Development of Second Generation Scaffolds for Iminium Ion Catalysis.

Ian L. Jones

A Thesis Submitted for the Degree of Doctor of Philosophy

at

Cardiff University

2006

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Dedicated to my Mother and Father.
Without their support, emotionally and financially,
I would never have discovered my full potential.

Basic research is like shooting an arrow into the air and, where it lands, painting a target.

--- Homer Adkins

An expert is a man who has made all the mistakes, which can be made, in a very narrow field.

--- Niels Bohr

Abstract

This thesis embraces two main sections that examine alternative architectures for the iminium ion catalysis of the Diels-Alder reaction – comprising acyclic and cyclic systems.

Chapter **1** provides an overview of iminium ion and enamine catalysed processes. Focus is on the structural requirements of catalysts for effective and efficient transformations. *Chapter* **2** highlights work carried out previously within the group and provides a more in depth review of the Diels-Alder reaction, the protocol adopted for comparing catalyst activity and methods by which results were analysed.

Chapter **3** describes the design and synthesis of a series of five membered cyclic catalysts based on the pyrazolidine subunit. These systems incorporated aspects of acyclic catalysts developed previously within the group to decrease reaction times and catalyst loadings. Reaction conditions were optimised with regards to solvent and acid co-catalyst. SAR studies of the cyclic and acyclic architectures lead to the expansion of the acyclic series within *Chapter* **4**. This resulted in the most active acyclic catalyst to date with a conversion of 98% after of six hours within the iminium ion catalysed Diels-Alder reaction.

Chapter **5** shows a combination of SAR studies and computer modelling that led to the design and synthesis of a series of six-membered cyclic analogues containing an α-heteroatom. These systems catalysed the Diels-Alder reaction more efficiently producing a conversion of 89% after three hours and 99% after six and would provide an effective architecture for the development of a chiral catalyst. A trend was discovered relating the electronic environment of a β-carbonyl incorporated into the catalyst structure and its associated activity with supporting evidence from an associated computational project.

Finally, *Chapter* **6** describes preliminary studies into the three proposed component steps of the iminium ion catalysed Diels-Alder reaction. ^{1}H NMR and UV spectroscopy was (and continues to be) used to examine these steps to gain valuable information regarding the mechanism of the catalytic cycle.

Acknowledgements

Firstly, I would like to thank my supervisor Dr. Nick Tomkinson for all his support and encouragement throughout my work at Cardiff University. It was his enthusiasm and excitement for chemistry has made my Ph.D. studies so enjoyable. I would also like to thank Dr. Richard Elliott from GSK, Harlow, for his guidance and for making my industrial placement so rewarding.

Many thanks go to all in lab 1.119 in Cardiff, both past and present members, especially to Dan, Claire and Julie who introduced me to the "ethics" of shared lab space. More recently to Niall, Antonio, Tim, Kerri, Huw and Marky B's group, and our post-docs Nonny, Eve, Jacky and Rob all of which have proved an excellent distraction from work on many occasions.

I would also like to thank all the analytical and technical staff at Cardiff University for all the help I've received, especially Rob, Robin, Gaz and Dave.

Outside of work special thanks goes to LL Dan, Ewan, 2/3 of Trian, Peter and Fractured who have fed and watered me, and provided entertainment with much merriment.

Finally, to my parents whose belief and support has been the driving force behind all of my achievements. They are the ones to blame for my being at university for so long.

There are many others who have helped (and hindered!) my Cardiff life, too many to mention but to you all I extend my gratitude.

TABLE OF CONTENTS

DETAILED TABLE OF CONTENTS

Abbreviations

Ac	acetyl
APcI	atmospheric pressure chemical ionisation
Ar	aromatic
atm.	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
b.pt.	boiling point
br	broad
Bu	butyl
cat.	catalyst
Cbz	benzyloxycarbonyl
column chromatography	flash column chromatography
Cy	cyclohexane
d	day(s)
d	doublet
DCA	dichloroacetic acid
DFT	density functional theory
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNPH	2,4-dinitrophenylhydrazine
Et	ethyl
ES	electrospray
ether	diethyl ether
EWG	electron withdrawing group
e.e.	enantiomeric excess
equiv. (eq.)	equivalent(s)
GC	gas chromatography
GLC	gas-liquid chromatography
hr.	hour(s)
HOMO	highest occupied molecular orbital

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	*iso*
IR	infra red
k	kilo
LA	Lewis acid
light petrol	petroleum ether 40–60 °C
Lit.	literature
LUMO	lowest unoccupied molecular orbital
M	molar
m	mass
m	multiplet
Me	methyl
min.	minute(s)
mmol	millimole(s)
NMR	nuclear magnetic resonance
MO	molecular orbital
mol	mole(s)
mp	melting point
MHz	megahertz
MS	mass spectrometry
Ms	mesyl
NCS	*N*-chlorosuccinimide
n	*normal*
n.d.	not determined
NFSI	*N*-fluorobenzenesulfonimide
NOESY	nuclear Overhauser enhancement spectroscopy
p	*para*
p	pentet
PES	potential energy surface
Ph	phenyl
PMP	*p*-methoxyphenyl
Pr	propyl
q	quartet

quant.	quantitative
RDS	rate determining step
r.t.	room temperature
s	singlet
SAR	structure-activity relationship
sept.	septet
SMP	(*S*)-2-methoxymethylpyrrolidine
sol^{n}.	solution
t	tertiary
t	triplet
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl
*p*TSA	*para*-toluene sulfonic acid
vol.	volume(s)
vs.	versus
z	charge
Å	Angstroms
Δ	heat
σ	sigma
*	chiral

Chapter 1: Introduction

1.1 Organic Chemistry

1.1.1 Chemical catalysis

Catalysis is a fundamental aspect of efficient and effective chemical transformations within all disciplines of chemistry. Its underlying principles are to increase reaction rates and therefore conversions, without affecting equilibria or causing alternative reaction routes to occur. Catalysis accounts for a large portion of research and spreads across the three traditional disciplines of organic, inorganic and physical chemistry.

1.1.2 Chiral molecules

Since the realisation that the spatial arrangements within molecules directly affects their fundamental properties, asymmetric catalysis has devoted itself to the preparation of chiral products and the control of their absolute configuration.[1] Undoubtedly, control of stereochemistry defines everything from simple interactions of molecules to the core of life as we perceive it. Production and definition of enantiomerically pure compounds is therefore paramount in organic chemistry particularly throughout the pharmaceutical industry where chiral compounds are needed to interact with chiral receptors where a stereogenic centre is present within the drug molecule. This, but not solely, has generated much need and interest for improved chemical control of organic reactions.

1.1.3 Organocatalysis

Enzymes within the body not only provide optically pure products but are also enormously efficient towards their specific chemical transformations. Whilst the chemist's toolbox of catalysts consists mostly of metal-containing species only about half of known enzymes contain metals in their active sites.[2] This indicates the significance for transformations to be carried out in the laboratory in the absence of metal. Consequently, organocatalysis is gaining appreciation within the organic community complementing existing bio- and metal-based catalysis. Examples of organocatalysis were reported from as early as 1960;[3] however it was not until the last decade that this branch of chemistry became the main focus of many research groups.[4]

The term organocatalysis encompasses the idea that the catalyst employed for a chemical transformation be comprised of only "organic" elements. However, today's understanding of an "organic catalyst" must also be cost effective relative to its metal-based competitors, and also environmentally friendly both in its production and application.

1.1.4 Asymmetric organocatalysis

With "Green Chemistry" fast becoming of utmost importance in our socially aware society, recent years have shown increased interest and development of small organic molecules to accelerate many reactions in place of their metal-containing equivalents. While metal based catalysis can be used for an extensive array of transformations with the ability for "fine tuning" to a particular substrate through the use of alternative coordinated ligands, there are several disadvantages such as the cost associated with large quantities of precious metals, toxicity and environmental issues resulting from chemical waste and possible metal contaminations residing in the products.[5]

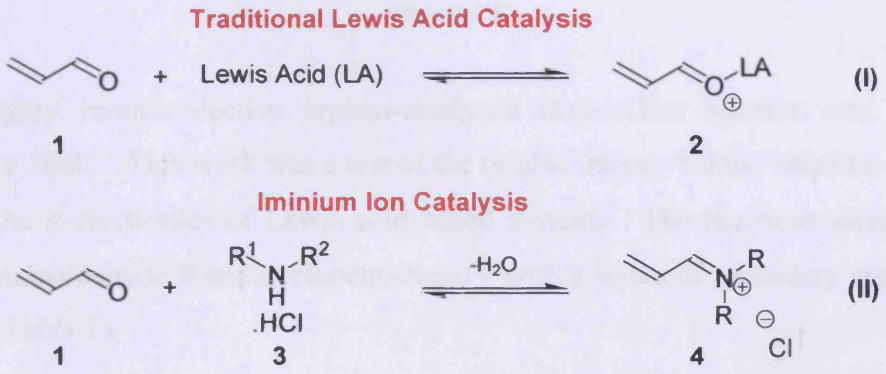
1.1.5 Aminocatalytic pathways

It is well known that structurally simple and stable chiral secondary amines and amino acids facilitate iminium ion and enamine based transformations with carbonyl compounds. Iminium ion catalysis utilises the increased reactivity of α,β-unsaturated carbonyl compounds to facilitate a multitude of organic transformations such as the Diels-Alder, [3+2] cycloaddition, cyclopropanations, and conjugate addition and reduction reactions.[6] Alternatively, enamine catalysis involves an enamine intermediate formed *via* the deprotonation of an iminium ion leading to an enhanced nucleophile which has a similar reaction portfolio to highly documented enolates.

Within this review both of these classes of catalysts will be examined. The emphasis will focus on the catalyst structural motifs drawn from current literature, and how this affects their catalytic ability.

1.2 Iminium Ion Catalysis

Iminium ion catalysis was derived from principles existing within analogous Lewis acid catalysis. The first example of this came from the laboratories of MacMillan who reasoned that LUMO-lowering activation and kinetic lability of ligand substitution that produces Lewis acid catalyst turnover (*Figure* 1, **I**) could be applied to carbogenic systems in an analogous fashion. With this in mind they hypothesised that reversible formation of iminium ions, such as **4**, from α,β-unsaturated carbonyl compounds, **1**, and secondary amines, **3** (*Figure* 1, **II**) would mimic the π-orbital dynamics of Lewis acid based catalysts. This provided the basis of an extremely powerful and general catalyst technology.[7]



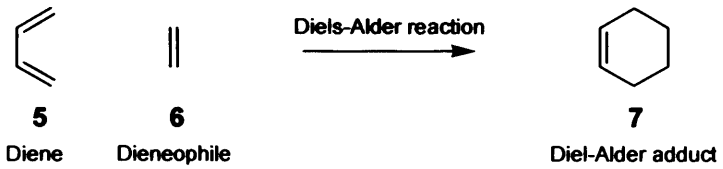
(*Figure* 1)

Due to the nature of iminium ion formation and properties of activated α,β-unsaturated carbonyl compounds this methodology was directed towards two main categories of reaction; cycloadditions and conjugate additions. This section is directed towards the investigation of structural motifs contained within these catalysts and the requirements for successful and effective transformations. This analysis includes the Diels-Alder reaction, [3+2]-dipolar cycloadditions, cyclopropanations, conjugate additions and conjugate reduction reactions. Literature findings are summarised with resulting conclusions combined as an overview of structural characteristics for effective iminium ion catalysis.

1.2.1 Cycloaddition reactions

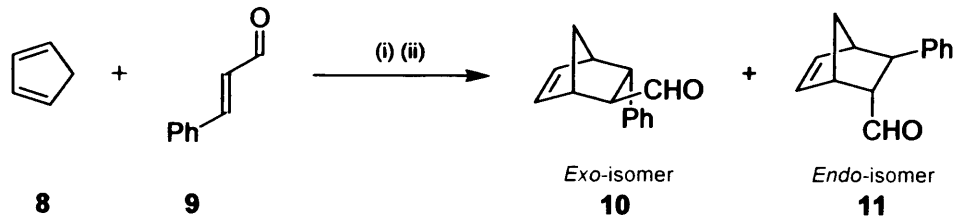
1.2.2 Diels-Alder reaction

The Diels-Alder reaction is a [4+2] cycloaddition reaction between a diene and a dieneophile (*Scheme* 1).



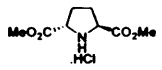
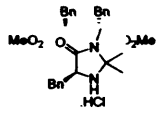
(*Scheme* 1)

The first highly enantioselective organo-catalysed Diels-Alder reaction was reported by MacMillan in 2000.[7] This work was a test of the original theory behind iminium ion catalysis mimicking the π-electronics of Lewis acid based systems. The reactions were carried out between cinnamaldehyde **8** and cyclopentadiene **9** with a series of secondary amine catalysts (*Scheme* 2) (*Table* 1).



(i) **16** (10 mol%), MeOH/H_2O (19:1), 23 °C. (ii) TFA, $CHCl_3$, H_2O, r.t., 2 hr., 99%, 93% e.e. (*exo*)

(*Scheme* 2)

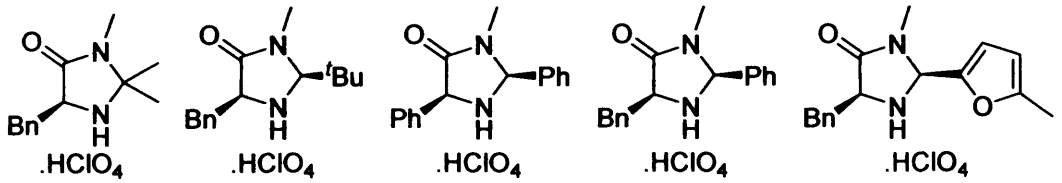
Entry	Catalyst[a]	Structure	Time hr	Yield[b] %	*exo*:*endo*[c]	*exo* e.e.[c] %
1	**12**	(S)-Pro-OMe.HCl	27	81	2.7:1	48
2	**13**	(S)-Abr-OMe.HCl	10	80	23:1	59
3	**14**		23	92	2.6:1	57
4	**15**		84	82	3.6:1	74
5	**16**		8	99	1.3:1	93

(*Table* 1)

(a) Reaction of *trans*-cinnamaldehyde **9** and cyclopentadiene **8** in methanol/water (19:1) at 23 °C with 10 mol% catalyst. (b) Isolated yield after chromatography. (c) Determined by GLC (Bodman Γ-AT).

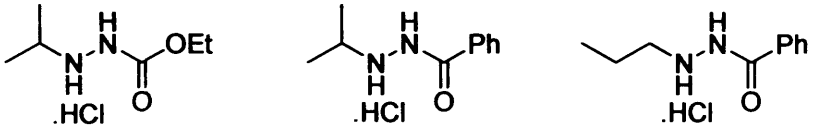
These results showed that secondary amines could be employed to catalyse reactions of α,β-unsaturated carbonyl compounds. Catalytic quantities of proline methyl ester hydrochloride **12** and abrine methyl ester hydrochloride **13** both provided good yields with moderate selectivities (*Table* 1, *entries* 1 & 2). Catalyst **14** gave similar results to proline methyl ester hydrochloride **12** which is perhaps to be expected due to the similarity between their structures (*Table* 1, *entry* 3). Compound **15** produced a good yield and selectivity, albeit requiring a long reaction period (*Table* 1, *entry* 4). The best results came from the imidazolidinone based structure **16** which provided a quantitative yield with excellent enantioselectivity after only eight hours under the reported reaction conditions (*Table* 1, *entry* 5). This work subsequently detailed the conversion of a series of dienes and cinnamaldehyde **9**, catalysed by **16**, in good yield and enantioselectivity throughout, showing **16** to be a general catalyst.

The imidazolidinone structure was later elaborated to the imidazolidinone based series of catalysts **17**, **18**, **19**, **20** and **21**.[8] Interestingly, **16** when employed as its perchlorate salt, **17**, showed poor yields for the Diels-Alder reaction of α,β-unsaturated ketones compared to its hydrochloride salt. Catalyst **21** provided the best results within this series.

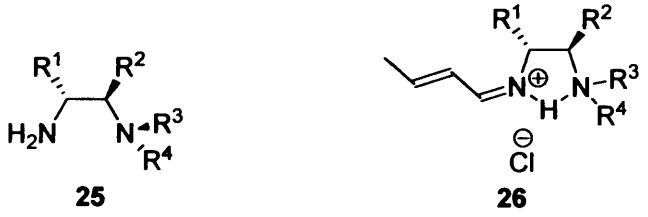


These imidazolidinone structures have since been used in ionic liquids,[9] adapted to polymer supports[10,11] and natural product synthesis[12] with excellent results.

Tomkinson produced a series of acyclic catalysts based on derivatised hydrazines **22**, **23** and **24**.[13] Use of the α-effect served as the reasoning for the increased catalytic ability of these molecules over similar linear molecules, with excellent yields observed for a range of substrates.



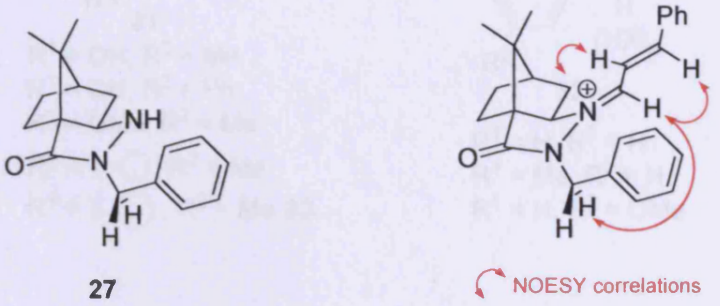
Alternative reported catalysts for this reaction include the use of 1,2-diamino structures based on **25**. These have been independently proposed by Ha[14] and Ishihara.[15] These structures are thought to catalyse the Diels-Alder reaction through intermediate iminium ion **26** with the hydrochloric acid co-catalyst acting as a Brønsted acid (*Figure* 2). Various R groups have been employed within these architectures with yields and enantioselectivities remaining high.



(*Figure* 2)

The final notable catalyst series comes from Ogilvie.[16] These tricyclic *N*-substituted structures, **27**, produce good enantioselectivities with moderate to high yields across a broad selection of dienophiles. Semiempirical calculations (PM3 in Spartan Pro) were carried out on the iminium ion intermediate which illustrated the lowest energy confomer (*Figure* 3)

accounting for the observed stereoselectivities. It is noteworthy however that no indication of reaction time is indicated within this report so it is difficult to assess the efficiency of this catalyst.

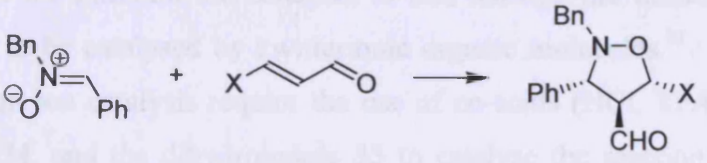


27

(*Figure* 3)

1.2.3 [3+2] Dipolar cycloaddition

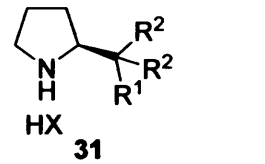
Literature examples of the [3+2] dipolar cycloaddition reactions are usually reported between the nitrone **28** and an electron deficient olefin **29** (*Scheme* 3). The imidazolidinone based systems of MacMillan have also been applied to this reaction with a good degree of success.[17] Reaction times are long (typically between 48-72 hours), however, yields are reasonable (45-77%) with generally good enantioselectivities. The most active imidazolidinone based catalyst was **16** as within the Diels-Alder reaction, with a similar rationale for observed selectivities being reported. Polymer bound variants of these catalysts have again been tested within this reaction, displaying slightly lower yields but retaining the enantioselectivities.[18]



28 **29** **30**

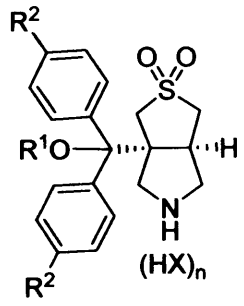
(*Scheme* 3)

Karlsson has investigated a range of catalysts directed towards this reaction based on the pyrrolidine **31** and the bicyclic pyrrolidine architecture **32**.[19] Within this report he suggests MacMillan's imidazolidinone based catalysts **16**, was a poor catalyst for cyclic dipolarophiles. Yields, diastereomeric ratios and enantioselectivities were generally high with the Karlsson system **33** providing the most active catalysts for this transformation.



