NH-Isoxazolidines as Organocatalysts

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You cannot teach a man anything; you can only help him find it within himself.

Galileo Galilei (1564-1642)

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To My Parents With Love

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Lastly and by no means least Rob, we started on this journey together eight years ago and throughout that time so much has changed. Thank you firstly for your friendship over the years; for your love, support and encouragement and for being by my side through thick and thin.

Declaration

I hereby certify that this thesis has not been submitted before, in whole or in part, to this or any other university for any degree and is, except where otherwise stated, the original work of the author.

Signed: _____ Date: _____

Linda Doyle

Abstract

This thesis describes the preparation and use of a range of *N*-unsubstituted bicyclic isoxazolidines as potential organocatalysts in iminium ion and enamine catalysis.

The first chapter gives an overview of state-of-the-art organocatalysis. Reactions are discussed in terms of the catalytic mechanism and a selection of reactions catalysed by each route is included.

The second chapter discusses the design of two generations of *N*-unsubstituted isoxazolidine frameworks as potential organocatalysts. The 1st generation, containing a spirocyclohexane adjacent to the secondary amine of an isoxazolidine ring proved difficult to prepare and debenzylation of the parent was problematic. The 2nd generation, based on an isoxazolidine ring fused to a second heterocycle, were successfully prepared and characterised by a combination of NMR spectroscopy, LC/TOF-MS, microanalytical data and x-ray crystallography where necessary.

In the third chapter the application of *NH*-isoxazolidines as catalysts in the Diels-Alder cycloaddition reaction, the Michael addition reaction and the Aldol condensation reaction is discussed. It has been demonstrated that the *NH*-isoxazolidines are effective in iminium ion catalysis and act as enantioselective organocatalysts for Diels-Alder reactions. The aldol reaction between acetone and *p*-nitrobenzaldehyde could not be promoted by the *NH*-isoxazolidines prepared in this thesis. Neither could these catalysts promote the Michael addition reaction with *trans*-β-nitrostyrene and a minor amount of the Michael addition product was observed with 1,1-bis(benzenesulfonyl)ethylene as the acceptor.

The fourth chapter details the experimental procedures and full characterisation of all new compounds described in this thesis.

The appendix carries details of the structures solved by x-ray crystallographic analysis and as a representative a case full description of structural determination of a bicyclic isoxazolidine is detailed.

Finally, a complete bibliography of articles referred to in this thesis is included.

Abbreviations

acac	Acetylacetonate
ACD	Advanced Chemistry Development
ACDC	Asymmetric counterion-directed catalysis
BHT	2,6-Di-*tert*-butyl-4-methylphenol
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bmim	1-Butyl-3-methylimidazolium
BNHP	1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate
Boc	*tert*-Butyloxycarbonyl
CAN	Ceric ammonium nitrate
Cbz	Carboxybenzyl
CSA	Camphorsulfonic acid
d.e.	Diastereoisomeric excess
DCA	Dichloroacetic acid
DCM	Dichloromethane
DME	Dimethyl ether
DMSO	Dimethylsulfoxide
DNBA	2,4-Dinitrobenzoic acid
EDG	Electron-donating group
EWG	Electron-withdrawing group
e.e.	Enantiomeric excess
e.r.	Enantiomeric ratio
FDA	Food and Drug Administration
Fmoc	Fluoren-9-ylmethoxycarbonyl
FO	Frontier orbital
GLC	Gas liquid chromatography
H-Bonding	Hydrogen bonding
HFIP	Hexafluoroisopropanol
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
LA	Lewis acid
LUMO	Lowest unoccupied molecular orbital

MTBE	Methyl-*tert*-butyl ether
n.d.	Not determined
n/a	Not available
NCS	*N*-Chlorosuccinimide
NFSI	*N*-Fluorodibenzenesulfonimide
NMN	*N*-Methylmalemide
NMP	*N*-Methylpyrrolidine
MO	Molecular orbital
PEG	Poly-(ethylene glycol)
RDS	Rate determining step
SOMO	Singly occupied molecular orbital
p-TsOH	*p*-Toluenesulfonic acid
TS	Transition state
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TCA	Trichloroacetic acid
TES	Triethylsilane
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TRIP	3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate
V.T.	Variable temperature

Introduction

1.1 Introduction

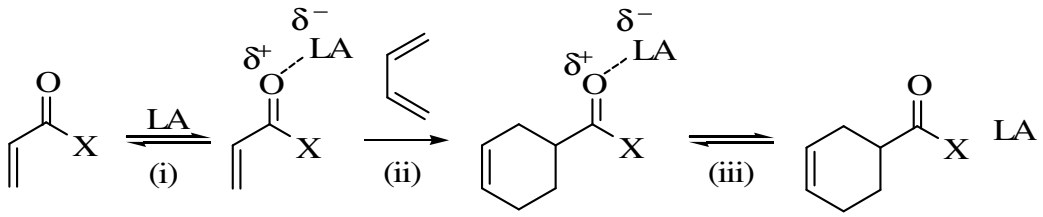
The value of asymmetric catalysis to organic synthesis is reflected in the awarding of the Nobel Prize in 2001 to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless.[1-3] In a time when the route to chiral compounds involved biochemical processes or the synthesis of racemic compounds followed by laborious resolution, these laureates showed that with a catalytic system comprising chiral ligands bound to metals a diverse range of organic transformations and industrial processes could be conducted with high levels of selectivity. The area of asymmetric catalysis has since expanded to include a variety of metal and organic mediated, catalytic enantioselective reactions and covers a wide range of reaction mechanisms and experimental conditions.[4-8]

In the pharmaceutical sector, stereoselective reactions are profoundly important because one or the other enantiomer of a compound can have beneficial or disastrous therapeutic effects. The awareness of this phenomenon intensified when the teratogenic effects of thalidomide, once prescribed to pregnant women, emerged in the 1960s. In 1992 the U.S. Food and Drug Administration (FDA) issued a policy on stereoisomeric drugs encouraging the commercialisation of clinical drugs as single enantiomers. From an economic standpoint the synthesis of enantiomerically pure compounds minimises the losses incurred from making racemic compounds. In 2006, 80% of small drugs approved by the FDA were chiral and 75% were single enantiomers.[9]

The area of transition metal catalysis has received much attention and a vast array of papers, books and reviews has been published in this area.[10-12] Most commonly in industry, transition metal complexes are used as asymmetric catalysts because of their high reactivity and high selectivity; however, they are not free from problems. The metals used are often expensive, they may be toxic and can be difficult to remove from the reaction products.[13]

Lewis acids have also found broad use as asymmetric catalysts for a variety of organic transformations. They generally exert their influence through activation of both conjugated and isolated π-systems toward nucleophilic attack.[14] The Diels-Alder reaction, shown in scheme 1, represents a typical Lewis acid catalysed reaction. The mechanism involves reversible binding of the Lewis acid to the electrophilic substrate resulting in redistribution of π-electrons toward the electropositive metal centre. This distribution of electrons lowers the energetic potential of the lowest unoccupied

molecular orbital, LUMO, resulting in an increased susceptibility toward combination with the highest occupied molecular orbital, HOMO, of the reaction partner, the diene in this case. Following bond formation, lability of the Lewis acid-product bond allows for catalyst turnover.



Scheme 1. Typical Lewis-acid catalysed Diels-Alder reaction.

While various types of Lewis acid-promoted reactions have been developed, and the reactions have been popular in industry, a significant drawback to their attractiveness lies in the requirement for strictly anhydrous conditions. More recently, however, Lewis acids have been developed which are stable in aqueous conditions.[15]

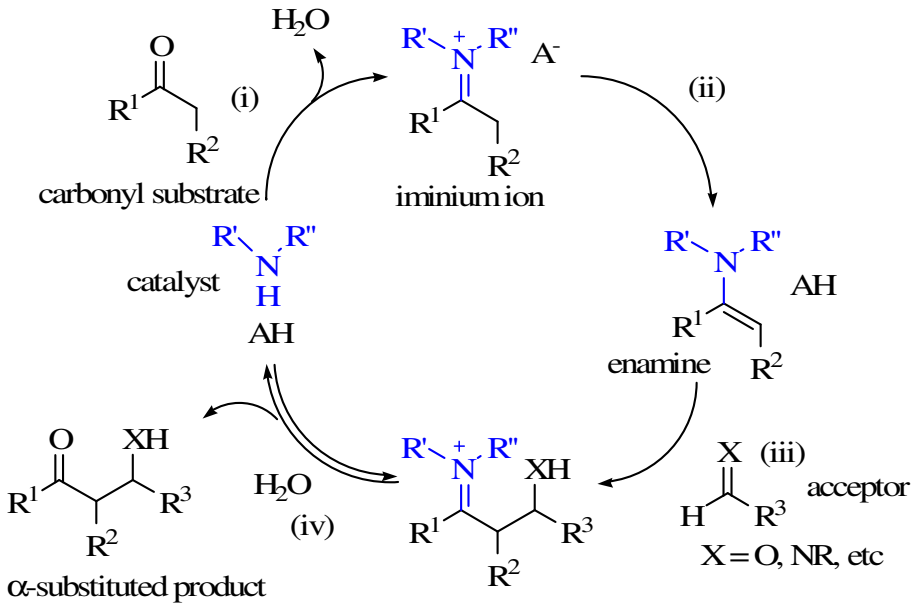
Ideally enantioselective catalysis should to be efficient, facile, reliable and economic if it is to be used widely in the pharmaceutical sector. There is a great hope that these requirements can be met by the employment of organocatalysts.

Organocatalysis is described as "the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom".[8] Unlike metal-ligand complexes, organocatalysts generally tolerate aerobic conditions and do not require rigorous exclusion of water. They tend to be inexpensive and possess a wider substrate scope than enzymes and can be used in a variety of organic solvents. Research in this area began in earnest in 2000 and in the intervening period numerous laboratories have contributed to develop the now large number of reactions which can be promoted by organocatalysts[7,16]. The remainder of this introduction aims to give an overview of the scope of organocatalysis as a tool for the modern synthetic chemist. The reactions are discussed in terms of the catalytic mechanism and are classified as follows: (i) Enamine Catalysis (ii) Iminium Ion Catalysis (iii) Counterion Catalysis (iv) Singly Occupied Molecular Orbital, SOMO, Catalysis and (v) Hydrogen-Bonding Catalysis. For each activating mechanism, a basic background and description is included together with a selection of reactions that have been catalysed by that particular route.

1.2 Enamine Catalysis

1.2.1 Introduction to Enamine Catalysis

Enamine catalysis is described as the catalysis, by primary or secondary amines, of electrophilic substitution reactions at the α-position of carbonyl compounds.[17] A generic example of activation by an enamine-based catalytic cycle is shown in scheme 2. The catalytic cycle involves (i) the formation of an iminium ion between a donor carbonyl compound and the amine-containing catalyst, (ii) the formation of an enamine intermediate from the iminium, (iii) C-C bond formation between the enamine and the acceptor substrate, and (iv) hydrolysis of the resulting iminium ion to release the product.



Scheme 2. Enamine catalytic cycle.

The key to enamine catalysis is the increase in the nucleophilicity that ensues from the conversion of the carbonyl substrate to the enamine. This transformation results in an increase in the energy of the HOMO and is comparable to Lewis acid activation of carbonyl substrates, figure 1a,b.

Enamine catalysis has three historic roots.[18] The first is the stoichiometric chemistry developed by Stork and others, which outlines the general utility of enamines as nucleophiles in organic synthesis.[19,20] The second is biochemical, with aldolases

exploiting enamine catalysis as an approach to carbon-carbon bond-formation.[21] The third and final pillar of enamine catalysis builds on the Hajos-Parrish[22] and Weichert, Sauer and Eder (*S*)-proline, **1**, catalysed aldol reaction.[23] Since the beginning of this millennium the field of asymmetric enamine catalysis has undergone an explosive growth and there are a number of excellent reviews in this area.[7,8,17,18,24-29] The author has endeavoured to select a variety of synthetic transformations to demonstrate the power of enamine catalysis.

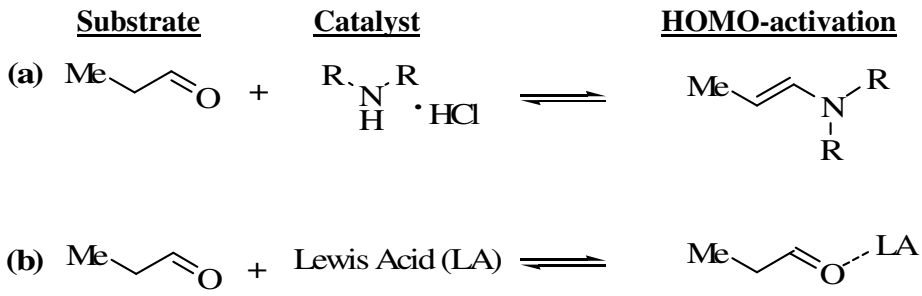


Figure 1. Carbonyl group HOMO activation **(a)** by primary or secondary amine organocatalysts and **(b)** by Lewis acids.

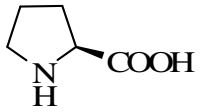


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Figure 2. (*S*)-Proline.

1.2.2 Aldol Reaction

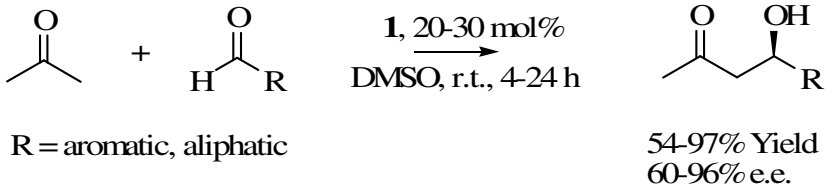
1.2.2.i Introduction

The aldol reaction is one of the most fundamental tools for the construction of new C-C bonds and consequently the ability to control its stereochemistry has attracted considerable interest.[30] Recently small chiral organic molecules have been found to catalyse the direct aldol addition of unmodified ketones to aldehydes with relatively high chemical and stereochemical efficiency.

1.2.2.ii Intermolecular aldolisations

The first amine-catalysed asymmetric direct intermolecular aldol reaction was reported by List *et al.* in 2000.[31] The reaction between excess acetone and aromatic or α-

branched aldehydes in DMSO was found to proceed in the presence of (*S*)-proline to furnish the products with high yields and enantioselectivities. α-Branched and α-trisubstituted aldehydes were found to be excellent substrates for this reaction, equation 1.



Equation 1. (*S*)-Proline catalysed intermolecular Aldol reaction.

A screen of potential catalysts for the aldol reaction between acetone and *p*-nitrobenzaldehdye, **2**, indicated that neither simple primary α-amino acids, e.g. **3**, nor acyclic *N*-methylated α-amino acids, e.g. **4**, were catalytically active and that (*S*)-proline was the most active catalyst for the reaction.[31,32] Among the "proline-type" cyclic α-amino acids only the thiazolidine carboxylic acid **5** was found to provide yields and enantioselectivities similar to those provided by (*S*)-proline, figure 3.[31]

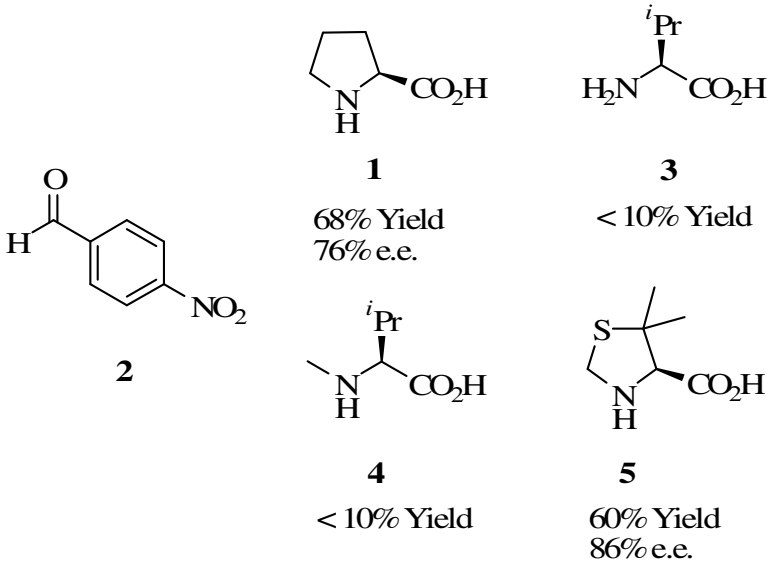


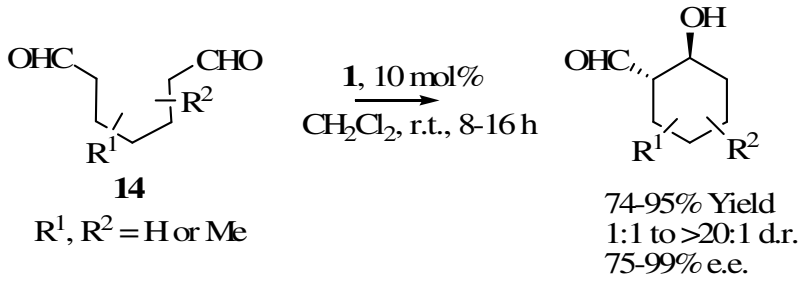
Figure 3. Potential catalysts for the aldol reaction between *p*-nitrobenzaldehyde, **2**, and acetone.

The mechanism for (*S*)-proline catalysed aldol reactions as proposed by Barbas, Lerner and List is shown in scheme 3. The initial step involves the formation of an N-C bond between the *N*-atom of proline and the carbonyl *C*-atom to give the intermediate, **6**. In the second step, elimination of H_2O leads to the zwitterion, **7**. The next step involves reprotonation of the carboxyanion and formation of the enamine, **8**, whose HOMO is higher in energy than that of acetone enhancing its nucleophilicity. The fourth step involves the formation of a new C-C bond with the aldehyde reaction partner, **9**, via transition state **10**. The transition state alignment is fixed by the catalyst so that *Re*-facial attack is preferred forming the iminium ion, **11**. Finally hydration and protonation at the pyrrolidine *N*-atom gives **12** and following proton transfer to the carboxylic acid the catalyst is reformed and the product **13** is released.

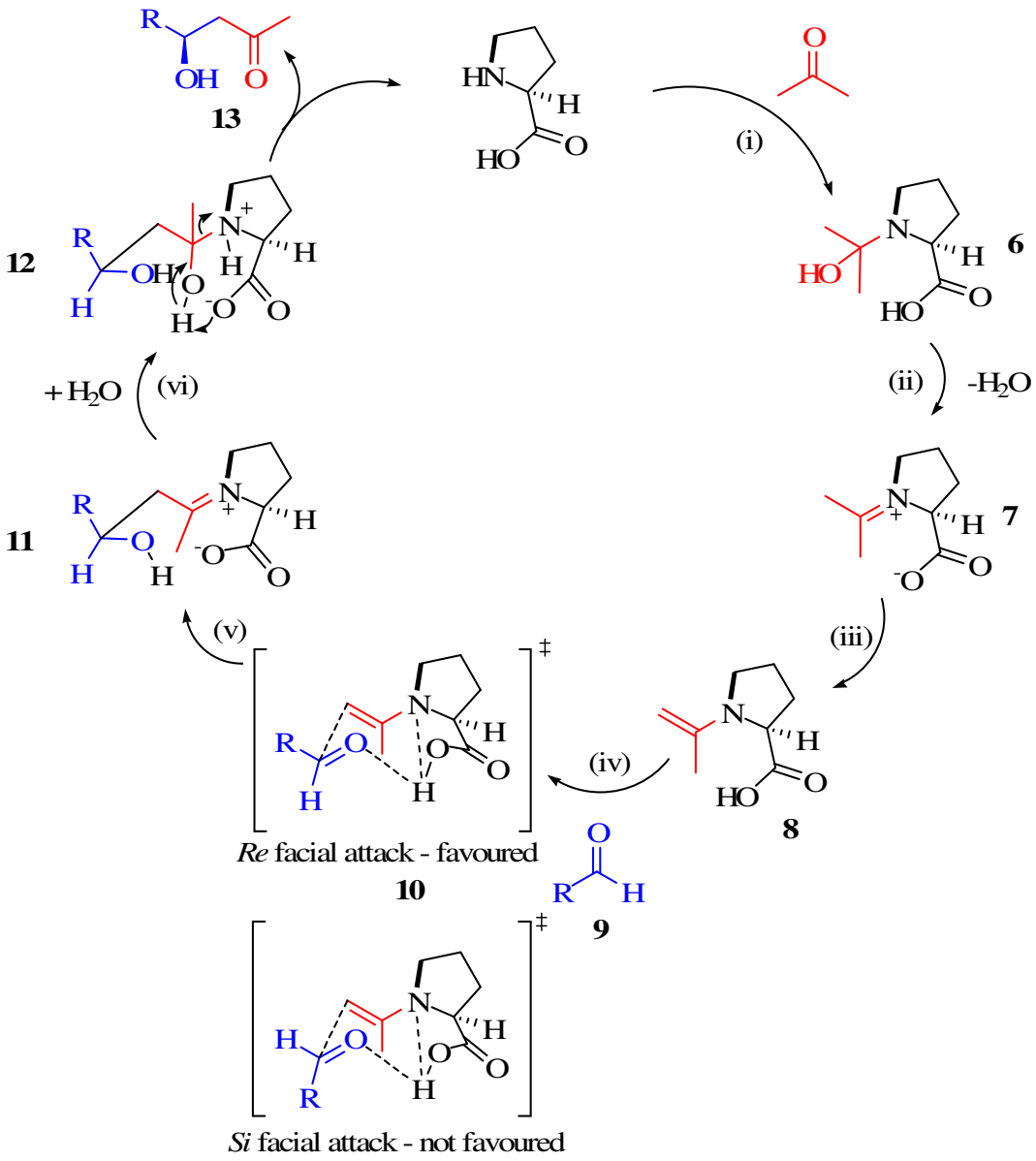
Ketones other than acetone can also be effective substrates in proline-catalysed aldolisations. However, if a large excess of the ketone component is required the synthetic utility can be limited by the availability of the ketone itself. Depending on the aldehyde partner enantioselectivities in the range of 41-85% e.e. have been achieved and diastereoselectivities up to >20:1 have also been recorded.[33-35]

1.2.2.iii Intramolecular aldolisations

A highly enantioselective aldolisation of dicarbonyl compounds was also reported, examples include the achiral heptanedials, **14**. Treatment of the heptanedials with (*S*)-proline furnished the corresponding hydroxyaldehydes with high enantioselectivities, equation 2.[36]



Equation 2. (*S*)-Proline catalysed intramolecular aldol reaction.



Scheme 3. Mechanism for the (*S*)-proline catalysed aldol reaction.

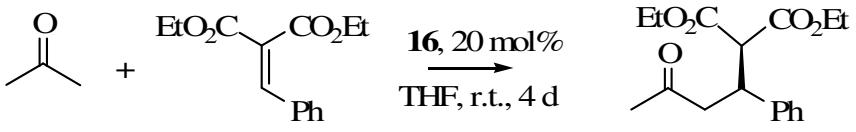
1.2.3 Michael Addition Reactions

1.2.3.i Introduction

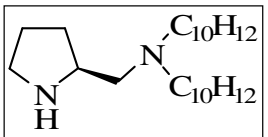
C-C bond formation by conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds is an important reaction in organic synthesis, versions of this reaction first reported in the 1900's involved catalysis by metalloprolinates.[37-40] This type of addition chemistry has continued to be an active area of research and in recent times organocatalysis has made significant contributions, of which a few examples are included in the following section.

1.2.3.ii α,β-Unsaturated carbonyl substrates as Michael acceptors

The addition of acetone to the highly activated Michael acceptor diethyl benzalmalonate, **15**, in DMSO was adopted as a model addition reaction by Barbas and co-workers.[41] (*S*)-Proline was found to catalyse the reaction; however the product was obtained in racemic form. A variety of chiral amines were subsequently screened in search of stereoselectivity and the hydrophobic diamine **16** was found to be the catalyst of choice yielding the product in 70% yield and with 64% e.e., equation 3.



15 70% Yield
64% e.e.



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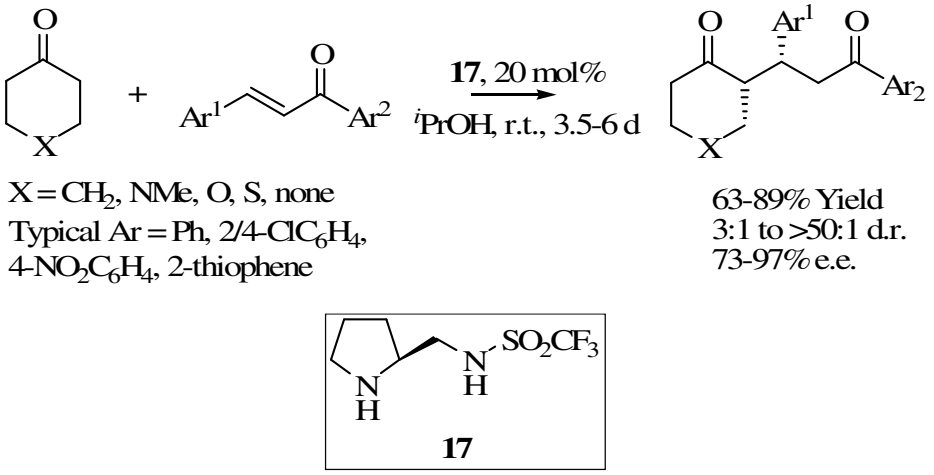
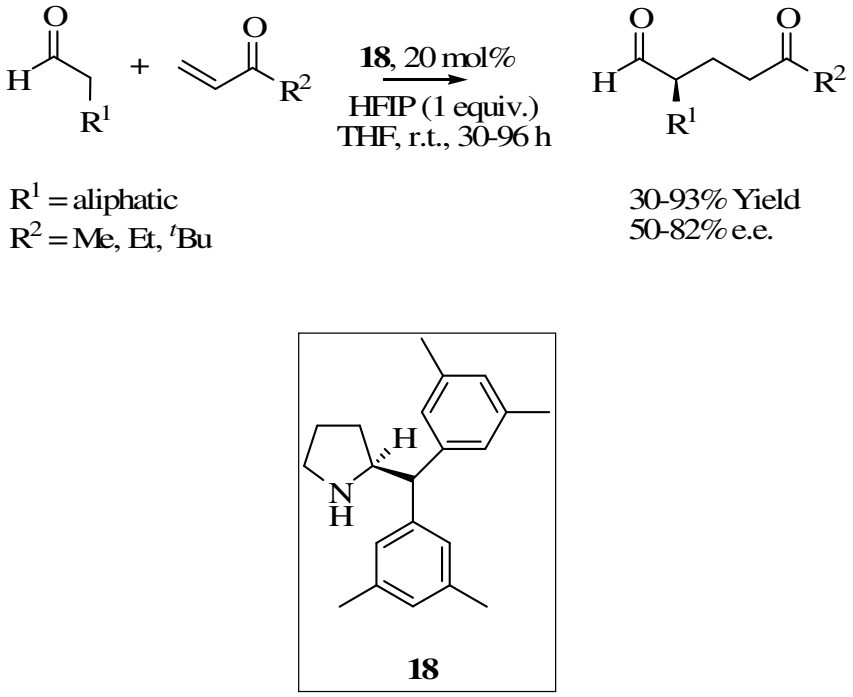
Equation 3. Organocatalysed Michael addition reaction between acetone and diethyl benzalmalonate.

Chiral diamines have also been found to be optimal catalysts for the Michael addition of cyclic ketones to α,β-unsaturated ketones.[42] As shown in equation 4, the proline sulfonamide **17** promoted the formation of the 1,5-dicarbonyl addition product with a high degree of stereoselectivity (>40:1 d.r. and up to 97% e.e.). Best results were observed for cyclic six-membered ketones and structural variation of the α,β-unsaturated ketones was tolerated without affecting the stereoselection.

Enantioselective conjugate addition of simple aldehydes to vinyl ketones have been developed with the pyrrolidine catalyst **18** bearing the bulky diaryl methyl group at the 2-position, highest yields and selectivities were observed using hexafluoroisopropanol (HFIP) as an additive. Product yields and selectivities were found to vary significantly with the size of the R group on the conjugated ketone, with methyl and ethyl vinyl ketone reacting faster and furnishing products with greater selectivity than that found for *tert*-butyl vinyl ketone, equation 5.[43]



Equation 4. Organocatalysed Michael addition of cyclic ketones to α,β-unsaturated ketones.

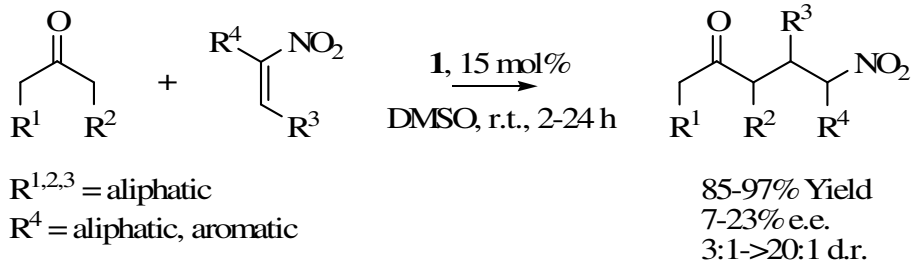


Equation 5. Enantioselective conjugate addition of simple aldehydes to vinyl ketones.

1.2.3.iii Nitroolefins as Michael acceptors

Intermolecular Michael reactions between ketones and nitroolefins were also catalysed by (*S*)-proline, equation 6.[44] Initial reactions were conducted in DMSO and although the reaction proceeded with low enantioselectivity, diastereoselectivity and chemical yields were high.

Protic solvents are most commonly used in proline-catalysed reactions thus it was anticipated that replacement of DMSO with an alcohol may increase the amount of dissolved proline and so promote the reaction. Accordingly, in methanol the selectivities were increased to 76% e.e. and up to 65:1 d.r.[45]

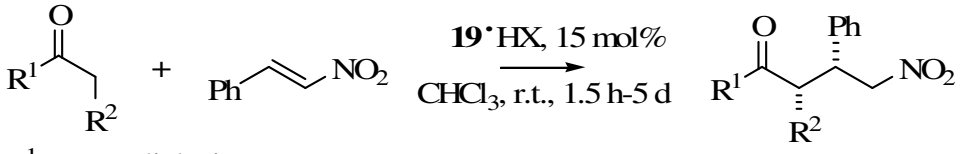


Equation 6. Intermolecular Michael reaction between ketones and nitroolefins catalysed by (S)-proline.

Diamines were also used as Michael addition catalysts.[46,47] In early examples Alexakis and Andrey employed the diamine **19** to catalyse the addition of a range of aldehydes and ketones to *trans*-β-nitrostyrene.[46] Enantioselectivities and diastereoselectivities of the resulting products were modest for most of the acyclic and cyclic ketone substrates (23-76% e.e.), but were excellent for the aldehydes. The addition of an acid co-factor was observed to effect an increase in the rate of the reaction by facilitating enamine formation and suppressing side reactions. Further, in the case of nonsymmetrical ketones, acid additives, such as *p*-toluenesulfonic acid or hydrochloride, the regioselectivity of the addition was found to be affected.[46]

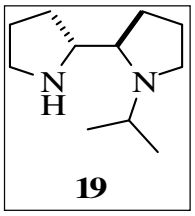
1.2.3.iv Vinyl sulfones as Michael acceptors

In 2005, Alexakis and Mossé reported the first asymmetric diamine catalysed Michael addition of aldehydes to vinyl sulfones. The adducts obtained in good yields had high enantioselectivities, equation 8.[48] In general the more hindered the aldehyde the better the stereoinduction.



R^1 = H or aliphatic
R^2 = aliphatic

R^1	HX	% Yield	% e.e.
H	None	99	61-66
H	HCl	86-99	67-79
Aliphatic	None	29-61	29-37
Aliphatic	HCl	55-95	25-76
Aliphatic	*p*-TsOH	74-99	23-48



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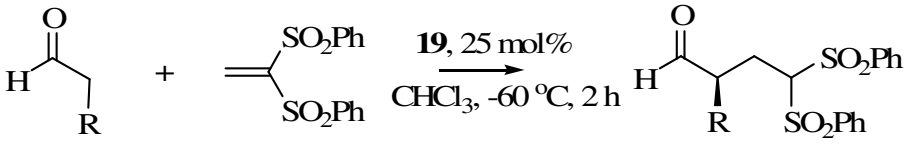
Equation 7. Organocatalysed Michael addition of a range of aldehydes and ketones to *trans*-β-nitrostyrene.



R = ^{i}Pr, ^{t}Bu, Me, Et

71-78% Yield
53-80% e.e.

Equation 8. Diamine catalysed Michael addition of aldehydes to vinyl sulfones.

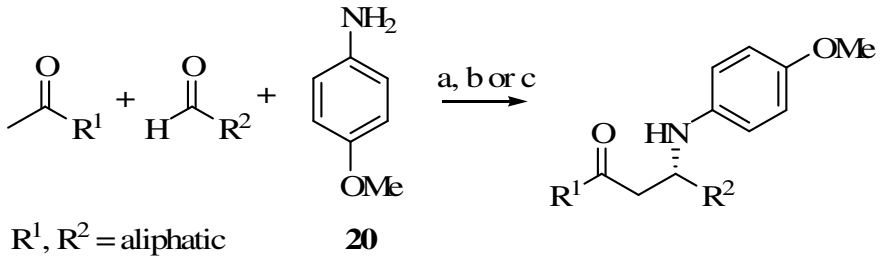
1.2.4 Mannich Reaction

1.2.4.i Introduction

The Mannich reaction is a valuable transformation for the construction of nitrogenous molecules; however the first catalytic asymmetric version was only developed in recent years and the direct three-component Mannich reaction stood as a major challenge for asymmetric catalysis.[49,50]

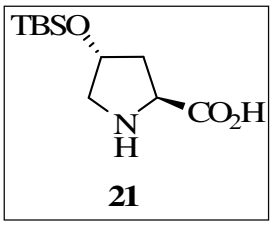
1.2.4.ii Direct Mannich reaction

In 2000, List published the first efficient organocatalytic asymmetric three-component Mannich reaction of acetone with *p*-anisidine, **20**, and a variety of aldehydes in DMSO.[51] The reaction was catalysed by (*S*)-proline and the products were obtained in good to excellent yields with up to 99% enantioselectivities, equation 9a. However, in some cases aldol addition and condensation products were observed as side products during the reaction. The substituted proline **21** was found to be an even more effective catalyst in the same reaction and accordingly the catalyst loading could be reduced to 5 mol% without compromising the enantioselectivity.[52] Interestingly, whilst (*S*)-proline was found inefficient for the direct catalytic Mannich reaction with electron-rich aldehydes, in the presence of **21** such substrates react well, equation 9b. The Mannich reaction of enolisable aldehydes with *p*-anisidine was also reported by Hayashi *et al.*[53] At room temperature the Mannich product was formed in less than 10% yield. Lowering the reaction temperature to -20 °C and changing the solvent to *N*-methyl-2-pyrrolidinone (NMP) caused an increase in reaction yield, diastereoselectivity and enantioselectivity, equation 9c.



Conditions	% Yield	% e.e.
a. 1, 35 mol%, DMSO, r.t., 12-48 h	70-99	61-85
b. 1 or **21**, 5 mol%, DMF, -20 °C, 20 h	**1** <5 **21** 48-63	n.d. 90-98
c. 1, 10 mol%, NMP, -20 °C then $NaBH_4$, MeOH	55-99[a]	71-99[a]

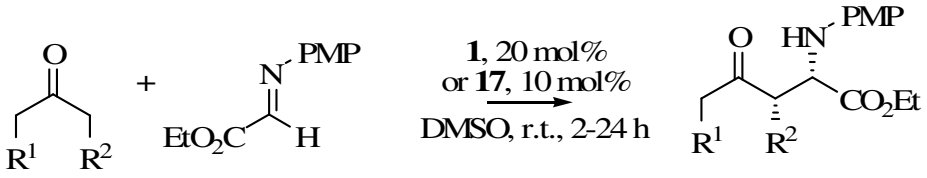
[a] Results for the corresponding alcohol.



Equation 9. Organocatalytic direct three-component Mannich reaction of acetone with *p*-anisidine and a variety of aldehydes in DMSO.

1.2.4.iii Indirect Mannich reaction

The indirect Mannich reaction between aldimines and ketones was shown to proceed with high stereoselectivity under the influence of (*S*)-proline, equation 10.[54] A solvent screen (acetone, $CHCl_3$, EtOAc, toluene, THF and 1,4-dioxane) revealed little solvent influence over yield and stereoselectivity. However, higher diasteroselectivities were achieved as the bulk of the aldehyde donor increased. The same reaction was catalysed by the proline sulfonamide **17** and whilst the product yields were higher similar stereoselectivities were noted.[55]



Typical R^1, R^2 = H, Me, -$(CH_2)_4$-,

Catalyst	% Yield	d.r.	% e.e.
1	47-85	>19:1	61-99
17	74-91	>19:1	96-99

Equation 10. Indirect Mannich reaction between aldimines and ketones.

1.2.5 *α-Heteroatom Functionalisation of Carbonyl Compounds*

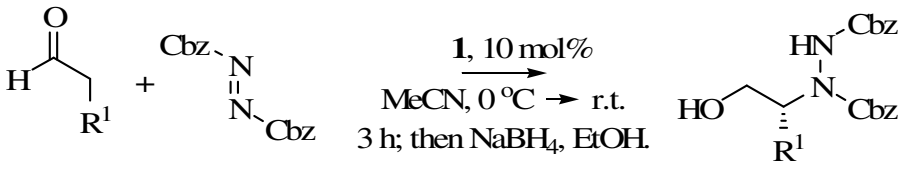
1.2.5.i Introduction

The stereochemical control of the transformation of a C-H bond to a stereogenic C-X (X = O, N, F, Cl, Br, S) bond adjacent to a carbonyl functionality is a fundamental challenge and of importance in chemistry and thus much effort has gone into this area in recent years.[56]

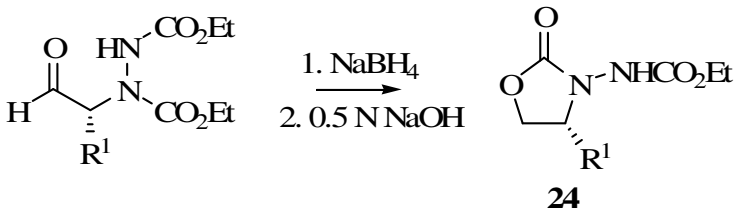
1.2.5.ii α-Amination of aldehydes

The first direct catalytic α-amination of aldehydes was reported independently by Jorgensen *et al*[57] and List[58] in 2002. In one case azodicarboxylates **22** were employed as the nitrogen electrophile with a slight excess of aldehyde. The reaction was catalysed by (*S*)-proline and the α-hydrazino aldehydes, **23**, were obtained directly in moderate to high yields and with high enantioselectivities, equations 11 and 12. In Jorgensen's work the hydrazine was immediately converted to corresponding *N*-aminoxazolidinones **24**

via reduction and cyclisation, equation 12. In a more recent development the proline sulfonamide **25** was identified as an alternative catalyst for the α-amination reaction, only 1 mol% was required to catalyse the reaction with good yields and enantioselectivities, however the use of branched aldehydes in the reaction lowered both the yield (18%) and enantioselectivity (61% e.e.).[59] Although in general the enantioselectivities are lower than those found with (*S*)-proline the attractive feature of **25** is the low catalyst loading.

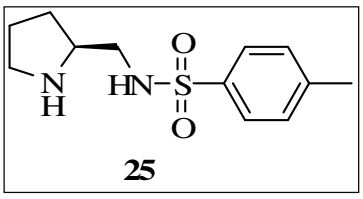


Equation 11. Organocatalytic α-amination of aldehydes with azodicarboxylates.



Catalyst	% Yield	% e.e.
1	57-92	89-95
25	58-88	80-87
	18[a]	61[a]

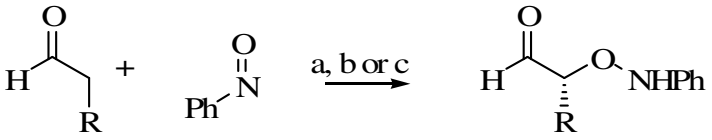
[a] $R^1 = {}^i Pr$



Equation 12. The reduction and cyclisation of the hydrazine to the corresponding N-aminoxazolidinones.

1.2.5.iii α-Oxygenation of aldehydes

(*S*)-Proline catalysed α-aminoxylation of aldehydes was reported simultaneously by Zhong[60], MacMillan[61] and Hayashi.[62] In Zhong's experiment 20 mol% of (*S*)-proline was employed, DMSO was selected as the solvent and the reaction was conducted at room temperature. Following reduction the alcohol was obtained in good yields and with high enantioselectivities, equation 13a.[60] In MacMillan's version the same level of enantioselectivity was achieved using much lower catalyst loading (typically 2-5 mol%, but 0.5 mol% is also possible) when conducting the reaction in $CHCl_3$ at 4 ^oC. The same group noted that considerable variation in the steric demands of the aldehyde could be tolerated without loss in efficiency or enantiocontrol, equation 13b.[61] Finally, Hayashi's procedure employed 30 mol% (*S*)-proline and acetonitrile as the reaction solvent at -20 ^oC; again similar enantioselectivities were observed, equation 13c.[62]



R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, Ph, Bn

Conditions	% Yield	% e.e.
a. 1, 20 mol%, DMSO, r.t., 10-20 mins then $NaBH_4$, EtOH	54-86[a]	94-99[a]
b. 1, 2-5 mol%, $CHCl_3$, 4 ^oC, 4h	76-95	97-99
c. 1, 30 mol%, CH_3CN, 0 to -20 ^oC, 24 h	53-81	95-99

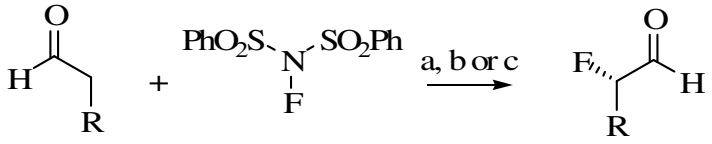
[a] Results for corresponding alcohol.

Equation 13. (*S*)-Proline catalysed α-aminoxylation of aldehydes.

1.2.5.iv α-Fluorination of aldehydes

The α-fluorination of aldehydes and ketones has been reported by a number of groups, the most popular approach involves reaction between *N*-fluorodibenzenesulfonimide (NFSI, **26**) and aliphatic aldehydes. Both the pyrrolidine, **27**, and the imidazolidinone, **28**, were found to be suitable catalysts. Only 1 mol% of **27** was required to obtain the products in good to high yields (55 to >95%) and excellent enantioselectivities (91-97% e.e.), equation 14a.[63] The imidazolidinone was used both alone in a stoichiometric amount, and together with an acid co-factor, e.g. dichloroacetic acid (DCA).[64,65] In the former case the reaction was conducted in DMF at 4 ^oC and products were obtained in moderate to good yields (40-97%) and with good to excellent enantioselectivities (86-

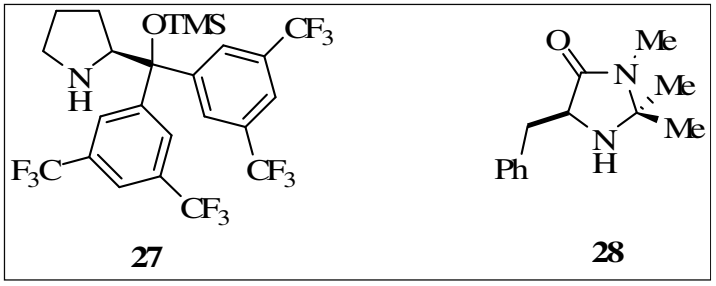
96% e.e.), equation 14b.[64] When used together with DCA as co-factor the catalyst loading was 20 mol% and a 10% ^{i}PrOH/THF solvent system was selected. Again good to excellent product yields (54-96%) and excellent enantioselectivities (91-99% e.e.) for the corresponding alcohol were observed, equation 14c.



26

Conditions	% Yield	% e.e.
a. 27, 1 mol%, MTBE, r.t., 1 h	53-95	91-97
b. 28, 1 equiv., DMF, 4 ^{o}C, 4 h	40-97	86-96
c. 28•DCA, 20 mol%, ^{i}PrOH/THF, -10 ^{o}C, 10-12 h then $NaBH_4$, DCM	54-96[a]	91-99[a]

[a] Results for corresponding alcohol.

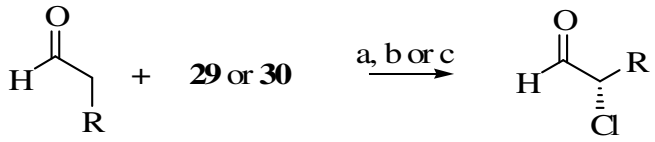


27 **28**

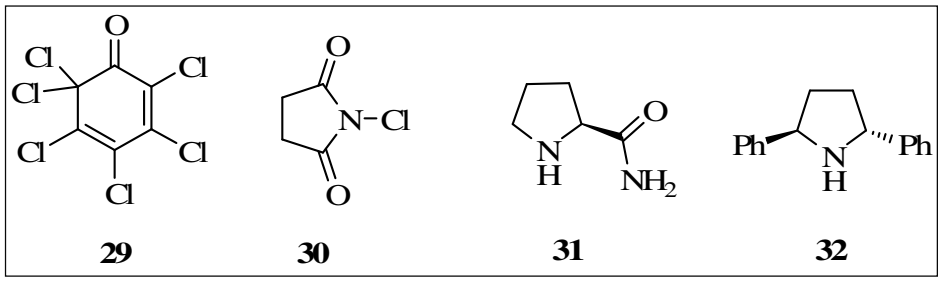
Equation 14. Organocatalytic α-fluorination of aldehydes and ketones.

1.2.5.v α-Chlorination of aldehdyes

Enantioselective α-chlorination of aldehydes was independently reported by MacMillan[66] and Jorgensen[67] in 2004. MacMillan's group found the reaction could be catalysed by the TFA salt of the chiral imidazolidinone **28** and perchlorinated quininone **29** was the chlorinating agent of choice. The reaction was compatible with a range of organic solvents without significant alteration of yield or enantioselectivity, equation 15a.[66] Jorgensen's group chose *N*-Chlorosuccinimide (NCS), **30**, as the chlorinating agent and either (*S*)-proline amide, **31**, or diphenylpyrrolidine, **32**, as catalysts, equation 15b,c.[67] Although the proline derivative **31** was a more active catalyst than the pyrrolidine **32**, in most cases the latter was found to induce higher enantioselectivities.



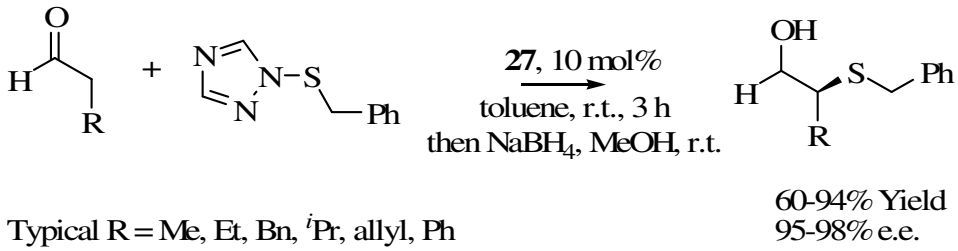
Conditions	% Yield	% e.e.
a. R = *n*-pent, cyclohexanone, Ph **28**•TFA, 5 mol%, acetone, -30 °C, 6-24 h	91-95	80-95
b. R = Me, Et, ^{i}Pr, ^{t}Bu, Bn, Allyl **31**, 10 mol%, CH_2Cl_2, r.t. or -24 °C, 1-10 h	90-99	70-95
c. R = Me, Et, ^{i}Pr, ^{t}Bu, Bn, Allyl **32**, 10 mol%, CH_2Cl_2, r.t. or -24 °C, 1-10 h	82-99	81-97



Equation 15. Enantioselective α-chlorination of aldehydes.

1.2.5.vi α-Sulfenylation of aldehydes and ketones

In 2004, Wang *et al.* reported the α-sulfenylation of aldehydes and ketones using commercially available electrophilic sulfur sources, e.g. *N*-(phenylthio)phthalimide, dimethylsulfide and diphenyldisulfides. The reaction was conducted with the diphenyl pyrrolidine **32**, and whilst yields in the range 42-88% were obtained no enantioselectivities were reported.[68] In the following year, however, Jorgensen presented the first stereoselective version of the reaction employing the diarylprolinol silyl ether **27** as the catalyst.[69] α,α-Disubstituted aldehydes were also shown to be suitable substrates for this reaction.



Equation 16. The α-sulfenylation of aldehydes and ketones.

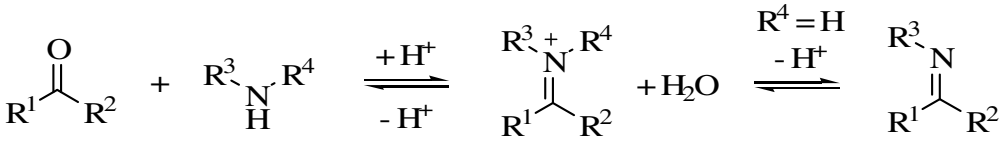
1.2.6 Concluding Remarks on Enamine Catalysis

Within only a few years since its conceptualisation, the area of enamine catalysis has developed very significantly. (*S*)-Proline has shown itself to be an efficient and widely applicable organocatalyst generally giving products in high chemical yields and with high enantioselectivities. The introduction of pyrrolidine-based catalysts increased the scope of reactions catalysed by enamine catalysis and in many cases the yields and enantioselectivities were increased when compared to (*S*)-proline. The excellent results outlined in the above section confirm that enamine catalysis has indeed established itself as a powerful means for asymmetric synthesis.

1.3 Iminium Catalysis

1.3.1 Introduction to Iminium Catalysis

The reversible formation of an iminium ion by condensation of an amine catalyst with a carbonyl substrate is central to iminium catalysis. The reaction was first discovered in 1864 by Schiff, and imines are also referred to as Schiff bases, scheme 4.[70] Primary amine-derived imines (R^4 = H) are basic ($pK_a \simeq 7$) and exist as iminium ions in acidic solution.[71]



Scheme 4. The formation of imines/Schiff bases.

Aldehydes and ketones also condense with secondary amines to form iminium cations, which can only be isolated as salts of strong acids. In iminium catalysis secondary amines tend to dominate the field, though catalysis by both primary and secondary amines has been demonstrated. For catalytic activity primary amines always require an acid co-catalyst but co-factors are also very commonly employed with secondary amine catalysts.

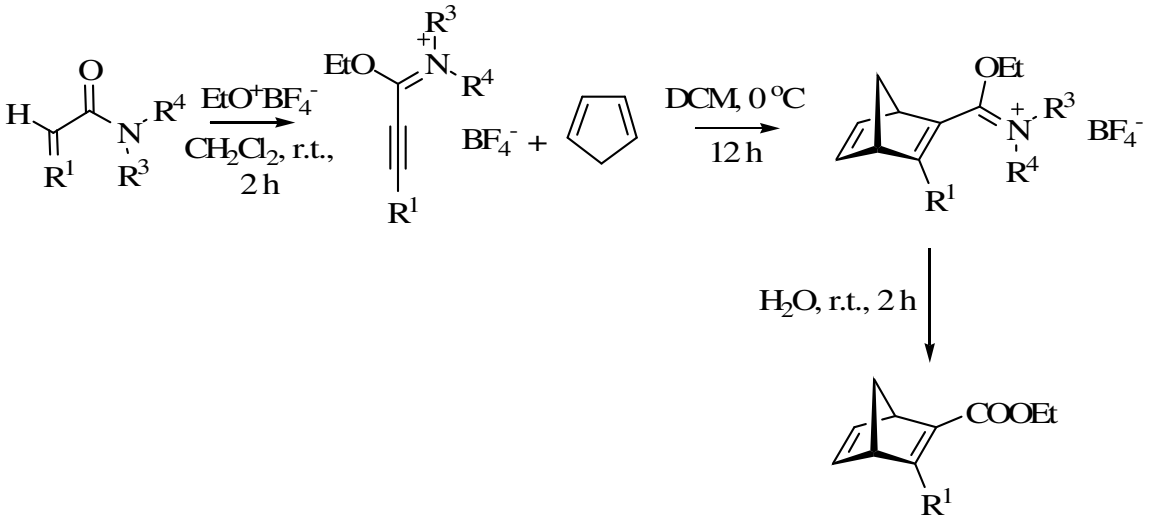
Since MacMillan's introduction of the imidazolidinone catalyst family in 2000, many cyclic amines, mainly substituted pyrrolidines, have been employed as iminium ion catalysts.[72] As in enamine catalysis, (*S*)-proline and its derivatives have been very popular, especially for a variety of ring forming and domino reactions. Iminium catalysis has been applied to a large range of reactions and the author attempts to illustrate its scope in the following sections.

1.3.2 Cycloaddition Reactions

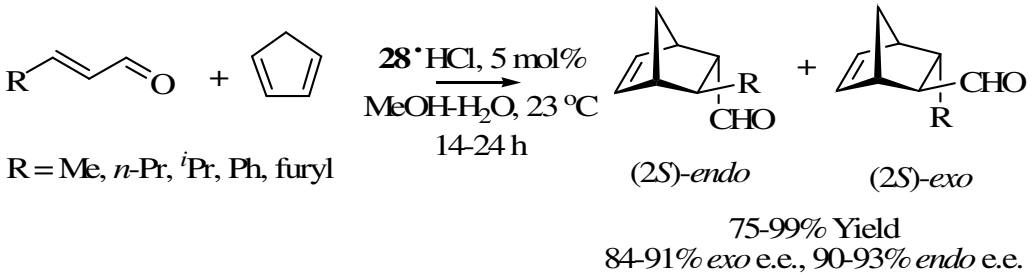
1.3.2.i [4+2]-Cycloadditions

Baume and Viche reported in 1976 that the [4+2]-cycloaddition of iminium salts with cyclopentadiene proceeded much more rapidly than the analogous Diels-Alder reaction with the parent carbonyl substrate.[73] However, as the iminium ions were pre-prepared and not *in situ* the reactions were not deemed catalytic. A number of years later Jung *et al.* reported the first enantioselective version of the same reaction which also involved preformed iminium ions, scheme 5.[74] Thus MacMillan's report on the reaction between cyclopentadiene and a range of α,β-unsaturated aldehydes, catalysed by the imidazolidinone **28**, is deemed the first example of an organocatalytic Diels-Alder reaction, equation 17.[72] The imidazolidinone catalysed reaction between a range of aldehydes and cyclopentadiene at room temperature formed the cycloaddition products in high yields (84-93%) and enantioselectivities (90-95% e.e.). Since this original publication, amine catalysed Diels-Alder reactions of α,β-unsaturated aldehydes have received much attention.[29,71]

The proposed catalytic cycle for the iminium ion catalysed Diels-Alder reaction is shown in scheme 6.[72] Initially a reactive iminium ion is formed by the condensation of the secondary amine catalyst with the α,β-unsaturated carbonyl compound. The iminium ion formed then undergoes [4+2]-cycloaddition with the diene in the key bond-formation process. Finally hydrolysis of the iminium ion releases the *endo* and *exo* products and regenerates the catalyst.

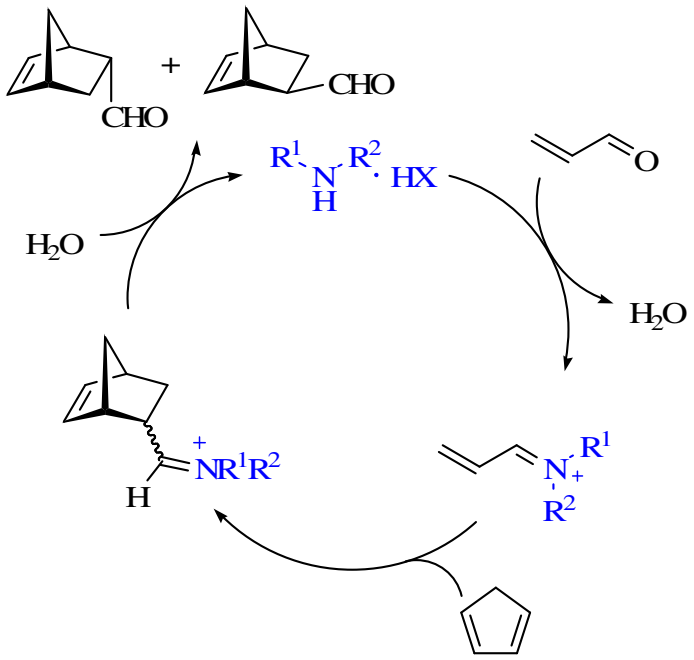


Scheme 5. The first enantioselective version of the [4+2] addition involving preformed iminium ions.

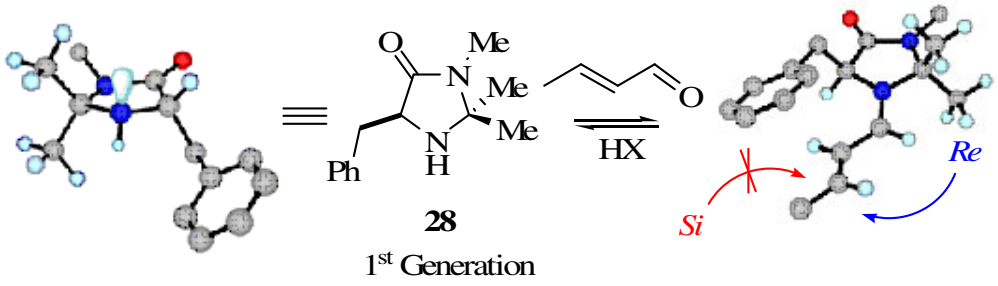


Equation 17. The Diels-Alder reaction between cyclopentadiene and a range of aldehydes.

MacMillan's first generation catalyst, the imidazolidinone **28**, was subject to kinetic studies which indicated that the overall rate of iminium catalysed-reactions was influenced by the efficiency of both the initial iminium ion formation and the carbon-carbon bond forming step.[75] As a result the imidazolidinone **33** was designed as a second generation catalyst with a view to more efficient formation of the iminium ion and consequently an increase in the reaction rate. In the new catalyst design the participating nitrogen lone pair is positioned away from structural impediments, a comparison between the two catalysts designs is shown in figure 4 and 5. It has also been found that the presence of a (5-methyl)furyl group at the 2-position of the imidazolidinone core permits enhanced catalysis of the Diels-Alder reaction with conjugate ketones, equation 18.[76]



Scheme 6. The proposed catalytic cycle for the iminium ion catalysed Diels-Alder reaction between acrolein and cyclopentadiene.



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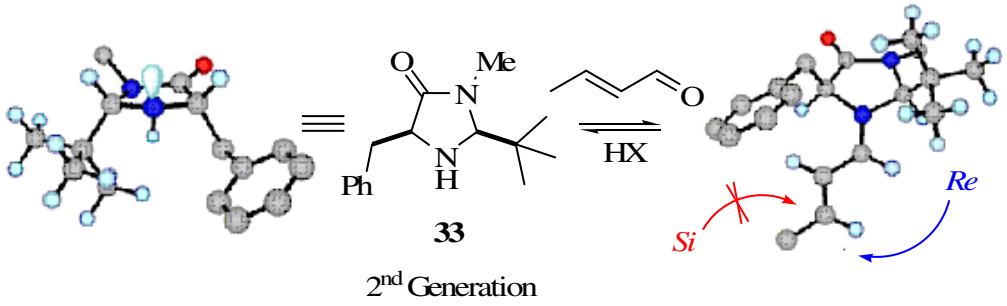
1st Generation

E-iminium geometry, *Re*-face exposed, *Si*-face sterically encumbered.

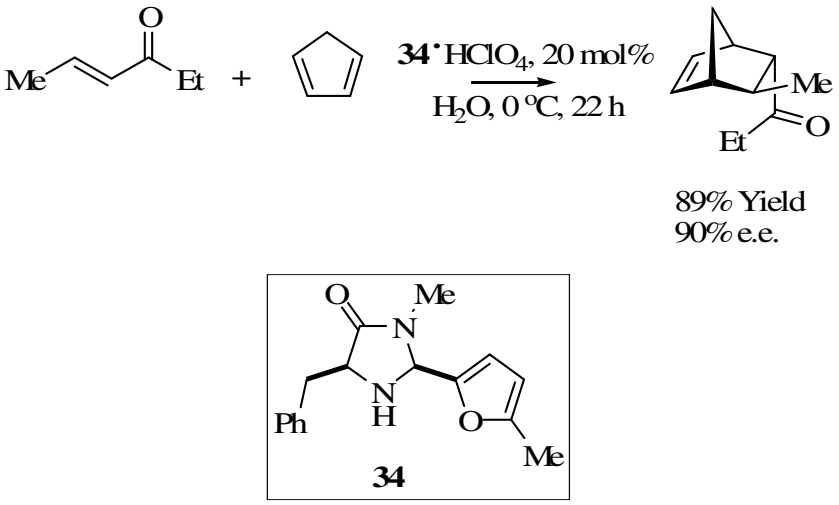
Figure 4. Computational model of the 1st Generation catalyst.



Nitrogen lone pair more exposed, leading to faster iminium ion formation.

Increased control of iminium ion geometry, *Re*-face more exposed.

Figure 5. Computational model of the 2nd Generation catalyst.



Equation 18. The Diels-Alder reaction with conjugate ketones in the presence of the 2nd generation catalyst.

The application of hydrazines as organocatalysts was proposed by both Tomkinson[77,78] and Ogilvie's groups.[79] In the design of hydrazine and hydroxylamine organocatalysts Tomkinson, Platts and co-workers endeavoured to improve the efficiency of the iminium catalysts by exploitation of the α-effect.[77,78]

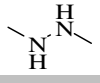
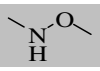
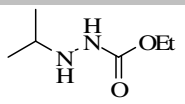
The α-effect is the significant increase in the nucleophilicity of a heteroatom by introducing an adjacent heteroatom. The origins of the observation are of some debate and several possible explanations have been offered including (i) the ground state of the nucleophile being destabilised by repulsion between the adjacent pairs of electrons[80]; (ii) stabilisation of the transition state by the adjacent pair of electrons[81,82] and (iii) the

adjacent pair of electrons reducing solvation of the nucleophile[83,84]. Since iminium ion formation involves a nucleophilic attack of the catalyst on the carbonyl substrate an increase in the nucleophilicity ought to render the catalyst more potent.

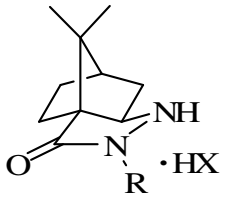
Tomkinson reported that simple hydrazines together with an acid co-factor catalyse the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene more efficiently than simple amines (Table 1, entry 1 *vs.* entries 2, 3 and 4) and that simple hydroxylamines were even more efficient (entry 2 *vs.* 3).[78] In further elaboration of the catalyst structure it was found that the introduction of an electron withdrawing group at the β-position made the hydrazine catalyst even more effective (entry 4).

Lemay and Ogilvie incorporated the hydrazine moiety into a chiral framework featuring a five-membered ring, a carbonyl group in the β-position and a bulky group positioned α- to the carbonyl in order to enhance selectivities. The camphor-derived hydrazine **35** is one example of their catalysts; together with an acid co-factor it was effective in promoting the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene. Both the yields and the enantioselectivity of the reaction products, summarised in figure 6, were found to be dependent on the nature of the acid co-factor, with stronger acids generally affording better results.[79] In iterative efforts to improve their catalyst Ogilive and co-workers altered the side chain and found that bulky substituents had a negative impact on both selectivity and reactivity, this was attributed to increased sterics during iminium ion formation.[85]

Table 1. Comparison of the efficiency of a range of organocatalysts containing an α-heteroatom in the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH or aqueous MeOH.[78]

Entry	Catalyst•HCl	Time (h)	% Yield of Diels-Alder product
1[a]		48	22
2[a,b]		72	48
3		72	80
4		6	90

[a] MeOH:H_2O 19:1 is used as the solvent. [b] Catalyst used as a *bis*-HCl salt.



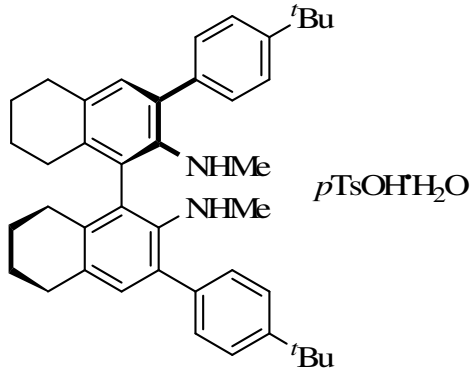
35

R	HX	pK_a [a]	% Yield	*endo* e.e.
Ph	$HClO_4$	-10	25	60
Bn	$HClO_4$	-10	90	82
CH_2-1-naphthyl	$HClO_4$	-10	82	74
Bn	CF_3CO_2H	-0.3	13	30
Bn	CF_3SO_3H	-14	89	88

[a] Values predicted with ACD™ labs.

Figure 6. The yields and enantioselectivities for the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in the presence of the hydrazine catalyst **35**.

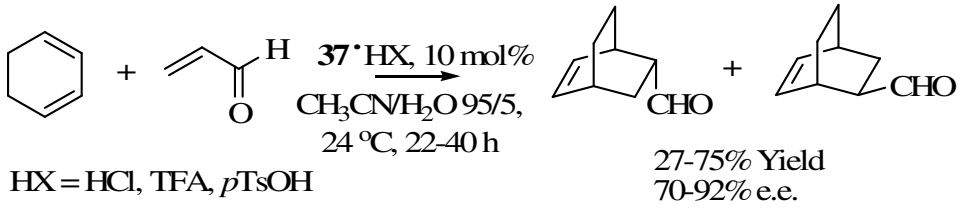
Maruoka and co-workers also strayed from pyrrolidine-based organocatalysts and have made an interesting contribution to the field in the development of an *exo*-selective binaphthyl-derived diamine catalyst, **36**, figure 7. Reaction between a variety of aldehydes and cyclopentadiene catalysed by **36** proceeded with good yields and stereoselectivities at -20 °C (72-99% yield, *exo/endo* 1.3:1 to >20:1, 56-98% *endo* e.e. and 82-95% *exo* e.e.).[86] Reaction times (45-160 hours) were reduced by raising the temperature, but with a compromise in enantioselectivity. Significantly, this catalyst did not have general utility for promoting the Diels-Alder reaction and was only effective with cyclopentadiene. Additionally dienophiles other than cinnamaldehyde furnished products with lower yields and enantioselectivities.

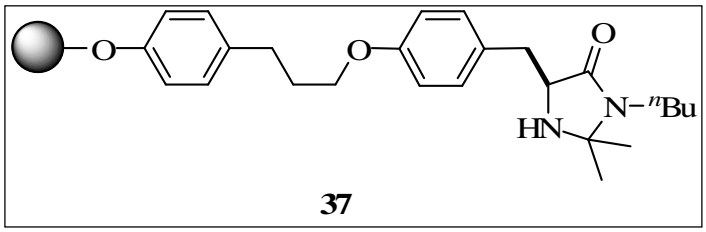


36

Figure 7. The binaphthyl-derived diamine catalyst.

Catalyst immobilisation on solid supports has been long established and many examples are known where turnover number and selectivity remain high after many applications. Once the reaction is complete the supported catalyst can be easily recycled following simple filtration. The first demonstration of supported organocatalysis by Cozzi and co-workers in 2002 involved the attachment of chiral imidazolidinone derivatives, such as **37**, to a poly(ethylene glycol) (PEG) polymer, equation 19.[87] A typical reaction promoted by this supported catalyst is the cycloaddition of cyclohexadiene to acrylaldehyde. After the third recycling of the catalyst, with TFA as the co-factor, the yield dropped from 61% to 38% but the enantioselectivity remained constant. In another demonstration Phiko and co-workers attached chiral imidazolidinone derived catalysts to JandaJel^{TM}, following one run, and a lowering of the catalyst loading from 20 mol% to 10 mol%, only a decrease of 5% in the yield of the reaction product was observed.[88]





37

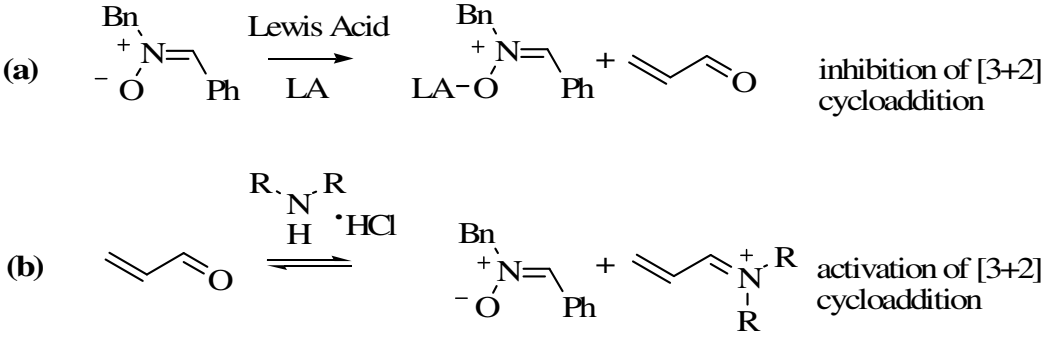
Equation 19. Solid-supported organocatalysis of the Diels-Alder reaction.

The hypothesis that ionic catalysts could be contained in a polar medium, such as an ionic liquid, also suggested an ease in recycling simply by extraction with a relatively non-polar organic solvent. In 2004, Kim and co-workers reported on the application of ionic liquids to organocatalysis.[89] The reaction between cinnamaldehyde and cyclopentadiene was selected for study in [Bmim]PF_6/H_2O and the results compared with those reported in MeOH/H_2O. Disappointingly, in the ionic liquid whilst the chemical yield remained excellent (99%) the enantioselectivity was somewhat reduced compared to the results found in aqueous MeOH (82% *endo* e.e. and 76% *exo* e.e., 99%

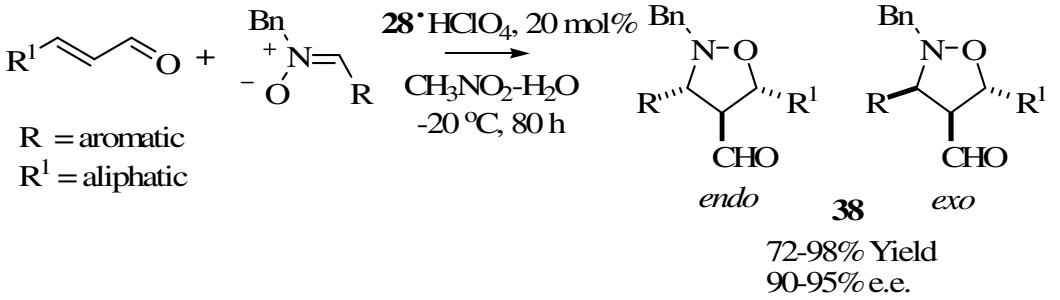
yield).[72] The potential for catalyst recycling in the ionic liquid was examined and on the second usage yields and enantioselectivities were found to be constant but using the same reaction beyond that both the yield and the enantioselectivity dropped considerably (77% yield, 57% *endo* e.e. and 56% *exo* e.e.).

1.3.2.ii [3+2]-Cycloadditions

The [3+2]-cycloaddition of nitrones to alkenes is an important synthetic route to isoxazolidines, however, promotion of [3+2] cycloadditions to α,β-unsaturated carbonyl substrates by Lewis acid catalysis has had limited success.[90] The impediment is that with one-point binding, coordination to the nitrone is favoured over coordination to the aldehyde substrate which effectively blocks the cycloaddition pathway, equation 20a. MacMillan and co-workers hypothesised that nitrones would be inert to organocatalysts enabling α,β-unsaturated aldehydes to undergo iminium activation, equation 20b. Accordingly the first organocatalytic [3+2]-addition promoted by the imidazolidinone **28**•$HClO_4$ was reported in 2000. The reaction between *N*-benzylnitrones and conjugated aldehydes afforded the isoxazolidines, **38**, in moderate to good yields and with good selectivities, equation 21.[91]



Equation 20. **(a)** Preferential Lewis acid coordination to nitrone and **(b)** preferential secondary amine coordination to α,β-unsaturated aldehydes.



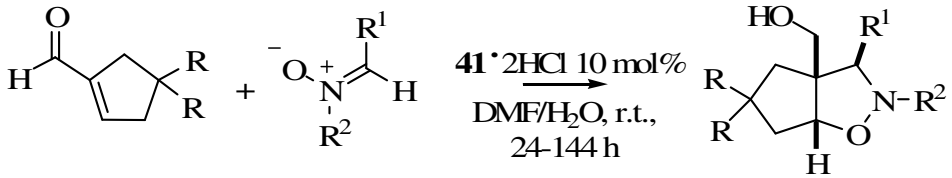
Equation 21. The [3+2] cycloaddition reaction between N-benzylnitrones and conjugated aldehydes.

More recently the polymer-supported organocatalyst **37** was used to promote a nitrone alkene [3+2]-cycloaddition reaction. In the Diels-Alder [4+2]-cycloaddition the supported catalyst had proven to be slightly inferior to the catalyst **28** in terms of yields and selectivity. The same pattern was observed when the ability of **37** to promote dipolar cycloaddition was compared with **28** (41-64% yield and 60-87% e.e.). During recycling the polymer supported catalyst retained the capacity for inducing enantioselectivity in the cycloaddition reaction while the chemical efficiency of the recovered catalyst slowly decreased. This was probably due to the degradation of the catalytic imidazolidinone under the reaction conditions.[92]

The scope of the polymer supported imidazolidinone in promoting dipolar cycloadditions was expanded by Karlsson and Hogberg to include the cyclic aldehydes **39** as dipolarophiles. The fused bicyclic isoxazolidines, **40**, were formed in modest to good yields under the influence of the diamine catalyst **41**•2HCl, equation 22.[93,94]

1.3.2.iii [3+3]-Cycloadditions

In 2005, Hsung *et al.* reported an intramolecular aza-[3+3] cycloaddition of vinylogous amides catalysed by pyrrolidine-based salts.[95] A variety of catalysts were screened and the pyrrolidine alcohol **42** afforded the tricyclic products **43** in high yields and with the greatest enantioselectivities, equation 23. (*S*)-Proline was observed to promote an intermolecular version of the [3+3] cycloaddition of α,β-unsaturated aldehydes. Using this methodology crotonaldehyde, **44**, was converted into the cyclic aldehydes, **45**, equation 24.[96]

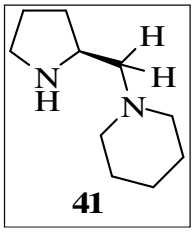


39

$R^{1,2}$ = aromatic, aliphatic

40

R	Temp (°C)	% Yield	% e.e.
H	-25 to 20	49-76	41-92
Me	20	19-38	37-48



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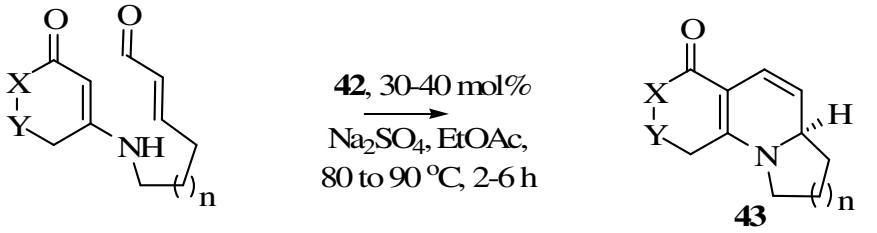
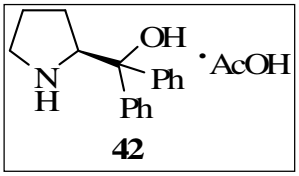
Equation 22. Dipolar cycloadditions in the presence of polymer supported imidazolidinones.



X = C, O, NMe
Y = C, O, C-Me, C-Me_2, C=O

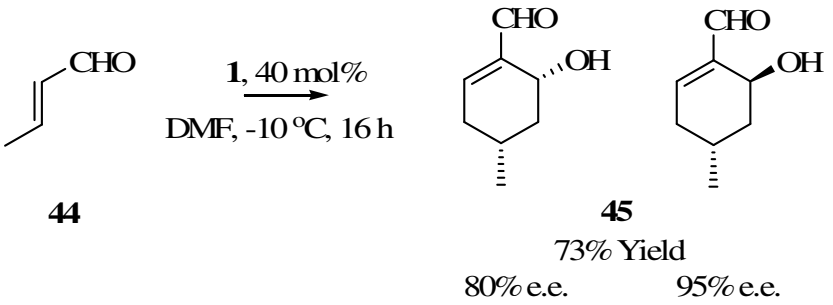
43

41-65% Yield
27:73 to 80:20 e.r.



42

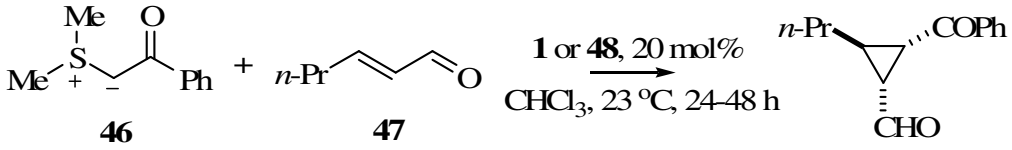
Equation 23. Intramolecular aza-[3+3] cycloaddition of vinylogous amides catalysed by pyrrolidine-based salts.



Equation 24. (*S*)-Proline promoted intermolecular [3+3] cycloaddition of α,β-unsaturated aldehydes.

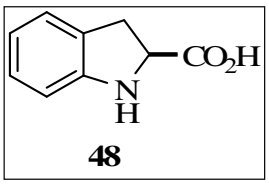
1.3.2.iv [2+1]-Cycloadditions

In 2005, MacMillan and co-workers published pioneering work on enantioselective cyclopropanation reactions based upon reaction of the sulfonium ylide, **46**, to the iminium activated α,β-unsaturated substrate, **47**, equation 25.[97] Imidazolidinones **28**•TFA and **33**•TFA failed to promote the reaction, however, (*S*)-proline, usually a poor catalyst for iminium activation, provided the cyclopropane products with good levels of conversion and moderate enantioselectivities. In a subsequent development the bicyclic indoline catalyst, **48**, was found to be a superior catalyst in terms of both conversions and enantioselectivities.



46 **47**

Catalyst	% Yield	% e.e.
1	72	46
48	78	94



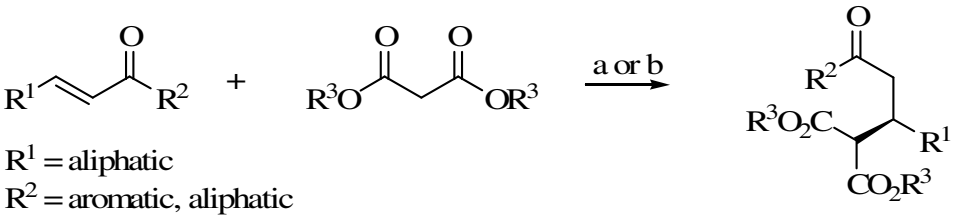
48

Equation 25. The first organocatalytic enantioselective cyclopropanation reaction.