31

R^1 = OH, R^2 = Me
R^1 = OH, R^2 = Ph
R^1 = OMe, R^2 = Me
R^1 =  , R^2 = Me
R^1 =  , R^2 = Me **33**

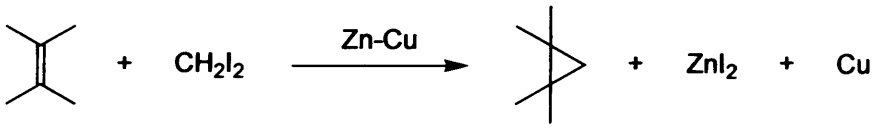


32

R^1 = H, R^2 = H
R^1 = Me, R^2 = H
R^1 = H, R^2 = OMe

1.2.4 Cyclopropanation

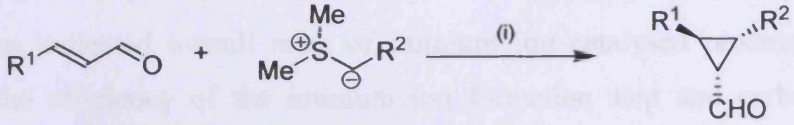
Cyclopropanation reactions are commonly carried out through the Simmons-Smith reaction involving the addition of an alkene and a carbene, created *in situ* with a zinc-copper couple (*Scheme* 4).[20]



(*Scheme* 4)
The Simmons-Smith reaction

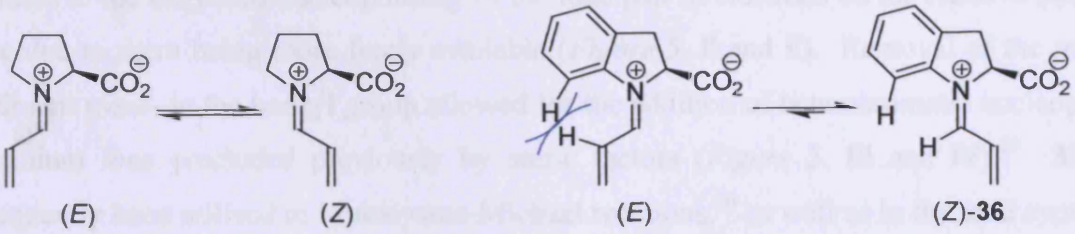
Literature reports of the iminium ion catalysis of this reaction are limited. MacMillan has shown the reaction to be catalysed by zwitterionic organic molecules.[21] Interestingly, most examples of iminium ion catalysis require the use of co-acids (HCl, TFA etc.) however, he has shown proline **34**, and the dihydroindole **35** to catalyse the reaction in good yield and enantioselectivity (*Scheme* 5). Increased enantioselectivities were seen with **35**, justified by a proposed intermediate iminium ion **36**. This intermediate acts to lower the Van der Waals interactions between the 3-H position and the substrate (*Figure* 4). No such interaction was possible within the structure of proline, **34**.

34 35



(i) Cat. (20mol%), $CHCl_3$, -10°C

(*Scheme* 5)



Poor iminium ion control

Van der Waals forces lead to *Z*-iminium ion formation

(*Figure* 4)

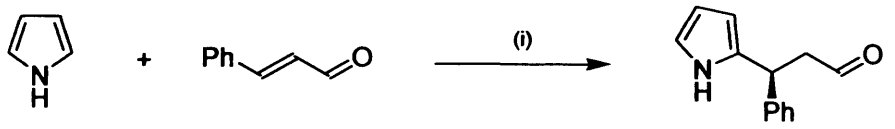
1.2.5 Addition reactions

Contained within this section is a discussion of conjugate addition reactions to iminium ions together with a more in-depth review of the conjugate hydride reduction.

1.2.6 Conjugate addition reactions

Examples within the literature of iminium ion catalysed conjugate addition reactions include a range of nucleophiles reacting with various α,β-unsaturated carbonyl compounds. MacMillan's initial study into Friedel-Crafts alkylation reactions represents the first enantioselective conjugate addition of pyrrole **37** using chiral amines as catalysts (*Scheme* 6).[22] This work demonstrated the ability of the imidazolidinone catalyst **16.TFA**; shown previously to be effective for the acceleration of cycloaddition reactions to also catalyse conjugate addition reactions.

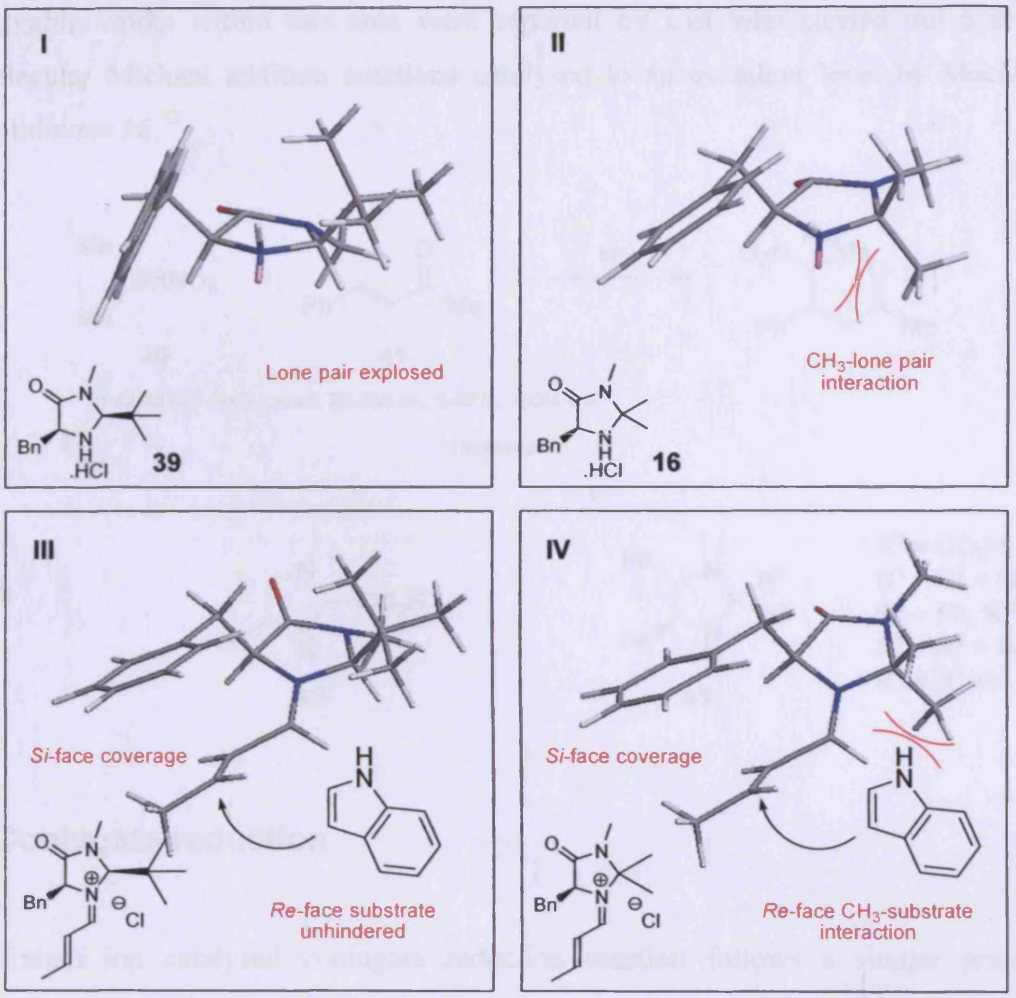
Various acid co-catalysts were employed with the best results being found from those of a lower pK_a value such as trichloro- and trifluoroacetic acid. A rationale similar to the Diels-Alder reaction was employed to explain the excellent stereoselectivities observed. MacMillan extended this work to encompass the addition reaction of indole-based substrates with the design of catalyst **39** from MM3[23] calculations.[24] Preliminary kinetic studies carried out within his group indicated overall rates of iminium ion catalysed processes were highly influenced by the efficiency of the iminium ion formation step and carbon-carbon bond forming events. This suggested that the improved rates of reaction observed with **39** were attributed to the increased nucleophilicity of the lone pair of electrons on the reactive nitrogen centre due to them being more freely available (*Figure* 5, **II** and **II**). Removal of the methyl substituent *trans*- to the benzyl group allowed for the addition of heteroaromatic nucleophiles to iminium ions precluded previously by steric factors (*Figure* 5, **III** and **IV**).[25] **39** has subsequently been utilised in Mukaiyama-Michael reactions,[26] as well as in the total synthesis of (-)-flustramine B[27] and in enantioselective organo-cascade reactions.[28]



37 **9** **38**

(i) **16.TFA** (20 mol%), THF-H_2O, 23 °C, 3hr., 78%, 81% e.e.

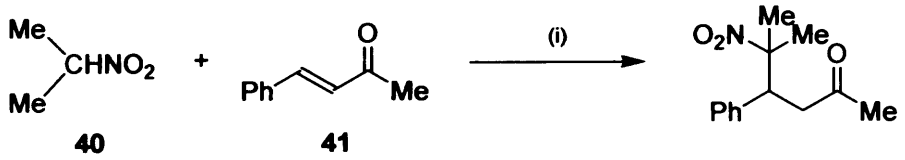
(*Scheme* 6)



(*Figure* 5)

Yamaguchi had shown that proline, as its rubidium salt, catalysed the addition of nitroalkanes to α,β-unsaturated carbonyl compounds.[29] Jørgensen screened a variety of chiral amines against the addition of 2-nitropropane **40** to benzylideneacetone **41** (*Scheme* 7).[30] Proline proved to be a poor catalyst for this transformation with low yield and enantioselectivity. MacMillan's imidazolidinone **16** also failed to effectively catalyse this reaction. However, Jørgensen developed an imidazolidine based catalyst containing an α-amino acid functionality **42**. While addition proceeded slowly, good yields and enantioselectivities were observed despite a mixture of diastereoisomers of **42** being used. He also developed a series of 1,2-diphenyl-1,2-diamine catalysts based on **43**, although yields were relatively poor. Jørgensen utilised catalyst **42** with a range of enones producing generally excellent yields and enantioselectivities but again long reaction times were required.[31]

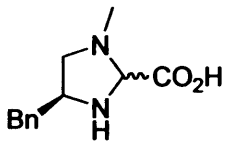
Final notable works within this area were reported by List who carried out a series of intramolecular Michael addition reactions catalysed to an excellent level by MacMillan's imidazolidinone **16**.[32]



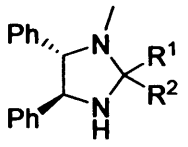
40 **41**

(i) **42/43** (20 mol%), neat, 20-180 hr., 3-87%, <80% e.e.

(*Scheme* 7)



42

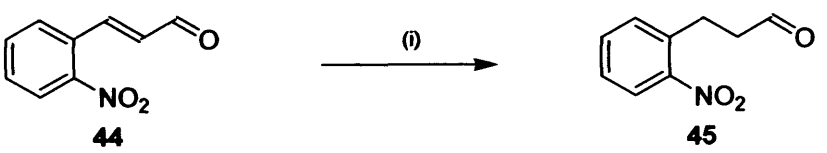


43

$R^1 = CO_2H$, $R^2 = H$
$R^1 = R^2 = CO_2Et$
$R^1 = Ph$, $R^2 = H$
$R^1 = R^2 = Me$
$R^1 = R^2 = H$

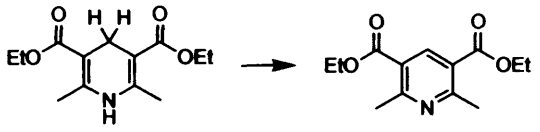
1.2.7 Conjugate reduction

The iminium ion catalysed conjugate reduction reaction follows a similar premise to conjugate additions. Formation of an iminium ion intermediate decreases the energy of the LUMO of the carbon-carbon double bond, increasing the rate of addition of a nucleophile. While conjugate additions make use of electron rich substrates the reduction required the use of hydride anions. Until recently these reductions required the use of metal catalysts with stoichiometric addition of metal hydrides. Conjugate reductions have been realised with various substrate classes however mild, general, chemoselective and catalytic variants applicable to α,β-unsaturated aldehydes were not described until recently. List proposed several ammonium salts to catalyse the conjugate reduction of *o*-nitrocinnamaldehyde **44** to **45** with the Hantzsch ester **46** providing the source of hydride (*Scheme* 8) (*Table* 2).[33]



44 45

(i) **47** (5 mol%), **46** (1.1 equiv.), THF, r.t., 6 hr. 94%.



46

(*Scheme* 8)

Entry	Catalyst[a]	Structure	Co-catalyst	Yield %
1	**47**		CF_3CO_2H	94
2	**48**		HCl	65
3	**49**		CF_3CO_2H	81
4	**50**		CF_3CO_2H	92
5	**51**		CF_3CO_2H	90
6	**52**		HCl	35

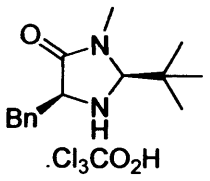
(*Table* 2)

(a) Reactions carried out in THF at room temperature for 6 hours with 5 mol% catalyst loading and 1.1 equivalents of **46**.

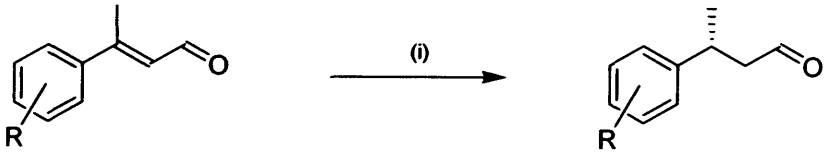
Interestingly, the most effective catalysts for this transformation were a mixture of cyclic and acyclic systems, with the best results seen with dibenzylamine **47** (*Table* 2, *entry* 1) as its trifluoroacetic acid salt. This catalyst was subsequently successfully used in the conjugate reduction of a series of α,β-unsaturated aldehydes with excellent yields.

List developed this chemistry further with the use of the imidazolidinone catalyst **53** to carry out this reduction in an asymmetric manner (*Scheme* 9).[34] This led to the introduction of an efficient asymmetric iminium ion catalysed conjugate reduction/intramolecular Michael reaction producing a series of five- and six-membered carbocycles in excellent yield and

enantioselectivity.[35] MacMillan simultaneously reported similar methodology expanding the library of workable substrates.[36]



53



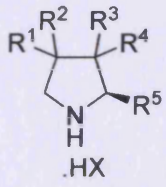
(i) **53** (10 mol%), **46** (1.02 equiv.), dioxane, 13 °C, 48 hr., 77-90%, 90-96% e.e.

(*Scheme* 9)

1.3 Iminium Ion Catalyst Motifs

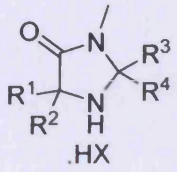
There exists a wide range of structures that have been shown to carry out a variety of iminium ion catalysed reactions effectively. Many were found to be generic and could be used to accelerate a variety of reactions with a broad range of substrates. Despite the importance of these transformations there has been little explanation offered within the literature regarding the relationship between catalyst structure and reactivity profile. Analysis of these structures reveals a series of interesting similarities.

In general, increases in effective rates of reaction were successfully achieved through the use of highly nucleophilic secondary nitrogen centres. Throughout the literature this has been obtained through the use of cyclic architectures to increase the availability of the nitrogen loan pair through ring strain. While some success has been observed with six-membered heterocycles within the iminium ion catalysed conjugate reduction reaction, all other cyclic catalysts were based on a five-membered heterocycle. Most successful generic catalysts were based on either the pyrrolidine or imidazolidinone skeleton, **54** and **55** respectively.



Pyrrolidine architecture

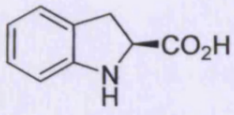
54



Imidazolidinone architecture

55

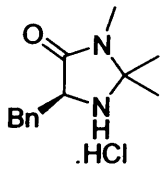
Pyrrolidine-based architectures were successfully employed in [3+2] dipolar cycloadditions and cyclopropanations. Substitution of the position adjacent to the reactive nitrogen centre accounted for the asymmetric induction observed through the proposed transition states. Interestingly, the cyclopropanation class of reactions were best catalysed by the zwitterionic proline derivative **35** with a dielectric effect controlling enantioselectivity.



35

Imidazolidinone architectures were found to be a more generic template for catalysis with good activities towards all iminium ion catalysed processes. Their use has been best exemplified in the Diels-Alder and conjugate addition reactions. Enantioselectivities were induced in products by the substitution of both of the positions adjacent to the reactive nitrogen centre. This substitution served either to favour the *cis*- or *trans*-isomer of the iminium ion through steric interactions, or by directing the incoming nucleophile by steric shielding (*Chapter* 1.2.6, *page* 12, *figure* 5).

Iminium ion catalysed processes require acidic conditions to proceed. Successful catalysts used acid co-catalysts as opposed to internal acids such as the carboxylic acid motif observed in enamine catalysed processes (Chapter 1.4, *page* 18). Catalysts employing co-acids with lower pK_a values, such as HCl and $HClO_4$ *verses* benzoic acid, delivered higher reactivity. The nature of acid co-catalyst was also shown to have a pronounced effect on the ability to catalyse certain types of reaction. The imidazolidinone catalyst **16** was an excellent catalyst for the Diels-Alder cycloaddition reaction but failed to catalyse conjugate addition reactions unless the trifluoroacetic acid derivative was employed. Success of the imidazolidinone based systems within iminium ion catalysed processes has led to their availability through commercial sources.

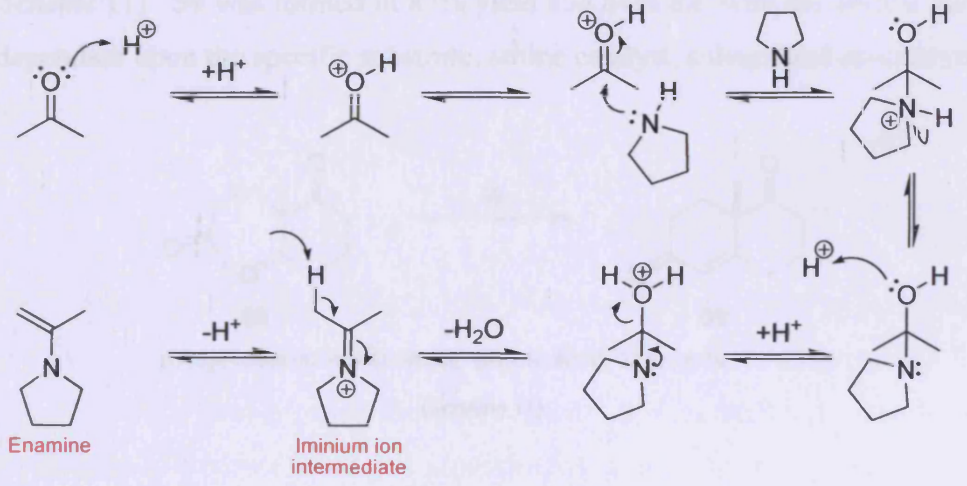


16

1.4 Enamine Catalysis

1.4.1 Enamine reactions

The literature shows a plethora of chemical transformations which can be accelerated through the use of enamine catalysis by simple nitrogen containing species. The mechanism of formation of an enamine is well published and understood (*Figure* 6).[37] Thus, this type of organocatalysis is ideal for a variety of chemical transformations that occur through the α-position of carbonyl compounds. Most notable reactions from the current literature are the aldol,[38] conjugate additions and their combination to form Robinson annulation products, the Mannich, α-substitutions,[39] Diels-Alder[40] and Claisen-Schmidt[41] reactions. This work will look in turn at each of these broad areas of chemistry and examine the necessary motifs employed within the catalyst structure for optimal reactivity.

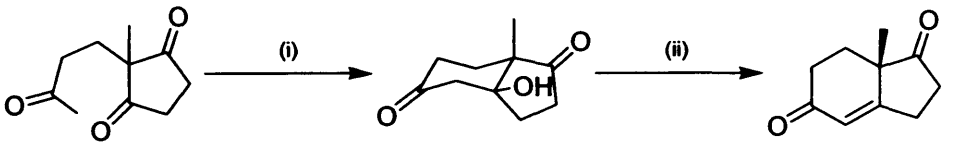


(*Figure* 6)

1.4.2 Early enamine catalysis

Proline was the pioneer of asymmetric enamine catalysis which was first reported in the early 1970's being utilised by Hajos, Parrish and Oliveto[3b] in the formation of the optically active bicyclic ketone **57** and independently by Eder, Sauer and Wiechert[42] for its homologue **59**. Both secured their targets though an intramolecular enamine catalysed aldol reaction.

Early investigations found the importance of the role of hydrogen-bonding in the transformation of **56** to **57** which lead to the use of polar aprotic solvents such as DMF. Importantly for the time Hajos, under a variety of conditions, described proline to catalyse the formation of **57** in high yield and with 57% e.e., providing a viable alternative to previous methods of classical chemical resolution (*Scheme* 10).[43]

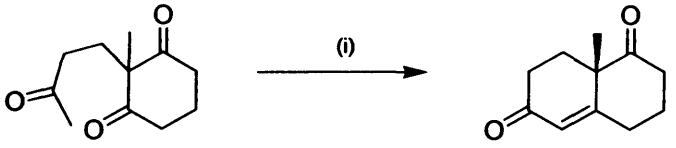


56 **(+)-57**

(i) (*S*)-Proline (3 mol%), DMF, 20 °C, 20 hr., 100%. (ii) *p*-TsOH, PhH, Δ, 15 min., 99%, 57% e.e.

(*Scheme* 10)

Eder, Sauer and Wiechert also showed a synthetic route through to **59** directly from the triketone **58** in the presence of (*S*)-proline **34** (10-200 mol%) in conjunction with an acid co-catalyst (*Scheme* 11). **59** was formed in 87% yield and 84% e.e. with the optical purity being strongly dependant upon the specific substrate, amine catalyst, solvent and co-catalyst.



58 **59**

(i) (*S*)-Proline (47 mol%), $HClO_4$, CH_3CN, 80 °C, 22 hr., 87%.

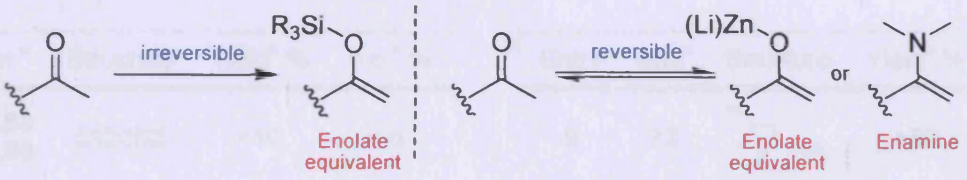
(*Scheme* 11)

This asymmetric proline-catalysed intramolecular aldol process, referred to as the Hajos-Parrish-Eder-Sauer-Wiechert reaction,[44] has been applied to the synthesis of numerous steroids and terpenoids since its first publication in the 1970's.[45] This reaction has also been carried out with polymer-bound (*S*)-proline.[46]

1.5 Enamine Catalysed Reactions

1.5.1 Aldol reaction

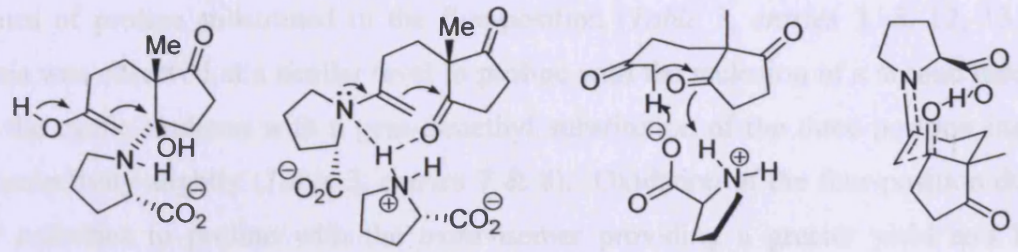
The aldol reaction is widely regarded to be one of the most important carbon-carbon bond forming reactions used in synthetic organic chemistry. The reaction is dominated by examples using preformed enolate equivalents or enolates formed *in situ* (*Figure* 7).[47] In recent years the asymmetric aldol reaction has become the most prolific area of enamine catalysis within the literature. The development carried out within this reaction has not only benefited its own area but also provided grounding for basic stereochemical aspects of other carbon-carbon bond forming reactions such as the Diels-Alder reaction and Michael addition. Despite this there still remains little evidence for the proposed enamine catalysed mechanism of this well known reaction.



(*Figure* 7)

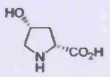
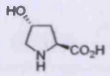
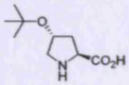
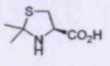
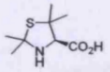
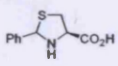
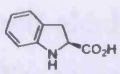
As discussed previously, the Hajos-Parrish-Eder-Sauer-Wiechert reaction involving proline was the first aldol reaction to be catalysed by this method (*Section* 1.4.2, *page* 18). However, the mechanism for this proline mediated reaction has been cause for much debate with a number of intermediates proposed. Hajos proposed the "activation" of one of the enantiotopic acceptor carbonyl groups as a carbinol amine (*Figure* 8, **A**).[3b] Much later Agami and colleagues proposed a side chain mechanism in which two molecules of proline participate in the intermediate; one as an enamine with the other as a proton transfer mediator (*Figure* 8, **B**).[48] Swaminathan *et al.* proposed a mechanism on the surface of crystalline proline in a heterogeneous aldolisation despite proline mediated aldol transformations mainly being homogeneous (*Figure* 8, **C**).[49] List challenged this latter intermediate more recently with the proposal of a mono-proline enamine mechanism (*Figure* 8, **D**).[50] A similar mechanism was proposed subsequently by Houk *et al.* on the basis of density functional theory (DFT) studies.

This last intermediate is currently thought to be the most accurate with increasing evidence for its existence being found.[51]



(*Figure* 8)

Work from List,[50] Barbas[38] and Yamamoto,[52] amongst others, has been directed towards the aldol reaction between acetone **60** and *p*-nitrobenzaldehyde **61** catalysed by a wide variety of secondary amines. A cross-section of the amines used in these studies is shown below (*Table* 3).

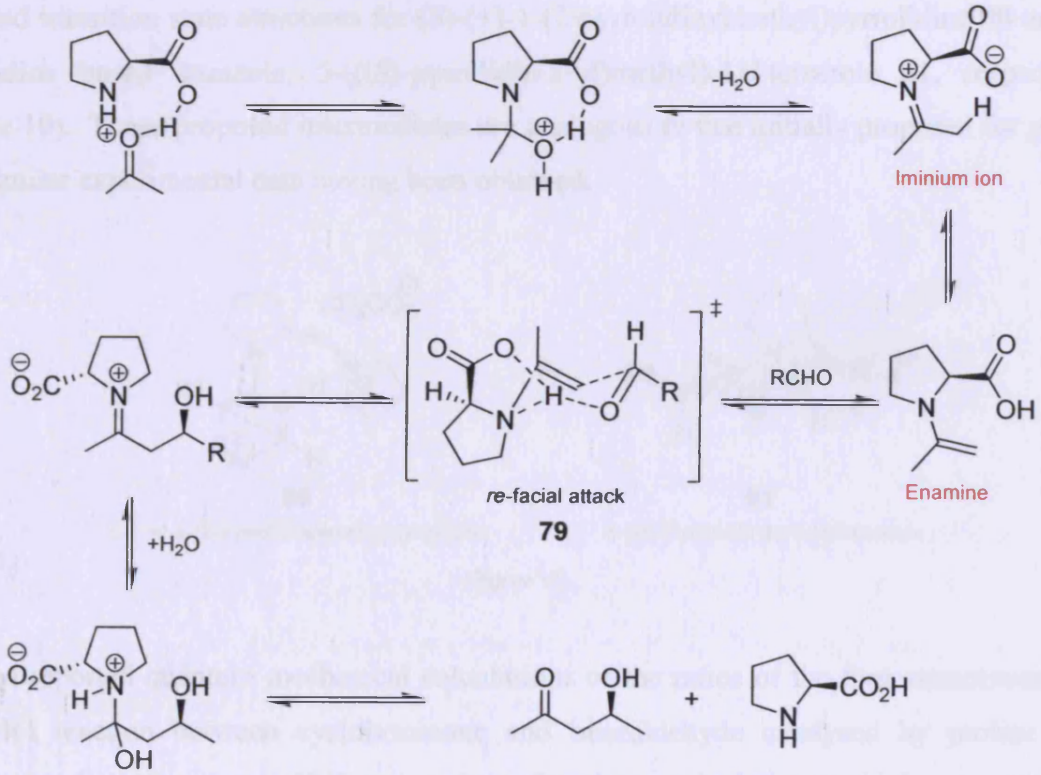
Entry	Cat.[a]	Structure	Yield[b] %	e.e.[c] %	Entry	Cat.[a]	Structure	Yield[b] %	e.e.[c] %
1	**62,63 64,65**	(*L*)-His, (*L*)-Val (*L*)-Tyr, (*L*)-Phe	<10	n.d.	9	**72**		>50	62
2	**66**		<10	n.d.	10	**73**		85	78
3	**67**		55	40	11	**74**		>50	62
4	**34**		68	76	12	**75**		<10	n.d.
5	**68**		<10	n.d.	13	**76**		<5	n.d.
6	**69**		<10	n.d.	14	**77**		<10	n.d.
7	**70**		67	73	15	**78**		26	61
8	**71**		66	86	16	**35**		<10	n.d.

(*Table* 3)

(a) Reaction typically between acetone **60** (20 vol.) and *p*-nitrobenzaldehyde **61** in DMSO with 20 mol% catalyst. (b) Isolated yields. (c) Determined *via* chiral-phase HPLC.

Results showed the primary amino acids, **62-65** and the acyclic secondary amine **66** to be poor catalysts for this reaction most probably because the rate of enamine formation was slow (*Table* 3, *entries* 1 & 2). This was also the case for four- and six-membered systems and analogues of proline substituted in the five-position (*Table* 3, *entries* 3, 5, 12, 13 & 14). Catalysis was observed at a similar level to proline with the inclusion of a second heteroatom within the cyclic skeleton with a gem-dimethyl substitution of the three-position increasing enantioselectivity slightly (*Table* 3, *entries* 7 & 8). Oxidation of the four-position displayed similar activities to proline with the *trans*-isomer providing a greater yield and level of asymmetric induction under the reaction conditions (*Table* 3, *entries* 9, 10 & 11).

To interpret these results further knowledge of the mechanism of enamine formation and subsequent aldol reaction originally proposed by List is required (*Mechanism* 1).[50]

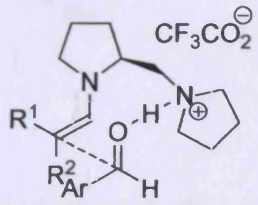


(*Mechanism* 1)

List proposed the key intermediate step in the enamine catalysed aldol reaction to be the enamine formed from (*S*)-proline and the ketone donor, **79**.[3b,53] The projected transition-state is analogous to the mechanism of the aldolase antibody 38C2, with the enamine attacking the carbonyl group of the acceptor with high enantiofacial selectivity imposed by the organised

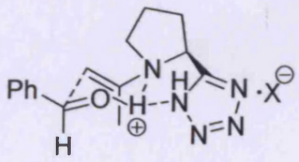
tricyclic hydrogen bonded framework.[54] This closely resembled a metal-free Zimmerman-Traxler type transition state. This mechanism, detailing intermediates, reflects the importance not only of the carboxylate proton, but its relative position compared to the acceptor group.[38]

This transition state is assumed for optimal catalysis of the reaction; therefore factors influencing geometry within the catalyst will have a pronounced affect on yield and enantioselectivity observed. Returning to the tabulated results above it is possible to attempt to rationalise the experimental results obtained. The four- and six-membered systems, **67** and **68**, would comprise alternative spatial arrangements between the carboxylate function and the transferable proton leading to less effective reactions. Substitution in the three- and four-position would have little effect on the yields as they are not proximal to the reactive centre, however, substitution of the five-position could have a significant effect on the reaction. Literature results adhere to these proposals. Barbas[55] and Yamamoto[56] have independently provided transition state structures for (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **80** and the pyrrolidine based tetrazole, 5-(((*S*)-pyrrolidin-2-yl)methyl)-1*H*-tetrazole **81,** respectively (*Figure* 10). These proposed intermediates are analogous to that initially proposed for proline with similar experimental data having been obtained.



80

(S)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine



81

5-((*S*)-Pyrrolidin-2-yl)-1*H*-tetrazole

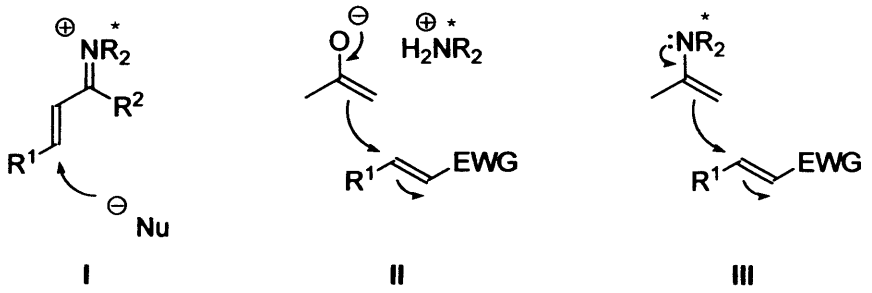
(*Figure* 10)

List has reported quantum mechanical calculations of the ratios of the four stereoisomers of the aldol reaction between cyclohexanone and benzaldehyde catalysed by proline **34**.[57] Experimental evidence provided comparison for these calculations which suggested the predictions for the proposed transition states to be correct.

MacMillan has also applied his imidazolidinone **18.HCl** to this methodology with good yields and stereoselectivities covering a range of donor and acceptor groups.[58] He has also contributed further examples of the proline catalysed aldol reaction.[59]

1.5.2 Conjugate addition

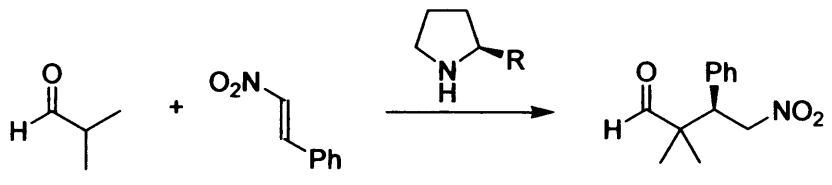
The conjugate addition reaction covers an enormous variety of substrates. Its various mechanisms, both catalysed and uncatalysed, are well understood and thoroughly documented throughout the literature and can be found in most undergraduate chemistry textbooks. A variety of catalysts can be employed for this reaction from metal-based Lewis acids to organocatalysts. In this section we will be focusing on the enamine catalysed Michael addition. Three possible mechanisms have been proposed for the amine-catalysed Michael reaction (*Scheme* 12). Chiral amines have been used to catalyse the asymmetric Michael reaction activating the acceptor *via* the formation of an iminium ion (*Scheme* 12, **I**), or as a base *via* an enolate which subsequently reacts with the acceptor (*Scheme* 12, **II**). The third mechanism utilises the transient activation of a carbonyl group through the formation of an enamine intermediate (*Scheme* 12, **III**).



I II III

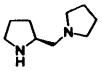
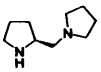
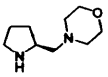
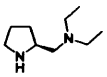
(*Scheme* 12)

Recently, notable work towards this enamine catalysed reaction has been reported from the groups headed by Alexakis,[60] Barbas[61] and List.[62] Frequently, catalysts involved in this work are based on substituted pyrrolidine scaffolds. Barbas reported on a variety of secondary amines to accelerate the direct asymmetric Michael reaction of α,α-disubstituted aldehydes, such as **82**, with β-nitrostyrenes **83** (*Scheme* 13). Notable results are shown below (*Table* 4).[63]



82 **83**

(*Scheme* 13)

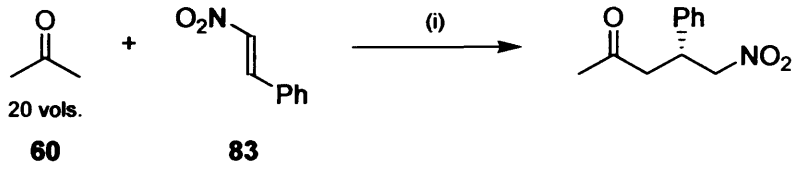
Entry	Catalyst[a]	Structure	Additive (equiv.)	Time hr	Yield %	e.e.[b] %
1[c]	**49**		AcOH (1.5)	12	84	n.d.
2	**34**		-	48	87	23
3	**84**		-	48	79	63
4	**85**		-	48	72	17
5	**86**		AcOH (0.3)	96	<1	65
6	**87**		AcOH (0.3)	96	82	21
7	**80**		-	0.5	90	50
8	**80**		TFA (0.3)	24	96	61
9	**88**		TFA (0.3)	96	19	73
10	**89**		TFA (0.3)	96	4	75

(*Table* 4)

(a) Reactions carried out in DMSO at room temperature. (b) Determined by HPLC using a CHIRALPAK AS-H column. (c) *Iso*butylaldehyde (1.2 equiv.) was used.

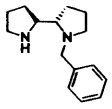
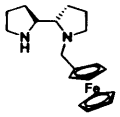
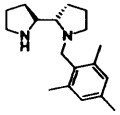
Generally, reactions were either slow or suffered from poor enantioselectivities with the use of bulky substituents on the pyrrolidine ring. The most notable catalyst for this transformation was (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **80** which gave an excellent yield after thirty minutes (*Table* 4, *entry* 7). Inclusion of 0.3 equivalents of trifluoroacetic acid as an additive was observed to increase the enantioselectivity of the reaction but lowered the reaction rate significantly (*Table* 4, *entry* 8). Solvent effects on the reaction between **82** and **83** with **80** as the catalyst were investigated resulting in excellent yields and moderate enantioselectivities. For example 96% yield and 68% e.e. was obtained with the use of a DMSO/ether (3:7) mixture after a twenty-four hour period .

Alexakis has reported a series of bipyrrolidine derivatives for use in the reaction of acetone **60** with β-nitrostyrene **83** (*Scheme* 14). Results are somewhat varied with generally a good yield but poor enantioselectivities being obtained as well as the reaction suffering from long reaction times (*Table* 5).