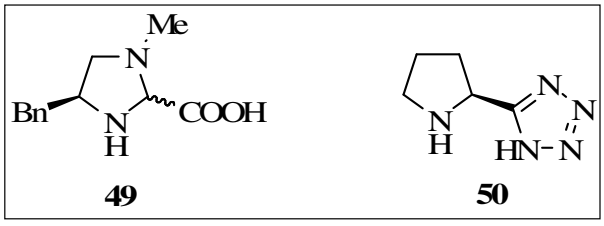
1.3.3 Michael Addition Reactions

1.3.3.i 1,3-Dicarbonyl compounds as Michael donors

Although additions of malonate nucleophiles to iminium ions had been reported from as early as 1991, the first organocatalytic reaction was not reported until 2003 when Jorgensen demonstrated an imidazolidine catalysed addition of malonates to acyclic enones, equation 26a.[37,39,98] It was observed that sterically hindered malonates afforded the addition products in low yields, whilst malonates free of steric impediments furnished excellent product yields with high enantioselectivities. Dibenzylmalonate was identified as the optimal substrate, whilst nonsymmetrical malonates furnished products in good yields but with low diastereoselectivity. With aliphatic and more sterically demanding enals the yields dropped significantly, and indeed, if steric bulk was introduced next to the ketone functionality the reactions failed to proceed. Ley and co-workers aspired to expand the utility of the reaction beyond dibenzyl malonate and to reduce the large excess of malonates employed. To this end they identified the pyrrolidinyl tetrazole, **50**, as a suitable catalyst for the addition of dimethyl and diethyl malonates to a range of enones, equation 26b.[99]



Conditions	% Yield	% e.e.
a. R^3 = Bn (8 equiv.); **49**, 10 mol%, r.t., 150-288 h	33-99	59-99
b. R^3 = Me (1.5 equiv.); **50**, 5 mol%, piperidine (1 equiv.), $CHCl_3$, r.t., 72 h	64-87	62-84

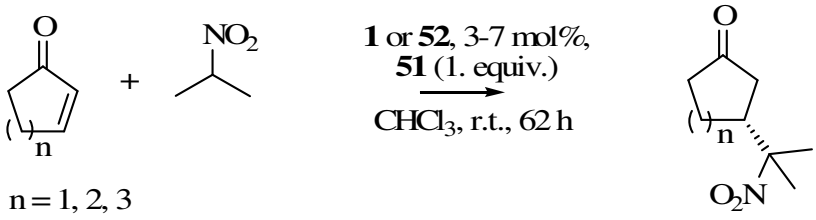


49 **50**

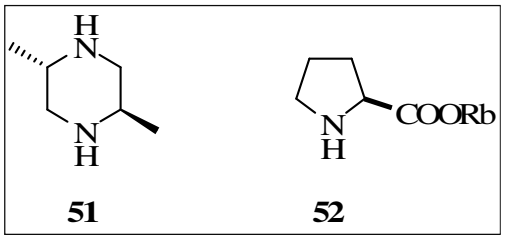
Equation 26. Iminium ion catalysed addition of malonates to acyclic enones.

1.3.3.ii Nitroalkanes as Michael donors

In 2000, Hanessian and Pham reported the first organocatalytic asymmetric conjugate addition of nitroalkanes to cyclic enones. (*S*)-Proline was the catalyst of choice and was used in conjuction with *trans*-2,5-dimethylpiperazine, **51**, as an additive. Products were obtained with high enantioselectivities and yields, well in excess of those results for the rubidium prolinate catalysis of the same reaction, equation 27.[40,100]



		% e.e.		
Catalyst	**n =**	**1**	**2**	**3**
1		75	93	86
52		12	59	73

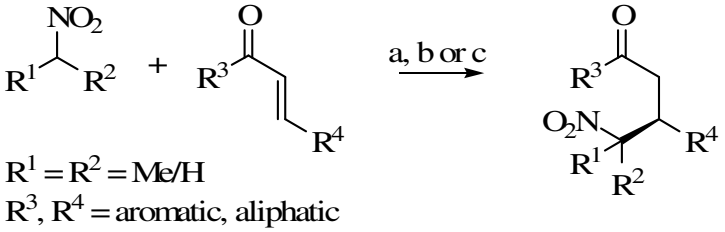


51 **52**

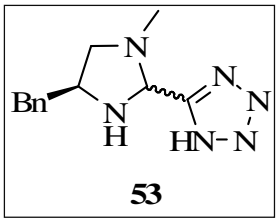
Equation 27. Organocatalytic asymmetric conjugate addition of nitroalkanes to cyclic enones.

Conjugate addition of nitroalkanes to various cyclic enones was also reported to be catalysed by the pyrrolidinyl tetrazole **50** in the presence of the amine additive **51**, equation 28a.[101] For example, reaction between cyclohexanone and 2-nitropropane yielded the addition product in 59% yield and 91% e.e. The yield of the conjugate addition product of nitroalkanes to acyclic β-substituted enones, catalysed by the chiral amine **49**, was shown to be strongly influenced by the size of the substitutent on the alkane.[102] The nitroalkanes were employed as the reaction solvent and were used in approximately twenty-fold excess, equation 28b. Three years later, Jorgensen reported the tetrazole appended imidazolidine catalyst **53** to be an equally viable catalyst for the conjugate addition of nitroalkanes to α,β-unsaturated enones.[103] The product yields and

selectivities were similar to those observed in the presence of the pyrrodinyl tetrazole **50**; however, the reaction times could be halved in most cases, equation 28c.



Conditions	% Yield	% e.e.
a. 50, 15 mol%, **51** (0.5 equiv.), CH_2Cl_2, r.t., 72 h	21-88	54-83
b. 49, 10 mol%, neat, r.t., 80-300 h	< 5-100	35-86
c. 53, 10 mol%, neat, r.t., 70-200 h	83-97	64-89



53

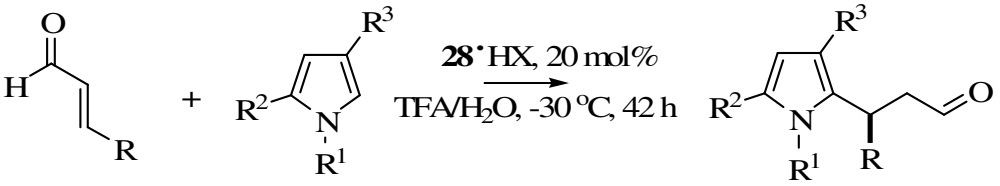
Equation 28. Conjugate addition of nitroalkanes to various cyclic enones.

1.3.3.iii Friedel-Crafts alkylation

One of the most noteworthy successes of organocatalysis lies in the development of asymmetric Friedel-Crafts alkylations which have been unsuccessful by traditional Lewis acid or metal mediated catalysis.[104] Thus, imidazolidinone promoted alkylation of pyrroles with several β-substituted enals was demonstrated and the adducts obtained in good yields and with high enantioselectivities, equation 29. The pyrrole core was shown to tolerate substitution at the 2- and 4-positions as well as different *N*-protecting groups without disturbing its reactivity.

Chen and co-workers reported organocatalytic Friedel-Crafts indole alkylation with aromatic or aliphatic enones catalysed by the TfOH salt of the diaminoquinoline **54**; reaction rates, product yields and enantioselectivities varied with the nature of the substituents on the reacting partners, equation 30.[105] Shortly afterwards a similar catalyst system was published using **55** along with a chiral co-catalyst.[106] Similar counterion-directed catalysis had been earlier reported by List and co-workers for the transfer hydrogenation of enones (see section 1.4).[107] A range of co-catalysts were

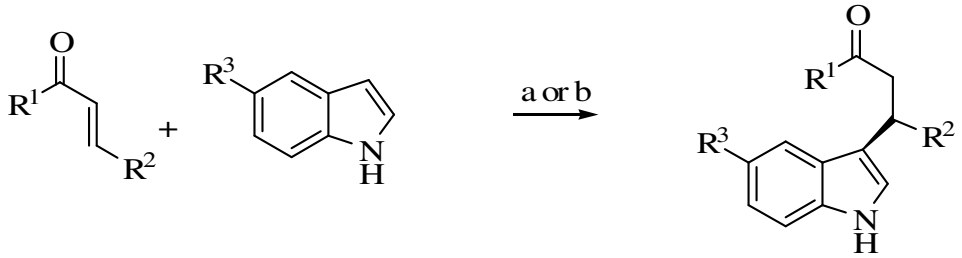
screened (TFA, *p*TsOH, CF_3SO_3H and various substituted *N*-Boc glycine co-catalysts) and *N*-Boc phenylglycine, **56**, exhibited the highest stereoselectivity. With this catalyst, the catalyst loadings were reduced by 10% while the reaction times remained comparable, with the yields and enantioselectivities being greater and more uniform.



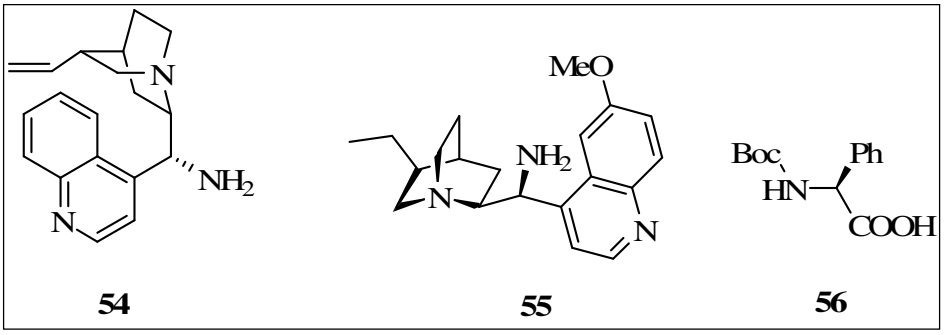
R = aromatic, aliphatic; R^1 = H, Me, Bn, Allyl; 68-87% yield [a]
R^2, R^3 = H, Bu, Pr; HX = TFA, $CNCH_2COOH$, TCA 89-97% e.e.

[a] Yields based upon isolation of corresponding alcohol after $NaBH_4$ reduction.

Equation 29. Imidazolidinone promoted alkylation of pyrroles with several β-substituted enals.



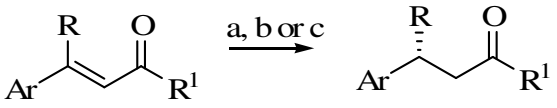
Conditions	% Yield	% e.e.
a. 54•2TfOH, 30 mol%, DCM/^{i}PrOH 85:15, -20 to 0 °C, 3-8 h	35-99	47-89
b. 55•2**56**, 20 mol%, toluene, r.t. to 70 °C, 24-96 h	56-98	70-96



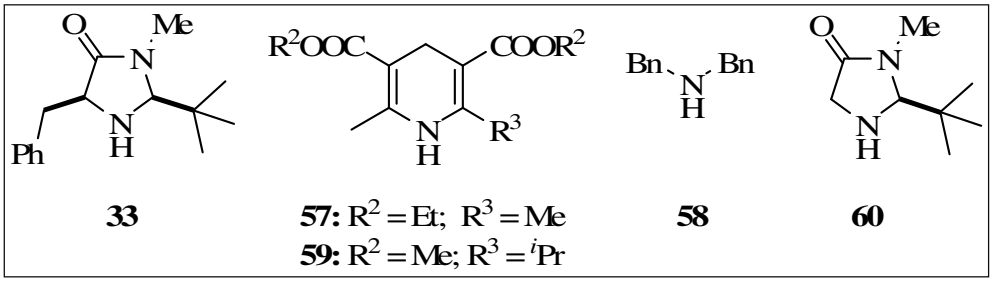
Equation 30. Organocatalytic Friedel-Crafts indole alkylation with aromatic or aliphatic enones.

1.3.3.iv Hydrogenation of enals

Organocatalytic transfer hydrogenation of enals with the Hantzsch ester, **57**, has been catalysed by the dibenzylammonium trifluoroacetate catalyst **58**, products were reported to be formed in high yields, equation 31a.[108,109] Shortly after the initial publication an enantioselective version of the reaction was reported employing the imidazolidinone catalyst **33**, and the modified Hantzsch ester **59**. Products were obtained in high yields with good enantioselectivities, equation 31b.[107] Subsequent studies by MacMillan and co-workers found that the benzylic side chain on the imidazolidinone was not necessary for good stereocontrol in this reaction and the 5-unsubstituted imidazolidinone, **60**, was effective for the generation of addition products with high enantioselectivities, equation 31c.[110] It was also noted that the outcome of the reaction was independent of the geometry of the enal substitution since the initial iminium salts rapidly isomerised.



Conditions	% Yield	% e.e.	e.r.
a. 58•TFA, 5 mol%, **57** (1.1 equiv.), THF, r.t., 5-6 h	81-96	-	-
b. 33•TCA, 10 mol%, **59** (1.1 equiv.), dioxane, 13 °C, 48 h	77-90	-	95:5 – 98:2
c. 60•2TFA, 20 mol%, **57** (1.2 equiv.), $CHCl_3$, -30 °C, 0.5-48 h	74-95	90-97	-



33 **57:** $R^2 = Et$; $R^3 = Me$ **58** **60**

59: $R^2 = Me$; $R^3 = {}^iPr$

Equation 31. Organocatalytic transfer hydrogenation of enals with the Hantzsch ester or modified Hantzsch ester.

1.3.4 Concluding Remarks on Iminium Catalysis

Iminium catalysis has been established as one of the key concepts in organocatalysis. It has been utilised in many synthetic transformations, of which only a small selection

were discussed here. The success of the approach can be garnered from the high yields and enantioselectivities of the products formed. However, improvements in turnover numbers are to be expected with continued research into iminium activation and iminium catalysis.

The concept of asymmetric counterion catalysis will be discussed next in section 1.4. Counterion catalysis can be considered a subset of classical iminium catalysis where the enantioselectivities of the reaction products arise due to the influence of a large chiral counterion.

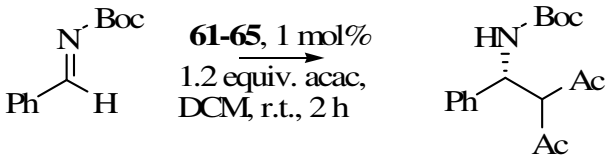
1.4 Counterion Catalysis

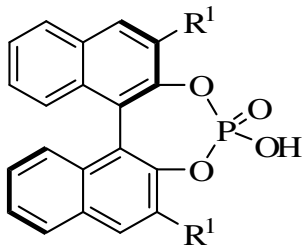
1.4.1 Introduction to Counterion Catalysis

Anions and cations play very important roles in chemical reactions as reagents, intermediates and products. In solution, ions and their oppositely charged counterions tend to form ion pairs and depending on the solvent the cations and anions within these pairs may be separated from each other by solvent molecules or may be close together, allowing one partner to influence or control the environment of the other.

1.4.2 Catalysed Reactions

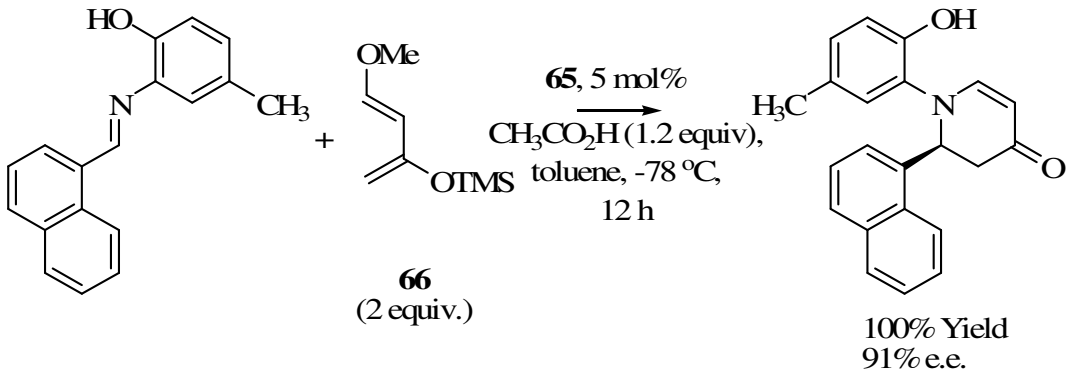
The potential of chiral binaphthyl-derived phosphoric acid derivatives, **61-64**, as stereodirecting counterions in organocatalysis was inspired by the discovery that these molecules function as highly efficient Brønsted acids in the catalysis of the direct Mannich reaction of acetylacetone with a range of arylimines, equation 32.[111,112] It was observed that the presence of β-naphthyl-phenyl groups in the 3- and 3'-positions of the binaphthyl core increased the enantiomeric excess of the product, with just 12% e.e. being observed with the parent **61** and 99% e.e. with the phenyl substituted **62**. The trisisopropylphenyl derivative (TRIP), **65**, was also found to be an effective Brønsted catalyst for the aza-Diels-Alder reaction of Danishefsky's diene **66**, equation 33.[113]





	R^1	% Yield	% e.e.
61	H	92	12
62	Ph	95	56
63	4-biphenyl	88	90
64	4-(β-Naph)-C_6H_4	99	95
65	-(2,4,6-^{i}Pr$_3$)-C_6H_2	-	-

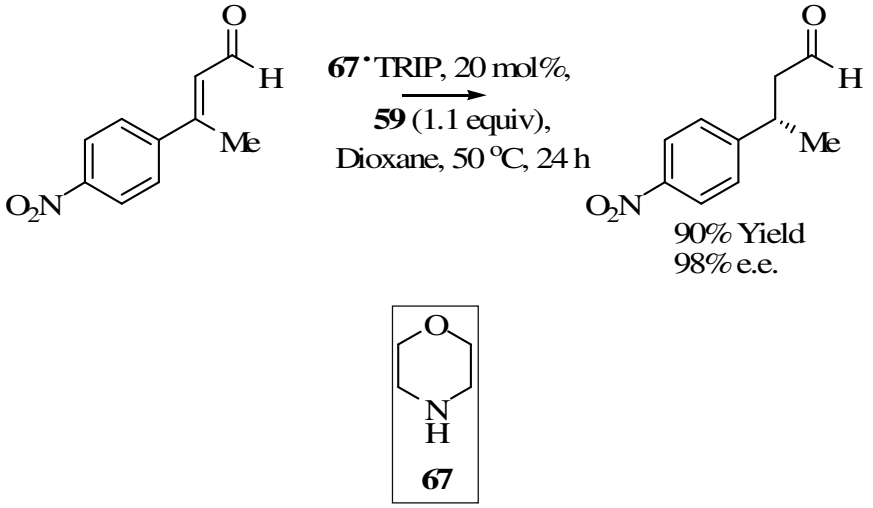
Equation 32. Brønsted acid catalysis of the direct Mannich reaction of acetylacetone with a range of arylimines.



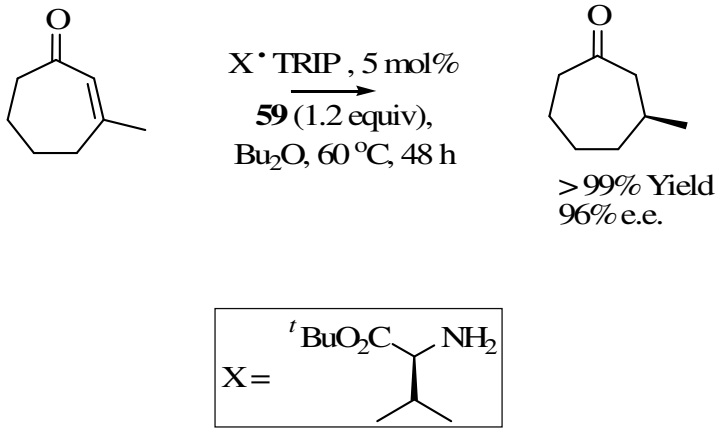
Equation 33. Brønsted acid catalysis of the aza-Diels-Alder reaction of Danishefsky's diene **66** in the presence of trisisopropylphenyl derivative (TRIP) **65**.

It was against this background that in 2006, List and co-workers introduced a novel variant in organocatalysis termed asymmetric counterion-directed catalysis, ACDC.[107] According to this concept, catalytic reactions that proceed via cationic intermediates can be conducted asymmetrically via the use of a chiral enantiomerically enriched anion incorporated into the catalyst. Thus, List developed a new salt, comprising the achiral amine morpholine, **67**, in conjunction with TRIP, which was found to catalyse highly enantioselective transfer hydrogenation from Hantzsch esters to α,β-unsaturated aldehydes, equation 34.[107,114,115] The product yield and enantioselectivity of the aldehyde is comparable to those obtained using the imidazolidinone salt **33**•Cl_3CO_2H (equation 31, section 1.3.3.*iv*). The reaction was subsequently extended to include α,β-

unsaturated ketone substrates.[115] In this case highest selectivities were recorded for reactions conducted under the influence of the valine ester salt of TRIP, equation 35.



Equation 34. TRIP catalysed enantioselective transfer hydrogenation from Hantzsch esters to α,β-unsaturated aldehydes.



Equation 35. The TRIP catalysed enantioselective transfer hydrogenation from Hantzsch esters to α,β-unsaturated ketone substrates.

1.4.3 Concluding Remarks on Counterion Catalysis

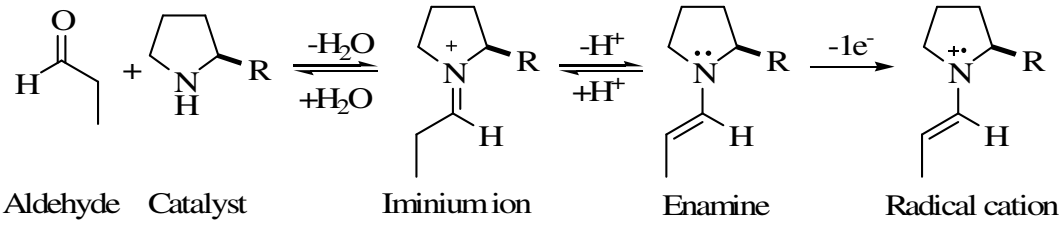
ACDC is a new strategy for highly enantioselective synthesis; research into this branch of organocatalysis is fast paced and looks promising to be of general utility.

1.5 SOMO Catalysis

1.5.1 Introduction to SOMO Catalysis

SOMO catalysis is amongst the most recently discovered activation modes in organocatalysis. In 2007 MacMillan and colleagues described a strategy for organocatalysis using radical intermediates - molecules that contain reactive single electrons.[116] SOMO catalysis is based on the idea that one-electron oxidation of an electron-rich enamine selectively generates a reactive radical cation with three π-electrons.[114] Upon reaction, amines and aldehydes form iminium ions which exist in equilibrium with the enamine species, scheme 7. However, enamines can be intercepted by an oxidising agent, which removes an electron from the intermediate to generate a positively charged radical. The radical is more susceptible to subsequent chemical attack than the original starting aldehyde or ketone.

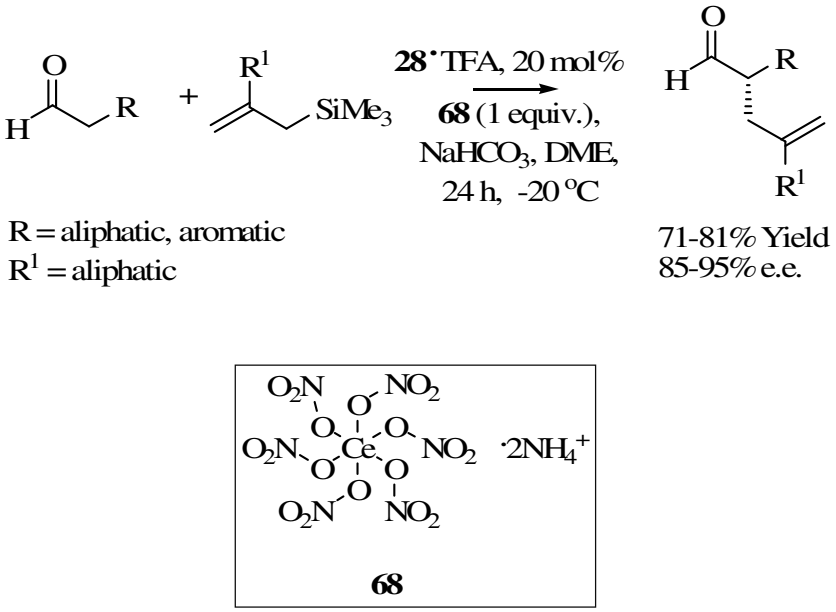
In comparison, enamine catalysis (section 1.2) raises the energy of the HOMO, whilst iminium ion catalysis (section 1.3) lowers the energy of the LUMO, these modes facilitate attack from reagents that respectively seek areas of negative or positive charge thus both these modes are based on the natural polarity of the reactants, which limits organocatalysis to transformations that are, at least in principle, also possible with metal-based catalysis.[117]



Scheme 7. The mechanism of SOMO catalysis.

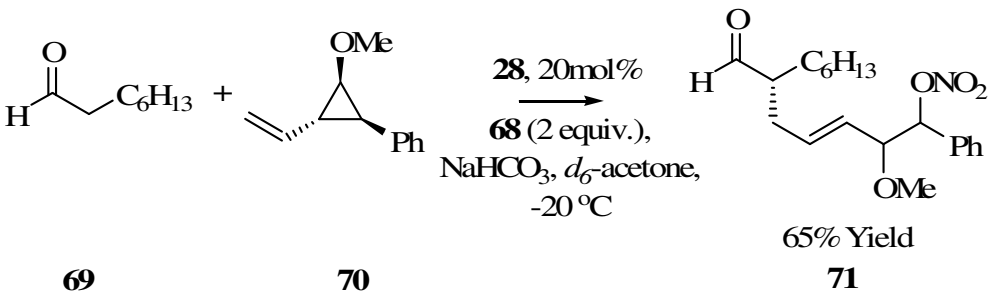
1.5.2 Catalysed Reactions

The first SOMO promoted organocatalytic reaction, aldehyde α-allylation, was reported in 2007, equation 36.[116] The catalytic system comprised of **28**•TFA (20 mol%) together with 1 equivalent of CAN, **68**, as the oxidising agent. A variety of chemical functionalities, including olefins, ketones, esters and carbamates were shown to be inert to the mild oxidising conditions.



Equation 36. SOMO promoted organocatalytic aldehyde α-allylation.

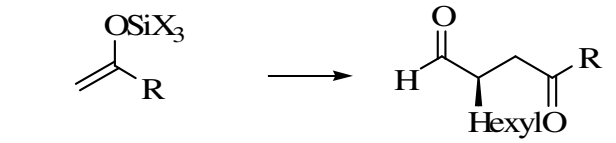
It has been previously noted by Newcomb *et al.* that cyclopropyl rings bearing a phenyl and alkoxy substituent could be expected to open in different ways depending on the reaction mechanism.[118,119] Thus phenyl groups stabilise an incipient radical centre more strongly than an alkoxy group. The author considered mechanistically that the product could have arisen by either a radical-mediated pathway or a cationic mechanism. The presentation of **71** in a 65% yield is in keeping with the scission of the benzylic cyclopropyl bond and not the α-methoxy cyclopropyl bond and the result is interpreted as involving a radical and not a cationic mechanism, equation 37. [116]



Equation 37. The radical clock reaction performed by MacMillan *et al.*

α-Enolation[120] and α-vinylation of aldehydes[121] with the silyl enol ether **75** or the vinyl potassium trifluoroborate salt **76** have been found successful with the same catalytic

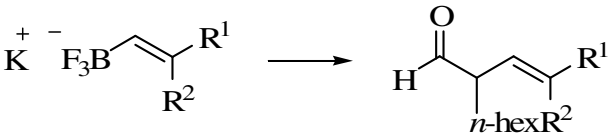
systems. Good to excellent yields and excellent enantioselectivities were observed in each case.



75

X = Me, ^{t}Bu, ^{t}BuPh$_2$
R = aliphatic, aromatic

55-85% Yield
86-96% e.e.



76

R^1 = aliphatic, aromatic
R^2 = H, Me

61-93% Yield
89-95% e.e.

Figure 8. SOMO catalysed α-Enolation and α-vinylation of aldehydes with the silyl enol ether **75** or the vinyl potassium trifluoroborate salt **76**.

1.5.3 Concluding Remarks on SOMO Catalysis

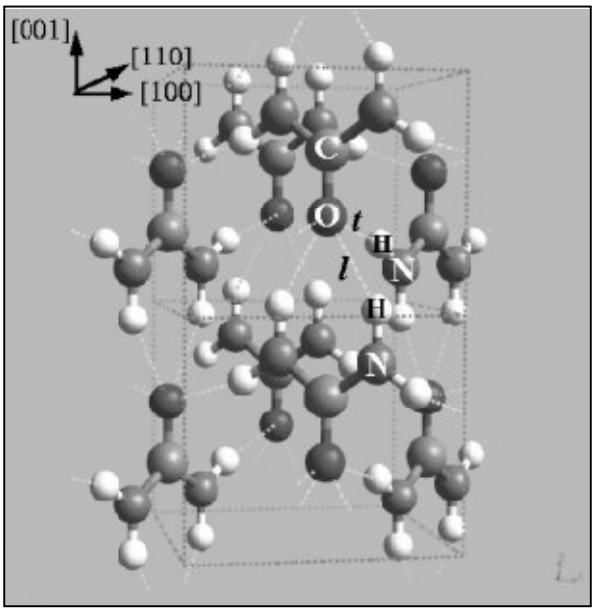
In the most recent demonstrations of SOMO activation, enantioselective α-arylation of aldehydes[122] and carbo-oxidation of styrenes have been reported.[123] SOMO activation is considered a highly promising strategy for asymmetric organocatalysis since numerous radical-based reactions can be carried out in a catalytic and asymmetric manner.[28]

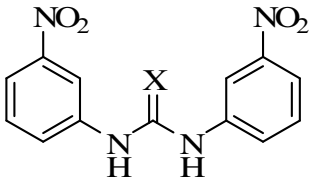
1.6 Hydrogen-Bonding Catalysis

1.6.1 Introduction to Hydrogen-Bonding Catalysis

Hydrogen-bonding (H-bonding) catalysis has been known for some time but has received little attention until recently.[124] In 1988 Etter *et al* discovered that *N,N'*-diarylureas bearing electron-withdrawing substituents, e.g. **77**, can readily form co-crystals with a variety of proton acceptors, including carbonyl compounds.[125] The hetero-molecular H-bonding between the *NH*-urea protons and the acceptor group, comes at the expense of the urea-urea (C=O, *NH*) homo-molecular network, figure 9.

Although urea carbonyl groups are reported to be reasonably good acceptors, Etter found that nearly any "external" acceptor is better than the carbonyl group in **77** and so with appropriate substituents hetero-molecular H-bonding dominates. Following from Etter's studies on efficient rigid bidentate H-bond donors and from the demonstration of binding between ureas and Lewis bases the foundation for the development of urea-based organocatalysis was laid.



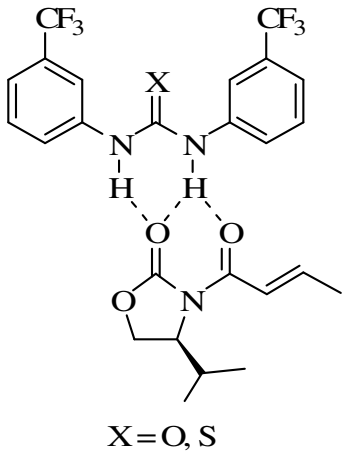


77 X = O, S

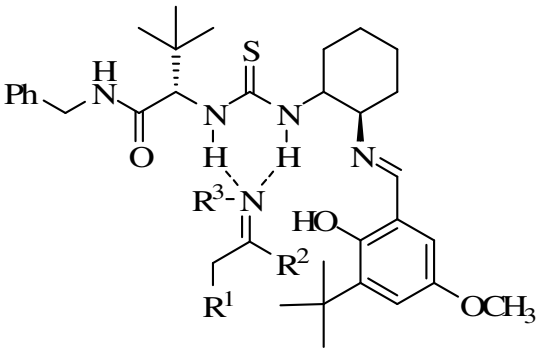
Figure 9. The structure of crystalline urea; all intermolecular bonds are N-H---O hydrogen bonds.[126]

The ability of ureas and thioureas to activate electrophiles by way of hetero-molecular H-bonding is parallel to Lewis acid activation. Whilst the stability energy contribution is only 1-6 kcal mol^{-1} the H-bonding interactions influence the conformational preferences by forming rigid three-dimensional structures and thus contribute effectively to the selectivity of molecular recognition.[127]

Curran and Kuo are the pioneers of H-bonding catalysis, initial reactions included sulfoxide allylations[128] and Claisen rearrangements.[129] Other groups have made significant contributions to the area including Schreiner's diarylthiourea catalysis of the Diels-Alder reaction[130] and Jacobsen's studies on the Strecker[131] and Mannich reactions.[132]



Activation of carbonyl species by a thiourea through H-bond formation.

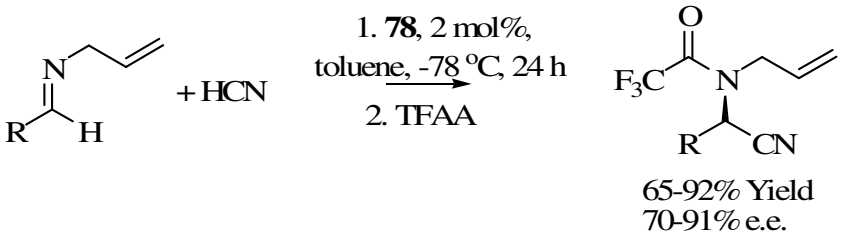


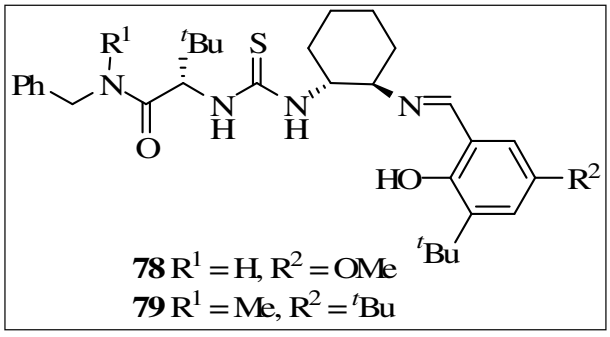
Activation of imines by a thiourea through H-bond formation.

Figure 10. Activation of electrophiles by way of hetero-molecular H-bonding.

1.6.2 Strecker Reaction

After three generations of catalyst development Jacobsen and Sigman established that the optimal catalyst for the Strecker reaction was the thiourea **78**. One example of this reaction, which is successful for a wide range of imines is shown in equation 38. The products are formed in good yields and with high enantioselectivities.[131]

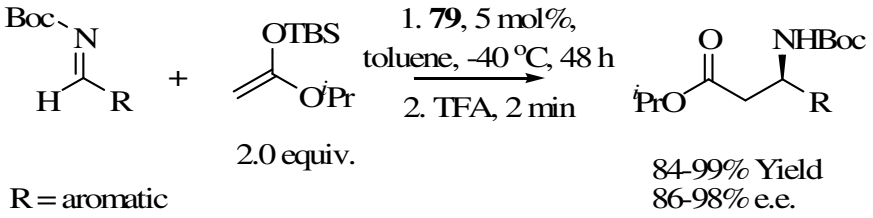




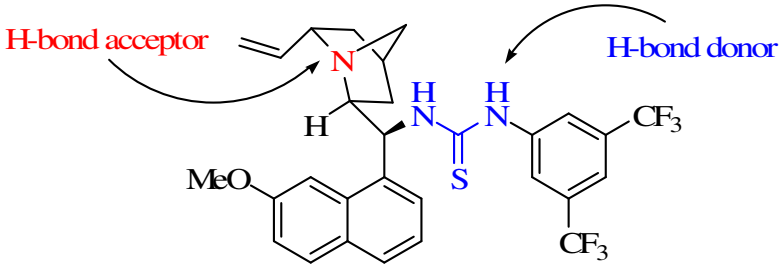
Equation 38. Organocatalysed Strecker reaction with a range of imines.

1.6.3 Mannich Reaction

Thiourea promoted asymmetric Mannich reaction of silyl ketene acetals catalysed by **79** was shown to be compatible with a wide range of *N*-Boc protected aromatic imines, in all cases excellent product yields and enantioselectivies were recorded, equation 39.[132] The Mannich reaction between malonates and *N*-Boc protected imines was also promoted by bifunctional cinchona alkaloid catalysts such as **80**. The bifunctionality in these catalysts results from the chiral thiourea H-bond donor and the chiral cinchona alkaloid H-bond acceptor. Again products were generally obtained in excellent yields (81-99%) and with high enantioselectivities (96-99%), figure 11.[133]



Equation 39. Thiourea promoted asymmetric Mannich reaction of silyl ketene acetals.

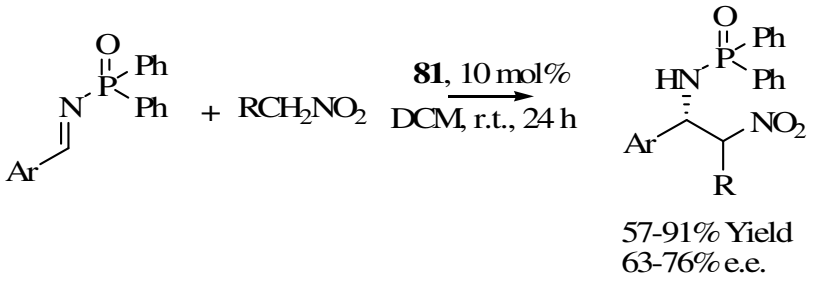


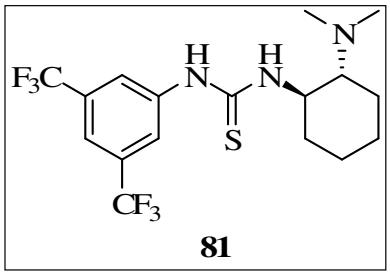
80

Figure 11. The bifunctionality of cinchona alkaloid catalysts.

1.6.4 Aza-Henry Reaction

The thiourea promoted aza-Henry reaction between imines and nitroalkanes has been shown to be compatible with a range of substrates, equation 40.[134] Thus, neither electron-donating nor electron-withdrawing groups on the aryl imine adversely affected the enantioselectivity of the reaction catalysed by **81**. Further, heteroaromatic rings and sterically hindered imines were also tolerated. In some cases a slight increase in the enantioselectivity was observed.





Equation 40. The thiourea promoted aza-Henry reaction between imines and nitroalkanes.

1.6.5 Addition Reactions

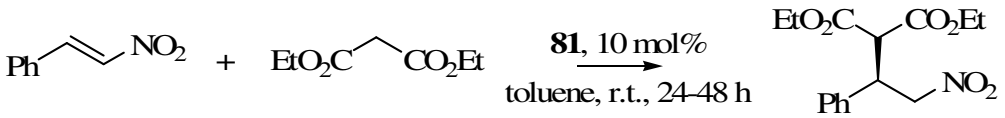
1.6.5.i 1,3-Dicarbonyl addition to nitroolefins

Takemoto *et al*. anticipated that the introduction of an additional basic and nucleophilic group to a thiourea catalytic framework might facilitate a synergistic interaction between the functional groups of the catalyst and thereby lead to a more efficient catalyst for the Michael reaction.[135,136] The reaction between *trans*-β-nitrostyrene and diethylmalonate was selected as a model for the study, equation 41. The results showed that the best catalyst **81** possesses both a thiourea and a tertiary amino group. The replacement of the 3,5-bis(trifluoromethyl)phenyl group of **81** with other aryl groups such as phenyl and 2-methoxy phenyl reduced H-bonding capability and resulted in a decrease in the enantioselectivity. Other successful thiourea catalysts bearing the tertiary amino group include **83**, which with just 1% loading promoted the reaction between a range of nitrostyrenes and 2,4-pentanedione. Product yields (82-92%) and enantioselectivities (83-97% e.e.) were high.[137]

1.6.5.ii Aldol reaction

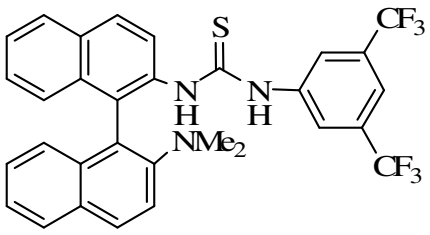
More recently, H-bonding functionalities have been introduced into pyrrolidine-based organocatalysts to promote aldol reactions. In 2003, the Houk-List model for the proline-catalysed aldol reaction suggested activation of the carbonyl acceptor by the

carboxylic acid group of (*S*)-proline through a single H-bond, figure 13a.[34,138] In the same year Gong, Wu and co-workers suggested **84** is capable of activation of the carbonyl acceptor through the formation of two H-bonds, figure 13b.[139] At room temperature (*S*)-proline and **84** catalyse the aldol reaction between acetone and 4-nitrobenzaldehyde equally well and with reasonable enantioselectivities, however, the amino alcohol **84** is a significantly better catalyst than (*S*)-proline at -25 °C furnishing the desired aldol product in good yield (66%) and with excellent enantioselectivities (93%), under the same conditions the (*S*)-proline promoted reaction proceeds to give only 6% yield of products.



86% Yield
93% e.e.

Equation 41. 1,3-Dicarbonyl addition between trans-β-nitrostyrene and diethylmalonate.

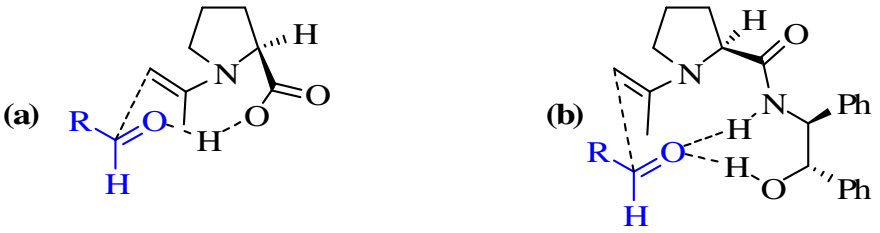


83

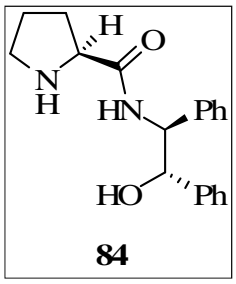
Figure 12. An example of thiourea catalysts bearing the tertiary amino group.

1.6.5.iii Mukaiyama-Aldol reaction

Chiral alcohols have also been investigated as organocatalysts; the diol **85** was successful in promoting the Mukaiyama-Aldol reaction between a range of aldehydes or ketones and the silyldienol ether, **86**. The yields and enantioselectivities of the reaction products varied with the nature of the carbonyl substrate and the presence or absence of the ammonium ion **87**, equation 42.[140]

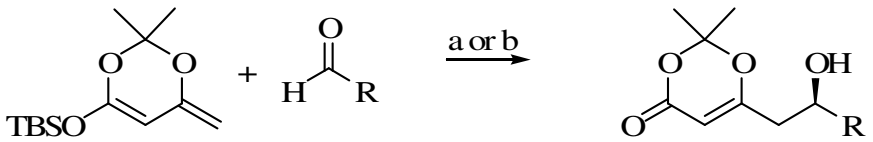


Catalyst	Temp (°C)	% Yield	% e.e.
1	25	68	76
	-25	6	70
84	25	89	69
	-25	66	93



84

Figure 13: **(a)** Houk-List model for (*S*)-proline-catalysed aldol reactions and **(b)** Gong-Wu double H-bonding catalyst

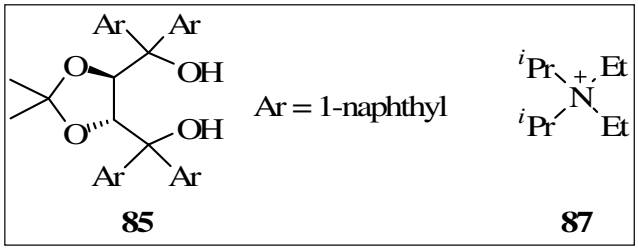


86

0-73% Yield
22-90% e.e.

R = aliphatic, aromatic

Conditions	% Yield	% e.e.
a. 85, 20 mol%, **87**, 10 mol%, toluene, 1N HCl, -80 °C, 1h	54-60	84-87
b. 85, 20 mol%, toluene, 1N HCl, -40 to -80 °C, 66-133 h	23-73	22-90



85 **87**

Equation 42. The Mukaiyama-Aldol reaction between a range of aldehydes or ketones and the silyldienol ether, **86**.

1.6.6 Concluding Remarks on H-Bonding Catalysis

Although thiourea-based catalysts are just over a decade old they have been demonstrated to be conformationally rigid catalytic templates, tunable from both steric and electronic standpoints. The addition of a second functional entity, e.g. a tertiary amine, provides a vast array of new opportunities in catalysis. Research in H-bonding catalysis continues to grow and holds promise for an ever-widening range of challenging and synthetically important processes.

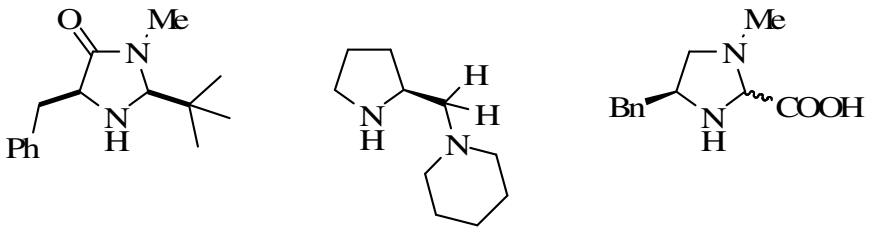
1.7 Conclusion

In the preceding sections the author has presented an overview of organocatalysis describing a selection of the number of the synthetic transformations which have been achieved. It was the intention of the author to use this introduction to describe the scope, successes and future potential for asymmetric organocatalysis as a tool for the synthetic chemist. More exhaustive information can be obtained from detailed reviews which are to be found in the literature.[7,8,18,24-29,71,130,141-145] The rest of this thesis will focus on the design and synthesis of *NH*-isoxazolidines as novel organocatalysts (Chapter 2) and their application in the organocatalysis of organic reactions (Chapter 3).

Catalyst Design

2.1 Introduction

It is significant that of the most successful iminium ion organocatalysts, including those developed by MacMillan[76,146], **33**, Karlsson and Hoberg[93,94], **41**, and Jorgensen[98,103], **49**, all possess a chiral five membered *N*-containing heterocycle. Effective enantiocatalysts are characterised by the following properties; (i) the chiral amine should undergo efficient and reversible iminium ion formation, (ii) it should have high levels of control of the iminium ion geometry, (iii) selective discrimination should be achieved in order to control the enantioselectivity of the reaction and (iv) catalyst preparation should be facile.[147] It has also been recognised that in order to gain high catalytic turnover it is necessary to have a highly nucleophilic nitrogen atom to accelerate the formation of the active iminium ion, which is the rate determining step of the catalytic cycle.[75]



33 **41** **49**

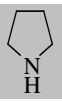
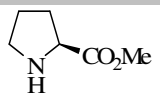
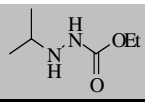
Figure 14. A range of successful iminium ion catalysts all possessing a chiral five membered *N*-containing heterocycle.

It is well established that the nucleophilicity of a heteroatom can be greatly increased by the introduction of an adjacent heteroatom. This is known as the α-effect and many theories have been furnished to explain this effect.[148] One view is that the electrostatic repulsions between an electron pair of the reacting atom and the free electron pair on the adjacent electronegative atom raise the ground state energy of the nucleophile, thus lowering the energy of activation.[149] In molecular orbital terms, this would imply a relatively high energy of the nucleophile HOMO that participates in bond formation. Another view is that the electron pair can act to stabilise charge deficiency at the transition state.[150]

In studying the potential of hydrazines and hydroxylamines as organocatalysts Tomkinson's group were the first to exploit the α-effect in search of organocatalysts which may be more reactive than the analogous amines and permit a departure from the

constraints of the five-membered ring design.[77,78] For example, *N,N'*-dimethylhydrazine was found to promote the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene with products being isolated in 48% yield after 72 hours at room temperature, table 2 entry 1. With the analogous hydroxylamine, entry 2, the reaction was much more successful and progressed to 80% over the same time period. These observations suggested that the *O*-heteroatom is a key influence in the enhancement of the catalytic activity. In parallel, the same group observed pyrrolidine to be an inferior catalyst to its 2-carbomethoxy derivative, entries 3 and 4. Against this background Tomkinson designed a new catalyst bearing both an α-heteroatom and a β-carbonyl, ethyl 1-methyl-2-(propan-2-yl)hydrazinecarboxylate, entry 5; with this double modification a significant increase in catalytic activity was observed and the Diels-Alder product was obtained in high yield after only 6 hours at room temperature.

Table 2. Catalysis of the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O (19:1).[78]

Entry	Catalyst•HCl	Time (h)	Product	
			% Yield	*Endo:Exo*
1[a]		72	48	32:68
2		72	80	34:66
3		24	9	32:68
4		48	85	29:71
5		6	74	34:66

[a] Catalyst used as a *bis*-HCl salt.

From these results it is clear that (i) the introduction of a heteroatom in the α-position caused an increase in the catalytic activity, (ii) oxygen is more efficient in this role than nitrogen and (iii) a carbonyl group β- to the nucleophilic *N*-atom increases the catalytic activity. It is against this scientific background that the novel work in this thesis was designed.

Our research group has wide experience in heterocyclic chemistry, and in particular in the synthesis of nitrogen containing rings.[151-155] Thus, we set about designing a new

generation of organocatalyst; the basic catalyst framework, centered around the isoxazolidine nucleus, is sketched in figure 15. Important structural features include (i) adjacent ring *N*- and *O*-atoms designed to confer enhanced nucleophilicity on the *N*-atom, (ii) a carbonyl group in the β'-position to enhance the reactivity and (iii) a large potentially stereodifferentiating group on one of the remaining positions close to the nucleophilic nitrogen atom. This is an attractive design since solubility problems observed with some organocatalysts can be circumvented whereby the isoxazolidine nucleus can be constructed as desired with either hydrophobic or hydrophilic substituents.

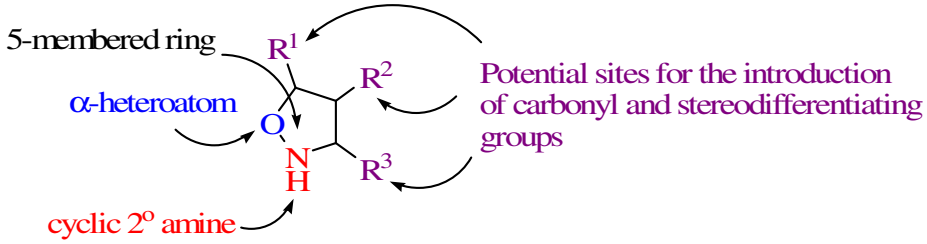
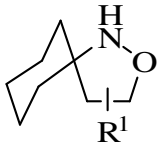


Figure 15. Outline of the basic catalytic framework.

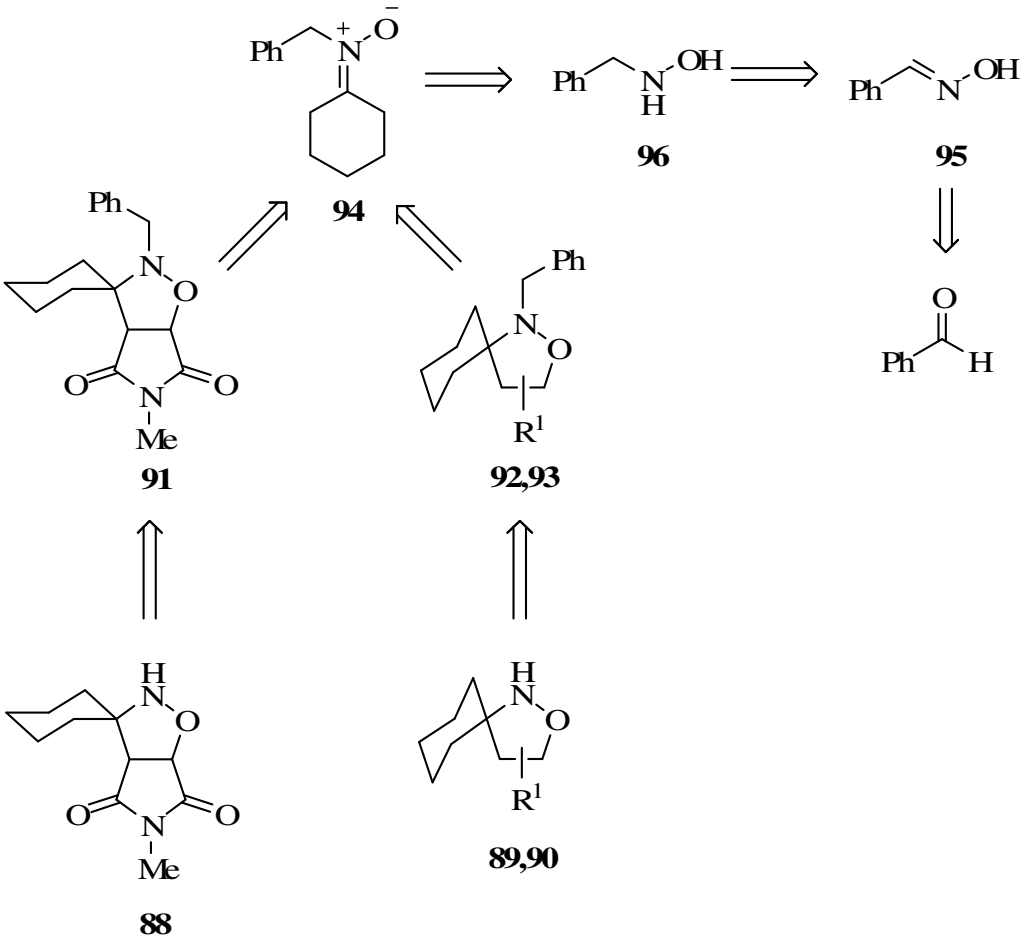
2.2 Synthesis of 1st Generation Isoxazolidine Containing Organocatalysts

The 1st generation organocatalysts, **88**-**90**, targeted had the basic framework outlined in figure 16 and bore a spirocyclohexane adjacent to the secondary amine. A retrosynthetic approach to the desired molecules is shown in scheme 9. Thus, the *NH*-cycloadducts **88**-**90** were to be acquired by debenzylation of **91-93**, themselves to be synthesised from the nitrone **94**. The nitrone, in turn was to be obtained by condensation of cyclohexanone with *N*-benzyl hydroxylamine.



88 $R^1 = C(O)NMeC(O)$
89 $R^1 = CO_2Me$
90 $R^1 = SO_2Ph$

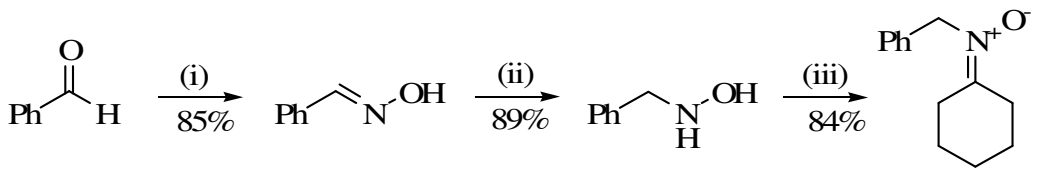
Figure 16. Targeted framework for the 1st generation isoxazolidine containing organcatalysts.



Scheme 9. Retrosynthetic analysis for the formation of the 1st generation organocatalysts.

2.2.1 Synthesis of Nitrone 94

Nitrone **94** was synthesised in three steps as shown in scheme 10. The first step involved condensation of benzaldehyde with hydroxylamine hydrochloride to form benzaldehyde oxime as a colourless oil in 85% yield, ^{1}H NMR spectral data for **95** was in agreement with that in the literature.[156] Reduction to the hydroxylamine **96** followed from treatment with sodium cyanoborohydride in acetyl chloride. The hydroxylamine was obtained as a yellow oil in 89% yield, again the ^{1}H NMR spectral data agreed with that reported in the literature.[157] Nitrone **94** is known in the literature and the reaction of hydroxylamine **96** and cyclohexanone was conducted in the presence of $ZnCl_2$ in DCM at room temperature. The nitrone **94** precipitated as a white solid from EtOAc and was obtained in 84% yield.[158]



95 **96** **94**

(i) NH_2OH•HCl, NaOAc, EtOH, 70 ^oC, 2 h

(ii) $NaBH_3CN$, CH_3COCl, MeOH, r.t., 15 min

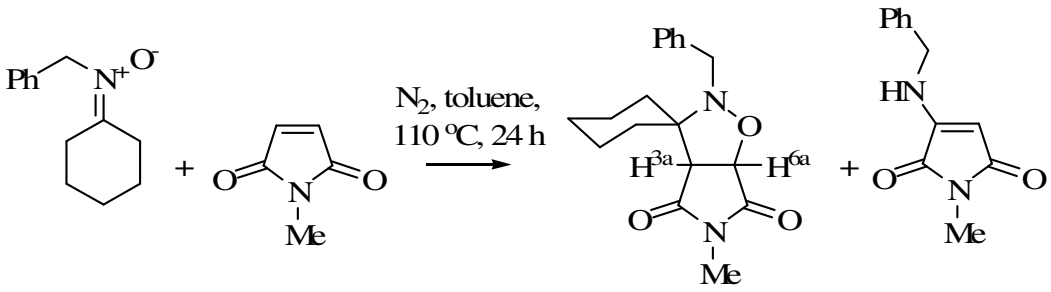
(iii) Cyclohexanone, $ZnCl_2$, anh. DCM, r.t., 1 h then 45 ^oC, 25 min

Scheme 10. Synthetic route to the formation of nitrone **94**.

2.2.2 Cycloaddition of Nitrone 94

2.2.2.i Cycloaddition to N-methylmalemide

The desired *N*-methylmalemide cycloadduct **91** was obtained following the reaction of the nitrone **94** with *N*-methylmalemide **97** in refluxing anhydrous toluene under a N_2 atmosphere for 24 hours. Following purification, **91** was obtained as a white solid in 41% yield; ^1H and ^{13}C NMR spectral data shown in figure 17 supports the structure. Characteristic peaks in the ^1H NMR spectrum include the doublet resonances at 4.70 and 3.50 ppm arising from the bridgehead protons H^{6a} and H^{3a}; signals at 75.3 and 54.1 ppm in the ^{13}C NMR are diagnostic of the corresponding *C*-atoms, C^{6a} and C^{3a}.



94 **97** **91** (41%) **98** (4%)

Equation 43. Cycloaddition of nitrone **94** and *N*-methylmalemide.

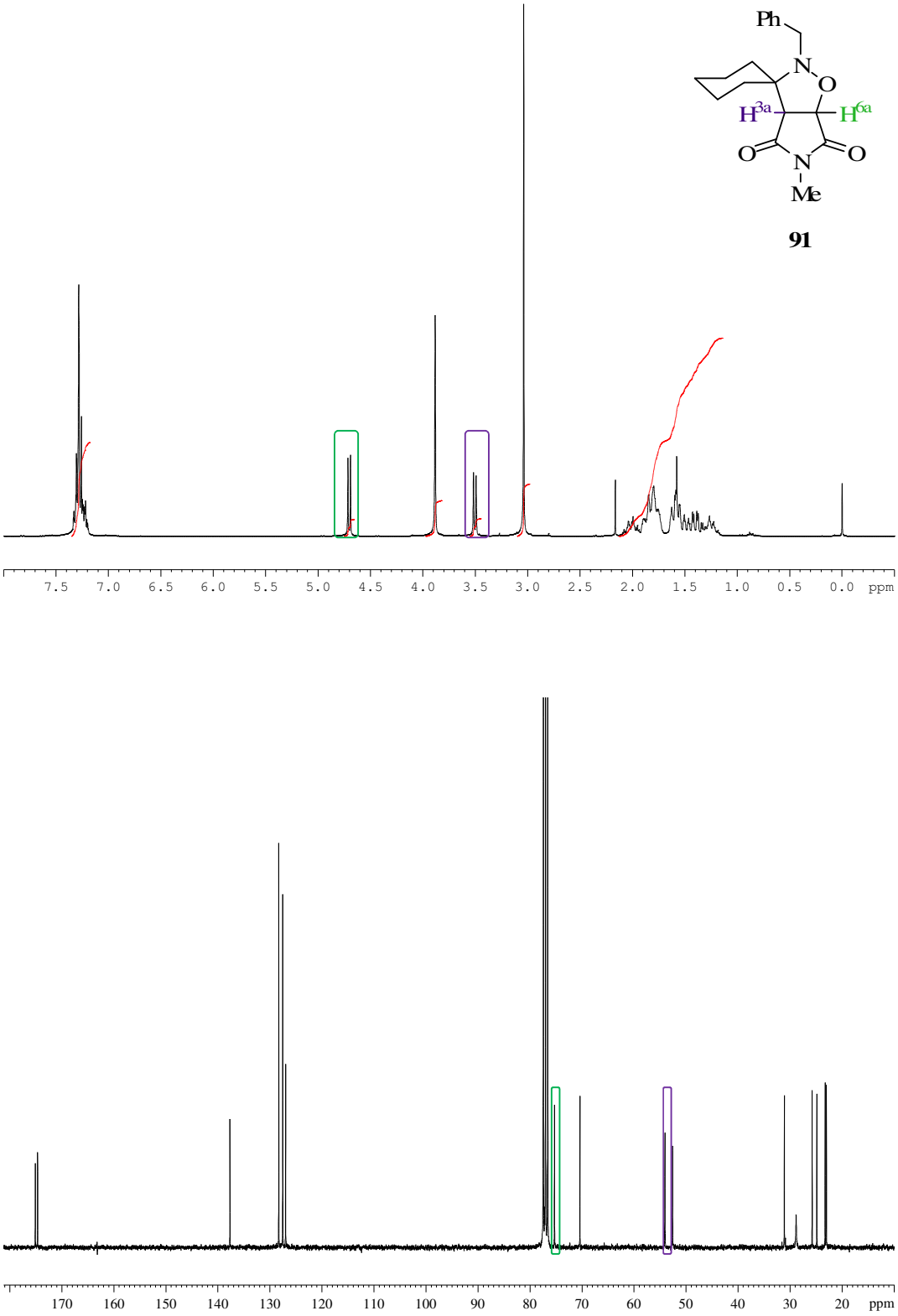


Figure 17. ^{1}H and ^{13}C NMR spectral data for the cycloadduct **91**.

The structure of a side product of the reaction, isolated as yellow crystals in 4% yield, was difficult to unambiguously assign. Fortunately, the crystals were of sufficient quality to permit characterisation by x-ray crystal structure determination. The x-ray crystal structure obtained, shown in figure 18, identifies the unknown compound as an addition product of *N*-benzylhydroxylamine with *N*-methylmalemide. The presence of residual *N*-benzylhydroxylamine **96**, which failed to separate during purification of the nitrone **94** accounts for the formation of **98**. A control experiment between *N*-methylmalemide and *N*-benzylhydroxylamine supported this hypothesis and following heating to reflux in toluene under a N_2 atmosphere for 24 hours **98** was formed in 8% yield. The x-ray crystal shows the C(1)-C(4) bond length to be 1.368 Å, confirming the presence of a double bond. A singlet at 4.86 ppm in the ^{1}H NMR spectrum represents the alkene type proton H^4.

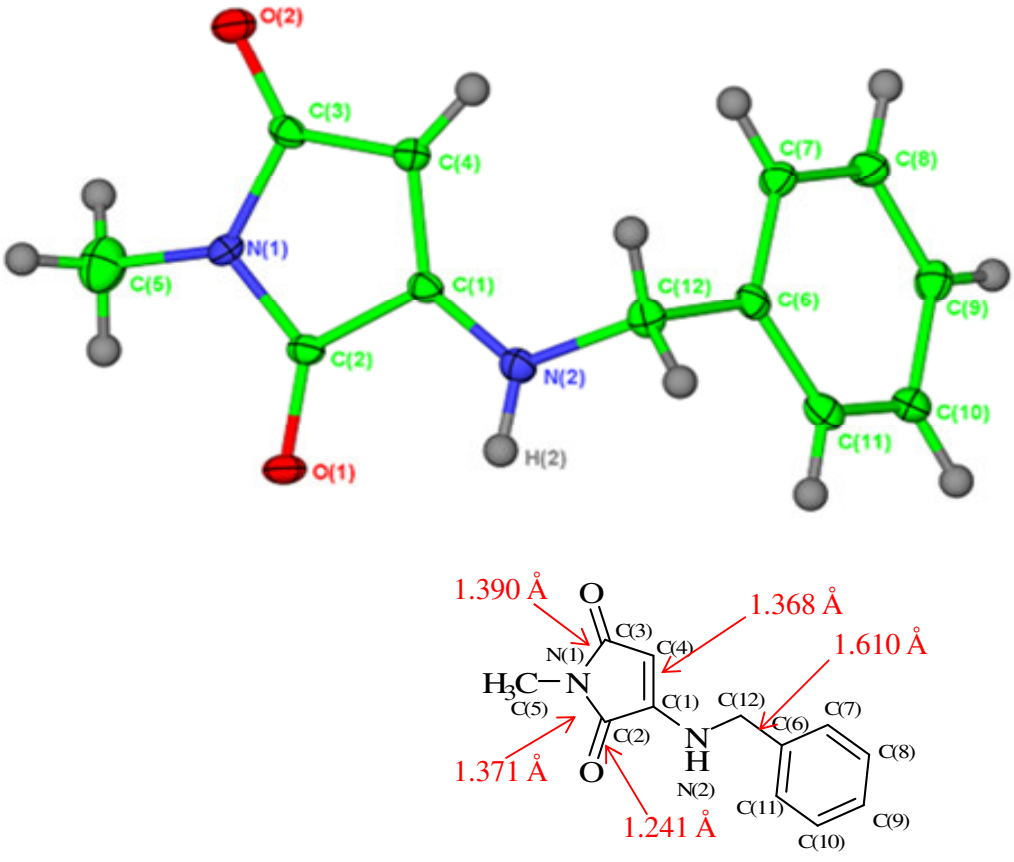


Figure 18. Crystal structure for compound **98**.

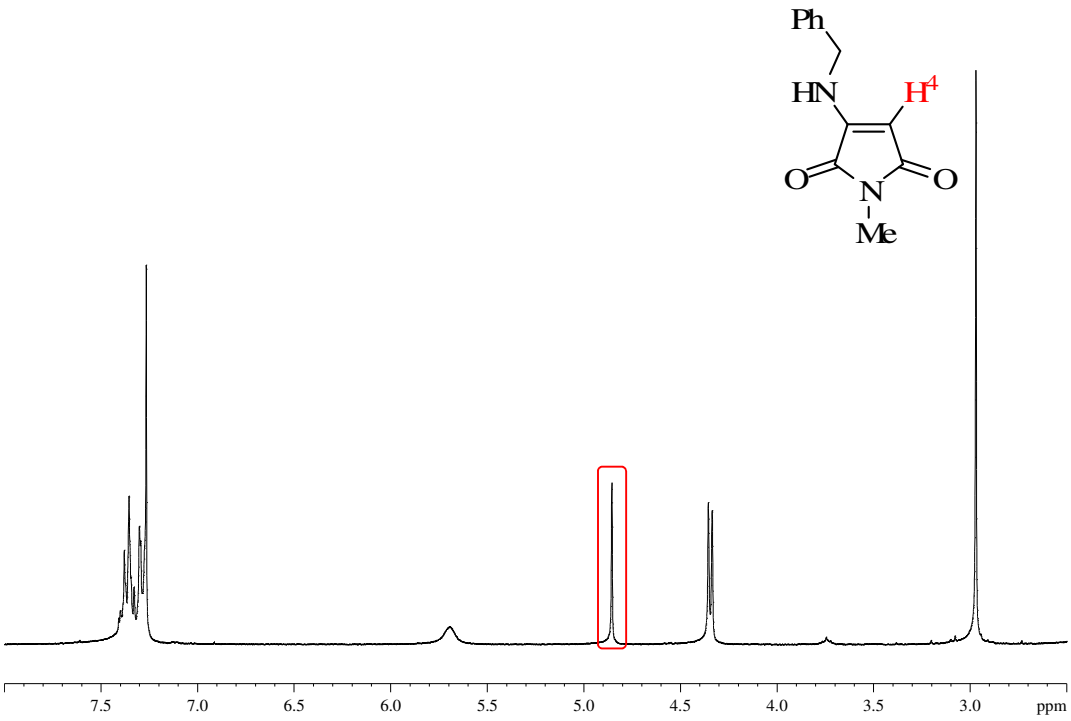


Figure 19. ^{1}H NMR spectral data for **98**.

2.2.2.ii Cycloaddition with methyl acrylate

The synthetic approach to **92** was similar to that discussed above for the bicycle **91**, however, the reaction of nitrone **94** with methyl acrylate was more sluggish and required heating to reflux under a N_2 atmosphere in a pressure tube for 37 hours. The product, **92**, was obtained as a yellow oil just in 13% yield, equation 44 and figure 20. The ^{1}H NMR spectral data of the crude product suggests a highly regioselective cycloaddition. Formation of the 5-substituted regioisomer is presumably favoured over the alternative 4-substituted compound due to steric hindrance imposed by the cyclohexane ring deterring formation of the latter. The presence of a doublet of doublets at 4.53 ppm in the ^{1}H NMR spectrum is characteristic of the H^5 isoxazolidine ring proton (as numbered in equation 44). The signals arising from the methylene group of the isoxazolidine ring at 3.72 and 51.1 ppm in the ^{1}H and ^{13}C NMR spectra respectively are indicative of a 5- and not a 4- substituted isomer.[159] No other cycloaddition products could be isolated from the reaction.

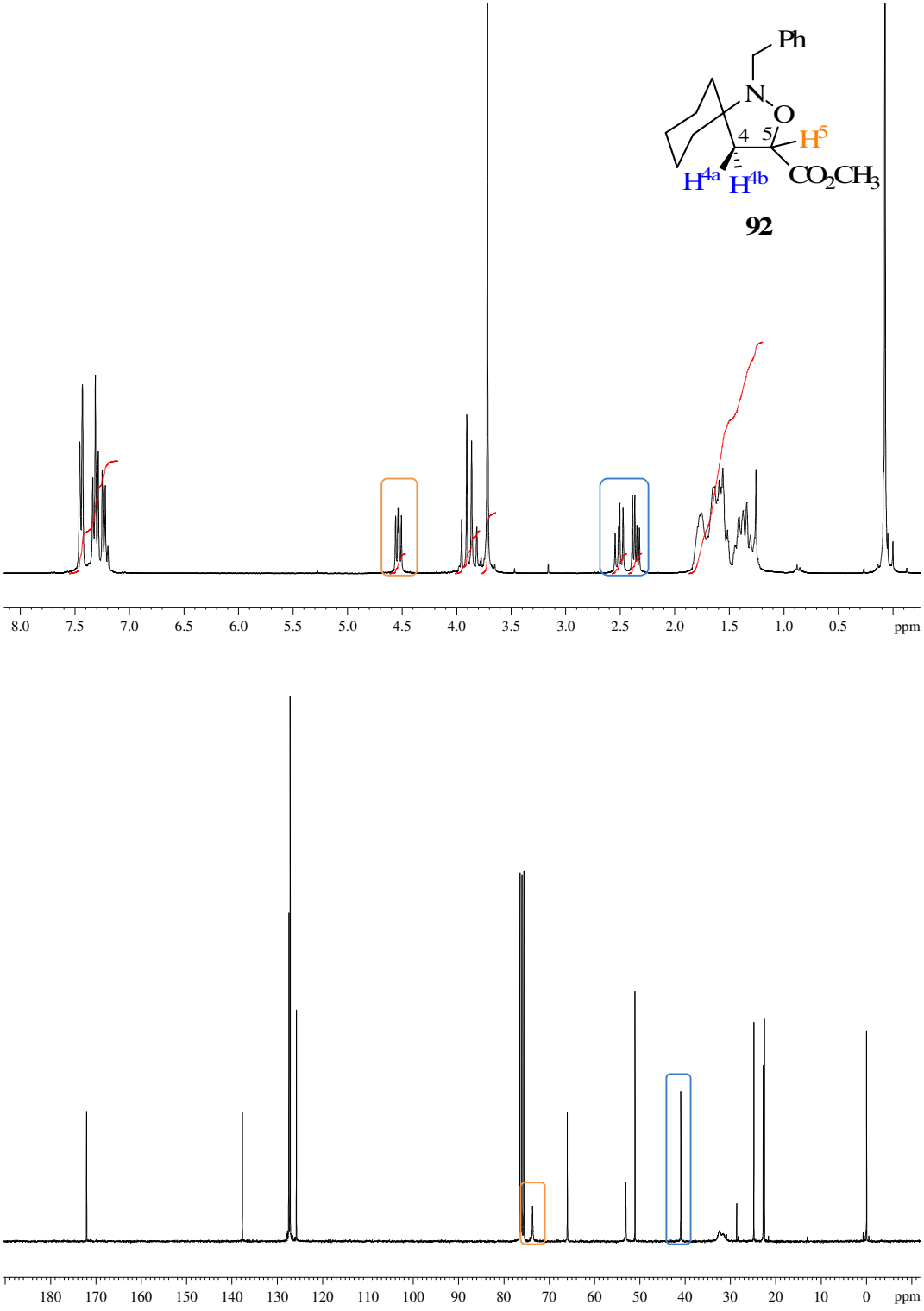
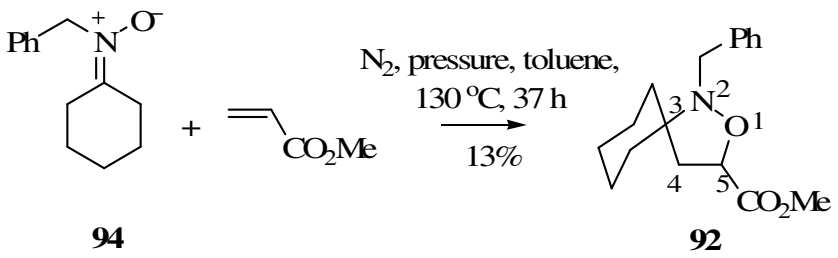


Figure 20. ^{1}H and ^{13}C NMR spectral data for the cycloadduct **92**.



Equation 44. Cycloaddition of nitrone **94** with methyl acrylate.

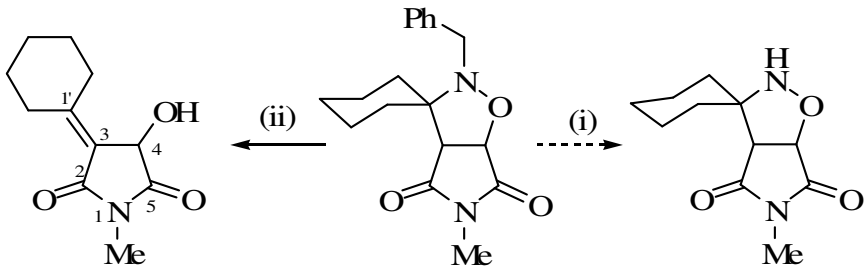
2.2.2.iii Cycloaddition with phenylvinyl sulfone

The attempted cycloaddition of the nitrone **94** with phenylvinyl sulfone proved difficult; with the employment of $CHCl_3$ as reaction solvent, and under a N_2 atmosphere, only a small percentage conversion to the cycloadduct was observed. Changing the solvent to the higher boiling toluene and applying pressure failed to increase the percentage conversion. Due to the small conversion to the cycloaddition product it was not possible to obtain a pure sample of the desired cycloadduct.

2.2.3 Attempted Deprotection of the Cycloadducts 91 and 92

The deprotection of **91** was attempted by following a literature procedure found to be successful for related compounds.[160] Thus, a sample of **91** was treated with anhydrous formic acid and palladium black in anhydrous MeOH at room temperature for 2.5 hours. TLC analysis of the reaction mixture showed the absence of any starting cycloadduct. Following filtration through celite, stirring with K_2CO_3 and work-up a yellow solid was obtained. Structural elucidation of this crude material through ^{1}H NMR was difficult due to the presence of very broad signals in $CDCl_3$, however it was clear that the desired compound was not present. The reaction was repeated under the same conditions, except on the second occasion the crude material was not basified with K_2CO_3. Once again the reaction product was difficult to analyse and the ^{1}H NMR spectrum comprised of broad signals. Purification by flash column chromatography yielded the product as colourless crystals in 31% yield. Once again, the ^{1}H NMR spectral data was clearly not consistent with the desired *NH*-isoxazolidine **88**, but was otherwise difficult to interpret. Fortunately, the crystals were suitable for x-ray diffraction and a single crystal x-ray structure determination revealed the product to be 3-cyclohexylidene-4-hydroxy-1-methylpyrrolidine-2,5-dione, **99**. Evidently the isoxazolidine ring had opened during the reaction and the presence of a hydroxy group at the 4-position in the x-ray crystal

structure confirmed the ring opening, figure 21. The x-ray data shows a bond length of 1.342 Å for the bond connecting C(7) to C(1) which is typical of a C=C double bond.[161] The C-OH bond length of 1.415 Å is a typical single bond length. The C-N bonds are different lengths; C(11)-N(4) is 1.414 Å and C(10)-N(4) is 1.358 Å, the shorter bond length indicates partial double bond character due to delocalisation over the C(10) carbonyl, figure 22.



99 **91** **88**

(i) HCOOH, MeOH, Pd black, r.t., 2.5 h, then K_2CO_3, 15 min, r.t.

(ii) HCOOH, MeOH, Pd black, r.t., 2.5 h

Scheme 11. Attempted deprotection of the bicycle **91**.

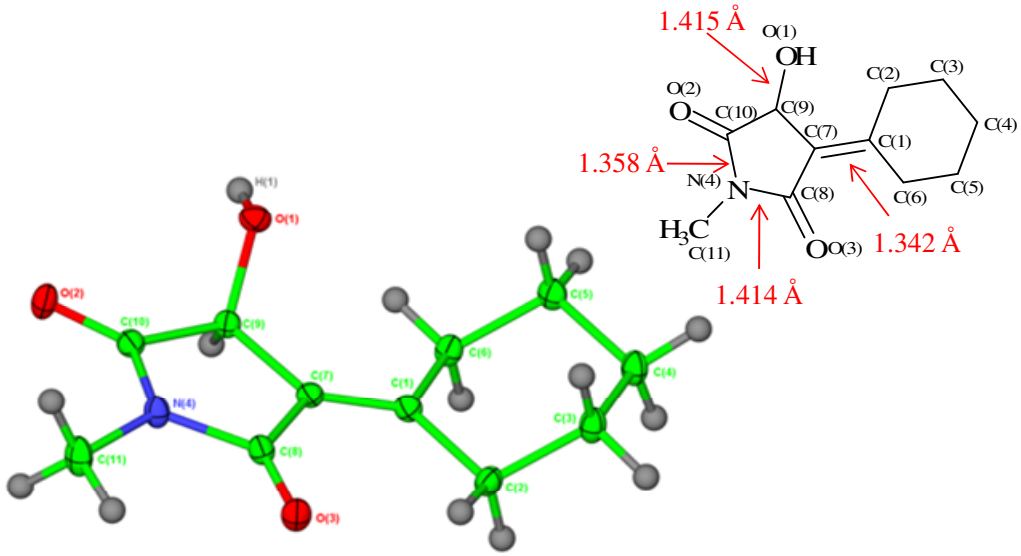


Figure 21. Crystal structure for **99**.

With the crystal structure determined the ^{1}H NMR spectral data of a sample of **99** in CD_3OD could be assigned. The methylene protons of the cyclohexane moiety are represented by five multiplets at ≃3.05, 2.92, 2.48, 2.32 and 1.61 ppm. The *N*-methyl

protons appeared at 2.87 ppm whilst the remaining CH proton was found at 3.21 ppm. The signals of the "alkene" carbon atoms appeared at 163.8 and 121.5 ppm for $C^{1'}$ and C^{3} respectively, $C^{1'}$ more deshielded due to resonance, and the C^{4} carbon atom is hidden beneath the solvent peak at 49.3 ppm, figure 23.