(i) **90-97** (15 mol%), *p*TSA.H_2O (15 mol%), r.t., 15 hr.-7 d, 25-89%, 3-30% e.e.

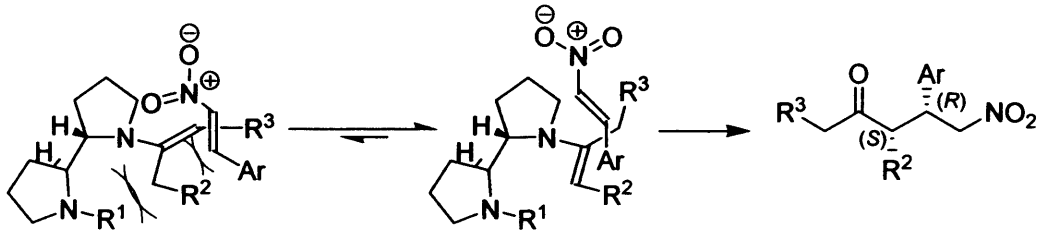
(*Scheme* 14)

Entry	Catalyst[a]	Structure	Time	Yield[b] %	e.e.[c] %
1	**90**		15hr	88	17
2	**91**		15hr	79	20
3	**92**		3d	91	17
4	**93**		3d	76	25
5	**94**		7d	25	3
6	**95**		7d	64	17
7	**96**		15hr	74	23
8	**97**		15hr	89	30

(*Table* 5)

(a) Reactions were carried out in acetone at room temperature with 15 mol% of the specified catalyst and 15 mol% *p*TSA.H_2O. (b) Isolated yield after chromatography. (c) Determined by GC with a Lipodex E column and configuration was resolved by comparison to literature data.

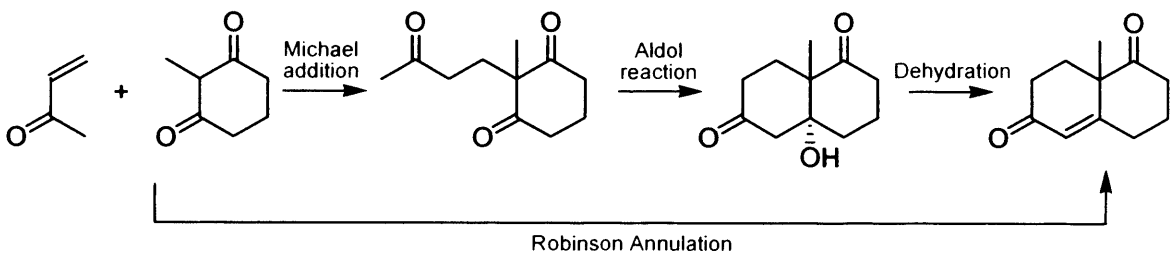
Yields were generally high but suffer from prolonged reactions times reinforcing Barbas' findings that bulky α-substituents on the reactive pyrrolidine ring slowed reaction rates. Enantioselectivities were poor, however, this was substrate specific as more highly substituted ketones provided elevated e.e.s and were *syn*-selective. Alexakis proposed a model for the *syn*-selectivities observed in accordance to Seebach's model (*Figure* 11).[64] Salunkha showed that use of proline **34** can approach these reactivities if used in conjunction with ionic liquids.[65]



(*Figure* 11)

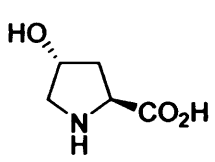
1.5.3 Robinson annulation

The Robinson Annulation is a useful reaction in the synthesis of six-membered rings in polycyclic compounds such as steroids (*Scheme* 15). It is the combination of a Michael addition and subsequent aldol reaction. Its mechanism is well understood and as its constituent reactions are also catalysed through enamine intermediates it is perhaps unsurprising that this reaction can be carried out in tandem making a one-pot enamine catalysed Robinson Annulation.

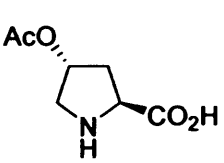


(*Scheme* 15)

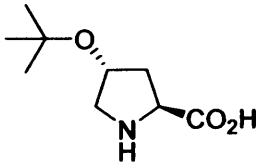
Barbas has shown (*S*)-proline **34** to accomplish this transformation in a yield of 49% with 76% e.e. in eighty-nine hours.[66] A series of substituted proline based compounds have also been employed by Barbas in the catalysis of this reaction. Compounds **73**, **98** and **74** have shown similar enantiomeric excesses (60-75%) to (*S*)-proline **34**, however, **67** showed less than 10% e.e. for the transformation; yields for reaction were not commented on. The poor e.e. observed from **67** indicates the possibility that spatial positioning of the acid functionality within these catalysts is paramount to increasing selectivities. Several primary amino acids failed to catalyse this reaction to any significant rate.



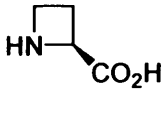
73



98

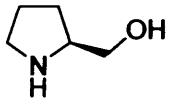


74

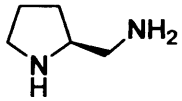


67

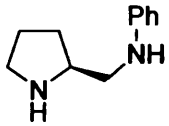
Interestingly, catalysts **84**, **100**, **101** and **80** catalyse the initial Michael addition and aldol reaction but failed, under the reaction conditions, to dehydrate to give the final product, indicating the requirement for the presence of an acidic proton on the catalyst.



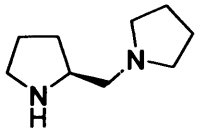
84



100



101

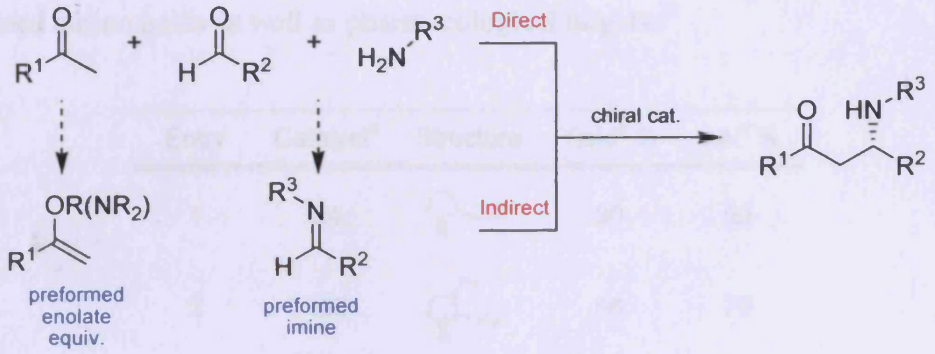


80

1.5.4 Direct Mannich reaction

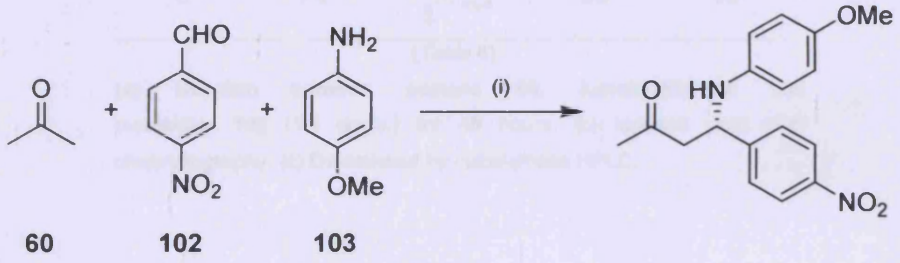
The asymmetric Mannich reaction is one of the most powerful methods for the production of chiral nitrogen-containing compounds through the combination of an amine, a ketone and an aldehyde (*Scheme* 16). The importance of its introduction into organic compounds is highlighted by the ubiquitous nature of nitrogen in pharmaceutical agents, agrochemical compounds and natural products. Formation of the products can be carried out through either direct or indirect variants. Direct methods require the use of unmodified ketones whereas the indirect processes utilise preformed enolate and/or imine equivalents. Precedent for non-catalytic methods include the addition of preformed enamines to imines.[67,68,69] With a secondary amine catalysed reaction there is the possibility for a cross-aldol reaction to occur

between the donor ketone and aldehyde or ketone acceptor (*Section* 1.5.1, *page* 21). However, it has been reasoned that the nucleophilic addition of an enamine is faster to an imine than an aldehyde, with imine formation of an aldehyde being faster with a primary imine than its aldolisation.[70]



(*Scheme* 16)

Proline **34** has commonly been used to catalyse the Mannich reaction. Early work within this area by List details its use to catalyse the reaction of acetone **60**, *p*-nitrobenzaldehyde **102** and *p*-anisidine **103** (*Scheme* 17).[71]

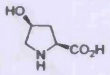
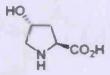
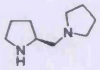


(i) (*S*)-Proline **34** (35 mol%), DMSO, 50%, 94% e.e.

(*Scheme* 17)

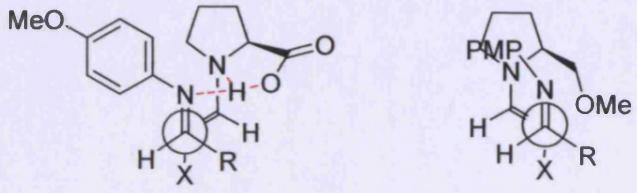
This methodology was extended by List to incorporate alternative amine and amino acid catalysts (*Table* 6). Substitution about the proline scaffold acted to reduce the selectivity within the reaction with 4-hydroxy compounds returning poor yields. Exclusion of the carboxylic acid functionality resulted in no enantioselectivity, suggesting its involvement in asymmetric induction. Extension of this series has been carried out independently by Barbas[72] and Córdova.[73] Within this work, Barbas proposed a chair-like transition state for catalysts containing the stereodirecting carboxylate functionality and also for (*S*)-2-methoxymethylpyrrolidine (SMP) (*Figure* 12). He suggested that the *si*-face of the imine was selectively attacked by the *re*-face of the enamine drawing the ethereal oxygen closer to the

imine nitrogen which he suggested, if protonated, could provide a favourable Coulombic interaction compensating for possible steric interactions between the pyrrolidine group of SMP and the PMP protecting group.[74] Barbas also showed the generality of proline as a catalyst synthesising a wide range of functionalise α-amino acids, γ-lactones, oxime-functionalised amino acids as well as pharmacological targets.[75]

Entry	Catalyst[a]	Structure	Yield[b] %	e.e.[c] %
1	**34**		90	93
2	**120**		56	76
3	**121**		22	12
4	**73**		22	15
5	**80**		26	0
6	**71**		60	16

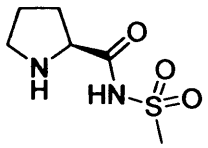
(*Table* 6)

(a) Reaction between acetone **60**, *iso*valeraldehyde and *p*-anisidine **103** (1.1 equiv.) for 48 hours. (b) Isolated yield after chromatography. (c) Determined by chiral-phase HPLC.



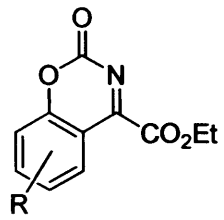
(*Figure* 12)

Wang has used the pyrrolidine-sulfonamide catalyst **104** in a range of polar aprotic solvents in good yields and excellent enantioselectivities.[76] In addition Hayashi telescoped the Mannich reaction with a hydride reduction of the aldehyde forming a series of 1,3-amino alcohols.[77]

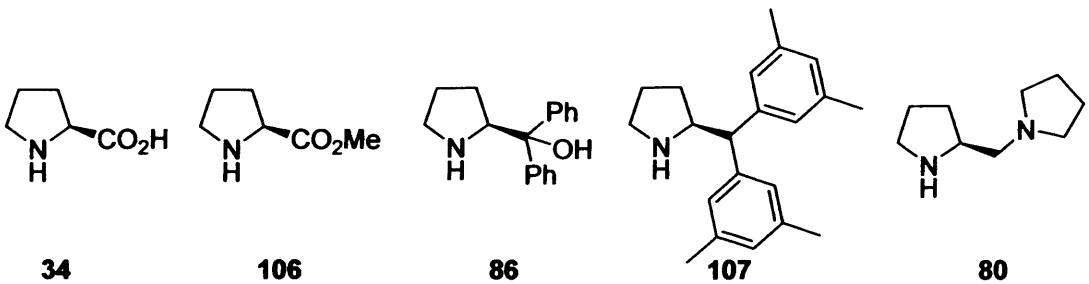


104

Other notable works within the area come from Jørgensen who examined the Mannich reaction directed towards substituted ketimines **105** with catalysts **34**, **106**, **86**, **107** and **80**.[78] Most active catalysts were **34** and **80** which provided yields of 84% and 56% with enantioselectivities of >82%. Catalysts not containing the stereodirecting carboxylate moiety appeared to benefit from Barbas' suggested Coulombic force attraction.



105



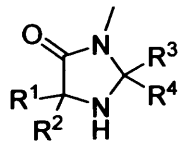
34 106 86 107 80

1.5.5 α–Substitution reactions

Within the literature α-substitution reactions include α-halogenation (fluoro and chloro), α-amination, α-aminomethylation, α-oxidation and α-alkylation. These methods will be dealt with separately completing this section of the review.

α-Halogenation

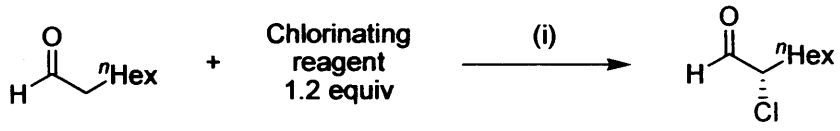
Halogenation of organic molecules is of particular interest within industrial chemical processes. Resistances to many metabolic transformations as well as the increased lipophilicity and stability of fluorine-containing compounds is utilised throughout the pharmaceutical and agricultural industry.[79] Today, many halogenating reagents are available on the market. However, despite the abundance of these reagents there are few examples in the literature of organocatalytic enantioselective halogenation reactions. Examples of metal-based process have been published within the last decade with Togni and Hintermann describing the first catalytic α-fluorination of β-ketoesters by chiral titanium complexes.[80] Since then the challenge of enantioselectively α-halogenating carbonyl compounds has been met by the groups of Barbas,[81] Bartoli,[82] Enders[39] and MacMillan.[83] Catalysts utilised in α-halogenation reactions fall into two main categories. Those based on the imidazolidinone structure **55** and those on proline-derived systems.



55

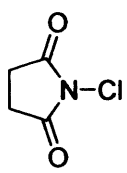
MacMillan has shown the use of (*S*)-proline **34** to catalyse the α-chlorination of aldehydes (*Scheme* 18).[83] Though furnishing an excellent yield at 4 °C with NCS, enantioselectivities were extremely poor with no reaction at -30 °C with **109** (*Table* 7, *entries* 1, 4 & 5). Use of imidazolidinones **110** and **111** demonstrated poor results with NCS, **108**, however, low temperatures combined with **109** displayed excellent yields and good enantioselectivities

(*Table* 7, *entries* 6 & 7). A proposed intermediate accounting for the increased enantioselectivity from **110** has been proposed (*Figure* 13).



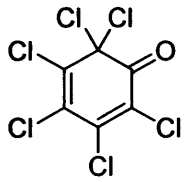
(i) **111** (5 mol%), $CHCl_3$, 4-(-)30 °C, 6 hr., 60-78%, 10-42% e.e.

(*Scheme* 18)



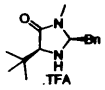
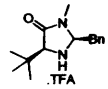
NCS

108



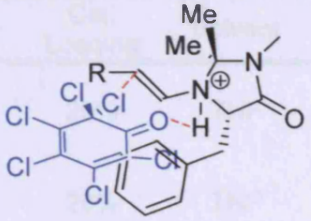
109

Chlorinating reagents

Entry	Catalyst[a]	Structure	Temp. °C	Time hr	Reagent	Conversion[b] %	e.e.[c] %
1	**34**		4	6	**108**	99	2
2	**110**		4	6	**108**	20	19
3	**111**		4	6	**108**	60	10
4	**34**		4	12	**109**	44	2
5	**34**		-30	30	**109**	n.d.	n.d.
6	**110**		-30	8	**109**	91	92
7	**111**		-30	6	**109**	78	42

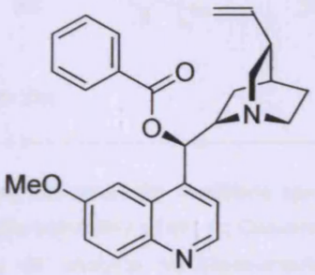
(*Table* 7)

(a) Reactions were run in $CHCl_3$ with 5 mol% catalyst loading. (b) Conversions were measured from an internal standard (benzyl methyl ether). (c) Determined by chiral GLC analysis using a Bodman Γ-TA column.

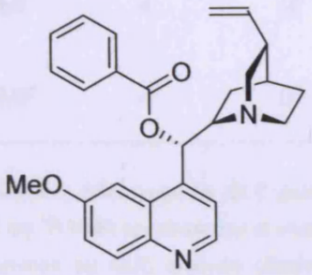


(*Figure* 13)

Alternative chiral amines **112** and **113** have been employed by Bartoli to catalyse α-chlorination reactions with excellent conversions of greater than 90% and enantioselectivities reaching 95%, however, these systems act as chiral-base catalysts, rather than through an enamine mechanism, and therefore will not feature further in this discussion.

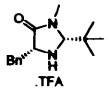


112



113

There is a broad selection of catalysts that have been reported for the catalytic α-fluorination of carbonyl compounds. MacMillan showed the use of the imidazolidinones **(114)** to catalyse the α-fluorination of aldehydes with NFSI with good results accompanied with short reaction times (*Table* 8, *entry* 2).[84] Barbas utilised pyrrolidine based structures in DMF but with varying results. Significantly, catalytic activity was removed with the inclusion of additional heteroatoms within the cyclic structure (*Table* 8, *entries* 3-7).

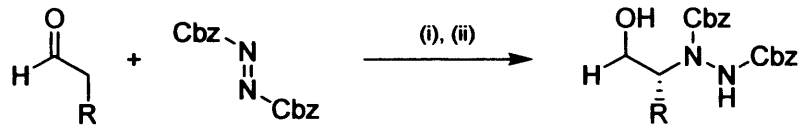
Entry	Catalyst[a]	Structure	Cat. Loading	Solvent	Time hr	Conv. %	e.e. %
1	**34**		20%	THF	4	79[b]	26[d]
2	**114**		20%	THF	0.3	96[b]	63[d]
3	**34**		30%	DMF	4	29[c]	29[e]
4	**85**		30%	DMF	4	30[c]	32[e]
5	**81**		30%	DMF	4	32[c]	30[e]
6	**71**		30%	DMF	4	trace	n.d.
7	**86**		30%	DMF	4	9[c]	50[e]
8	none	-	-	DMF	4	0[c]	0[e]

(*Table* 8)

(a) Reactions were run under the conditions specified. (b) Conversion determined by GLC analysis relative to an internal standard (benzyl methyl ether). (c) Conversion determined my ^{1}H NMR spectroscopy of crude reaction mixtures and correlated to GC analysis. (d) Enantiomeric excess determined by GLC analysis (Bodman Γ-TA column). (e) Enantiomeric excess determined by GLC analysis (Bodman γ-TA column).

α-Amination

Throughout the literature this class of reaction is catalysed solely by proline **34**. List[85] and Jørgensen have independently carried out the α-amination of a series of aldehydes, **115**, with the aza-electrophile **116** (*Scheme* 19). Excellent yields and enantioselectivities (90-99% yield, >90% e.e.) were recorded throughout, highlighting the diverse nature of proline as an organocatalyst. Both authors have suggested the same transition state to explain the observed asymmetric induction (*Figure* 14).[86]

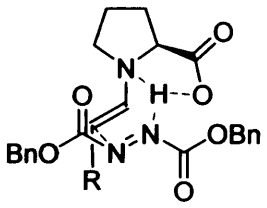


115 **116**

R = ^{i}Pr, ^{n}Pr, ^{n}Bu, Me, Et, Bn.