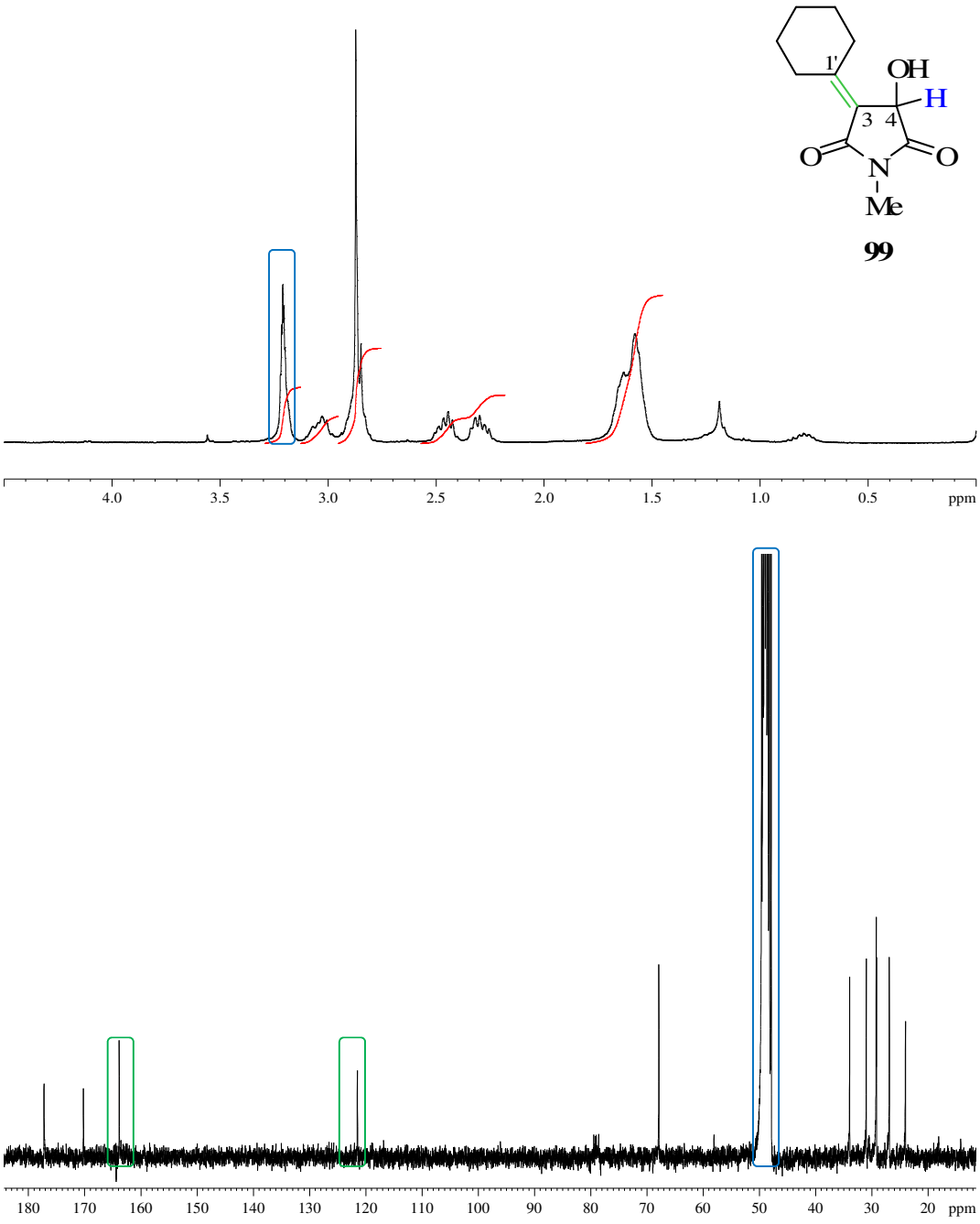
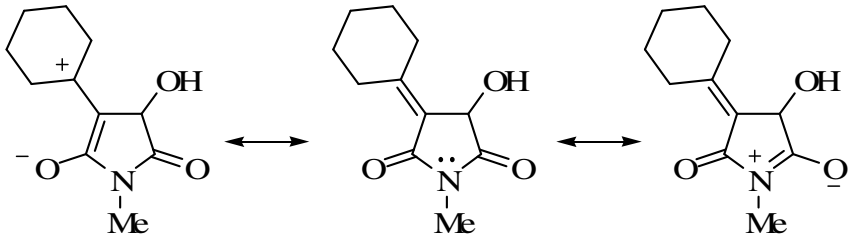


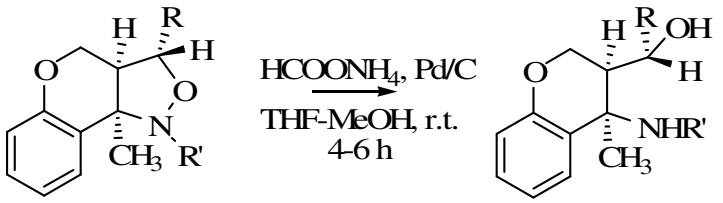
Figure 23. ^{1}H and ^{13}C NMR (CD_3OD) spectral data of **99**.



99

Figure 22. Resonance structures available for **99**.

It is proposed that **99** arises from the reductive cleavage of the heterocyclic N-O bond of **91** followed by elimination of the protonated *N*-benzyl group. Structures related to **99** have been previously reported though none by way of reductive cleavage.[162-164] Reductive cleavage of isoxazolidine rings is however a common synthetic tool for forming amino alcohols, one such transformation, shown in equation 45, is effected by treatment of **101** with ammonium formate and Pd/C in MeOH-THF (3:1).[165]



101a-e **100a-e**

$R = H, CH_3, Ph; R' = H, CH_3$

Equation 45. Reductive cleavage of isoxazolidines.

2.2.4 Conclusion

As a consequence of (i) the failed cycloaddition between the *N*-benzyl nitrone **94** and phenyl vinyl sulfone, (ii) the low yield of the cycloaddition product with methyl acrylate and (iii) the difficulties encountered during the debenzylation of the *N*-methylmalemide cycloadduct, **91**, further efforts to synthesise the first generation catalyst design were terminated.

2.3 Synthesis of 2nd Generation Isoxazolidine Containing Organocatalysts

2.3.1 Introduction

The second generation catalysts comprised bicyclic frameworks as sketched in figure 24. The frameworks A, B and C all consist of an isoxazolidine ring fused to a second heterocycle. The differences in the three frameworks are in the nature of the second ring. Frameworks A and B bear a lactone and a lactam ring respectively, both introduce a β'-carbonyl into the structure, while framework C has a pyrrolidine ring. The synthetic approach to each of the frameworks will be discussed in the following sections.

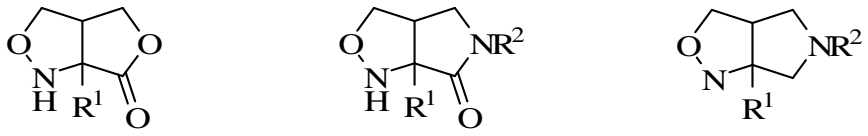


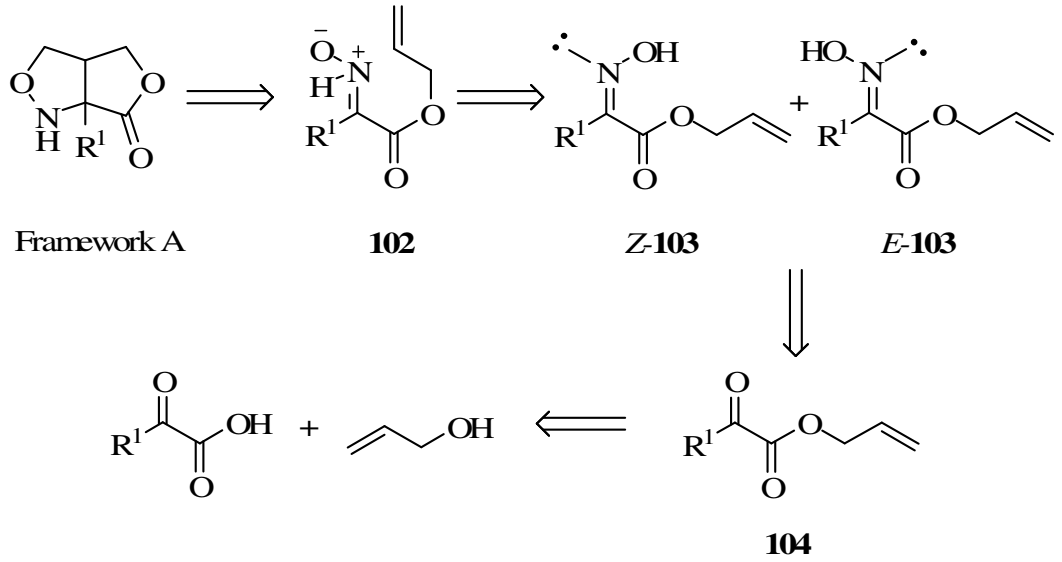
Figure 24. Frameworks for the 2nd generation isoxazolidine containing organocatalysts.

2.3.2 Lactone Fused Isoxazolidine; Framework A

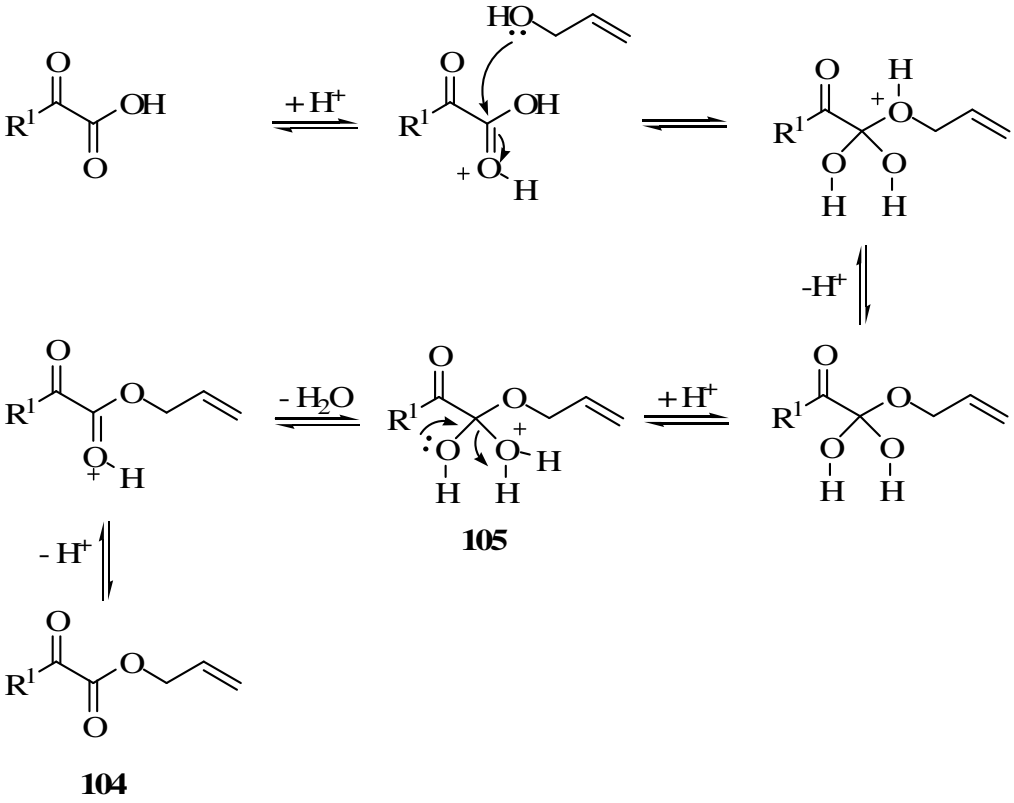
This section describes the preparation of the family of bicyclic isoxazolidines with framework A by the route summarised in the retrosynthetic approach in scheme 12. The bicycle is formed from cycloaddition of the transiently generated *NH*-nitrone **102** which arises by tautomerisation of the parent oxime **103**.[166] The oxime in turn is synthesised from the α-keto ester **104**. The ester is formed from condensation between the corresponding acid and allyl alcohol.

2.3.2.i α-Keto ester preparation

The preparation of α-keto esters from α-keto acids and allyl alcohols by an acid catalysed esterification reaction has been previously documented.[167] Following the literature precedent *para*-toluene sulfonic acid (*p*-TsOH) was employed as catalyst in toluene with the use of a Dean-Stark trap. The general mechanism for an esterification reaction is shown in scheme 13. Initial protonation of the carbonyl group of the α-keto acid promotes nucleophilic attack by the alcohol. The hydrogen transfer step afforded the intermediate **105** with loss of water and deprotonation yielding the α-keto ester **104**.



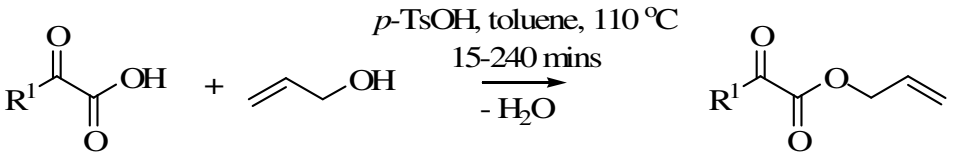
Scheme 12. Retrosynthetic analysis for the formation of framework A.



Scheme 13. Mechanism for the formation of the α-keto-esters **104a-f**.

Six α-keto esters **104a-f** were prepared, the yields were good varying from 81-91%. The condensation products of allyl alcohol with benzoylformic acid, **104a**, thiophene-2-

glyoxylic acid, **104c**, and 2-nitrophenyl pyruvic acid, **104d**, are known and the data obtained was in agreement with the literature[167,168], yields are summarised in table 3.



106 **104**

a. R^1 = Ph; **b.** R^1 = 2-furyl, **c.** R^1 = 2-thienyl,

d. R^1 = *o*-nitrobenzyl, **e.** $R^1 = CH_2Ph$, **f.** $R^1 = 2,4,6\text{-}(CH_3)_2C_6H_2$

Equation 46. Synthetic route for the formation of the α-keto esters.

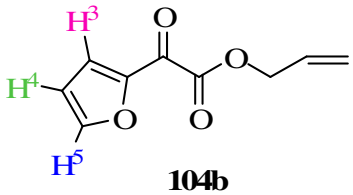
Table 3. Isolated yields of α-keto esters **104a-f**.

Substrate	R^1	Time (min)	Product (% Yield)
106a	Ph	240	**104a** (90)
106b	2-furyl	20	**104b** (87)
106c	2-thienyl	25	**104c** (84)
106d	*o*-nitrobenzyl	20	**104d** (91)
106e	CH_2Ph	25	**104e** (81)
106f	$2,4,6\text{-}(CH_3)_3C_6H_2$	15	**104f** (90)

As a representative case the ^{1}H NMR spectrum of **104b**, the 2-furyl α-keto ester, is shown in figure 25. Each of the three aromatic protons appeared as doublet of doublets, with H^3 and H^5 downfield at 7.72 and 7.77 ppm respectively, and H^4 more upfield at 6.63 ppm. A multiplet for the CH proton of the alkene resonates between 6.08 and 5.95 ppm and the OCH_2 protons appear as a doublet at 4.85 ppm whilst the terminal alkene protons each appear as a doublet of doublets between 5.48 and 5.33 ppm.

The benzyl substituted ester **104e** presented as a 1:1 mixture of the keto and enol forms. The ester could not be purified and the ^{1}H NMR spectrum of the crude product showed two sets of doublets at ≃4.8 ppm representing the OCH_2 protons of the keto and enol forms. Peaks at 6.62 and 4.16 ppm were observed for the enol C<u>H</u>Ph and keto C<u>H</u>$_2$Ph protons, respectively. The enol C<u>H</u>Ph peak appeared broad at the base indicating the presence of an OH peak at the same resonance. Upon shaking with D_2O the peak appeared sharper and a decrease in the integration was observed, figure 26. The

presence of the OH peak was confirmed by a broad OH stretch in the IR spectrum at ≃3225 cm^{-1}.



104b

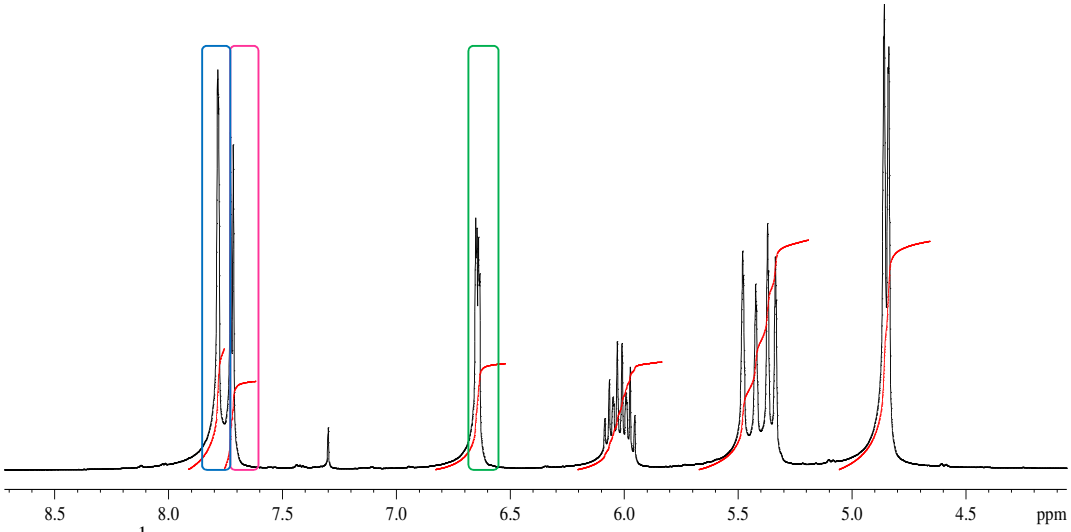


Figure 25. ^{1}H NMR spectrum for the 2-furyl α-keto ester **104b**.

2.3.2.ii Oxime preparation

Oximes are simple derivatives of the carbonyl functional group; a general mechanism for an oximation reaction is shown in scheme 14. The reaction involves nucleophilic attack at the carbonyl group by hydroxylamine affording the intermediate **107**, which *via* protonation affords the addition compound **108** with a hydroxyl and amino group attached to the same carbon atom. Following and deprotonation and protonation, dehydration and loss of a proton the oxime is generated.

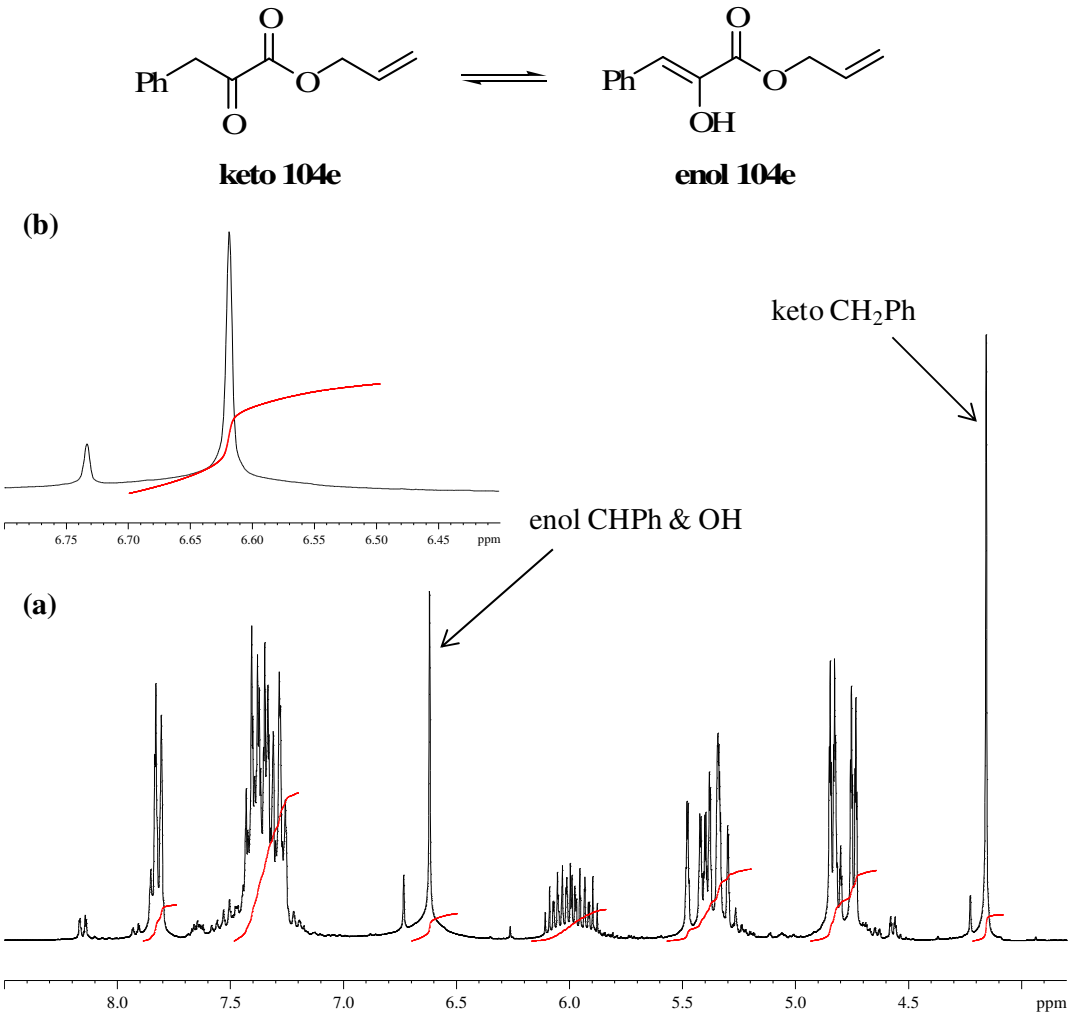
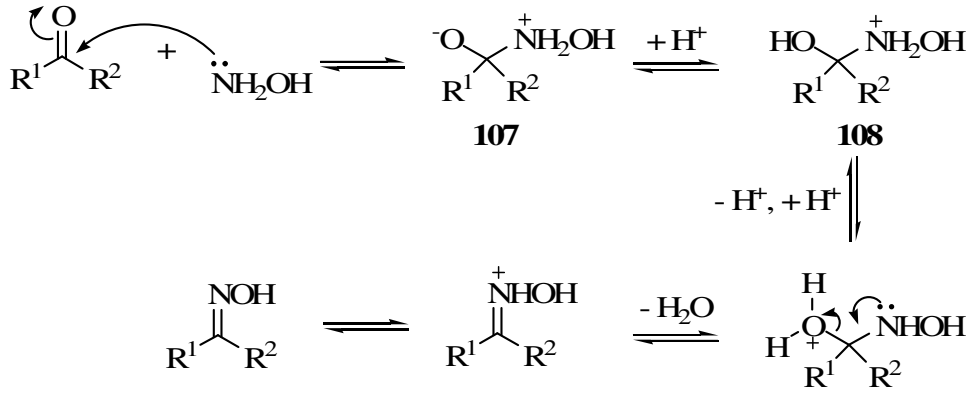


Figure 26. ^{1}H NMR spectral data showing **(a)** the keto and enol forms of **104e** and **(b)** the disappearance of the OH peak post D_2O shake.



Scheme 14. Mechanism for oxime formation from α-keto esters.

Oxime geometry is assigned on the basis of the atoms bound to the C=N double bond, the bond is assigned a *Z*-configuration when the two groups with the higher priority are on the same side of the double bond. If the two groups are on opposite sides, the molecule is given an *E*-configuration, figure 27. In comparing the furyl and thienyl oximes there is a change in relative priorities of the groups connected to the oxime double bind, however, in the interest in consistency in graphical presentation, in both cases those oximes have the hydroxyl group on the same side as the alkenyl chain are considered Z-oxime isomers and those with the heteroaryl and the hydroxyl group on the same side are labelled as *E*-isomers.

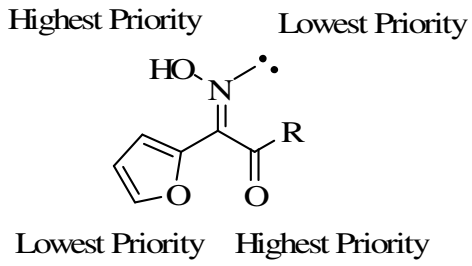
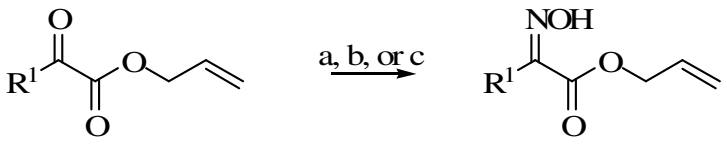


Figure 27. Assignment of priorities of the oximes.

The geometrical oximes **103a** were synthesised in H_2O, the hydroxylamine was commercially available as the hydrochloride salt and sodium acetate was used as base (equation 47(iii)).[166] The oximes **103b-e** were prepared in EtOH with NH_2OH•HCl and pyridine as base (equation 47(i)). Geometrical oxime isomers were obtained for **103b&c** but **103d&e** formed only the *E*-oximes isomer.[167,168] In all cases the reactions progressed well and the oximes could be isolated in satisfactory yields. The attempted oximation of **104f** was more problematic; the reaction failed in H_2O (equation 47(iii)) and only progressed slowly in EtOH (condition (i)). ^{1}H NMR spectral analysis of the crude reaction products showed much crowding in the aromatic region suggesting the formation of one or more undesired products. The reaction was repeated with a higher boiling alcohol ^{t}BuOH (82.4 ^{o}C)[169] as solvent and with a larger excess of the reagents (2.2 equiv.). The reaction progressed selectively, albeit quiet slowly to furnish the desired oximes. ^{i}PrOH (82.3 ^{o}C)[169] was subsequently found to be the best reaction solvent leading to the desired products in 70% yield after 56 hours reaction (equation 47(ii)).

E- and *Z*-isomers of the phenyl and 2-thienyl oximes, **103a&c**, were separable by flash column chromatography and a pure sample of each was obtained. In the case of **103a** the *Z*-isomer was the major component by a factor of ≃4:1 whilst the 2-thienyl oximes, *E*- and *Z*-**103c**, were obtained in approximately equal amounts. The isomers of the 2-furyl derivative **103b** were inseparable and presented with an *E*:*Z* ratio of 1:1.4. For illustrative purposes the ^{1}H NMR spectrum of a mixture of the *E*- and *Z*-geometrical oximes of **103b** is shown in figure 28. The spectrum shown is taken from a fraction enriched in the minor *E*-isomer. The aromatic protons of the *E*-isomer resonate in similar positions to the corresponding protons of the parent α-keto ester **106b**. For the *Z*-isomer the aromatic protons H^4 and H^5 are slightly more shielded than the corresponding protons in the *E*-isomer. However there is a significant difference in the resonance position of H^3, the proton experiences a large upfield shift (≃ 1 ppm) with respect to that observed in the *E*-isomer. This deshielding is attributed to the proximity of H^3 to the hydroxy group in the *E*-isomer.



104a-f **103a-f**

(i) NH_2OH•HCl, pyridine, EtOH, 70 ^oC

(ii) NH_2OH•HCl, pyridine, ^{i}PrOH, 85 ^oC

(iii) NH_2OH•HCl, NaOAc, H_2O, 70 ^oC

a. R^1 = Ph; **b.** R^1 = 2-furyl, **c.** R^1 = 2-thienyl, **d.** R^1 = *o*-nitrobenzyl, **e.** R^1 = CH_2Ph, **f.** R^1 = 2,4,6-$(CH_3)_2C_6H_2$.

Equation 47. Synthetic route to the formation of the oximes **103a-f**.

Table 4. Preparation of the substituted oximes **103a-f**.

Substrate	R^1	Conditions	Time	Oxime *E:Z* (% Yield)
104a	Ph	iii	4 h	**103a** (21:77)
104b	2-furyl	i	20 min	**103b** (99)[a]
104c	2-thienyl	i	25 min	**103c** (43:40)
104d	*o*-nitrobenzyl	i	20 min	**103d** (97)
104e	CH_2Ph	i	25 min	**103e** (75)
104f	2,4,6-$(CH_3)_3C_6H_2$	ii	56 h	**103f** (8:62)[b]

[a] %Yield is quoted for a mixture of isomers as separation could not be achieved. [b] After 17 days at r.t. *Z*-**103f** had all converted to *E*-**103f**.

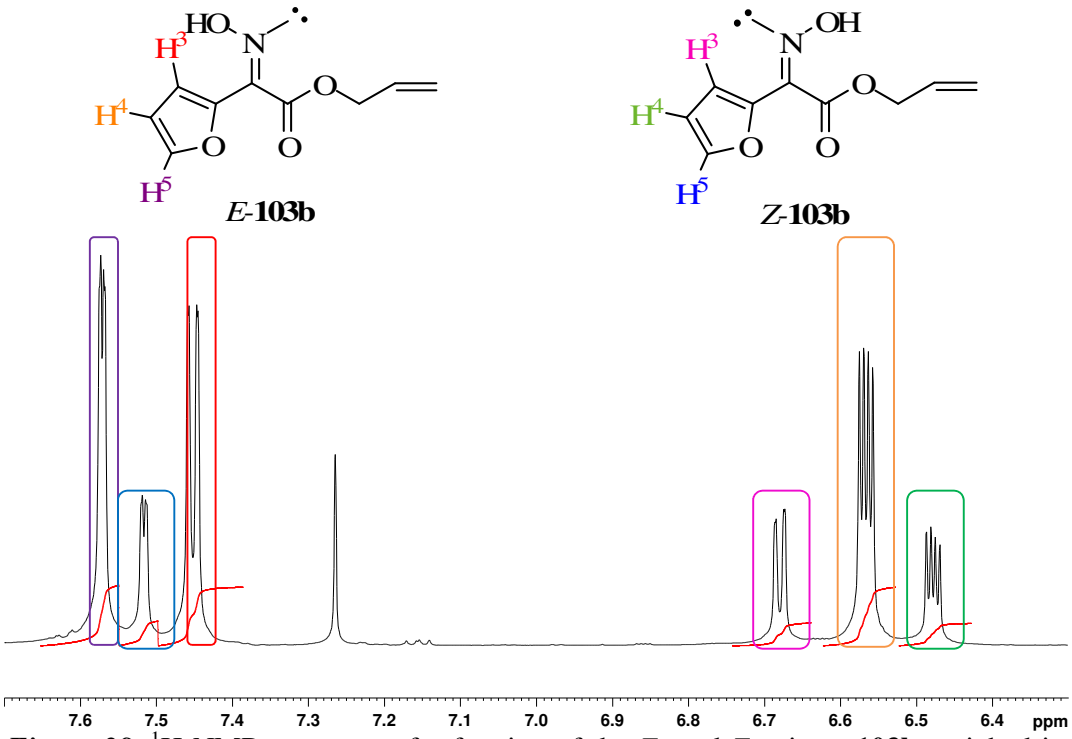


Figure 28. ^{1}H NMR spectrum of a fraction of the *E*- and *Z*-oximes **103b** enriched in the minor *E*-103b.

In the case of the mesityl oximes, **103f**, the *Z*-isomer was the major component in a newly prepared sample. This oxime was found to be geometrically unstable upon standing in solution ($CDCl_3$) at room temperature and after 17 days on the bench it had fully converted to the *E*-isomer. When stored neat at -20 ^oC the *Z*-isomer, a pale yellow oil, was found to be fully stable. The ^{1}H NMR spectral data for the *E*- and *Z*-isomers is very similar, the only discernable difference being in the resonance position of the CH_3

peaks with the *o*-CH_3 and *p*-CH_3 protons observed as singlets at 2.14 and 2.30 ppm for the *E*-isomer and at 2.23 and 2.22 ppm for the *Z*-isomer, figure 29.

For this series of oximes geometrical assignment was on the basis of their ^{13}C NMR data. Comparison of the ^{13}C resonance positions of the α-carbon of the *E*- and *Z*- oxime isomers can be used to assist in structural assignment as the ^{13}C resonance positions of the C-atom of C=N ketone oximes are known to depend on their steric configuration. This parameter can be used to distinguish between geometrical isomers. The ^{13}C chemical shifts of a range of aldehyde oximes, ketone oximes and ketone oxime *O*-vinyl ethers reported in the literature indicate that the sterically more compressed *E*-isomer resonates upfield with respect to the corresponding *Z*-isomer.[170] The ^{13}C NMR spectrum of the 2-furyl oximes **103b** exhibited the α-C signals at 140.0 and 142.6 ppm and following the above guidelines the major isomer can be assigned as the *Z*-isomer and the minor as the *E*-isomer, table 5.

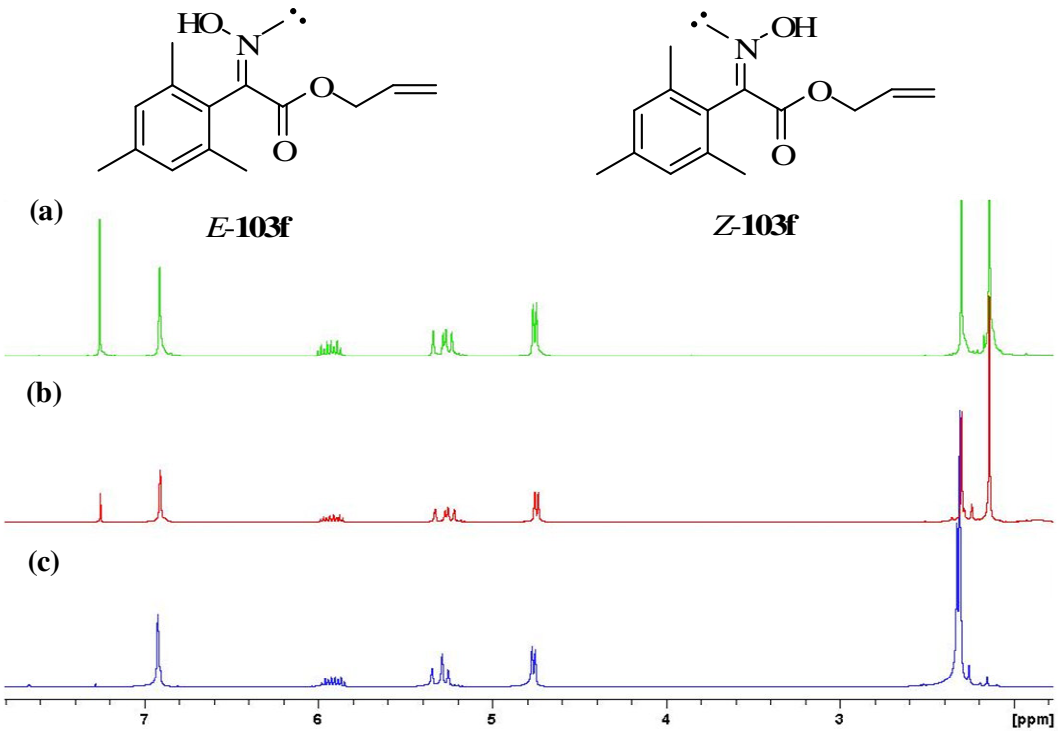


Figure 29. ^{1}H NMR spectral data for **(a)** *E*-**103f**, **(b)** *Z*-**103f** (converted to *E*-**103f**) after 17 days at r.t. standing in $CDCl_3$ and **(c)** *Z*-**103f** after 19 days neat at -20 ^{o}C.

Table 5. ^{13}C resonance positions for the α-C of the oxime isomers of **103a-f**.

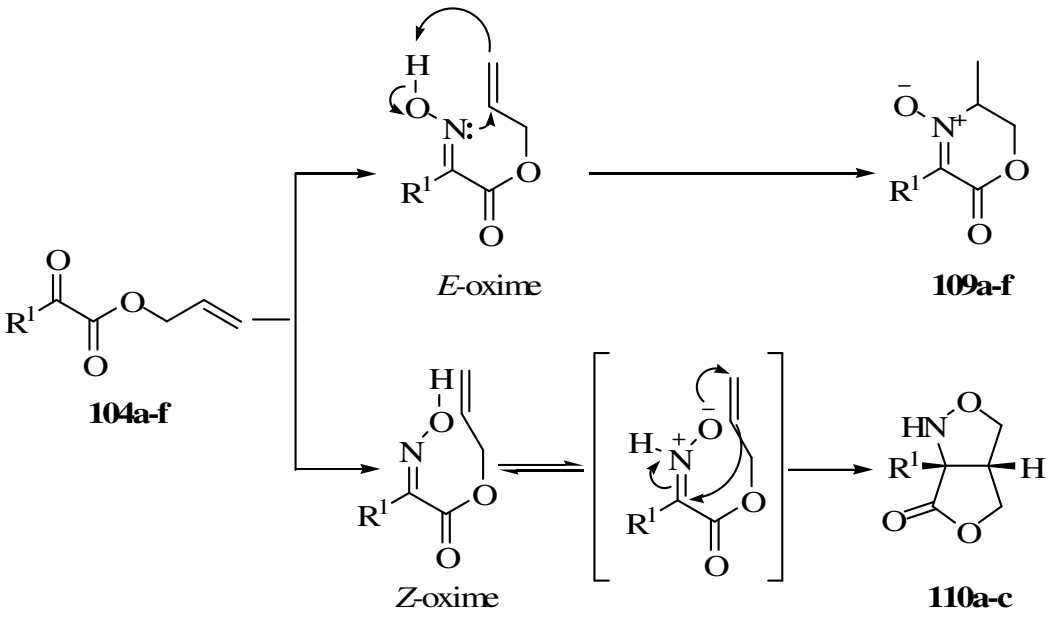
Oxime	^{13}C resonance of α-C (ppm)	Δ (*E,Z*), ppm
E-**103a**	129.9	1.00
Z-**103a**	130.9	
E-**103b**	140.0	2.60
Z-**103b**	142.6	
E-**103c**	127.9	5.80
Z-**103c**	133.9	
E-**103d**	130.5	-
E-**103e**	135.6	-
E-**103f**	126.6	1.40
Z-**103f**	128.0	

a. R^1 = Ph; **b.** R^1 = 2-furyl, **c.** R^1 = 2-thienyl, **d.** R^1 = *o*-nitrobenzyl, **e.** R^1 = CH_2Ph, **f.** $R^1 = 2,4,6\text{-}(CH_3)_2C_6H_2$.

2.3.2.iii Reaction of oxime isomers

The synthetic route to isoxazolidine formation from oximes is based on the observation by Heaney *et al.* that the geometrical isomers of certain δ-alkenyl oximes show differential reactivity *e.g.* the *E*-isomer **103a** reacts exclusively to furnish the six-membered cyclic dipole **109a** *via* a concerted 1,3-azaprotio cyclotransfer mechanism, whilst the *Z*-isomer reacts *via* a 1,2-prototropy-cycloaddition sequence furnishing fused isoxazolidine **110a**, scheme 15.[166,168]

The *N*-oxides **109a-f** are important building blocks for the construction of ring fused heterocycles, however they do not possess the necessary functionalities for organocatalytic activity and consequently were of no further interest to the current study. As discussed in section 2.3.1.ii the α-keto esters **104a-f** react to furnish either a single *E*-oxime isomer, **103d&e**, or a mixture of *E*- and *Z*-oxime isomers, **103a-c&f**. Thermal reactivity of the α-keto oximes was investigated with the hypothesis that, if these oximes are configurationally stable then *E*-isomers would react by an intramolecular 1,3-azaprotio cyclotransfer mechanism forming nitrones, **109a-f**, whilst *Z*-isomers would participate in a tandem 1,2-prototropy-cycloaddition sequence furnishing fused bicyclic isoxazolidines, **110a-c**.



a. R^1 = Ph; **b.** R^1 = 2-furyl, **c.** R^1 = 2-thienyl, **d.** R^1 = *o*-nitrobenzyl, **e.** R^1 = CH_2Ph, **f.** R^1 = 2,4,6-$(CH_3)_2C_6H_2$.

Scheme 15. Thermal reactivity of the oxime isomers to form the nitrone **109a-f** or the bicycles **110a-c**.

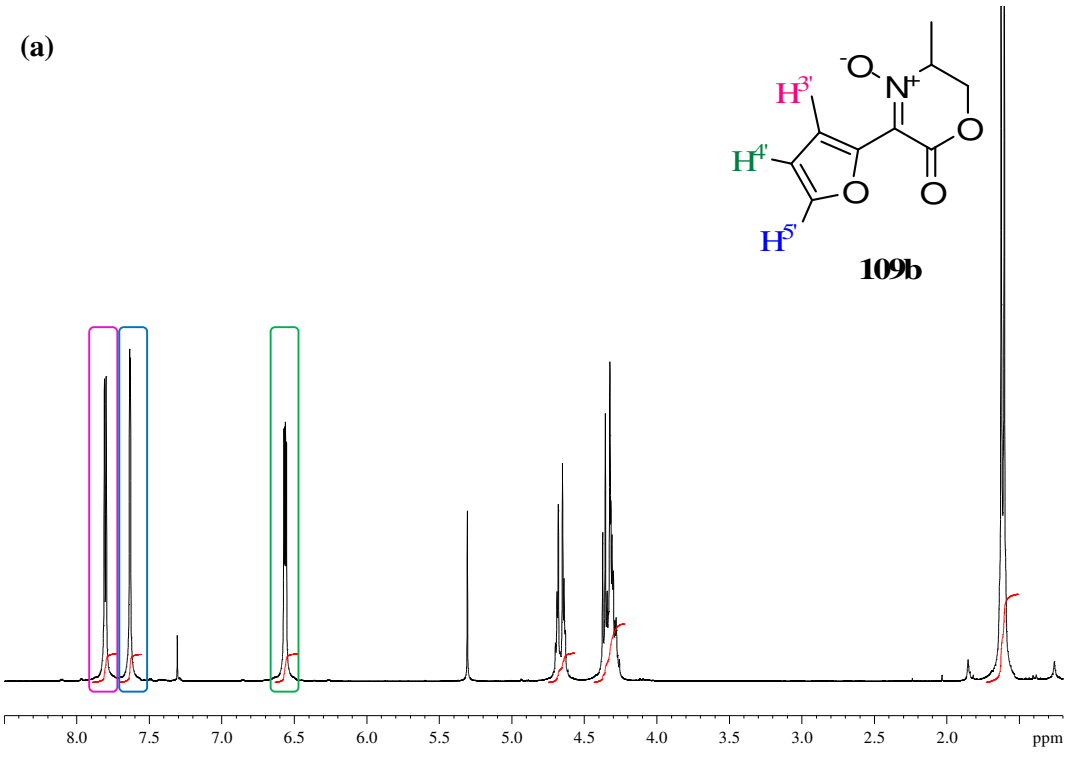
The 2-furyl geometrical oxime isomers **103b** were inseparable by flash column chromatography, accordingly a xylene solution of the mixed isomers in an *E:Z* 1:1.4 ratio was heated to reflux in the presence of hydroquinone for 24 hours. Examination of the ^{1}H NMR spectral data for the crude reaction products suggested conversion to the nitrone **109b** and the bicycle **110b**. Separation of the products of the reaction furnished the nitrone **109b** in 56% yield and the desired bicycle **110b** in 20% yield. The ^{1}H NMR spectral data for both compounds is shown in figure 30a,b. A diagnostic signal for the nitrone **109b** is the CH_3 resonance which is observed as a doublet at 1.61 ppm and the ring protons between ≃4.3 and 4.7 ppm characterise the nitrone ring. There are also interesting differences between the aromatic protons of the bicycle and the nitrone; for the nitrone $H^{3'}$ and $H^{5'}$ present as doublets at 7.80 and 7.63 ppm with $H^{4'}$ as a doublet of doublets upfield at 6.56 ppm. In contrast the aromatic protons of the bicycle **110b** resonate as a doublet at 7.46 ppm ($H^{5'}$), a doublet for $H^{3'}$ appears at 6.64 ppm and $H^{4'}$ shows as a doublet of doublets at 6.42 ppm. The shielding of $H^{3'}$ is assumed to be due to its proximity to the β'-carbonyl group. Assignment of the ring H^{α} and H^{β} protons is made with reference to the C^{6a}-Ph analogue, **110a**, previously prepared within the group.[171]

In the case of the 2-thienyl oximes **103c**, thermal activation of the *E*-isomer upon heating to reflux in xylene, in the presence of hydroquinone, resulted in the formation of the nitrone **109c**, as the sole product of the reaction, in 79% yield after 24 hours. The *Z*-isomer on the other hand was found not to be configurationally stable at elevated temperatures. Following heating in xylene (140 ^{o}C) a mixture of the nitrone **109c** (41% yield) and the fused bicycle **110c** (21% yield) was obtained.

The *o*-nitrobenzyl and benzyl oximes **103d&e** were available only as the *E*-isomer, under thermal activation these cyclised to form the nitrones **109d&e** exclusively.

As may have been expected on the grounds of its geometrical instability at room temperature, heating *Z*-**103f** to reflux in xylene resulted in the formation of the nitrone **109f**. The exclusive formation of the nitrone is presumed to be due to a ready conversion of the *Z*-isomer to the *E*-isomer under the reaction conditions.

Similarities in the resonance positions of the cycloaddition products, which are formed diastereospecifically, allow the stereochemical assignment of **110b** and **110c** as being *cis*-fused which is extrapolated from the results of NOEDS studies performed on **110a**, figure 31.[168]



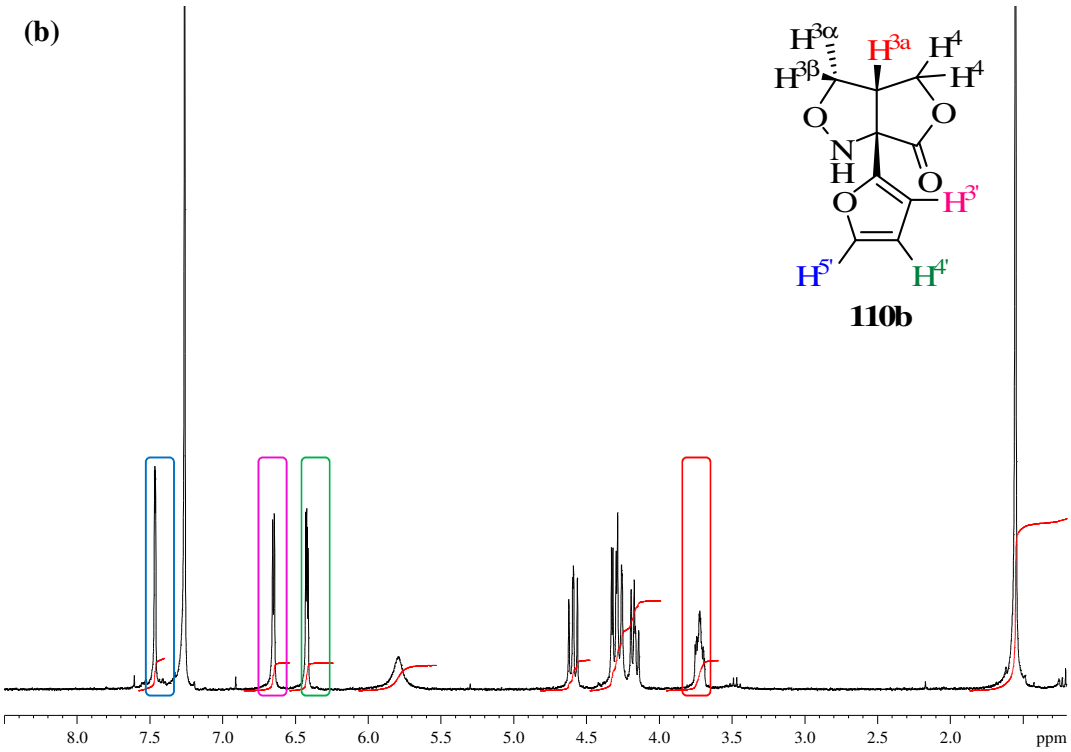


Figure 30. ^{1}H NMR spectral data of **(a)** the cyclic nitrone **109b** and **(b)** the bicyclic isoxazolidine **110b**.

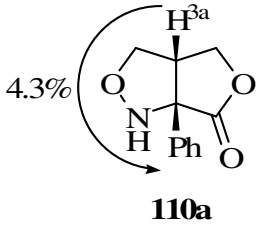
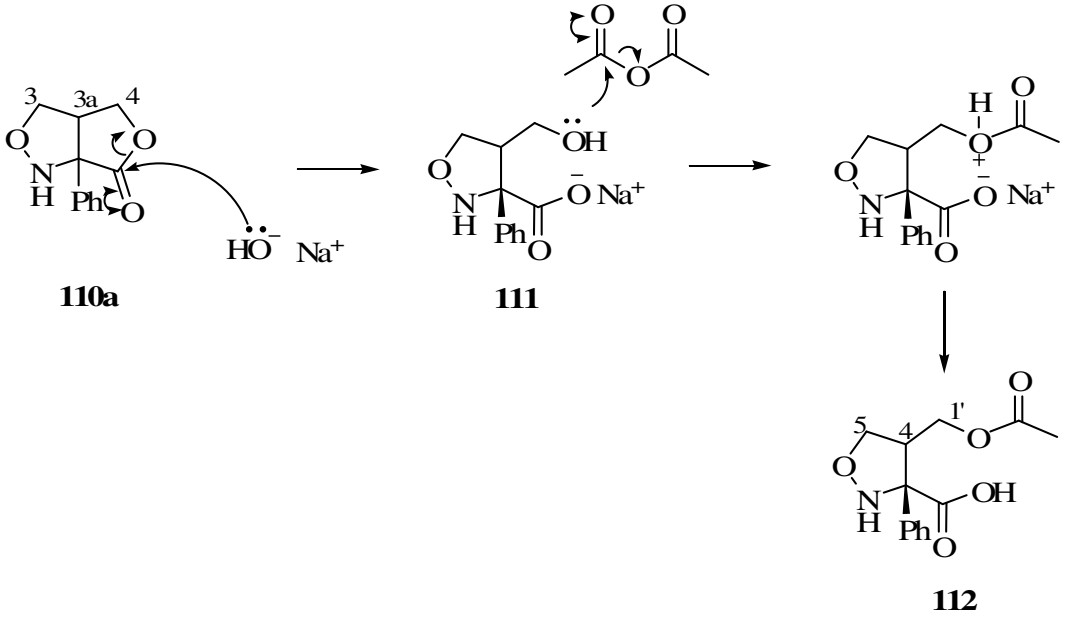


Figure 31. NOEDS studies performed on **110a**.

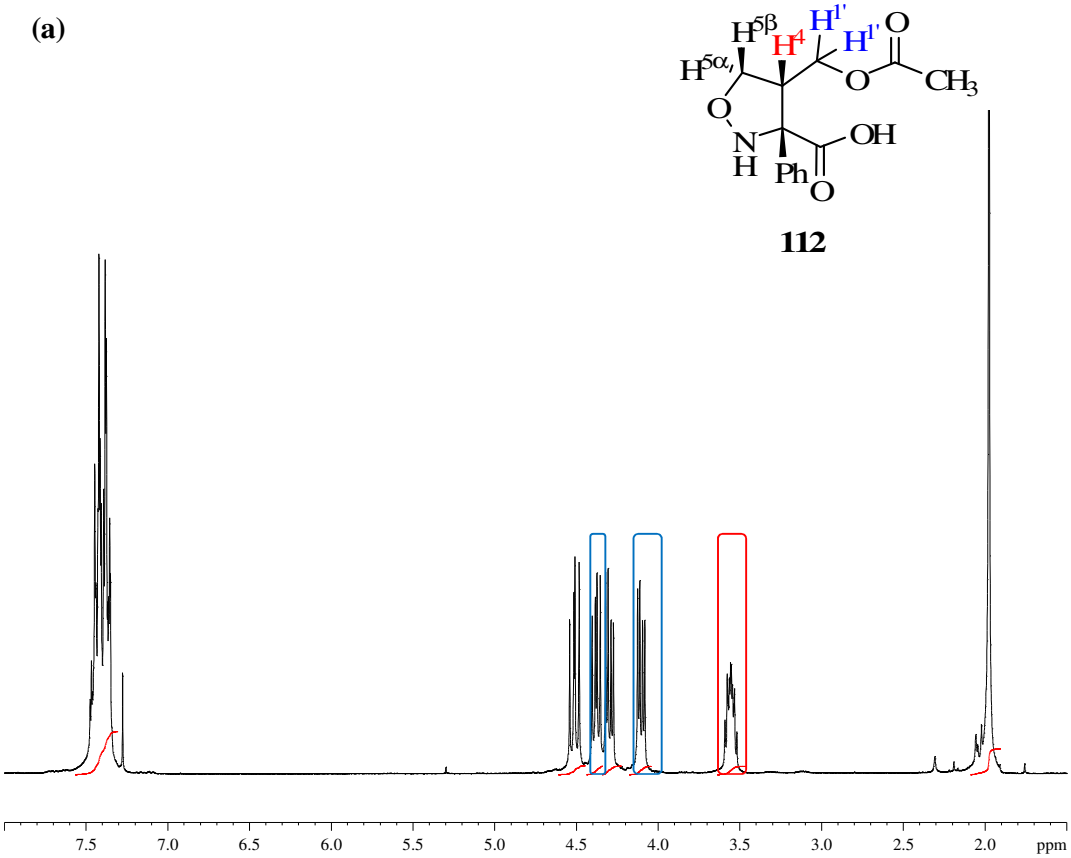
2.3.2.iv Opening of the lactone ring

To remove the constraints of the fused ring system the lactone ring of **110a** was subjected to ring opening. Following literature reports on the opening of various sized lactone rings, **110a** was heated to reflux with NaOH in MeOH for 4 hours to form the sodium carboxylate **111**.[172] Subsequently treatment with acetic anhydride (5 hours, 60 ^{o}C) yielded the desired **112** in 81% yield. A mechanism for the transformation is proposed in scheme 16. It involves initial opening of the lactone ring with sodium hydroxide resulting in the formation of the sodium carboxylate **111**.The newly formed alcohol attacks acetic anhydride and proton transfer results in **112**. ^{1}H NMR spectral

data confirms the structure of **112** with the methyl group of the ester appearing at 1.98 ppm and 22.3 ppm in the ^{13}C spectra.



Scheme 16. Mechanism for the ring opening of the lactone ring.



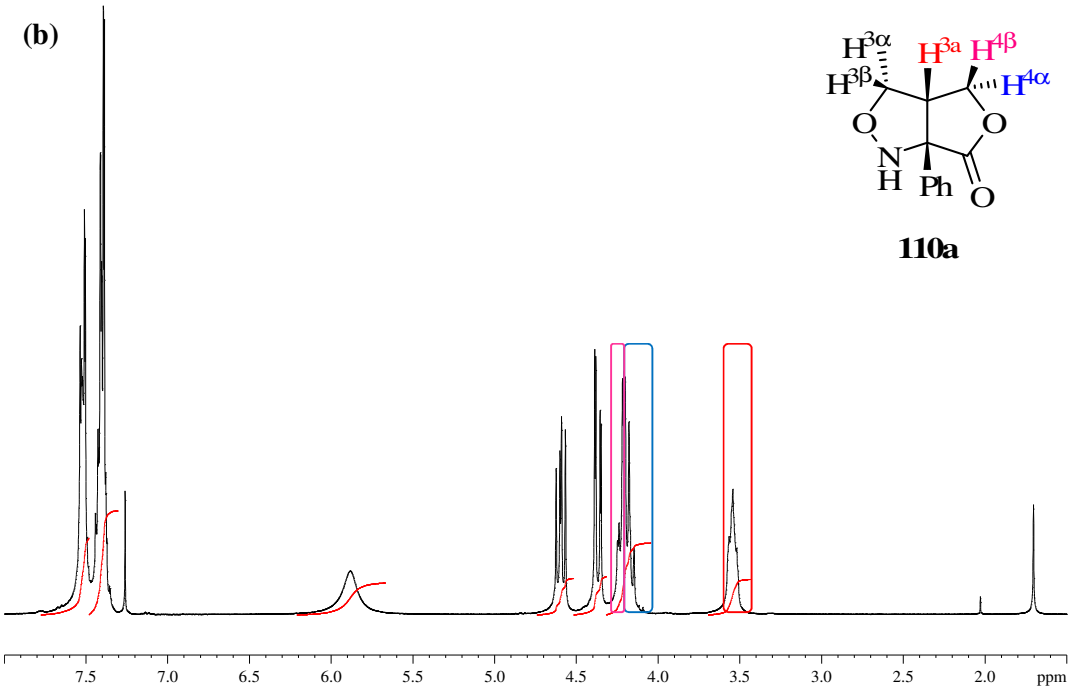
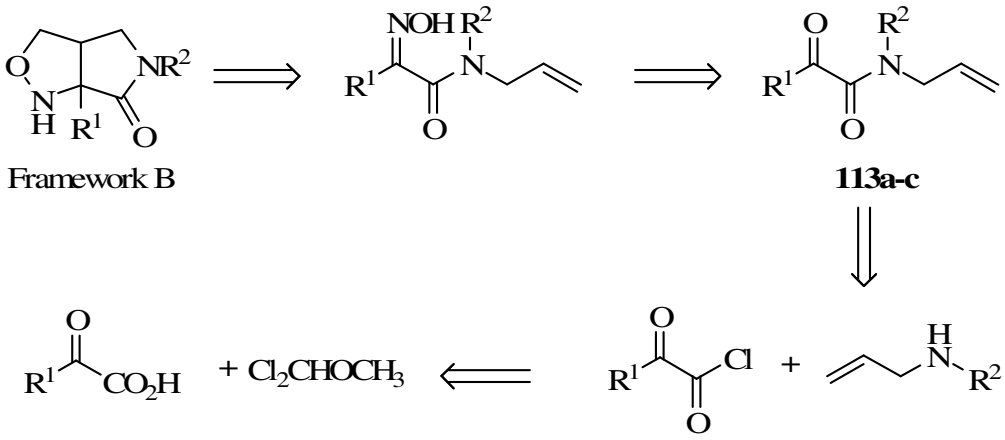


Figure 32. ^{1}H NMR spectral data for **(a) 112** and **(b) 110a**.

2.3.3 Lactam Fused Isoxazolidines; Framework B

The retrosynthetic approach to the lactam fused isoxazolidines, framework B, is outlined in scheme 17.

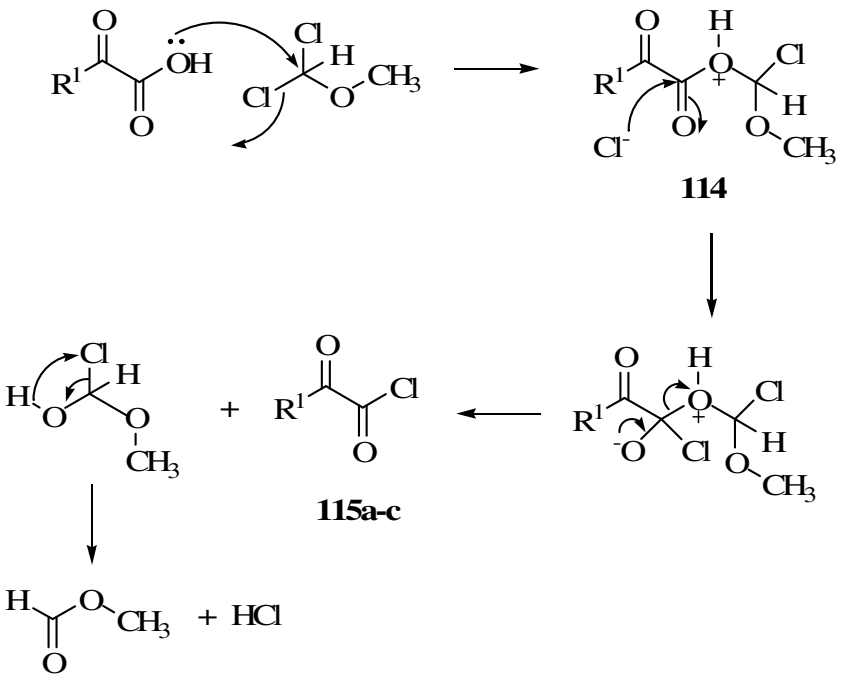


Scheme 17. Retrosynthetic route to the formation of the lactam-fused isoxazolidines.

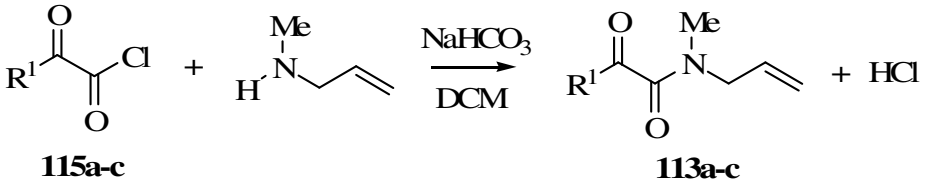
2.3.3.i α-Keto amide preparation

The first step towards the preparation of the lactam fused isoxazolidines required the preparation of the amides **113a-c**. Carboxylic acids are often derivatised to the corresponding acid chlorides prior to amidation. The chlorine atom is a better leaving group than hydroxy, consequently, acid chlorides are much more reactive with nucleophiles than their parent acid.[161] The synthesis of acid chlorides normally involves the use of thionyl chloride ($SOCl_2$), phosphorous trichloride (PCl_3) or phosphorous pentachloride (PCl_5) as the chlorinating agent, with PCl_3 and PCl_5 largely restricted to aromatic carboxylic acids.[173] However, these conditions proved unsuccessful for the preparation of the acid chlorides of pyruvic or benzoylformic acid, and only low yields of the desired compounds were obtained.[174] The use of α,α-dichloromethyl methyl ether (Cl_2CHOCH_3) as a chlorinating agent for the preparation of acid chlorides has previously been demonstrated by Ottenheijm; using this reagent acyl halides generally result in high yields and with sufficient purity to negate the need for stringent purification.[175] A mechanism for chlorination with this reagent is proposed in scheme 18. It involves the initial attack of the acid hydroxyl group on the dichloride resulting in formation of the charged species **114**; degradation affords HCl (which can be trapped using a water/acid trap) and methyl formate, which is easily removed on a rotary evaporator at room temperature (b.p. 31.5 ^{o}C).[169]

The acid chlorides **115a-c** prepared by this approach were used without further purification, table 6. Reaction with *N*-methyl allyl amine in the presence of $NaHCO_3$ yielded the desired α-keto amides, equation 48.



Scheme 18. Mechanistic route to the preparation of the acid chlorides **115a-c**.



115a-c **113a-c**

a. R^1 = Ph; **b.** R^1 = 2-furyl, **c.** R^1 = 2-thienyl

Equation 48. Synthetic route to the formation of the α-keto amides.

Table 6. Isolated Yields of α-keto amides **113a-c**.

Substrate	R^1	Products (% Yield)	Rotamer Ratio
115a[153]	Ph	**113a** (96)	1:1.1
115b	2-furyl	**113b** (88)	1:1.1
115c	2-thienyl	**113c** (75)	1:1.1

^{1}H NMR spectral data for the α-keto amides **113a-c** show a doubled signal set indicating that in solution ($CDCl_3$, r.t.) isomerisation is occurring about the amide bond. In total there are four possible conformations of the tertiary amides **113a-c**, two for each rotamer which are shown in figure 33. The terms *syn* and *anti* refer to the arrangement about the OC-CO bond whilst *cis/trans* is used to indicate the geometry about the amide "double bond".[161,176,177]

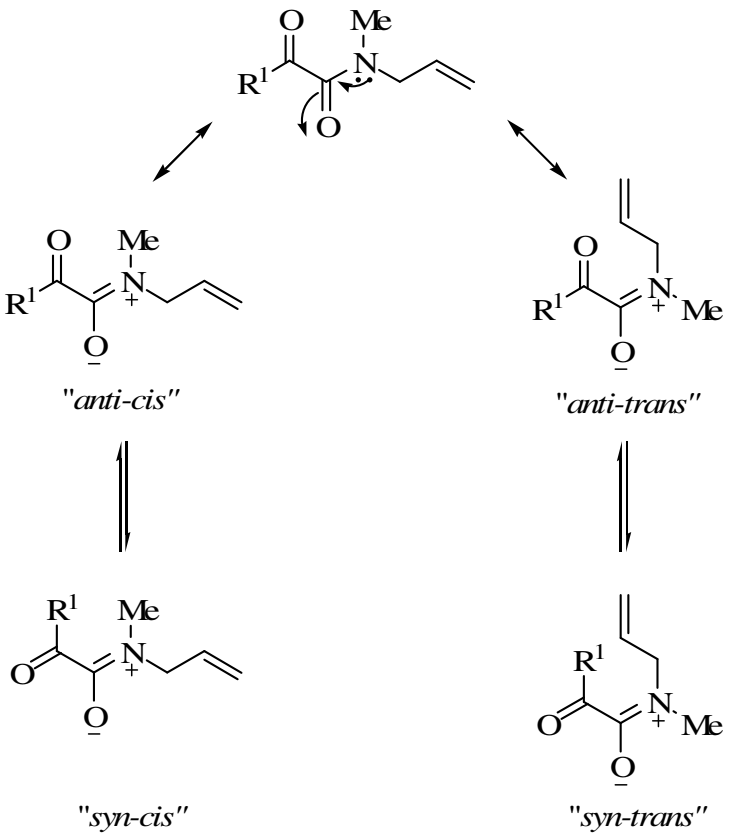


Figure 33. Conformations available to α-keto amides.

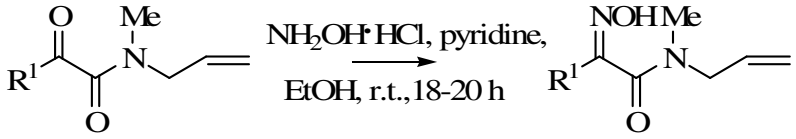
Bach has performed *ab initio* molecular orbital studies on primary and tertiary α-keto amides, his work suggests primary amides [NH_2-C(O)C(O)-H] exist as a minimum in the *anti* conformation.[176] The *syn* conformation exists as a local minimum, 7.2 kcal/mol higher in energy than the *anti* conformation. It is well accepted that the main factor contributing to the energy difference between the *syn* and *anti* conformers is the repulsion between the oxygen lone pairs and the O=C-C=O dihedral angles are typically between 90° and 150° in crystals of fully substituted α-keto amides.[177] With these findings it is proposed that only amide conformers having *anti* displacement of the carbonyl groups need to be considered for tertiary amides **113a-c** and that the two rotamers seen in solution at room temperature are the *anti-cis* and *anti-trans* forms.

As a typical example the ^{1}H and ^{13}C NMR spectra of **113b** are shown in figure 34. The existence of amide rotameric forms is evident in the duplication of signals, most clearly seen for the *N*-methyl protons which resonate at 2.81 and 2.75 ppm and the NCH_2 protons which appear at 3.90 and 3.68 ppm. It is noteworthy that duplication of signals

is most obvious for the protons closest to the amide bond; duplication of signals is not observed for the protons on the carbon atoms of the aryl ring or of the alkene.

2.3.3.ii Oxime preparation

The oximes **116a-c** were prepared in an analogous fashion to that described above for the α-keto ester substrates **103a-f**, section 2.3.2.ii. Thus, reaction of the corresponding α-keto amides, **113a-c**, with hydroxylamine hydrochloride and pyridine in EtOH effected the desired functional group transformation, equation 49. Oxime **116a** formed as the *Z*-isomer selectively (38%), no *E*-isomer was returned from the reaction. The 2-furyl oximes **116b** returned as a 1.2:1 ratio of *E*- and *Z*-isomers in good yield, however the geometrical isomers were impossible to separate by flash column chromatography. The 2-thienyl oximes **116c**, obtained in 88% yield, were also present as an inseparable mixture of geometrical isomers in a 3:2 ratio, table 7. Oxime geometry was assigned on the basis of ^{13}C NMR data.[170] Thus the α-C resonance for *E*-**116b** rotamers were observed at 142.5 and 142.6 ppm whilst the corresponding resonance for the *Z*-isomer was more downfield at 143.3 ppm.



113a-c **116a-c**

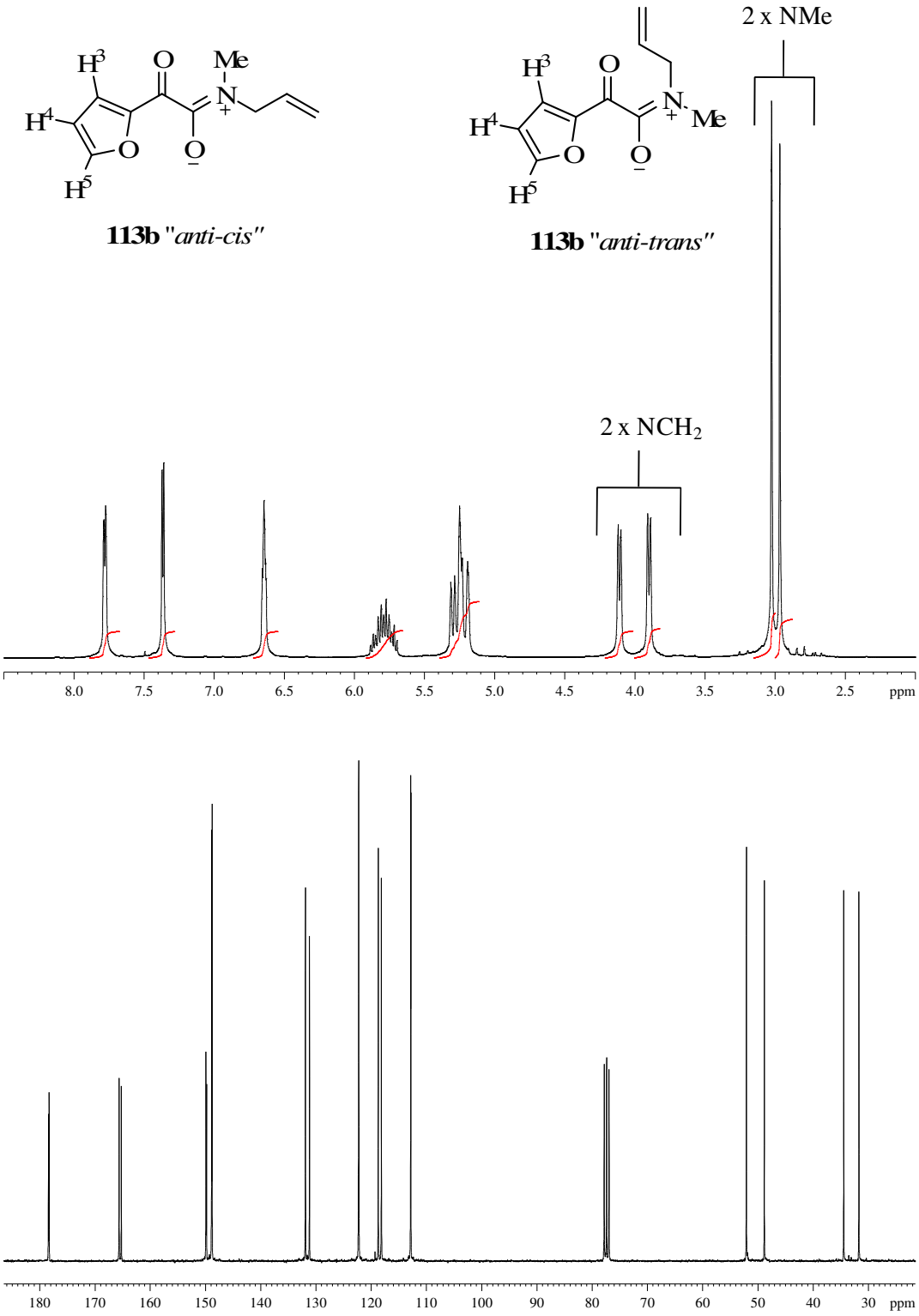
a. R^1 = Ph; **b.** R^1 = 2-furyl, **c.** R^1 = 2-thienyl.

Equation 49. Synthetic route to the formation of the oxime isomers **116a-c**.

Table 7. Preparation of the substituted oximes **116a-c**.

Substrate	R^1	Product (% Yield)	*E:Z* Ratio	Rotameric Ratio
113a	Ph	**116a** (39)	0:1	*Z*-1:1.3
113b	2-furyl	**116b** (76)[a]	1.1:1	*E*-1:1.3 *Z*-1:1.2
113c	2-thienyl	**116c** (88)[a]	1.3:1	*E*-1:1.3 *Z*-1:1

[a] %Yield quoted is for an isolated mixture of isomers. **a.** R^1 = Ph; **b.** R^1 = 2-furyl, **c.** R^1 = 2-thienyl.



113b "*anti-cis*" **113b** "*anti-trans*"

Figure 34. ^{1}H and ^{13}C NMR spectral data for **113b** showing doubled signal sets.

2.3.3.iii Amidooxime rotamers

The presence of both rotamers of the substituted *Z*-**116b** is evident on examination of ^{1}H and ^{13}C NMR spectral data. The oximes present a greater range of H-bonding opportunities than their keto parents but it is likely that the same factors operate to control the number of rotameric forms which present for the tertiary amines. The ^{1}H and ^{13}C NMR spectra for the geometrical isomers of **116b** are shown in figure 35. As is the case with the parent α-keto amide **113b**, ^{1}H and ^{13}C NMR spectral data show duplication of signals for each oxime. The NCH_2 protons appear as a doublet at 4.17 ppm for the *E*-isomer and as two sets of doublets at 3.84 and 3.88 ppm for the *Z*-isomer. Four NCH_3 singlet peaks are observed in the range 3.06-2.92 ppm.

2.3.3.iv Reaction of amidooxime isomers

Cyclisation of the α-keto amide oximes **116** was promoted by thermal activation and the bicyclic fused isoxazolidines **117a-c** and nitrones **118a-c** formed in good yields. The tertiary amidooxime **116a**, on heating in xylene in the presence of hydroquinone (140 ^{o}C, 24 h), furnished the bicyclic isoxazolopyrrolidinone **117a** in 66% yield as described in the literature.[153] The *E*- and *Z*-thienyl isomers **116c** were separable and were reacted individually in refluxing xylene in the presence of hydroquinone under a nitrogen atmosphere for 90 hours. The *E*-isomer cyclised to the nitrone **118c**, a brown oil, in 71% yield whilst the *Z*-isomer formed the bicycle **117c** in 86% yield, also as a brown oil. The 2-furyl geometrical isomers were inseparable by flash column chromatography. Accordingly, a xylene solution of the mixed isomers was heated at reflux in the presence of hydroquinone under a N_2 atmosphere for 100 hours to yield the bicycle, **117b**, as a brown solid, and the nitrone **118b**. The bicycle could clearly be isolated (44%), however the nitrone **118b** was obtained as an enriched sample together with the bicycle, figure 36.

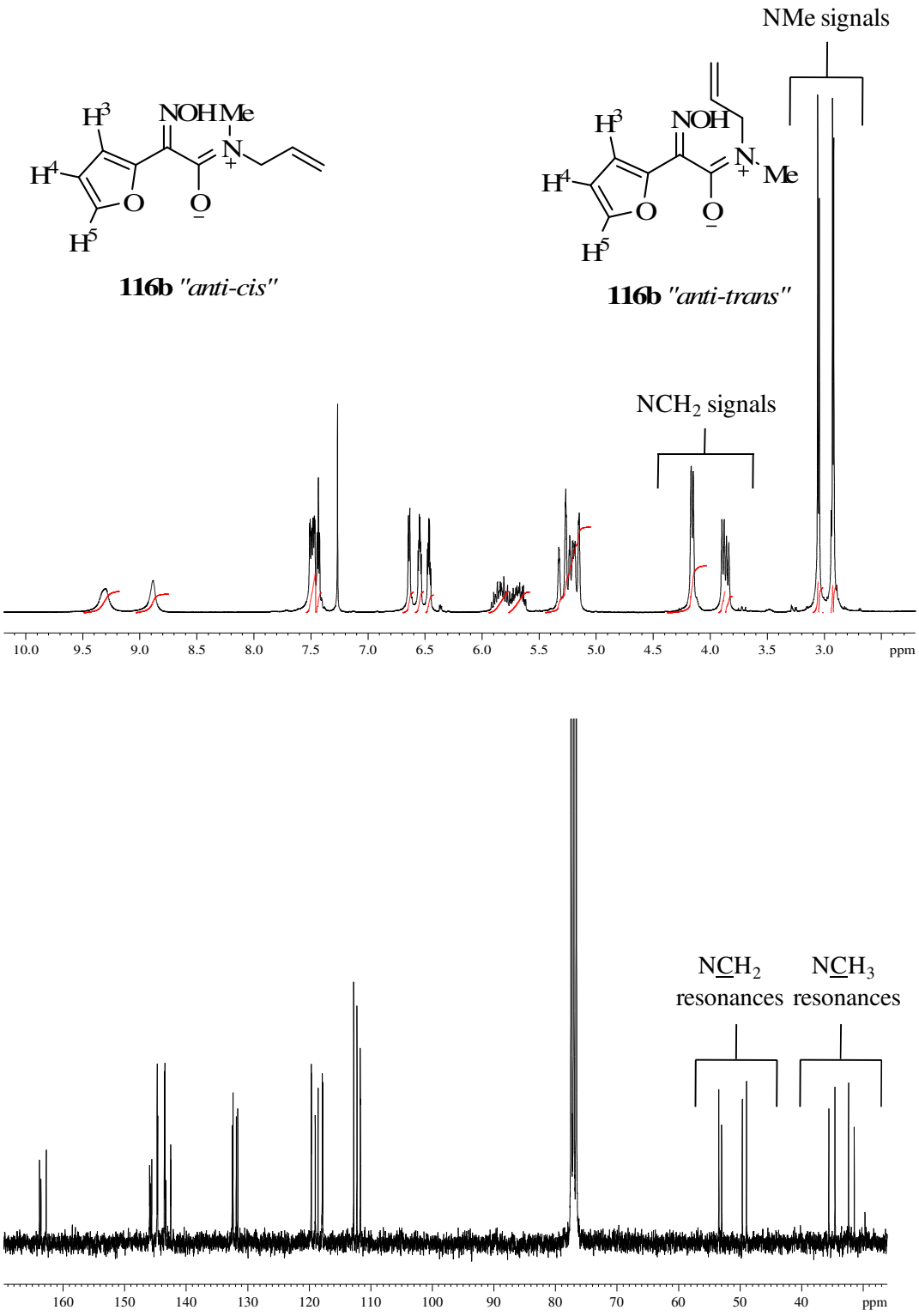


Figure 35. ^{1}H and ^{13}C NMR spectral data for the *E*- and *Z*- isomers of **116b** showing doubled peaks for each isomer.

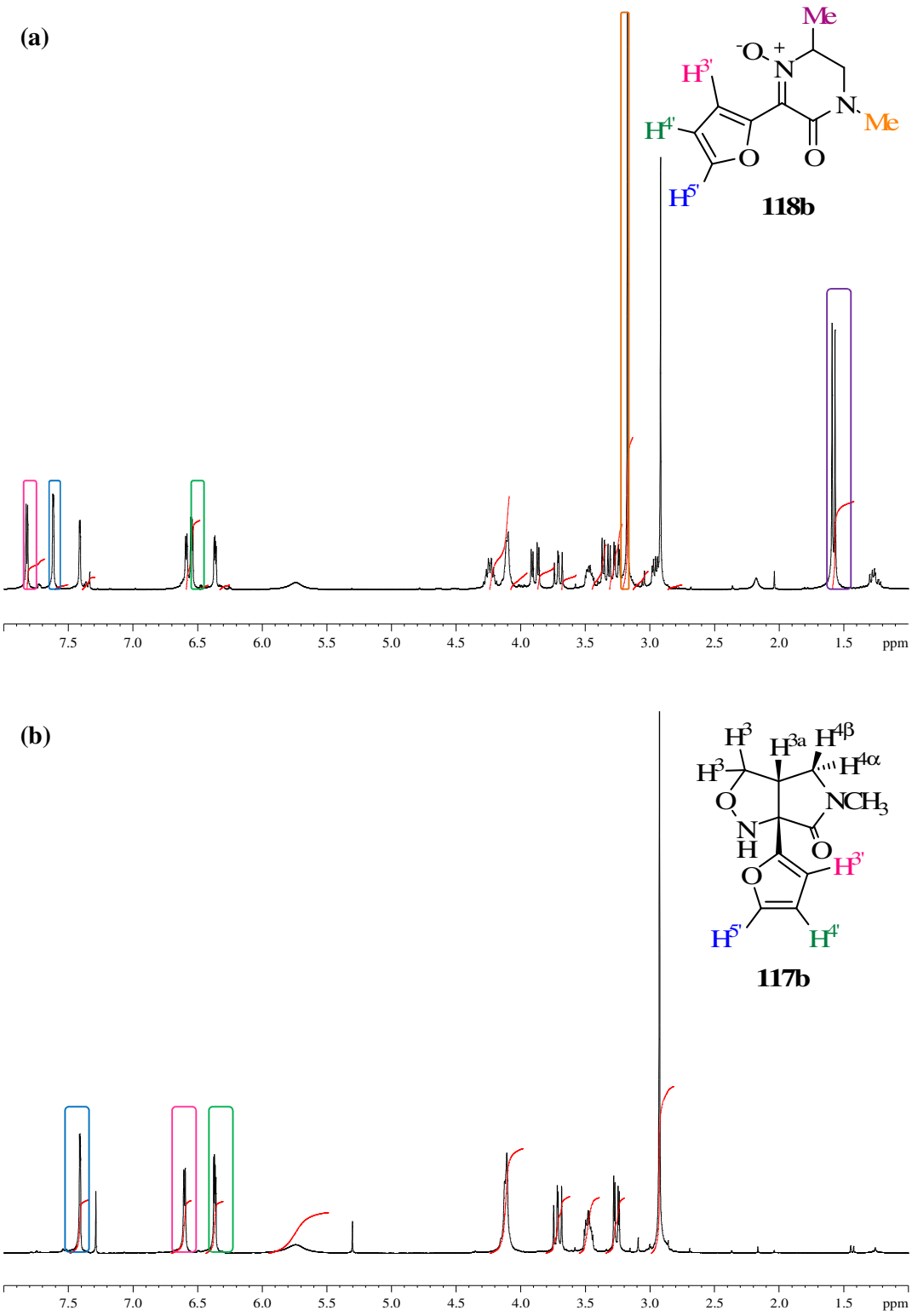


Figure 36. ^{1}H NMR spectral data for **(a) 118b** as an enriched sample together with **117b** and **(b) 117b**.

Stereochemical assignment of **117b** as being a *cis*-fused 5,5-bicycle is made with reference to the C^{6a}-Ph analogue **117a** previously prepared within the group.[153] Comparisons are made due to the similarity in the resonance positions of the protons attached to the ring. That **117a** was *cis*-fused was surmised on the basis of the enhancement observed on both H^{3a} and the ArH following irradiation of H^{4b}. Significantly an x-ray crystal determination on the same compound confirms this assignment, figure 37a,b.

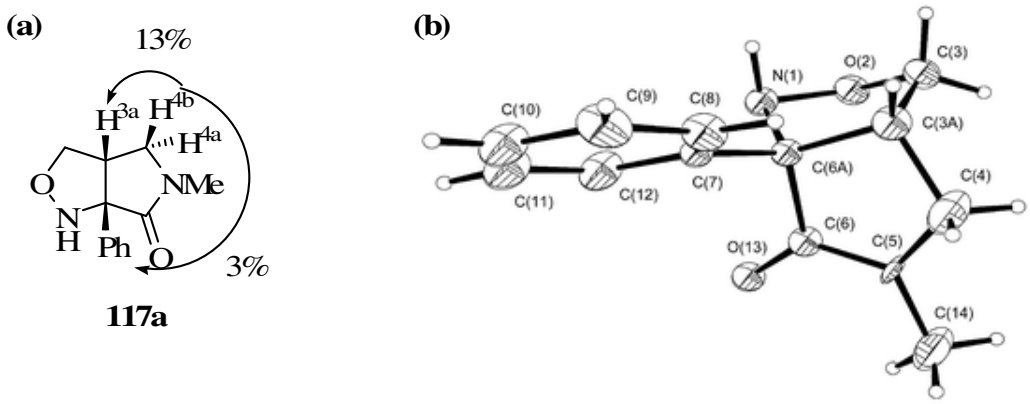
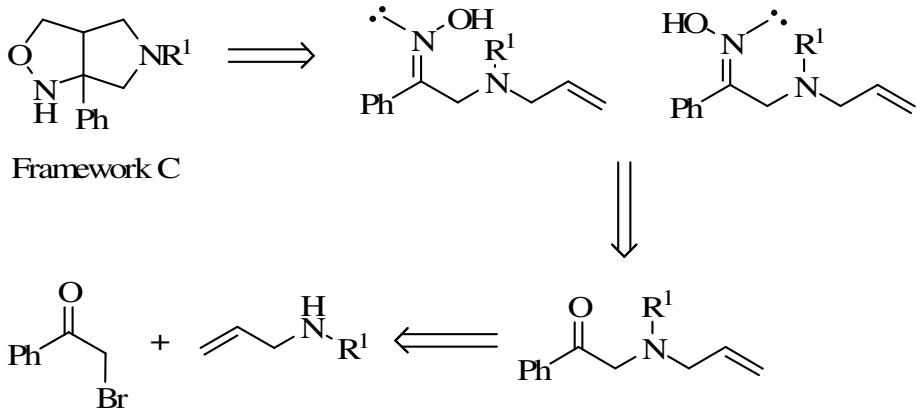


Figure 37. **(a)** NOEDS data and **(b)** crystal structure for **117a**.

2.3.4 Pyrrolidine Fused Isoxazolidines; Framework C

This section of the chapter is devoted to the preparation of the pyrrolidine fused isoxazolidines, framework C. The synthetic approach adopted is outlined in the retrosynthetic analysis in scheme 19.



Scheme 19. Retrosynthetic analysis for the formation of pyrrolidine fused isoxazolidines.

2.3.4.i β-Keto amine preparation

The preparation of the cycloadducts of the framework C, which lack the β'-carbonyl present in frameworks A and B, required the formation of the amines **119a&b** from 2-bromoacetophenone and the corresponding allylamine, **120a&b**. The *N*-methyl derivative **119a** was synthesised in 98% yield following stirring of a solution of 2-bromoacetophenone and *N*-methylallylamine, **120a**, in DCM at room temperature for 10 minutes. The *N*-phenyl derivative **119b** has previously been prepared and ^{1}H NMR spectral data of the material obtained during this project agrees with that in the literature; yields are summarised in table 8.[178]

120a,b **119a,b**

a. R^1 = Me, **b.** R^1 = Ph

Equation 50. Synthetic route to the preparation of β-keto amines.

Table 8. Isolated yields of β-keto amines **119a&b** prepared according to equation 50.

Substrate	R^1	Reaction Time	Product (% Yield)
120a	Me	10 mins	**119a** (98)
120b	Ph	30 h	**119b** (99)

The ^{1}H and ^{13}C NMR spectral data for the keto amine **119a**, are shown in figure 38. The *N*-methyl protons resonate at 2.25 ppm and a singlet at 3.69 ppm is diagnostic of the CH_2 group located between the amine and the carbonyl carbon. The *N*-methyl carbon is located at 42.7 ppm, and resonances at 60.9 and 63.1 ppm are observed for the methylene carbon atoms.

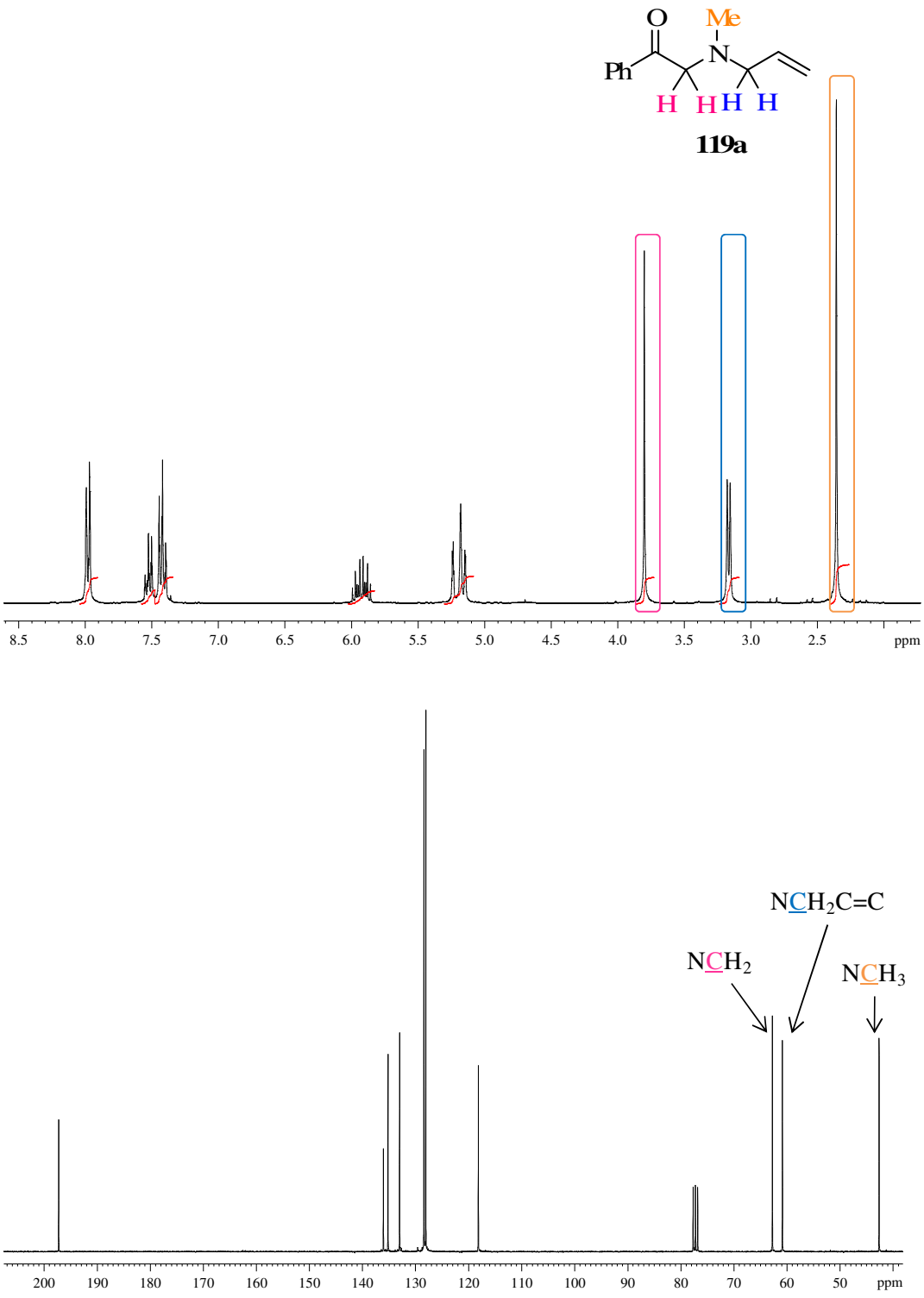


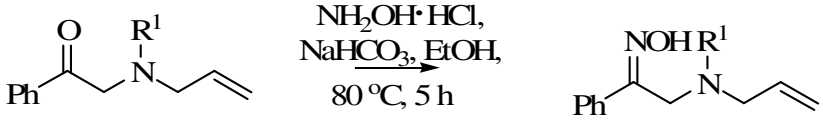
Figure 38. ^{1}H and ^{13}C NMR spectral data for the β-keto amine **119a**.

2.3.4.ii Oxime preparation

The oximes **121a&b** were prepared from the reaction of the β-keto amines **119a&b** with NH_2OH•HCl in refluxing EtOH in the presence of $NaHCO_3$. The oximes of **121b** are not novel compounds having previously been synthesised from the reaction of **119b** and NH_2OH•HCl in H_2O with NaOH as base in 81% yield.[178] Gratifyingly with EtOH as solvent and $NaHCO_3$ as base the yield was improved to 100%. The change in conditions was also found to have an influence on the geometrical ratio with the EtOH reaction being more selective for the desired *Z*-isomer, and an *E*:*Z* ratio of 1:1.3 was observed compared to 1:1 in the literature.

The *E*- and *Z*-*N*-methyl aminooxime isomers **121a** were separable by flash column chromatography and pure samples of each were obtained. However, the analogous *N*-phenyl oximes **121b** were inseparable.

Oxime geometry is assigned on the basis of ^{13}C NMR data and comparison of the ^{13}C resonance positions of the α-C for the *E*- and *Z*-isomers of **121a** permitted the assignment of the major compound as the *Z*-isomer (135.7 ppm), the α-carbon atom of the *E*-isomer resonated upfield at 132.6 ppm.[170] The ^1H and ^{13}C NMR spectral data for both the *E*- and *Z*-oximes of **121a** are shown in figure 39; the *N*-methyl protons resonate as singlets at 2.24 and 2.34 ppm and the CH_2 protons of the allylic moiety appear as doublets at 3.03 and 3.13 ppm. The $NCH_2C{=}N$ protons appear as a singlet at 3.38 ppm for the *E*-isomer whilst for the *Z*-isomer they occur downfield at 3.77 ppm.



119a,b **121a,b**

a. R^1 = Me, **b.** R^1 = Ph

Equation 51. Synthetic route for the preparation of the oximes **121a,b**.

Table 9. Isolated yields of the *E*- and *Z*-isomers **121a,b**.

Substrate	R^1	% Yield (*E:Z*)	*E:Z*
119a	Me	**121a** (17:45)	1:2
119b	Ph	**121b** (100)[a]	1:1.3

[a] %Yield is quoted for a mixture of isomers as separation could not be achieved.

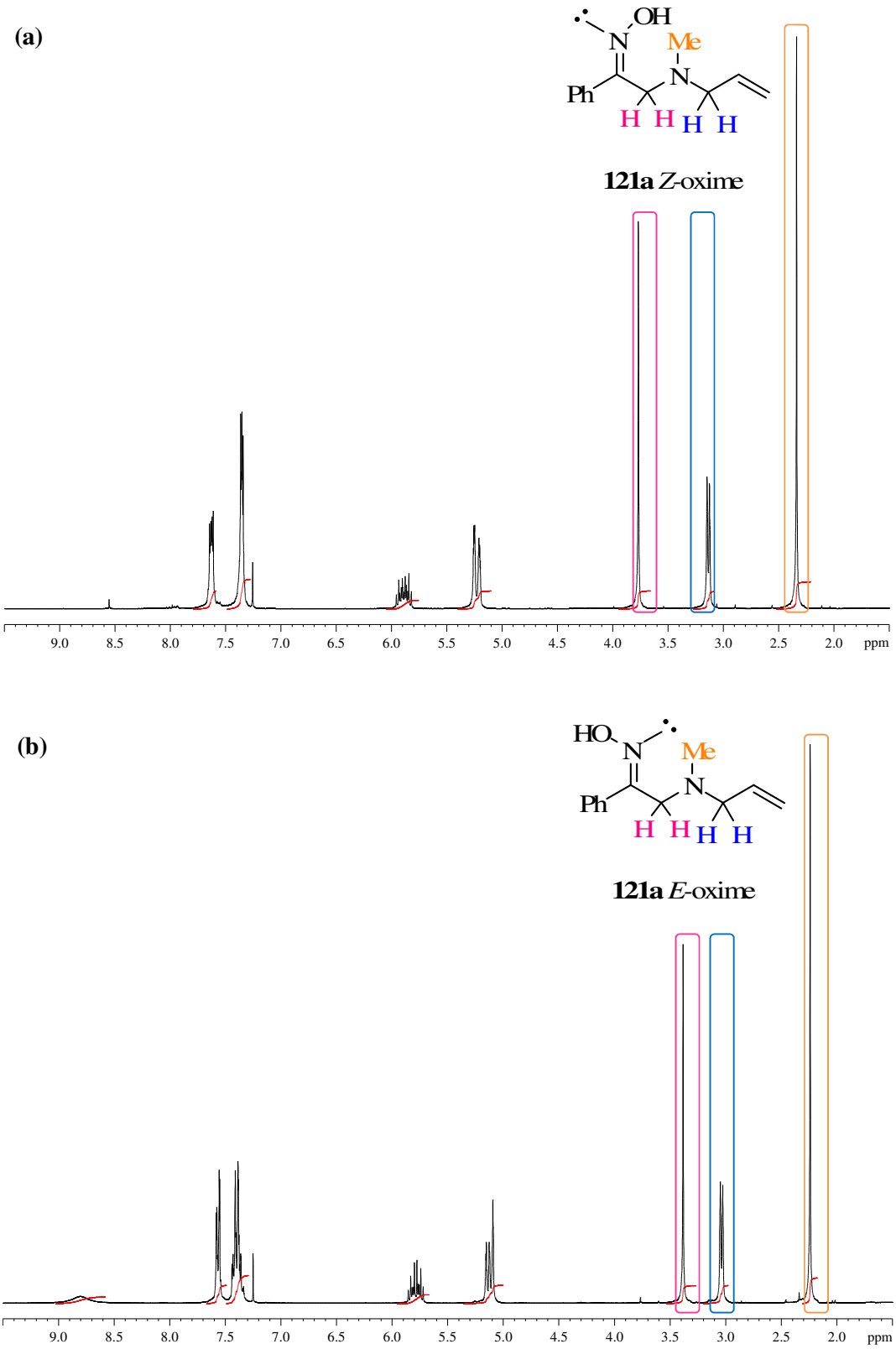


Figure 39. ^{1}H NMR spectrum for **(a)** *Z*-**121a** and **(b)** *E*-**121a**.

2.3.4.iii Reaction of oxime isomers

The *N*-phenyl pyrrolidine fused isoxazolidine **122b** was prepared in 57% yield according to literature reports upon heating of a mixture of *E*- and *Z*-isomers, **121b**, to reflux in toluene for 8 hours.[178] The *N*-methyl analogue **122a** was prepared in the same manner and was isolated in 62% yield. The bicycles **122a,b** both gave very broad ^{1}H NMR spectral peaks at room temperature and accordingly these were hard to assign. From the literature it is known that the broad peaks for **122b** are due to the presence of two conformers of the bicycle at room temperature, figure 40. Accordingly a series of V.T. NMR experiments were conducted on these substrates. At -50 ^{o}C the emergence of two sets of sharp peaks was observed and the conformers of **122a** and **112b**[178] were estimated to be present in an 1:6 ratio.

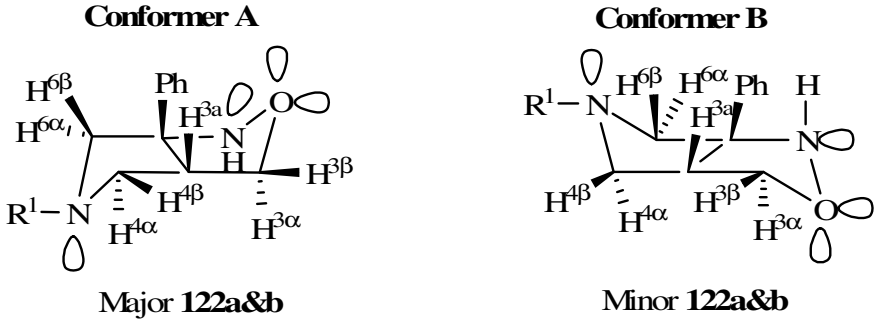


Figure 40. The two conformers available to the bicycles **122a,b**.

Conformational mobility of the *N*-methyl pyrrolidine bicycle **122a** was followed by a detailed analysis of the low-temperature ^{1}H NMR spectra, table 10 and figure 41. The main diagnostic feature of the conformers is the absence of a vicinal coupling interaction between the bridgehead hydrogen atom H^{3a} and one of the protons on an adjacent carbon; for conformer A the "missing" coupling constant refers to one of the protons on the NCH_2 ($J_{3a,4}$) and conversely for conformer B the coupling to one of the protons on CH_2O ($J_{3a,3}$) is almost absent. Due to the overlapping of many of the peaks it was difficult to accurately measure many of the *J* values for the two conformers. However, in the minor conformer of **122a** coupling between H^{3a} and one of the protons on C^3 is <1 Hz ($J_{3a,3\beta}$). This is not the case for the major conformer where each of the protons on H^3 have a coupling constant of ≃8.4 Hz to the bridgehead hydrogen H^{3a}, both H^{3a} and H^{3b} appear as a triplet. The coupling constants between H^{3a} and $H^{4\alpha/\beta}$ cannot be determined.

In a 5-membered ring, a small $^{3}J_{HH}$ value indicates a *trans* relationship between the relevant protons; it also fixes the conformation of the envelope so that the out-of-plane atom (*N* on the pyrrolidine ring or *O* on the isoxazolidine ring) is *anti* to the bridgehead substituents.[178] The other 5-membered ring therefore, must have the opposite conformation, with the out-of-plane *N*- or *O*-atom *syn* to the bridgehead substituents. It is also established that the orientation of the *NH* of the isoxazolidine moiety is always pseudoaxial.

The ^{1}H NMR spectral data for **122a** at -50 ^{o}C also shows two sharp signals at 5.48 and 5.22 ppm for the NH proton in each conformer; resonances at and 2.42 and 2.35 ppm are characteristic of the *N*-methyl protons of the major and minor conformer respectively. At room temperature only one NCH_3 resonance is observed, figure 41.

Table 10. ^{1}H NMR data - chemical shift positions and coupling constants for the major and minor conformers of **122a&b**, recorded at -50 ^{o}C in $CDCl_3$.

H	122a (δ)		122b (δ)[178]	
	Major Conformer	**Minor Conformer**	**Major Conformer**	**Minor Conformer**
1 (NH)	5.48	5.22	5.40	5.47
3α	4.58	4.22	3.55	4.13
3β	3.59	3.80	4.54	-
3a	3.21	3.42	3.35	-
4α	3.21	-	3.66	-
4β	2.60	-	3.40	-
6α	3.14	-	3.82	-
6β	3.01	-	3.14	-
		***J* Hz**		
3α, 3β	8.4	9.0	8	9
3α, 3a	8.4	0	7	<1
3β, 3a	8.0	7.7	8	-
4α,4β	9.7	-	9	-
4α,3a	-	-	<1	8
4β,3a	6.8	-	7	-
6α,6β	10.8	-	11	-

- = unknown (could not be determined from spectrum).

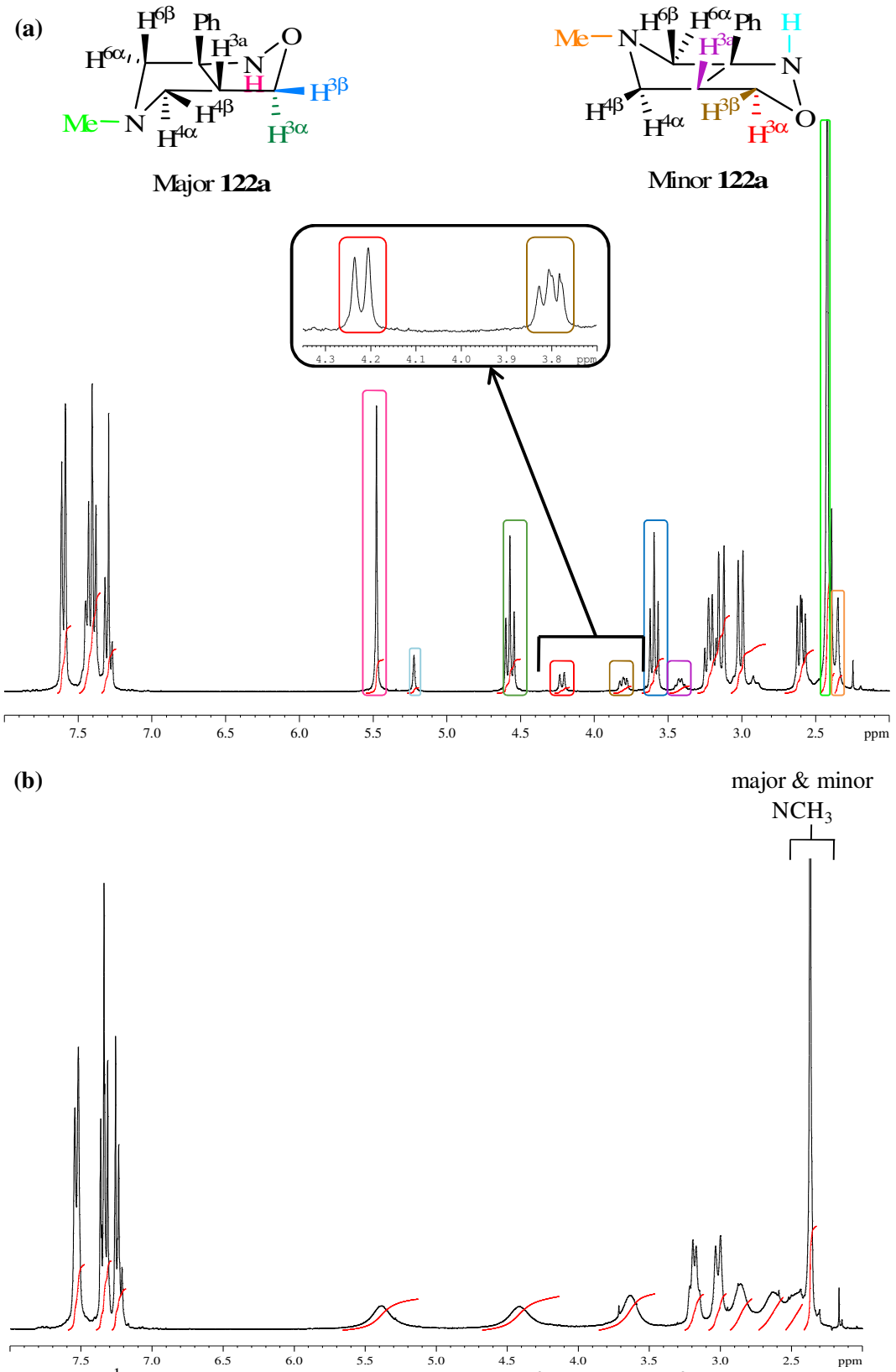


Figure 41. ^{1}H NMR spectral data for **122a** at **(a)** -50 °C and **(b)** 25 °C.

2.4 Salt Formation

An examination of the literature on iminium ion catalysis indicates the organocatalyst is commonly employed together with an acid co-factor. With this in mind we set out to examine the ease of salt formation with each of the three isoxazolidine fused frameworks described in the preceding sections.

2.4.1 Salt formation with the Lactone Fused Isoxazolidines, Framework A

The HCl salt of the isoxazolo-lactone **110a** was initially targeted. The bicycle was stirred at room temperature in a 0.02 M methanolic HCl solution. However, ^{1}H NMR spectral analysis, melting point determination and TLC analysis all suggested returned starting material. Accordingly, the solution was heated to 40 ^{o}C, again to no apparent avail. In the next attempt to make the HCl salt, anhydrous HCl gas was bubbled through a solution of **110a** in dry Et_2O. Unfortunately, once again no difference could be detected by TLC analysis, m.p. determination or ^{1}H NMR spectral analysis of the material pre or post reaction, figure 42. The choice of a HCl salt, from the standpoint of ^{1}H NMR spectral analysis is less than ideal as the counterion has no peaks in the ^{1}H NMR spectrum. At this point it was considered advantageous to choose a co-factor where for any ensuing salt the counterion would possess its own characteristic peaks in the ^{1}H NMR spectrum. (+)-10-Camphorsulfonic acid (CSA) was selected for this reason. It did not escape our attention that this acid is optically active and diastereoisomeric salts may have resulted. Further, we were aware that a chiral counterion may have some stereochemical influence on the reactions we wished to study with the new organocatalyst.

The (+)-10-CSA salt was prepared by dissolving an equimolar amount of **110a** and (+)-10-CSA in hot acetone. Upon cooling, a white solid precipitated which was analysed by ^{1}H NMR spectroscopy. From a sample prepared in d_6-DMSO the ^{1}H NMR spectrum, shown in figure 43, was only very slightly different to the "addition" spectra of the component isoxazolidine and (+)-10-CSA, however, there was no evidence of the expected doubling of peaks due to the presence of diastereoisomeric salts.

In contrast, a comparison of the spectral data for **110a** and its proposed (+)-10-CSA salt in $CDCl_3$ showed clear differences, figure 44. A downfield shift in the resonance position of all the protons of the isoxazolidine moiety is observed; again no doubling of

the peaks was noticed. As (+)-10-CSA alone is not soluble in $CDCl_3$ a comparison with the parent (+)-10-CSA was not possible. The differential solubility of (+)-10-CSA and the salt prepared with **110a** is also interpreted as confirmation of salt formation.

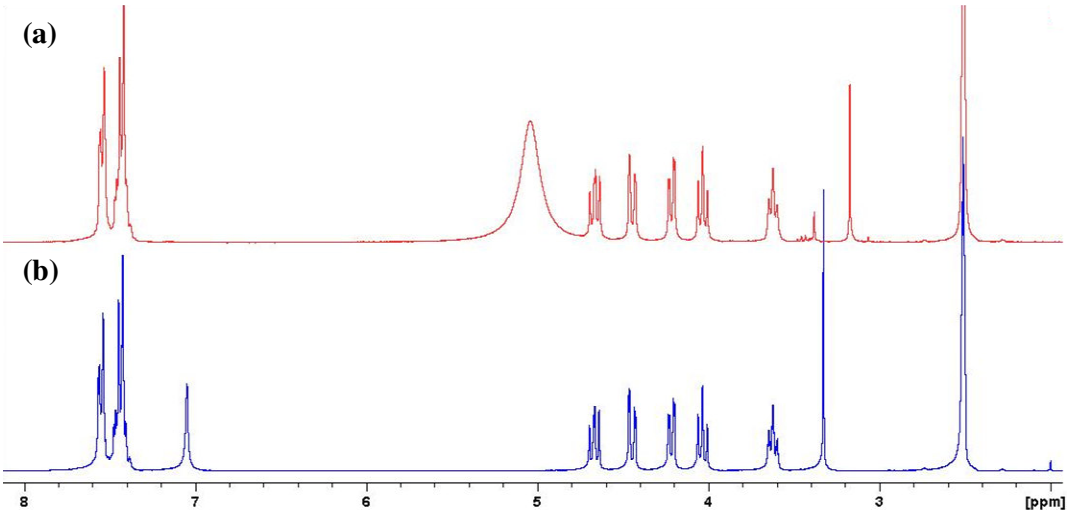


Figure 42. ^{1}H NMR spectra (d_6-DMSO) for **(a)** the returned starting material following efforts to prepare the HCl salt and **(b)** the lactone-fused isoxazolidine **110a**.

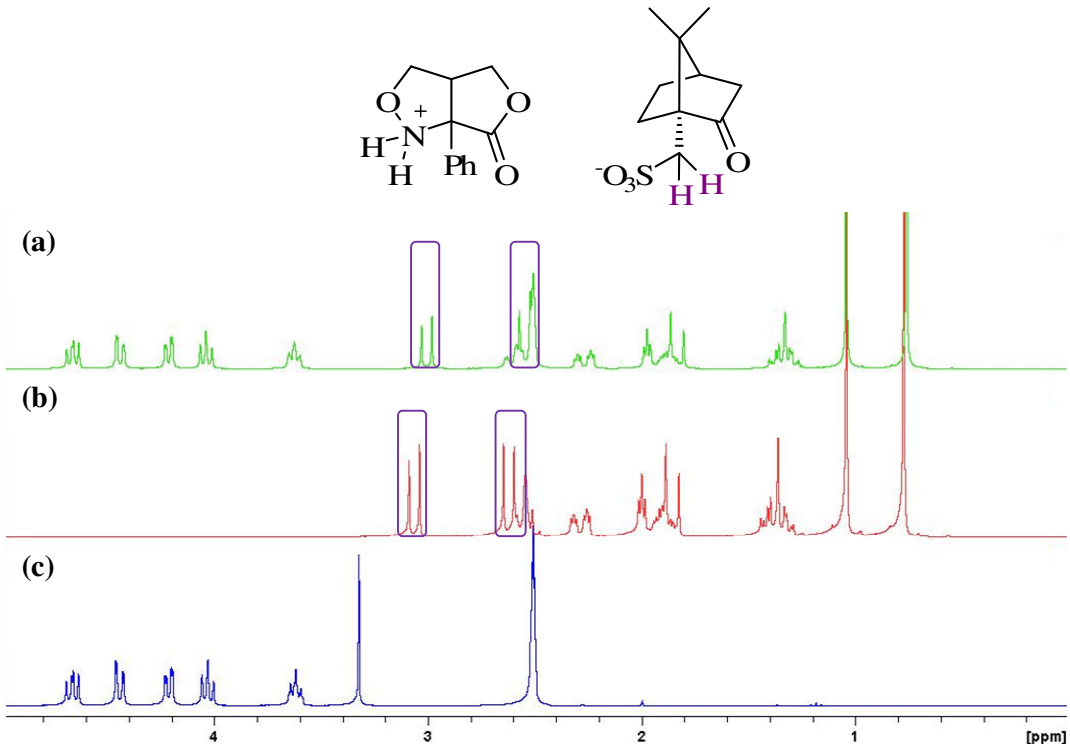


Figure 43. ^{1}H NMR spectral data (d_6-DMSO) of the (+)-10-CSA and isoxazolidinium region of **(a) 110a•**(+)-10-CSA salt, **(b)** (+)-10-CSA and **(c)** isoxazolidine **110a**.

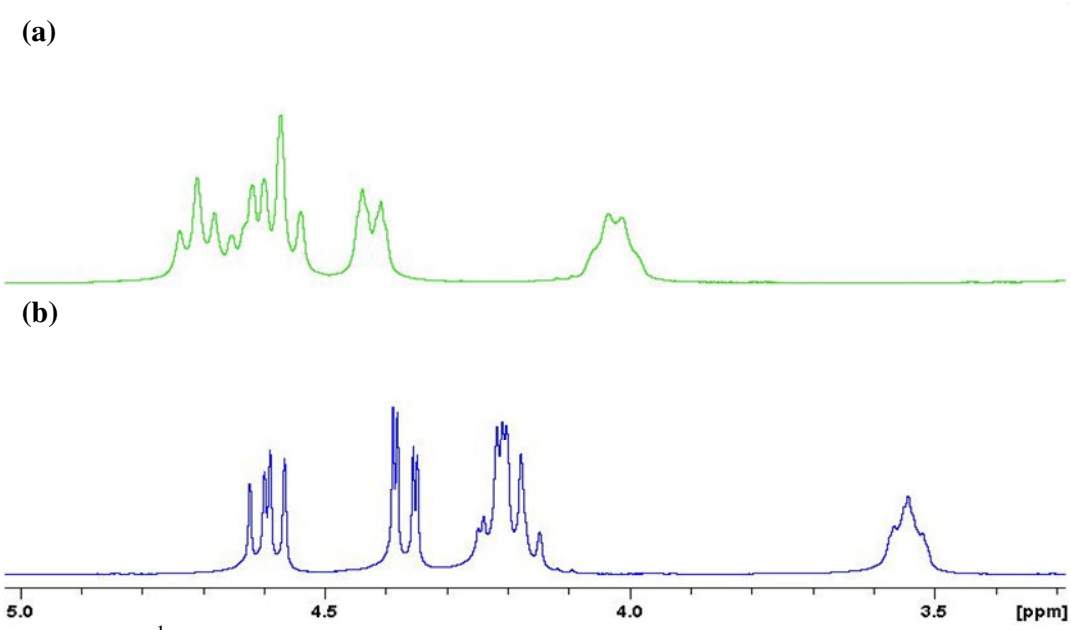


Figure 44. ^{1}H NMR spectral data ($CDCl_3$) of the isoxazolidinium region of **(a)** **110a**•(+)-10-CSA salt and **(b)** isoxazolidine **110a**.

The observation of only one set of peaks for the diastereoisomeric salts is possibly due to the formation of a solvent separated ion pair. Ions may exist in solution as either a contact pair or a solvent separated pair; in a contact pair the cation and anion are in close contact with each other whilst in the solvent separated pair the ions are separated by the solvent, figure 45.[179] Doubling of ^{1}H NMR peaks would not be expected in solvent separated ions. A comparison of the ^{1}H NMR spectra of the individual diastereoisomeric salt pairs, separately to be discussed later in section 2.4.4, (-)-**110a**•(+)-10-CSA and (-)-**110a**•(-)-10-CSA in DMSO show these salts to be identical by ^{1}H NMR spectroscopy, figure 46.

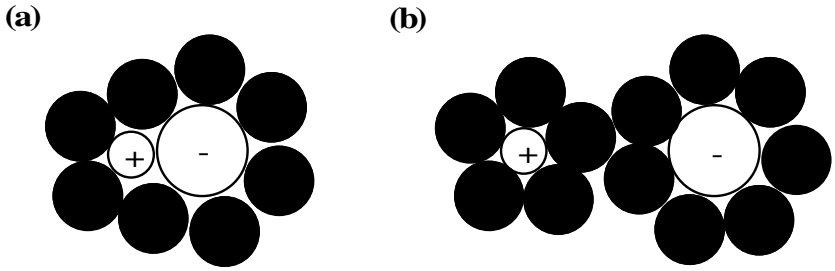


Figure 45. Schematic representation of **(a)** a solvated contact ion pair and **(b)** a solvent separated ion pair.

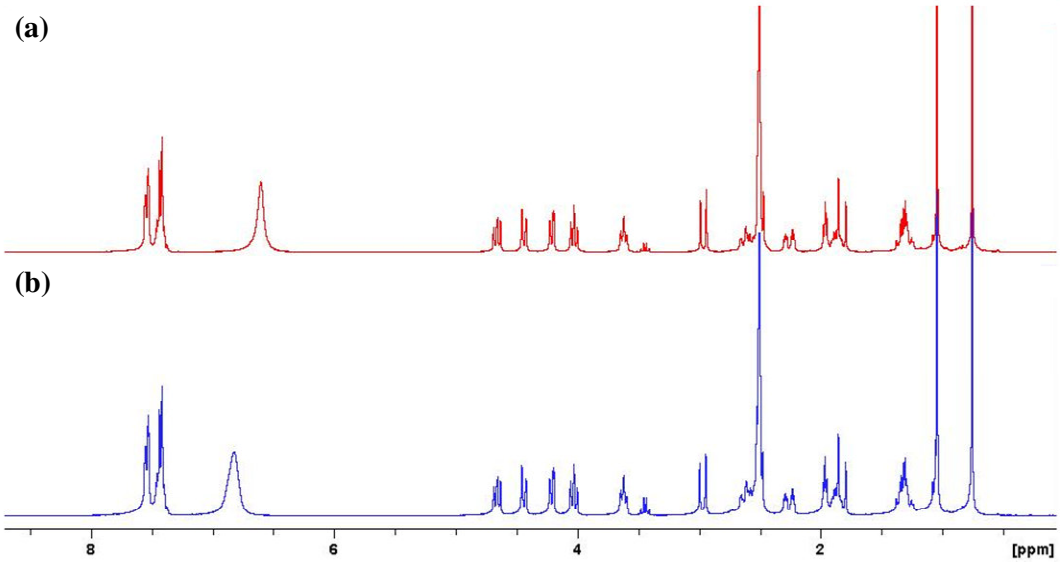


Figure 46. ^{1}H NMR spectral data (d_6-DMSO) of **(a) (-)-110a•**(-)-10-CSA and **(b) (-)-110a•**(+)-10-CSA.

The (+) and (-)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (BNHP) salts of **110a** were also synthesised. In common with the (+)-10-CSA salt the **110a•**(+)-BNHP phosphate salt was insoluble in $CDCl_3$ and ^{1}H NMR spectra of each component recorded in DMSO are shown in figure 47. An examination of the spectra shows the salt "appears" as little more than an "addition" of the signals of the two components. In CD_3OD however, small differences between the resonance signals of the salt and those of the parent bicycle were observed, figure 48. In particular, an upfield shift is noted for H^4 and a downfield shift for the remaining isoxazolidine ring protons.

2.4.2 Salt formation with the Lactam Fused Isoxazolidines, Framework B

The (+)-10-CSA salt of the bicycle **117a** was synthesised in the same manner as described above for **110a**. A 1:1 mixture of **117a** and (+)-10-CSA was dissolved in hot acetone and upon cooling the solution the salt precipitated at room temperature. A comparison of the ^{1}H NMR spectra of the parent bicycle and the precipitated material showed distinct shifts in the peaks associated with the protons of the bicyclic framework, a notable shift was also observed in the SCH_2 protons of **117a•**(+)-10-CSA when compared to the parent (+)-10-CSA, figure 49.

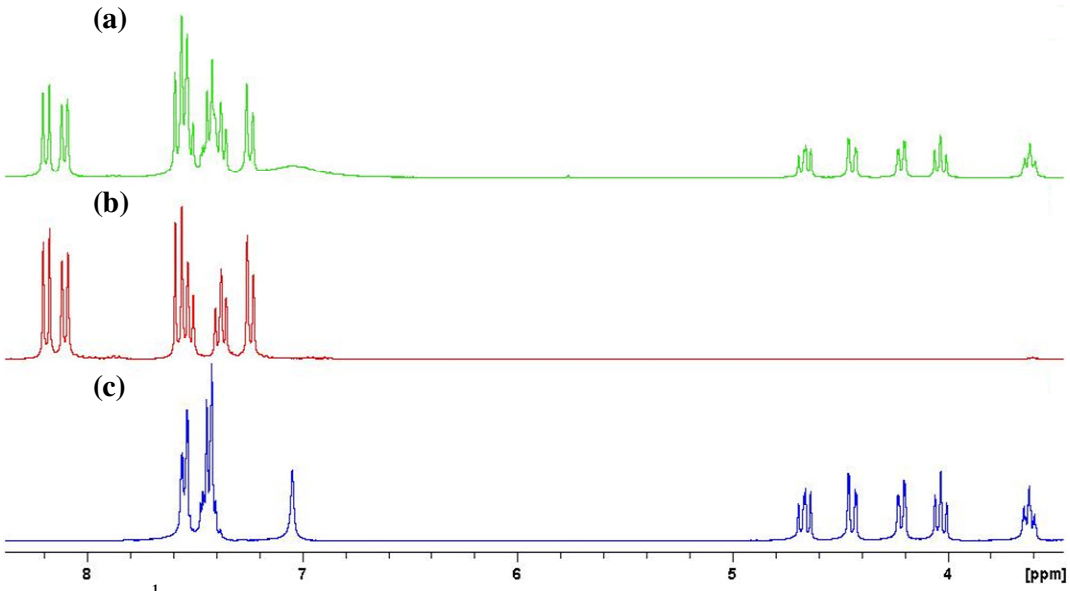


Figure 47. ^{1}H NMR spectral data (d_6-DMSO) of **(a) 110a•**(+)-BNHP, **(b)** (+)-BNHP and **(c)** isoxazolidine **110a**.

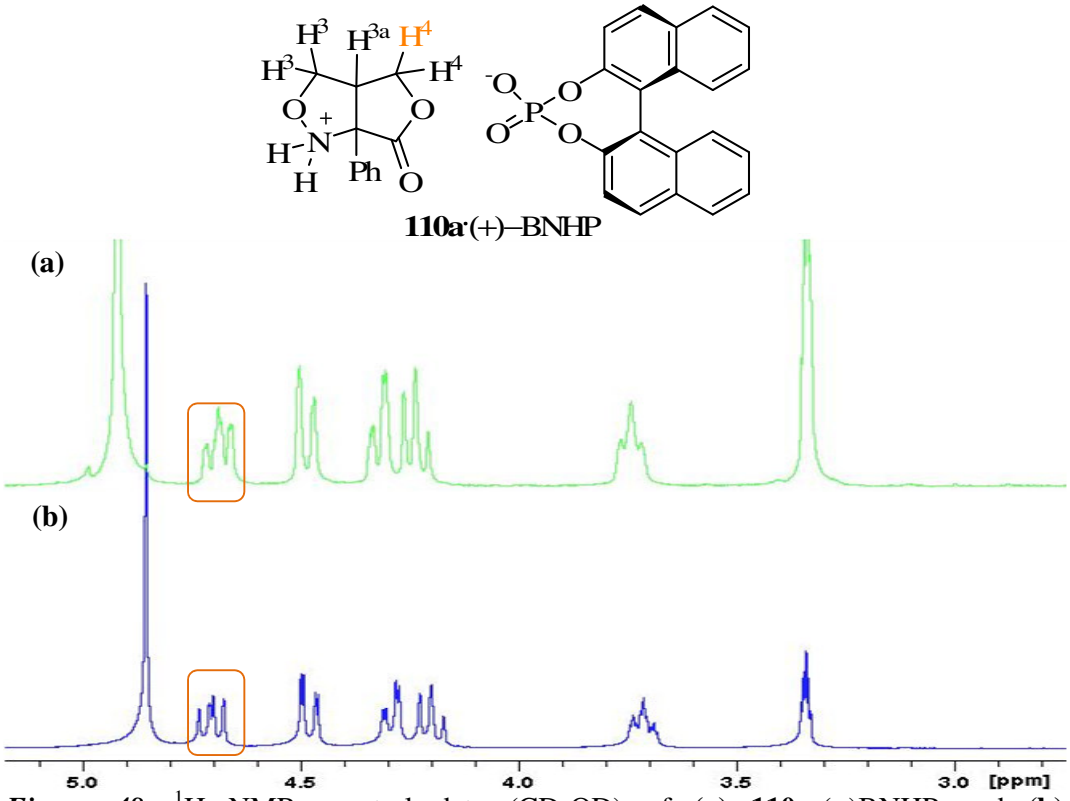


Figure 48. ^{1}H NMR spectral data (CD_3OD) of **(a) 110a•**(+)BNHP and **(b)** isoxazolidine **110a**.

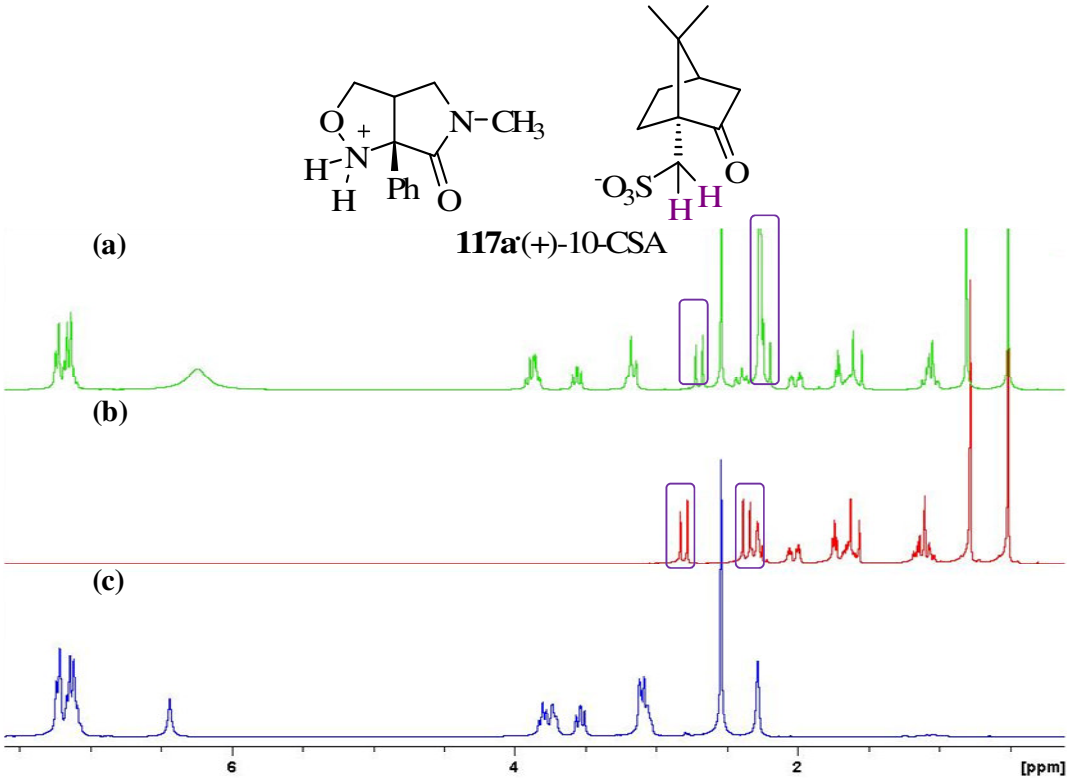
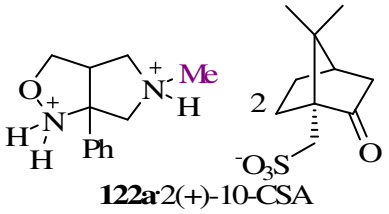


Figure 49. ^{1}H NMR spectral data (d_6-DMSO) for **(a) 117a•**(+)-10-CSA, **(b)** (+)-10-CSA and **(c) 117a**.

2.4.3 Salt formation with Pyrrolidine Fused Isoxazolidines, Framework C

The (+)-10-CSA salts of **122a&b** were obtained by the same approach as outlined above. The white solids which precipitated from the acetone solution of either **122a** or **122b** and (+)-10-CSA were collected and analysed by ^{1}H NMR spectroscopy. Both the (+)-10-CSA salts displayed broad signals for the protons associated with the bicyclic rings, which were impossible to assign. The broad appearance is due to the presentation of the bicycle in two distinct conformations. V.T. ^{1}H NMR analysis failed to deliver any improvement in resolution. One noticeable feature in the ^{1}H NMR spectrum of the **122a•**(+)-10-CSA salt was the apparent absence of the signal at 2.37 ppm which represented the *N*-methyl protons of the parent **122a**, figure 50a,b. A broad singlet overlapping with one of the SCH_2 protons at 3.08 ppm, is likely to represent these protons in the salt; the downfield shift with respect to the parent **122a** suggests that salt formation may have occurred at the more basic pyrrolidine *N*-atom rather than at the isoxazolidine *N*-atom. Advanced Chemistry Development (ACD^{TM}) labs predict the pK_a of the parent isoxazolidine to be ≃5.49 whilst the pK_a of an *N*-methyl pyrrolidine ring is

≃10.55, figure 51. A downfield shift in the resonance of the *N*-methyl protons and of the protons on the adjacent carbon atom, $H^{4\alpha,\beta}$ and $H^{6\alpha,\beta}$, is considered consistent with salt formation on the pyrrolidine ring. However, due to the broadness of the peaks this hypothesis could not be confirmed.



122a•2(+)-10-CSA

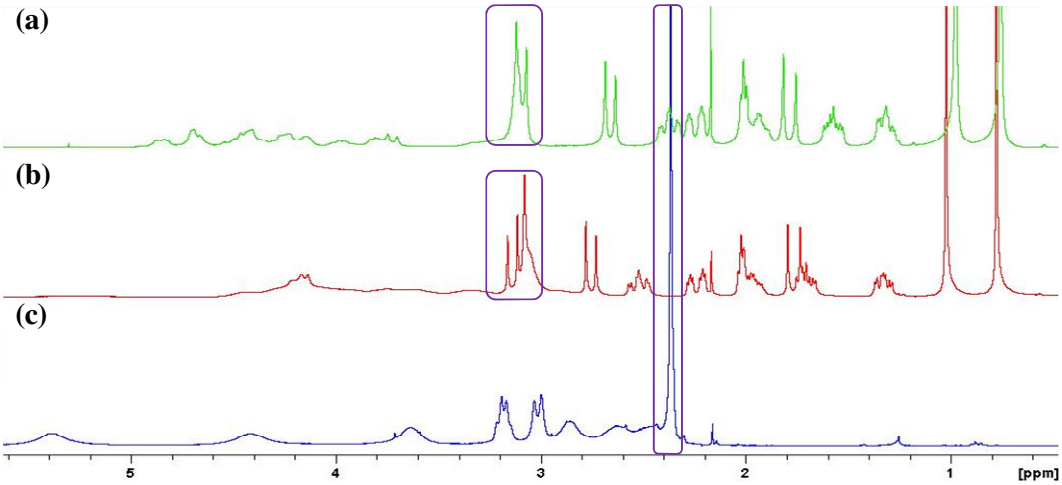
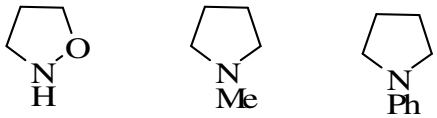


Figure 50. ^{1}H NMR spectral data of **(a) 122a**•2(+)-10-CSA, **(b) 122a**•(+)-10-CSA and **(c) 122a**.



pK_a	5.49	10.55	5.68

Figure 51. ACD^{TM} predicted pK_a values for the isoxazolidine, *N*-methyl and *N*-phenyl pyrrolidine rings.

An examination of the ^{13}C NMR spectra of **122a** and its (+)-10-CSA salt indicated a slight shift in the resonances of the *N*-methyl carbon atom. In **122a** the *N*-methyl carbon atom resonated at 41.2 ppm whilst in **122a**•(+)-10-CSA the signal representing this atom was deshielded to 41.7 ppm supporting the possibility that the salt had formed at the pyrrolidine ring. We hypothesised that the addition of two moles of (+)-10-CSA to

122a ought to give a *N,N'-bis*-salt. As with the "*mono*-salt" the ^{1}H NMR spectrum of the proposed *bis*-salt **122a**•2(+)-10-CSA appears very broad, especially in the region characteristic of the bicycle protons. Indeed it proved impossible to assign these signals. In the ^{13}C NMR the NCH_3 peak appeared at 41.7 ppm - the same position as it presented in the *mono*-salt. This is as expected since the *bis*-salt also contains a quaternary *N*-atom in the pyrrolidine ring.

The formation of the *mono*-salt by protonation at the desired isoxazolidine *N*-atom for the phenyl substituted pyrrolidine-bicycle **122b** is supported by the ^{1}H NMR spectral data. Comparison of the spectrum of the *mono*-salt and the parent **122b** show the former to be less well resolved than the latter. In the aromatic region a slight shift is observed between the protons of **122b**•(+)-10-CSA and the parent bicycle. A more noticeable downfield shift can be seen in the region characteristic of the bicycle protons, figure 52. The *bis*-salt, **122b**•2(+)-10-CSA, was prepared for the sake of comparison with its *N*-methyl analogue **122a**•2(+)-10-CSA. From comparison of the spectra a distinct downfield shift in the resonance position of the aromatic protons is noticeable for the *bis*-salt when compared to both the *mono*-salt and the parent indicating the formation of the second salt at the pyrrolidine *N*-atom.

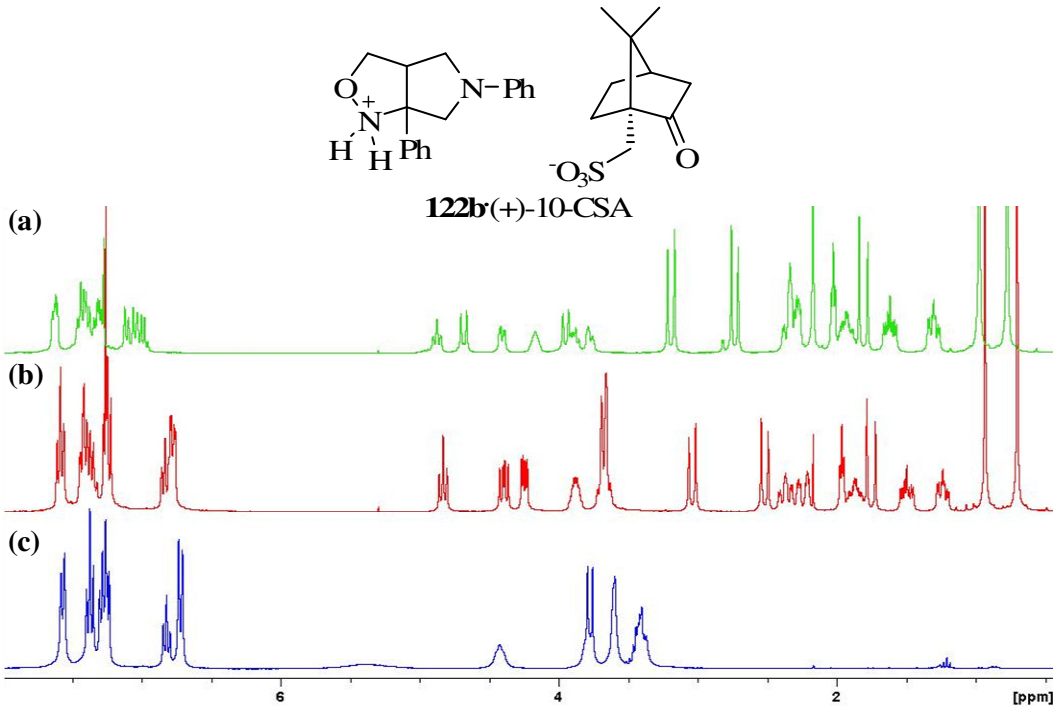
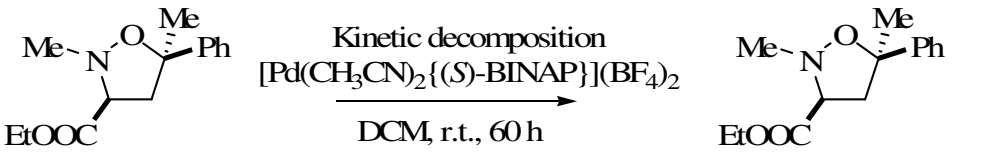


Figure 52. ^{1}H NMR spectral data for **(a) 122b**•2(+)-10-CSA **(b) 122b**•(+)-10-CSA and **(c) 122b**.

2.4.4 Resolution of the Bicyclic Isoxazolidines

The resolution of isoxazolidines has received little attention to date. In one report resolution of **123** was achieved by kinetic decomposition of a Pd-BINAP complex, equation 52.[180] However, the reaction was of long duration, 60 hours, and the products required purification by flash column chromatography. Only 48% of the resolved isoxazolidine (+)-**123** was obtained with high optical purity (99% e.e.). This is not a viable route from the perspective of this author's research since the second isomer was destroyed.

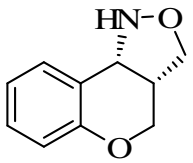


racemic *cis*-**123** (R)/(S) *cis*-**123**

+ decomposition products

Equation 52. Resolution of isoxazolidines by kinetic decomposition.

In a second and more conventional approach, classical resolution of the isoxazolidine **124** was achieved by salt formation with (+)-10-CSA. Classical resolution of organic compounds is common practice in both research and industry and leads to diastereomers, often with high yields and diastereoselectivities. In the case of **124** sequentially precipitating crops were found to comprise individual samples of (+)(+) and (+)(-) diastereoisomeric salts in high yields and with high diastereoselectivities.[181,182] This method was more suited to our needs as it provides crops of each diastereomer from which enantiomerically pure compounds could be obtained.



124

Figure 53. Benzopyranoisoxazolidine used in classical resolution with (+)-10-CSA.

In an attempt to obtain diastereoisomerically pure CSA salts of the lactone-fused isoxazolidine **110a**, it was combined with (+)-10-CSA in either a 1:1 or a 1.6:1 ratio and dissolved in warm acetone. Upon cooling, the resulting crops were collected and optical rotation measurements and/or HPLC analysis was used to ascertain the purity of the individual crops. From the trial involving the bicycle and (+)-10-CSA in a 1:1 ratio, the (+)-**110a**•(+)-10-CSA salt was obtained in 62% yield, $[\alpha]^{25}_{D}$= +75 (c. 0.0023, MeOH), whilst the experiment with a higher loading of **110a** yielded (+)-**110a**•(+)-10-CSA in just 56%, $[\alpha]^{25}_{D}$= +74 (c. 0.0072, MeOH). In both cases it was difficult to obtain the (-)-**110a**•(+)-10-CSA salt in high diastereoselectivity from the alternative crops. However applying the same method to the resolution of the (-)-10-CSA salts the (-)-**110a**•(-)-10-CSA salt could be obtained in 44% yield, $[\alpha]^{25}_{D}$= -64 (c. 0.002, MeOH).

Treatment of the (+)-**110a**•(+)-10-CSA and the (-)-**110a**•(-)-10-CSA in turn with 1 M NaOH, followed by extraction with DCM gave pure samples of (+)-**110a**, $[\alpha]^{25}_{D}$= +112 (c. 0.0010, MeOH) and (-)-**110a**, $[\alpha]^{25}_{D}$= -110 (c. 0.0064, MeOH), in quantative yields, as illustrated in the HPLC traces shown in figure 54. The enantiomerically pure (+)- and (-)-**110a** could be combined with either (+)- or (-)-10-CSA to provide samples of all four diastereoisomeric salts, which were tested as potential organocatalysts for the Diels-Alder reaction.

In an attempt to increase the yields obtained for the crops, the resolution was attempted with EtOAc, this was not as successful and the (+)-**110a**•(+)-10-CSA and (-)-**110a**•(-)-10-CSA salts were obtained in just 20% and 37% respectively.

The resolution of the 2-thienyl lactone-fused isoxazolidine, **110c**, was attempted with (+)-10-CSA in both acetone and EtOAc, however diastereoisomeric enrichment was not observed for any of the resultant crops from either mixture.

Resolution of the lactam-fused isoxazolidine **117a** under similar conditions also failed.

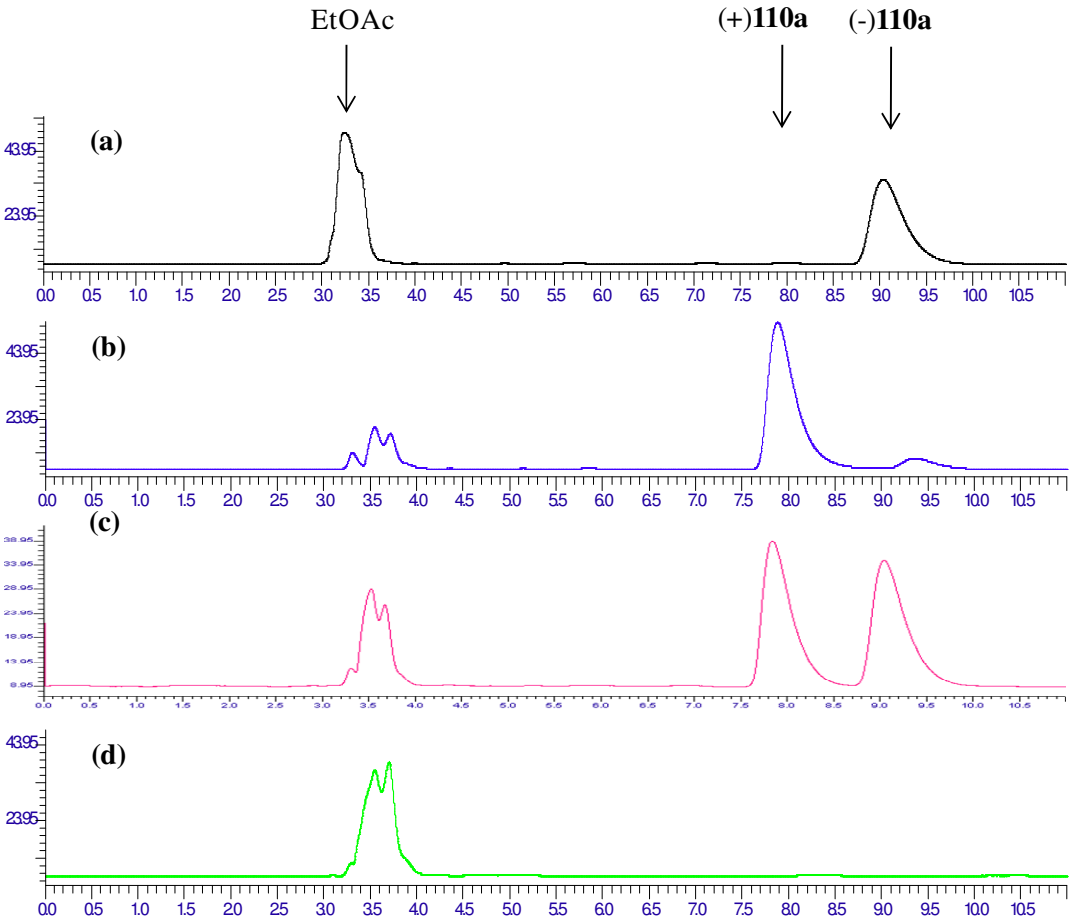


Figure 54. HPLC trace of **(a)** (-)-**110a** **(b)** (+)-**110a** **(c)** racemic **110a** and **(d)** EtOAc.

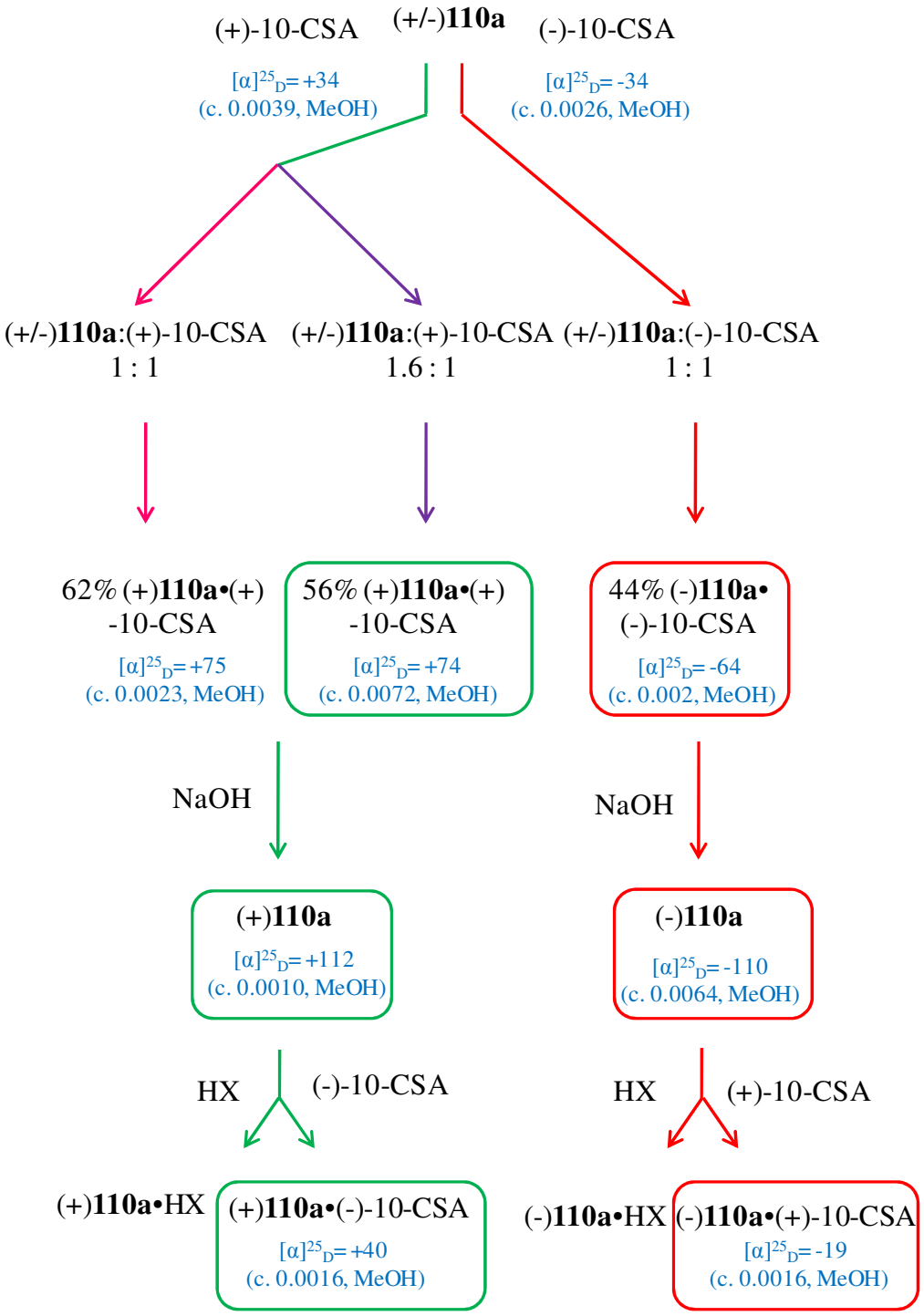


Figure 55. Route to obtain all 4 diastereoisomeric salts of **110a** with either (+)- or (-)-10-CSA.

2.5 Conclusion

The formation of the organocatalytic framework based on *N*-unsubstituted isoxazolidines was attempted. Difficulties were encountered in the synthesis of the 1st generation catalysts where the final step required debenzylation of the *N*-benzyl cycloadduct **91**. As a result a 2nd generation of organocatalysts were designed, these were formed by a tandem 1,2-prototropy cyclisation process from parent δ-alkenyl oxime substrates and thus were obtained *N*-unsubstituted. By varying the linker between the oxime and the alkene functionalities three different frameworks, lactone, lactam and pyrrolidine-fused isoxazolidines, were prepared. A ring-opened version of the lactone-fused isoxazolidine **110a** was also prepared.

Classical resolution with (+)-10-CSA was successful for the generation of diastereoisomerically pure salts, and from these enantiomerically pure isoxazolidines were obtained; HPLC analysis indicated the success of the resolution. With the (+)- and (-)- forms of the isoxazolidine **110a** available all four diastereoisomeric salts were formed and tested as potential organocatalysts.

The next chapter will discuss the application of these compounds as novel catalysts in the Diels-Alder cycloaddition reaction, the Michael addition reaction and the Aldol condensation reaction.

Results and Discussion

3.1 Introduction

In the previous chapter the synthetic route to the three isoxazolidine frameworks designed as organocatalysts was discussed, this chapter will cover the application of these compounds in promotion of the Diels-Alder reaction, by way of iminium ion catalysis, and the attempted catalysis of both the aldol condensation and Michael addition reactions, by means of enamine catalysis.

3.2 Iminium Ion Catalysis

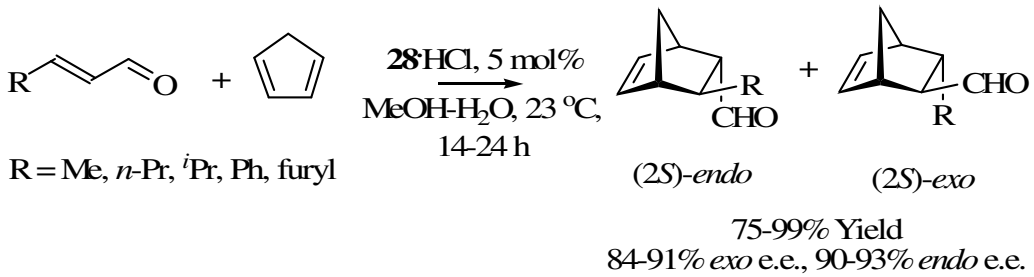
3.2.1 Introduction

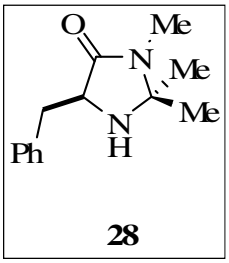
Iminium ion catalysis was first introduced in 2000 by the MacMillan research group when the imidazolidinone **28** was used to catalyse the Diels-Alder reaction between a range of α,β-unsaturated aldehydes and cyclopentadiene at room temperature. The cycloaddition products were observed to form in high yields (84-91%) and with very good enantioselectivities (90-93% e.e.), equation 53.[72] Since this original publication amine catalysed Diels-Alder reactions of α,β-unsaturated aldehydes have received much attention (see section 1.3.2). It is evident from the literature that the Diels-Alder reaction is frequently the reaction of choice for the initial testing of the activity of novel organocatalysts, we concurred with this choice and so we began our testing.

3.2.2 Diels-Alder reaction

3.2.2.i Introduction

The Diels-Alder reaction is a valuable transformation for the construction of complex carbocycles and to a lesser extent heterocycles. Arguably it represents one of the most powerful ring forming methodologies in organic chemistry.[183] It is a [4 + 2] addition of a diene to a dienophile forming a new ring. The driving force of the reaction is the formation of two new σ-bonds, which are energetically more stable than the π-bonds sacrificed for the reaction. The Diels-Alder reaction proceeds by a pericyclic mechanism. It takes place in a single step with a cyclic flow of electrons, as shown in figure 56. As it is a one-step reaction there are no intermediates but one transition state which has six delocalised π-electrons.[161]





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Equation 17. The Diels-Alder reaction between cyclopentadiene and a range of aldehydes catalysed by the imidazolidinone **28**.

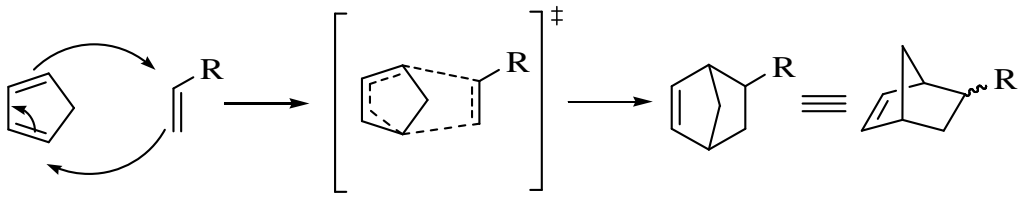


Figure 56. The pericyclic mechanism of the Diels-Alder reaction.

The diene component in the Diels-Alder reaction can be open-chain or cyclic and can bear a range of substituents; however, it must be able to adopt the s-*cis* conformation. Many open-chain dienes are in the s-*trans* conformation but react through the equilibrium s-*cis* form, figure 57. Cyclic dienes that are fixed in the s-*cis* conformation are exceptionally good Diels-Alder substrates.

A clear understanding of concerted cycloaddition reactions developed as a result of the formulation of the mechanism within the framework of molecular orbital (MO) theory. Consideration of the MO's of reactants and products reveal that in many cases a smooth transformation of the orbitals of the reactants to those of the products is possible.

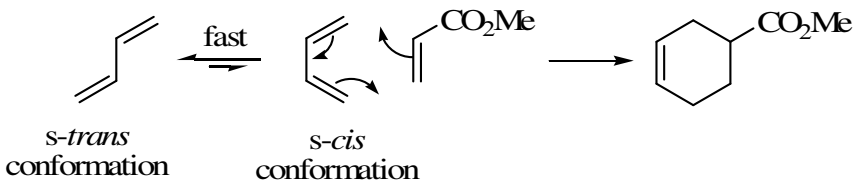


Figure 57. Conversion between *s*-trans and *s*-cis open-chain dienes.

3.2.2.ii Frontier orbital description

From a frontier orbital point of view the Diels-Alder reaction is described as the reaction of two different π-bond containing molecules to form a new cyclic molecule by rearrangement of the π-electrons and the formation of two new σ-bonds. The reaction occurs between the HOMO of one reactant and the LUMO of the other. From the MO symmetry of the reactants, figure 58, it can be seen that the reaction can proceed with the HOMO of the diene and the LUMO of the dienophile or the LUMO of the diene and HOMO of the dienophile, figure 59. Normally electron flow is from the HOMO of the diene to the LUMO of the dienophile as these orbitals are generally the closest in energy. Most Diels-Alder reactions use electron-deficient dienophiles, which have low-lying LUMOs, and electron-rich dienes, which have high energy HOMOs. This combination gives the most effective overlap in the transition state.

Two modes of orbital overlap, termed suprafacial and antarafacial overlap, allow for the simultaneous formation of two σ-bonds. Suprafacial bond formation occurs if both σ-bonds form on the same side of the π-system, whilst antarafacial bond formation occurs when the two σ-bonds form on opposite sides of the π-system. Cycloaddition reactions that form 4-, 5- or 6-membered rings must occur by suprafacial overlap; due to geometrical constraints antarafacial overlap is not possible.

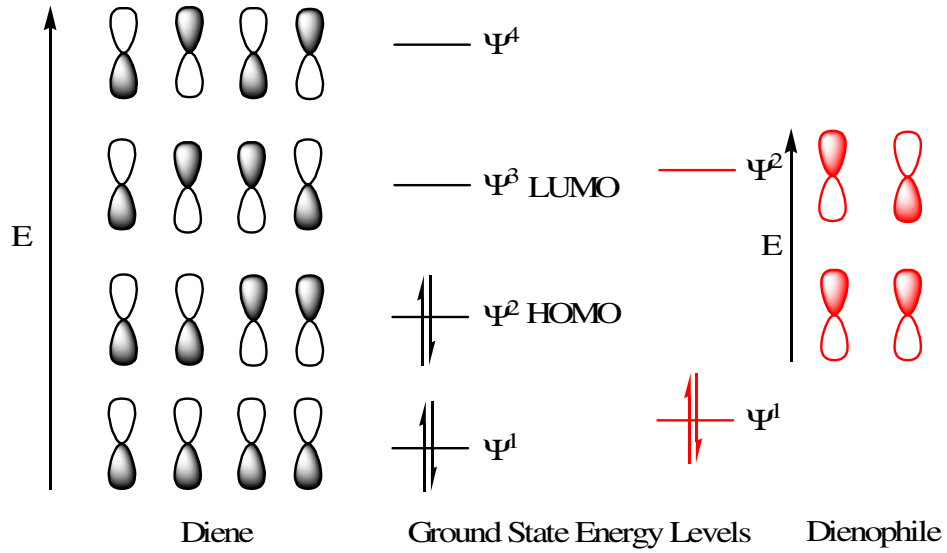


Figure 58. Molecular orbitals of the diene and the dienophile in the ground state.

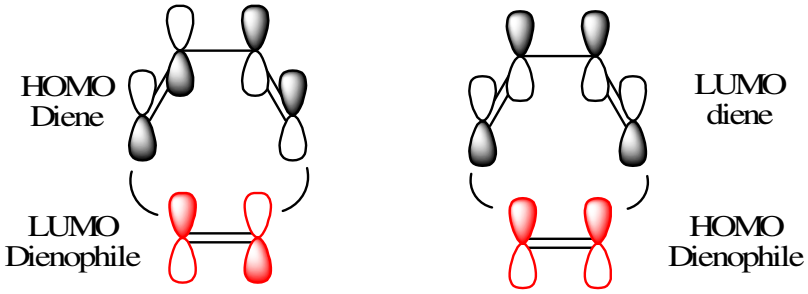


Figure 59. Orbital overlap of the HOMO/LUMO of the diene with the LUMO/HOMO of the dienophile.

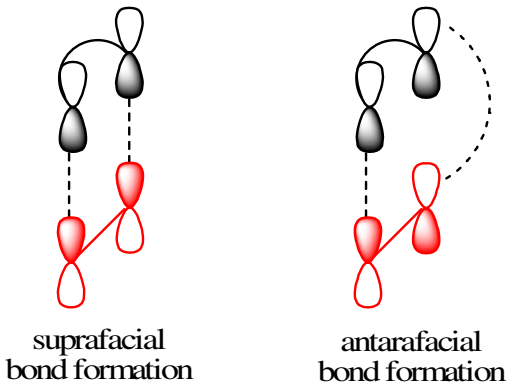


Figure 60. Suprafacial and antarafacial overlap of the diene and dienophile.

3.2.2.iii Reactivity and substituent effects

The reactivity of the Diels-Alder reaction depends on the energy separation of the HOMO-LUMO of the diene and dienophile, the smaller the energy difference the lower the TS energy of the reaction. There is a strong electronic substituent effect on the Diels-Alder reaction. The most reactive dienophiles for simple dienes are those having electron-withdrawing groups (EWG) and quinines, maleic anhydride and nitroalkenes are amongst the most reactive dienophiles. Electron-rich dienes have high-energy HOMOs that interact strongly with the LUMOs of electron-poor dienophiles. When the substituent pattern is reversed and the diene is electron-poor, the strongest interaction is between the dienophile HOMO and the diene LUMO, resulting in a reverse electron demand Diels-Alder reaction, figure 61.