(i) (*S*)-Proline **34** (10 mol%), CH_3CN. (ii) EtOH, $NaBH_4$, 90-99%, >90% e.e.

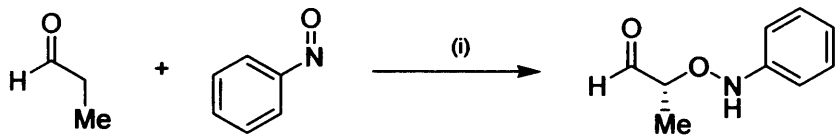
(*Scheme* 19)



(*Figure* 14)

α-(Amino)oxylation

The catalytic α-oxidation of carbonyl compounds by organocatalysts is still very much in its infancy. The first example of α-oxidation of aldehydes came from the laboratories of MacMillan in their continuing programme to develop broadly useful organic catalysts for asymmetric synthesis.[87] Proline was used successfully for the asymmetric α-oxyamination of propanal **117** with nitrosobenzene **118** (*Scheme* 20). This work was amenable to a variety of substrates with good yields and excellent stereocontrol.



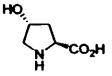
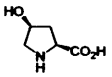
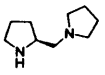
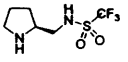
117 **118** **119**

(i) (*S*)-Proline **34** (10 mol%), $CHCl_3$, 4 °C, 20 mins., 88% yield, 97% e.e.

(*Scheme* 20)

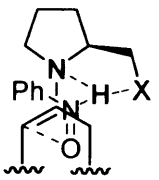
Following the initial work by MacMillan, the laboratories of Córdova[88] and Wang[89] published further studies in this developing area employing nitrosobenzene **118** in the asymmetric α-oxyamination of cyclohexanone. Córdova examined a series of pyrrolidine based catalysts whereas Wang focused on the pyrrolidine sulfonamide-based organocatalyst **123** (*Table* 9). These combined results highlight some interesting factors regarding this reaction. It appears

that catalysts which do not incorporate an acidic proton fail to catalyse this reaction to any significant degree implying that a proton donor plays a pivotal role in the reaction mechanism. Secondly, as enantioselectivities of these protic catalysts are >99% the active intermediate must involve hydrogen-bonding to transfer chirality from the catalyst to the products. Both Córdova and Wang within their groups have proposed similar transition states whose structure can be generalised (*Figure* 15). Córdova has extended this process to the α-oxylation of aldehydes *via* removal of the aniline subunit from **119** with Adams catalyst forming cis-1,2-cyclohexanediol in excellent yields of up to 96%.[90] This is an excellent method for introducing additional functionality into carbonyl containing compounds.

Entry	Catalyst[a]	Structure	Yield[b] %	e.e.[c] %
1	**34**		70	>99
2	**120**		64	>99
3	**73**		66	>99
4	**121**		67	>99
5	**122**		trace	n.d.
6	**80**		trace	n.d.
7	**85**		trace	n.d.
8	**123**[d]		84	>99

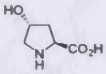
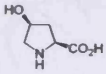
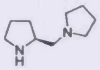
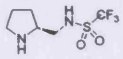
(*Table* 9)

(a) Reactions were carried out in DMSO at room temperature for 2-24 hours with 20 mol% catalyst. (b) Isolated yields after chromatography. (c) Determined by chiral-phase HPLC (d) Reaction time of 20 mins.



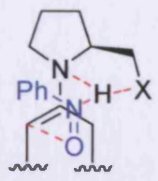
(*Figure* 15)

that catalysts which do not incorporate an acidic proton fail to catalyse this reaction to any significant degree implying that a proton donor plays a pivotal role in the reaction mechanism. Secondly, as enantioselectivities of these protic catalysts are >99% the active intermediate must involve hydrogen-bonding to transfer chirality from the catalyst to the products. Both Córdova and Wang within their groups have proposed similar transition states whose structure can be generalised (*Figure* 15). Córdova has extended this process to the α-oxylation of aldehydes *via* removal of the aniline subunit from **119** with Adams catalyst forming cis-1,2-cyclohexanediol in excellent yields of up to 96%.[90] This is an excellent method for introducing additional functionality into carbonyl containing compounds.

Entry	Catalyst[a]	Structure	Yield[b] %	e.e.[c] %
1	**34**		70	>99
2	**120**		64	>99
3	**73**		66	>99
4	**121**		67	>99
5	**122**		trace	n.d.
6	**80**		trace	n.d.
7	**85**		trace	n.d.
8	**123**[d]		84	>99

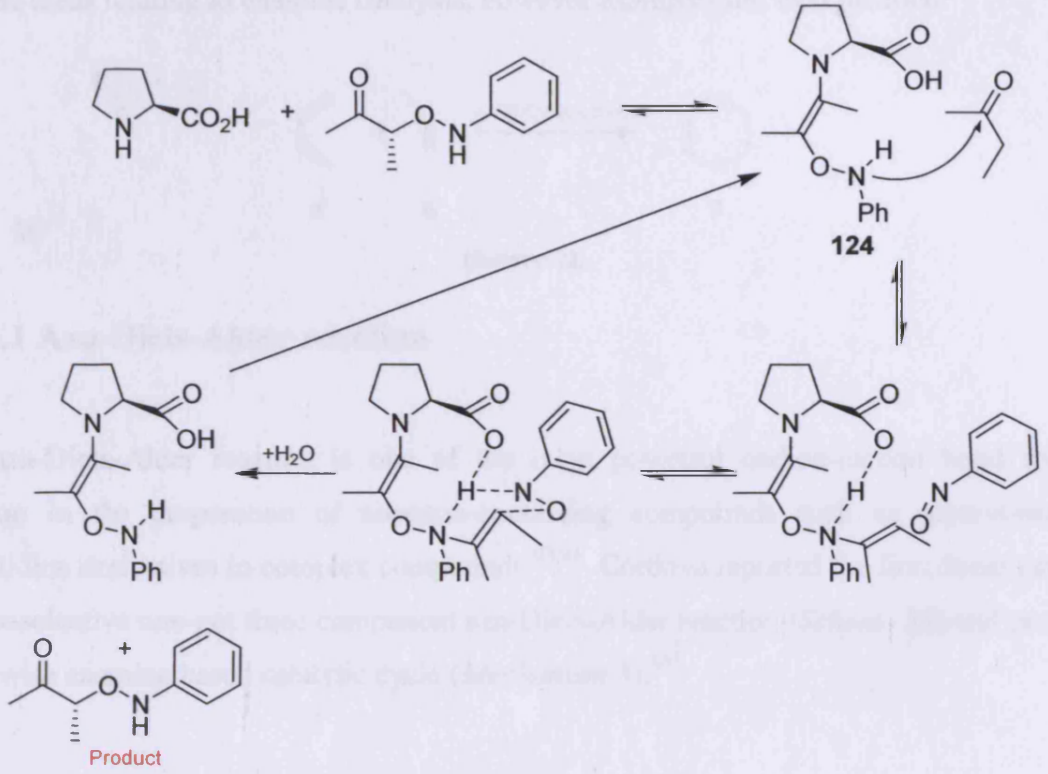
(*Table* 9)

(a) Reactions were carried out in DMSO at room temperature for 2-24 hours with 20 mol% catalyst. (b) Isolated yields after chromatography. (c) Determined by chiral-phase HPLC (d) Reaction time of 20 mins.



(*Figure* 15)

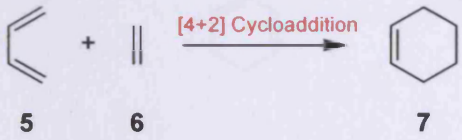
Work carried out by Blackmond suggested that this reaction is auto-catalytic with the rate of this reaction being enhanced by the proline-product species **124** (*Scheme* 21).[91] This enhancement in reactivity was shown by a positive non-linear enhancement of the enantiomeric excess observed within reactions containing non-homochiral mixtures of proline.[92] Blackmond also proposed a mechanism for the product induction within her studies (*Mechanism* 2).



(*Mechanism* 2)

1.5.6 Diels-Alder reaction

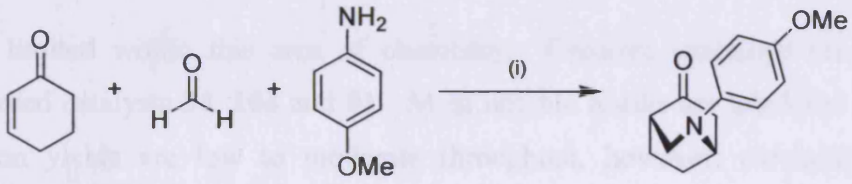
This area of enamine catalysis covers two types of reaction. The aza-Diels-Alder reaction and the inverse electron demand Diels-Alder reaction. The Diels-Alder reaction itself is dealt with in greater detail later (*Section* 2.2.3, *page* 54). It is a [4+2] cycloaddition between a diene **5** and a dieneophile **6**, forming cyclohexene **7** (*Scheme* 22). There is limited literature in these areas relating to enamine catalysis, however examples are well justified.



(*Scheme* 22)

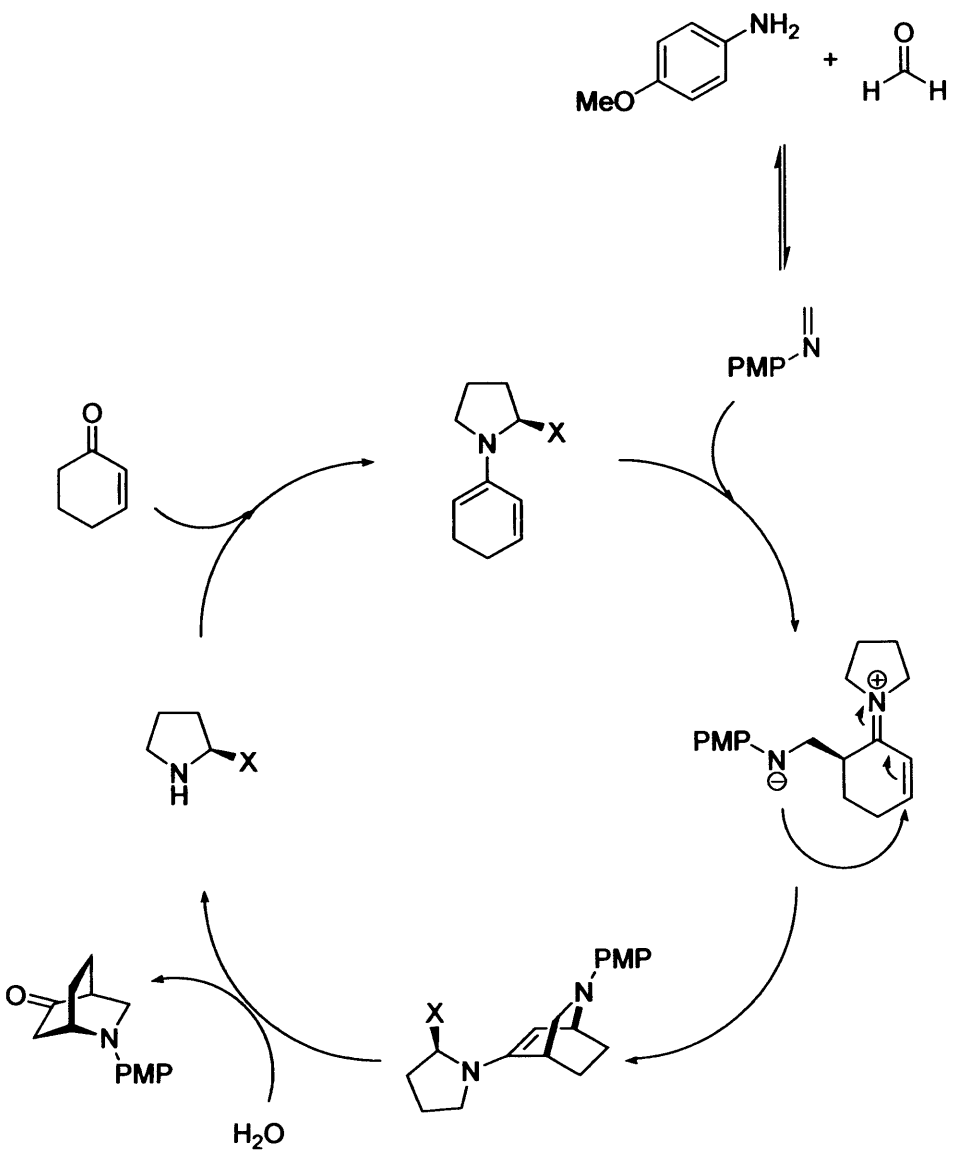
1.5.6.1 Aza-Diels-Alder reaction

The aza-Diels-Alder reaction is one of the most powerful carbon-carbon bond forming reaction in the preparation of nitrogen-containing compounds such as piperidines and quinolidine derivatives in complex compounds.[93,94] Córdova reported the first direct catalytic enantioselective one-pot three component aza-Diels-Alder reaction (*Scheme* 23) and proposed a stepwise enamine based catalytic cycle (*Mechanism* 3).[40]



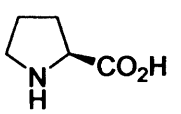
(i) (*S*)-Proline (30 mol%), DMSO, r.t., 24 hr., 30%, 99% e.e.

(*Scheme* 23)

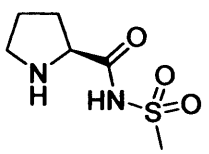


(*Mechanism* 3)

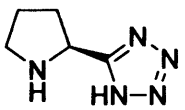
Literature is limited within this area of chemistry. Córdova examined the use of three pyrrolidine based catalysts **34**, **104** and **81**. Most notable results are tabulated below (*Table* 10). Reaction yields are low to moderate throughout, however, elevated temperatures increase yield without loss of enantioselectivity (*Table* 10, *entry* 1). Furthermore, proline **34** was applied to alternative substrates ranging from substituted and different sized α,β-unsaturated cyclic carbonyl compounds and alternative anilines with high yields and enantioselectivities throughout.



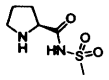
34



104



81

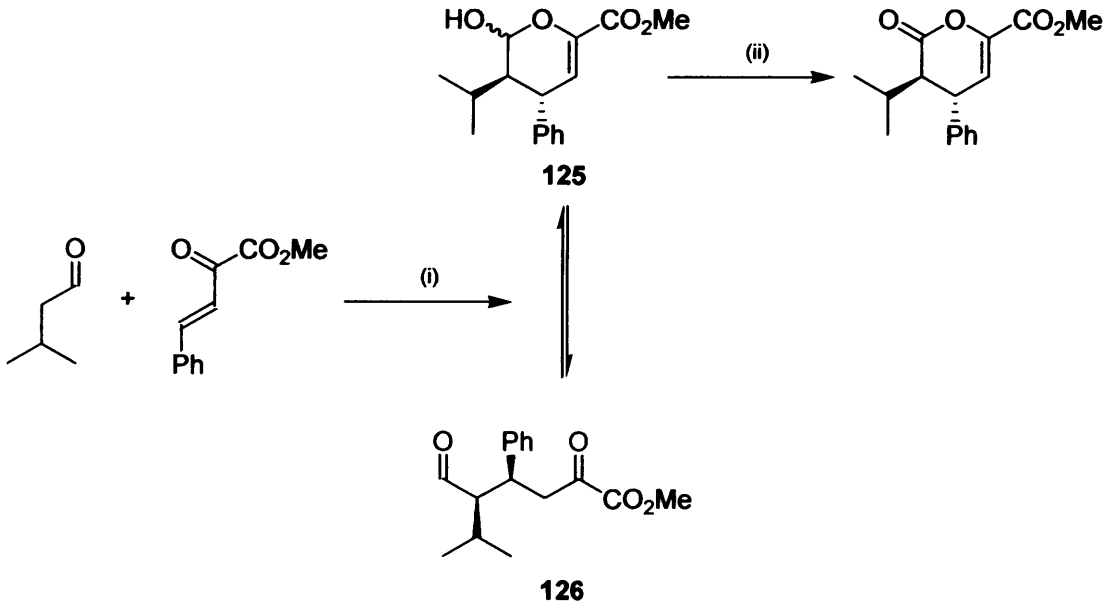
Entry	Catalyst[a]	Structure	Time hr	Temp.	Yield[b] %	e.e.[c] %
1	**34**		24	50 °C	52	99
2	**34**		24	r.t.	30	99
3	**104**		48	r.t.	31	94
4	**81**		24	r.t.	61	99

(*Table* 10)

(a) Reaction conditions outlined in *Scheme* 23. (b) Isolated yield after chromatography. (c) Determined by chiral-phase HPLC analysis.

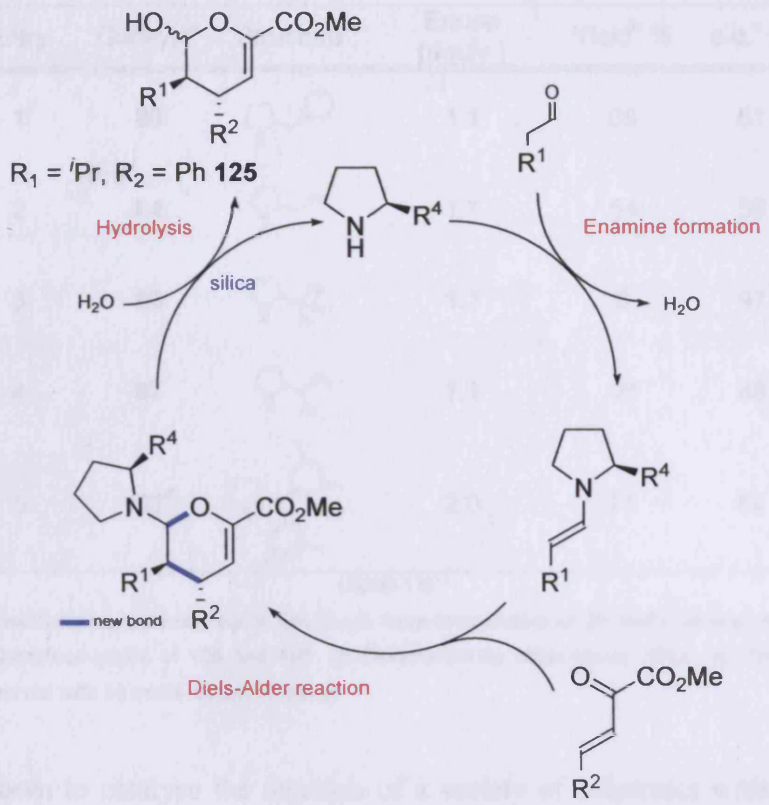
1.5.6.2 Inverse-electron demand Diels-Alder reaction

This involves the incorporation of electron-rich alkenes as opposed to the standard electron poor dieneophiles usually required for this class of reaction. Jørgensen developed methodology for the enantioselective hetero-Diels-Alder reaction (*Scheme* 24) and a possible catalytic cycle (*Mechanism* 4).[95]



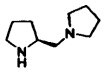
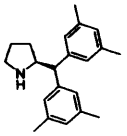
(i) Amine catalyst (20 mol%), silica, solvent. (ii) PCC oxidation.