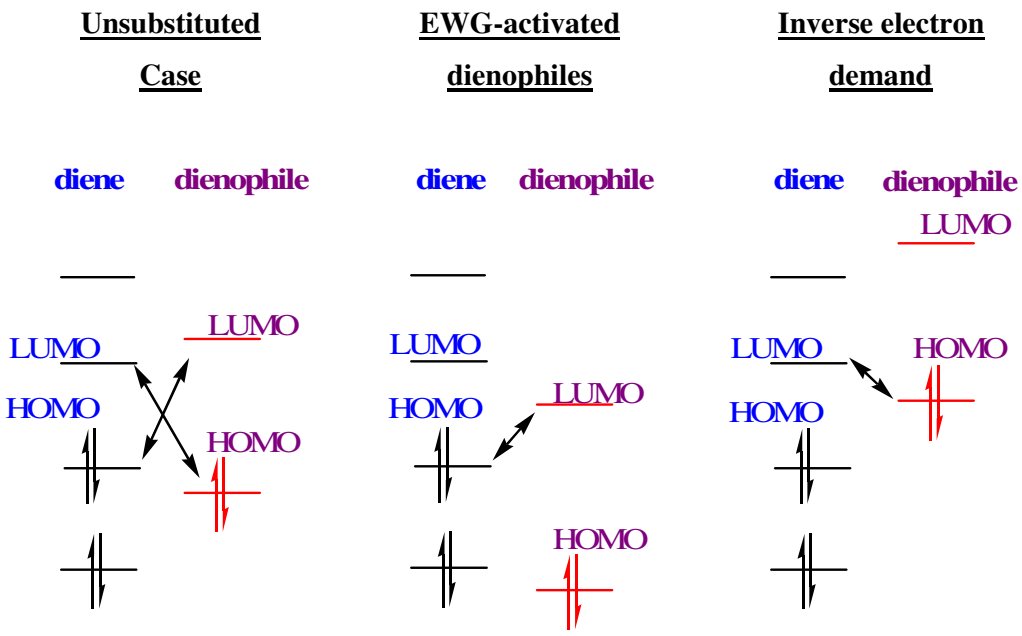


Figure 61. HOMO and LUMO diene and dienophile interactions for substituted reactants.

3.2.2.iv Stereoselectivity

For an unsymmetrical dienophile there are two possible alignments in the transition state, the *endo* and *exo*. In the *endo* TS the reference substituent is oriented toward the π-orbitals of the diene, figure 62. In the *exo* TS the substituent is oriented away from the π-system, making it less hindered. The *endo* mode of addition is usually preferred when an EWG such as a carbonyl is present on the dienophile, however, frequently a mixture of both stereoisomers is formed and sometimes the *exo* product dominates. The preference for the *endo* TS is considered to be the result of secondary orbital interactions between the dienophile substituent and the π-electrons of the diene; dipolar and Van der Waals attractions may also be involved. Secondary orbital overlap is when the *p*-orbitals of the EWG on the dienophile overlap with those of the central carbon atoms of the diene stabilising the *endo* TS with respect to the *exo* TS, it does not lead to bond formation but does contribute to lowering the energy of the *endo* TS, making it the kinetic product, figures 63 & 64.

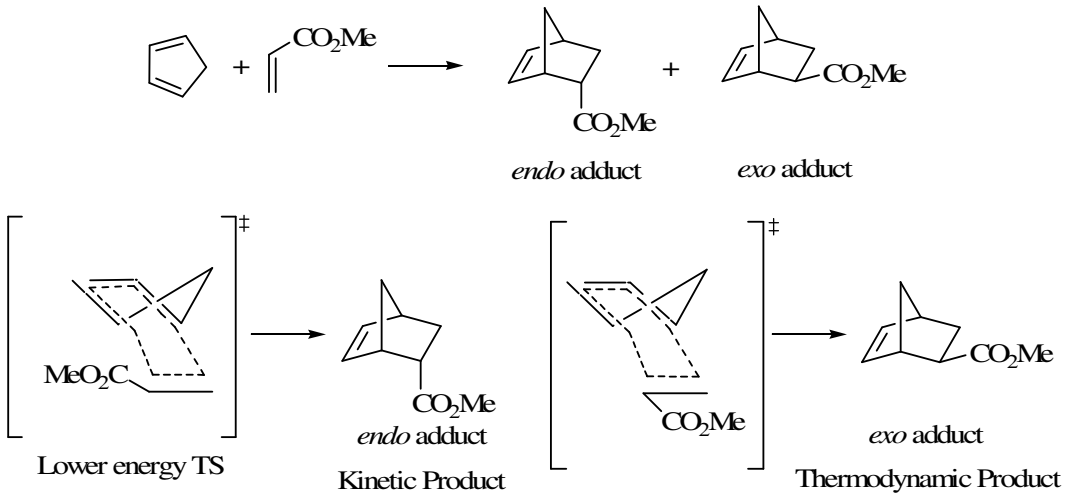


Figure 62. Orientation of the *exo* and *endo* transition states.

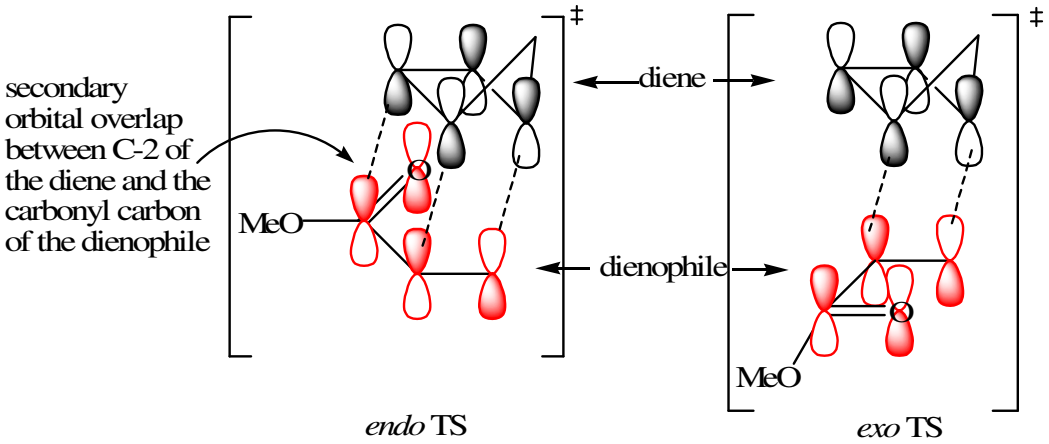


Figure 63. Secondary orbital overlap leading to the lower energy of the *endo* TS.

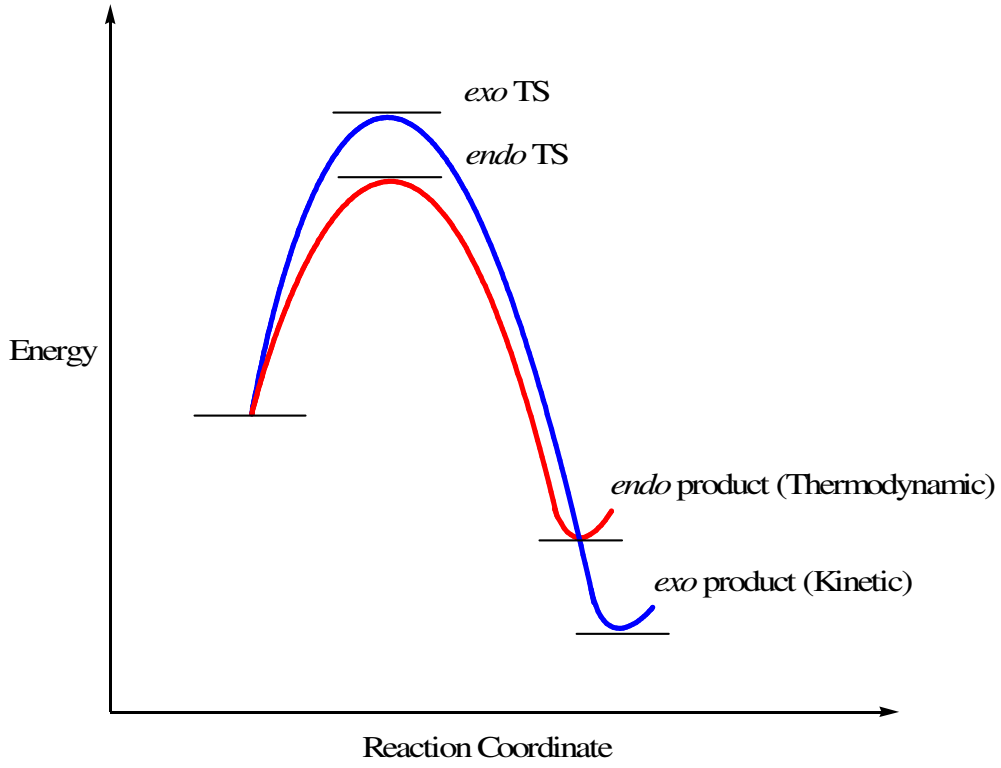


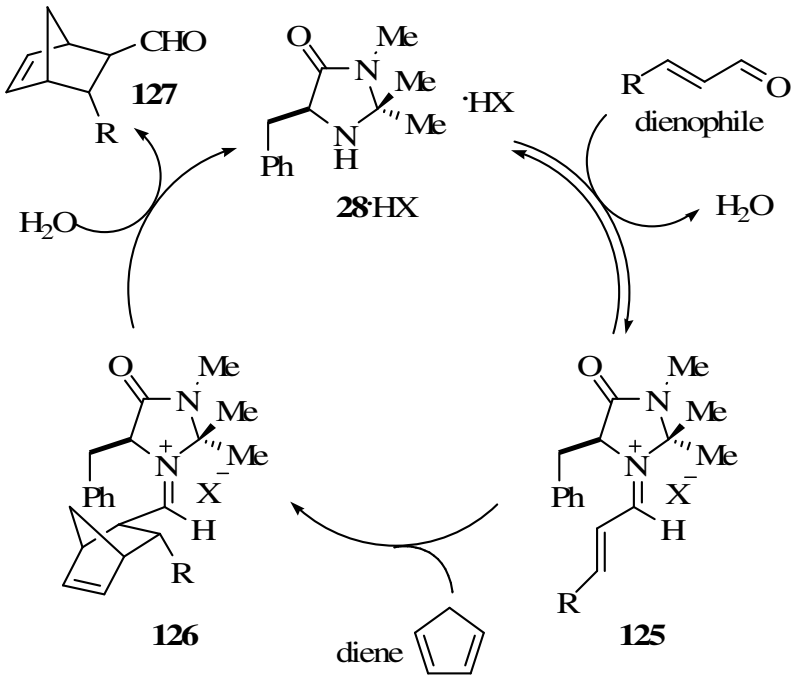
Figure 64. Reaction coordinate diagram for a typical Diels-Alder reaction.

3.2.3 Organocatalysis and the Diels-Alder Reaction

Catalytic enantioselective variants of the Diels-Alder reaction have received unprecedented attention.[5,71,183,184] In line with the mechanistic rationale of LUMO-lowering iminium activation MacMillan hypothesised that the iminium ion **125**, generated from the secondary amine **28** and an α,β-unsaturated aldehyde, could be

activated towards cycloaddition with an appropriate diene, scheme 20. The initial Diels-Alder product, the iminium ion cycloadduct **126**, would hydrolyse in the presence of water to yield the enantioenriched product **127** and regenerate the catalyst **28**.

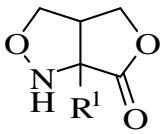
In 2002 the first highly enantioselective amine-catalysed Diels-Alder reaction was published by the MacMillan group[72] and since then many computational studies have been carried out to decipher the mechanism of iminium ion promoted Diels-Alder reactions.[185-187] It is noteworthy that the selectivity of the Diels-Alder reaction which proceeds via organocatalysis is the reverse of that normally observed *i.e.* the *exo* product generally dominates.



Scheme 20. Iminium ion catalytic cycle of the Diels-Alder reaction.

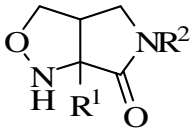
3.2.3.i.a Catalytic activity and the nature of the catalyst

Initially the Diels-Alder reaction was tested using racemic catalysts and not enantiomerically pure versions in order to obtain the optimal reaction conditions. The reaction between cinnamaldehyde and cyclopentadiene with a 10 mol% loading of the catalyst in MeOH:H_2O (19:1) at room temperature was selected as the test conditions to explore the potential of the racemic *NH*-isoxazolidines **110**, **117** and **122** to promote iminium ion catalysis.[72,78,188,189]



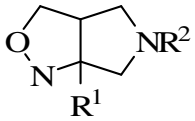
A

110



B

117



C

122

110/117 a. R = Ph; **b.** R = 2-furyl; **c.** R = 2-thienyl; **122 a.** R = Me; **b.** R = Ph

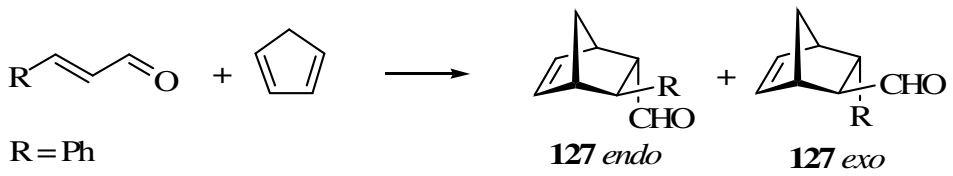
Figure 65. The three catalytic frameworks synthesised and tested as potential catalysts for the Diels-Alder reaction.

The bicyclic isoxazolidinium salt **110a•**(+)-10-CSA was first studied, it was stirred with cinnamaldehyde in MeOH:H_2O (19:1) at 25 ^oC for 5 minutes to initiate iminium ion formation. Freshly cracked cyclopentadiene was added to the stirring mixture which was left to react at 25 ^oC for 48 hours. The volatiles were removed under reduced pressure and the resulting residue was hydrolysed in a $CHCl_3$, H_2O and TFA (2:1:1) solution for two hours followed by neutralisation with $NaHCO_3$. Following work-up, ^1H NMR spectral analysis showed the reaction had gone to completion and the Diels-Alder products were obtained in 96% isolated yield. The diastereoisomeric *endo:exo* ratio was 39:61, the selectivity towards the *exo* product supports the hypothesis that the reaction had proceeded via iminium ion catalysis. Three control reactions confirmed the identity of the catalytic system. The first control involving only cinnamaldehyde and cyclopentadiene failed to produce any products. In the second and third experiments it was found neither **110a** nor (+)-10-CSA alone (10 mol%) were able to promote cycloaddition. Thus, it can be concluded that the catalytic activity requires both the isoxazolidine **110a** and the acid co-factor.

3.2.3.i.b The influence of time

Since the reaction had reached completion at 48 hours it was deemed prudent to seek a reduced reaction time. It was subsequently found that after 24 hours the reaction was complete and the products were isolated in 85% yield. Following further experimentation it was discovered that 6 hours was sufficient to effect complete conversion of starting materials and to furnish the Diels-Alder products in 85% yield, table 11 entries 1-3. Reducing the reaction time further to 4 and 2 hours was accompanied by a reduction in isolated yields, to 75% and 61% respectively.

Significantly the *exo*-isomer dominated in all cases. Thus, it was concluded that a reaction time of 6 hours was optimal for completion of the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene when catalysed by **110a•**(+)-10-CSA in aqueous MeOH.



Equation 54. The Diels-Alder reaction between cinnamaldehyde and a range of aldehydes.

Table 11. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O (19:1) at 25 ^oC catalysed by **110a•**(+)-10-CSA (10 mol%).

Entry	Time (h)	% Conversion[a]	127 R = Ph	
			% Yield	*endo:exo*[b]
1	48	97	96	39:61
2	24	94	85	40:60
3	6	93	86	40:60
4	4	84	75	36:64
5	2	71	61	36:64

[a] % Conversion determined by ^{1}H NMR spectral analysis of the ratio of the aldehyde peaks of the starting material to the *endo* and *exo* adducts. [b] Ratio determined by ^{1}H NMR spectral analysis of the integration of the *endo* and *exo* peaks. ^{1}H NMR spectral data for the Diels-Alder products is shown in figure 66.

3.2.3.i.c Optimisation of catalyst loading

Although 10 mol% is a fairly typical catalyst loading recent publications have employed organocatalysts at lower loadings. In one example the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by the imidazolidinone **28** yielded the products in 99% yield after 8 hours with 10 mol% catalyst. Upon lowering the loading to 5 mol% there was little compromise in product yields, albeit with a significant increase in reaction time to 21 hours.[72]

After 6 hours with just 1 mol% of **110a•**(+)-10-CSA the reaction between cinnamaldehyde and cyclopentadiene only proceeded to 9% conversion, the products were not isolated due to the small % conversion of reactants, table 12 entry 1.

Increasing the time to 24 hours increased the yield a little and the products were isolated in 16% yield. Raising the loading of the catalyst to 5 mol% significantly promoted the reaction and the products were isolated in a moderate 51% yield. When compared to state of the art results in the literature these yields are not competitive, thus, it was decided that for the catalytic framework under study a 10 mol% loading of the catalyst was optimal and future studies were based on this observation.

Table 12. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by **110a•**(+)-10-CSA in MeOH:H_2O (19:1) at 25 ^oC, with varying catalyst loading.

Entry	110a•(+)-10-CSA (mol%)	Time (h)	% Conversion	% Yield	*endo:exo*
1	1	6	9	-	43:57
2	1	24	23	16	51:49
3	5	6	65	51	39:61
4	5	24	89	73	41:59
5	10	6	93	86	40:60

3.2.3.i.d Influence of solvent

To this point the Diels-Alder reactions discussed in this thesis have been performed in MeOH:H_2O (19:1). This solvent mixture represents the most common choice for iminium ion promoted Diels-Alder reactions. However, there are reports of other useful solvents for related studies.[72,78,79,190,191]

The Diels-Alder reaction between cinnamaldehyde and cyclopentadiene promoted by **110a•**(+)-10-CSA (10 mol%) was repeated in a range of solvents as shown in table 13. In alcoholic solvents it was observed that as the length of the carbon chain or the steric bulk of the alkyl group increased the yield of the product decreased. For example, in MeOH the products were formed in 88% yield whilst in the bulkier ^{t}BuOH the products were observed in only 20% yield, entries 1-6. It is anticipated that the bulky solvents negatively impact on the rate of iminium ion formation and the ability of the iminium ion and the diene to align properly. Significantly, no decrease in yield was observed with anhydrous MeOH as the reaction solvent when compared to MeOH:H_2O. This observation will be discussed in further detail in section 3.2.3.iii. No cycloaddition products were observed in pure H_2O, entry 7.

Reactions in aprotic solvents such as dioxane and DMSO were less successful than in aqueous MeOH and a decrease in product yield was observed to just 26% and 18%

respectively, entries 8 and 9. The poor yields may be attributed to the inability of these solvents to participate in hydrogen bonding.

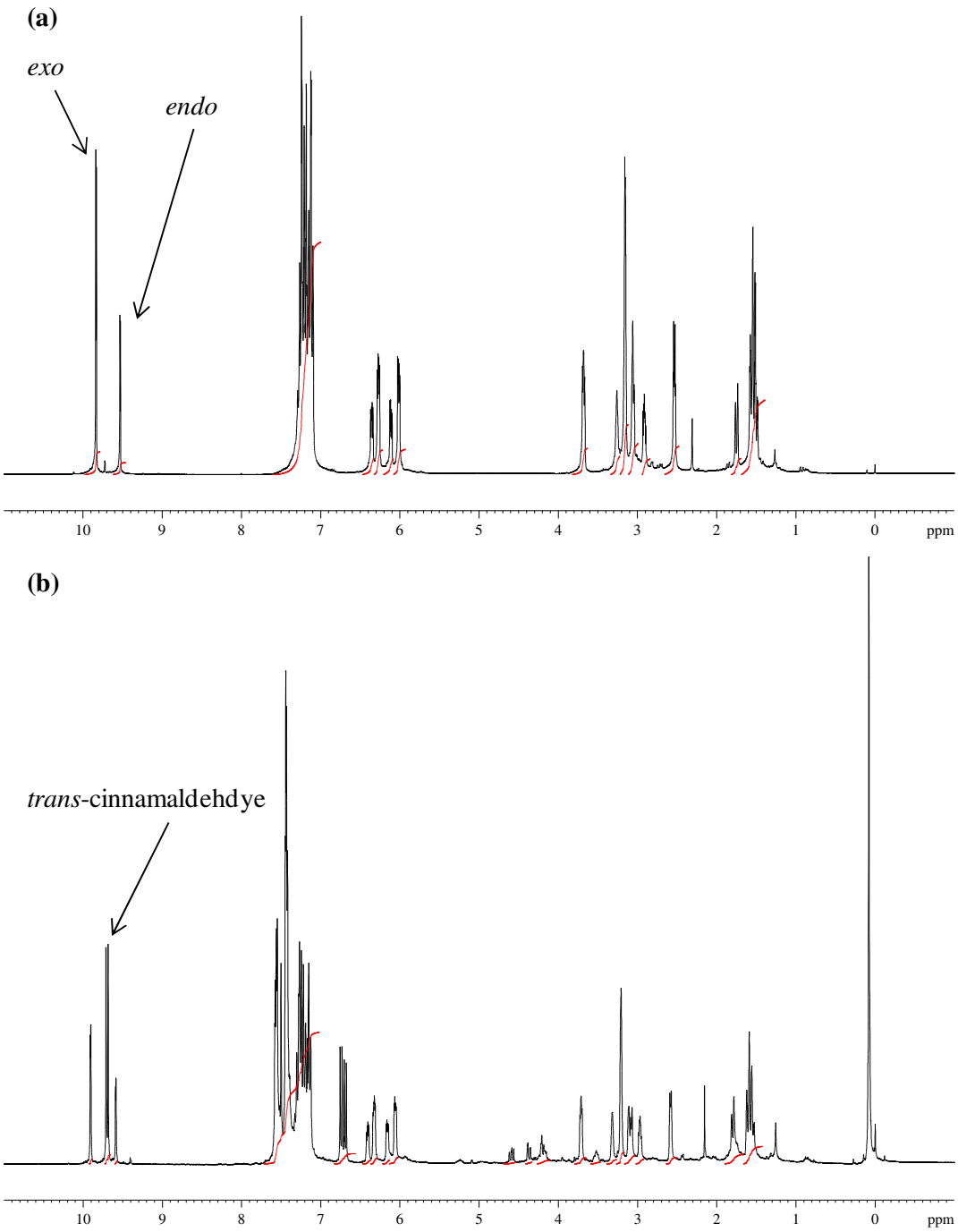


Figure 66. ^{1}H NMR spectra showing **(a)** an isolated mixture of *endo* and *exo* Diels-Alder adducts **127** and **(b)** the crude reaction mixture from the Diels-Alder reaction.

Reactivity was also very poor in chlorinated solvents and reduced cycloaddition yields were observed when compared to reactions run in aqueous MeOH. $CHCl_3$ was a slightly less useful solvent than CH_2Cl_2 and the products were isolated in 52% and 70% respectively, entries 8 and 9. Interestingly, in these chlorinated solvents the *endo*/*exo* selectivities were much poorer than those observed for aqueous MeOH.

Reactions conducted in Et_2O and toluene also resulted in moderate to low yields of the Diels-Alder products with little or no selectivity observed in toluene, entries 12 and 13.

Analysing the above results it can be concluded that for the lactone-fused isoxazolidinium salt **110a**•(+)-10-CSA, MeOH:H_2O (19:1) is, in terms of yield and diastereoselectivity, the solvent of choice for catalysis of the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene.

Table 13. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by **110a**•(+)-10-CSA (10 mol%) at 25 ^{o}C, for 6 hours with varying solvents.

Entry	Solvent	% Conversion	% Yield	*endo:exo*
1	MeOH:H_2O (19:1)	93	86	38:62
2	MeOH	92	88	39:61
3	EtOH	91	78	40:60
4	^{i}PrOH	74	60	39:61
5	2-BuOH	51	43	46:54
6	^{t}BuOH	25	20	43:57
7	H_2O	0	0	-
8	Dioxane	43	26	48:52
9	DMSO	30	18	34:66
10	CH_2Cl_2	73	70	48:52
11	$CHCl_3$	66	52	49:51
12	Et_2O	54	37	43:57
13	Toluene	55	46	50:50

3.2.3.i.e Variation of the acid co-factor

To this point (+)-10-CSA has been the only co-factor discussed and in this section the influence of a range of alternative co-factors, in conjunction with **110a**, will be considered. It is anticipated that the counterion could have a significant effect on the yield and selectivity of the reaction, table 14.[75,78,79,189-193]

The **110a**•(+)-10-CSA salt to this point has been employed as a preformed salt formed by the addition of **110a** and (+)-10-CSA to hot acetone. Allowing the solution to cool to room temperature resulted in the precipitation of the salt as a white solid which was characterised by NMR spectroscopy and used to catalyse the Diels-Alder reaction

between cinnamaldehyde and cyclopentadiene. In order to establish if it was necessary to preform the salt a control reaction involving simply adding the two components to the reaction mixture was conducted. The result of this experiment, in which a 91% conversion to the Diels-Alder products (*endo*:*exo* 37:63) was observed after 24 hours, confirms the equal success of the reaction independently of whether the catalytic system was preformed or not. Due to the technical ease of *in situ* salt formation all future reactions are performed with a 1:1 mixture of the salt components.

Table 14. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O (19:1) at 25 ^oC for 6 hours, catalysed by **110a** (10 mol%) and a range of co-factors (10 mol%).

Entry	Co-factor (10 mol%)	% Conversion	% Yield	*endo:exo*	Acid Co-Factor pK_a[a]
1	(+)-10-CSA	86	77	44:56	1.17
2	(-)-10-CSA	84	66	42:58	1.17
3	L-Tartaric Acid	0	0	-	2.98
4	D-Tartaric acid	0	0	-	2.98
5	TFA	32	25	38:62	0.5
6	H_2SO_4	78	60	39:61	-3
7	HCl	66	52	38:62	-8
8	$HClO_4$	88	82	40:60	-10

[a] pK_a values were calculated using ACD^{TM} labs.

In addition to (+)-10-CSA its enantiomer (-)-10-CSA was examined as well as the optically active D- and L-tartaric acids. As expected, with (-)-10-CSA as co-factor the reaction progressed to a similar extent as observed with (+)-10-CSA. However, neither of the tartaric acid salts of **110a** were able to catalyse the reaction, entries 1-4.

The attempted preparation of the preformed **110a•**HCl salt was discussed in section 2.4.1 and as no difference could be detected by TLC analysis, m.p. determination or ^1H NMR spectral analysis of the material formed when compared to the starting **110a** it was considered that salt formation had not occurred. However, catalytic activity of the *in situ* HCl salt along with the salts for the achiral acids, TFA, sulphuric acid, and $HClO_4$, was explored, entries 5-8. In the case of the achiral acids a general trend correlating lower pK_a values of the acids with a higher yield of Diels-Alder products was noted. $HClO_4$ was the only acid comparable to (+)-10-CSA, in this case the Diels-Alder products were obtained in 82% yield and with similar diastereoselectivities.

Since the **110a•**(+)-10-CSA salt afforded the Diels-Alder products in the greatest yield and with the possibility of the optical purity of the CSA component introducing selectivity into the reaction it was identified as the co-factor of choice for further studies of the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene.

3.2.3.i.f The use of alternative dienophiles

In an effort to examine the generality of the catalytic properties of the lactone fused isoxazolidinium salt, **110a•**(+)-10-CSA, to promote the Diels-Alder reaction a range of dienophiles was examined in conjunction with cyclopentadiene. The first tested were the electron poor *o*- and *p*-nitrocinnamaldehyde. Reaction of *o*-nitrocinnamaldehyde with cyclopentadiene in the presence of **110•**(+)-10-CSA afforded the Diels-Alder products in 52% yield, interestingly with a slight preference for the *endo* stereoisomer. On the other hand *p*-nitrocinnamaldehyde was a more reactive substrate and cycloaddition to cyclopentadiene in the presence of **110a•**(+)-10-CSA gave the cycloaddition products in an 86% yield with a selectivity for the *exo* adduct, table 15 entries 1 and 2. The nitro group is a mesomeric electron withdrawing group, -M, and in the *ortho* and *para* positions it increases the electronegativity of the carbonyl oxygen and the electropositivity of the carbonyl carbon making it more susceptible to nucleophilic attack from the secondary amine; as a result it may be considered to promote iminium ion formation. The reduced yield with the *o*-nitro substituent may simply be due to structural impediment.

The electron-rich *o*- and *p*-methoxycinnamaldehyde were next tested. Reaction between cyclopentadiene and *o*-methoxycinnamaldehdyde afforded the Diels-Alder products in 83% yield with a 3:2 preference for formation of the *exo* adduct. This compares favourably with that obtained for the parent reaction between cinnamaldehyde and cyclopentadiene (86% yield, *endo:exo* 38:62). Surprisingly, however, reaction with *p*-methoxycinnamaldehdye was much less efficient and reaction products were obtained in just 16% yield.

The large difference observed in the isolated yields for the adducts formed from *o*- and *p*-methoxycinnamaldehyde may be attributed to the *ortho*-effect. It is proposed that in the *ortho*-position the methoxy group may form an intermolecular H-bond to the NH of the isoxazolidine ring, as shown in figure 67. This could be advantageous in two ways, firstly it increases the nucleophilicity of the *N*-atom and secondly it positions the

isoxazolidine ring closer to the carbonyl group thereby facilitating, in a pseudo-intramolecular fashion, the formation of the iminium ion.

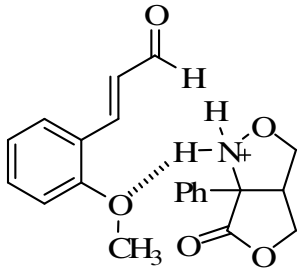


Figure 67. The proposed intermolecular H-bond between the methoxy group and the NH of the isoxazolidine ring.

Table 15. The Diels-Alder reaction between cyclopentadiene and substituted cinnamaldehydes catalysed by **110a•**(+)-10-CSA (10 mol%) for 6 hours at 25 ^{o}C in MeOH:H_2O (19:1).

Entry	Dienophile	% Conversion	% Yield	*endo:exo*
1	*o*-nitrocinnamaldehdye	61	52	55:45
2	*p*-nitrocinnamaldehdye	88	86	40:60
3	*o*-methoxycinnamaldehyde	96	83	40:60
4	*p*-methoxycinnamaldehyde	26	16	38:62

3.2.3.ii.a Lactone fused isoxazolidines; framework A (R= furyl and thienyl)

Six lactone fused isoxazolidines were designed as potential organocatalysts for study in this research although, as outlined in the preceding chapter, only three were successfully synthesised. The difference between the three frameworks lies in the nature of the aryl group at the bridgehead position. With **110a**, **110b** and **110c** bearing phenyl, furyl and thienyl aromatic groups respectively. This R group has the potential to block one face during iminium ion formation and therefore it was hypothesised that if enantiopure samples were available this group may have a role in influencing the stereoselectivity as well as the yield of the Diels-Alder reaction. The results of the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene under the influence of these three substituted isoxazolidine lactones are summarised in table 16.

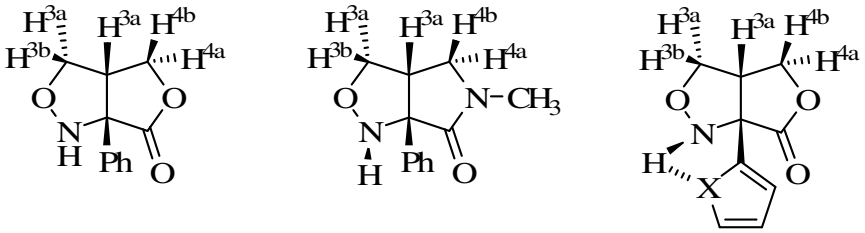
Table 16. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O (19:1), at 25 ^oC for 6 hours.

Entry	Catalyst•(+)-10-CSA (10 mol%)	% Conversion	% Yield	*endo:exo*
1	**110a** (R = Ph)	93	86	38:62
2	**110b** (R = 2-furyl)	40	35	43:57
3	**110c** (R = 2-thienyl)	62	60	43:57

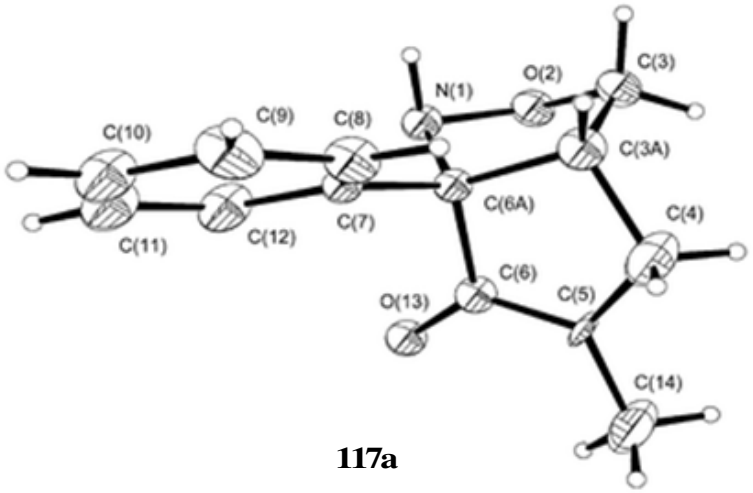
The 2-furyl substituted isoxazolidinium salt, **110b**•(+)-10-CSA, was a less effective catalyst than its phenyl counterpart and the cycloadducts were obtained in just 35% yield, however, the diastereoselectivity was still marginally in favour of the *exo* adduct, entries 1 and 2. The 2-thienyl substituted isoxazolidinium salt, **110c**•(+)-10-CSA, was more effective than its furyl analogue in catalysis of the reaction and the products were obtained in a modest 60% yield with the same preference for the *exo* adduct.

The differences in the yield may be attributed to the orientation of the R group in relation to the *N*-atom of the isoxazolidine ring. It has been demonstrated that the positioning of the lone pair of electrons of the *N*-atom away from structural impediments improves efficiency for iminium ion formation.[75]

NOEDS experiments conducted on **110a** confirmed the expected *cis* fusion at the ring junction with irradiation of H^{3a} causing a 4.3% enhancement on the aromatic protons. The same relative stereochemical orientation would be expected for the furyl and thienyl substituted analogues.[168] A crystal structure obtained for the related lactam-fused isoxazolidine **117a** indicated the positioning of the *NH*-hydrogen of the isoxazolidine *cis* to both H^{3a} and the phenyl substituent, again it is assumed that lactone isoxazolidines **110a-c** would present with the same orientation, figure 68.[153] In this orientation intramolecular H-bonding between the heteroatom on the aryl group (furyl or thienyl) and the isoxazolidine NH is possible and the resulting "tetracycle" structure may impede the rate of iminium ion formation thus lowering the catalytic activity of these molecules, figure 68. The lower catalytic activity of the 2-furyl substituted bicycle, **110b**, compared to the 2-thienyl analogue, **110c**, may be attributed to the greater electronegativity of the *O*-atom when compared to the *S*-atom. Due to its greater electronegativity the *O*-atom will form a stronger H-bond than the *S*-atom and the resulting "tetracycle" may be tighter and more effective at hindering the formation of the iminium ion.



110a **117a** **110b** X = O
c X = S



117a

Figure 68. A crystal structure obtained for the related lactam-fused isoxazolidine **117a** and proposed H-bonding in the furyl and thienyl substituted lactone-fused isoxazolidines.

3.2.3.ii.b Lactam fused isoxazolidines; framework B (R = phenyl, furyl and thienyl)

The isoxazolidine fused bicycles were synthesised with the catalytic role of the isoxazolidine ring in mind, however, the fused ring may also play an important role in the reactivity and stereoselectivity of the catalysed reactions. In order to test the role of the fused ring a second class of bicyclic isoxazolidines with a fused lactam ring was synthesised. The lactam ring selected possesses an *N*-methyl group.

The lactam fused salt, **117a**•(+)-10-CSA, displayed a similar level of catalytic activity in promotion of the Diels-Alder reaction between cyclopentadiene and cinnamaldehyde to that observed with the lactone fused analogue **110a**•(+)-10-CSA (88% *v.s.* 86%), table 17. In each case the Diels-Alder products were obtained with a preference for formation of the *exo*-adduct.

The 2-furyl and 2-thienyl lactam salts, **117b**•(+)-10-CSA and **117c**•(+)-10-CSA, had similar catalytic activity to their lactone analogues and the Diels-Alder products were

obtained in ≃50% yield. As observed for the lactone-fused series, both heteroaromatic substituted molecules were less effective catalysts than their phenyl bearing parent.

Table 17. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O (19:1) for 6 hours at 25 ^oC with a range of catalysts.

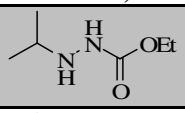
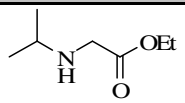
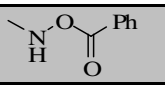
Entry	Catalyst•(+)-10-CSA (10 mol%)	% Conversion	% Yield	*endo:exo*
1	**110a** (R = Ph)	93	86	38:62
2	**117a** (R = Ph)	95	86	35:65
3	**117b** (R = 2-furyl)	53	48	39:61
4	**117c** (R = 2-thienyl)	49	46	41:49

3.2.3.ii.c Pyrrolidine fused isoxazolidines; framework C (R = methyl and phenyl)

During the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by **110a**•(+)-10-CSA it was noted that with anhydrous MeOH as reaction solvent a slightly superior product yield was observed when compared to the reaction carried out in MeOH:H_2O (19:1), table 13 entries 1 and 2. This finding was unexpected as literature precedent suggests that in the majority of cases the introduction of H_2O to the reaction solvent is accompanied by an increase in the reaction yield and selectivity.[72,78]

In a deviation from the norm an increase in the yield of Diels-Alder cycloaddition products has also been noted for catalysts bearing a β-carbonyl group, as summarised in table 18.[78] The catalysts employed in this study were used as HCl salts, all carried a β-carbonyl group and in each case an increase in the catalytic activity was observed in anhydrous MeOH with respect to aqueous MeOH. Comparable *exo/endo* selectivities were also observed.

Table 18. The Diels-Alder reaction between cinnamaldehyde and cyclopentadiene at room temperature for 6 hours in wet or dry MeOH.[78]

Entry	Catalyst•HCl (10 mol%)	Solvent	% Yield	*endo:exo*
1		MeOH:H_2O 19:1	74	34:66
2		MeOH	97	33:67
3		MeOH:H_2O 19:1	3	34:66
4		MeOH	5	35:65
5		MeOH:H_2O 19:1	13	34:66
6		MeOH	28	35:65

Against this background it was deemed interesting to explore the catalytic activity of **110•**CSA and **117•**CSA in both anhydrous and aqueous MeOH and the results are summarised in table 19. In aqueous MeOH, in the presence of **110a•**(+)-10-CSA, the reaction proceeded to 86% yield after 6 hours at 25 ^{o}C, however in the total absence of H_2O the products were delivered in approximately the same yield, entries 1 and 2. As after 6 hours, in both cases, the reaction had gone so far toward completion it was difficult to draw any conclusion as to whether the reaction proceeded better or worse in the absence of H_2O. Since it was already established that the reaction was incomplete after 4 hours, table 11 entry 4, the reactions were re-examined after this time period. In both cases an increase in the catalytic activity was observed in the absence of H_2O, entries 3 and 4.

The same experiments were repeated with the furan and thiophene bearing isoxazolidinium salts **110b•**(+)-10-CSA and **110c•**(+)-10-CSA. The reduced activity of these salts make them ideal to either confirm or negate any role for the β'-carbonyl group in the catalytic cycle. Again, in both cases the yield of the Diels-Alder products increased in the absence of H_2O, confirming the results obtained with **110a•**(+)-10-CSA, entries 5-8.

The reaction catalysed by the lactam fused isoxazolidine **117a•**(+)-10-CSA salt reached completion after 6 hours in both anhydrous MeOH and in aqueous MeOH thus no comment can be made regarding the role of the solvent and the β'-carbonyl group on the activity of the catalyst.

Table 19: Diels-Alder reaction between cinnamaldehyde and cyclopentadiene for 6 hours at 25 ^{o}C in anhydrous or aqueous MeOH.

Entry	Catalyst•(+)-10-CSA (10 mol%)	Solvent	% Conversion	% Yield	*endo:exo*
1	**110a**	MeOH:H_2O 19:1	93	86	38:62
2	**110a**	Anh. MeOH	92	88	39:61
3	**110a**[a]	MeOH:H_2O 19:1	84	75	36:64
4	**110a**[a]	Anh. MeOH	91	82	36:64
5	**110b**	MeOH:H_2O 19:1	40	35	43:57
6	**110b**	MeOH	52	47	45:55
7	**110c**	MeOH:H_2O 19:1	62	60	43:57
8	**110c**	MeOH	91	86	41:59
9	**117a**	MeOH:H_2O 19:1	95	86	35:63
10	**117a**	Anh. MeOH	96	85	34:66

[a] Reaction was stopped after 4 hours.

In an attempt to further establish if there was a role for the β'-carbonyl functionality in the catalytic cycle pyrrolidine fused isoxazolidines **122a&b**, framework C, were prepared and their activity explored. The pyrrolidine ring lacks the β'-carbonyl which is present in both the lactone and lactam fused bicycles and thus it would serve to provide information on the role of the solvent and/or any role for the second fused heterocycle ring.

Two pyrrolidine fused isoxazolidines were synthesised, the first possessed an *N*-methyl substituent, **122a,** while the other bore an *N*-phenyl substituent, **122b**. Both were explored as organocatalysts for the Diels-Alder reaction between cyclopentadiene and cinnamaldehyde. In both aqueous and anhydrous MeOH **122a**•(+)-10-CSA failed to promote the Diels-Alder reaction, table 20 entries 1 and 2. This was an unexpected result as **122a** can be considered to share the required features of an organocatalyst that make **110** so active - a cyclic 2^{o} amine bearing an α-heteroatom (the isoxazolidine ring). Upon further consideration of the structure of the bicyclic framework and with cognizance of the calculated pK_a values (ACD labs^{TM}) for the isoxazolidine ring at 5.49 and of the *N*-methyl pyrrolidine ring at 10.55 we considered salt formation had most likely occurred at the pyrrolidine nitrogen rather than the isoxazolidine nitrogen and thus no catalytic activity was expected as the free isoxazolidine is not an efficient catalyst. Accordingly, a second equivalent of (+)-10-CSA was added to **122a** in an attempt to form an *N,N'-bis*-salt. Repeating the Diels-Alder reaction in the presence of **122a**•2(+)-10-CSA in MeOH:H_2O (19:1) lead to a huge improvement in the yield of

cycloaddition products to 65%. When the same reaction was conducted in anhydrous MeOH products formed in just 52% yield, entries 3 and 4. The observed decrease in the yield in the absence of water is in stark contrast to the increase observed for reactions catalysed by the lactone and lactam fused isoxazolidinium salts. Taken together these observations point to a role for the fused lactone/lactam ring in the catalytic activity of **110•**CSA and **117•**CSA.

The products of the Diels-Alder reaction promoted by the *mono*-CSA salt of the *N*-phenyl substituted pyrrolidine, **122b•**(+)-10-CSA, were obtained in 64% yield following reaction in aqueous MeOH. A significant decrease in yield to 31% was observed in anhydrous MeOH, entries 5 and 6. The *bis*-salt of **122b** was also synthesised, for comparison purposes. The ability of **122b•**2(+)-10-CSA to promote the Diels-Alder reaction was essentially the same as the *mono*-salt in both MeOH:H_2O (19:1) (62%) and in anhydrous MeOH (43%). Taken together with the results summarised in table 19 these results support a role for a β'-carbonyl in iminium ion formation with **110•**CSA and **117•**CSA salts.

Thus, in summary catalysts bearing a β'-carbonyl group function best in anhydrous conditions whilst those devoid of this functionality function best in aqueous alcoholic solvent.

Table 20. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene at 25 ^oC for 6 hours in anhydrous or aqueous MeOH.

Entry	Catalyst•(+)-10-CSA (10 mol%)	Solvent	% Conversion	% Yield	*endo:exo*
1	**122a**	MeOH:H_2O 19:1	1	-	-
2	**122a**	Anh. MeOH	1	-	-
3	**122a**[a]	MeOH:H_2O 19:1	74	65	38:62
4	**122a**[a]	Anh. MeOH	58	52	42:58
5	**122b**	MeOH:H_2O 19:1	70	64	38:62
6	**122b**	Anh. MeOH	35	31	30:70
7	**122b**[a]	MeOH:H_2O 19:1	65	62	39:61
8	**122b**[a]	Anh. MeOH	46	43	44:56

[a] Employed as a *bis*-salt.

3.2.3.iii The role of water and iminium ion formation

3.2.3.iii.a The role of water

The Diels-Alder reaction is often quoted as an example of a reaction that is little influenced by solvent. However, this is not fully justified since H_2O can have a large effect on the rate of the reaction.[194,195] It is now known that the acceleration of the Diels-Alder reaction by aqueous media is a general phenomenon which can result in up to 12,800 fold accelerations.[196,197] Two effects are believed to contribute to this observed rate acceleration. The first effect is an enforced hydrophobic interaction where the hydrophobic diene and dienophile are forced into close proximity. The term enforced is used to distinguish the hydrophobic bonding of the diene and the dienophile during the activation process for the cycloaddition from hydrophobic interactions that lead to complexes of different geometry and complexes in which the components may be separated by H_2O molecules. The second effect involves H-bonding interactions where water forms H-bonds to the activating group of the dienophile which strengthens the electron-withdrawing capacity and thereby decreases the HOMO-LUMO gap between the diene and dienophile. The relative extent to which these two factors influence the rate of the Diels-Alder reaction depends on the particular reaction under study.

The selectivity of the Diels-Alder reaction can also be affected by H_2O as solvent choice. For example the reaction between 3-buten-2-one and cyclopentadiene in a range of aqueous solvents and in H_2O shows the *endo/exo* ratio to be greatly altered in preference for the *endo* adduct as the H_2O component of the solvent increases (MeOH/H_2O *endo:exo* 10:1 and H_2O *endo:exo* 21:1).[197,198]

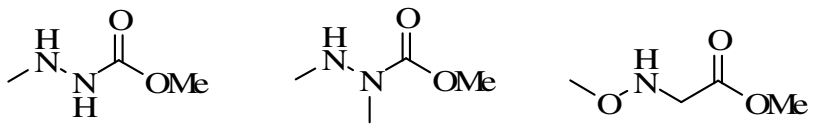
3.2.3.iii.b Iminium ion formation

One important factor that determines the efficiency of amine catalysts in asymmetric enantioselective reactions is the reversible formation of iminium ions between the secondary amine and α,β-unsaturated carbonyl compounds.[185] Hydrolysis to the products of the reaction generally occurs smoothly and does not have any influence on the new chiral centre generated in the previous step of the reaction.[185] A kinetic study proposed that the initial iminium ion formation step and the C-C bond forming steps are the key influences on the overall rate of the reaction.[75] Computational studies on iminium ion formation between dimethylhydrazine•HCl and acrolein suggested the

reaction profile outlined in figure 69.[199] In TS1 the amine catalyst has transferred a proton to the chloride anion and the transferring proton is H-bonded to the free nitrogen of the amine and also to the carbonyl oxygen of the α,β-unsaturated aldehyde substituent. A metastable intermediate separates TS1 and TS2. In this state a H_2O molecule bridges the HCl and the carbonyl with proton transfer from HCl to the carbonyl oxygen taking place at TS2 leading to formation of the aminol. The aminol structure contains the newly formed N-C bond and the proton has transferred from the amine to the carbonyl oxygen atom. The final TS involves the elimination of H_2O from the aminol intermediate to form the iminium ion.

It is in the intermediate between TS1 and TS2 that H_2O performs its role by bridging the hydrogen chloride and the carbonyl group. Thus, the H_2O can be thought to act as a "proton shuttle" between HCl and the carbonyl oxygen. The energy difference between the metastable intermediate and TS2 was calculated at just 10 kJ mol^{-1} and this is the only step in iminium ion formation that appears to require the presence of a H_2O molecule.

Computational studies on catalysts including **127**-**129** containing a β-carbonyl group were also carried out but the role of H_2O in their iminium ion formation was not discussed.[199]



127 **128** **129**

Figure 70. Computational studies on catalysts **127-129** containing a β-carbonyl group were also carried out.

We have shown that in our bicyclic *NH*-isoxazolidines, **110**, **117** and **122**, those catalysts bearing a β'-carbonyl group, **110** and **117**, function best in anhydrous conditions whilst those devoid of this functionality, **122**, function best in aqueous MeOH. In order to better understand the role of the β'-carbonyl in iminium ion formation the predicted structures for the metastable intermediate were extrapolated and the structures shown in figure 71a-e were proposed for the bicyclic *NH*-isoxazolidines in the presence and absence of H_2O.

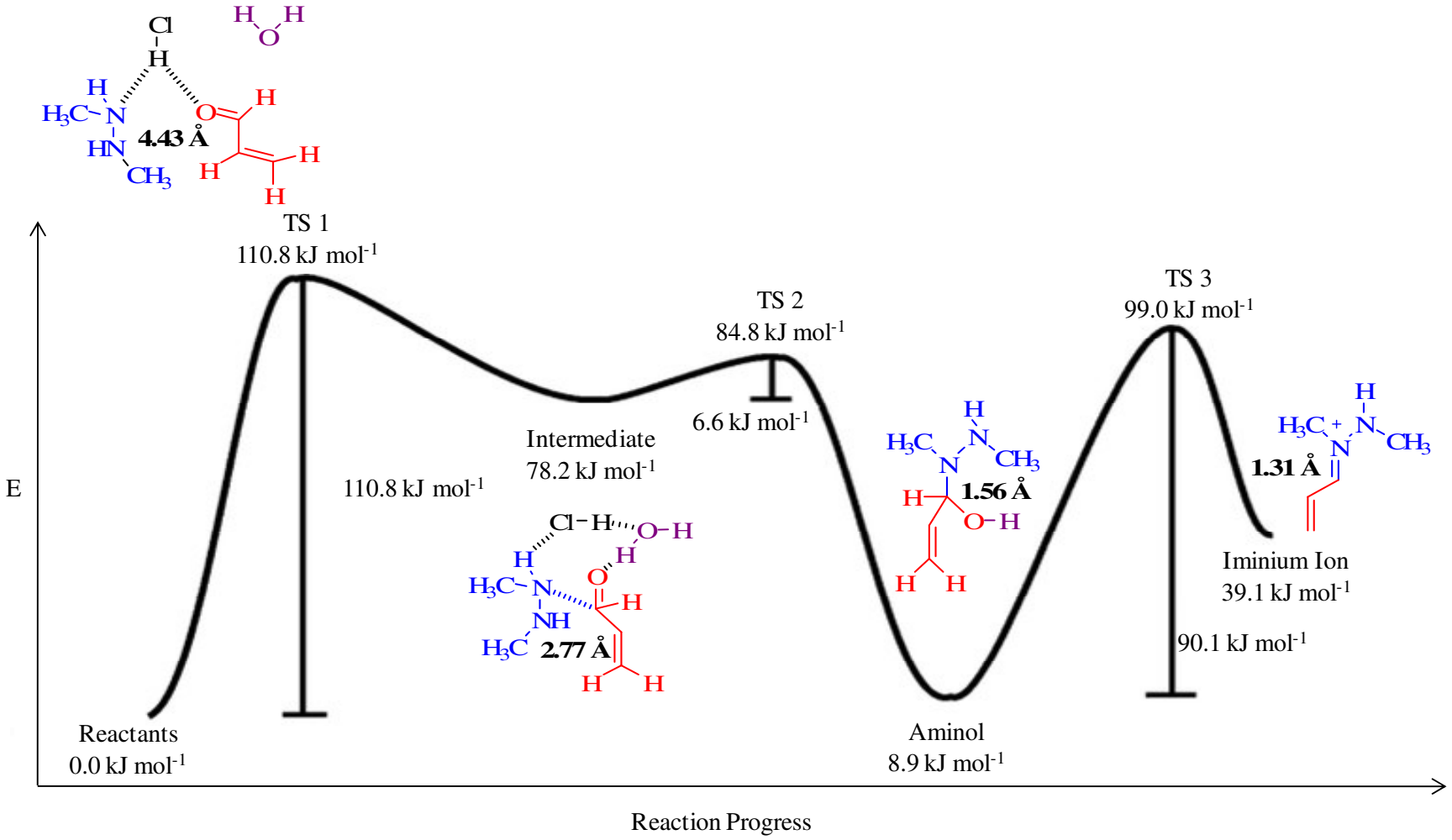


Figure 69. Reaction profile of the reaction between dimethylhydrazine•HCl and acrolein.

It is proposed that the metastable intermediate for **110a**•(+)-10-CSA in anhydrous conditions would involve (+)-10-CSA bridging between the β'-carbonyl of **110a** and the carbonyl group of the dienophile allowing the transfer of the proton. In the absence of the H_2O molecule tighter intramolecular H-bonds would be expected and the location of the lone pair of electrons of the *N*-atom on the same face as the β'-carbonyl facilitate the formation of the iminium ion, figure 71a. The 2-furyl and 2-thienyl analogues, **110b** and **110c**, are postulated to have similar H-bonding in the absence of H_2O, figure 71c. In the presence of H_2O, using a structure similar to that in the literature, the H-bonding outlined in figure 71d is predicted. The metastable intermediate of **122b**•(+)-10-CSA, which lacks a β'-carbonyl, in H_2O would be similar to that in the literature, figure 71e.

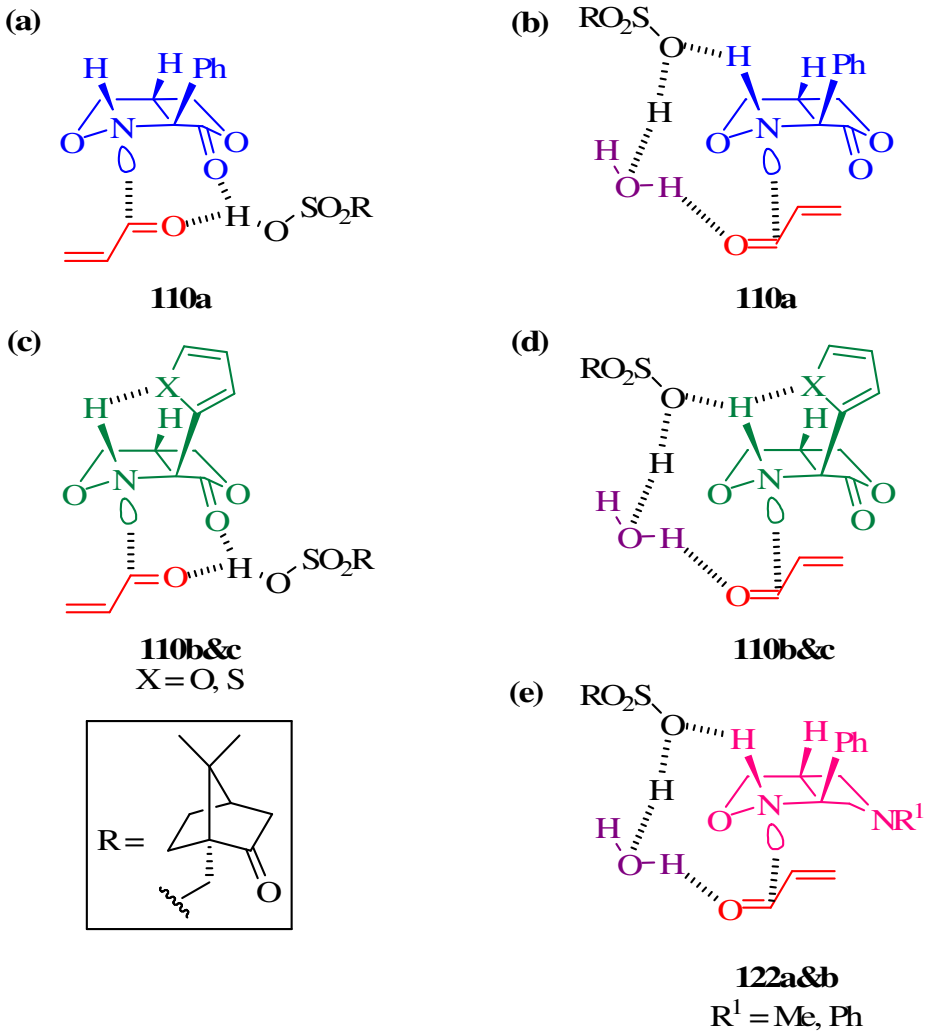


Figure 71. Proposed metastable intermediates formed between cinnamaldehyde, (+)-10-CSA and (a) 110a in the absence of H_2O, (b) 110a in the presence of H_2O, (c) 110b&c in anhydrous conditions, (d) 110b&c in aqueous conditions and (e) 112a&b in aqueous conditions.

3.2.3.iii.c ^{1}H NMR studies on iminium ion formation

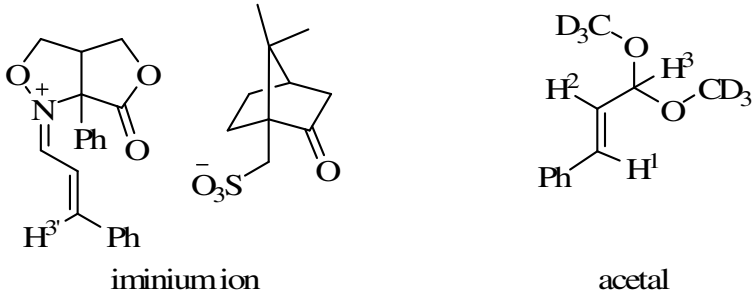
In an attempt to confirm the existence of an intermediate iminium ion in the reaction between cinnamaldehyde and cyclopentadiene catalysed by the isoxazolidine **110a•**CSA the reaction was followed by ^{1}H NMR spectroscopy. Measurements were made in CD_3OD and in CD_3OD:D_2O (19:1). Thus, a solution of **110a•**(+)-10-CSA and cinnamaldehyde in a 1:1 ratio in either CD_3OD or CD_3OD/D_2O was monitored by ^{1}H NMR spectroscopy with spectra recorded every few minutes. The formation of the dimethylacetal of cinnamaldehyde was noted alongside iminium ion formation.

It is noteworthy that after just four minutes at room temperature in CD_3OD the iminium ion and the dimethylacetal of cinnamaldehyde are present in a 1:2 ratio, with the diagnostic $^+$N=C<u>H</u> peak of the iminium ion observed at 8.10 ppm and the dimethylacetal C<u>H</u>=CHPh peak visible at 6.20 ppm. The absence of the diagnostic aldehyde peak (C<u>H</u>O, 9.70 ppm) of the cinnamaldehyde suggests complete conversion to the dimethylacetal and iminium ion, figure 72. Analysis was carried out over sixty minutes with spectra recorded every four minutes and no change in the ratio was observed. As the dimethylacetal is formed from the reaction of cinnamaldehyde and CD_3OD no methoxy peaks are visible in the ^{1}H NMR spectrum. The ^{1}H^{1}H COSY, shown in figure 73, highlights the proton coupling of the iminium ion and of the dimethylacetal. A search of the literature gives the assignment of the *E*-isomer, (CD_3CN 8.64 (1H, *J* = 10.6 Hz, $H^{1'}$), 8.12 (1H, *J* = 15.2 Hz, $H^{3'}$), 7.32 (1H, dd *J* = 10.6 & 15.2 Hz, $H^{2'}$)), whilst data for the *Z*-isomer could not be obtained and as a result the geometry of the iminium ion formed could not be unambiguously assigned.[200-202]

The ratio, in CD_3OD/D_2O, of the iminium ion to the dimethylacetal showed sensitivity to temperature, figure 74. At -30 ^{o}C the iminium ion was favoured over the dimethylacetal with an observed 5:2 ratio; as the solution was heated to +25 ^{o}C the amount of acetal gradually decreased to a final ratio of 3:1. Upon further heating to +40 ^{o}C the equilibrium continued to shift towards the iminium ion (4:1). Thus, the equilibrium at both low and high temperatures favours the iminium ion. The presence of this equilibrium between the iminium ion and dimethylacetal is consistent with the high yield (96%) of cycloaddition products, thus, as the iminium ion is consumed by cycloaddition to cyclopentadiene, the equilibrium is re-established between the dimethylacetal and the iminium ion.

From the data collected it can be concluded that the formation of the dimethylacetal and the iminium ion of **110a•**(+)-10-CSA and cinnamaldehyde is fastest, and reaches

completion almost immediately in anhydrous MeOH. When water is present an equilibrium is established between the iminium ion, the dimethylacetal and cinnamaldehyde and the position of the equilibrium is significantly influenced by temperature.



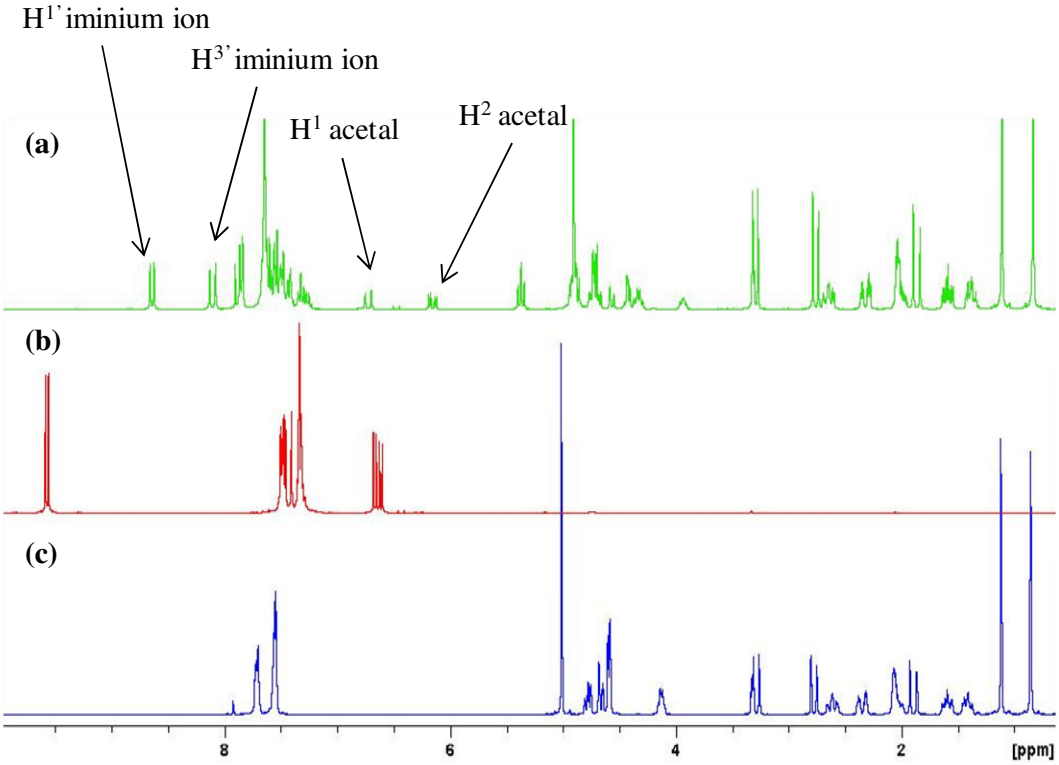


Figure 72. ^{1}H NMR spectra in CD_3OD of **(a)** the iminium ion formed between **110a•**(+)-10-CSA and cinnamaldehyde after 4 minutes at 25 °C **(b)** *trans*-cinnamaldehyde and **(c) 110a•**(+)-10-CSA.

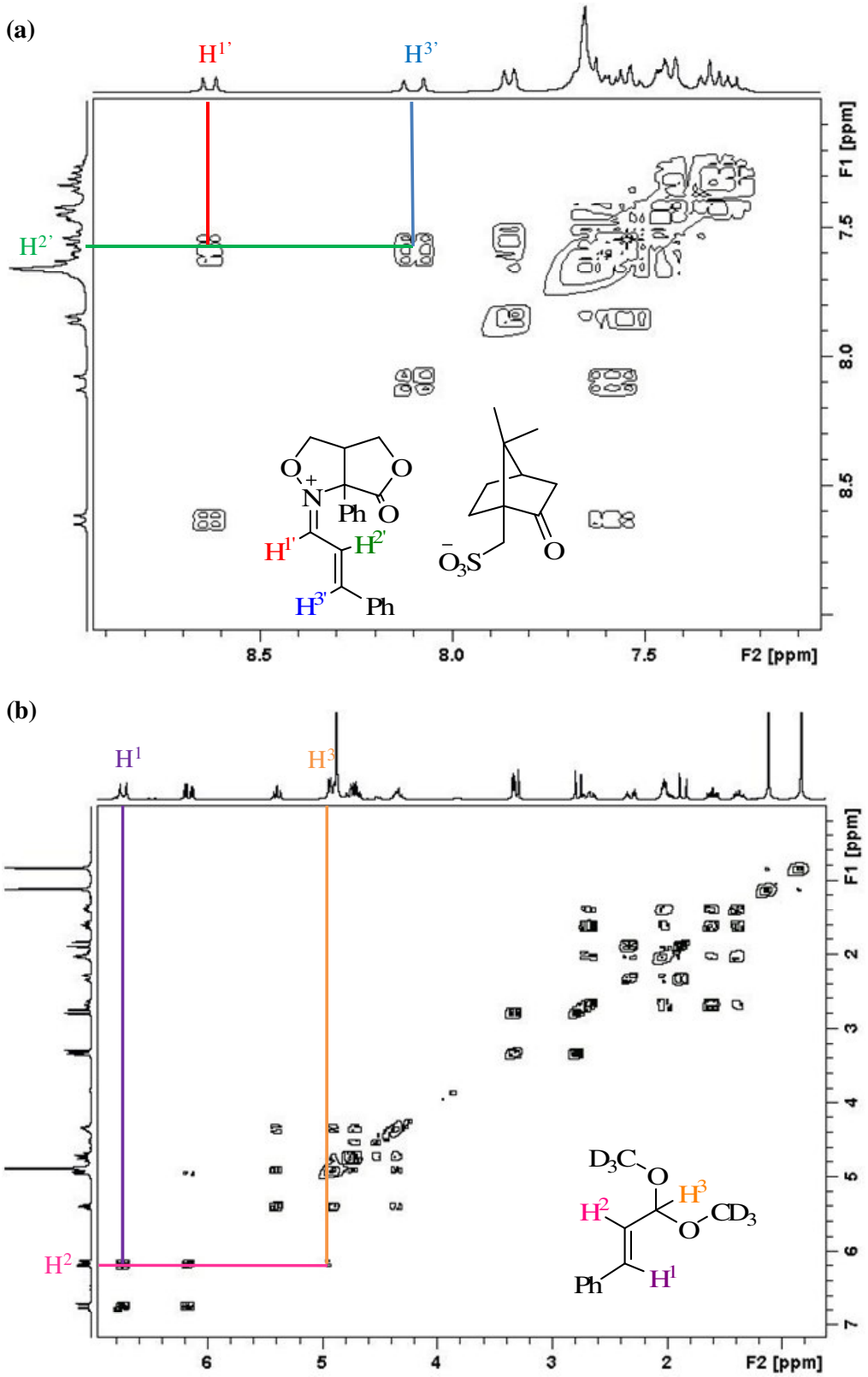


Figure 73. H-H COSY highlighting **(a)** coupling in the iminium ion and **(b)** in the acetal.

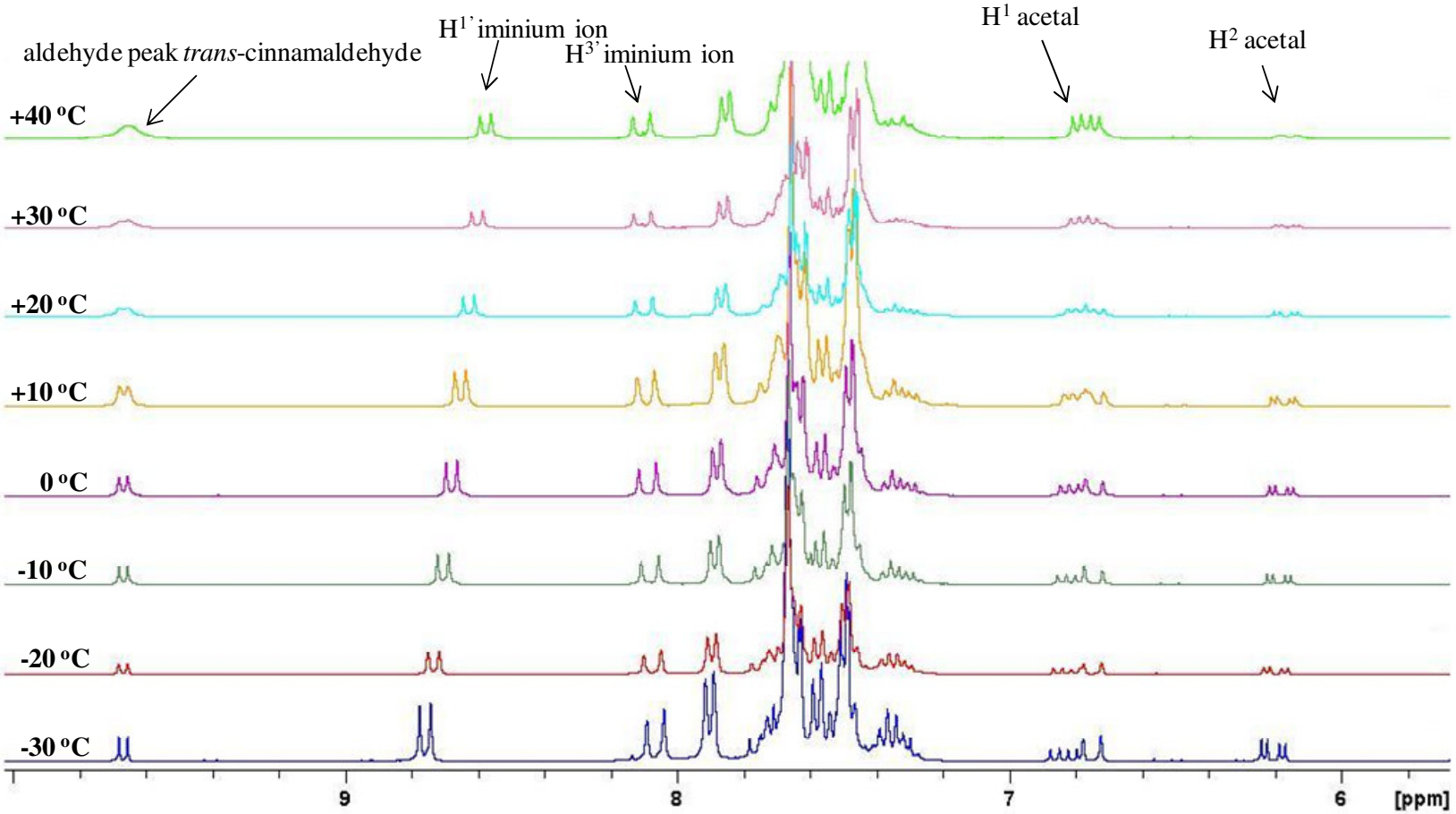


Figure 74. V.T. ^{1}H NMR spectra of the iminium ion and dimethylacetal formed between **110a•**(+)-10-CSA and *trans*-cinnamaldehyde in the range of -30 ^{o}C to +40 ^{o}C, recorded in CD_3OD:D_2O (19:1).

3.2.4 Diels-Alder Reaction in the Presence of Resolved Salts

The Diels-Alder reaction between cinnamaldehyde and cyclopentadiene, promoted by the lactone and lactam fused isoxazolidines, **110a** and **117a**, have furnished cycloaddition products in yields comparable, and in some cases superior, to those reported in the literature. In all reactions discussed to date the catalysts were formed from racemic isoxazolidines and it was deemed prudent to explore their potential for enantioselective organocatalytic activity. To this end, as discussed in chapter 2, the racemic lactone fused isoxazolidine **110a** was subjected to classical resolution. Thus individual samples of each of the enantiomers of **110a** were obtained following base treatment of each of the diastereoisomeric salts ((+)-**110a**•(+)-10-CSA and (-)-**110a**•(-)-10-CSA). It was anticipated that the Diels-Alder reaction would proceed with some degree of enantioselectivity in the presence of an enantiomerically pure isoxazolidinium salt.

The diastereoselectivity of a catalysed reaction is dependent on the relationship of the components of the catalytic diastereoisomeric salt with the salts referred to as matched and mismatched pairs.[203] With matched pairs the stereochemical biases of the catalyst components are alike and both prefer the formation of the same stereoisomer, mismatched pairs however afford low diastereoselectivity.

Enantioselectivities of the Diels-Alder products were determined by G.C. analysis, where separation was achieved on a SUPLECO β-Dex column (30 m x 0.25 mm x 0.25 μm) and retention times for the *exo* isomers were 10.31 and 10.52 minutes, the *endo* isomer eluted at 10.79 and 10.96 minutes, G.C. traces are shown in figure 75.

A control Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O (19:1) was performed in the presence of the racemic (±)-**110a**•(±)-10-CSA salt. After 6 hours at 25 ^{o}C the cycloaddition products were obtained in 76% yield and slight enhancements in the selectivities were observed with the *endo* and *exo* adducts obtained with 6% and 3% e.e. respectively.

The Diels-Alder reaction promoted by the (+)-10-CSA salt of racemic **110a** in MeOH:H_2O (19:1) also proceeded with little enantioselectivity and the *exo* and *endo* additives were obtained in 2% and 0.3% e.e. respectively. Changing the co-factor to (-)-10-CSA each adduct was found with ≃5% e.e. The low e.e. values suggest the optically active counterion was unable to confer selectivity on the reaction, table 21 entries 2 and 3.

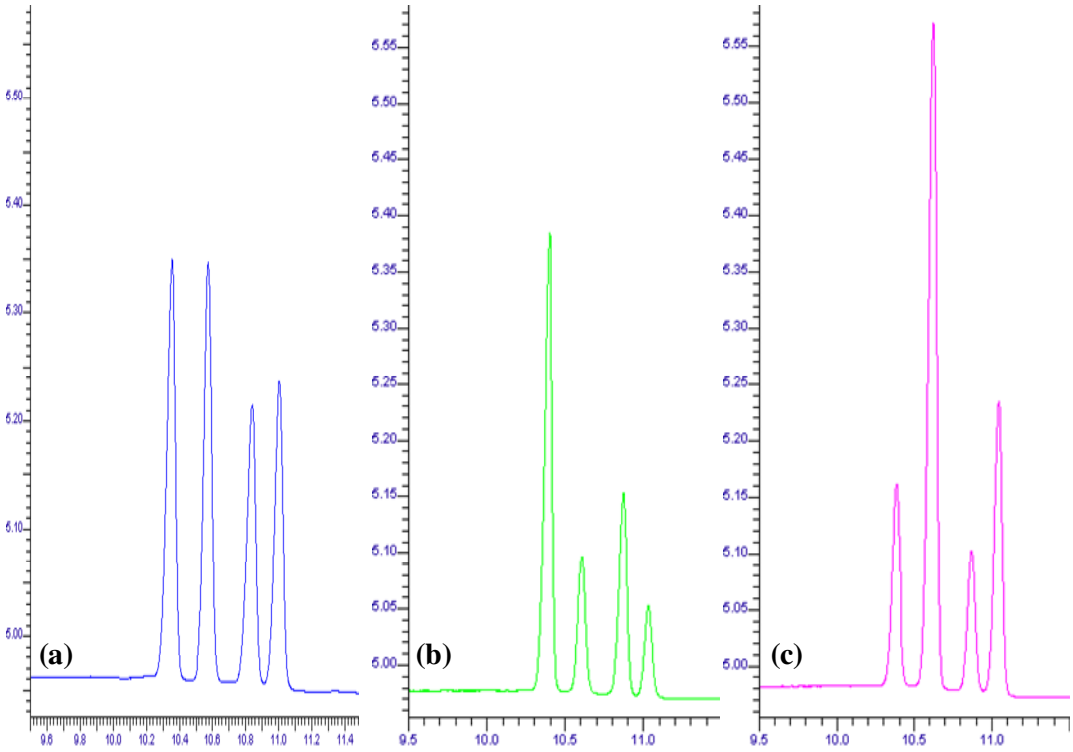


Figure 75. G.C. trace for the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by **(a)** (±)-**110a**•(+)-10-CSA, **(b)** (+)-**110a**•(+)-10-CSA and **(c)** (-)-**110a**•(+)-10-CSA in MeOH:H_2O (19:1).

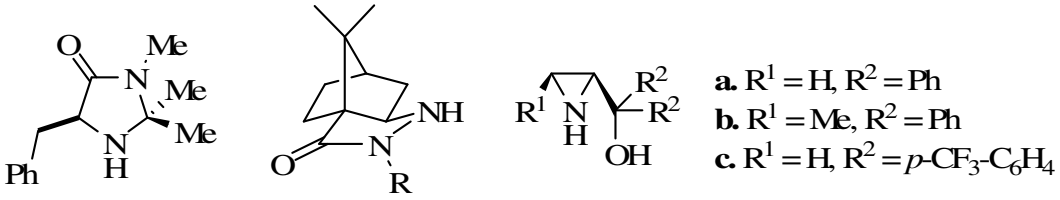
Table 21. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O 19:1 at 25 ^oC for 6 hours catalysed by a range of resolved salts.

Entry	Catalyst (10 mol%)	% Conversion	% Yield	*endo:exo*	*endo* e.e.[a]	*exo* e.e.[a]
1	(±)-**110a**•(±)-10-CSA	86	76	38:62	6	3
2	(±)-**110a**•(+)-10-CSA	93	86	38:62	0.3	2
3	(±)-**110a**•(-)-10-CSA	84	82	38:62	5	5
4	(+)-**110a**•(+)-10-CSA	92	84	37:63	41	58
5	(+)-**110a**•(-)-10-CSA	90	83	37:63	40	58
6	(-)-**110a**•(+)-10-CSA	82	74	38:62	37	42
7	(-)-**110a**•(-)-10-CSA	83	69	39:61	37	54

[a] For opposite enantiomers of **110a** the stereochemistry of the e.e.'s is reversed.

Salts formed from the (+)-enantiomer of **110a** with either (+)- or (-)-10-CSA were found to promote the reaction with enantioselectivities that were approximately equal. In each case moderate selectivity was observed; 41% e.e. for the *endo* adduct and 58% e.e. for the *exo* adduct. Similar results were obtained when (-)-**110a** was employed as catalyst together with either (+)- or (-)-10-CSA, entries 6 and 7. For these combinations enantioselectivities of the resultant products was somewhat lower than that observed with the corresponding (+)-**110a** salts and the *exo* and *endo* adducts were obtained with 42% and 37% e.e. respectively.

The enantioselectivies observed are comparable to those reported in the literature for similar reactions. Thus, the hydrazine **35** with CSA as a co-catalyst, promoted the reaction of cinnamaldehyde with cyclopentadiene and the *endo* isomer of the cycloaddition product was observed in 57% e.e. The e.e. of the *exo* adduct was not quoted.[79] Neither was the aziridinium salt, **130**•HCl, a superior enantioselective catalyst under its influence the *exo* and *endo* adducts were obtained with a 24-51% e.e.[190] The range in the enantioselectivities is attributable to the influence of the R groups on the catalyst. With the imidazolidinone **28**•HCl 93% e.e. was observed for both *exo* and *endo* adducts.[72]



28 **35** **130**

Figure 76. Successful iminium ion catalysts for the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene.