(*Scheme* 24)



(*Mechanism* 4)

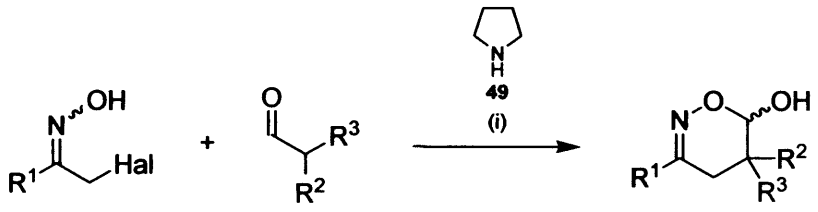
Jørgensen showed a series of substituted five-membered cyclic amines to catalyse this reaction (*Table* 11). As seen in previous reactions optimal catalysis is carried out with the use of the pyrrolidine based skeleton. The popular catalyst (*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine **80** performs relatively well under the reaction conditions with modest yield and enantioselectivity (*Table* 11, *entry* 1). This is also the case for (*S*)-(+)-2-pyrrolidinemethanol **84** suggesting that this reaction benefits from a proximal lone pair of electrons (*Table* 11, *entry* 2). Inclusion of bulky substituents α- to the reactive centre appeared to preclude the reaction reducing the overall yield substantially (*Table* 11, *entry* 3). Interestingly, **86** showed increased enantioselectivity which was retained in the case of (*S*)-(-)-2-(diphenylmethyl) pyrrolidine **87** but displayed a greater yield (*Table* 11, *entry* 4). Finally, the dimesityl analogue (*S*)-2-(bis(3,5-dimethylphenyl)methyl)pyrrolidine **107** provided excellent enantioselectivity and a greater yield (*Table* 11, *entry* 5). This did require a greater number of equivalents of enone, however, only half the catalyst loading was necessary (10 mol% *vs.* 20 mol%).

Entry	Catalyst[a]	Structure	Enone (equiv.)	Yield[b] %	e.e.[c] %
1	**80**		1.1	69	51
2	**84**		1.1	54	56
3	**86**		1.1	6	97
4	**87**		1.1	46	88
5	**107**[d]		2.0	71	87

(*Table* 11)

(a) Reactions were carried out in CH_2Cl_2 at room temperature at 20 mol% catalyst loading. (b) Combined yields of **125** and **126**. (c) Determined by chiral-phase HPLC. (d) Reaction carried out with 10 mol% catalyst loading.

107 was also shown to catalyse the reaction of a variety of substrates with all yields above 50% and excellent enantioselectivities being observed throughout. In later work, Jørgensen detailed the first catalytic inverse-electron demand hetero-Diels-Alder reaction of nitroso alkenes using pyrrolidine, **49**, as the organocatalyst (*Scheme* 25).[96] In the absence of chiral catalysts enantioselectivities were not recorded. Yields were good, ranging from 50-89% for a variety of substrates, perhaps indicating that in this instance, substitution about the catalyst ring plays little part in the reaction itself.



R^1 = Ph, *p*-MeO-C_6H_4, *p*-NO_2-C_6H_4, EtO_2C.
R^2 = ^{i}Pr, ^{n}Pr, Et, H, Bn.
R^3 = H, Me, Ph
Hal = Cl, Br

(i) Pyrrolidine **49** (10 mol%), $NaOAc.3H_2O$ (2eq), CH_2Cl_2, r.t., 24-72 hr., 50-89%.

(*Scheme* 25)

1.6 Enamine Catalyst Motifs

As with iminium ion catalysis, enamine catalysed reactions can be accelerated by a range of amines. Many were found to be generic and could be used to catalyse a number of reactions. Inspection of these systems reveals certain structural motifs essential for catalytic activity. As with iminium ion catalysis, it is self-evident that a secondary nitrogen centre was essential for enamine catalysis.

Throughout the majority of the reported enamine catalysed reactions examined, all effective and efficient catalysts contained the reactive nitrogen centre within a five-membered heterocycle. It has long been established that one of the determining factors in enamine catalysis is the nucleophilicity of this centre. This made the incorporation of the reactive site within a five-membered heterocycle paramount for effective catalysis, although this increase in reactivity through exposure of the nitrogen's loan pair has it's limits. Incorporation of the reacting centre in a four-membered cycle has yet to produce a successful catalyst.

Proposed mechanisms for these transformations highlighted the requirement of a Brønsted base. This was seen to facilitate the transfer of protons within the reaction (proton shuttle) and therefore its spatial positioning and directing properties within reaction intermediates is fundamental in the acceleration of transformations. Additionally, the associated chirality of this group is important as proposed transition states defined the absolute configuration of the products. Positioning of a Brønsted base adjacent to the reactive nitrogen centre not only served to accelerate transformations but to convey chirality to the products. Correct spatial positioning of this group within the transition state requires the rigid scaffold supplied by the five-membered cyclic structure. High levels of catalysis can be found in the absence of this acidic moiety utilising the rationale of Coulombic forces between electron pairs to provide active transition states. Even so, all catalysts required the presence of a proton source; be it a carboxylic acid or acid co-catalyst.

Many reactions are tolerant of additional substitution about the heterocyclic ring. This is reaction specific with additional functionality increasing the yield of some reactions whilst reducing others. Generally, five-membered cyclic catalysts are tolerant to substitution in the three- and/or four-positions. Reduced activities are universally found with either a substituted

five-position or quaternary two-position. Proposed transition states show these substitution patterns serve only to increase steric hindrance of the reactive nitrogen-centre, retarding enamine formation.

A *gem*-dimethyl group in the three-position was observed to increase catalytic activity within the aldol reaction. It has been postulated that this was due to a slight alteration in the catalyst geometry. Many catalysts also benefited from the inclusion of an additional heteroatom either within (or *exo* to) the cycle. This has been assumed to increase solvent interactions, or as a possible alternative proton source.

The majority of successful catalysts employed throughout the literature were based on the proline scaffold. There are also a number of examples of excellent catalysis utilising the imidazolidinone structure in conjunction with an acid co-catalysts, however this second type of scaffold was best suited to iminium ion catalysed processes.

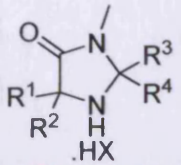
1.7 General Aminocatalysis Structures.

It was of little surprise that many of the structural requirements for a successful iminium ion catalyst is reflected for effective enamine catalysts. This is due to the belief that in enamine formation the substrates pass through an iminium ion intermediate. Both classes of catalysts benefited from an increase in nucleophilicity of the reactive nitrogen centre. Generally, this increase came from inclusion of the reactive nitrogen centre within the constraints of a five-membered cyclic structure. As a result structural motifs for iminium ion and enamine catalysts are similar, with substitution adjacent to the reactive nitrogen centre accounting for the asymmetric induction observed.

The rate determining step in iminium ion formation was assumed to be the initial attack of the nucleophilic nitrogen centre on the carbonyl of the substrate. Enantioselectivities were proposed to occur from controlling the *cis*/*trans*-geometry of the iminium ion through steric interactions in conjunction with steric shielding, directing the trajectory of the incoming nucleophile. Therefore, examples of iminium ion catalysts contained bulky substituents adjacent to the reactive nitrogen centre. Acidic conditions required for successful iminium ion catalysis were provided through the inclusion of an acid co-catalyst with higher reactivities observed with acids of a lower pK_a.

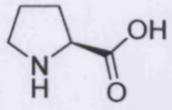
Alternatively, the rate determining step for the enamine catalysed processes was assumed to be the proton transfer from an internal acid group of the catalyst to the substrate within a pre-formed enamine. Therefore, enamine catalysts required an internal acidic group acting as a proton source within the reaction. This transition state has also been proposed as a rationale for observed enantioselectivities. Enamine catalysis was often intolerant to additional substitution of the cyclic structure.

Generally, successful iminium ion catalysts were based on the imidazolidinone architecture **(55),** whereas enamine processes were accelerated by proline based systems **(34)**.



Imidazolidinone architecture
Generic iminium ion catalyst

55



Proline
Generic enamine catalyst

34

Chapter 2: Establishing General Protocol

2.1 Chemical Catalysis

Over the past 30 years, enantioselective catalysis has become one of the most important frontiers in exploratory synthetic research.[97] Organometallic catalysis has delivered a plethora of transformations; however organocatalysis, until recently, was still very much in its infancy. The last decade has seen the development of organocatalysis and in particular aminocatalysis with investigation into this nubile area of chemistry leading to a multitude of asymmetric transformations. These aminocatalytic processes have been described as biomimetic strategies exemplified by enzymatic processes such as the Class I aldolases (enamine catalysis) and ketoacid decarboxylases (iminium ion catalysis).

A wide variety of amino based catalysts have been reported in the recent literature, however, while detailed explanation of their asymmetric induction exists, there is little evidence regarding the benefit to catalysis of certain structural motifs.

The work herein is aimed at exploring the diverse nature of aminocatalysis and utilises a continuing structure-activity relationships (SAR) study to develop an understanding of these systems.

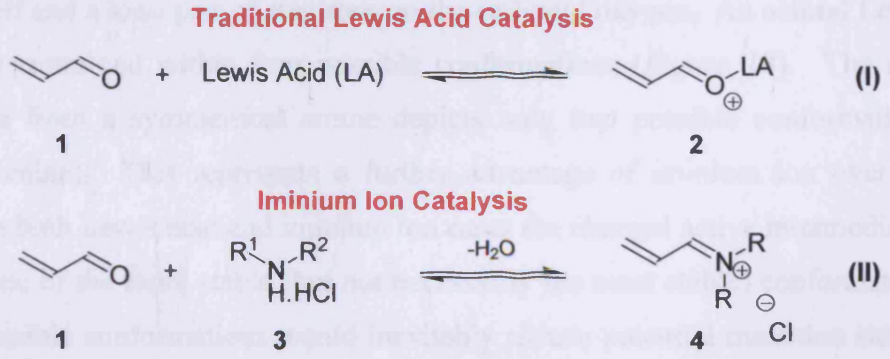
> *"While decreasing catalyst loading and reaction time remained the ultimate objective of this work, we aimed to generate a greater understanding of iminium ion catalysed processes."*

2.1.1 Amino catalysis and α,β-unsaturated carbonyl compounds

The carbonyl is one of the most well understood functional groups and is key to many organic transformations. The multitude of reactions that have been carried out on this group is comprehensive. Its ability to react through various proximal centres depending upon reaction conditions has led to numerous books, articles and papers contributing to its understanding. Reactions involving this functionality have been commonly catalysed by metal-containing species *via* Lewis or Brønsted acids and bases. When reacted with a Lewis acid the carbonyl moiety **1** can form a charged complex **2** (*Figure* 16). This complexation decreases the energy of the lowest unoccupied molecular orbital (LUMO). This lowering in energy increases reactivity towards certain reaction pathways as reviewed in chapter one.

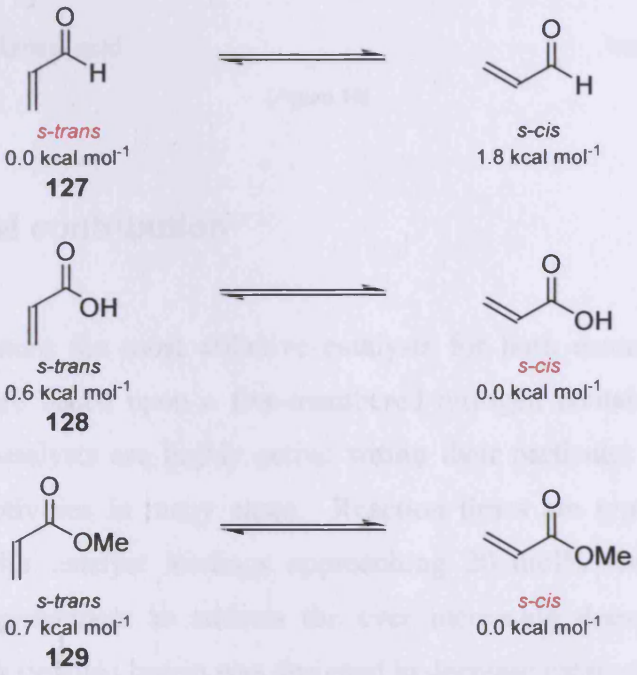
> *"If the already broad spectrum of Lewis acid based catalysis can be used for such transformations, what is the driving force for research into iminium ion catalysis of the same processes?"*

There are many advantages of iminium ion catalysed reactions over Lewis acid processes. The most prevalent is that Lewis acid catalysis frequently requires low reaction temperatures combined with the exclusion of molecular oxygen and moisture from reactions. This highlights the main advantage of iminium ion processes as these reactions can be carried out at room temperature in the presence of air and moisture. In addition, reaction products can also differ *via* the two methods (*See Chapter* 2.2.7, *page* 56).



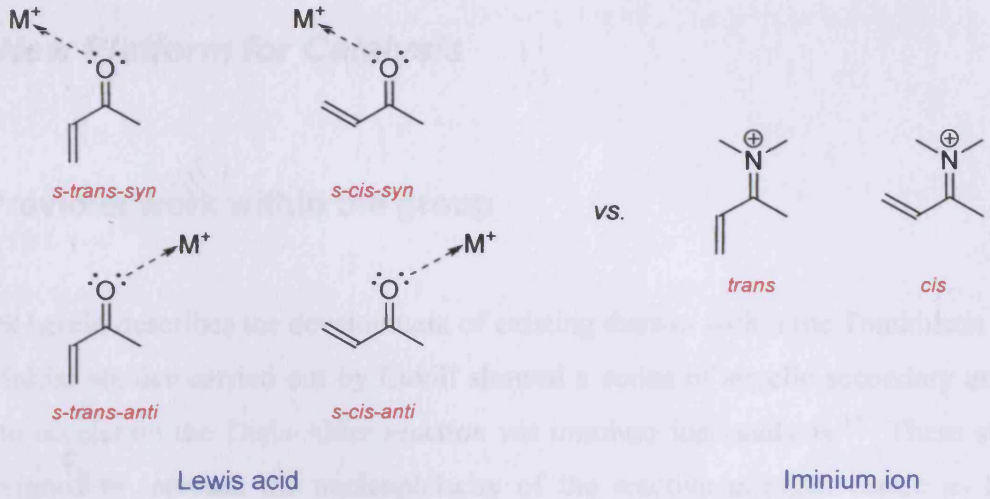
(*Figure* 16)

The α,β-unsaturated carbonyl itself exists in several conformations (*Figure* 17). Transition energies between such conformations are well known and have been published previously.[98] This conformational preference within a variety of functional groups has also been addressed showing the *s-trans* conformation to be most stable in simple α,β-unsaturated aldehydes such as acrolein **1**. Carboxylic acids, such as acrylic acid **128** and esters (methyl acrylate **129**) prefer the *s-cis* arrangement. The organic chemist should therefore be mindful of these preferences when designing catalysts for such systems.



(*Figure* 17)

As seen previously, the iminium ion π-electronics closely approximate those of traditional Lewis acid activation (*Figure* 16). These Lewis acid species chelate through a σ-interaction between itself and a lone-pair of electrons on the carbonyl oxygen. An achiral Lewis acid can therefore be restrained within four possible conformations (*Figure* 18). The nature of an iminium ion from a symmetrical amine depicts only two possible conformations (with a symmetric amine). This represents a further advantage of iminium ion over Lewis acid catalysis. In both Lewis acid and iminium ion cases the charged active intermediate is certain to exist in one of the more stable (but not necessarily the most stable) conformation. Hence, lowering possible conformations would inevitably reduce potential transition states allowing for greater control of the reaction.



(*Figure* 18)

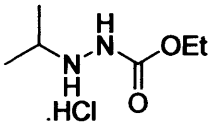
2.1.2 Fundamental contribution

Throughout the literature the most effective catalysts for both enamine and iminium ion catalysed processes are based upon a five-membered nitrogen containing heterocycle (*See Chapter* 1). These catalysts are highly active within their particular reactions and induce excellent enantioselectivities in many cases. Reaction times are typically in the order of twenty-four hours with catalyst loadings approaching 20 mol% leaving opportunity for development and improvement to address the ever increasing demands of the chemical community. The work detailed herein was designed to decrease catalyst loadings and reaction times through the design and synthesis of more active catalysts. This process required greater insight into the iminium ion catalytic cycle and a better understanding of iminium ion processes.

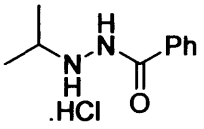
2.2 A New Platform for Catalysis

2.2.1 Previous work within the group

The work herein describes the development of existing themes within the Tomkinson research group. Initial studies carried out by Cavill showed a series of acyclic secondary amines **22** and **23** to accelerate the Diels-Alder reaction *via* iminium ion catalysis.[13] These structures were designed to increase the nucleophilicity of the reactive nitrogen centre as literature precedent indicated the initial attack of the amine onto the carbonyl group was the rate determining step for iminium ion processes.[24] This increased nucleophilicity was realised through the incorporation of an α-heteroatom.



22



23

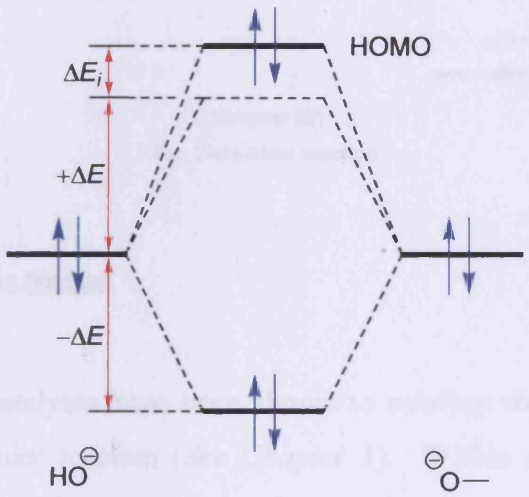
2.2.2 The α-effect

The α-effect is defined as the positive deviation of an α-nucleophile (an α-nucleophile being an unshared pair of electrons on an atom adjacent to the nucleophilic site) from the Brønsted-type plot of log K_{nuc} versus pK_a constructed for a series of normal related nucleophiles.[99] More generally is can be considered to be "*the influence of an atom bearing a lone pair of electrons on the reactivity of the adjacent site.*" This enhanced reactivity was first reported in 1947 but did not receive its name until 1962 when Edwards and Pearson coined the term α-effect.[100]

The origins of these observations still remain debated with several plausible explanations being offered. These include:

- Destabilisation of the ground state of the nucleophile due to repulsion of adjacent pairs of electrons.[101]
- Stabilisation of the transition state by the extra pair of electrons.[102]
- Reduced solvation of the reactive site due to the proximity of the extra pair of electrons.[103]
- Electron pair-pair repulsion raising the nucleophile's highest occupied molecular orbital (HOMO).[104]

This phenomenon is generally believed to have several origins. However, pair-pair repulsion is often cited as the foundation of the α-effect. The theoretical basis of this can be described as the overall increase in energy of the system (ΔE_i) through the linear combination of atomic orbitals of two atoms both containing a lone pair of electrons (*Figure* 19). The increased nucleophilicity can then arise from either (a) the overall increase in energy of the molecule's ground state (ΔE_i) or, (b) the increase in energy ($\Delta E+\Delta E_i$) of the HOMO itself. Frontier Molecular Orbital (FMO) theory suggests the rate enhancements observed are due to reduction in the energy difference between the HOMO and the LUMO of the reacting substrate allowing for a greater overlap of orbitals.