3.2.4.i.a Temperature

The influence of temperature in the control of enantioselectivity of a reaction is well acknowledged. Generally, lowering the temperature of a reaction results in enhanced enantioselectivities but often at the cost of increased reaction time. Thus, in search of improved selectivity the Diels Alder reaction between cinnamaldehyde and cyclopentadiene in the presence of enantiopure **110a** with either (+)- or (-)-10-CSA as

the co-factor was repeated at 0 and -20 ^{o}C, results are summarised in table 22. It can be seen that lowering the reaction temperature to 0 ^{o}C results in a marginal improvement in enantioselectivities over those observed at 25 ^{o}C. At -20 ^{o}C a further small increase in enantioselectivity was observed. It is significant however that much longer reaction times are required to bring the reactions closer to completion at 0 ^{o}C. The further improvement in selectivity at -20 ^{o}C was accompanied by a sharp decrease in the conversion to products even after a 72 hour reaction time.

Table 22. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by **110a•**CSA diastereoisomeric salts in 10 mol% loading.

Entry	Catalyst (10 mol%)	Temp(^{o}C)	Time (h)	% Conversion	% Yield	*endo:exo*	*endo e.e.*	*exo e.e.*
1	**(±)-**110a**•(+)-10-CSA**	0	48	94	86	36:64	2	0.5
2	**(+)-**110a**•(+)-10-CSA**	0	48	96	82	36:64	42	59
3	**(+)-**110a**•(-)-10-CSA**	0	48	95	84	38:62	37	61
4	**(-)-**110a**•(+)-10-CSA**	0	48	90	79	37:63	41	55
5	**(-)-**110a**•(-)-10-CSA**	0	48	88	65	37:63	41	54
6	**(±)-**110a**•(+)-10-CSA**	-20	72	40	38	37:63	2.2	1.7
7	**(+)-**110a**•(+)-10-CSA**	-20	72	63	52	36:64	45	64
8	**(+)-**110a**•(-)-10-CSA**	-20	72	56	42	36:64	44	65
9	**(-)-**110a**•(+)-10-CSA**	-20	72	56	49	37:63	44	56
10	**(-)-**110a**•(-)-10-CSA**	-20	72	76	71	38:62	44	57

3.2.4.i.b Solvent

It is also widely known that the selectivity of a reaction can vary hugely depending on the choice of reaction solvent. With this in mind the test case reactions were repeated in a range of solvents which have already been reported to give high enantioselectivities for Diels-Alder reactions.[78,189,204]

With toluene as the reaction solvent the yield of Diels-Alder products was significantly lowered, table 23. The enantioselectivities also decreased in all cases. A wide range in the conversions and isolated yields was observed, this range was, at least in part, due to

issues with the solubility of the catalytic salts in toluene. None of the diastereoisomeric salts were observed to be fully soluble in toluene, however, upon addition of cinnamaldehyde, the iminium ion/salt mixture persisted. It was observed that whilst solubility generally improved the yields observed for the reaction mixtures reflected the degree of solubility in toluene. The loss in selectivity and yield indicated that toluene was not a suitable solvent for the catalysis of the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene by *NH*-isoxazolidines of general type **110a•**CSA.

Table 23. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in toluene at 25 ^{o}C for 6 hours.

Entry	Catalyst (10 mol%)	% Conversion	% Yield	*endo:exo*	*endo e.e.*	*exo e.e.*
1	(±)-**110a•**(+)-10-CSA	70	61	51:49	1.6	3
2	(±)-**110a•**(-)-10-CSA	57	55	51:49	4	4
3	(+)-**110a•**(+)-10-CSA	16	14	45:55	11	21
4	(+)-**110a•**(-)-10-CSA	28	19	46:54	3	31
5	(-)-**110a•**(+)-10-CSA	71	64	48:52	0.8	19
6	(-)-**110a•**(-)-10-CSA	18	12	43:57	8	16

In dioxane the chemical yields were also suppressed in comparison with those found from the reaction performed in aqueous MeOH. However, more significantly, in dioxane the products were obtained almost without any diastereoselectivity and the *exo* and *endo* adducts were isolated in a ≃1:1 ratio. A difference is also noted in the enantioselectivities and both the (+)-**110a•**CSA and (-)-**110a•**CSA salts yielded products with higher enantioselectivities for the *endo* adduct than for the *exo* adduct. This is a reversal of the result obtained in aqueous MeOH and in toluene, table 24. For the products formed under influence of the (+)- and (-)-10-CSA salts of **110a** the e.e. of the *exo* adducts were approximately 4%, whilst the e.e. of the *endo* adducts was much greater at ≃30%. Salts produced from (-)-**110a** and either (+)- or (-)-10-CSA were much less effective at inducing enantioselectivity into the reaction.

When the reactions were performed in Et_2O the cycloadduct yields were poor, again this is likely due to problems of solubility of the catalytic system. Diastereoselectivities

were also reduced in comparison to the results found in aqueous MeOH, table 25. The enantioselectivities were low for the *endo* product and modest for the *exo* product. For the catalytic system comprising of the salts based on (+)-**110a** the highest e.e. was observed with the (+)-**110a**•(-)-10-CSA combination, yielding, in this case, the *exo* cycloadduct with an e.e. of 35%.

Table 24. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in dioxane at 25 ^{o}C for 6 hours.

Entry	Catalyst	% Conversion	% Yield	*endo:exo*	*endo e.e.*	*exo e.e.*
1	(±)-**110a**•(+)-10-CSA	45	32	50:50	3	6
2	(±)-**110a**•(-)-10-CSA	45	33	49:51	5	6
3	(+)-**110a**•(+)-10-CSA	46	45	47:53	32	4
4	(+)-**110a**•(-)-10-CSA	48	30	49:51	30	0.4
5	(-)-**110a**•(+)-10-CSA	35	28	52:48	13	4
6	(-)-**110a**•(-)-10-CSA	33	27	51:49	13	5

Table 25. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in Et_2O at 25 ^{o}C for 6 hours.

Entry	Catalyst (10 mol%)	% Conversion	% Yield	*endo:exo*	*endo e.e.*	*exo e.e.*
1	(±)-**110a**•(+)-10-CSA	52	49	50:50	2	2.9
2	(±)-**110a**•(-)-10-CSA	57	56	48:52	1.9	4
3	(+)-**110a**•(+)-10-CSA	28	25	46:54	8	30
4	(+)-**110a**•(-)-10-CSA	41	36	47:53	4	35
5	(-)-**110a**•(+)-10-CSA	36	32	43:57	9	21
6	(-)-**110a**•(-)-10-CSA	34	29	41:59	12	18

The results obtained to this point in the promotion of the Diels-Alder reaction by the diastereoisomeric isoxazolidinium•CSA salts in a range of solvents clearly show the

greatest successes in aqueous MeOH with up to 83% isolated cycloadduct yield for the reaction catalysed by (+)-**110a**•(-)-10-CSA. The diastereoselectivities and the enantioselectivities were also highest in aqueous MeOH. The cycloaddition products from reactions catalysed by either (+)-**110a**•(+)-10-CSA or (+)-**110a**•(-)-10-CSA were obtained with reasonable enantioselectivities with the *endo* adduct obtained in 40% e.e. and the *exo*-adduct in 58% e.e. Lowering the temperature to -20 ^{o}C was accompanied by an improvement in enantioselectivity up to 45% e.e. for the *endo* adduct and 65% for the *exo*-adduct. However, to obtain similar yields of cycloaddition products at this temperature 72 hours of reaction time was required.

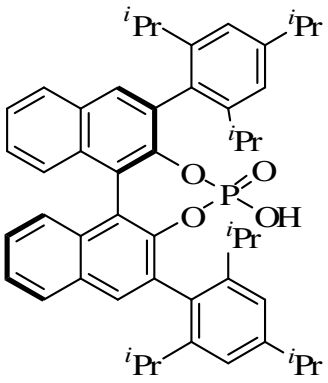
3.2.5 The Diels-Alder Reaction and Counterion Catalysis

All the catalysts tested on the Diels-Alder reaction so far selected CSA as the co-factor and in particular for reactions in MeOH/H_2O, where there was no issue with selective solubility of one of the diastereoisomeric catalytic systems over the other, a pattern emerges where the enantioselectivities of the reactions promoted by either (+)-**110a** or (-)-**110a** appear independent of the choice of (+)- or (-)-10-CSA as the co-factor. These observations further support the earlier indications that CSA is unable to play a significant role in the control of the enantioselectivity of the Diels-Alder reaction under study. As the enantioselectivity appears to be controlled by the isoxazolidinium core of the diastereoisomeric salt and the CSA appears to exert no influence over the enantioselectivity of the reaction the idea of matched and mismatched pairs does not apply to the **110a**•CSA diastereoisomeric salts.

However, with the concept of counterion catalysis being accepted it was deemed valuable to explore the ability of alternative optically active co-factors, in conjunction with either (+)- or (-)-**110a** as a catalytic system in place of CSA.

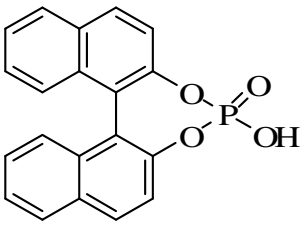
In iminium ion catalysis it is typical for the organocatalyst to comprise of a chiral organic component and an achiral counterion. The use of achiral organic components in conjunction with chiral counterions, termed counterion catalysis, has been discussed in section 1.4 and more recently the sterically hindered chiral phosphoric acid derivative TRIP, **65**, has been shown to introduce enantioselectivity into organocatalysed reactions where the organic component is achiral.[107,115,116] (*R*)-TRIP is commercially available and was purchased for this project, it is expensive at €249 for 100 mg and thus, prior to

testing its potential as a co-factor to the isoxazolidine family a cheaper analogue, **131**, was explored. Initially (±)-**131** was tested as co-factor alongside (±)-**110a** and the resulting Diels-Alder products were obtained in moderate yields and with diastereoselectivities similar to those observed with CSA. However, as both the catalyst and co-factor were racemic there was no opportunity to consider enantioselectivity. Disappointingly the catalytic system comprising either (+)- or (-)-**131** with (±)-**110a** failed to induce enantioselectivity into the Diels-Alder reaction, table 26.



$pK_a = 1.12$

65



$pK_a = 1.14$

131

Figure 77. (*R*)-TRIP and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate.

Table 26. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O (19:1) at 25 ^oC for 6 hours.

Entry	Catalyst (10 mol%)	% Conversion	% Yield	*endo:exo*	*endo* e.e.	*exo* e.e.
1	(±)-**110a**•(±)-**131**	65	53	38:62	0.4	1.8
2	(±)-**110a**•(+)-**131**	62	57	35:65	0.4	1.3
3	(±)-**110a**•(-)-**131**	50	42	39:61	0.5	1.9
4	(+)-**110a**•(+)-**131**	66	52	38:62	45	59
5	(+)-**110a**•(-)-**131**	56	47	39:61	39	58
6	(+)-**110a**•(±)-**131**	65	42	39:61	35	56
7	(-)-**110a**•(+)-**131**	31	27	39:61	37	54
8	(-)-**110a**•(-)-**131**	38	32	39:61	26	48

The Diels-Alder reaction was also performed in the presence of all four **110a•131** diastereoisomeric salts, entries 4-8. Moderate enantioselectivities were observed for all pairings. Upon comparison with the **110a•**CSA salts enantioselectivities were found to

be very similar suggesting optically pure **131** was not able to induce asymmetric counter ion catalysis in this reaction.

An attempt to improve the selectivity by repeating the reaction in toluene proved fruitless as no conversion to the products was observed. This was probably due to the very limited solubility of **131** in the solvent.

Despite the disappointing results with **131** it was decided to explore the catalytic activity of the (*R*)-TRIP salt of **110a**. Aqueous MeOH was the solvent of choice due to the insolubility of **131** in toluene. The isoxazolidine was used in both its racemic form as well as in optical pure (+)- or (-)-forms, results are summarised in table 27. After 6 hours reaction in MeOH:H_2O (19:1) under the influence of **110a•**(*R*)**-**TRIP the Diels-Alder reaction had progressed to a very limited extent, just 5-11%. Due to the low conversion no attempt was made to isolate the products. The enantioselectivities of the reaction were judged by GC analysis of the crude reaction products. Under the influence of the (*R*)-TRIP salt of racemic **110a** both the *exo* and *endo* cycloaddition products were found with just 9% e.e., entry 1. The low enantioselectivities indicate a limited role for (*R*)-TRIP in controlling the selectivity of the reaction. The Diels-Alder reaction promoted by (+)-**110a•**(*R*)-TRIP resulted in adducts with enantioselectivities slightly lower than those observed with (+)-10-CSA in MeOH:H_2O (19:1), table 21. In the presence of (-)-**110a•**(*R*)-TRIP the e.e. of the *endo* adduct was similar to that previously observed for (+)- or (-)-10-CSA salts of (-)-**110a**, however, the *exo* adducts were obtained with reduced selectivity.

Table 27. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O 19:1 at 25 ^{o}C for 6 hours.

Entry	Catalyst (10 mol%)	% Conversion	% Yield	*endo:exo*	*endo e.e.*	*exo e.e.*
1	(±)-**110a•**(*R*)-TRIP	11	-	45:55	9	9
2	(+)-**110a•**(*R*)-TRIP	5	-	32:68	25	51
3	(-)-**110a•**(*R*)-TRIP	6	-	45:55	34	22

When the results obtained with the chiral phosphoric acid derivatives **131** and (*R*)-TRIP are compared with their CSA analogues it seemed highly likely that the co-factor was not significantly influencing the enantioselectivity of the reaction. In order to test this hypothesis two final test reactions were performed employing (+)-**110a** as catalyst with

HCl or $HClO_4$ as achiral co-factors, results are summarised in table 28. In combination with (+)-**110a** the Diels-Alder products were obtained in high yields and with moderate enantioselectivities. Enantioselectivities were similar for the two salts, they also compared favourably with those obtained with the chiral counterions. The similarity in the enantioselectivies of the resultant cycloadducts confirms the hypothesis that the selectivity of the reaction between cinnamaldehyde and cyclopentadiene is controlled by the isoxazolidinium core of the two component system **110a•**HX and that the nature of the counterion has little or no influence on the selectivity of the reaction.

Table 28. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene in MeOH:H_2O (19:1) for 6 hours at 25 ^oC.

Entry	Catalyst	% Conversion	% Yield	*endo:exo*	*endo e.e.*	*exo e.e.*
1	(+)-**110a•**$HClO_4$	93	91	38:62	32	51
2	**(+)-110a•**HCl	87	78	37:63	38	56

3.2.6 Conclusion

In summary, we have demonstrated the success of *NH*-isoxazolidinium salts as catalysts for the iminium ion activation of the Diels-Alder reaction between a variety of aldehydes and cyclopentadiene. The optimised conditions were found to be 6 hours reaction time at 25 ^oC in aqueous MeOH with 10 mol% loading of the catalyst.

The phenyl substituted lactone fused isoxazolidine **110a** in conjunction with CSA catalysed the reaction between cinnamaldehyde and cyclopentadiene more efficiently than its furyl or thienyl analogues, **110b** and **110c**. Similarly, of the lactam fused isoxazolidinium salts, the phenyl substituted **117a•**CSA was a better catalyst than the furyl or thienyl analogues **117b** and **117c**. Both the lactone and lactam fused isoxazolidinium families showed superior catalytic performance in anhydrous solvents. The hypothesis that the β'-carbonyl moiety on these frameworks may be adopting the role played by a H_2O molecule in the catalytic cycle was tested by the preparation of pyrrolidine fused isoxazolidine catalytic frameworks. The *N*-methyl substituted pyrrolidine fused isoxazolidine **122a** was first investigated and the CSA salt was prepared, however, it was unable to catalyse the Diels-Alder reaction. Examination of the structure of this 1:1 complex showed salt formation involving the pyrrolidine ring *N*-atom. Following the addition of a second mole of (+)-10-CSA the *bis*-salt was found

to be catalytically active and the Diels-Alder products could be isolated in a moderate yield (65%). The reduced cycloaddition yields from reactions promoted by pyrrolidine fused isoxazolidines support a role for the β'-carbonyl of **110** and **117** in assisting in iminium ion formation.

Classical resolution of **110a** by way of either the (+)- or (-)-CSA salts yielded separate samples of (+)- and (-)-**110a** and the enantiomerically pure isoxazolidines were examined for potential as enantioselective organocatalysts together with a range of chiral and achiral counterions. Enantioselectivies in the range of 13-65% e.e. and 3-45% e.e. were obtained for the *exo* and *endo* adducts respectively for reactions catalysed by either the (+)- or (-)-10-CSA salts of **110a**, the highest enantioselectivities were observed in aqueous MeOH. Lowering the temperature to -20 ^{o}C did little to increase the enantioselectivity of the reaction but had a detrimental effect on the yield. The introduction of chiral phosphoric acid derivatives **131** and TRIP as potential chiral co-factors also failed to influence the enantioselectivity of the reaction. A control reaction employing either (+)- or (-)-**110a** with achiral co-factors confirmed that the observed selectivity is governed by the isoxazolidine moiety alone, with the counterion appearing to have little or no influence.

Thus, it can be concluded from this section that bicyclic *NH*-isoxazolidines have the potential to act as enantioselective organocatalysts for reactions that proceed by way of iminium ion intermediates. At this point it was deemed interesting to see if the same frameworks could support catalysis by the enamine route.

3.3 Enamine Catalysis

Enamine catalysis, as discussed in section 1.2.1, is described as the catalysis, by primary or secondary amines, of electrophilic substitution reactions in the α-position of carbonyl compounds.[17] Since the introduction of this type of catalysis in 2000 there has been an explosion of activity in the field and the range of reactions and catalysts continues to expand. This section will discuss the potential of the *NH*-isoxazolidine framework to promote such reactions.

3.3.1 Aldol Reaction

3.3.1.i Introduction

The aldol reaction is a powerful methodology for the construction of new carbon-carbon bonds. The reaction components typically include, as a pro-nucleophile, an enolisable aldehyde, ketone or carboxylic acid derivative and a carbonyl electrophile, usually an aldehyde and more rarely a ketone, figure 78.[30] Frequently, in addition to carbon-carbon bond formation, one or two new stereocenters are created during the aldol reaction, thus, the control of both the absolute and relative configuration of the products is crucial. Many groups, chiral or achiral, present (a) on either substrate, (b) on metal centres in the enolate intermediate **A**, or (c) on the catalyst/promoter can play a role in controlling the product stereochemistry.

Recently small chiral organic molecules have been found to catalyse the direct aldol addition of unmodified ketones to aldehydes with relatively high chemical and stereochemical efficiency.[30,31,33,205]

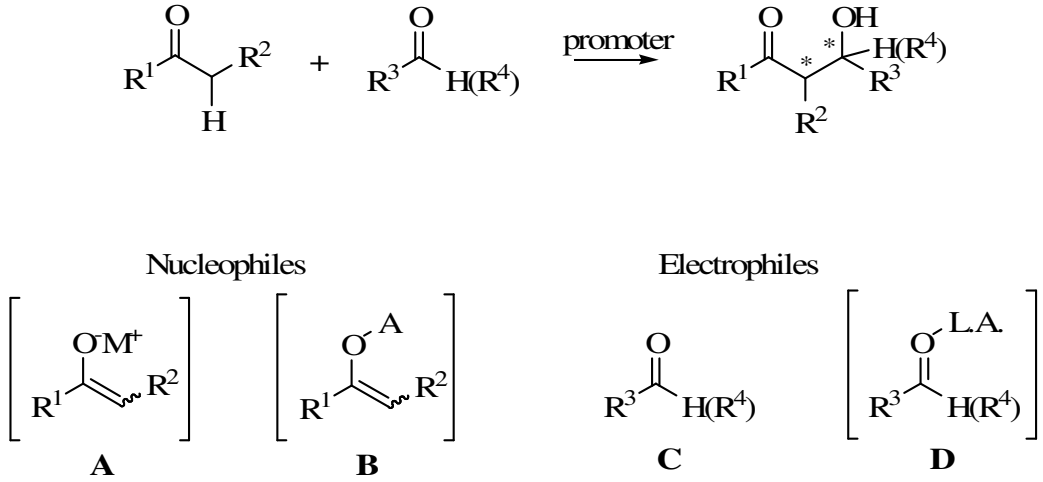


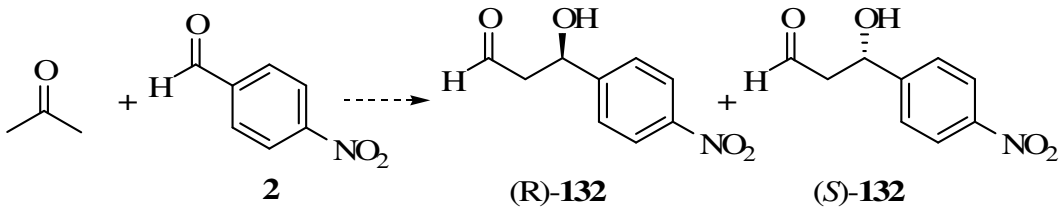
Figure 78. The enantioselective aldol reaction.

3.3.1.ii Organocatalysis and the aldol reaction

Whilst the first catalytic enamine activation noted outside of biochemistry was the Hajos-Parrish reaction catalysed by proline, the underlying principle of enamine activation remained undeveloped for a further 25 years before the pioneering work of Barbas and co-workers revealed that proline catalysis could be extended to the direct enantioselective intermolecular aldol reaction between ketones and aldehydes.[31,206]

Subsequent to this important publication more than 50 manuscripts have been published on the subject of enamine-catalysed aldol reactions.[8,18,25,26,29,145,207] In 2000 MacMillan and co-workers developed the first direct enantioselective aldehyde-aldehyde crossed-aldol reaction via enamine activation exploiting either proline or imidazolidinone catalysts.[76,208-210]

There are many examples of organocatalysts in the literature which, whilst initially designed to promote iminium ion catalysis were subsequently found to be successful as enamine catalysts. Thus, it was deemed prudent to test the isoxazolidines prepared in this research for their ability to promote the aldol reaction. An examination of the literature indicated that the best choice of substrates for initial studies were acetone and *p*-nitrobenzaldehyde, **2**, in DMSO, equation 55.[31,205,211]



Equation 55. The aldol reaction between acetone and *p*-nitrobenzaldehdye.

The procedure for the reaction involved the addition of *p*-nitrobenzaldehdye to a mixture of acetone and DMSO followed by the catalyst and the resulting mixture was stirred at room temperature for 24-144 hours. Initially as a control the literature results were verified in our hands with (*S*)-proline employed as the catalyst. The desired aldol product (*R*)-**132** was obtained in 52% yield after 144 hours. Whilst this yield is slightly less than the 68% reported in the literature it confirms our ability to perform the reaction, table 29.[31]

Unfortunately, **110a•**(+)-10-CSA completely failed to promote the aldol reaction. Even with catalyst loading up to 30 mol% and reaction times of up to 10 days the reaction still failed. Neither did an increase in reaction temperature to 40 ^{o}C help to promote the reaction. No conversion to the desired products was observed in any case, entries 3 and 4.

Neither were the lactam-fused, **117a**, nor the pyrrolidine-fused isoxazolidines, **122a&b**, able to catalyse the reaction. The ring-opened **112**, either on its own or as the (+)-10-CSA salt, was also found to be catalytically inactive, entries 5-11.

Table 29. Aldol reaction between acetone and *p*-nitrobenzaldehyde in DMSO at r.t.

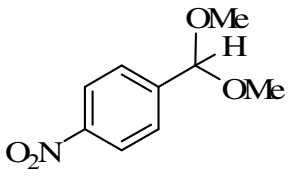
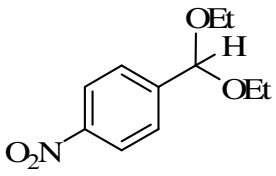
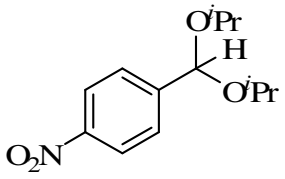
Entry	Catalyst (20 mol%)	Time (h)	% Yield of aldol product
1	**1**	144	52
2	**110a**•(+)-10-CSA	24	0
3	**110a**•(+)-10-CSA[a]	240	0
4	**110a**•(+)-10-CSA[a,b]	24	0
5	**117a**•(+)-10-CSA	24	0
6	**122a**•(+)-10-CSA	24	0
7	**122a**•2(+)-10-CSA	24	0
8	**122b**•(+)-10-CSA	24	0
9	**122b**•2(+)-10-CSA	24	0
10	**112**[c]	48	0
11	**112**•(+)-10-CSA[c]	48	0

[a] 30 mol% loading of catalyst. [b] Reaction performed at 40 °C. [c] 10 mol% loading of catalyst.

In considering the probable reasons for the failed reactions the solvent was identified as one possible difficulty. We had previously noted that the Diels-Alder reaction catalysed by **110a**•(+)-10-CSA was rather sluggish in DMSO (table 13) and so it was decided to experiment with the aldol reaction in a range of solvents and the results are summarised in table 30.

Initially, MeOH and aqueous MeOH were employed as these solvents were most successful for the promotion of the Diels-Alder reaction. However, again no catalytic activity was observed and the dominant reaction was the formation of the acetal of *p*-nitrobenzaldehyde, **133**. In a further attempt at reaction in polar solvents more bulky alcohols were explored as solvents. However, acetal formation was also observed for reactions conducted in EtOH and ^{i}PrOH and in addition to **134** and **135** only starting materials were returned. In ^{t}BuOH no reactions occured.

Control reactions confirmed that *p*-nitrobenzaldehdye is inert to acetal formation in the absence of CSA. Thus, simply on stirring in MeOH, entry 5, or in the presence of the isoxazolidine, entry 6, no reaction occurred. In the presence of (+)-10-CSA alone acetal formation resulted, entry 7.

133 **134** **135**

Figure 79. The range of acetals formed during the attempted enamine catalysed aldol reaction.

Table 30. Aldol reaction between acetone and *p*-nitrobenzaldehdye catalysed by **110a**•(+)-10-CSA (20 mol%) at room temperature.

Entry	Solvent	Time (h)	Products	
			Aldol	Acetal
1	MeOH	49	-	**133**
2	MeOH:H_2O 19:1	55	-	**133**
3	EtOH	67	-	**134**
4	^{i}PrOH	67	-	**135**
4	^{t}BuOH	67	-	**-**
5[a]	MeOH	48	-	**-**
6[b]	MeOH	48	-	**-**
7[c]	MeOH	48	-	**133**

[a] No catalyst was used. [b] **110a** was used as the additive. [c] (+)-10-CSA was used as the additive.

All attempts at the aldol reaction in DMF:H_2O (19:1), in pure H_2O and in CH_2Cl_2 failed and in each case the starting materials were returned unchanged, table 31 entries 1-3. In $CHCl_3$, the conversion of the aldehyde to the diethyl acetal is accounted for through the presence of a small percentage of EtOH present as a stabiliser in commercial $CHCl_3$.

Table 31. Aldol reaction between acetone and *p*-nitrobenzaldehyde catalysed by **110a**•(+)-10-CSA (20 mol%) at room temperature.

Entry	Solvent	Time (h)	Product
1	DMF:H_2O (19:1)	56	Returned S.M.
2	H_2O	55	Returned S.M.
3	CH_2Cl_2	71	Returned S.M.
4	$CHCl_3$	71	**134**

3.3.1.iii Conclusion

The aldol reaction between acetone and *p*-nitrobenzaldehyde could not be promoted by the *NH*-isoxazolidines prepared in this thesis and as an alternative to explore the potential for enamine mediated organocatalysis we turned our attention to the Michael addition reaction.

3.3.2 Michael addition reaction

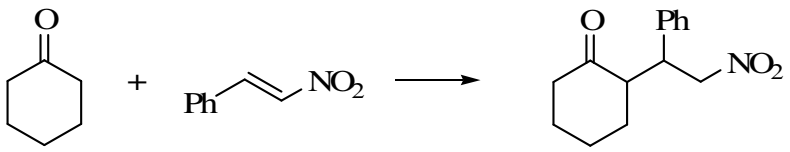
Michael addition reactions are powerful tools for the generation of new C-C bonds and the importance of this transformation has stimulated significant interest in the development of catalytic, asymmetric versions of the reaction.[4,7,24,145,212-214]

3.3.2.i Organocatalysis and the Michael addition reaction

The first examples of enamine promoted Michael addition reactions with proline as the organocatalyst furnished the products in good chemical yield but proved disappointing in terms of enantiocontrol.[34,41,87,212,215] In the subsequent search for more selective enamine catalysts diamines[41,42,46,48] and imidazolidinones (initially developed for iminium catalysis) have proven valuable catalysts.[216]

3.3.2.i.a trans-β-Nitrostyrene as Michael acceptor

We began our study into the potential of *NH*-isoxazolidine as catalysts for the Michael addition reaction by looking at the reaction between *trans*-β-nitrostyrene and cyclohexanone. The reaction, first catalysed by (*S*)-proline (15 mol%) in 2001 yielded the product in 94% but with low enantioselectivity (23% e.e.).[34] The diamine **19**•2HCl in $CHCl_3$ was less effective in terms of chemical yield, but it was more enantioselective (74% e.e.).[46] These substrates have been selected by many groups as test case examples of Michael addition reactions.[217-226]



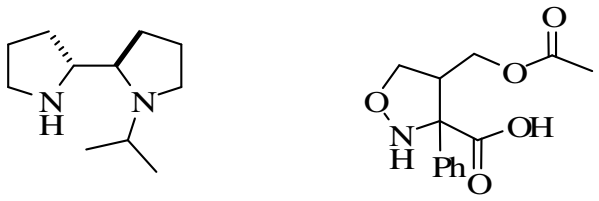
Equation 56. The Michael addition reaction between cyclohexanone and *trans*-β-nitrostyrene.

Efforts to demonstrate isoxazolidinium promoted Michael addition reactions of cyclohexanone and *trans*-β-nitrostyrene employed 10 mol% of **110a**•(+)-10-CSA at room temperature. After 51 hours in $CHCl_3$ the starting material was returned unchanged, table 32 entry 1. As the majority of enamine catalysts do not require an acid co-catalyst the reaction was repeated in the presence of just **110a**.[34,46,224,227] However, once again starting materials were returned, entry 2.

The reaction was repeated exploring the potential of the monocyclic **112** both on its own and together with (+)-10-CSA. After 63 hours reaction at room temperature the starting materials were returned unchanged both with the parent **112** and its CSA salt, entries 3 and 4.

Table 32. Attempted Michael addition reaction between *trans*-β-nitrosytrene and cyclohexanone at room temperature with 10 mol% catalyst loading.

Entry	Catalyst (10 mol%)	Solvent	Time (h)	Product
1	**110a**•(+)-10-CSA	$CHCl_3$	63	Returned S.M.
2	**110a**	$CHCl_3$	51	Returned S.M.
3	**112**•(+)-10-CSA	$CHCl_3$	63	Returned S.M.
4	**112**	$CHCl_3$	63	Returned S.M.
5	**110a**•(+)-10-CSA	Brine	51	Returned S.M.
6	**110a**	Brine	51	Returned S.M.
7	**112**•(+)-10-CSA	Brine	52	Returned S.M.
8	**112**	Brine	52	Returned S.M.
9	**110a**	DMSO	51	Returned S.M.
10	**112**	DMSO	51	Returned S.M.
11	**110a**•(+)-10-CSA	DMSO	52	Returned S.M.
12	**112**•(+)-10-CSA	DMSO	52	Returned S.M.
13	**110a**•(+)-10-CSA	MeOH:H_2O 19:1	81	Returned S.M.
14	**110a**•(+)-10-CSA	MeOH	81	Returned S.M.
15	**110a**•(+)-10-CSA	H_2O	81	Returned S.M.

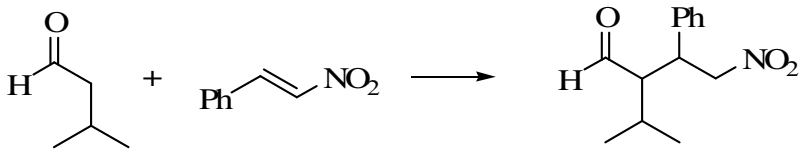


19 **112**

Figure 80. Alternative catalysts for the attempted promotion of the Michael addition reaction between *trans*-β-nitrosytrene and cyclohexanone.

According to the literature Michael Addition reactions have been successful in brine[228] and DMSO[44], subsequently the reaction was repeated in these solvents. In neither case was any catalysis observed, entries 5-12. Finally both anhydrous and wet MeOH as well as H_2O were examined as solvents for the isoxazolidine promoted Michael addition reaction, entries 13-15.[45] In each case ^1H NMR spectral analysis indicated only unchanged starting materials. Even after 81 hours duration there was no evidence for formation of Michael addition products.

As the reaction between *trans*-β-nitrostyrene and cyclohexanone could not be promoted by the *NH*-isoxazolidines an aldehyde partner was considered. Promotion of the Michael reaction between *trans*-β-nitrostyrene and isovaleraldehyde, by enamine catalysis was first reported in 2001.[227] The diamine **136** functioned as catalyst, the reaction was conducted in THF at room temperature and after 3 days the product was furnished in 78% yield with 72% e.e. Since the initial report many related examples have been published.[229-232]



Equation 57. The Michael addition reaction between *trans*-β-nitrostyrene and isovaleraldehyde.

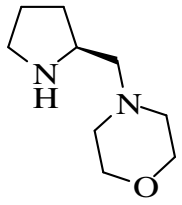


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Figure 81. The successful diamine organocatalyst for the reaction between *trans*-β-nitrostyrene and isovaleraldehyde.

A survey of the literature revealed $CHCl_3$ to be the most successful solvent for organocatalysed Michael addition to aldehydes in terms of both yield and enantioselectivity, thus, it was selected to study the isoxazolidine promoted reaction between isovaleraldehdye and *trans*-β-nitrostyrene.[46,231,232] Potential catalytic systems

include the isoxazolidine **110a**, its CSA salt, **110a•**(+)-10-CSA, the monocycle, **112**, and its salt, **112•**(+)-10-CSA. Disappointingly, in all cases after 48 hours starting materials were returned unchanged, table 33 entries 1-4. Altering the solvent to MeOH, aqueous MeOH or H_2O also failed to promote the reaction, entries 5-10.

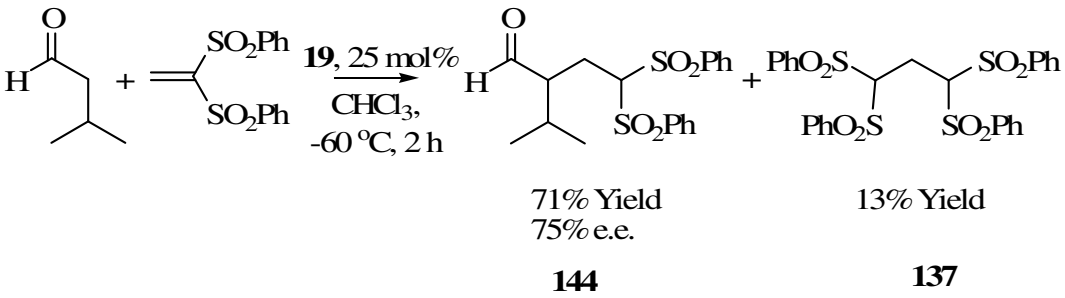
Since the isoxazolidine failed to catalyse the Michael addition of either aldehyde or ketone substrates to *trans*-β-nitrostyrene a stronger Michael acceptor was explored.

Table 33. Attempted Michael addition reaction between *trans-β*-nitrostyrene and isovaleraldehyde at room temperature with 15 mol% catalyst loading.

Entry	Catalyst (15 mol%)	Solvent	Time (h)	Product
1	**110a**	$CHCl_3$	53	Returned S.M.
2	**110a•**(+)-10-CSA	$CHCl_3$	48	Returned S.M.
3	**112**	$CHCl_3$	48	Returned S.M.
4	**112•**(+)-10-CSA	$CHCl_3$	48	Returned S.M.
5	**110a**	MeOH:H_2O 19:1	53	Returned S.M.
6	**110a•**(+)-10-CSA	MeOH:H_2O 19:1	90	Returned S.M.
7	**110a**	MeOH	53	Returned S.M.
8	**110a•**(+)-10-CSA	MeOH	90	Returned S.M.
9	**110a**	H_2O	53	Returned S.M.
10	**110a•**(+)-10-CSA	H_2O	90	Returned S.M.

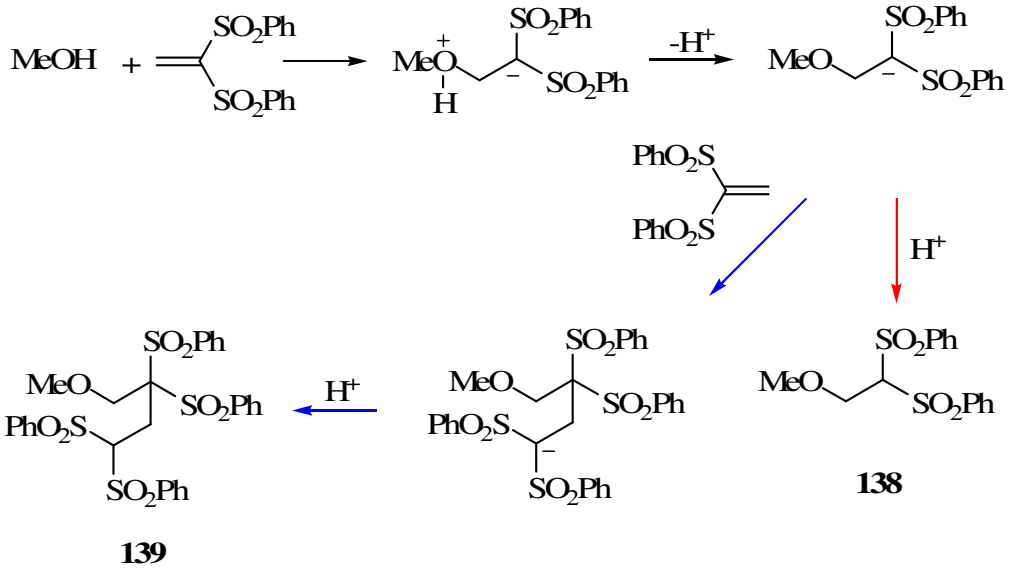
3.3.2.i.b Vinyl sulfones as Michael acceptors

Due to the failure of isoxazolidine based catalysts to promote Michael addition to *trans*-β-nitrostyrene 1,1-bis(benzenesulfonyl)ethylene was identified as a more reactive acceptor. 1,1-Bis(benzenesulfonyl)ethylene can be considered to be doubly activated and there are literature reports on the addition of isovaleraldehyde to this acceptor catalysed by a range of pyrrolidine based catalysts.[48] The highest yields and enantioselectivities were furnished under the influence of **19** at room temperature (65% yield and 57% e.e), however, at -60 ^{o}C after 2 hours the enantioselectivity increased to 75% e.e. The self-reaction of 1,1-bis(benzenesulfonyl)ethylene to form the by-product **137** in 18% yield was also noted, equation 58. Since the original publication a further handful of reports on addition to this substrate with alternative organocatalysts have appeared.[224,231,233,234]



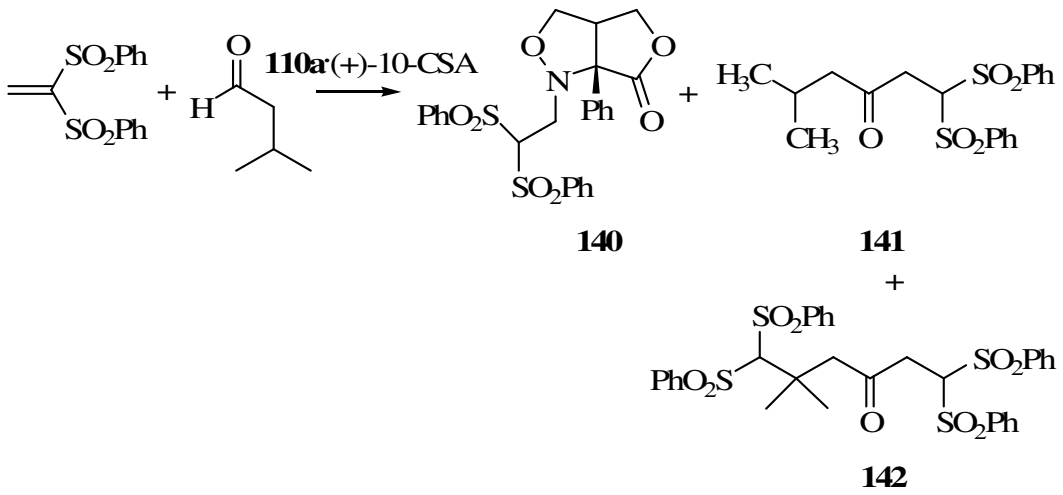
Equation 58. The Michael addition reaction between isovaleraldehyde and 1,1-bis(benzenesulfonyl)ethylene.

The potential of **110a**•(+)-10-CSA to promote the reaction between isovaleraldehyde and 1,1-bis(benzenesulfonyl)ethylene was initially attempted in MeOH at room temperature. In the presence of **110a**•(+)-10-CSA (10 mol%) two products, **138** and **139**, arising from MeOH addition to the sulfone were observed in a 3:2 ratio after 5 hours reaction at room temperature, the products could not be isolated and no Michael products were present. In a control reaction 1,1-bis(benzenesulfonyl)ethylene was stirred alone in MeOH at room temperature and under these conditions **137**, **138** and **139** were obtained in a 1:28:14 ratio. A mechanism accounting for the formation of **138** and **139** invokes MeOH attack on 1,1-bis(benzenesulfonyl)ethylene, quenching of the initial reaction leads to **138**, alternatively the intermediate can attack a second mole of 1,1-bis(benzenesulfonyl)ethylene leading to the highly substituted **139**, scheme 21.



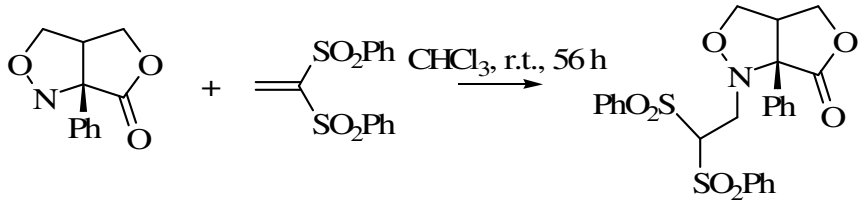
Scheme 21. Proposed mechanistic route to the formation of the methanol by-products of the Michael addition reaction.

As MeOH proved a most reactive solvent in combination with 1,1-bis(benzenesulfonyl)ethylene subsequent reactions were explored in $CHCl_3$. Indeed it is known from the literature that the organocatalysed Michael addition reaction of 1,1-bis(benzenesulfonyl)ethylene and isovaleraldehyde is successful in $CHCl_3$.[48] Accordingly, the reaction to probe **110a**•(+)-10-CSA as a catalyst for this system was repeated in $CHCl_3$. Initially the acceptor was added to a stirred solution of **110a**•(+)-10-CSA in $CHCl_3$ followed by addition of the aldehyde. The resulting solution was stirred at room temperature for 5 hours after which ^{1}H NMR spectral analysis showed the presence of three new products identified as **140**, **141** and **142** in a 1:4:2 ratio which could not be isolated from the reaction mixture; none of the desired Michael addition products were formed, equation 59.



Equation 59. The attempted Michael addition reaction between 1,1-bis(benzenesulfonyl)ethylene and isovaleraldehyde by **110a**.

The first product, **140**, simply arose from the addition of isoxazolidine **110a** to 1,1-bis(benzenesulfonyl)ethylene. To support this hypothesis, a control reaction between **110a** and 1,1,-bis(benzenesulfonyl)ethylene in $CHCl_3$ was conducted, and **140** resulted in 96% yield, equation 60. Following this observation the reaction protocol was revised, and to minimise the formation of **140** it was planned that in future experiments the aldehyde should be added first to the solution of catalyst prior to the introduction of the acceptor.

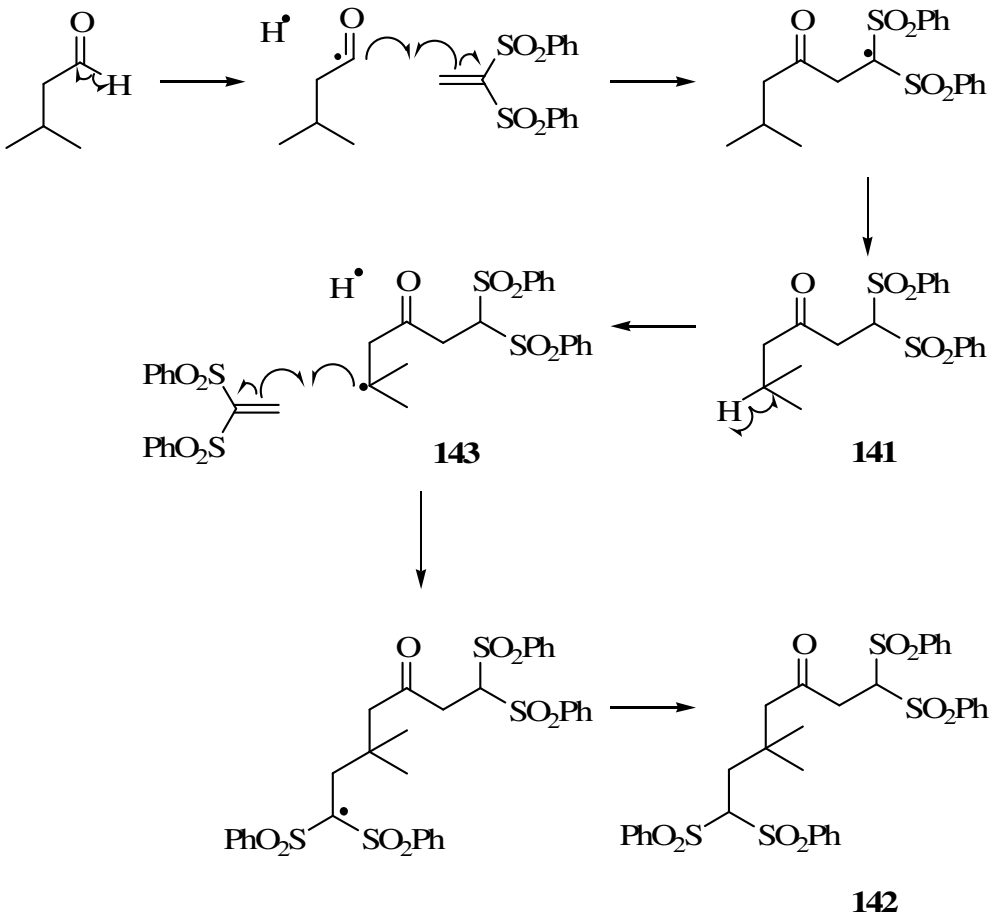


110a **140**

Equation 60. The synthetic route to the addition of the isoxazolidine **110a** to 1,1-bis(benzenesulfonyl)ethylene.

The products **141** and **142** are believed to arise as a result of a radical mediated reaction between the starting materials. A plausible mechanism for their formation is shown in scheme 22. Initiation of the reaction may involve homolytic cleavage of the aldehyde C-H bond. The resulting carbon radical may attack 1,1-bis(benzenesulfonyl)ethylene and termination furnishes 5-methyl-1,1-bis(phenylsulfonyl)hexan-3-one, **141**. This first formed product was postulated to be an intermediate en route to **142**. Homolytic C-H bond cleavage may form the radical **143**, which, in turn, may attack a second molecule of 1,1-bis(benzenesulfonyl)ethylene. Finally termination would yield **142**.

In an effort to probe the intermediacy of radical species the influence of atmospheric oxygen on the progress of the reaction was examined and thus the experiments were re-run in an inert atmosphere. In a close parallel to the conditions found successful by Mossé and Alexakis anhydrous $CHCl_3$ filtered over basic alumina was employed and the reactions were run under an argon atmosphere.[48] The reaction was explored with a 25 mol% loading of **110a**. Under these revised conditions after two hours at room temperature the desired Michael addition product **144** was observed as a minor product amongst numerous other reaction products which included **140**, **141** and **142**, table 34 entry 1. Since the proportion of the desired Michael addition product, as judged by ^1H NMR spectral analysis of the crude mixture, was minor it was deemed not to be a viable synthetic approach and the reaction products were not purified.



Scheme 22. Proposed radical route to the formation of the *bis*- and the *tetrakis*-(phenylsulfones) **141** and **142**.

In a further revision of the protocol the aldehyde was added by syringe to a pre-mixed air free solution of 1,1-bis(benzenesulfonyl)ethylene and **110a** in $CHCl_3$. Under these conditions a slight improvement in the ratio of **144** to the *bis*- and the *tetrakis*-(phenylsulfones), **141** and **142**, was observed, however starting materials remained a significant portion of the crude reaction products, entry 2.

There is precedent in the literature that lowering of reaction temperatures has been effective in minimising radical induced product formation[235] and thus the reaction between isovaleraldehyde and 1,1-bis(benzenesulfonyl)ethylene was repeated at 0 ^{o}C. After 5 hours these components again failed to yield a significant amount of the desired Michael addition product. The *bis*-(phenylsulfone), **141**, and the *tetrakis*-(phenylsulfone), **142**, dominated the product mixture, entry 3. Even at -50 ^{o}C only a minor amount of the Michael addition product and the tetrasulfone, **137**, were present

after 2 hours. An increase in the reaction time to 28.5 hours resulted in the formation of *bis*-(phenylsulfone), **141**, and *tetrakis*-(phenylsulfone), **142**, with no evidence for any Michael addition product, entries 4 and 5.

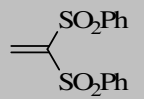
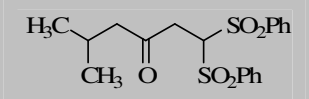
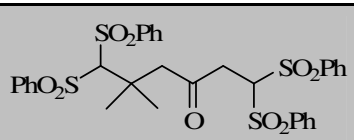
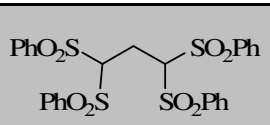
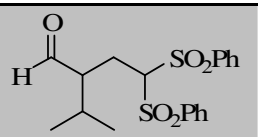
In a further effort to minimise formation of *bis*- and *tetrakis*-(phenylsulfones), **141** and **142**, 2,6-di-*tert*-butyl-4-methylphenol (BHT), **145**, was employed as a radical inhibitor. It is reported in the literature that BHT completely closed off the radical mediated reaction between butanal and a vinyl sulfonate which in its absence yielded the ketone **146** in 40% yield, equation 61.[236]

Thus, it was hypothesised that addition of BHT may prevent formation of the *bis*- and *tetrakis*-(phenylsulfones) and result in more selective formation of **144**. The reaction was repeated and prior to the addition of the aldehyde the radical trap BHT was added. The reaction was performed under atmospheric conditions at room temperature for 2 hours. After this time ^{1}H NMR spectral analysis indicated the presence of a small amount of the *N*-substituted isoxazolidine **140** and the desired conjugate addition product in a 1:1 ratio, however, the starting 1,1-bis(benzenesulfonyl)ethylene was the major component amongst the product mixture, entry 6.

With the addition of BHT at 0 ^{o}C formation of the radical promoted products, **141** and **142**, could be ceased. However, at this low temperature most of the 1,1-bis(benzenesulfonyl)ethylene remained unreacted, entry 7. After 26.5 hours under the same conditions formation of the *bis*- and *tetrakis*-(phenylsulfones) was noted. However, once again the dominant feature of the reaction products was returned 1,1-bis(sulfonylethylene), entry 8.

In summary, **110a** was rather ineffective in promotion of the Michael reaction between 1,1-bis(benzenesulfonyl) ethylene and isovaleraldehyde. The desired product could only be obtained under very stringent experimental conditions, and even then, only in very small amounts.

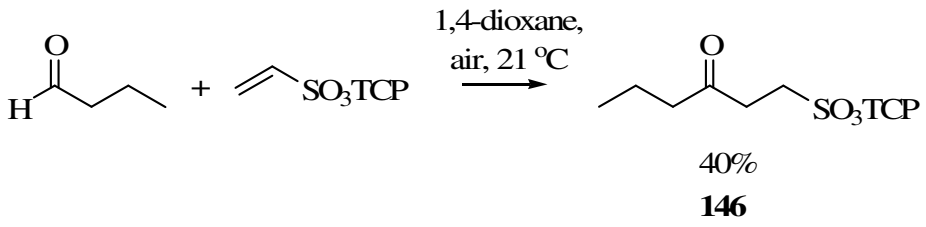
Table 34. Attempted Michael addition reaction between 1,1-bis(benzenesulfonyl)ethylene and isovaleraldehdye under the influence of **110a** (25 mol%) in anh. $CHCl_3$.[*]

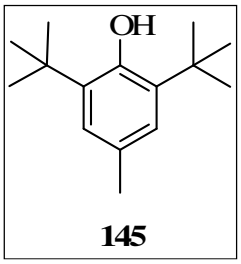
		Product[#]					
Entry	**Time (h)**	 Starting Material	 **141**	 **142**	 **137**	 **144**	
1	2	0	30	11	9	1	
2[a]	2	2	25	5	7	1	
3[a,b]	5	0	50	8	2	1	
4[c]	28.5	0	27	14	1	-	
5[c]	2	12	-	-	1	1	
6[d]	2	21	-	-	1	1	
7[b,d]	8	35	-	-	1	12	
8[b,d]	26.5	12	4	1	1	5	

[a]Addition of aldehyde through a syringe. [b] Reaction carried out at 0 ^oC. [c] Reaction carried out at -50 ^oC. [d] Addition of BHT.

[*] Solvent filtered over alumina at room temperature, reaction conducted in an argon atmosphere.

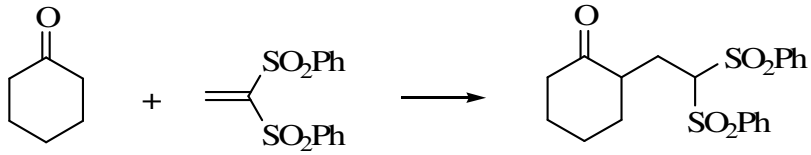
[#] Values reported refer to the relative ratios of the indicated products as measured from ^1H NMR spectra of crude reaction mixtures.



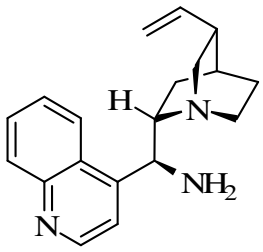


Equation 61. The BHT inhibited radical mediated reaction between butanal and a vinyl sulfonate.

Finally, an attempt was made to promote the Michael addition reaction between 1,1-bis(benzenesulfonyl)ethylene and cyclohexanone. The organocatalysis of Michael addition reactions between ketones and vinyl sulfones is a recent finding.[237] Of the catalysts tested **146**•PhCOOH proved the most successful and the reaction conducted in $CHCl_3$ at 0 °C afforded the desired addition product in 94% yield and with 92% e.e. Sensitivity to solvent was noted in that the enantioselectivity was reduced in MeOH to 27% e.e.



Equation 62. The Michael addition reaction between cyclohexanone and 1,1-bis(benzenesulfonyl)ethylene.



146

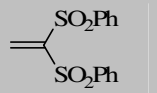
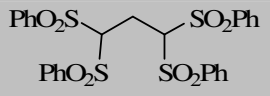
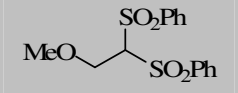
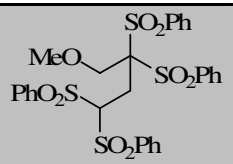
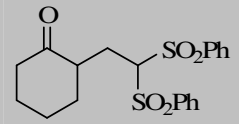
Figure 83. Chichona-derived primary amine catalyst.

The attempted reaction of these two substrates in the presence of **110a** was investigated in MeOH. The product mixture comprised unreacted 1,1-bis(benzenesulfonyl)ethylene, the self reaction product **137**, **138** and **139**, the products of solvent addition, table 35 entry 1.

Repeating the reaction with 10 mol% of the isoxazolidinium salt **110a•**(+)-10-CSA yielded the desired product **147** alongside **138** and **139** in a ratio of 5:8:1, entry 3.

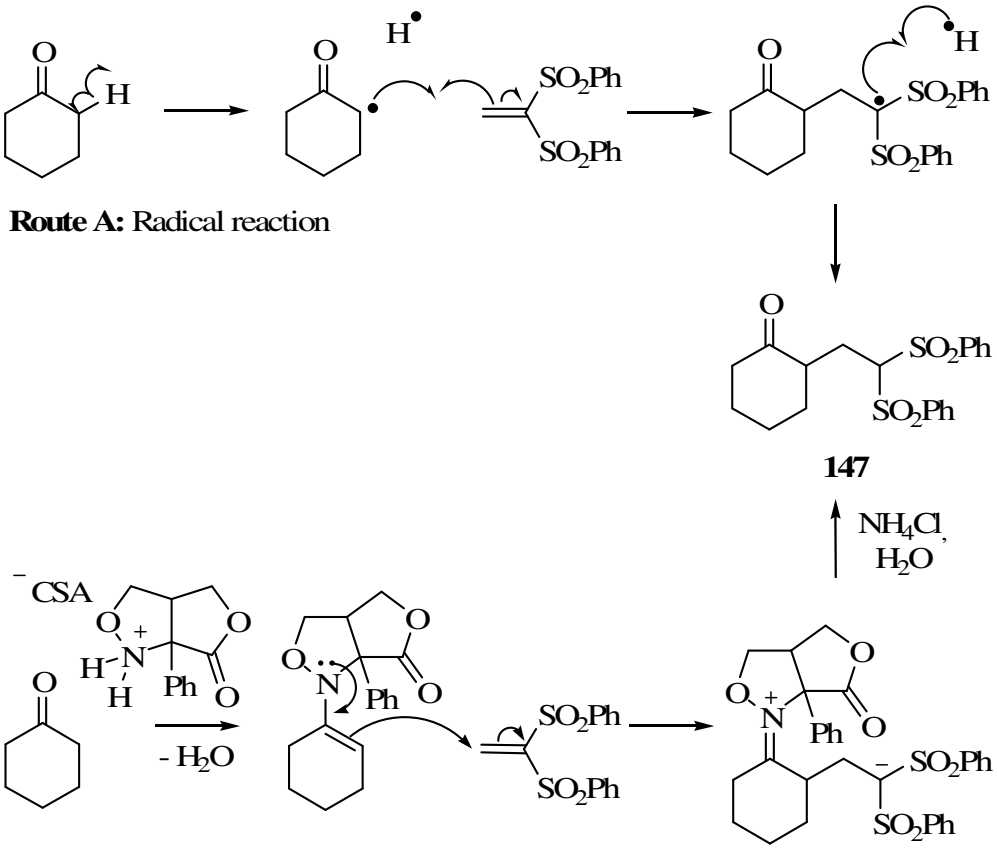
As noted previously in this authors hands reaction between 1,1-bis(benzenesulfonyl)ethylene and isovaleraldehyde afforded 5-methyl-bis(phenylsulfone) and 5-methyl-tetrakis(phenylsulfone) **141** and **142** which are believed to arise via a radical pathway, rather than the desired conjugate addition product. As cyclohexanone is symmetrical the product arising from a radical pathway is identical to that which would result from a Michael addition reaction. In order to ascertain which mechanism lead to the formation of **147** the reaction was repeated in the presence of the radical inhibitor BHT. In the presence of this additive a reduced amount of the "conjugate addition" product formed and the relative amount of by-products increased. On this basis it is concluded that the dominant mechanism leading to **147** was radical mediated.

Table 35. Attempted Michael addition reaction between cyclohexanone and 1,1-bis(benzenesulfonyl)ethylene in MeOH at room temperature with 10 mol% loading of the proposed catalyst.

			Product[#]				
			 Starting Material	 **137**	 **138**	 **139**	 **147**
Entry	**Time (h)**	**Catalyst**					
1	49	**110a**	5	1	3	28	-
2	51	(+)-10-CSA	3	1	5	42	-
3	56	**110a**•(+)-10-CSA	4	-	8	1	5
4[a]	51	**110a**•(+)-10-CSA	3	-	1	6	4

[a] BHT added.

[#] Values reported refer to the relative ratios of the indicated products as measured from ^{1}H NMR spectra of crude reaction mixtures.



Scheme 23. Proposed routes to the formation of the product of the Michael addition reaction between cyclohexanone and 1,1-bis(benzenesulfonyl)ethylene.

3.3.3 Conclusion

Neither the parent isoxazolidine **110a** nor its CSA salt were effective in promotion of the Michael addition reaction of isovaleraldehyde or cyclohexanone to *trans*-β-nitrostyrene. A very minor amount of the Michael addition product was observed between 1,1-bis(benzenesulfonyl)ethylene and isovaleraldehyde. A false positive was noted in the case of 1,1-bis(benzenesulfonyl)ethylene and cyclohexanone. However, the product was subsequentially established to have its origins in a radical promoted reaction.

Concluding Remarks

A range of *NH*-isoxazolidine organocatalysts were designed and prepared by a tandem 1,2-prototropy cycloaddition process from parent δ-alkenyl oxime substrates. By varying oxime structure three different bicyclic isoxazolidine frameworks were prepared bearing, as the second ring, a lactone, a lactam and a pyrrolidine-fused ring. One monocyclic isoxazolidine was also synthesised. Classical resolution with either (+)- or (-)-10-CSA was successful for the generation of diastereoisomerically pure salts of the lactone-fused family and from these enantiomerically pure isoxazolidines were obtained.

From the organocatalysis discussed in this thesis it is clear that *NH*-isoxazolidines are effective for the iminium ion activation of the Diels-Alder reaction. Considerable effort was directed to the identification of optimal reaction conditions. Studies were performed to find the optimal reaction time, catalyst loading and the most efficient solvent. In addition a range of acid co-factors and dienophiles were examined. Following these studies it was found that the highest cycloaddition yields (96%) were obtained after just 6 hours reaction at room temperature in MeOH/MeOH:H_2O (19:1) employing a 10% loading of the catalyst with (+)-10-CSA as the acid co-factor. In the presence of resolved salts the enantioselectivities of the [4 + 2] products were moderate, ≃42% *endo* ee and 59% *exo* e.e. rising to ≃45% *endo* e.e. and 64% *exo* e.e. at -20 ^{o}C. By exploring the potential for counterion ion catalysis it was concluded that any enantioselectivity observed was as a result of the organic core of the catalyst and that the counterion had little or no influence on stereoselectivity.

Enamine catalysis of the aldol reaction was unsuccessful and largely returned starting material. In some cases, acetal formation was observed through aldehyde reaction with the solvent. Attempted catalysis of the Michael addition reaction between nitroalkenes and either aldehydes or ketones was also unsuccessful. Vinyl sulfones were slightly better substrates and a very minor amount of the Michael addition product between 1,1-bis(benzenesulfonyl)ethylene and isovaleraldehyde was isolated. However, the major products from reaction between these compounds were subsequentially identified as arising by means of a radical reaction.

Although much has been reported in this thesis there remains much scope for future research in this area and if continuing with this subject I suggest the following areas merit attention.

(i) In an attempt to increase the enantiocontrol of the reaction a new generation of the catalyst would be designed with bulky groups such as ^{t}Bu or triphenylmethyl positioned at the fusion position of the isoxazololactone bicycle.

(ii) An isoxazolidine ring could be prepared with a β-carbonyl group, this would allow comparison of the reactivity with the current catalysts which bear a β'-carbonyl group.

(iii) With the knowledge that the catalysts are not effective in enamine catalysis future studies should concentrate on expanding the range of iminium ion promoted reactions to explore the versatility of *NH*-isoxazolidines as catalysts. Broadening the range of reactions should include cascade or domino reactions. Attractive features of such synthetic approaches include the avoidance of intermediate isolation and of protection/deprotection strategies, and hence cascade/tandem approaches are less time consuming and less costly.

(iv) Major limitations of asymmetric organocatalysis are the long reaction times and high catalyst loadings. There is a growing interest in microwave-assisted organic synthesis and in the issue of microwave effects and it would be important to explore the impact of microwave activation on that catalytic activity of the *NH*-isoxazolidines described in the preceding chapters.

I have enjoyed my time carrying out the research for this thesis and hope to one day return to this area.

Experimental

4.1 Instrumentation

Solvents were dried and purified in accordance with established procedures.[169]

Melting points were measured on a Stuart Scientific (Bibby) Melting Point SMPI apparatus and are uncorrected.

Infrared (IR) Spectra were recorded on a Perkin Elmer System 2000 FT spectrometer. Solid samples were finely ground with an excess of dry potassium bromide and liquid/oil samples were added to an excess of Nujol.

All NMR spectra were recorded on a Bruker Avance spectrometer at a probe temperature of 25 ^{o}C, unless otherwise stated, operating at 300 MHz for the ^{1}H nucleus and 75.5 MHz for the ^{13}C nucleus. Low temperature NMR spectroscopy experiments were carried out by cooling the probe with liquid nitrogen blow off. Spectra were recorded in deuteriochloroform ($CDCl_3$) unless otherwise stated. Tetramethylsilane (TMS) was used as internal standard in all cases. Chemical shifts are given in ppm downfield from the internal standard and coupling constants are given in Hz. Data were reported as follows: chemical shift, integration, multiplicity, coupling constants and assignment (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, td = triplet of doublets and br = broad). ^{13}C NMR spectra were recorded with complete proton decoupling.

Microanalytical data were provided by The Microanalytical Laboratory, National University of Ireland Cork, Cork, Ireland and The Microanalytical Laboratory, University College Dublin, Belfield, Dublin 4, Ireland. Samples were analysed on an Exeter Analytical CE-440 elemental analyser in oxygen with helium carrier gas at 975 °C in a combustion tube and are within ±0.5% of the calculated carbon, hydrogen and nitrogen content of the desired molecular formula.

Mass spectrometry was carried out on a LC/TOF-MS model 6210 Time-Of-Flight LC/MS with an electrospray source positive and negative (ESI+/-), capillary 3,500 V, nebuliser spray 30 psig, drying gas 5 L/min and source temperature 325 ^{o}C. The

fragmentor was used at 175 V. The LC was a model 1200 Series and injection volumes were typically 10μL. An Agilent Eclipse XBD-C18 column, 5-micron in diameter was employed. The mobile phase comprised A (MeCN with 0.1 % formic acid) and B (0.1 % formic acid in water) with gradient was 5% A to 100% over 15 minutes at a flow rate of 0.5 mL/min. All samples were found to be within 5 ppm of the desired value.

Flash column chromatography was performed using silica gel 60 (Merck, 0.040-0.063 mm) on a Buchi Automated Flash system comprising of a fraction collector C-660 Buchi UV Monitor C-630, Buchi Pump Module C-601 and Buchi Pump Manager C-615. Analytical thin layer chromatography was carried out on aluminium sheets pre-coated with Merck TLC Silica gel 60 F_{254}, developed sheets were visualised using a portable UVItec CV-006 lamp ($\lambda = 254$).

Analytical chiral gas-phase chromatography (GC) was performed on a Perkin-Elmer Clarus 500 equipped with a flame ionization detector using a CHIRALDEX B-DA β-Dex 110 fused silica capillary column (30 m x 0.25 mm x 0.25 μm).

High Performance Liquid Chromatography (HPLC) was performed on a Perkin-Elmer Totalchrom v.6.2.0.0.1 or Gilson analytical HPLC column using a CHIRALCEL OD analytical column in both cases (250 x 4.6 mm).

Optical rotations were measured on an Optical Activity AA 100 polarimeter in a 20 dm polarimeter tube.

Reactions at 25 ^{o}C were carried out in a Grant W14 water bath without stirring. Low-temperature reactions were carried out in an ethanol bath and the temperature was controlled by a Julabo FT920 cooler.

All compounds were named by ACD^{TM} or IUPAC method. In comparing the furyl and thienyl oximes **103b,c** and **116b,c** there is a change in relative priorities of the groups connected to the oxime double bind, however, in the interest in consistency in graphical presentation, in both cases those oximes have the hydroxyl group on the same side as the alkenyl chain are considered Z-oxime isomers and those with the heteroaryl and the hydroxyl group on the same side are labelled as *E*-isomers.

Rotamers are referred to as major and minor except where they are present in a 1:1 ratio and are referred to as a and b.

4.2 Experimental

4.2.1 Synthesis of 1st Generation catalysts

Synthesis of Benzaldehyde oxime (95)[156]

A mixture of benzaldehyde (6.518 g, 0.061 moles), sodium acetate (5.527 g, 0.067 moles) and NH_2OH•HCl (4.691 g, 0.067 moles) in EtOH (100 cm^3) was heated under reflux for two hours. The solution was cooled, evaporated and the residue taken up in H_2O (50 cm^3). The solution was washed with DCM (3 x 30 cm^3) and the extract was dried over $MgSO_4$ and evaporated to yield the crude product as a pale yellow oil (6.281 g, 85%). ^{1}H NMR spectral data agrees with that in the literature.

Synthesis of *N*-Benzylhydroxylamine (96)[157]

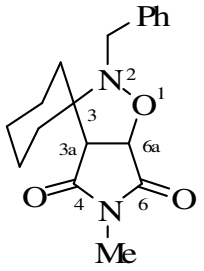
N-Benzylhydroxylamine was synthesised in 86% yield as previously described and ^{1}H NMR spectral data agrees with that in the literature.

Synthesis of *N*-benzyl-*N*-cyclohexylideneamine oxide (94)[158]

The titled product was prepared according to literature reports in 84% yield.

Cycloaddition of nitrone (94) and *N*-methylmalemide; formation of 2'-benzyl-5'-methyl-3a'*H*-spiro[cyclohexane-1,3'-pyrrolo[3,4-*d*][1,2]oxazole]-4',6'(5'*H*,6a'*H*)-dione (91)

A solution of **94** (1.000 g, 0.005 moles) and *N*-methylmalemide (1.293 g, 0.011 moles) in anh. toluene (100 cm^3) was heated at reflux under a N_2 atmosphere for 24 hours. The reaction mixture was cooled to r.t. and the solvent was removed by rotary evaporation to afford a yellow oil which was **91** as white crystals (0.638 g, 41%).



^{1}H NMR ($CDCl_3$): (δ) 7.33-7.19 (5H, m, ArH), 4.70 (1H, d J = 7.5, H^{6a}), 3.88 (2H, s, NCH_2Ph), 3.50 (1H, d J = 7.5, H^{3a}), 3.04 (3H, s, CH_3), 2.09-1.19 (10H, m, C_6H_{10}).

^{13}C NMR ($CDCl_3$): (δ) 175.1, 174.7 (C^6 & C^4), 137.7 (Q ArC), 128.3, 127.5, 127.0 (3xArC), 75.3 (C^{6a}), 70.4 (C^3), 54.1 (C^{3a}), 52.6 (NCH_2), 31.6, 30.9, 28.9, 23.3, 23.0 (5xCH_2), 24.9 (NCH_3).

IR (KBr): (cm^{-1}) 3457, 2945, 1694, 1453, 1286.

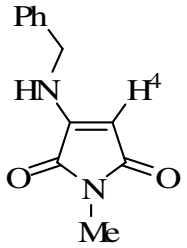
µ analysis:	Found:	C 68.75%	H 6.98%	N 8.84%
	$C_{18}H_{22}N_2O_3$ requires:	C 68.75%	H 7.06%	N 8.91%

m.p.: 151-155 ^{o}C (Et_2O:hexane 1:1)

LC/TCOF-MS: $(M + Na)^+$ requires 338.1554 g/mol, found 338.1567 g/mol, difference (3.69 ppm).

Preparation of 3-(benzylamino)-1-methyl-1H-pyrrole-2,5-dione (98)

A mixture of *N*-benzylhydroxylamine **96** (0.578 g, 0.005 moles) and *N*-methyl malemide (0.522 g, 0.005 moles) in toluene (50 cm^3) was heated at reflux under a N_2 atmosphere for 24 hours. The solution was allowed to cool and the solvent was removed by rotary evaporation to yield the crude product which was purified by flash column chromatography (Et_2O:hexane 1:1) yielding **98** as a yellow solid (0.078, 8%).



^{1}H NMR ($CDCl_3$): (δ) 7.40-7.02 (5H, m, ArH), 5.69 (1H, br s, NH), 4.86 (1H, s, H^4), 4.34 (2H, d *J* = 5.8, $C\underline{H}_2Ph$), 2.97 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): (δ) 172.5, 167.6 (2xC=O), 149.1 (C=$\underline{C}$N), 135.7 (Q ArC), 129.0, 128.3, 127.7 (3xArC), 85.5 ($\underline{C}$H=C), 48.4 (NCH_2), 23.5 (NCH_3).

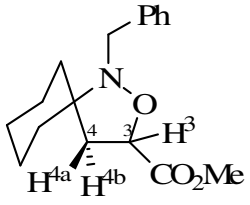
IR (KBr): (cm^{-1}) 3323, 1701, 1626, 1456, 1394.

μ analysis: Found: C 66.23% H 5.54% N 12.22%

$C_{12}H_{12}N_2O_2 \bullet 0.5(CH_3)_2C=O$ requires: C 66.38% H 5.86% N 12.14%

Cycloaddition of nitrone (94) and methylacrylate; formation of methyl 1-benzyl-2-oxa-1-azaspiro[4.5]decane-3-carboxylate (92)

A mixture of **94** (0.300 g, 1.470 x 10^{-3} moles) and methyl acrylate (0.665 g, 7.450 x 10^{-3} moles) in dry toluene (20 cm^3) was heated at reflux under N_2 and pressure for 37 hours. The solution was allowed to cool to r.t. and the reaction solvent was evaporated to yield the crude product, which was purified by flash column chromatography (hexane:Et_2O, 3:2) to yield the pure product as a yellow oil (0.053 g, 13%).



^{1}H NMR ($CDCl_3$): (δ) 7.45-7.20 (5H, m, 5xArH), 4.56-4.51 (1H, dd *J* = 9.5 & 6.6, H^3), 3.93 (1H, d *J* = 14.2, NCH_2), 3.84 (1H, d *J* = 14.2, NCH_2), 3.72 (3H, s, OCH_3), 2.55-2.47 (1H, dd *J* = 12.5 & 9.5, $H^{4a/b}$), 2.39-2.33 (1H, 12.5 & 6.6, $H^{4a/b}$), 1.79-1.26 (10H, m, C_6H_{10}).

^{13}C NMR ($CDCl_3$): (δ) 172.0 (C=O), 137.7 (Q ArC), 127.8, 127.4, 125.7 (3xArC), 73.7 (C^3), 66.0 (C^5), 53.1 (NCH_2), 51.1 (OCH_3), 41.0 (C^4), 28.7, 28.3, 24.9, 22.8, 22.6 (5xCH_2).

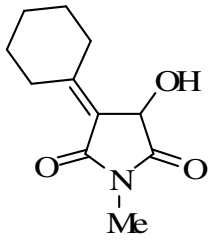
IR (nujol): (cm^{-1}) 2888, 1741, 1456, 1376, 1261, 1202, 1029, 802, 695.

Attempted cycloaddition of nitrone (94) and phenyl vinyl sulfone; 3/4-(phenylsulfonyl)-2-oxa-1-azaspiro[4.5]decane (93)

A mixture of **94** (1.000 g, 0.005 moles) and phenyl vinyl sulfone (0.992 g, 0.005 moles) in anh. toluene (60 cm^3) was heated at reflux under N_2 for 38 hours to yield the crude product which was purified using flash column chromatography (hexane:Et_2O 3:2) to give uncharacterised white crystals.

Attempted deprotection of *N*-benzyl group of 2'-benzyl-5'-methyl-3a'*H*-spiro[cyclohexane-1,3'-pyrrolo[3,4-*d*][1,2]oxazole]-4',6'(5'*H*,6a'*H*)-dione (91). Preparation of 3-cyclohexylidene-4-hydroxy-1-methylpyrrolidine-2,5-dione (99)

To a solution of **91** (0.050 g, 0.165 x 10^{-3} moles) in anh. MeOH (6.5 cm^3) at r.t. was added anh. formic acid (0.6 cm^3, 1.590 x 10^{-2} moles). Palladium black (0.180 g, 1.700 x 10^{-1} moles) was added to the rapidly stirring solution and stirring continued at r.t. After 2.5 hours the reaction mixture was filtered through celite, washed with MeOH (25 cm^3) and concentrated *in vacuo* to yield a yellow oil. The crude product was purified by flash column chromatography (Et_2O:hexane 1:1) to yield **98** and **99**. The former as yellow crystals (8%), the latter as white crystals (31%).



99

^{1}H NMR (CD_3OD): (δ) 7.81 (1H, br s, OH), 3.21 (1H, d *J* = 1.5, C<u>H</u>OH), 3.07-3.00 (2H, m, 2xC<u>H</u>C=C), 2.87 (3H, s, NCH_3), 2.49-2.26 (2H, m, 2xC<u>H</u>C=C), 1.91-1.43 (6H, m, 3xCH_2).

^{13}C NMR (CD_3OD): (δ) 177.2, 170.2 (2xC=O), 163.8 (<u>C</u>=CCOH), 121.5 (C=<u>C</u>COH), 49.3 (CHOH), 34.0, 31.0, 29.2, 29.1, 26.9 (5xCH_2), 24.0 (NCH_3).

IR (KBr): (cm^{-1}) 3380, 2854, 1652, 1451, 1378, 1263, 1072.

m.p.: 110-116 ^oC

LC/TCOF-MS: $(M + H)^+$ requires 211.1157 g/mol, found 211.1155 g/mol, difference (-0.84 ppm).

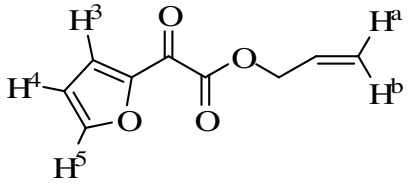
4.2.2 Synthesis of 2nd Generation catalysts

Preparation of prop-2-en-1-yl oxo(phenyl)acetate (104a)[166,168]

Allyl 2-oxo-2-phenylacetate was prepared according to literature reports in 91% yield and ^{1}H NMR spectral data was consistent with that reported.

Preparation of prop-2-en-1-yl furan-2-yl(oxo)acetate (104b)

A solution of α-oxo-2-furanacetic acid (2.500 g, 0.018 moles) and allyl alcohol (1.555 g, 0.027 moles) in toluene (75 cm^3) in the presence of a catalytic amount of *p*-TsOH was stirred with heating at reflux using a Dean-Stark apparatus for 20 hours. The solution was washed with sat. aq. $NaHCO_3$ (20 cm^3) and H_2O (20 cm^3) and the organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude title product as a dark yellow oil (2.800 g, 87%), which was used without further purification.



^{1}H NMR ($CDCl_3$): (δ) 7.78-7.77 (1H, dd *J* = 1.6 & 0.6, H^5), 7.73-7.72 (1H, dd *J* = 3.7 & 0.6 H^3), 6.64-6.63 (1H, dd *J* = 3.7 & 1.6, H^4), 6.09-5.95 (1H, m, C<u>H</u>=CH_2), 5.49-5.32 (2H, m, CH=C<u>H</u>$_2$), 4.85 (2H, d *J* = 5.9, OCH_2).

^{13}C NMR ($CDCl_3$): (δ) 170.8 (ArC=O), 160.7 (OC=O), 149.7 (Q ArC), 149.6 (C^5), 130.6 (<u>C</u>H=CH_2), 124.8 (C^3), 120.1 (<u>C</u>H$_2$=CH), 113.1 (C^4) 67.0 (OCH_2).

IR (Nujol): (cm^{-1}) 3793, 2951, 1675, 1576, 1457.

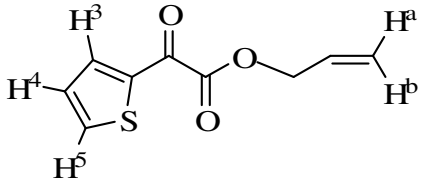
μ analysis:	Found:	C 59.26%	H 4.56%
	$C_9H_8O_4$•0.1H_2O requires:	C 58.86%	H 4.50%

R_f: 0.25 (hexane:EtOAc 9:1)

LC/TCOF-MS: $(M + NH_4)^+$ requires 198.0761 g/mol, found 198.0711 g/mol, difference (4.96 ppm).

Preparation of prop-2-en-1-yl oxo(thiophene-2-yl)acetate (104c)[167]

The α-keto ester **104c** was prepared according to literature methods in 84% yield.



^{1}H NMR ($CDCl_3$): (δ) 8.13-8.11 (1H, dd *J* = 3.9 & 1.1, H^3), 7.84-7.82 (1H, dd *J* = 4.9 & 1.1, H^5), 7.21-71.18 (1H, dd *J* = 4.9 & 3.9, H^4), 6.09-5.96 (1H, m, $\underline{C}H=CH_2$), 5.48-5.42 (1H, dd *J* = 17.2 & 1.3, H^b), 5.37-5.33 (1H, dd *J* = 10.4 & 1.3, H^a), 4.85 (2H, d *J* = 5.9, OCH_2).

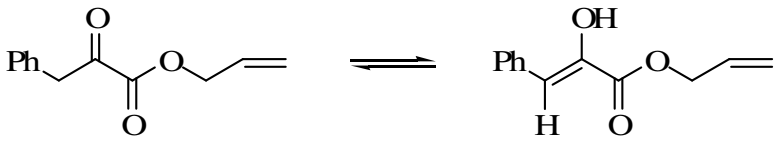
^{13}C NMR ($CDCl_3$): (δ) 176.1 (ArC=O), 161.3 (OC=O), 139.1 (Q ArC), 137.5 ($\underline{C}H=CH_2$), 137.3, 130.7, 128.7 (3xArC), 120.1 ($\underline{C}H_2=CH$), 67.0 (OCH_2).

Synthesis of prop-2-en-1-yl 3-(2-nitrophenyl)-2-oxoproponate (104d)[167]

Prop-2-en-1-yl 3-(2-nitrophenyl)-2-oxoproponate **104d** was prepared according to literature reports in 94% yield.

Preparation of prop-2-en-1-yl 2-oxo-3-phenylpropanoate (104e)

A solution of phenylpyruvic acid (2.500 g, 0.015 moles), allyl alcohol (1.471 g, 0.025 moles) and a catalytic amount of *p*-TsOH in toluene (60 cm^3) was stirred with heating at reflux with a Dean-Stark apparatus for 25 minutes. The solution was allowed to cool to r.t. prior to washing with sat. aq. $NaHCO_3$ (20 cm^3) and H_2O (20 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude product as a yellow oil (3.110 g, 81%) which could not be further purified.



Keto Enol

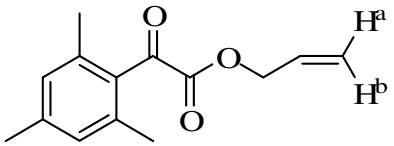
^{1}H NMR ($CDCl_3$): (δ) 7.85-7.26 (10H, m, $ArH_{[keto\ \&\ enol]}$), 6.63 (1H, br s, $OH_{[enol]}$), 6.62 (1H, s, $C\underline{H}Ph_{[enol]}$), 6.11-5.88 (2H, m, $C\underline{H}=CH_{2[keto\ \&\ enol]}$), 5.48-5.30 (4H, $C\underline{H}_2=CH_{[keto\ \&\ enol]}$), 4.85-4.73 (4H, $OCH_{2[keto\ \&\ enol]}$), 4.16 (2H, s, $CH_2Ph_{[keto]}$).

^{13}C NMR ($CDCl_3$): (δ) 164.9, 159.5 ($OC=O_{[keto\ \&\ enol]}$), 156.3 ($CH_2\underline{C}=O_{[keto]}$), 143.8 ($\underline{C}HPh_{[enol]}$), 138.1, 137.5 (Q $ArC_{[keto\ \&\ enol]}$), 130.4, 130.1, 129.4, 129.2, 129.1, 128.8, 128.5, 128.1, 128.0, 127.6 ($10xArC_{[keto\ \&\ enol]}$), 111.4 ($CHPh_{2[enol]}$), 131.4, 130.6 ($\underline{C}H=CH_{2[keto\ \&\ enol]}$), 118.8, 118.2 ($OCH_{2[keto\ \&\ enol]}$), 69.7 ($COH_{[enol]}$), 66.4, 66.1 ($\underline{C}H_2=CH_{[keto\ \&\ enol]}$), 44.8 ($CH_2Ph_{[keto]}$).

IR (Nujol): (cm^{-1}) 3225, 2952, 2587, 1736, 1455, 1274, 1177.

Formation of prop-2-en-1-yl oxo(2,4,6-trimethylphenyl)acetate (104f)

A solution of mesitylglyoxylic acid (1.000 g, 5.202 x 10^{-3} moles) and allyl alcohol (0.453 g, 7.804 x 10^{-3} moles) in toluene (25 cm^3) was heated to reflux in the presence of a catalytic amount of *p*-TsOH. A Dean-Stark apparatus was employed and after 15 minutes the reaction mixture was cooled to r.t., washed with sat. aq. $NaHCO_3$ (15 cm^3) and H_2O (15 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield the title product as a yellow oil (1.087 g, 90%) which was used without further purification.



^{1}H NMR ($CDCl_3$): (δ) 6.86 (2H, s, ArH), 5.99-5.88 (1H, m, $C\underline{H}=CH_2$), 5.40-5.34 (1H, dd *J* = 17.2 & 1.0, H^b), 5.30-5.26 (1H, dd *J* = 10.4 & 1.0, H^a), 4.75 (2H, d *J* = 5.9, OCH_2), 2.27 (3H, s, *p*-$ArCH_3$), 2.24 (6H, s, 2x*o*-$ArCH_3$).

^{13}C NMR ($CDCl_3$): (δ) 191.7 ($Ar\underline{C}=O$), 162.4 (C=O), 141.1 (*p*-ArC), 136.3 (*o*-ArC), 133.1 (Q ArC), 130.7 ($\underline{C}H=CH_2$), 129.1 (*m*-ArC), 120.0 ($\underline{C}H_2=CH$), 66.8 ($\underline{C}H_2O$), 21.2 (*p*-$ArCH_3$), 19.4 (*o*-$ArCH_3$).

IR (nujol): (cm^{-1}) 2854, 1737, 1610, 1460, 1377, 1297, 1201.

μ analysis: Found: C 72.19% H 6.90%

$C_{14}H_{16}O_3$ requires: C 72.39% H 6.95%

R_f: 0.33 (hexane:EtOAc 4:1)

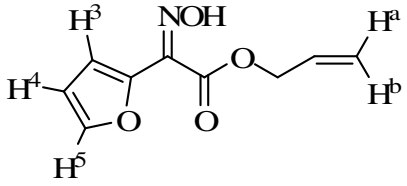
LC/TCOF-MS: $(M + H)^+$ requires 233.1172 g/mol, found 233.1182 g/mol, difference (4.17 ppm).

Synthesis of prop-2-en-1-yl (2*E*)-(hydroxyimino)(phenyl)ethanoate (*E*-103a) and prop-2-en-1-yl (2*Z*)-(hydroxyimino)(phenyl)ethanoate (*Z*-103a)[166,168]

E- and *Z*-**103a** were prepared according to literature reports in 21% and 77% yields respectively and ^{1}H NMR spectral data of each isomer was consistent with that reported.

Synthesis of prop-2-en-1-yl (2*E*)-furan-2-yl(hydroxyimino)ethanoate (*E*-103b) and prop-2-en-1-yl (2*Z*)-furan-2-yl(hydorxyimino)ethanoate (*Z*-103b)

A solution of **104b** (2.788 g, 0.015 moles), NH_2OH•HCl (1.614 g, 0.023 moles) and pyridine (2.714 g, 0.023 moles) in EtOH (140 cm^3) was stirred with heating at reflux for 3 hours. Following cooling to r.t. the solution was evaporated and the residue taken up in DCM (50 cm^3), washed with sat. aq. $NaHCO_3$ (50 cm^3) and H_2O (50 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude product as a mixture of *E*- and *Z*-oxime isomers (*E:Z* 1:1.4) as a brown oil (2.900 g, 99%), which proved impossible to separate by flash column chromatography.



^{1}H NMR ($CDCl_3$): (δ) *E*-oxime isomer 10.23 (1H, br s, OH), 7.57 (1H, d *J* = 1.5, H^5), 7.45 (1H, d *J* = 3.5, H^3), 6.58-6.56 (1H, dd *J* = 3.5 & 1.5, H^4), 6.08-5.94 (1H, m, C<u>H</u>=CH_2), 5.46-5.40 (1H, dd *J* = 17.2 & 1.3, H^b), 5.33-5.29 (1H**,** dd *J* = 10.4 & 1.3, H^a), 4.84 (2H, d *J* = 5.8, OCH_2).

***Z*-oxime isomer** 10.21 (1H, br s, OH), 7.52 (1H, d *J* = 1.5, H^5), 6.68 (1H, d *J* = 3.5, H^3), 6.49-6.47 (1H, dd *J* = 3.5 & 1.5, H^4), 6.08-5.94 (1H, m, C<u>H</u>=CH_2), 5.48-5.43 (1H, dd *J* = 17.2 & 1.3, H^b), 5.35-5.31 (1H**,** dd *J* = 10.4 & 1.3, H^a), 4.88 (2H, d *J* = 5.8, OCH_2).

^{13}C NMR ($CDCl_3$): (δ) *E*-oxime isomer 161.9 (C=O), 144.1 (C^5), 142.3 (C=N), 140.0 (Q ArC), 131.2 (CH_2=<u>C</u>H), 119.8 (C^3), 119.4 (<u>C</u>H_2=CH), 111.9 (C^4), 66.7 (CH_2O).

***Z*-oxime isomer** 161.3 (C=O), 145.1 (C=N), 144.9 (C^5), 142.6 (Q ArC), 130.9 (CH_2=<u>C</u>H), 119.7 (<u>C</u>H_2=CH), 113.1 (C^3), 111.8 (C^4), 66.8 (CH_2O).

IR (Nujol): (cm^{-1}) 3152, 2854, 1737, 1649, 1461, 1377, 1308, 1225, 1157, 1052.

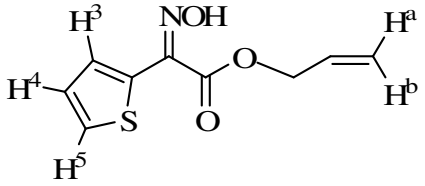
μ analysis:	Found:	C 53.24%	H 4.49%	N 6.70%
	$C_9H_9NO_4$•H_2O requires:	C 52.97%	H 4.93%	N 6.86%

R_f: 0.39 (hexane:EtOAc 3:2)

LC/TCOF-MS: $(M + Na)^+$ requires 219.0456 g/mol, found 219.0464 g/mol, difference (4.09 ppm).

Preparation of prop-2-en-1-yl (2*E*)-(hydroxyimino)(thiophen-2-yl)ethanoate (*E*-103c) and prop-2-en-1-yl (2*Z*)-(hydroxyimino)(thiophen-2-yl)ethanoate (*Z*-103c)[167]

The *E*- (40% yield) and *Z*-oxime isomers (43% yield) were prepared according to the literature.



***E*-oxime isomer**

^{1}H NMR ($CDCl_3$): (δ) 10.69 (1H, br s, OH), 8.18-8.15 (1H, dd *J* = 4.0 & 0.9, H^3), 7.63-7.61 (1H, dd *J* = 5.0 & 0.9, H^5), 7.17-7.14 (1H, dd *J* = 5.0 & 4.0, H^4), 6.12-6.01 (1H, m, C<u>H</u>=CH_2), 5.49-5.42 (1H, dd *J* = 17.2 & 1.2, H^b), 5.36-5.32 (1H, dd *J* = 10.4 & 1.2, H^a), 4.86 (2H, d *J* = 5.9, OCH_2).

^{13}C NMR ($CDCl_3$): (δ) 162.9 (C=O), 141.8 (C=N), 133.5 (C^3), 131.1 (C^5), 131.2 (<u>C</u>H=CH_2), 127.9 (Q ArC), 126.5 (C^4), 119.7 (<u>C</u>H_2=CH), 66.9 (OCH_2).

***Z*-oxime isomer**

^{1}H NMR ($CDCl_3$): (δ) 9.37 (1H, br s, OH), 7.37-7.35 (1H, dd *J* = 5.1 & 1.0, H^5), 7.21-7.19 (1H, dd *J* = 3.8 & 1.0, H^3), 7.05-7.02 (1H, dd *J* = 5.1 & 3.8, H^4), 6.08-5.95 (1H, m, C<u>H</u>=CH_2), 5.45-5.42 (1H, dd *J* = 17.2 & 1.3, H_b), 5.35-5.31 (1H, dd *J* = 10.4 & 1.3, H_a), 4.89 (2H, d *J* = 5.9, OCH_2).

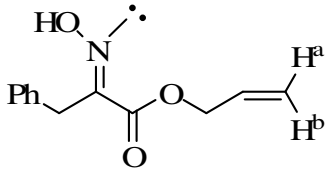
^{13}C NMR ($CDCl_3$): (δ) 162.7 (C=O), 146.9 (C=N), 133.7 (Q ArC), 130.9 (C̲H=CH_2), 129.1 (C^3), 128.4 (C^5), 127.5 (C^4), 119.9 (C̲H_2=CH), 66.7 (OCH_2).

Preparation of prop-2-en-1-yl (2*Z*)-2-(hydroxyimino)-3-(2-nitrophenyl) propanoate (*E*-103d)[167]

Prop-2-en-1-yl (2*E*)-2-(hydroxyimino)-3-(2-nitrophenyl)propanoate **103d** was prepared according to the literature in 91% yield.

Preparation of prop-2-en-1-yl (2*E*)-2-(hydroxyimino)-3-phenylpropanoate (*E*-103e)

A mixture of **104e** (1.600 g, 0.008 moles), NH_2OH•HCl (0.654 g, 0.009 moles) and pyridine (0.744 g, 0.009 moles) in EtOH (35 cm^3) was heated with stirring at reflux for 3 hours. The mixture was allowed to cool to r.t. prior to evaporation. The residue was taken up in DCM (20 cm^3) and the solution was washed with sat. aq. $NaHCO_3$ (15 cm^3) and H_2O (15 cm^3) and the organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude product as a yellow oil, which was purified by flash column chromatography (hexane:Et_2O 1:1) to yield the *E*-oxime isomer as a white solid (1.271 g, 75%).



^{1}H NMR ($CDCl_3$): (δ) 9.45 (1H, br s, NOH), 7.33-7.21 (5H, m, 5xArH), 5.98-5.89 (1H, m, C̲H=CH_2), 5.36-5.30 (1H, dd *J* = 17.0 & 1.1, H^b), 5.28-5.25 (1H, dd *J* = 10.6 & 1.1, H^a), 4.71 (2H, d *J* = 5.8, CH_2O), 3.99 (2H, s, CH_2Ph).

^{13}C NMR ($CDCl_3$): (δ) 163.0 (C=O), 151.1 (C=N), 135.6 (Q ArC), 131.3 (C̲H=CH_2), 129.2, 128.6, 126.7 (3xArC), 119.3 (C̲H_2=CH), 66.5 (OCH_2), 30.6 (C̲H_2Ph).

IR (KBr): (cm^{-1}) 3243, 1726, 1449, 1311.

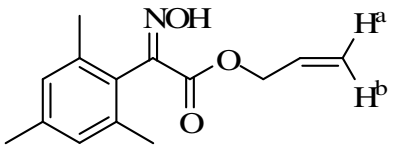
μ analysis:	Found:	C 68.08%	H 7.21%	N 5.15%
	$C_{12}H_{13}NO_3$ requires:	C 67.98%	H 6.93%	N 5.66%

m.p.: 59-62 °C

LC/TCOF-MS: $(M + Na)^+$ requires 242.0787 g/mol, found 242.0779 g/mol, difference (0.8 ppm).

Synthesis of prop-2-en-1-yl (2*E*)-hydroxyimino)(2,4,6-trimethylphenyl)ethanoate (*E*-103f) and prop-2-en-1-yl (2*Z*)-hydroxyimino)(2,4,6-trimethyl phenyl)ethanoate (*Z*-103f)

A mixture of **104f** (0.561 g, 2.417 x 10^{-3} moles), pyridine (0.421 g, 0.430 cm^3, 5.322 x 10^{-3} moles) and NH_2OH•HCl (0.370 g, 5.324 x 10^{-3} moles) in ^{i}PrOH (11 cm^3) was heated with stirring at reflux for 56 hours. The mixture was allowed to cool to r.t. prior to evaporation to dryness. The residue was taken up in DCM (10 cm^3) and the organics were washed with sat. aq. $NaHCO_3$ (5 cm^3) and H_2O (5 cm^3), dried ($MgSO_4$), filtered and evaporated to yield the crude product as a yellow oil. Purification by flash column chromatography (hexane:EtOAc 9.5:0.5) yielded the *E*-isomer as a cream solid (0.042 g, 8%) and the *Z*-isomer as a yellow oil (0.314 g, 62%) together with unreacted **104f**.



***E*-oxime isomer**

^{1}H NMR ($CDCl_3$): (δ) 8.65 (1H, br s, NOH), 6.91 (2H, s, 2xArH), 6.00-5.87 (1H, m, C<u>H</u>=CH_2), 5.34-5.28 (1H, dd *J* = 17.2 & 1.3, H^b), 5.27-5.23 (1H, dd *J* = 10.4 & 1.3, H^a), 4.75 (2H, d *J* = 5.8, OCH_2), 2.30 (3H, s, *p*-CH_3), 2.14 (6H, s, *o*-CH_3).

^{13}C NMR ($CDCl_3$): (δ) 162.8 (<u>C</u>=O), 151.9 (<u>C</u>=N), 139.2 (*p*-ArC), 135.6 (*o*-ArC), 131.3 (<u>C</u>H=CH_2), 128.2 (*m*-ArC), 126.6 (Q ArC), 119.2 (<u>C</u>H_2=CH), 66.4 (OCH_2), 21.2 (*p*-CH_3), 19.5 (*o*-CH_3).

IR (KBr): (cm^{-1}) 3258, 2923, 1735, 1410, 1199.

µ analysis:	Found:	C 68.10%	H 7.04%	N 5.62%
	$C_{14}H_{17}NO_3$ requires:	C 67.98%	H 6.93%	N 5.66%

m.p.: 83-87 ^{o}C

LC/TCOF-MS: $(M + Na)^+$ requires 248.1281 g/mol, found 248.1285 g/mol, difference (1.5 ppm).

***Z*-oxime isomer**

^{1}H NMR ($CDCl_3$): (δ) 11.11 (1H, br s, NOH), 6.89 (2H, s, *m*-ArH), 5.93-5.80 (1H, m, $\underline{C}H=CH_2$), 5.30-5.26 (1H, dd *J* = 12.7 & 1.4, H^b), 5.24-5.22 (1H, dd *J* = 5.9 & 1.4, H^a), 4.72 (2H, d *J* = 5.7, OCH_2), 2.29 (3H, s, *p*-$ArCH_3$), 2.23 (6H, s, *o*-CH_3).

^{13}C NMR ($CDCl_3$): (δ) 163.0 (C=O), 148.7 (C=N), 139.1 (*p*-ArC), 137.4 (*o*-ArC), 130.6 ($\underline{C}H=CH_2$), 128.5 (*m*-ArC), 128.0 (Q ArC), 119.5 ($\underline{C}H_2=CH$), 66.2 (OCH_2), 21.1 (*p*-$ArCH_3$), 19.8 (*o*-$ArCH_3$).

IR (Nujol): (cm^{-1}) 3266, 2924, 1736, 1612, 1456, 1287.

R_f: 0.40 (hexane:EtOAc 4:1)

LC/TCOF-MS: $(M + Na)^+$ requires 270.1101 g/mol, found 270.1108 g/mol, difference (2.58 ppm).

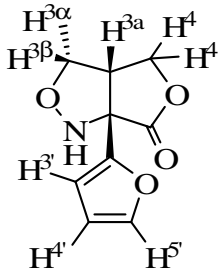
Preparation of 6a-phenyltetrahydro-3*H*,6*H*-furo[3,4-*c*][1,2]oxazol-6-one (109a) and 5-methyl-3-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one 4-oxide (110a)

Method I: The title compound was prepared as reported in the literature following separation of the geometrical *E*- and Z-oximes of **103a** and reaction of a pure sample of the *Z*-isomer under thermal conditions in 53% yield[166,168].

Method II: A 1:5 mixture of the crude *E*- and *Z*-oxime isomers (2.000 g, 0.010 moles) was heated neat at 160 ^oC for 2 hours to form the crude product as a dark brown oil. The oil was purified by flash column chromatography (EtOAc:hexane 3:2) and recrystallised from EtOAc to yield the title product **110a** as white crystals (0.840 g, 42%) and **109a** as a brown solid (0.460 g, 23%).

Synthesis of 6a-(furan-2-yl)tetrahydro-3*H*,6*H*-furo[3,4-*c*][1,2]oxazol-6-one (110b) and 3-(furan-2-yl)-5-methyl-5,6-dihydro-2*H*-1,4-oxazine-1-one 4-oxide (109b)

A mixture of *E*- and *Z*-**103b** (1.000 g, 0.005 moles) in xylene (300 cm^3) was heated with stirring at reflux in the presence of hydroquinone (1.0%, w/v, 3.000 g) under N_2 for 24 hours. The solution was allowed to cool to r.t., the xylene was removed under vacuum and the crude product was taken up in $CHCl_3$ (150 cm^3) and left at r.t. for 30 minutes. After any remaining hydroquinone had precipitated the solution was filtered and evaporated to yield the crude product which was purified by flash column chromatography (hexane:EtOAc 1:1) to yield **110b** as a brown solid (0.200 g, 20%) and **109b** as a brown solid (0.551 g, 56%).



110b

^{1}H NMR ($CDCl_3$): (δ) 7.46 (1H, d *J* = 1.9, $H^{5'}$), 6.64 (1H, d *J* = 3.3, $H^{3'}$), 6.43-6.41 (1H, dd *J* = 3.3 & 1.9, $H^{4'}$), 5.79 (1H, br s, NH), 4.62-4.56 (1H, dd *J* = 9.6 & 8.3, H^4), 4.33-4.26 (2H, m, $H^{3\beta\&4}$), 4.20-4.14 (1H, dd *J* = 9.1 & 6.5, $H^{3\alpha}$), 3.75-3.67 (1H, m, H^{3a}).

^{13}C NMR ($CDCl_3$): (δ) 173.1 (C=O), 144.2 (C^{6a}), 143.9 ($C^{5'}$), 111.3 ($C^{4'}$), 110.8 ($C^{3'}$), 70.2 (Q ArC), 69.9 (C^4), 48.1 (C^{3a}), 29.7 (C^3).

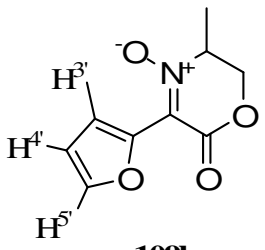
IR (KBr): (cm^{-1}) 3384, 2849, 1766, 1377, 1194.

μ analysis: Found: C 51.26% H 4.46% N 6.50%

$C_9H_9NO_4 \bullet 0.75H_2O$ requires: C 51.82% H 4.71% N 6.71%

m.p.: 69-74 °C

LC/TCOF-MS: $(M + H)^+$ requires 196.0540 g/mol, found 196.0548 g/mol, difference (3.60 ppm).



109b

^{1}H NMR ($CDCl_3$): (δ) 7.80 (1H, d *J* = 3.5, $H^{3'}$), 7.63 (1H, d *J* = 1.6, $H^{5'}$), 6.57-6.56 (1H, dd *J* = 3.5 & 1.6, $H^{4'}$), 4.70-4.63 (1H, m, C<u>H</u>CH_3), 4.37-4.26 (2H, m, CH_2), 1.61 (3H, d *J* = 6.7, CH_3).

^{13}C NMR ($CDCl_3$): (δ) 156.5 (C=O), 144.7 ($C^{5'}$), 143.6 (C=N), 127.2 (Q ArC), 118.3 ($C^{3'}$), 111.6 ($C^{4'}$), 67.0 (CH_2), 64.0 (<u>C</u>HCH_3), 14.2 (CH_3).

IR (KBr): (cm^{-1}): 3426, 2837, 1716, 1526, 1286, 1280, 1207.

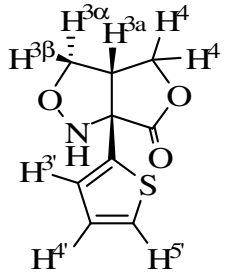
μ analysis:	Found:	C 55.78%	H 4.76%	N 6.94%
	$C_9H_9NO_4$ requires:	C 55.37%	H 4.65%	N 7.18%

m.p.: 68-72 ^oC

LC/TCOF-MS: $(M + H)^+$ requires 196.0604 g/mol, found 196.0613 g/mol, difference (4.30 ppm).

Preparation of 6a-(thiophene-2-yl)tetrahydro-3*H*,6*H*-furo[3,4-*c*][1,2]oxazol-6-one (110c) and 5-methyl-3-(thiophen-2-yl)-5,6-dihydro-2*H*-1,4-oxazin-2-one 4-oxide (109c)

A solution of *Z*-**103c** (0.233 g, 1.104 x 10^{-3} moles) in xylene (70 cm^3) was heated to reflux in the presence of hydroquinone (1.0%, w/v, 0.700 g) under N_2 for 46 hours. The solution was allowed to cool to r.t., the xylene was removed *in vacuo* and the residue was taken up in $CHCl_3$ (50 cm^3) and left to stand at r.t. for 30 minutes. After any remaining hydroquinone had precipitated the $CHCl_3$ solution was filtered and evaporated to yield the crude product which was purified by flash column chromatography (hexane:Et_2O 1:3.5) to give **110c** as a pale brown solid (0.051 g, 22%), **109c** as a brown solid (0.096 g, 41%) and unreacted *Z*-oxime (0.034 g, 15%).



110c

^{1}H NMR ($CDCl_3$): (δ) 7.40-7.38 (1H, dd *J* = 5.1 & 1.2, $H^{5'}$), 7.29-7.27 (1H, br dd *J* = 3.5 & 1.2, $H^{3'}$), 7.07-7.04 (1H, dd *J* = 5.1 & 3.8, $H^{4'}$), 5.76 (1H, br s, NH), 4.65-4.59 (1H, dd *J* = 9.7 & 7.1, $H^{3\alpha}$), 4.39-4.34 (1H, dd *J* = 9.7 & 2.4, $H^{3\beta}$), 4.30-4.19 (2H, m, H^4), 3.63-3.57 (1H, m, H^{3a}).

^{13}C NMR ($CDCl_3$): (δ) 175.3 (C=O), 134.6 (Q ArC), 127.7 ($C^{4'}$), 127.3 ($C^{3'\&5'}$), 78.7 (C^4), 72.5 (C^{6a}), 70.6 (C^3), 50.51 (C^{3a}).

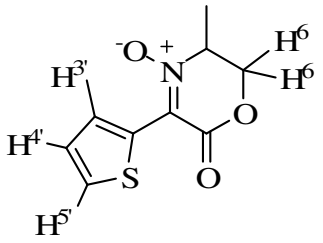
IR (KBr): (cm^{-1}) 3197, 3070, 2923, 1764, 1481, 1384, 1234, 983.

µ analysis: Found: C 50.51% H 4.98% N 6.06%

$C_9H_9NO_3S•0.25H_2O$ requires: C 50.13% H 4.44% N 6.49%

m.p.: 135-140 °C

LC/TCOF-MS: $(M + K)^+$ requires 249.9935 g/mol, found 249.9937 g/mol, difference (0.97 ppm).



109c

^{1}H NMR ($CDCl_3$): (δ) 8.49-8.47 (1H, dd *J* = 4.2 & 1.1, $H^{3'}$), 7.53-7.51 (1H, dd *J* = 5.1 & 1.1, $H^{5'}$), 7.24-7.21 (1H, dd *J* = 5.1 & 4.2, $H^{4'}$), 4.70-4.64 (2H, m, H^6), 4.44-4.33 (1H, m, C<u>H</u>CH_3), 1.66 (3H, d *J* = 6.6, CH_3).

^{13}C NMR ($CDCl_3$): (δ) 157.5 (C=O), 132.8 ($C^{3'}$), 130.6 ($C=N^+$), 129.2 ($C^{5'}$), 129.0 (Q ArC), 127.2 ($C^{4'}$), 67.0 (<u>C</u>HCH_3), 63.2 (CH_2), 14.4 (CH_3).

IR (cm^{-1}): 3426, 1731, 1538, 1446, 1401, 1360, 1273.

µ analysis: Found: C 51.99% H 4.57% N 6.32%

$C_9H_9NO_3S•^{0.5}C_3H_6O$ requires: C 51.85% H 4.69% N 6.20%

m.p.: 119-123 °C

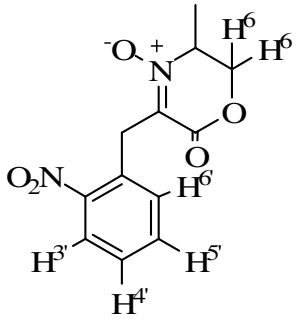
LC/TCOF-MS: $(M + Na)^+$ requires 234.0195 g/mol, found 234.0202 g/mol, difference (5.70 ppm).

Preparation of 5-methyl-3-(thiophen-2-yl)-5,6-dihydro-2*H*-1,4-oxazin-2-one 4-oxide (109c)

A solution of *E*-**103c** (0.200 g, 9.476 x 10^{-4} moles) in xylene (60 cm^3) was heated to reflux in the presence of hydroquinone (1.0%, w/v, 0.600 g) under N_2 for 24 hours. The solution was allowed to cool to r.t., the xylene was removed *in vacuo* and the crude product was taken up in $CHCl_3$ (50 cm^3) and left to stand at r.t. for 30 minutes. After any remaining hydroquinone had precipitated the solution was filtered and evaporated to yield the crude product which was purified by flash column chromatography (hexane:Et_2O 1:3.5) to give the title product as a brown solid (0.157 g, 79%).

Preparation of 5-methyl-3-(2-nitrobenzyl)-5,6-dihydro-2*H*-1,4-oxazin-2-one 4-oxide (109d)

A solution of **103d** (0.500 g, 1.893 x 10^{-3} moles) was heated to reflux in xylene (150 cm^3) in the presence of hydroquinone (1.0% w/v, 1.500 g) for 28 hours under N_2. The solution was allowed to cool to r.t, evaporated and the residue was taken up in $CHCl_3$ (50 cm^3). After 30 minutes any precipitated hydroquinone was removed by filtration and the solvent evaporated to yield the crude product as a yellow oil which was purified by flash column chromatography (hexane:EtOAc 1:1) to yield the title product as a yellow solid (0.149 g, 50%).



^{1}H NMR ($CDCl_3$): (δ) 7.94-7.91 (1H, dd *J* = 8.7 & 1.7, $H^{3'}$), 7.55-7.52 (1H, ddd *J* = 9.4, 7.5 & 1.7, $H^{5'}$), 7.42-7.37 (2H, m, $H^{3'\&5'}$), 4.63-4.58 (1H, dd *J* = 12.2 & 3.6, H^6), 4.35 (2H, s, $C\underline{H}_2Ar$), 4.32-4.26 (1H, dd *J* = 12.2 & 5.9, H^6), 4.20-4.10 (1H, m, $C\underline{H}CH_3$), 1.53 (3H, d *J* = 6.8, CH_3).

^{13}C NMR ($CDCl_3$): (δ) 159.0 (C=O), 149.6 (Q ArC), 135.7 ($C=N^+$), 133.0 ($C^{5'}$), 131.7 ($C^{4'/6'}$), 130.2 ($C^{2'}$), 128.0 ($C^{4'/6'}$), 124.8 ($C^{3'}$), 67.3 (C^6), 63.7 ($\underline{C}HCH_3$), 28.6 ($C\underline{H}_2Ph$), 14.3 (CH_3).

IR (KBr): (cm^{-1}) 2923, 1727, 1520, 1342, 1265.

μ analysis: Found: C 52.92% H 5.11% N 9.70%

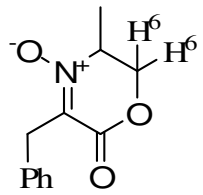
$C_{12}H_{12}N_2O_5 \bullet 1/2H_2O$ requires: C 52.75% H 4.80% N 10.20%

m.p.: 68-74 °C

LC/TCOF-MS: $(M + Na)^+$ requires 288.0669 g/mol, found 288.0678 g/mol, difference (3.00 ppm).

Preparation of 3-benzyl-5-methyl-5,6-dihydro-2*H*-1,4-oxazin-2-one 4-oxide (109e)

A solution of *E*-**103e** (0.158g, 7.207 x 10^{-4} moles) was heated at reflux in xylene (50 cm^3) in the presence of hydroquinone (1% w/v, 0.500 g) under N_2 for 24 hours to yield the crude product which was purified by flash column chromatography (EtOAc:hexane 3:2) to yield **109e** as a yellow solid (0.038 g, 24%).



^{1}H NMR ($CDCl_3$): (δ) 7.37-7.19 (5H, m, ArH), 4.57-4.52 (1H, dd *J* = 12.0 & 3.5, H^6), 4.26-4.20 (1H, dd *J* = 12.0 & 5.8, H^6), 4.19-4.11 (1H, m, C<u>H</u>CH_3), 4.02 (2H, s, C<u>H</u>$_2$Ph), 1.53 (3H, d *J* = 6.8, CH_3).

^{13}C NMR ($CDCl_3$): (δ) 158.2 (C=O), 134.6 ($C=N^+$), 133.7 (Q ArC), 128.6, 127.6, 124.7 (3xArC), 66.6 (C^6), 62.8 (<u>C</u>HCH_3), 29.9 (<u>C</u>H_2Ph), 13.4 (CH_3).

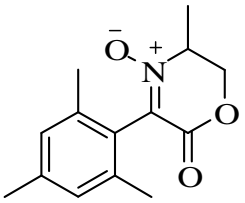
IR (KBr): (cm^{-1}): 3402, 1703, 1553, 1495, 1453, 1382, 1362.

m.p.: 88-94 ^oC

LC/TCOF-MS: $(M + H)^+$ requires 220.0968 g/mol, found 220.0964 g/mol, difference (-1.80 ppm).

Preparation of 5-methyl-3-(2,4,6-trimethylphenyl)-5,6-dihydro-2*H*-1,4-oxazin-2-one 4-oxide (109f)

A solution of *E*-**103f** (0.050 g, 2.022 x 10^{-4} moles) was heated in xylene (15 cm^3) to reflux in the presence of hydroquinone (1 mol% w/v, 0.150 g) for 24 hours. The reaction was allowed to cool to r.t. prior to evaporation. The residue was taken up in $CHCl_3$ (15 cm^3) and left to stand at r.t. for 30 minutes. After any remaining hydroquinone had precipitated the solution was filtered and evaporated to yield the crude product as a pale brown solid (0.045 g, 89%).



^{1}H NMR ($CDCl_3$): (δ) 6.92 (2H, s, *m*-ArH), 4.74-4.68 (1H, dd *J* = 12.2 & 3.4, OCH_2), 4.38-4.23 (1H, dd *J* = 12.2 & 4.0, OCH_2), 4.29-4.20 (1H, m, C<u>H</u>CH_3), 2.29 (3H, s, *p*-CH_3), 2.12 (3H, s, *o*-CH_3), 2.09 (3H, s, *o*-CH_3), 1.66 (3H, d *J* = 6.9, CHC<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$): (δ) 157.6 (C=O), 139.2 ($C=N^+$), 136.2, 135.6, 134.9 (4xQ ArC), 127.9 (*o*-ArC), 66.1 (CH_2), 63.6 (<u>C</u>HCH_3), 20.2 (*p*-CH_3), 18.3, 17.9 (2x*o*-CH_3), 13.8 (CH_3).

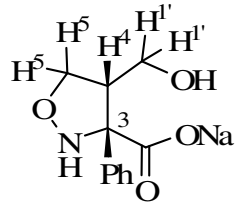
IR (KBr): (cm^{-1}) 3415, 2920, 1722, 1611, 1722, 1534, 1464, 1350, 1282, 1201, 1142.

m.p.: 101-109 ^oC

LC/TCOF-MS: $(M + H)^+$ requires 249.1314 g/mol, found 239.1304 g/mol, difference (-3.73 ppm).

Preparation of sodium 4-(hydroxymethyl)-3-phenyl-1,2-oxazolidine-3-carboxylate (111)

A solution of **110a** (0.100 g, 4.876 x 10^{-4} moles) and NaOH (0.024 g, 5.900 x 10^{-4} moles) in MeOH (5 cm^3) was stirred at reflux for 4 hours. The cooled solution was concentrated to dryness giving a white powder (0.140 g) which was used without further purification.



^{1}H-NMR (d_6-DMSO): (δ) 7.70 (2H, d *J* = 7.4, *o*-ArH), 7.23-7.18 (2H, dd *J* = 7.4 & 7.2, *m*-ArH), 7.12-7.10 (1H, d *J* = 7.2, *p*-ArH), 3.93-3.89 (1H, br dd *J* = 7.9, H^5), 3.71-3.64 (1H, dd *J* = 11.1 & 8.2, $H^{1'}$), 3.48-3.43 (1H, dd *J* = 11.1 & 5.2, $H^{1'}$), 3.30-3.25 (1H, dd *J* = 14.0 & 7.9, H^5), 2.87-2.78 (1H, m, H^4).

^{13}C-NMR (d_6-DMSO): (δ) 171.8 (C=O), 146.9 (Q ArC), 127.4 (*o*-ArC), 126.6 (*m*-ArC), 125.1 (*p*-ArC), 76.0 (C^3), 73.3 (C^5), 61.6 ($C^{1'}$), 57.3 (C^4).

IR (KBr): (cm^{-1}) 3427, 2963, 1603, 1377, 1068, 801.

μ analysis: Found: C 50.32% H 4.56% N 4.67%

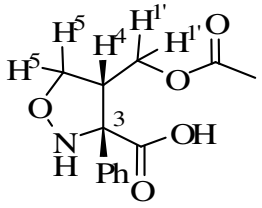
$C_{11}H_{10}NO_5Na•0.5CH_3OH$ requires: C 50.19% H 4.39% N 5.08%

m.p.: 127-133 °C

LC/TCOF-MS: $(2M + Na)^+[-H_2O]$ requires 523.0700 g/mol, found 523.0699 g/mol, difference (-0.22 ppm).

Preparation of (3*S*)-4-[(acetyloxy)methyl]-3-phenyl-1,2-oxazolidine-3-carboxylic acid (112)

A solution of **111** was stirred in Ac_2O (10 cm^3) for 5 hours at 60 °C. The reaction mixture was evaporated to dryness, ice-water (15 cm^3) was added to the residue prior to extraction with Et_2O (2 x 10 cm^3). The organic layer was collected, dried ($MgSO_4$), filtered and evaporated to yield the title product as a pale yellow solid, (0.748 g, 81%) which required no further purification.



^{1}H-NMR ($CDCl_3$): (δ) 7.47-7.35 (5H, m, 5xArH), 4.54-4.48 (1H, dd *J* = 9.8 & 7.6, H^5), 4.40-4.35 (1H, dd *J* = 9.0 & 5.9, $H^{1'}$), 4.32-4.27 (1H, dd, *J* = 9.8 & 4.4, H^5), 4.13-4.08 (1H, dd, *J* = 9.0 & 4.0, $H^{1'}$), 3.59-3.52 (1H, m, H^4), 1.98 (3H, s, CH_3).

^{13}C-NMR ($CDCl_3$): (δ) 172.1 (C=O), 166.8 (C=O), 135.2 (Q ArC), 129.4, 128.7, 125.7 (3xArC), 72.5 (C^3), 70.3 ($C^{1'}$), 67.3 (C^5), 56.1 (C^4), 22.3 (CH_3).

IR (KBr): (cm^{-1}) 3510, 2994, 1766, 1655, 1449, 1373, 1347, 1229, 1182, 972, 755.

m.p.: 137-141 °C

LC/TCOF-MS: $(M + Na)^+$ requires 288.0842 g/mol, found 288.0831 g/mol, difference (-3.88 ppm).

Synthesis of oxo(phenyl)acetyl chloride (115a)[153]

The title compound was prepared by known methods and was obtained in 100% yield. It was used immediately. Spectral data was consistent with that in the literature.

Preparation of furan-2-yl(oxo)acetyl chloride (115b)[175]

α-Oxo-2-furanacetic acid (0.200 g, 0.001 moles) was stirred neat under Ar at r.t. for 10 minutes. α,α-Dichloromethylmethyl ether (0.494 g, 0.004 moles, 0.39 cm^3) was added dropwise and evolution of HCl started. The mixture was heated in an oil bath at 50 ^oC for 30 minutes and then allowed to cool to r.t. Methyl formate was removed on a rotatory evaporator using an ice-cooled water bath to yield the product as a pungent brown oil (0.226 g, 100%), which was immediately reacted.

Preparation of oxo(thiophen-2-yl)acetyl chloride (115c)[175]

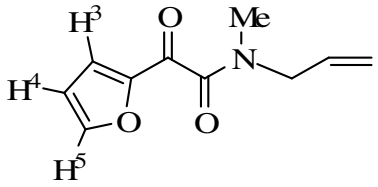
Thiophene-2-glyoxylic acid (1.000 g, 0.006 moles) was stirred at r.t. in the absence of solvent under N_2 for 15 minutes. α,α-Dichloromethyl methyl ether (2.205 g, 0.019 moles) was added dropwise and evolution of HCl started. The mixture was heated in an oil bath at 50 ^oC for 30 minutes before cooling to r.t. Methyl formate was removed on a rotatory evaporator using an ice-cooled water bath to yield the product as a brown oil (1.126 g, 100%), which was used immediately.

Preparation of *N*-methyl-2-oxo-2-phenyl-*N*-(prop-2-en-1-yl)acetamide (113a)[153]

The title product **113a** was prepared according to literature reports and obtained in 96% yield.

Preparation of 2-(furan-2-yl)-*N*-methyl-2-oxo-*N*-(prop-2-en-1-yl)acetamide (113b)

To a mixture of *N*-methylallylamine (1.442 g, 0.020 moles) and $NaHCO_3$ (1.706 g, 0.020 moles) in DCM (30 cm^3) at 0 ^oC was added dropwise a solution of **115b** (2.491 g, 0.015 moles) in DCM (8 cm^3). The mixture was stirred at r.t. for 1 hour prior to washing with H_2O (20 cm^3). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed by rotary evaporation to yield the crude product as a brown oil (2.658 g, 88%). Rotamer ratio: 1.1:1.



^{1}H NMR ($CDCl_3$): (δ) 7.57-7.56 (2.1H, m, $H^{5}_{[major\ rot.\ \&\ minor\ rot.]}$), 7.15 (2.1H, d *J* = 3.5, $H^{3}_{[major\ rot.\ \&\ minor\ rot.]}$), 6.44-6.42 (2.1H, m, $H^{4}_{[major\ rot.\ \&\ minor\ rot.]}$), 5.65-5.50 (2.1H, m, $C\underline{H}=CH_{2[major\ rot.\ \&\ minor\ rot.]}$), 5.48-4.97 (4.2H, m, $C\underline{H_2}=CH_{[major\ rot.\ \&\ minor\ rot.]}$), 3.90 (2.2H, d *J* = 5.8, $NC\underline{H}_{2[major\ rot.]}$), 3.68 (2H, d *J* = 5.8, $NC\underline{H}_{2[minor\ rot.]}$), 2.81 (3H, s, $NCH_{3[minor\ rot.]}$), 2.75 (3.3H, s, $NCH_{3[major\ rot.]}$).

^{13}C NMR ($CDCl_3$): (δ) 178.4 & 178.3 ($ArC=O_{[major\ rot.\ \&\ minor\ rot.]}$), 165.6 & 165.2 ($NC=O_{[major\ rot.\ \&\ minor\ rot.]}$), 150.1 & 149.9 (2xQ $ArC_{[major\ rot.\ \&\ minor\ rot.]}$), 148.8 ($C^5$), 131.9 & 131.6 ($\underline{C}H=CH_{2[major\ rot.\ \&\ minor\ rot.]}$), 122.3 ($C^3$), 119.3 & 119.2 ($\underline{C}H_2=CH_{[major\ rot.\ \&\ minor\ rot.]}$), 112.8 ($C^4$), 52.1 ($NCH_{2[major\ rot.]}$), 48.8 ($NCH_{2[minor\ rot.]}$), 34.5 ($NCH_{3[minor\ rot.]}$), 31.7 ($NCH_{3[major\ rot.]}$).

IR (nujol): (cm^{-1}) 2854, 1654, 1568, 1462, 1377.

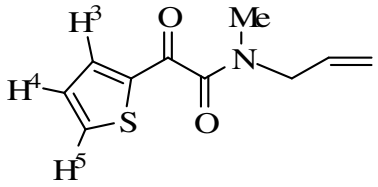
μ analysis:	Found:	C 59.75%	H 5.60%	N 6.94%
	$C_{10}H_{11}NO_3 \bullet 0.5H_2O$ requires:	C 59.40%	H 5.73%	N 6.63%

R_f: 0.31 (4:1 hexane:EtOAc)

LC/TCOF-MS: $(M + Na)^+$ requires 216.0631 g/mol, found 216.0639 g/mol, difference (3.70 ppm).

Preparation of *N*-methyl-2-oxo-*N*-(prop-2-en-1-yl)-2-(thiophen-2-yl)acetamide (113c)

To a cooled solution of *N*-methylallylamine (0.651 g, 0.009 moles) and $NaHCO_3$ (0.770 g, 0.009 moles) in DCM (4 cm^3) at 0 °C was added dropwise a solution of **115c** (1.126 g, 0.006 moles) in DCM (4 cm^3). The mixture was stirred at r.t. for 1 hour before washing with H_2O (5 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude title product as a brown oil (1.013 g, 75%). Rotamer ratio: 1.1:1.



^{1}H NMR ($CDCl_3$): (δ) 7.83-7.78 (2.1H, m, $H^{3\&5}_{[major\ rot.\ \&\ minor\ rot.]}$), 7.28-7.16 (2.1H, m, $H^{4}_{[major\ rot.\ \&\ minor\ rot.]}$), 5.89-5.73 (2.1H, m, $C\underline{H}CH_{2[major\ rot.\ \&\ minor\ rot.]}$), 5.32-5.18 (4.2H, m, $C\underline{H}_2{=}CH_{[major\ rot.\ \&\ minor\ rot.]}$), 4.13 (2H, d *J* = 6.0, $NCH_{2[minor\ rot.]}$), 3.90 (2.2H, d *J* = 5.9, $NCH_{2[major\ rot.]}$), 3.05 (3.3H, s, $CH_{3[major\ rot.]}$), 2.98 (3H, s, $CH_{3[minor\ rot.]}$).

^{13}C NMR ($CDCl_3$): (δ) 183.4, 183.3 ($Ar\underline{C}{=}O_{[major\ rot.\ \&\ minor\ rot.]}$), 166.1, 165.7 ($N\underline{C}{=}O_{[major\ rot.\ \&\ minor\ rot.]}$), 140.3, 140.2 (2xQ $ArC_{[major\ rot.\ \&\ minor\ rot.]}$), 136.5, 136.4 ($C^{3}_{[major\ rot.\ \&\ minor\ rot.]}$), 136.2, 136.1 ($C^{5}_{[major\ rot.\ \&\ minor\ rot.]}$), 132.2, 131.4 ($\underline{C}H{=}CH_{2[major\ rot.\ \&\ minor\ rot.]}$), 128.7, 128.6 ($C^{4}_{[major\ rot.\ \&\ minor\ rot.]}$), 119.0, 118.7 ($\underline{C}H_2{=}CH_{[major\ rot.\ \&\ minor\ rot.]}$), 52.5, 49.1 ($NCH_{2[major\ rot.\ \&\ minor\ rot.]}$), 34.8, 32.0 ($NCH_{3[major\ rot.\ \&\ minor\ rot.]}$).

IR (Nujol): (cm^{-1}) 3286, 3086, 2932, 1852, 1760, 1659, 1408, 1355, 1287.

μ analysis:	Found:	C 55.32%	H 5.25%	N 6.01%
	$C_{10}H_{11}NSO_2{\bullet}0.5H_2O$ requires:	C 55.07%	H 5.55%	N 6.42%

R_f: 0.33 (hexane:EtOAc 9:1)

LC/TCOF-MS: $(M + K)^+$ requires 248.0142 g/mol, found 248.0148 g/mol, difference (2.52 ppm).

Synthesis of *Z*-2-(hydroxyimino-*N*-methyl-2-phenyl-*N*-(prop-2-en-2-yl)ethanamide (*Z*-116a)[153]

The *Z*-aldoxime was prepared from **113a** in 39% yield and spectral data was consistent with that reported in the literature.

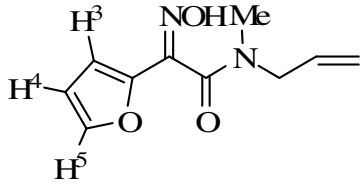
Synthesis of *E*-2-(furan-2-yl)-2-(hydroxyimino)-*N*-methyl-*N*-(prop-2-en-1-yl)ethanamide (*E*-116b) and *Z*-2-(furan-2-yl)-2-(hydroxyimino)-*N*-methyl-*N*-(prop-2-en-1-yl)ethanamide (*Z*-116b)

A mixture of **113b** (4.995 g, 2.587 x 10^{-3} moles), pyridine (2.237 g, 2.828 x 10^{-3} moles) and $NH_2OH{\bullet}HCl$ (1.968 g, 2.828 x 10^{-3} moles) in EtOH (500 cm^3) was stirred with heating at reflux for 20 hours. The solution was cooled to r.t. prior to evaporation under reduced pressure. The residue was taken up in DCM (150 cm^3) and the organics were

washed with sat. aq. $NaHCO_3$ (50 cm^3) and H_2O (50 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield the title product, a brown oil, as a mixture of oxime isomers (Major:Minor 1.1:1), which failed to separate by flash column chromatography (4.088 g, 76%).

Major-oxime isomer rotamer ratio: 1.3:1.

Minor-oxime isomer rotamer ratio: 1.2:1.



^{1}H NMR ($CDCl_3$): (δ)

NOH Major-oxime isomer 9.30 (1.1H, br s, $OH_{[major\ rot.\ \&\ minor\ rot.]}$)

Minor-oxime isomer 8.89 (1H, br s, $OH_{[major\ rot.\ \&\ minor\ rot.]}$)

Aromatic Protons

7.51-7.47 (2.2H, m, $H^{3\&5}{}_{[major\ rot.\ \&\ minor\ rot.]}$) Major Oxime Isomer

6.64 (1.1H, m, $H^4{}_{[major\ rot.\ \&\ minor\ rot.]}$) Major Oxime Isomer

7.45-7.43 (1H, m, $H^5{}_{[major\ rot.\ \&\ minor\ rot.]}$) Minor Oxime Isomer

6.56-6.45 (2H, m, $H^{3\&4}{}_{[major\ rot.\ \&\ minor\ rot.]}$) Minor Oxime Isomer

C<u>H</u>=CH_2 Major Oxime Isomer 5.91-5.76 (1.1H, m, C<u>H</u>=$CH_{2[major\ rot.\ \&\ minor\ rot.]}$)

Minor Oxime Isomer 5.75-6.62 (1H, m, C<u>H</u>=$CH_{2[major\ rot.\ \&\ minor\ rot.]}$)

CH_2=CH Major & Minor Oxime Isomer 5.33-5.15 (4.4H, m, CH_2=$CH_{[major\ rot.\ \&\ minor\ rot.]}$)

NCH_2 Major Oxime Isomer 4.17 (2.2H, d J = 5.5, $NCH_{2[major\ rot.\ \&\ minor\ rot.]}$)

Minor Oxime Isomer 3.84 (2H, dd J = 6.2, $NCH_{2[minor\ rot.]}$)

NCH_3 Major Oxime Isomer 2.93 (3H, s, $NCH_{3[minor\ rot.]}$), 2.92 (3.9H, s, $NCH_{3[major\ rot.]}$)

Minor Oxime Isomer 3.06 (3.6H, s, $NCH_{3[major\ rot.]}$), 3.05 (3H, s, $NCH_{3[minor\ rot.]}$).

^{13}C NMR ($CDCl_3$): (δ)

C=O Major- *&* Minor-oxime isomer 163.8, 163.6, 162.8

QC

(C=N & Q ArC) Major- & Minor-oxime isomer 146.0, 145.9, 145.8, 145.6, 143.55, 143.3, 142.6, 142.5

Aromatic Carbons:

$C^{3\&5}$	Major-oxime isomer 144.8, 144.7, 143.6, 143.5;
C^{4}	Major-oxime isomer 112.8
C^{5}	Minor-oxime isomer 119.7, 119.6
$C^{3\&4}$	Minor-oxime isomer 112.3, 111.7
($\underline{C}H=CH_2$)	Major-oxime isomer 131.9, 131.6; 132.6, 132.4
($\underline{C}H_2=CH$)	Major-oxime isomer 119.1, 118.6; Minor-oxime isomer 117.9, 117.8
(NCH_2)	Major-oxime isomer 49.6, 49.0; Minor-oxime isomer 53.4, 53.0
(NCH_3)	Major-oxime isomer 35.5, 34.6; Minor-oxime isomer 32.4, 31.4

IR (Nujol): (cm^{-1}) 2924, 1654, 1463, 1377, 1154, 963.

R_f: 0.18, 0.41 (7:3 hexane:EtOAc)

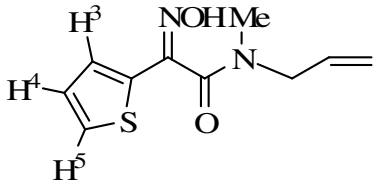
LC/TCOF-MS: $(M + K)^+$ requires 247.0480 g/mol, found 247.0488 g/mol, difference (3.61 ppm).

Preparation of (2*E*)-2-(hydroxyimino)-*N*-methyl-*N*-(prop-2-en-1-yl)-2-(thiophen-2-yl)ethanamide (*E*-116c) and (2*Z*)-2-(hydroxyimino)-*N*-methyl-*N*-(prop-2-en-1-yl)-2-(thiophen-2-yl)ethanamide (*Z*-116c)

A solution of **113c** (1.100 g, 5.255 x 10^{-3} moles), pyridine (0.492 g, 0.503 cm^3, 6.212 x 10^{-3} moles) and NH_2OH•HCl (0.432 g, 6.217 x 10^{-3} moles) in EtOH (110 cm^3) was heated with stirring at reflux for 18 hours. The solution was allowed to cool to r.t. prior to evaporation under reduced pressure and the residue was taken up in DCM (50 cm^3). The organic layer was washed with sat. aq. $NaHCO_3$ (25 cm^3), then H_2O (25 cm^3) and were dried ($MgSO_4$), filtered and evaporated to yield the crude product, a yellow oil as a mixture of geometrical oxime isomers (*E:Z* 1.3:1) which were separated by flash column chromatography (hexane:EtOAc 3:7) to yield the *E*-isomer as a yellow oil (0.225 g, 20%), the *Z*-isomer as a brown oil (0.286 g, 24%) and unreacted **113c**.

E-oxime isomer rotamer ratio: 1.3:1.

Z-oxime isomer rotamer ratio: 1:1



***E*-oxime isomer**

^{1}H NMR ($CDCl_3$): (δ) 10.22 (2H, br s, $OH_{[rot.\ a\ \&\ rot.\ b]}$), 7.58 (2H, d J = 5.1, $H^{5}_{[rot.\ a\ \&\ rot.\ b]}$), 7.40 (2H, d J = 3.8, $H^{3}_{[rot.\ a\ \&\ rot.\ b]}$), 7.11-7.06 (2H, m, $H^{4}_{[rot.\ a\ and\ rot.\ b]}$), 5.94-5.81 (1H, m, $C\underline{H}=CH_{2[rot.\ a]}$), 5.74-5.61 (1H, m, $C\underline{H}=CH_{2[rot.\ b]}$), 5.31-5.13 (4H, m, $\underline{CH_2}=CH_{[rot.\ a\ \&\ rot.\ b]}$), 4.17 (2H, d J = 5.9, $NCH_{2[rot.\ a]}$), 3.88 (2H, d J = 6.0, $NCH_{2[rot.\ b]}$), 3.08 (3H, s, $NCH_{3[rot.\ a]}$), 2.93 (3H, s, $NCH_{3[rot.\ b]}$).

^{13}C NMR ($CDCl_3$): (δ) 165.1 ($C=O_{[rot.\ a]}$), 164.8 ($C=O_{[rot.\ b]}$), 146.8, 146.7 ($C=N_{[rot.\ a\ \&\ rot.\ b]}$), 132.5 ($\underline{C}H=CH_{2[rot.\ b]}$), 132.0 ($\underline{C}H=CH_{2[rot.\ a]}$), 131.9 ($C^{3}_{[rot.\ a]}$), 131.8 ($C^{3}_{[rot.\ b]}$), 131.1 ($C^{5}_{[rot.\ a]}$), 130.9 ($C^{5}_{[rot.\ b]}$), 128.8, 128.7 (Q $ArC_{[rot.\ a\ \&\ rot.\ b]}$) 126.2, 126.1 ($C^{4}_{[rot.\ a\ \&\ rot.\ b]}$), 118.9 ($\underline{C}H_2=CH_{[rot.\ a]}$), 118.3 ($\underline{C}H_2=CH_{[rot.\ b]}$), 53.7 ($NCH_{2[rot.\ a]}$), 49.8 ($NCH_{2[rot.\ b]}$), 35.9 ($NCH_{3[rot.\ a]}$), 32.5 ($NCH_{3[rot.\ b]}$).

IR (Nujol): (cm^{-1}) 3233, 1737, 1627, 1394, 1417, 1342, 982.

R_f: 0.27 (hexane:EtOAc 1:1)

LC/TCOF-MS: $(M + H)^+$ requires 225.0692 g/mol, found 225.0702 g/mol, difference (4.40 ppm).

***Z*-oxime isomer**

^{1}H NMR ($CDCl_3$): (δ) 9.89 (2.3H, br s, $OH_{[major\ rot.\ \&\ minor\ rot.]}$), 7.31-7.29 (2.3H, dd J = 4.7 &1.0, $H^{5}_{[major\ rot.\ \&\ minor\ rot.]}$), 7.17-7.16 (2.3H, dd J = 3.4 & 1.0, $H^{3}_{[major\ rot.\ \&\ minor\ rot.]}$), 7.02-6.98 (2.3H, m, $H^{4}_{[major\ rot.\ \&\ minor\ rot.]}$), 5.88-5.75 (1.3H, m, $C\underline{H}=CH_{2[major\ rot.]}$), 5.72-5.54 (1H, m, $C\underline{H}=CH_{2[minor\ rot.]}$), 5.32-5.11 (4.6H, m, $C\underline{H_2}=CH_{[major\ rot.\ \&\ minor\ rot.]}$), 4.16 (2.6H, d J = 5.3, $NCH_{2[major\ rot.]}$), 3.80 (2H, d J = 5.9, $NCH_{2[minor\ rot.]}$), 3.04 (3H, s, $NCH_{3[minor\ rot.]}$), 2.88 (3.9H, s, $CH_{3[major\ rot.]}$).

^{13}C NMR ($CDCl_3$): (δ) 163.3 ($C=O_{[major\ rot.\ \&\ minor\ rot.]}$), 147.9 ($C=N_{[major\ rot.\ \&\ minor\ rot.]}$), 133.7 (Q $ArC_{[minor\ rot.]}$), 133.5 (Q $ArC_{[major\ rot.]}$), 131.5 ($\underline{C}H=CH_{2[minor\ rot.]}$), 130.2 ($\underline{C}H=CH_{2[major\ rot.]}$), 127.8 ($C^{3}_{[minor\ rot.]}$), 127.6 ($C^{3}_{[major\ rot.]}$), 126.8 ($C^{5}_{[major\ rot.]}$), 126.7 ($C^{5}_{[minor\ rot.]}$), 126.5 ($C^{4}_{[major\ rot.]}$), 126.4 ($C^{4}_{[minor\ rot.]}$), 118.2 ($\underline{C}H_2=CH_{[minor\ rot.]}$), 117.0

($\underline{C}H_2$=$CH_{[major\ rot.]}$), 52.1 ($NCH_{2[minor\ rot.]}$), 48.0 ($NCH_{2[major\ rot.]}$), 33.6 ($NCH_{3[major\ rot.]}$), 30.5 ($NCH_{3[minor\ rot.]}$).

IR (Nujol): (cm^{-1}) 3244, 2246, 1622, 1488, 1416, 1348, 1265.

R_f: 0.33 (hexane:EtOAc 1:1)

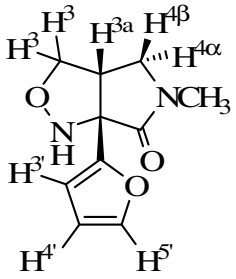
LC/TCOF-MS: $(M + H)^+$ requires 225.0692 g/mol, found 225.0702 g/mol, difference (4.40 ppm).

Preparation of 5-methyl-6a-phenyltetrahydro-6*H*-pyrrolo[3,4-*c*][1,2]oxazol-6-one (117a)[153]

The title compound was prepared according to the literature in 66% yield.

Synthesis of 6a-(furan-2-yl)-5-methylhexahydro-6H-pyrrolo[3,4-c][1,2]oxazol-6-one (117b) and 3-(furan-2-yl)-1,5-dimethyl-5,6-dihydropyrazin-2(1H)-one 4-oxide (118b)

A solution of *E*- and *Z*-**116b** (1.003 g, 4.817 x 10^{-3} moles) in toluene (310 cm^3) was heated to reflux under a N_2 atmosphere for 100 hours. The solution was allowed to cool to r.t. prior to evaporation yielding the crude products, which were purified by flash column chromatography (EtOAc:DCM 4:1) to yield the bicycle **117b** as a orange solid (0.441 g, 44%) and the nitrone **118b** (0.170 g, 16%) which could not be separated from **117b**.



117b

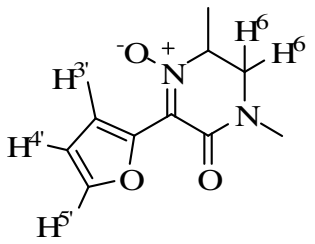
^{1}H NMR ($CDCl_3$): (δ) 7.41-7.40 (1H, dd *J* = 1.9 & 0.8, $H^{5'}$), 6.60 (1H, d *J* = 3.3, $H^{3'}$), 6.38-6.36 (1H, dd *J* = 3.3 & 1.9, $H^{4'}$), 5.74 (1H, br s, NH), 4.15-4.11 (2H, m, H^3), 3.75-3.68 (1H, dd *J* = 10.1 & 8.3, $H^{4\beta}$), 3.65-3.44 (1H, m, H^{3a}), 3.28-3.24 (1H, dd *J* = 10.1 & 2.6, $H^{4\alpha}$), 2.92 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): (δ) 170.2 (C=O), 148.2 (Q ArC), 143.0 ($C^{5'}$), 110.9 ($C^{4'}$), 109.8 ($C^{3'}$), 79.2 (C^{3}), 72.8 (C^{6a}), 52.5 (C^{4}), 44.8 (C^{3a}), 30.3 (NCH_3).

IR (KBr): (cm^{-1}) 3435, 3224, 3118, 2876, 1676, 1496, 1403.

m.p.: 109-115 °C

LC/TCOF-MS: $(M + K)^+$ requires 247.0280 g/mol, found 247.0485 g/mol, difference (2.26 ppm).



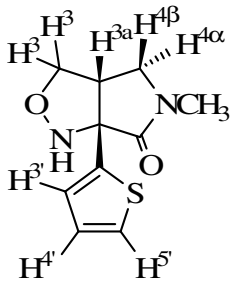
118b

^{1}H NMR ($CDCl_3$): (δ) 7.81 (1H, d *J* = 3.5, $H^{3'}$), 7.62 (1H, d *J* = 1.8, $H^{5'}$), 6.55-6.53 (1H, dd *J* = 3.5 & 1.8, $H^{4'}$), 4.28-4.18 (1H, m, C<u>H</u>CH_3), 3.91-3.86 (1H, dd *J* = 13.7 & 4.3, H^{6}), 3.37-3.30 (1H, dd *J* = 13.7 & 5.2, H^{6}), 3.17 (3H, s, NCH_3), 1.57 (3H, d *J* = 6.8, CHC<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$): (δ) 153.8 (C=O), 144.5 ($C=N^+$), 143.0 ($C^{3'}$), 129.8 (Q ArC), 118.1 ($C^{5'}$), 110.5 ($C^{4'}$), 64.9 (<u>C</u>HCH_3), 52.9 (NCH_2), 34.8 (NCH_3), 15.6 (CCH_3).

Preparation of 5-methyl-6a-(thiophen-2-yl)hexahydro-6H-pyrrolo[3,4-c][1,2]oxazol-6-one (117c)

A solution of *Z*-**116c** (0.0774 g, 3.451 x 10^{-3} moles) in xylene (24 cm^3) was heated at reflux in the presence of hydroquinone (0.240 g, 1 mol% w/v) under N_2 for 90 hours. The solution was allowed to cool to r.t. and left to stand prior to evaporation. The residue was taken up in $CHCl_3$ (15 cm^3) and left at r.t. for 30 minutes. After any remaining hydroquinone had precipitated the solution was filtered and the solvent was evaporated to yield the crude product which was separated and purified by flash column chromatography (EtOAc:hexane 4:1) to yield **117c** as a brown oil (0.067 g, 86%).



^{1}H NMR ($CDCl_3$): (δ) 7.32-7.30 (1H, dd *J* = 5.1 & 1.0, $H^{5'}$), 7.22-7.21 (1H, br d *J* = 3.7, $H^{3'}$), 7.01-6.98 (1H, dd *J* = 5.1 & 3.7, $H^{4'}$), 4.19-4.08 (2H, m, H^3), 3.79-3.73 (1H, dd *J* = 10.3 & 7.8, $H^{4\beta}$), 3.41-3.37 (1H, m, H^{3a}), 3.32-3.27 (1H, dd *J* = 10.3 & 2.0, $H^{4\alpha}$), 2.91 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): (δ) 170.4 (C=O), 136.9 (Q ArC), 126.2 ($C^{4'}$), 125.0 ($C^{5'}$), 123.1 ($C^{3'}$), 79.4 (C^3), 73.1 (C^{6a}), 51.4 (C^4), 47.1 (C^{3a}), 29.8 (NCH_3).

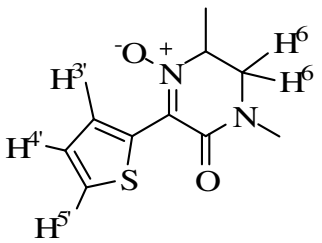
IR (KBr): (cm^{-1}) 3436, 3183, 2924, 1677, 1503, 1404, 1678.

R_f: 0.36 (EtOAc:hexane 3:2)

LC/TCOF-MS: $(M + NH_4)^+$ requires 242.0958 g/mol, found 242.0951 g/mol, difference (-2.86 ppm).

Preparation of 1,5-dimethyl-3-(thiophen-2-yl)-5,6-dihydropyrazin-2(1H)-one 4-oxide (118c)

A solution of *E*-**117c** (0.078 g, 3.496 x 10^{-3} moles) in xylene (24 cm^3) was heated to reflux in the presence of hydroquinone (0.240 g, 1 mol% w/v) under N_2 for 90 hours. The solution was allowed to cool to r.t. and left to stand prior to evaporation and the residue was taken up in $CHCl_3$ (15 cm^3) and left at r.t. for 30 minutes. After any remaining hydroquinone had precipitated the solution was filtered and the solvent was evaporated to yield the crude product which was separated and purified by flash column chromatography (EtOAc:hexane 4:1) to yield **118c** as a brown oil (0.056 g, 71%).



^{1}H NMR ($CDCl_3$): (δ) 8.66 (1H, d *J* = 4.2, $H^{3'}$), 7.46 (1H, d *J* = 5.1, $H^{5'}$), 7.20-7.17 (1H, dd *J* = 5.1 & 4.2, $H^{4'}$), 4.36-4.26 (1H, m, C<u>H</u>CH_3), 3.89-3.83 (1H, dd *J* = 13.5 & 4.4, H^6), 3.36-3.30 (1H, dd *J* = 13.5 & 5.4, H^6), 3.19 (3H, s, NCH_3), 1.59 (3H, d *J* = 6.8, CH_3).

^{13}C NMR ($CDCl_3$): (δ) 158.5 (C=O), 133.0 ($C=N^+$), 132.8 ($C^{3'}$), 130.4 (Q ArC), 128.7 ($C^{5'}$), 126.8 ($C^{4'}$), 63.6 (<u>C</u>HCH_3), 49.9 (CH_2), 35.2 (NCH_3), 15.6 (CH<u>C</u>H_3).

IR (KBr): (cm^{-1}) 3585, 2980, 2244, 1652, 1485, 1389, 1056, 913.

μ analysis: Found: C 52.09% H 5.36% N 11.54%

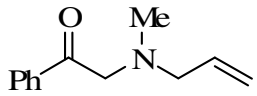
$C_{10}H_{12}N_2SO_2$•$0.25H_2O$ requires: C 52.55% H 5.51% N 12.25%

R_f: 0.27 (EtOAc:hexane 7:1)

LC/TCOF-MS: $(M + H)^+$ requires 225.0698 g/mol, found 226.0720 g/mol, difference (1.80 ppm).

Synthesis of 2-[methyl(prop-2-en-1-yl)amino]-1-phenylethanone (119a)

A solution of 2-bromoacetophenone (2.030 g, 1.020 x 10^{-2} moles) in DCM (23 cm^3) was injected slowly to a stirred solution of *N*-methylallylamine (5.000 g, 7.040 x 10^{-2} moles) in DCM (68 cm^3) at r.t. After complete addition and a further 10 minutes stirring at r.t. the solution was washed with H_2O (3 x 30 cm^3), dried ($MgSO_4$), filtered and evaporated to yield the crude product as a yellow oil (1.820 g, 98%) which required no further purification.



^{1}H-NMR ($CDCl_3$): (δ) 7.89-7.85 (2H, m, *m*-ArH), 7.44-7.38 (1H, m, *p*-ArH), 7.34-7.25 (2H, m, *o*-ArH), 5.88-5.74 (1H, m, C<u>H</u>=CH_2), 5.13-5.03 (2H, m, C<u>H$_2$</u>=CH), 3.69 (2H, s, NC<u>H$_2$</u>CO), 3.05 (2H, d *J* = 6.6, NC<u>H$_2$</u>CH), 2.25 (3H, s, NCH_3).

^{13}C-NMR ($CDCl_3$): (δ) 197.3 (C=O), 136.7 (Q ArC), 135.5 (CH_2=<u>C</u>H), 132.7 (*p*-ArC), 128.8 (*o*-ArC), 128.4 (*m*-ArC), 118.2 (<u>C</u>H_2=CH), 63.1 (<u>C</u>H_2C(O)), 60.9 (N<u>C</u>H_2CH), 42.7 (NCH_3).

IR (Nujol): (cm^{-1}) 3451, 2960, 2572, 1741, 1647, 1455, 1169, 1040.

R_f: 0.27 & 0.41 (hexane:EtOAc 3:2)

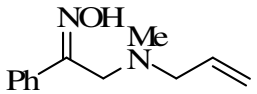
LC/TCOF-MS: $(M + H)^+$ requires 190.1226 g/mol, found 190.1219 g/mol, difference (-3.81 ppm).

Synthesis of 1-phenyl-2-[phenyl(prop-2-en-1-yl)amino]ethanone (119b)[178]

The title compound, prepared according to the literature was obtained as a yellow solid in 99% yield.

Preparation of *N*-[(2*E*)-2-(hydroxyimino)-2-phenylethyl]-*N*-methylprop-2-en-1-amine (*E*-121a) and *N*-[(2*Z*)-2-(hydroxyimino)-2-phenylethyl]-*N*-methylprop-2-en-1-amine (*Z*-121a)

To a solution of **119a** (0.314 g, 1.6606 x 10^{-3} moles) in EtOH (5 cm^3) was added $NaHCO_3$ (0.157 g, 1.8118 x 10^{-2} moles) and NH_2OH•HCl (0.128 g, 1.8098 x 10^{-3} moles). The mixture was heated at 80 ^oC for 3.5 hours. The solution was cooled to r.t., concentrated *in vacuo* and taken up in DCM (10 cm^3). The organic layer was washed with H_2O (2 x 10 cm^3), dried ($MgSO_4$), filtered and concentrated to yield the crude product as a yellow oil (0.289 g, 85%), as a mixture of *E*- and *Z*–oxime isomers (*E:Z* 1:2) which were separated by flash column chromatography (hexane:EtOAc 7:3) to give the *E*-isomer (0.026 g, 17%) and the Z-isomer (0.152 g, 45%) both as yellow oils.



***E*-oxime isomer**

^{1}H-NMR ($CDCl_3$): (δ) 8.75 (1H, br s, OH), 7.58-7.50 (2H, m, *o*-ArH), 7.44-7.36 (3H, m, *m*-&*p*-ArH), 5.86-5.72 (1H, m, C<u>H</u>=CH_2), 5.16-5.09 (2H, m, $C\underline{H_2}$=CH), 3.38 (2H, s, $C\underline{H_2}$C=N), 3.03 (2H, d, *J* = 6.5, $NC\underline{H_2}CH$), 2.24 (3H, s, NCH_3).

^{13}C-NMR ($CDCl_3$): (δ) 155.5 (C=N), 135.4 (<u>C</u>H=CH_2), 132.6 (Q ArC), 129.0, 128.1 (*m*-&*p*-ArC), 126.5 (*o*-ArC), 117.8 (<u>C</u>H_2=CH), 60.6 ($N\underline{C}H_2CH$), 60.3 ($N\underline{C}H_2C$=N), 42.1 (NCH_3).

IR (Nujol): (cm^{-1}) 2854, 1463, 1377, 1154.

µ analysis:	Found:	C 69.10%	H 7.62%	N 12.72%
	$C_{12}H_{16}N_2O$•0.25H_2O requires:	C 69.01%	H 7.97%	N 13.41%

R_f: 0.32 (hexane:EtOAc 1:1)

LC/TCOF-MS: $(M + Na)^+$ requires 227.1155 g/mol, found 227.1164 g/mol, difference (3.93 ppm).

***Z*-oxime isomer**

^{1}H-NMR ($CDCl_3$): (δ) 12.38 (1H, br s, OH), 7.66-7.60 (2H, m, *o*-ArH), 7.38-7.33 (3H, m, *m*-&*p*-ArH), 5.96-5.82 (1H, m, C<u>H</u>=CH_2), 5.26-5.20 (2H, m, C<u>H_2</u>=CH), 3.77 (2H, s, C<u>H_2</u>C=N), 3.13 (2H, d, *J* = 6.7, NC<u>H_2</u>CH), 2.34 (3H, s, NCH_3).

^{13}C-NMR ($CDCl_3$): (δ) 154.2 (C=N), 135.7 (Q ArC), 133.5 (<u>C</u>H=CH_2), 129.1, 128.5 (*m*-&*p*-ArCH), 126.5 (*o*-ArCH), 119.6 (<u>C</u>H_2=CH), 60.3 (N<u>C</u>H_2), 54.8 (N<u>C</u>H_2C=N), 41.8 (NCH_3).

IR (Nujol): (cm^{-1}) 2854, 1463, 1377, 1154.

μ analysis: Found: C 69.51% H 7.77% N 13.13%

$C_{12}H_{16}N_2O$•$0.25H_2O$ requires: C 69.01% H 7.97% N 13.41%

R_f: 0.39 (hexane:EtOAc 3:2)

LC/TCOF-MS: $(M + NH_4)^+$ requires 227.1601 g/mol, found 227.1603 g/mol, difference (1.11 ppm).

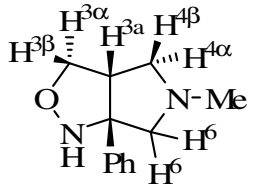
Synthesis of *N*-[(2*E*)-2-(hydroxyimino)-2-phenylethyl]-*N*-(prop-2-en-1-yl)aniline (*Z*-121b) and *N*-[(2*Z*)-2-(hydroxyimino)-2-phenylethyl]-*N*-(prop-2-en-1-yl)aniline (*E*-121b)

To a stirred solution of **119b** (0.310 g, 0.001 moles) in EtOH (8 cm^3) was added NH_2OH•HCl (0.109 g, 0.002 moles), $NaHCO_3$ (0.132 g, 0.002 moles) and the mixture was stirred with heating at reflux for 3 hours. The mixture was cooled to r.t., concentrated and dissolved in DCM (10 cm^3). The organic layer was washed with H_2O (2 x 5 cm^3), dried ($MgSO_4$), filtered and evaporated to yield the crude product as a yellow solid (0.325 g, 100%) with an *E:Z* ratio of 1:1.3. ^{1}H NMR spectral data was in agreement with the literature[178].

Preparation of 5-methyl-6a-phenylhexahydro-1*H*-pyrrolo[3,4-*c*][1,2]oxazole (122a)

A mixture of *E*- and *Z*-**121a** (1:1.6) (1.080 g, 5.270 x 10^{-3} moles) in toluene (370 cm^3) was heated at reflux for 15 hours. The solution was cooled to r.t. and concentrated to yield the crude product, which was purified by flash column chromatography (Et_2O:MeOH 9:1) and was obtained as a yellow solid (0.660 g, 62%) which was

configurationally mobile at r.t. At -50 °C ^{1}H NMR spectra indicated a major:minor conformer ratio of 6:1.



^{1}H-NMR ($CDCl_3$, -50 °C): (δ) Major conformer: 7.61-7.27 (5H, m, 5xArH), 5.48 (1H, s, NH), 4.60-4.55 (1H, dd *J* = 8.4 & 8.4, $H^{3\beta}$), 3.62-3.57 (1H, dd *J* = 8.4 & 8.0, $H^{3\alpha}$), 3.25-3.18 (2H, m, $H^{3a\&4\alpha}$), 3.14 (1H, d *J* = 10.8, H^6), 3.01 (1H, d *J* = 10.8, H^6), 2.62-2.57 (1H, dd *J* = 9.7 & 6.8, $H^{4\beta}$), 2.42 (3H, s, NCH_3).

Minor conformer: 7.62-7.27 (5H, m, 5xArH), 5.22 (1H, s, NH), 4.22 (1H, d *J* = 9.0, $H^{3\alpha}$), 3.83-3.78 (1H, dd J = 9.0 & 7.7, $H^{3\beta}$), 3.45-3.39 (1H, m, H^{3a}), 3.25-3.18 (1H, m, $H^{4/6}$), 2.92 (2H, m, $H^{4/6}$), 2.62-2.57 (1H, m, $H^{4/6}$), 2.35 (3H, s, NCH_3).

^{13}C-NMR ($CDCl_3$): (δ) 142.3 (Q ArC), 128.4, 127.0, 125.6 (3xArC), 78.4 (CH_2), 77.9 (C^{6a}), 65.4, 60.5 (2xCH_2), 55.0 (C^{3a}), 40.1 (NCH_3), 28.6.