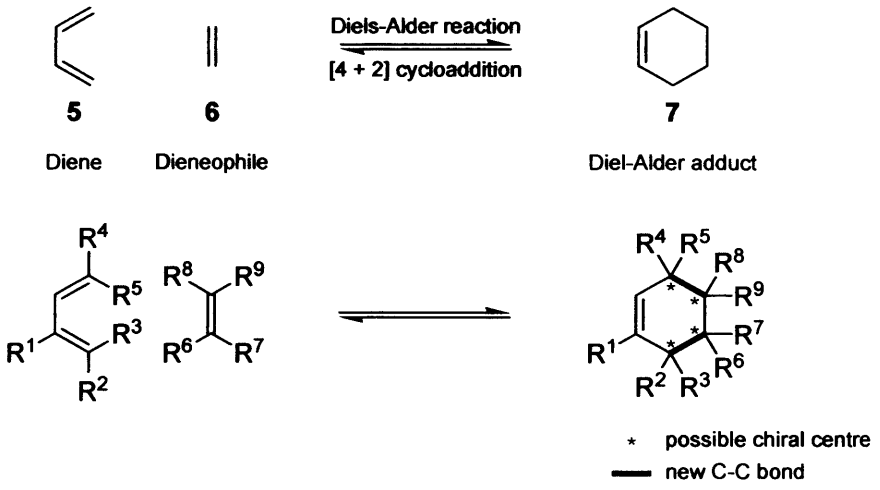


(*Figure* 19)

The nature of these individual effects and the exact conditions they operate under are yet to be unambiguously identified. Nonetheless, the physical properties of the α-effect are indisputable and can be used to explain certain chemical reactivity profiles.[105] Therefore, the α-effect was employed to increase the catalytic ability of these scaffolds.

2.2.3 Diels-Alder test reaction

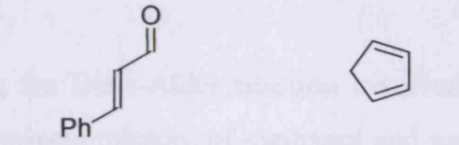
Upon successful synthesis of target catalysts their performance was evaluated *via* their ability to catalyse the Diels-Alder reaction. A plethora of literature regarding catalysis of this reaction exists.[106] This was used to provide a direct comparison of our work with commercially available and reported systems. This highly diverse reaction has been utilised throughout natural product synthesis and within the pharmaceutical industry.[107] It is a [4+2] cycloaddition of a diene **5** and a dieneophile **6** (*Scheme* 26) but on more detailed inspection it can be seen this reaction constructs up to four contiguous chiral centres and two new carbon-carbon bonds in one step.



(*Scheme* 26)
The Diels-Alder reaction

2.2.4 Diels-Alder substrates

Secondary amine based catalysts have been shown to catalyse the reaction of a variety of substrates in the Diels-Alder reaction (*See Chapter* 1). Within our work we adopted the reaction between cyclopentadiene **8** and *trans*-cinnamaldehyde **9** within our standard protocol to compare the activities of the catalysts prepared. Literature precedent utilising these substrates typically required twenty-four hours with 10 mol% catalyst loading allowing for reasonable reaction rates to be achieved providing room for improvement.[7] More importantly, background reaction between these two substrates is minimal allowing for more accurate comparison of individual catalysts.

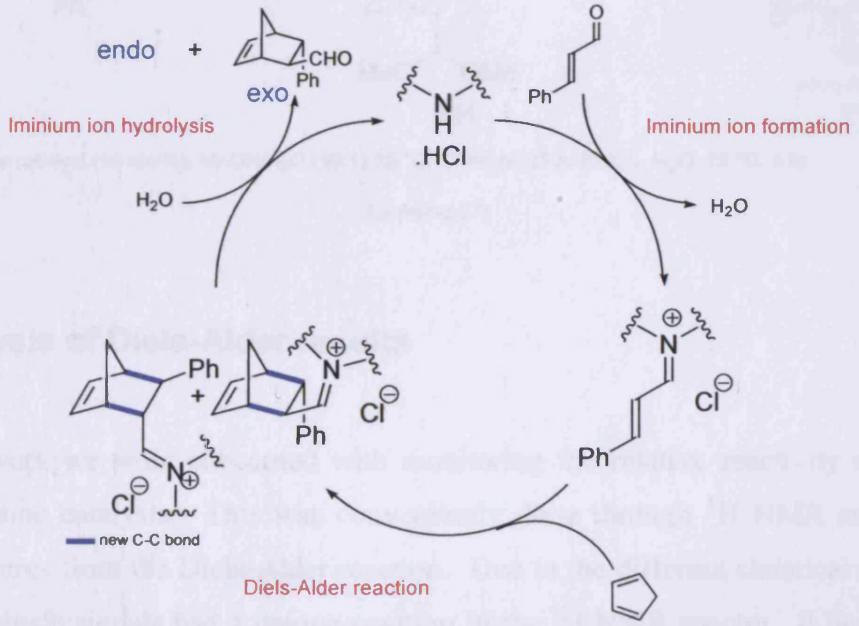


trans-cinnamaldehyde **9**

cyclopentadiene **10**

2.2.5 Diels-Alder catalytic cycle

The mechanism for the iminium ion catalysed Diels-Alder reaction has been proposed (*Mechanism* 5).[7] Nucleophilic attack of the nitrogen lone pair of the catalyst on the carbonyl moiety initiates this process. This first step produces our iminium ion and has been suggested to be the rate determining step (RDS) of the reaction.[24] The energy of the LUMO of the iminium ions carbon-carbon double bond is lowered sufficiently to provide a greater overlap with the HOMO of the diene, cyclopentadiene **8**. This increased overlap serves to accelerate [4+2] cycloaddition, forming our product precursors as their iminium ion. Finally, the initial molecule of water produced by iminium ion formation can hydrolyse the Diels-Alder adduct precursor regenerating the catalyst.

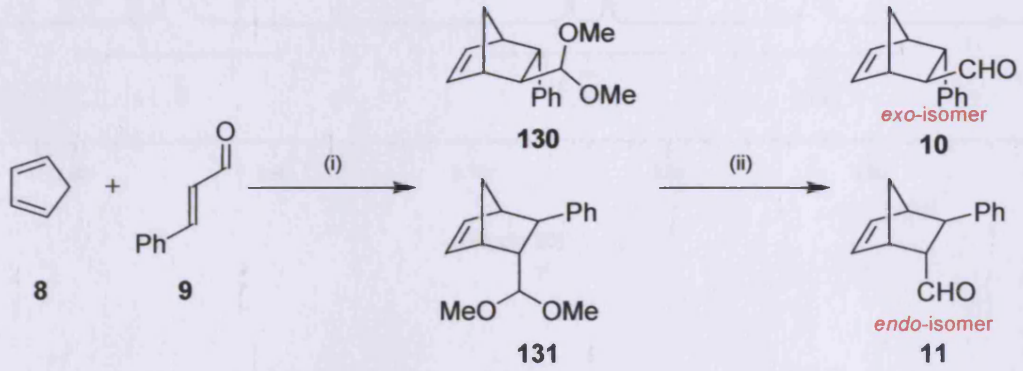


(*Mechanism* 5)

Diels-Alder catalytic cycle

2.2.6 Catalytic procedure

The procedure for following the Diels-Alder reaction involved the combination of catalyst with cinnamaldehyde **9** in a solvent mixture of methanol and water (19:1). This mixture was allowed to stir for five minutes initiating iminium ion formation. Cyclopentadiene **8** was then added in a single aliquot and the resulting reaction was sealed and maintained at 25 °C for a period of twenty-four hours after which time the reaction was stopped *via* removal of volatiles under reduced pressure. Aqueous work-up resulted in a mixture of products, dimethyl acetals **130** and **131** together with the desired reaction products **10** and **11**. These intermediates were subsequently hydrolysed with trifluoroacetic acid (TFA) in a mixture of chloroform and water. Complete hydrolysis was realised within four hours with subsequent purification of the products *via* chromatography affording the target compound 3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde as its *exo*-**10** and *endo*-**11** isomers (*Scheme* 27).



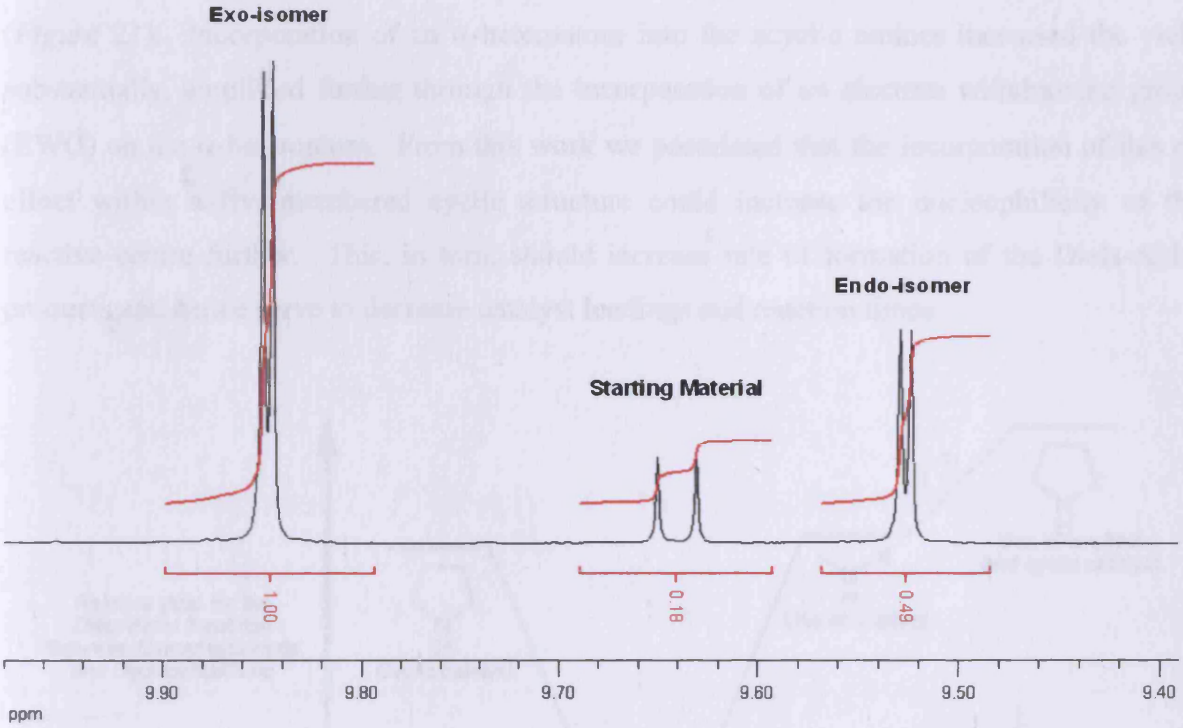
(i) Amine catalyst (10 mol%), MeOH/H_2O (19:1),25 °C, 24 hr. (ii) TFA, $CHCl_3$, H_2O, 25 °C, 4 hr.

(*Scheme* 27)

2.2.7 Analysis of Diels-Alder results

Within our work we were concerned with monitoring the relative reactivity of a series of secondary amine catalysts. This was conveniently done through ^{1}H NMR analysis of the reaction mixtures from the Diels-Alder reaction. Due to the different chemical environments the three aldehyde signals had a unique position in the ^{1}H NMR spectra. It has been shown that the signals corresponding to the *exo*-**10** and *endo*-**11** isomer appeared at δ9.85 and δ9.53 respectively with cinnamaldehyde **9** at δ9.64 (*Figure* 20).[108] Integration of these signals gave the *exo*:*endo* ratio of the Diels-Alder products and later was used to calculate conversions

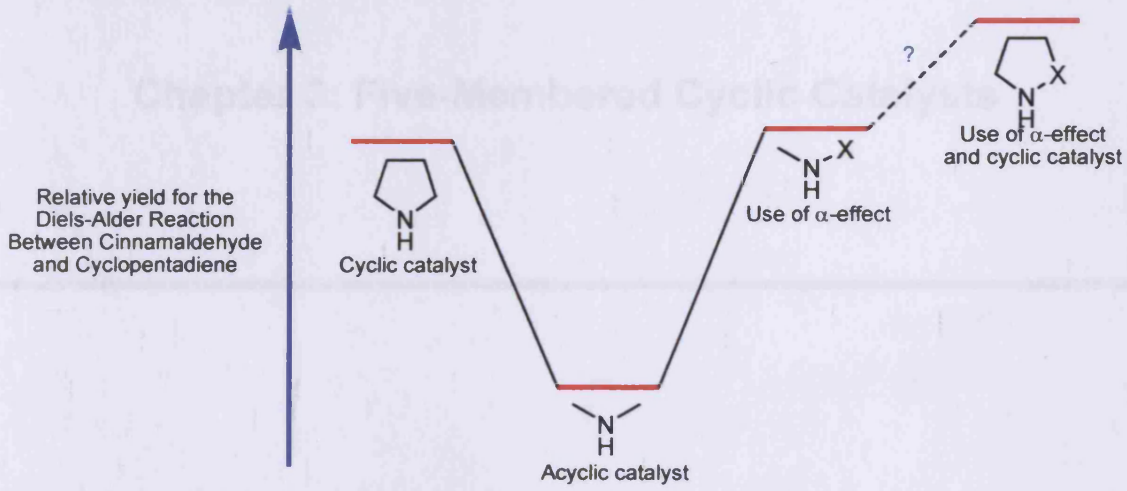
from crude reaction mixtures. The relative integrations of product peaks could also indicate the type of catalysis that occurred. While not exclusive, iminium ion catalysis generally favoured the *exo*-isomer whereas Lewis acid catalysis favoured the *endo*-isomer.



(*Figure* 20)

2.3 Catalyst Design Concept

The work of Cavill showed when moving from a secondary amine, contained within a cyclic structure to an acyclic analogue there was a dramatic decrease in Diels-Alder reaction yield (*Figure* 21). Incorporation of an α-heteroatom into the acyclic amines increased the yield substantially, amplified further through the incorporation of an electron withdrawing group (EWG) on the α-heteroatom. From this work we postulated that the incorporation of this α-effect within a five-membered cyclic structure could increase the nucleophilicity of the reactive centre further. This, in turn, should increase rate of formation of the Diels-Alder products and hence serve to decrease catalyst loadings and reaction times.



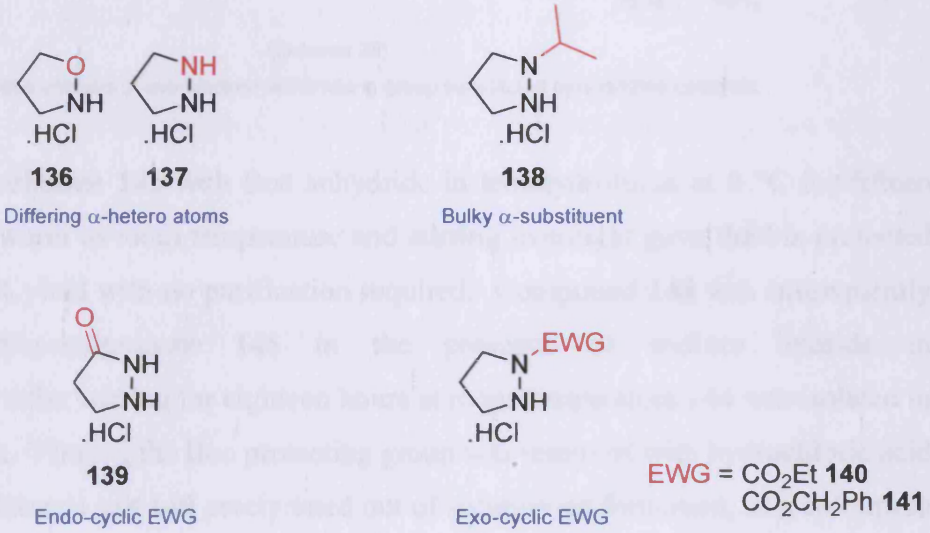
(*Figure* 21)

Chapter 3: Five-Membered Cyclic Catalysts

3.1 Proposed Catalytic Design

3.1.1 Five-membered heterocycles

Our initial aim within this project was to discover if the combination of the α-effect within a five-membered nitrogen containing heterocycle would led to an increase in reactivity and allow for the subsequent design and preparation of a chiral catalyst. To this end we selected a series of target compounds **136-141** (*Figure* 22), based on the pyrazolidine unit with which to test our original hypothesis. The targets incorporated a variety of characteristics which could reasonably be expected to affect catalytic ability of the compounds. These characteristics fell into four distinct classes of compounds.



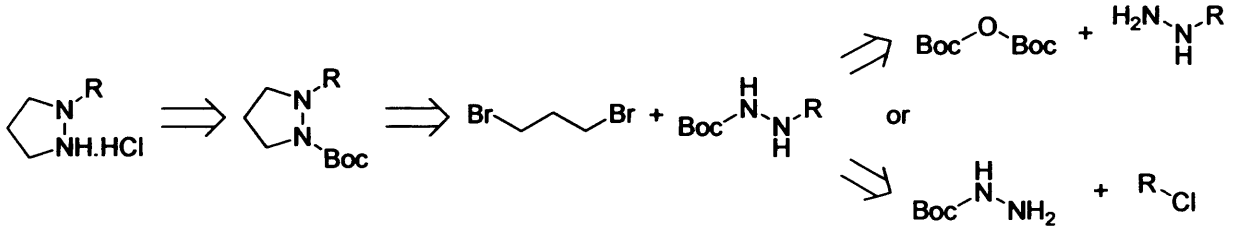
(*Figure* 22)

Initially, optimisation of the α-heteroatom was explored. Previous work detailed increased catalytic ability from systems containing an α-nitrogen centre over α-oxygen. Molecules **136** and **137** were proposed to examine this effect within a cyclic series. Previous work within the group found the inclusion of an electron withdrawing group attached to the α-heteroatom increased catalytic ability. To test this, two series of catalysts were proposed incorporating either an *exo*- or *endo*-electron withdrawing group bound to the heterocycle; structures **139**, **140** and **141**. Finally, we wanted to investigate the influence of an alkyl-substituted α-heteroatom, **138**. As an aside to this we needed to examine the effect of increased sterics

around the reactive nitrogen centre, an important factor in the design of a future chiral catalyst.

3.1.2 *Exo*-electron withdrawing group syntheses

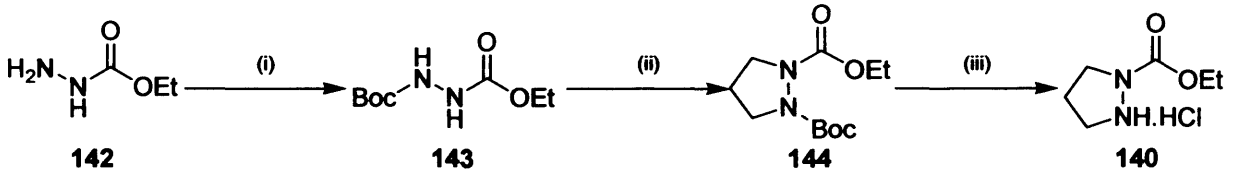
Retrosynthetic analysis of the substituted pyrazolidine compound **140** showed a viable synthetic route through to this cyclic system (*Scheme* 28).[109] Boros *et al.* synthesised this and similar molecules in the preparation of aminobicyclopyrazolones.[110] Dutta and Morley have since utilised this synthesis for use in α-aza-peptides.[111]



(*Scheme* 28)

Retrosynthetic analysis of *exo*-electron-withdrawing group substituted pyrazalidine catalysts.

Treatment of ethyl carbazate **142** with Boc anhydride in tetrahydrofuran at 0 °C for fifteen minutes allowing to warm to room temperature and stirring overnight gave the bis-protected hydrazine **143** in 97% yield with no purification required. Compound **143** was subsequently reacted with 1,3-dibromopropane **145** in the presence of sodium hydride in dimethylformamide. After stirring for eighteen hours at room temperature **144** was isolated in 74% after purification. Finally, the Boc protecting group was removed with hydrochloric acid in ether. The hydrochloride salt **140** precipitated out of solution on formation, as a colourless solid, furnishing the desired catalyst in an overall yield of 71% for the three steps (*Scheme* 29).