IR (KBr): (cm^{-1}) 3420, 2972, 2795, 1663, 1448, 1264, 1164.

μ analysis:	Found:	C 70.40%	H 7.63%	N 13.43%
	$C_{12}H_{16}N_2O$ requires:	C 70.55%	H 7.90%	N 13.72%

m.p.: 77-80 °C

LC/TCOF-MS: $(M + H)^+$ requires 205.1335 g/mol, found 205.1343 g/mol, difference (3.50 ppm).

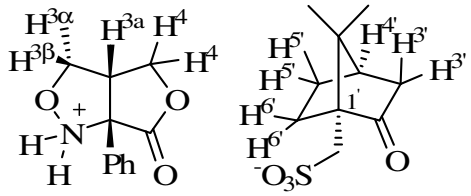
Synthesis of 5,6a-diphenylhexahydro-1*H*-pyrrolo[3,4-*c*][1,2]oxazole (122b)

A solution of the *E*- and *Z*-**121b** (0.682 g, 0.003 moles) in toluene (230 cm^3) was heated at reflux for 8 hours. The solution was cooled to r.t. and concentrated to yield the crude product which was purified by column chromatography (Et_2O:hexane 2:3) to yield the title product as a yellow solid (0.389 g, 57%). ^{1}H NMR spectral data is in agreement with that in the literature[178].

4.2.3 Salt Formation

Preparation of (6a*S*)-6-oxo-6a-phenyltetrahydro-1*H*,3*H*-furo[3,4-*c*][1,2]oxazol-1-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methane sulfonate (110a•(+)-10-CSA)

Hot acetone (1 cm^3) was added to a mixture of **110a** (0.100 g, 4.876 x 10^{-4} moles) and (+)-10-CSA (0.133 g, 4.876 x 10^{-4} moles). The resulting solution was allowed to stir at r.t. until the title salt precipitated as a white solid (0.228 g, 98%).



^{1}H NMR (d_6-DMSO): (δ) 7.56-7.52 (2H, m, ArH), 7.50-7.37 (3H, m, ArH), 4.69-4.63 (1H, dd *J* = 9.7 & 7.2, H^4), 4.46-4.42 (1H, dd *J* = 9.7 & 1.8, H^4), 4.23-4.19 (1H, dd *J* = 8.7 & 2.2, $H^{3\alpha}$), 4.07-4.01 (1H, dd *J* = 8.7 & 8.7, $H^{3\beta}$), 3.66-3.59 (1H, m, H^{3a}), 3.01 (1H, d *J* = 14.8, $C\underline{H}_2S$), 2.63-2.50 (2H, m, $C\underline{H}_2S$ & $H^{5'/6'}$), 2.31-2.23 (1H, m, $H^{3'}$), 1.99-1.80 (3H, m, $H^{3'}$, $H^{4'}$ & $H^{5'/6'}$), 1.40-1.25 (2H, m, $H^{5'\&6'}$), 1.04 (3H, s, CH_3), 0.76 (3H, s, CH_3).

^{13}C NMR (d_6-DMSO): (δ) 215.7, 176.1 (2xC=O), 134.2 (Q ArC), 128.7, 128.6, 126.7 (3xArC), 78.6 (C^3), 75.3 (C^{6a}), 70.1 (C^4), 58.0 ($C^{1'}$), 47.9 (C^{3a}), 47.0 ($\underline{C}H_2S$), 42.2 ($C^{3'}$), 42.1 ($C^{4'}$), 38.6 ($\underline{C}(CH_3)_2$), 26.3, 24.2 ($C^{5'\&6'}$), 19.9, 19.4 (2xCH_3).

^{15}N NMR (d_6-DMSO): (δ) 173.6.

IR (KBr): (cm^{-1}) 3451, 2952, 2530, 1781, 1734, 1451, 1386, 1231.

μ analysis:	Found:	C 57.58%	H 6.22%	N 3.23%
	$C_{21}H_{27}NSO_7$ requires:	C 57.62%	H 6.21%	N 3.20%

m.p.: 153-158 °C

LC/TCOF-MS: $(M + Na)^+$ requires 460.1400 g/mol, found 460.1405 g/mol, difference (1.06 ppm).

Classical resolution of 110a with (+)-10-CSA (1:1)

The racemic mixture was resolved by applying the method by Abiko *et al.*[181,182] In our case, as the authors found, separate crops fell from solution as the (+)(+) and the (-)(+) when the (±)**110a**•(+)-10-CSA salt was used.

(±)**110a** (0.234 g, 1.143 x 10^{-3} moles) and (+)-10-CSA (0.266 g, 1.143 x 10^{-3} moles) were dissolved in warm acetone (13.5 cm^3).

- After stirring for 26 hours at r.t., the 1st crop of the white solid was collected (0.145 g, 58%) $[\alpha]^{25}_D$= +76 (c. 0.0023, MeOH).
- The mother liquor and washings were concentrated to ≃7 cm^3 and left to stir at r.t. for 4 hours to afford the 2nd crop (0.010 g, 4%) $[\alpha]^{25}_D$= +74 (c. 0.0072, MeOH).
- The mother liquor and washings were concentrated to ≃3.5 cm^3 and left to stir at r.t. for 26 hours to afford the 3rd crop (0.011 g, 5%) $[\alpha]^{25}_D$= +56 (c. 0.0006, MeOH).

Total yield of (+)-**110a**•(+)-10-CSA based on the first two crops was 62%.

Classical resolution of 110a with (+)-10-CSA (1.6:1)

(±)**110a** (0.234 g, 1.143 x 10^{-3} moles) and (+)-10-CSA (0.457g, 1.967 x 10^{-3} moles) were dissolved in warm acetone (19 cm^3).

- After stirring at r.t. for 26 hours the 1st crop of white solid was collected (0.089 g, 26%) $[\alpha]^{25}_D$= +72 (c. 0.0011, MeOH).
- The mother liquor and washings were concentrated to ≃8 cm^3 and after 30 minutes at r.t. the 2nd crop precipitated (0.045g, 13%) $[\alpha]^{25}_D$= +75 (c. 0.0011, MeOH).
- Resolution was repeated as above and afforded the following crops: 3rd (0.049 g, 14%) $[\alpha]^{25}_D$= +68 (c. 0.0010, MeOH),
- 4th (0.009 g, 3%) $[\alpha]^{25}_D$= +78 (c. 0.0070, MeOH),
- 5th (0.003 g, 1%) $[\alpha]^{25}_D$= +44 (c. 0.0007, MeOH),
- 6th (0.015 g, 4%) $[\alpha]^{25}_D$= +39 (c. 0008, MeOH).

Total yield of (+)-**110a**•(+)-10-CSA after 6 recrystallisations was 56%.

Classical resolution of 110a with (-)-10-CSA (1:1)

(±)110a (1.500 g, 7.314 x 10^{-3} moles) and **(-)**-10-CSA (3.199 g, 7.314 x 10^{-3} moles) were dissolved in warm acetone (58 cm^3).

- Stirring at r.t. for 26 hours the 1st crop was collected (0.321 g, 20%) $[\alpha]^{25}_D$= -74 (c. 0.002, MeOH).

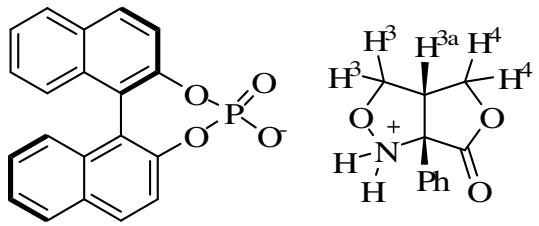
- The mother liquor and washings were concentrated to ≃49 cm^3 and stirred at r.t. for 69 hours to afford the second crop (0.144g, 9%) $[\alpha]^{25}_D$= -78 (c. 0.0099, MeOH).
- The collection/concentration process was repeated as above affording the following crops: 3rd (0.093 g, 6%) $[\alpha]^{25}_D$= +21 (c. 0.008, MeOH),
- 4th (0.240, 15%) $[\alpha]^{25}_D$= -75 (c. 0.0011, MeOH),
- 5th (0.276g, 17%) $[\alpha]^{25}_D$= +36 (c. 0.0014, MeOH).

Total yield of (-)-**110a**•(-)-10-CSA after 5 recrystallisations was 44%.

(+)-**110a** $[\alpha]^{25}_D$= +112 (c. 0.0010, MeOH) and (-)-**110a** $[\alpha]^{25}_D$= -110 (c. 0.0064, MeOH) were obtained quantitatively by treatment of the (+)-**110a**•(+)-10-CSA and (-)-**110a**•(-)-10-CSA salts with 1M NaOH and extraction with CH_2Cl_2.

Preparation of (6a*S*)-6-oxo-6a-phenyltetrahydro-1*H*,3*H*-furo[3,4-*c*][1,2]oxazol-1-ium (+)-1,1'-binaphthyl-2,2'-diylhydrogen phosphate (110a•(+)-BNHP)

To a mixture of **110a** (0.050 g, 2.438 x 10^{-4} moles) and (*S*)-(+)-1,1'-binaphthyl-2,2'-diylhydrogen phosphate (0.085 g, 2.438 x 10^{-4} moles) was added hot MeOH (8 cm^3). The resulting solution was stirred at r.t. for 15 hours prior to evaporation to dryness to yield the product as a white solid (0.135 g, 100%).



^{1}H NMR (CD_3OD): (δ) 8.09 (2H, d *J* = 8.9, ArH), 7.99 (2H, d *J* = 8.2, ArH), 7.60-7.55 (4H, m, ArH), 7.49-7.29 (5H, m, ArH), 7.27-7.22 (4H, m, ArH), 4.68-4.61 (1H, m, H^3), 4.47-4.44 (1H, m, H^3), 4.43-4.19 (2H, m, H^4), 3.75-3.68 (1H, m, H^{3a}).

^{13}C NMR (CD_3OD): (δ) 176.2 (C=O), 147.6, 147.5, 132.3, 132.2, 142.1 (5xQ ArC), 131.6, 130.8, 129.3, 129.1, 128.9, 128.3, 126.5, 126.4, 125.3, 121.4, 120.5 (11xArC), 79.0 (C^4), 75.6 (C^{6a}), 71.2 (C^3), 48.0 (C^{3a}).

IR (KBr): (cm^{-1}) 3410, 1777, 1590, 1507, 1326, 1231.

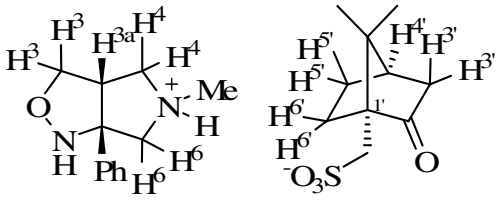
μ analysis:	Found:	C 66.45%	H 4.61%	N 2.23%
	$C_{31}H_{24}NPO_7$•$0.5H_2O$ requires:	C 66.19%	H 4.48%	N 2.49%

m.p.: 110-119 °C

LC/TCOF-MS: $(M + K)^+$ requires 592.0922 g/mol, found 592.0943 g/mol, difference (3.53 ppm).

Preparation of (6a*S*)-5-methyl-6-oxo-6a-phenylhexahydro-1*H*-pyrrolo[3,4-*c*][1,2]oxazol-1-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methane sulfonate (117a•(+)-10-CSA)

117a (0.200 g, 9.169 x 10^{-3} moles) and (+)-10-CSA (0.213g, 9.169 x 10^{-3} moles) were dissolved in hot acetone (1.6 cm^3) and the solution was allowed to cool to r.t. until the salt precipitated as a white solid (0.384 g, 93%).



^{1}H NMR (d_6-DMSO): (δ) 7.48-7.39 (5H, m, ArH), 6.48 (2H, br s, $^+NH_2$), 4.16-4.06 (2H, m, H^3), 3.83-3.77 (1H, dd *J* = 10.5 & 7.5, $H^{4\beta}$), 3.44-3.38 (2H, br m, $H^{3a\&4\alpha}$), 2.91 (1H, d *J* = 9.8, SCH_2), 2.78 (3H, s, NCH_3), 2.67-2.43 (2H, m, $C\underline{H}_2S$ & $H^{5/6}$), 2.30-2.21 (1H, m, $H^{3'}$), 1.97-1.78 (3H, m, $H^{3'}$, $H^{4'}$ & $H^{5'/6'}$), 1.36-1.24 (2H, m, $H^{5'\&6'}$), 1.04 (3H, s, CH_3) 0.75 (3H, s, CH_3).

^{13}C NMR (d_6-DMSO): (δ) 216.0, 170.3 (2xC=O), 136.0 (Q ArC), 128.4, 128.2, 126.6 (3xArC), 78.7 (C^3), 76.6 (C^{6a}), 58.1 ($C^{1'}$), 51.5 (C^4), 47.1 (C^{3a}), 46.8 (CH_2S), 42.2 ($C^{3'}$), 40.3 ($C^{4'}$), 39.8 ($\underline{C}(CH_3)_2$), 29.8 (NCH_3), 26.3, 24.1 ($C^{5'\&6'}$), 20.0, 19.5 (2xCH_3).

IR (KBr): (cm^{-1}) 3455, 2929, 2645, 1741, 1711, 1590, 1504, 1451, 1267.

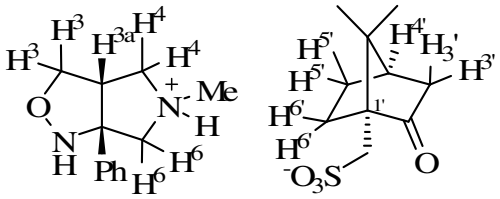
μ analysis:	Found:	C 58.70%	H 6.71%	N 6.11%
	$C_{22}H_{30}N_2SO_6$ requires:	C 58.66%	H 6.72%	N 6.22%

m.p.: 180-186 °C

LC/TCOF-MS: $(M + K)^+$ requires 491.1452 g/mol, found 491.1456 g/mol, difference (0.78 ppm).

Preparation of (6a*S*)-5-methyl-6a-phenylhexahydro-1*H*-pyrrolo[3,4-*c*][1,2]oxazol-5-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methane sulfonate (122a•(+)-10-CSA)

122a (0.250 g, 1.230 x 10^{-3} moles) and (+)-10-CSA (0.290 g, 1.230 x 10^{-3} moles) were dissolved in warm acetone (2 cm^3).The resulting solution was allowed to stir at r.t. until the title product precipitated as a white solid (0.540 g, 100%). ^{1}H NMR spectral data was difficult to assign, even at -50 ^{o}C, due to the presence of very broad peaks.



^{1}H-NMR ($CDCl_3$): (δ) 11.01 (1H, br m, $^+$N<u>H</u>Me), 7.52-7.28 (5H, m, 5xArH), 5.03 (1H, br s, NH), 4.44-3.32 (7H, br m, H^3, H^4, H^6 & H^{3a}), 3.14 (1H, d, *J* = 14.5, SCH_2), 3.08 (3H, br s, $^+$NHC<u>H</u>$_3$), 2.75 (1H, d *J* = 14.5, SCH_2), 2.57-2.47 (1H, br m, $H^{6'}$), 2.29-2.17 (1H, m, $H^{3'}$), 2.04-1.93 (2H, m, $H^{4'}$ & $H^{5'}$), 1.80-1.66 (2H, m, $H^{3'\&6'}$), 1.37-1.29 (1H, m, $H^{5'}$), 1.02 (CH_3), 0.78 (CH_3).

^{13}C-NMR ($CDCl_3$): (δ) 216.2 (C=O), 138.41 (Q ArC), 128.1, 127.3, 125.2 (3xArC), 77.7, 63.8, 59.4 ($C^{3,4\&6}$), 57.4 ($C^{1'}$), 52.9 (C^{3a}), 46.4 ($C^{3'}$), 41.9 <u>C</u>$(CH_3)_2$, 41.6 ($C^{4'}$), 40.2 (NCH_3), 26.0 ($C^{5'}$), 23.5 ($C^{6'}$), 18.8, 18.7 (2xCH_3).

IR (KBr): (cm^{-1}) 3447, 3224, 2975, 2497, 1735, 1457, 1240.

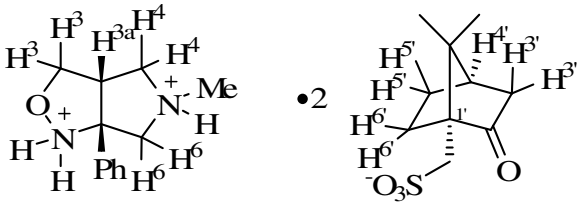
µ analysis:	Found:	C 60.55%	H 7.41%	N 6.27%
	$C_{22}H_{32}N_2SO_5$ requires:	C 60.49%	H 7.39%	N 6.42%

m.p.: 170-176 ^{o}C

LC/TCOF-MS: $(M + H)^+$ requires 437.2105 g/mol, found 437.2216 g/mol, difference (2.52 ppm).

Preparation of (6a*S*)-5-methyl-6a-phenylhexahydro-1*H*-pyrrolo[3,4-*c*][1,2]oxazole-1,5-diium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methane sulfonate (122a•2(+)-10-CSA)

The bicycle **110a** (0.201g, 9.846 x 10^{-4} moles) and (+)-10-CSA (0.460g, 1.980 x 10^{-3} moles) were added to warm acetone (1.6 cm^3). Upon cooling to r.t. the racemic *bis*-salt precipitated as a yellow solid (0.660g, 100%).



^{1}H-NMR ($CDCl_3$): (δ) 10.71 (1H, br d, $^+$NHMe), 7.98 (1H, br s, $^+$NH), 7.61-7.41 (5H, m, 5xArH), 4.89-3.70 (7H, br m, H^3, H^{3a}, H^4 & H^6), 3.12-3.07 (5H, br m, NHC<u>H_3</u> & 2xSCH), 2.65 (2H, d *J* = 14.7, 2xSCH), 2.24-2.22 (4H, m, 2x$H^{6'}$ & 2x$H^{3'}$), 2.03-1.89 (4H, m, 2x$H^{4'}$ & 2x$H^{5'}$), 1.77 (2H, m, 2x$H^{3'}$), 1.62-1.53 (2H, m, 2x$H^{6'}$), 1.36-1.26 (2H, m, 2x$H^{5'}$), 0.98 (6H, s, 2xCH_3), 0.76 (6H, s, 2xCH_3).

^{13}C-NMR ($CDCl_3$): (δ) 216.9, 207.1 (2xC=O), 129.8 (Q ArC), 129.5, 129.4, 127.1 (3xArC), 77.9, 75.9, 63.7 ($C^{3,4\&6}$), 59.7 ($C^{1'}$), 50.7 (C^{3a}), 47.6 (SCH_2), 42.6 ($C^{3'}$), 41.9 ($C^{4'}$), 41.7 ($^+NCH_3$), 40.7 (<u>C</u>$(CH_3)_2$), 26.9 ($C^{5'}$), 24.6 ($C^{6'}$), 19.8 (CH_3), 19.7 (CH_3).

IR (KBr): (cm^{-1}) 3451, 2960, 2572, 1741, 1647, 1455, 1169, 1040.

μ analysis: Found: C 65.57% H 6.46% N 5.41%

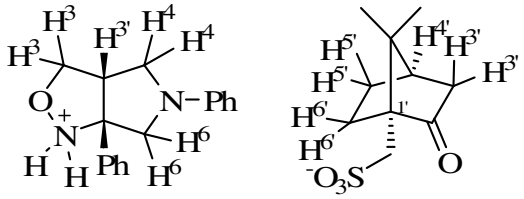
$C_{32}H_{48}N_2S_2O_9$ requires: C 65.01% H 6.88% N 5.62%

m.p.: 97-106 °C

LC/TCOF-MS: $(M + Na)^+$ requires 691.2693 g/mol, found 691.2689 g/mol, difference (-0.65 ppm).

Synthesis of (6a*S*)-5,6a-diphenylhexahydro-1*H*-pyrrolo[3,4-*c*][1,2]oxazol-1-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate (122b•(+)-10-CSA)

A solution of **122b** (0.202 g, 7.589 x 10^{-4} moles) and (+)-10-CSA (0.176 g, 7.589 x 10^{-4} moles), dissolved in hot acetone (1.2 cm^3) was allowed to cool with stirring at r.t. until the salt precipitated from solution. The salt was filtered and dried to yield the title product as a brown solid (0.365 g, 97%).



^{1}H NMR ($CDCl_3$): (δ) 8.85 (2H, br s, $^{+}NH_2$), 7.61-7.56 (2H, m, ArH), 7.39-7.30 (3H, m, ArH), 7.27-7.22 (2H, m, ArH), 6.85-6.76 (3H, m, ArH), 4.86-4.81 (1H, dd *J* = 8.3 & 8.3, H^3), 4.42-4.36 (1H, dd *J* = 7.4 & 3.9, H^4), 4.27-4.23 (1H, dd *J* = 8.3 & 4.0, H^3), 3.92-3.85 (1H, m, H^{3a}), 3.73-3.62 (3H, m, H^4 & H^6), 3.03 (1H, d *J* = 14.8, SCH_2), 2.51 (1H, d *J* = 14.8, SCH_2), 2.42-2.32 (1H, ddd *J* = 14.9, 12.0 & 3.8, $H^{6'}$), 2.29-2.20 (1H, m, $H^{3'}$), 1.98-1.95 (1H, m, $H^{5'}$), 1.93-1.81 (1H, m, $H^{4'}$), 1.75 (1H,br d *J* = 18.3, $H^{3'}$), 1.54-1.45 (1H, ddd *J* = 4.7, 9.3 & 14.9, $H^{6'}$), 1.28-1.2 (1H, m, $H^{5'}$), 0.93 (3H, s, CH_3), 0.70 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$): (δ) 216.7 (C=O), 146.9, 135.2 (2xQ ArC), 129.3, 129.3, 126.7, 126.7, 119.4, 114.7 (6xArC), 78.9 (C^{6a}), 78.2 (C^3), 59.0 (C^6), 58.3 ($C^{1'}$), 54.6 (C^4), 50.3 (C^{3a}), 47.9 ($\underline{C}(CH_3)_2$), 47.4 (SCH_2), 42.8 ($C^{3'}$), 42.6 ($C^{4'}$), 26.9 ($C^{5'}$), 24.6 ($C^{6'}$), 19.9, 19.7 (2xCH_3).

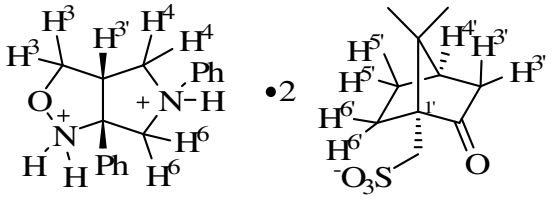
IR (KBr): (cm^{-1}) 3424, 2958, 2663, 1741, 1600, 1501, 1197, 1038, 756.

μ analysis:	Found:	C 64.69%	H 6.75%	N 5.46%
	$C_{27}H_{34}N_2SO_5$ requires:	C 65.01%	H 6.88%	N 5.62%

m.p.: 110-118 ^{o}C.

Synthesis of (6a*S*)-5,6a-diphenylhexahydro-1*H*-pyrrolo[3,4-*c*][1,2]oxazole-1,5-diium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate (122b•(+)-10-CSA)

The isoxazolidine **122b** (0.150 g, 5.636 x 10^{-4} moles) and (+)-10-CSA (0.262 g, 1.127 x 10^{-3} moles) were dissolved in hot acetone (1.8 cm^3) and stirred with cooling to r.t. until the salt precipitated from solution. The salt was filtered and dried to yield the title product as a dark green solid (0.390 g, 95%).



^{1}H NMR ($CDCl_3$): (δ) 10.56 (2H, br s, $^+NH_2$), 7.63-7.01 (12H, m, 12xArH), 4.90-4.85 (1H, dd J = 8.3 & 8.3, H^3), 4.76-4.72 (1H, dd *J* = 12.0 & 2.5, H^4), 4.45 (1H, br dd *J* = 8.3 & 2.6, H^3), 4.20-4.19 (1H, m, H^{3a}), 3.97 (1H, d *J* = 12.0, H^6), 3.94-3.74 (2H, m, H^4), 3.18 (2H, d *J* = 14.8, 2xSCH), 3.71 (2H, d *J* = 14.8, 2xSCH), 2.40-2.25 (4H, m, 2x$H^{3'}$ & 2x$H^{6'}$), 2.02-1.87 (4H, m, 2x$H^{4'}$ & 2x$H^{5'}$), 1.77 (2H, d *J* = 18.4, 2x$H^{3'}$), 1.62-1.53 (2H, m, 2x$H^{6'}$), 1.33-1.25 (2H, m, 2x$H^{5'}$), 0.97 (6H, s, 2xCH_3), 0.76 (6H, s, 2xCH_3).

^{13}C NMR ($CDCl_3$): (δ) 217.4, 207.2 (2xC=O), 144.3, 133.8 (2xQ ArC), 133.6, 129.7, 129.4, 127.3, 127.2, 117.12 (16xArC), 79.41 (C^{6a}), 77.4 (C^3), 60.01 (C^6), 58.4 ($C^{1'}$), 57.6 (C^4), 49.8 (C^{3a}), 48.2 ($\underline{C}(CH_3)_2$), 47.8 (SCH_2), 42.8 ($C^{3'}$), 42.6 ($C^{4'}$), 26.9 ($C^{5'}$), 25.0 ($C^{6'}$), 19.8, 19.7 (2xCH_3).

IR (KBr): (cm^{-1}) 3415, 2960, 1744, 1600, 1415, 1154, 1038.

m.p.: 84-96 °C.

4.2.4 Organocatalysis of the Diels-Alder Reaction

Typical Diels-Alder Reaction

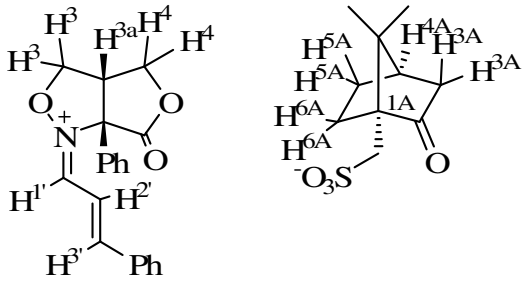
To a solution of the organic catalyst (7.576 x 10^{-5} moles, 10 mol%) and acid co-factor (7.576 x 10^{-5} moles, 10 mol%) in MeOH:H_2O 19:1 (0.78 cm^3) was added trans-cinnamaldehyde (0.100 g, 7.576 x 10^{-4} moles) and the resulting solution was stirred at r.t. for 5 minutes. To this solution was added freshly cracked cyclopentadiene (0.150 g, 2.273 x 10^{-3} moles, 3 eq.) in a single aliquot and the solution was stirred at 25 °C for a further 6 hours. The reaction solvent was evaporated and hydrolysis followed by stirring a $CHCl_3$ (2 cm^3), TFA (1 cm^3) and H_2O (1 cm^3) solution of the residue for 3 hours at r.t. The solution was then neutralised with sat. aq. $NaHCO_3$, the organic layer was extracted with DCM (2x10 cm^3), washed with H_2O (5 cm^3), dried ($MgSO_4$), filtered and evaporated to yield the crude product as a brown oil. Purification by flash column chromatography followed (hexane:EtOAc 98:2). ^{1}H NMR spectral data of the crude reaction mixtures was used to establish the extent of conversion of the starting material

as well as the product *exo:endo* ratio through the integration of the signals representing the aldehyde protons. ^{1}H NMR data for the cycloaddition products was consistent with previously reported literature values.[77]

The diastereoisomeric and enantiomeric ratios were determined by chiral GC analysis using a SUPLECO β-Dex column (30 m x 0.25 mm x 0.25 μm), (160 ^{o}C then 2 ^{o}C/min to 200 ^{o}C), retention time; *exo* isomers: 10.31 & 10.52 min, *endo* isomers: 10.79 & 10.96 min.

Isolation of (1*E*,6a*S*)-6-oxo-6a-phenyl-1-[(2*E*)-3-phenylprop-2-en-1-ylidene]tetrahydro-1*H*,3*H*-furo[3,4-*c*][1,2]oxazol-1-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate and [(1E)-3,3-dimethoxyprop-1-en-1-yl]benzene

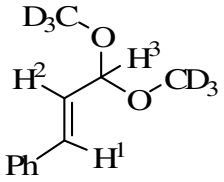
A mixture of **110a•**(+)-10-CSA (0.040 g, 9.2 x 10^{-5} moles) and *trans*-cinnamaldehyde (0.012 g, 9.2 x 10^{-5} moles) were dissolved in CD_3OD (0.5 cm^3) at r.t. Almost immediately the iminium ion and acetal formed in a 1:1.2 ratio.



110a iminium ion

^{1}H NMR (CD_3OD): (δ) 8.62 (1H, d *J* = 10.0, $H^{1'}$), 8.10 (1H, d *J* = 15.5, $H^{3'}$), 7.85-7.23 (11H, m, 10xArH & $H^{2'}$), 5.42-5.37 (1H, dd *J* = 8.5 & 8.5, H^{3}), 4.94-4.67 (4H, m, H^{3a}, H^{3} & 2xH^{4}), 3.33 (1H, d *J* = 14.8, SCH), 2.76 (1H, d *J* = 14.8, SCH), 2.72-2.62 (1H, m, C^{6A}), 2.36-2.27 (1H, m, H^{3A}), 2.05-1.94 (2H, m, H^{5A} & H^{4A}), 1.86 (1H, d *J* = 18.3, H^{3A}), 1.65-1.56 (1H, m, H^{6A}), 1.42-1.33 (1H, m, H^{5A}), 1.12 (3H, s, CH_3), 0.83 (3H, s, CH_3).

^{13}C NMR (CD_3OD): (δ) 216.9 (C=O), 169.1 (C=O), 161.9 ($C^{3'}$), 153.6. ($C^{1'}$), 134.1 ($C^{2'}$), 131.3-126.4 (8xArC), 77.3, 68.4 ($C^{3\&4}$), 58.2 (C^{1A}), 50.7 (C^{3a}), 47.4 ($\underline{C}(CH_3)_2$), 46.8 (SCH_2), 42.6 (C^{4A}), 42.3 (C^{3A}), 26.4 (C^{6A}), 24.4 (C^{5A}), 19.1, 18.8 (2xCH_3).



^{1}H NMR (CD_3OD): (δ) 7.85-7.23 (5H, m, 5xArH), 6.73 (1.2H, d *J* = 16.2, H^1), 6.20-6.13 (1.2H, dd *J* = 16.2 & 5.2, H^2), 4.94-4.67 (1H, m, H^3).
^{13}C NMR (CD_3OD): (δ) 133.4 (C^3), 131.3-126.4 (4xArC), 125.4 (C^2), 103.3 (C^1), 58.2 OCD_3).

4.2.5 Attempted organocatalysis of the Aldol Reaction

Typical Aldol Reaction

To a mix of solvent (2 cm^3) and acetone (0.5 cm^3) was added 4-nitrobenzaldehyde (0.038 g, 2.500 x 10^{-4} moles) followed by **110a•**(+)-10-CSA (20 mol%, 0.044 g, 1.000 x 10^{-4} moles) and the mixture was stirred at r.t. for 24 hours, sat. aq. NH_4Cl was added and extraction with EtOAc (2 x 5 cm^3) followed. The organic layer was dried ($MgSO_4$), filtered and evaporated to yield returned starting material and various acetals.

Formation of 1-(dimethoxymethyl)-4-nitrobenzene (133)[238,239]

The typical aldol condensation reaction procedure was performed in MeOH to yield **133** as a yellow oil (0.020 g, 40%). ^{1}H NMR spectral data was in accordance with the literature.

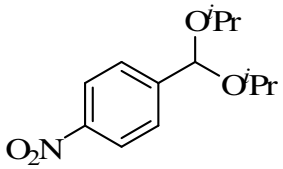
Synthesis of 1-(diethoxymethyl)-4-nitrobenzene (134)[240,241]

Typical aldol reaction procedure was carried out in EtOH to yield **134** as a yellow oil (0.025 g, 45%). ^{1}H NMR spectral data in accordance with that in the literature.

1-[*bis*(propan-2-yloxy)methyl]-4-nitrobenzene (135)[240]

4-Nitrobenzaldehdye (0.100 g, 6.617 x 10^{-4} moles) was stirred in ^{i}PrOH (8 cm^3) in the presence of (+)-10-CSA (0.031 g, 1.323 x 10^{-4} moles, 20 mol%) at r.t. for 72 hours. The solution was evaporated under reduced pressure and the residue was taken up in DCM

(10 cm^3). The organic layer was washed with sat. aq. NH_4Cl (5 cm^3) then H_2O (5 cm^3) and was dried ($MgSO_4$), filtered and evaporated to yield the crude product which was purified by flash column chromatography (hexane:EtOAc 4:1) to yield **135** as a yellow oil (0.058g, 36%).



^{1}H-NMR ($CDCl_3$): (δ) 8.21 (2H, d *J* = 8.6, *m*-ArH), 7.69 (2H, d *J* = 8.6, *o*-ArH), 5.63 (1H, s, C<u>H</u>O^{i}Pr), 3.99-3.87 (2H, m, OC<u>H</u>$(CH_3)_2$), 1.21 (6H, d *J* = 6.3, O(C<u>H</u>$_3)_2$), 1.19 (6H, d *J* = 6.2, O(C<u>H</u>$_3)_2$)

^{13}C-NMR ($CDCl_3$): (δ) 146.8, 146.6 (2xQ ArC), 129.5 (*o*-ArC), 122.4 (*m*-ArC), 97.1 (<u>C</u>HO^{i}Pr), 67.4 (O<u>C</u>H$(CH_3)_2$), 23.5, 22.8 (O(<u>C</u>H$_3)_2$).

IR (KBr): (cm^{-1}) 2973, 1609, 1524, 1348.

R_f: 0.42 (hexane:EtOAc 9:1)

4.2.6 Attempted organocatalysis of the Michael Addition Reaction

General Procedure 1: Addition of isovaleraldehyde to 1,1-bis(benzenesulfonyl)ethylene)

To a solution of **110a** (0.005 g, 2.438 x 10^{-5} moles) in anhydrous $CHCl_3$ filtered over basic alumina (2 cm^3) under Ar, was added isovaleraldehyde (0.210 g, 0.262 cm^3, 2.438 x 10^{-3} moles, 10 eq). The solution was left to stir at r.t. for 10 mins prior to the addition of 1,1-bis(benzenesulfonyl)ethylene (0.075 g, 2.438 x 10^{-4} moles). Stirring was continued at r.t. for 2 hours after which the solution was hydrolysed with sat. aq. NH_4Cl (2 cm^3). The layers were separated and the aqueous phase was extracted with DCM (2 x 3 cm^3), the combined organic layers were dried ($MgSO_4$), filtered and concentrated to yield the crude reaction products.

General Procedure 2: Addition of cyclohexanone to 1,1-bis(benzenesulfonyl)ethylene

To a mixture of **110a** (0.005 g, 2.438 x 10^{-5} moles) and (+)-10-CSA (0.006 g, 2.438 x 10^{-5} moles) in MeOH (0.125 cm^3) under Ar, was added cyclohexanone (2eq, 50 µl,

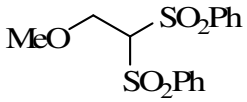
4.876 x 10^{-2} moles) followed by 1,1-bis(benzenesulfonyl)ethylene (0.075 g, 2.438 x 10^{-4} moles). The reaction was stirred at r.t. for 56 hours, after which it was hydrolysed with sat. aq. NH_4Cl and the organic material extracted with DCM (2 x 5 cm^3), washed with H_2O (5 cm^3), dried ($MgSO_4$), filtered and evaporated to yield the crude product.

Synthesis of 2-[2,2-bis(phenylsulfonyl)ethyl]cyclohexanone (147)

Prepared according to the general procedure 2; the crude product was purified by flash column chromatography (SiO_2, hexane:EtOAc 3:2) to yield the titled product as a cream solid (0.068 g, 68%). ^{1}H NMR spectral data was consistent with that in the literature[237].

Synthesis of 1,1'-[(2-methoxyethane-1,1-diyl)disulfonyl]dibenzene (138) and 1,1,3,3-tetrakis(bis(sulfonylethylene))4-methoxybutane (139)

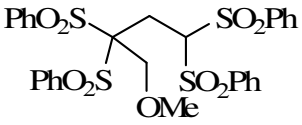
A solution of 1,1-bis(benzenesulfonyl)ethylene (0.050 g, 1.6214 x 10^{-4} moles) in MeOH (1.5 cm^3) was stirred at r.t. for 2.5 hours. Upon evaporation of the solvent the crude product was obtained as a yellow oil consisting of **138**, **139** and unreacted 1,1-bis(benzenesulfonyl)ethylene, which could not be separated.



138

^{1}H-NMR ($CDCl_3$): (δ) 8.19-7.54 (10H, m, 10xArH), 4.69-4.66 (1H, t *J* = 4.5, CH), 4.33 (2H, d *J* = 4.5, CH_2), 3.13 (3H, s, OCH_3).

^{13}C-NMR ($CDCl_3$): (δ) 139.2, 129.7, 129.0, 128.8 (4xArC), 83.3 (CH), 66.8 (CH_2), 58.9 (CH_3).



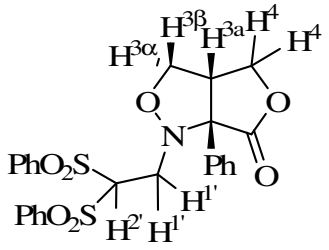
139

^{1}H-NMR ($CDCl_3$): (δ) 7.99-7.52 (20H, m, ArH), 4.69-4.67 (1H, t *J* = 4.8, CH), 3.63-3.58 (2H, s, CH_2OCH_3), 3.31 (2H, d J = 4.8, CH_2), 3.12 (3H, s, OCH_3).

^{13}C-NMR ($CDCl_3$): (δ) 153.6 (QC), 138.9, 138.6, 138.1, 137.8 (4xQ ArC), 135.0, 134.8, 134.7, 134.5, 129.9, 129.7, 129.6, 129.5, 129.3, 129.2, 129.0, 128.9 (12xArC), 83.3 (CH), 66.8 (CH_2), 58.9 (OCH_3), 58.4 (CH_2O).

Synthesis of (6a*S*)-6a-phenyl-1-[2,2-bis(phenylsulfonyl)ethyl]tetrahydro-3*H*,6*H*-furo[3,4-*c*][1,2]oxazol-6-one (140)

A solution of 1,1-bis(benzenesulfonyl)ethylene (0.050 g, 1.621 x 10^{-4} moles) and **110a** (0.033 g, 1.621 x 10^{-4} moles) in $CHCl_3$ (1.5 cm^3) was stirred at r.t. for 56 hours. The solvent was evaporated to yield the crude product which was purified by flash column chromatography (hexane:EtOAC 3:2) to yield the title product as a white solid (0.080 g, 96%).



^{1}H NMR ($CDCl_3$): (δ) 7.92-7.42 (15H, m, 15xArH), 4.95-4.92 (1H, dd *J* = 6.5 & 3.6, $H^{2'}$), 4.42-4.37 (1H, dd *J* = 9.8 & 6.1, $H^{3\alpha}$), 4.29-4.25 (1H, dd *J* = 9.8 & 1.1, $H^{3\beta}$), 4.20-4.14 (1H, dd *J* = 9.4 & 9.4, H^4), 3.87-3.82 (1H, dd *J* = 9.4 & 2.6, H^4), 3.81-3.75 (1H, dd *J* = 15.0 & 3.6, $H^{1'}$), 3.5-3.4 (2H, m, $H^{3a\&1'}$).

^{13}C NMR ($CDCl_3$): (δ) 173.5 (C=O), 138.5, 138.3 (2xQ ArC), 134.6 (ArC), 134.4 (Q ArC), 131.7, 129.7, 129.6, 129.5, 129.2, 129.1, 128.9, 127.8 (8xArC), 81.1 ($C^{2'}$), 73.0 (C^4), 70.3 (C^3), 51.8 (C^{6a}), 47.0 ($C^{1'}$).

IR (KBr): (cm^{-1}) 3557, 2923, 1763, 1448, 1312, 1156.

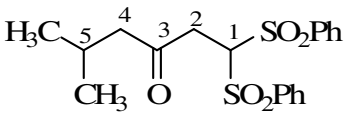
μ analysis:	Found:	C 56.25%	H 5.13%	N 2.51%
	$C_{25}H_{23}NS_2O_7 \bullet H_2O$ requires:	C 56.48%	H 5.12%	N 2.63%

m.p.: 70-78 °C

LC/TCOF-MS: $(M + K)^+$ requires 552.0548 g/mol, found 552.0543 g/mol, difference (-0.81 ppm).

Synthesis of 5-methyl-1,1-bis(phenylsulfonyl)hexan-3-one (141) and 1,1,6-tris(bis(phenylsulfonyl))-5-[bis(phenylsulfonyl)methyl]-5-methylhexan-3-one (142)

A mixture of isovaleraldehyde (0.210 g, 0.262 cm^3, 2.438 x 10^{-3} moles, 10 eq) and 1,1-bis(benzenesulfonyl)ethylene (0.075 g, 2.438 x 10^{-4} moles) were stirred in $CHCl_3$ (2 cm3) at r.t. for 2 hours. The solvent was evaporated to yield the crude product as a 2:1 mixture of **141**:**142** which could not be separated.

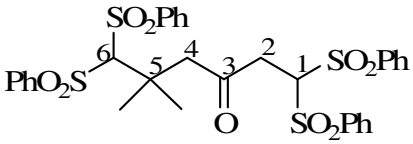


141

^{1}H NMR ($CDCl_3$): (δ) 7.91-7.49 (10H, m, 10xArH), 5.47-5.43 (1H, t *J* = 6.8, H^1), 3.28 (2H, d *J* = 5.8, H^4), 3.28 (2H, d *J* = 6.8, H^2), 2.21-2.09 (1H, m, H^5), 0.92 (6H, d *J* = 6.6, 2xCH_3).

^{13}C NMR ($CDCl_3$): (δ) 201.1 (C=O), 129.6, 128.1, 127.4 (3xArC), 78.7 (C^1), 50.3 (C^4), 36.2 (C^2), 23.6 (C^5), 20.6 (CH_3).

IR (KBr): (cm^{-1}) 3427, 2954, 1723, 1447, 1331, 1156, 1080.



142

^{1}H-NMR ($CDCl_3$): (δ) 7.92-7.54 (20H, m, ArH), 5.42-5.38 (1H, t *J* = 5.9, H^1), 4.74 (1H, s, H^6), 3.20 (2H, d *J* = 5.9, H^2), 2.61 (2H, s, H^4), 1.02 (6H, s, 2xCH_3).

Appendix

5.1 Crystal Data

The x-ray crystal structures for compounds **98** and **99** were solved by Prof. Pat McArdle and Dr. Mary Mahon of the University of Bath, this contribution is gratefully acknowledged.

5.1.1 Crystal Data for 98

Table 36. Crystal data and structure refinement for **98**.

Identification code	k06pma1
Empirical formula	$C_{12}H_{12}N_2O_2$
Formula weight	216.24
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 5.5410(1) Å
	b = 19.0880(4) Å β = 98.680(1) ^{o}
	c = 10.1480(2) Å
Volume	1061.01(4) $Å^3$
Z	4
Density (calculated)	1.354 Mg/m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	456
Crystal size	0.25 x 0.08 x 0.08 mm
Theta range for data collection	3.79 to 25.68 ^{o}.
Index ranges	-6<=h<=6; -23<=k<=23; -12<=l<=12
Reflections collected	16054
Independent reflections	2007 [R(int) = 0.0576]
Reflections observed (>2σ)	1829
Data Completeness	0.997
Absorption correction	Multiscans
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2007 / 24 / 202
Goodness-of-fit on F^2	1.187
Final R indices [I>2σ(I)]	R_1 = 0.0633 wR_2 = 0.1435
R indices (all data)	R_1 = 0.0771 wR_2 = 0.1477
Largest diff. peak and hole	0.343 and -0.394 e.$Å^{-3}$

Table 37. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

Atom	x	y	z	U(eq)
O(1)	2584(4)	-529(1)	151(2)	33(1)
O(2)	-1681(4)	-797(1)	3624(2)	37(1)
N(2)	4907(4)	428(1)	2158(2)	29(1)
N(1)	44(15)	-804(4)	1715(7)	29(2)
C(12)	5919(5)	983(2)	3062(3)	32(1)
C(1)	3010(6)	36(2)	2355(4)	26(1)
C(2)	1912(7)	-455(2)	1256(5)	27(1)
C(3)	-126(9)	-557(2)	2990(4)	27(1)
C(4)	1707(6)	-35(2)	3389(3)	29(1)
C(5)	-1578(17)	-1310(5)	963(9)	57(3)
C(6)	4499(8)	1648(3)	2787(6)	29(1)
C(7)	2675(8)	1836(2)	3537(5)	31(1)
C(8)	1218(6)	2428(2)	3183(3)	36(1)
C(9)	1606(6)	2831(2)	2080(4)	35(1)
C(10)	3510(11)	2651(3)	1348(6)	37(1)
C(11)	4887(5)	2080(2)	1722(3)	33(1)
O(2A)	1800(5)	-729(2)	-320(3)	62(3)
N(2A)	3297(5)	386(2)	3977(3)	51(2)
O(1A)	-654(5)	-588(2)	3771(3)	60(3)
N(1A)	160(50)	-744(14)	1560(20)	28(6)
C(12A)	5150(20)	911(6)	4006(12)	50(3)
C(1A)	2530(20)	31(6)	2883(14)	28(3)
C(2A)	500(40)	-491(12)	2825(18)	68(8)
C(3A)	1940(30)	-517(8)	832(15)	29(4)
C(4A)	3280(20)	-20(6)	1668(12)	39(3)
C(5A)	-1520(20)	-1295(7)	987(13)	5(3)
C(6A)	4330(40)	1590(13)	3117(19)	49(7)
C(7A)	2260(40)	1952(12)	3210(20)	68(8)
C(8A)	1590(30)	2525(10)	2444(19)	79(6)
C(9A)	3030(30)	2697(9)	1548(17)	29(5)
C(10A)	4940(30)	2274(8)	1384(14)	128(12)
C(11A)	5780(30)	1787(8)	2226(14)	63(3)

Table 38. Bond lengths [Å] and angles [°] for **98**.

O(1)-C(2)	1.241(5)	**O(2)-C(3)**	1.238(6)
N(2)-C(1)	1.329(4)	**N(2)-C(12)**	1.457(4)
N(1)-C(2)	1.371(8)	**N(1)-C(3)**	1.393(8)
N(1)-C(5)	1.456(7)	**C(12)-C(6)**	1.499(6)
C(1)-C(4)	1.368(5)	**C(1)-C(2)**	1.512(6)
C(3)-C(4)	1.436(6)	**C(6)-C(7)**	1.400(6)
C(6)-C(11)	1.401(8	**C(7)-C(8)**	1.404(6)
C(8)-C(9)	1.401(5)	**C(9)-C(10)**	1.420(6)
C(10)-C(11)	1.352(6)	**O(2A)-C(3A)**	1.228(14)
N(2A)-C(1A)	1.316(13)	**N(2A)-C(12A)**	1.431(12)
O(1A)-C(2A)	1.243(15)	**N(1A)-C(2A)**	1.359(19)
N(1A)-C(3A)	1.39(2)	**N(1A)-C(5A)**	1.465(14)
C(12A)-C(6A)	1.61(2)	**C(1A)-C(4A)**	1.362(14)
C(1A)-C(2A)	1.500(17)	**C(3A)-C(4A)**	1.407(14)
C(6A)-C(11A)	1.352(14	**C(6A)-C(7A)**	1.354(15)
C(7A)-C(8A)	1.360(15)	**C(8A)-C(9A)**	1.338(15)
C(9A)-C(10A)	1.361(1	**C(10A)-C(11A)**	1.3004
C(1)-N(2)-C(12)	123.5(3	**C(2)-N(1)-C(3)**	108.2(5)
C(2)-N(1)-C(5)	125.6(7)	**C(3)-N(1)-C(5)**	126.1(7)
N(2)-C(12)-C(6)	111.0(3	**N(2)-C(1)-C(4)**	133.8(3)
N(2)-C(1)-C(2)	118.5(4)	**C(4)-C(1)-C(2)**	107.7(3)
O(1)-C(2)-N(1)	126.6(5)	**O(1)-C(2)-C(1)**	126.5(3)
N(1)-C(2)-C(1)	106.9(4)	**O(2)-C(3)-N(1)**	120.5(4)
O(2)-C(3)-C(4)	128.9(3)	**N(1)-C(3)-C(4)**	110.6(5)
C(1)-C(4)-C(3)	106.6(3)	**C(7)-C(6)-C(11)**	118.4(5)
C(7)-C(6)-C(12)	121.2(6)	**C(11)-C(6)-C(12)**	120.3(4)
C(6)-C(7)-C(8)	120.1(5)	**C(9)-C(8)-C(7)**	119.6(3)
C(8)-C(9)-C(10)	120.1(4)	**C(11)-C(10)-C(9)**	118.7(4)
C(10)-C(11)-C(6)	123.0(4)	**C(1A)-N(2A)-C(12A)**	121.2(8)
C(2A)-N(1A)-C(3A)	112.8(14)	**C(2A)-N(1A)-C(5A)**	128.1(17)
C(3A)-N(1A)-C(5A)	118.3(16)	**N(2A)-C(12A)-C(6A)**	114.3(11)
N(2A)-C(1A)-C(4A)	134.2(11)	**N(2A)-C(1A)-C(2A)**	121.3(13)
C(4A)-C(1A)-C(2A)	104.4(12)	**O(1A)-C(2A)-N(1A)**	131.7(17)
O(1A)-C(2A)-C(1A)	122.6(16)	**N(1A)-C(2A)-C(1A)**	105.4(13)
O(2A)-C(3A)-N(1A)	117.1(12)	**O(2A)-C(3A)-C(4A)**	138.4(14)
N(1A)-C(3A)-C(4A)	104.0(13)	**C(1A)-C(4A)-C(3A)**	112.8(12)
C(11A)-C(6A)-C(7A)	120.0(19)	**C(11A)-C(6A)-C(12A)**	117.0(17)
C(7A)-C(6A)-C(12A)	123.0	**C(6A)-C(7A)-C(8A)**	122(2)
C(9A)-C(8A)-C(7A)	116.4(18)	**C(8A)-C(9A)-C(10A)**	119.5(16)
C(11A)-C(10A)-C(9A)	123.5(10)	**C(10A)-C(11A)-C(6A)**	116.5(12)

Table 39. Anisotropic displacement parameters ($Å^2$ x 10^3) for **98**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2a^{*2}U11$ + ... + 2 h k a* b* U12].

Atom	U11	U22	U33	U23	U13	U12
O(1)	36(1)	39(1)	28(1)	2(1)	15(1)	1(1)
O(2)	40(1)	39(1)	35(1)	3(1)	16(1)	1(1)
N(2)	28(1)	28(1)	32(1)	-3(1)	8(1)	1(1)
N(1)	35(3)	27(2)	27(2)	5(2)	11(2)	-3(1)
C(12)	29(2)	31(2)	35(2)	-2(1)	3(1)	1(1)
C(1)	31(2)	24(2)	25(2)	1(1)	8(2)	6(1)
C(2)	30(2)	27(2)	25(2)	3(2)	9(2)	6(1)
C(3)	35(2)	25(2)	22(2)	1(1)	5(2)	10(2)
C(4)	31(2)	28(2)	29(2)	-1(1)	9(1)	0(1)
C(5)	56(4)	51(4)	62(4)	2(2)	-1(2)	-9(2)
C(6)	25(2)	31(2)	31(3)	-10(2)	3(2)	-6(1)
C(7)	33(2)	28(2)	34(2)	5(2)	9(2)	2(2)
C(8)	38(2)	32(2)	41(2)	4(1)	16(1)	8(1)
C(9)	39(2)	29(2)	36(2)	3(2)	1(1)	-1(1)
C(10)	46(3)	35(2)	33(2)	-6(2)	15(2)	-4(2)
C(11)	33(2)	37(2)	28(2)	-9(2)	3(1)	0(1)

Table 40. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **98**.

Atom	x	y	z	U(eq)
H(2)	5588	348	1443	35(9)
H(12A)	7643	1065	2955	38
H(12B)	5881	835	3993	38
H(4)	1964	212	4210	35
H(5A)	-1588	-1235	6	86
H(5B)	-3235	-1251	1173	86
H(5C)	-1003	-1785	1202	86
H(7)	2424	1562	4286	38
H(8)	-23	2555	3689	43
H(9)	595	3224	1820	42
H(10)	3808	2927	610	44
H(11)	6178	1966	1240	39
H(2A)	2657	299	4702	50
H(12C)	6591	701	3691	60
H(12D)	5652	1061	4941	60
H(4A)	4571	252	1412	46
H(5A1)	-3041	-1082	552	8
H(5A2)	-1865	-1610	1697	8
H(5A3)	-767	-1562	329	8
H(7A)	1242	1802	3829	82
H(8A)	169	2789	2540	95
H(9A)	2717	3111	1030	35
H(10A)	5695	2338	614	153
H(11A)	7337	1581	2216	76

5.1.2 Crystal data for 99

Table 41. Crystal data and structure refinement for **99**.

Identification code	linda2
Empirical formula	C11 H15 N O3
Formula weight	209.24
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P21ab
Unit cell dimensions	a = 7.5640(4) Å
	b = 9.1400(4) Å
	c = 14.8700(9) Å
Volume	1028.04(9) $Å^3$
Z	4
Density (calculated)	1.352 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	448
Crystal size	0.20 x 0.20 x 0.15 mm
Theta range for data collection	3.53 to 27.47 °.
Index ranges	-9<=h<=9; -11<=k<=11; -19<=l<=19
Reflections collected	14860
Independent reflections	2341 [R(int) = 0.0497]
Reflections observed (>2σ)	2050
Data Completeness	0.994
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.90
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2341 / 1 / 139
Goodness-of-fit on F^2	1.083
Final R indices [I>2σ(I)]	R_1 = 0.0416 wR_2 = 0.0977
R indices (all data)	R_1 = 0.0493 wR_2 = 0.1015
Absolute structure parameter	-1.3(11)
Largest diff. peak and hole	0.242 and -0.197 e.$Å^{-3}$

Table 42. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

Atom	x	y	z	U(eq)
O(1)	6203(2)	986(1)	8966(1)	32(1)
O(2)	7221(2)	3651(1)	9977(1)	36(1)
O(3)	7979(2)	4515(1)	6988(1)	35(1)
N(4)	7505(2)	4379(1)	8511(1)	29(1)
C(1)	8281(2)	1157(2)	7142(1)	27(1)
C(2)	8548(3)	1494(2)	6161(1)	34(1)
C(3)	7304(3)	588(2)	5566(1)	35(1)
C(4)	7452(3)	-1042(2)	5765(1)	35(1)
C(5)	7143(3)	-1353(2)	6757(1)	33(1)
C(6)	8412(3)	-460(2)	7349(1)	31(1)
C(7)	7958(2)	2154(2)	7783(1)	25(1)
C(8)	7840(2)	3763(2)	7655(1)	28(1)
C(9)	7707(2)	1852(2)	8774(1)	26(1)
C(10)	7466(2)	3372(2)	9181(1)	28(1)
C(11)	7511(3)	5951(2)	8684(1)	40(1)

Table 43. Bond lengths [Å] and angles [°] for **99**.

O(1)-C(9)	1.415(2)	**O(2)-C(10)**	1.2246(18)
O(3)-C(8)	1.210(1)	**N(4)-C(10)**	1.358(2)
N(4)-C(8)	1.414(2)	**N(4)-C(11)**	1.4591(19)
C(1)-C(7)	1.342(2)	**C(1)-C(2)**	1.505(2)
C(1)-C(6)	1.513(2)	**C(2)-C(3)**	1.534(3)
C(3)-C(4)	1.523(2)	**C(4)-C(5)**	1.521(2)
C(5)-C(6)	1.537(3)	**C(7)-C(8)**	1.486(2)
C(7)-C(9)	1.512(2)	**C(9)-C(10)**	1.527(2)
C(10)-N(4)-C(8)	113.28(13)	**C(10)-N(4)-C(11)**	122.51(14)
C(8)-N(4)-C(11)	123.39(13	**C(7)-C(1)-C(2)**	125.02(14)
C(7)-C(1)-C(6)	122.07(14)	**C(2)-C(1)-C(6)**	112.90(13)
C(1)-C(2)-C(3)	111.45(14)	**C(4)-C(3)-C(2)**	111.80(15)
C(5)-C(4)-C(3)	111.07(13)	**C(4)-C(5)-C(6)**	111.15(15)
C(1)-C(6)-C(5)	111.13(14)	**C(1)-C(7)-C(8)**	126.33(14)
C(1)-C(7)-C(9)	126.26(13)	**C(8)-C(7)-C(9)**	107.38(13)
O(3)-C(8)-N(4)	121.77(14)	**O(3)-C(8)-C(7)**	131.43(15)
N(4)-C(8)-C(7)	106.80(13)	**O(1)-C(9)-C(7)**	113.57(13)
O(1)-C(9)-C(10)	109.49(13)	**C(7)-C(9)-C(10)**	103.59(11)
O(2)-C(10)-N(4)	124.90(15)	**O(2)-C(10)-C(9)**	126.20(14)
N(4)-C(10)-C(9)	108.86(13)		

Table 44. Anisotropic displacement parameters ($Å^2$ x 10^3) for **99**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2 a^{*2}$ U11 + ... + 2 h k a* b* U12]

Atom	U11	U22	U33	U23	U13	U12
O(1)	34(1)	29(1)	33(1)	6(1)	-2(1)	-3(1)
O(2)	57(1)	28(1)	24(1)	-3(1)	2(1)	2(1)
O(3)	53(1)	24(1)	28(1)	5(1)	-1(1)	-3(1)
N(4)	39(1)	22(1)	25(1)	-1(1)	-4(1)	2(1)
C(1)	29(1)	25(1)	27(1)	2(1)	-2(1)	-1(1)
C(2)	47(1)	29(1)	25(1)	0(1)	5(1)	-3(1)
C(3)	55(1)	26(1)	25(1)	0(1)	-3(1)	1(1)
C(4)	50(1)	25(1)	29(1)	-4(1)	-2(1)	2(1)
C(5)	46(1)	21(1)	33(1)	0(1)	0(1)	0(1)
C(6)	43(1)	23(1)	27(1)	1(1)	1(1)	4(1)
C(7)	28(1)	24(1)	24(1)	4(1)	-2(1)	-1(1)
C(8)	33(1)	25(1)	26(1)	0(1)	-4(1)	-1(1)
C(9)	31(1)	22(1)	25(1)	1(1)	-1(1)	1(1)
C(10)	30(1)	27(1)	27(1)	1(1)	-1(1)	-1(1)
C(11)	65(1)	21(1)	32(1)	-2(1)	-7(1)	3(1)

Table 45. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **99**.

Atom	x	y	z	U(eq)
H(1)	6466	352	9352	38
H(2A)	9789	1283	5994	40
H(2B)	8329	2548	6055	40
H(3A)	6071	910	5668	42
H(3B)	7595	765	4926	42
H(4A)	6570	-1582	5402	42
H(4B)	8642	-1392	5591	42
H(5A)	7319	-2409	6875	40
H(5B)	5907	-1104	6915	40
H(6A)	8124	-627	7991	37
H(6B)	9640	-796	7246	37
H(9)	8791	1380	9027	32
H(11A)	6378	6238	8950	59
H(11B)	7686	6479	8117	59
H(11C)	8472	6190	9101	59

5.2 Detailed analysis of spectral data in support of representative members of bicyclic isoxazolidines.

In order to characterise the novel compounds prepared in this thesis various NMR spectral techniques were employed; ^{1}H, ^{13}C DEPT (45, 90, 135), homonuclear and heteronuclear COSY. For all compounds initially the ^{1}H NMR spectra were examined, resonance positions, multiplicity and relative integrations were recorded. Peaks were assigned based on resonance position and multiplicity. Homonuclear COSY data highlighted coupling between the protons and the ^{13}C peaks were assigned with the help of DEPT (45, 90 135) spectra and heteronuclear COSY spectra.

NMR spectral data of 6a-(furan-2-yl)-5-methylhexahydro-6H-pyrrolo[3,4-c][1,2]oxazol-6-one, 117b.

Included below is the NMR data obtained for the 2-furyl lactam fused bicycle **117b** which was used to assign peaks and characterise **117b**.

The use of the relative integrations and coupling constants in the ^{1}H NMR spectrum and a range of additional NMR spectra were used to assign the peaks. In the ^{1}H NMR spectrum the aromatic peaks are located between 6.4-7.5 ppm, the NH proton is the broad peak at ≃5.75 ppm, the four peaks between ≃4.2 and 3.2 ppm are those belonging to the protons attached to the bicycle and the largest peak, integrating for three protons, at 2.92 ppm is that of the *N*-methyl protons, figure 84.

Upon examination of the $^{1}H^{1}H$ COSY spectrum, coupling is observed between all of the aromatic protons. Accordingly these were assigned on a combination of their resonance positions and coupling constants, figure 84 & table 46. Typical resonance positions for an unsubstituted furan ring show the proton closest to the O-atom (H^{α}) to be the most downfield proton at ≃7.4 ppm[242], in our structure this represents $H^{3'}$. In an unsubstituted system the H^{β} is more shielded due to resonance around the ring and as a result the doublet of doublets at ≃6.37 ppm corresponds to $H^{4'}$ leaving the doublet of doublets at ≃6.60 ppm representing $H^{5'}$. The observed coupling constants confirm the peak assignments with 1.8 Hz a typical coupling constant between H^{α} and H^{β} and 3.5 Hz for that between H^{β} and $H^{\beta'}$.

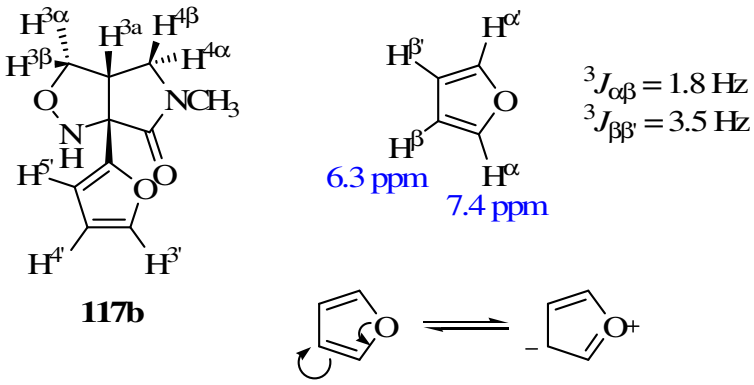


Figure 84. Typical coupling constants for the furan ring.

Table 46. Coupling constants observed for the aromatic peaks located between 7.41 and 6.36 ppm.

Entry	Peak (ppm)	Multiplicity	Coupling Constants (Hz)		Proton
1	7.41-7.40	dd	1.9	0.8	$H^{3'}$
2	6.60	d	3.3	-	$H^{5'}$
3	6.38-6.36	dd	3.3	1.9	$H^{4'}$

- = unknown (could not be determined from spectrum).

The $^1H^1H$ COSY spectrum indicates the presence of coupling between the multiplet located at 3.65-3.44 ppm and all other ring protons; as this is the only proton that couples to every other ring proton it can be assigned as H^{3a}, figure 86. The most downfield peak of the ring protons, representing two protons, shows coupling only to itself and H^{3a} and due to its more downfield location can be assigned as $H^{3\alpha\&3\beta}$. The $^{13}C^1H$ correlation spectrum confirmed the protons represented by this signal are indeed attached to the same carbon atom. The peaks located between 3.75-3.68 ppm and 3.28-3.24 ppm represent $H^{4\alpha}$ and $H^{4\beta}$. Assignment of these protons is made with reference to the C^{6a}-Ph analogue **117a** previously prepared within the group and again the $^{13}C^1H$ COSY confirms the protons are attached to the same carbon atom, figure 87.

Assignment of the ring H^{α} and H^{β} protons is made with reference to the C^{6a}-Ph analogue, **110a**, previously prepared within the group and stereochemical assignment of **117b** as being a *cis*-fused 5,5-bicycle is also made with reference to **117a**. That **117a** was *cis*-fused was surmised on the basis of the enhancement observed on both H^{3a} and the ArH following irradiation of $H^{4\beta}$. Significantly an x-ray crystal determination on the same compound confirms this assignment.

The ^{13}C spectrum, figure 88, can be assigned with help of DEPT 45, 135 and CH correlation spectra. The most downfield peak at 170.2 ppm can be assigned to the carbonyl carbon and the *N*-methyl carbon is very noticeable at 30.3 ppm, DEPT 135 confirms this assignment. Due to the assignment of the aromatic protons from the ^{1}H NMR spectrum the $^{13}C^{1}H$ COSY indicates the peaks at 143.0, 110.9 and 119.8 represent $C^{3'}$, $C^{4'}$ and $C^{5'}$ respectively. The DEPT 135 spectrum indicates two CH_2 carbon atoms at 79.2 and 52.5 ppm and a glance at the $^{13}C^{1}H$ COSY shows the peak at 79.2 ppm to be that of C^{3} whilst the peak at 52.5 ppm can be assigned as C^{4}. The $^{13}C^{1}H$ COSY also indicates the peak at 44.8 ppm represents C^{3a}. The two peaks remaining belong to quaternary carbon atoms and can be assigned as Q ArC (142.8 ppm) and C^{6a} (72.8 ppm).

Similar methods were used to assign the NMR spectra of all the compounds discussed in this thesis.

^{1}H NMR ($CDCl_3$): (δ) 7.41-7.40 (1H, dd *J* = 1.9 & 0.8, $H^{3'}$), 6.60 (1H, d *J* = 3.3, $H^{5'}$), 6.38-6.36 (1H, dd *J* = 3.3 & 1.9, $H^{4'}$), 5.74 (1H, br s, NH), 4.15-4.11 (2H, m, H^{3}), 3.75-3.68 (1H, dd *J* = 10.1 & 8.3, $H^{4\beta}$), 3.65-3.44 (1H, m, H^{3a}), 3.28-3.24 (1H, dd *J* = 10.1 & 2.6, $H^{4\alpha}$), 2.92 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): (δ) 170.2 (C=O), 148.2 (Q ArC), 143.0 ($C^{3'}$), 110.9 ($C^{4'}$), 109.8 ($C^{5'}$), 79.2 (C^{3}), 72.8 (C^{6a}), 52.5 (C^{4}), 44.8 (C^{3a}), 30.3 (NCH_3).

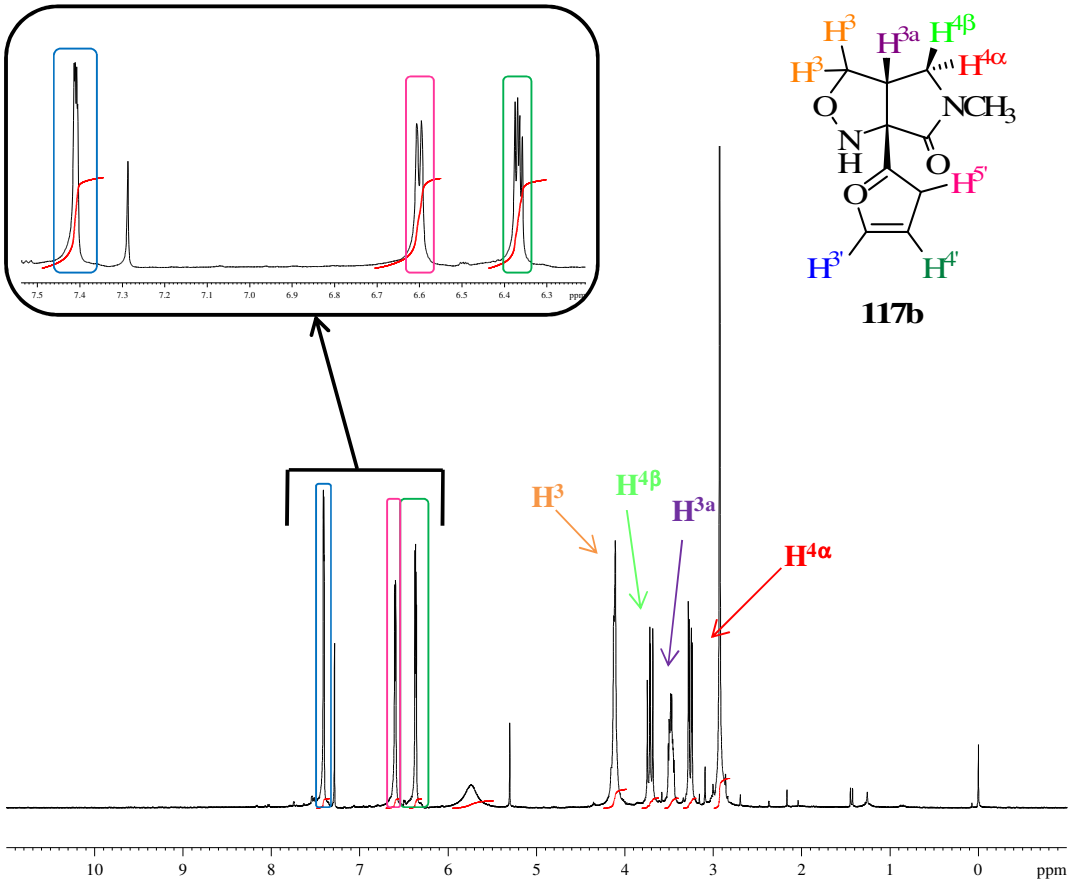


Figure 85. ^{1}H NMR spectrum for **117b**.

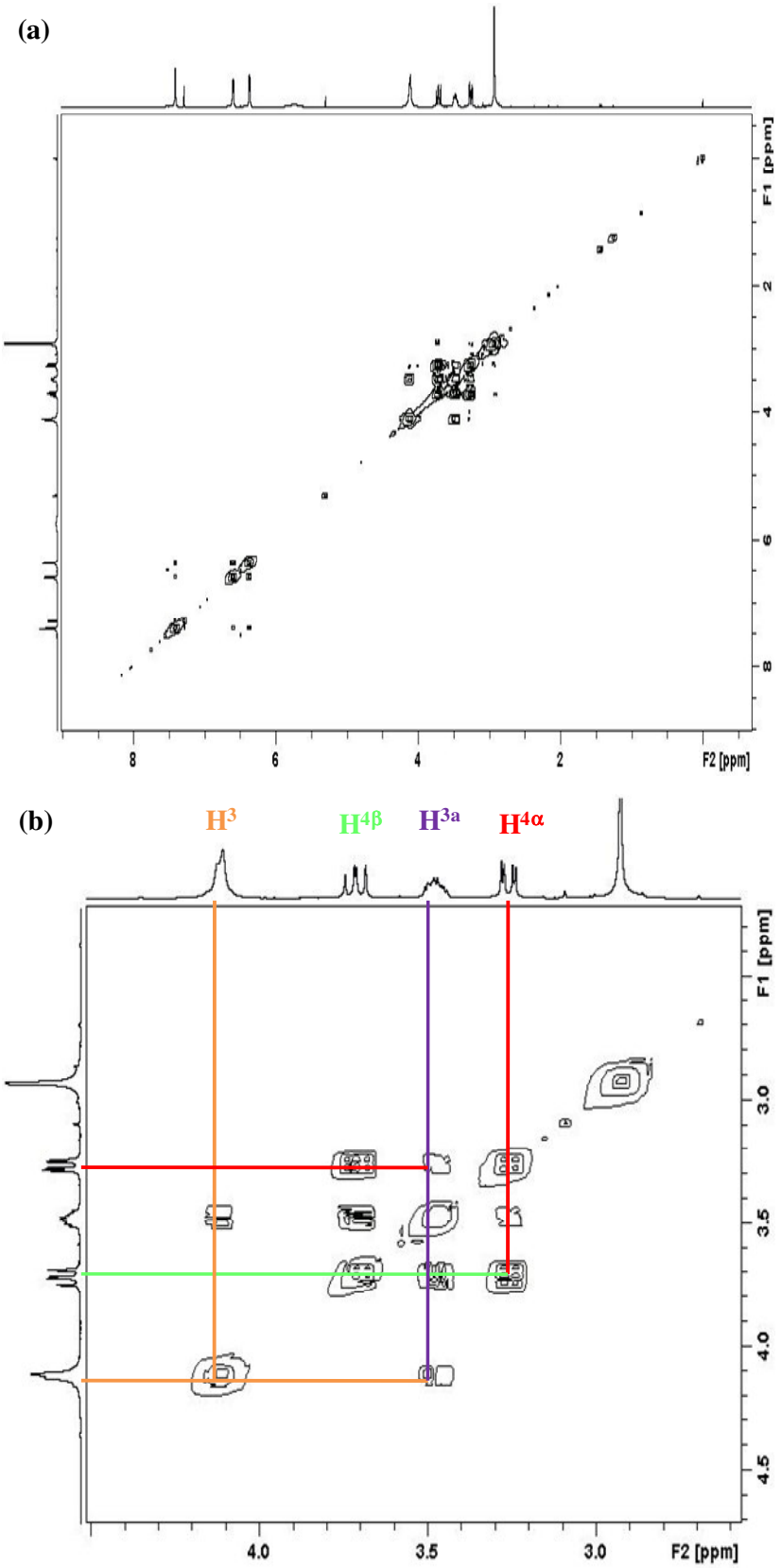


Figure 86. $^{1}H^{1}H$ COSY **(a)** for **117b** and **(b)** highlighting the isoxazolidine protons.

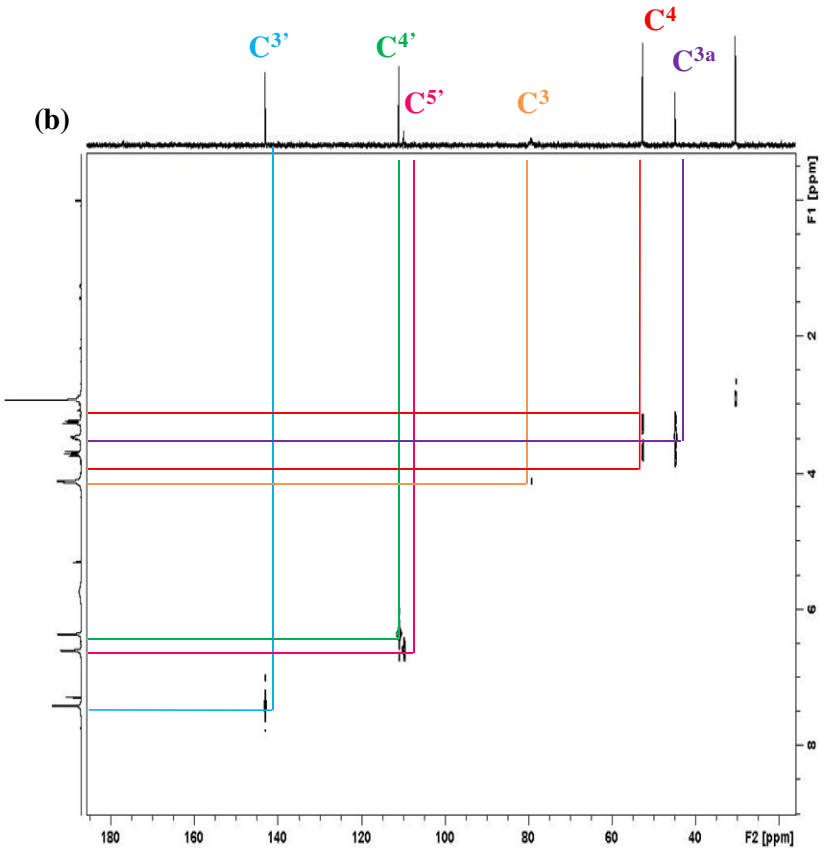


Figure 87. $^{1}H^{13}C$ COSY for **117b**.

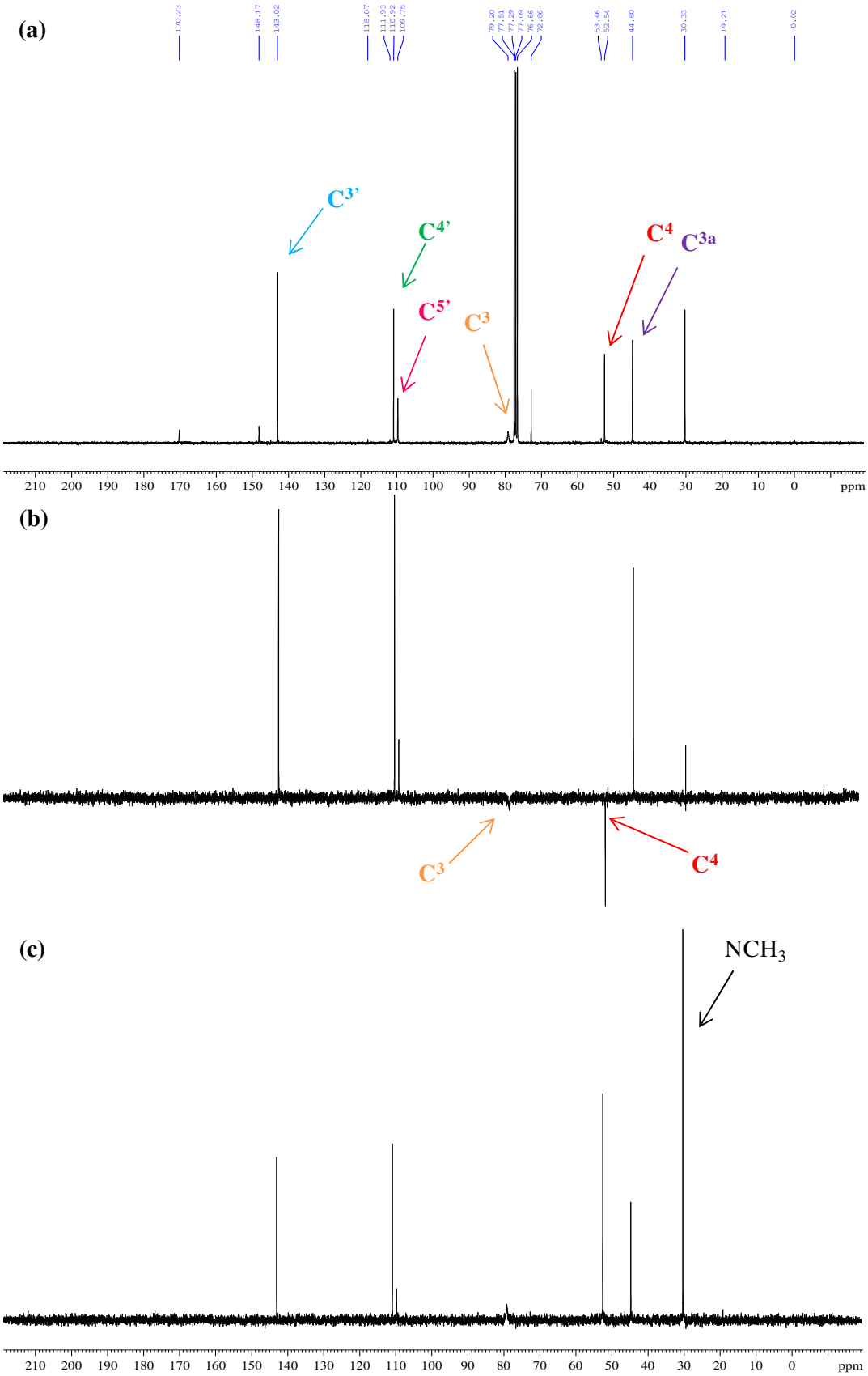


Figure 88. **(a)** ^{13}C spectrum, **(b)** DEPT 135 and **(c)** DEPT 45 for **117b**.

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