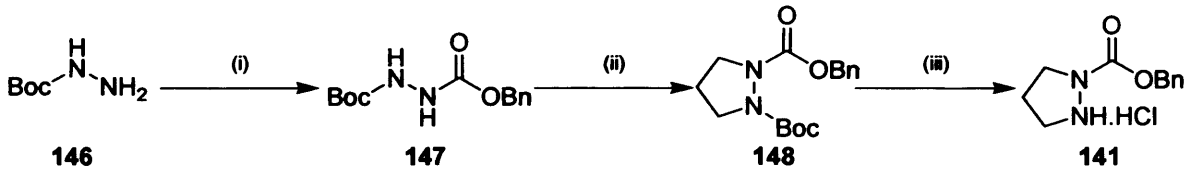


142 **143** **144** **140**

(i) BocOBoc, THF, 0 °C (30 min), r.t., 14 hr., 97%. (ii) NaH, DMF, dibromopropane **145**, r.t., 18 hr., 76%. (iii) 2M hydrochloric acid in ether, r.t., 24 hr., 96%.

(*Scheme* 29)

Compound **141** was formed in an analogous fashion. Carboxybenzyl protection of *tert*-butyl carbazate **146** proceeded at room temperature to give **147** in 91% after twenty-four hours. *N'*-*tert*-butyl ester benzyl carbazate **147** was then submitted to a cyclisation reaction with 1,3-dibromopropane **145** to give *tert*-butyl benzyl pyrazolidine-1,2-dicarboxylate, **148**, in an isolated yield of 79%. Again, Boc deprotection with hydrochloric acid in ether resulted in **141** as a colourless solid in an overall yield of 46% for the three steps (*Scheme* 30).

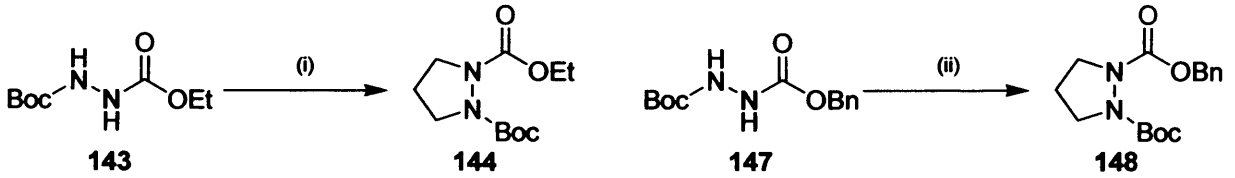


146 **147** **148** **141**

(i) Benzylchloroformate, $CHCl_3$, NaOH (aq), r.t., 24 hr., 91% (ii) NaH, DMF, dibromopropane **145**, r.t., 18 hr., 54% (iii) 2M hydrochloric acid in ether, r.t., 24 hr., 94%.

(*Scheme* 30)

Variations of this synthesis were subsequently employed to secure viable routes through to the majority of our initial targets. However, the key cyclisation step with sodium hydride and 1,3-dibromopropane **145** frequently provided inconsistent yields and difficult purifications to isolate adequate quantities of the desired products. Boros *et al.* had included within their work a phase-transfer method for the synthesis of **148** using tetraethylammonium bromide.[110] This involved reflux of the substrates in a mixture of toluene and a highly concentrated solution of aqueous sodium hydroxide (50% w/w). In our hands this resulted in a reaction which allowed for easier monitoring by TLC and consistent scalable yields to be obtained. This method was not without its disadvantages as reactions were required to be constantly monitored to avoid degradation of the products which occurred upon prolonged heating. Repetition of these reactions allowed for a much improved understanding of the chemistry leading to successful increase output and purity of compounds (*Scheme* 31).



143 **144** **147** **148**

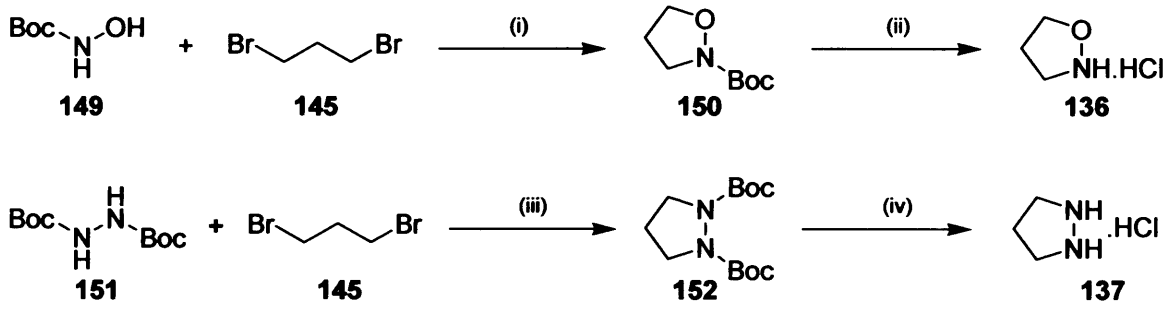
(i) Dibromopropane **145**, PhMe, NaOH (aq, 50% w/w sol^{n}.), NEt_4Br, 100 °C, 90 min., 81%.

(ii) Dibromopropane **145**, PhMe, NaOH (aq, 50 % w/w sol^{n}.), NEt_4Br, 100 °C, 80 min., 79%.

(*Scheme* 31)

3.1.3 Alternative α-heteroatoms

This methodology was subsequently employed in the synthesis of the compounds **136** and **137** derived from *tert*-butyl *N*-hydroxycarbamate **149** and di-*tert*-butyl hydrazodiformate **151** respectively (*Scheme* 32). This formed **150** and **152** with subsequent deprotection of the *tert*-butyloxycarbonyl nitrogen centres with hydrochloric acid in ether giving the desired catalysts **136** and **137** as their salts as colourless powders in overall yields of 15% and 71% respectively. Elemental analysis of compound **137** revealed the ratio of hydrochloride salt to catalyst to be 1.70. Boros *et al.* originally found this ratio to be 1.72.

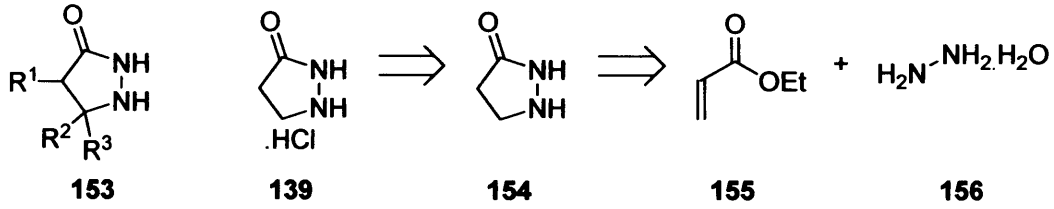


(i) PhMe, NaOH (aq. 50% w/w), NEt_4Br, Δ, 90 min., 17%. (ii) 2M hydrochloric acid in ether, r.t., 24 hr., 89%. (iii) PhMe, NaOH (aq. 50% w/w), NEt_4Br, Δ, 90 mins, 74%. (iv) 2M hydrochloric acid in ether, r.t., 24 hr., 96%.

(*Scheme* 32)

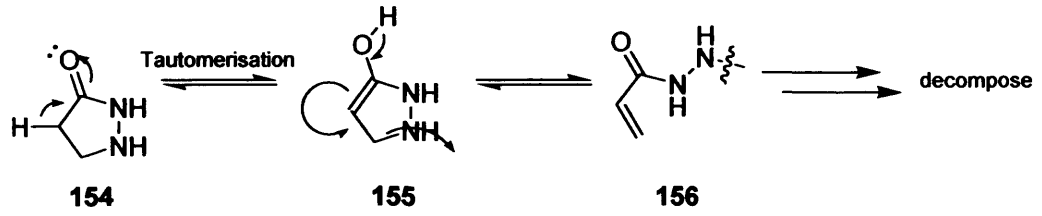
3.1.4 *Endo*-electron withdrawing group syntheses

Retrosynthetic analysis of **139** suggested that synthesis could be achieved from hydrazine **156** and ethyl acrylate **155** (*Scheme* 33). We believed conjugate addition of the nucleophilic hydrazine **156** to the acrylate **155** followed by intramolecular cyclisation should provide rapid access to amine **154**.



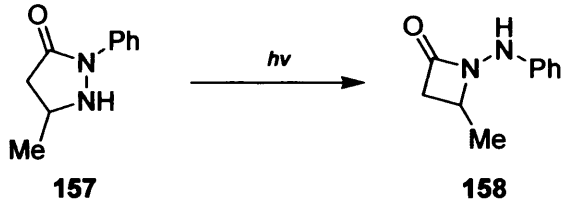
(*Scheme* 33)

A mixture of ethyl acrylate **155** and hydrazine hydrate **156** was refluxed in ethanol. Purification of the crude reaction mixture resulted in an isolated yield of 16% of the desired pyrazolidinone **154**. This yield is poor, yet consistent with the literature precedent for this transformation.[112] The product **154** was an extremely viscous yellow oil and readily decomposed to an intractable mixture of compounds even when stored under an inert atmosphere at -4 °C. A possible explanation for the low yield could be the decomposition of the product during purification. On the mildly acidic silica gel used in the chromatography tautomerisation of **154** could occur forming intermediate **155**. Degradation and decomposition of which could follow from **156** (*Scheme* 34). White showed in his synthesis of similar molecules that substitution at positions R^1-R^3 of **153** increased isolable quantities of the products.



(*Scheme* 34)

Evidence for decomposition post-purification had been detailed by Ege who showed that when irradiated **157** undergoes a ring contraction forming **158** in 70-80% yield (*Scheme* 35).[113]

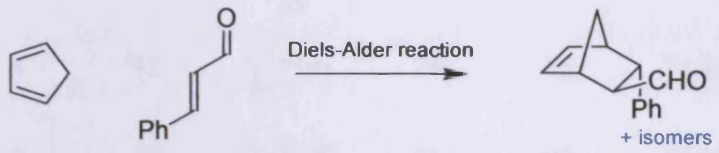


(*Scheme* 35)

This photolytic decomposition route was also shown to occur with various substitutions about the cyclic structure.[114] It was therefore decided at this point not to continue with synthesis of **139** and **138** but concentrate on testing of compounds already prepared within the cyclic series.

3.2 Catalysis: Initial Investigations

With suitable catalysts prepared we tested our initial hypothesis within the Diels-Alder reaction (*Scheme* 36) between cinnamaldehyde **9** and cyclopentadiene **8**.



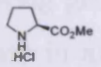
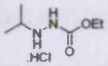
8 Diene | **9** Dieneophile | **10** Diel-Alder adduct

(*Scheme* 36)

3.2.1 Five-membered heterocycles

Initially, catalysts **136**, **137**, **140** and **141** were examined under the catalytic conditions described previously. We decided to test our compounds against the commercially available catalysts proline methyl ester hydrochloride **12** and MacMillan's imidazolidinone based catalyst **16** to give an indication of expected activity within these reactions. These catalysts were chosen due to their prolific use throughout the literature in amine catalysis.[115] Reactions were carried out in the absence of any catalyst to show the background reaction under our employed conditions. Triethylamine hydrochloride **159** was also examined to indicate any possible catalysis from the hydrochloric acid portion of the catalyst. Finally, we included catalyst **22** from previous work to indicate the reactivity of the acyclic compounds.

Initial results from the Diels-Alder reaction between *trans*-cinnamaldehyde **9** and cyclopentadiene **8** are outlined below (*Table* 12).

Entry	Catalyst[a]	Structure	Time hr	Yield[b] %	*exo*:*endo*[c]
1	none	-	48	7	36:64
2	**159**	NEt_3.HCl	48	7	37:63
3	**16**		24	98	56:44
4	**12**		24	85	71:29
5	**22**		24	90	65:35
6	**140**		24	38	67:33
7	**141**		24	34	68:32
8	**137**[d]		24	15	45:55
9	**136**		24	8	66:34

(*Table* 12)

(a) Reactions were carried out in methanol/water (19:1) at 25 °C with 10 mol% catalyst. (b) Isolated yield after chromatography. (c) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixtures. (d) 1.7 equiv. HCl.

The exclusion of any catalyst (*Table* 12, *entry* 1) regardless of the presence of the protic acid co-catalyst (*Table* 12, *entry* 2) showed the background reaction to proceed to a maximum of 7% with an extended reaction time of forty-eight hours. These examples exhibited *exo*:*endo* ratios in favour of the *endo*-adduct as could be expected in the absence of iminium ion catalysis. MacMillan's oxazolidinone based catalyst **16** performed exceptionally well under these conditions resulting in a near quantitative yield after twenty-four hours with the *exo*-product predominating slightly over the *endo*, a characteristic feature of iminium ion catalysis (*Table* 12, *entry* 3). This ratio was reflected to a greater degree in the case of proline methyl ester **12** (*Table* 12, *entry* 4) with an isolated yield of 85%. The acyclic substituted hydrazide **22** explored previously within the group also performed well under these conditions with a yield of 90% isolated in an *exo*:*endo* ratio of 65:35. These results defined the target for our heterocyclic analogues.

Initial testing of the prospective five-membered nitrogen containing heterocycles, **136**, **137**, **140** and **141**, in the Diels-Alder reaction failed to deliver the expected increase in reactivity based on our initial hypothesis. Out of the four catalysts prepared **136**, **137**, **140** and **141**, those containing an *exo*-electron withdrawing group, **140** and **141** preformed best with yields after twenty-four hours of 38% and 34% respectively (*Table* 12, *entries* 6 & 7). Both suggested iminium ion catalysis denoted by *exo*:*endo* ratios in favour of the *exo*-isomer. The incorporation of an electron withdrawing group attached to the α-heteroatom in these cyclic systems served to increase the activity in a similar manner to that observed in the acyclic series.[13] Without this electron withdrawing group present in the catalyst architecture the isolated yields for the reaction were poor (*Table* 12, *entries* 8 & 9).

3.2.2 Optimisation of conditions

While the initial results obtained from the catalytic investigation did not prove as successful as we had hoped, the reaction conditions employed were those optimised for an alternative catalyst, **16**. Optimisation of the reaction conditions towards our catalysts could possibly produce results closer to our initial expectations. To this end we decided to alter the solvent and acid co-catalyst employed.

3.2.2.1 Solvent optimisation

Within the literature the use of a methanol/water mixture (19:1) as the solvent was required for optimal catalyst reactivity.[7] It was proposed that water was necessary for the hydrolysis of the iminium ion Diels-Alder adduct to facilitate catalyst turnover. We repeated the catalytic tests in a variety of typical laboratory bench solvents to discover their effects on reactivity in the Diels-Alder reaction. Comparison was carried out between the polar protic solvents methanol and water along with a variety of polar aprotic solvents; acetonitrile, dimethylformamide and dimethyl sulfoxide, in addition to the apolar aprotic solvent dichloromethane. The reaction was also carried out in the absence of solvent. These choices of solvent systems provided us with an adequate platform to assess solvent effects on the Diels-Alder reaction. All other reactions conditions other than the solvent employed remained constant and the results obtained are tabulated below (*Table* 13).

Entry	Solvent[a]	Homogeneous	Time hr	Yield[b] %	*exo*:*endo*[c]
1	MeOH	Yes	24	53	69:31
2	MeOH/H_2O (19:1)	Yes	24	34	68:32
3	^{i}PrOH	Yes	24	31	69:31
4	MeCN	Yes	24	27	65:35
5	Neat	Yes	24	25	54:46
6	CH_2Cl_2	Yes	24	24	56:44
7	DMSO	Yes	24	18	66:34
8	DMF	Yes	24	15	70:30
9	H_2O	No	24	12	50:50

(*Table* 13)

(a) Reactions were carried out in the specified solvent at 25 °C with 10 mol% of catalyst **141**. All solvents were dried prior to reaction with the exception of water. (b) Isolated yield after chromatography. (c) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixtures.

Although yields remained low, the results highlighted some interesting factors regarding this reaction. Primarily, the use of dry methanol afforded the desired products in a yield of 53% (*Table* 13, *entry* 1). This showed a substantial increase in reactivity over the methanol/water mixtures used previously; *c.f.* 34%. Use of *iso*-propanol gave the desired products in a yield of 31% (*Table* 13, *entry* 3). This gave a good indication that the iminium ion catalysed Diels-Alder reaction proceeded better in polar protic solvents. A possible explanation for the lower reactivity of the catalyst in *iso*-propanol may be the slower conversion of the iminium ion Diels-Alder adducts to the corresponding acetals, resulting in slower catalyst turnover, although we have no direct evidence for this.

The absence of solvent or use of dichloromethane showed poor yields for the reaction (*Table* 13, *entries* 5 & 6). The use of water failed to provide the product in satisfactory yield (*Table* 13, *entry* 9) although it is worth noting that this reaction was bi-phasic. Acetonitrile, dimethyl

sulfoxide and dimethylformamide (*Table* 13, *entries* 4, 7 & 8) indicated iminium ion catalysis to have occurred by inspection of the *exo*:*endo* ratio of products, albeit relatively slowly.

It is plausible that higher yields were observed in alcohol based solvent systems as the final step of the catalytic cycle required hydrolysis of the iminium ion of the Diels-Alder adduct. This can be carried out with water (forming the target product) or by the solvent (forming the corresponding acetal). Due to the abundance of nucleophiles within the alcohol based reaction mixtures the hydrolysis of the intermediate iminium ions could be faster. This would increase regeneration of the amine and hence its ability to catalyse subsequent reactions.

3.2.2.2 Acid co-catalyst optimisation

In order to examine the effect of the co-acid catalyst, we formed the free-amine of our most active five-membered cyclic system, **140**, with a simple separation between ethyl acetate and aqueous sodium hydrogen carbonate, and reacted it under our standard catalytic conditions with the formation of a variety of salts of the catalytic amine *in situ* (*Table* 14).

Entry	Co-acid[a]	pK_a[b]	mol%	Yield[c] %	*exo*:*endo*[d]
1	HCl	-7.0	10	56	68:32
2	$HClO_4$	-10	10	55	59:41
3	*p*TSA	0.7	10	46	62:38
4	TFA	0.5	10	18	71:29
5	Benzoic	4.2	10	trace	n.d.
6	none	-	-	trace	n.d.

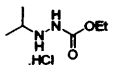
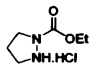
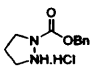
(*Table* 14)

(a) Reactions were run at 25 °C for 24 hours with 10 mol% catalyst **140** with acid salts produced *in situ*. (b) Values for the free acid in water at 25 °C. (c) Isolated yield after chromatography. (d) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixtures.

Examination of the results showed acids with a lower pK_a value generally catalysed the Diels-Alder reaction to a greater extent. The data suggested that effective acceleration of the reaction could occur with acids of a pK_a value of 1.0 and below. From these results we decided the best acid to have within the reaction mixture would be hydrochloric acid.

3.2.3 Standard reaction conditions

With the optimisation of solvent and co-acid complete we resubmitted the cyclic catalysts prepared previously to the Diels-Alder reaction for re-evaluation (*Table* 15).

Entry	Catalyst[a]	Structure	Time hr	Yield[b] %	*exo*:*endo*[c]
1	**22**		24	90	66:34
2	**140**		24	56	68:32
3	**141**		24	53	69:31
4	**137**[d]		24	36	29:71
5	**136**		24	7	67:33

(*Table* 15)

(a) Reactions were carried out in methanol at 25 °C with 10 mol% catalysts. (b) Isolated yield after chromatography. (c) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixtures. (d) 1.7 equiv. HCl.

The use of dry methanol as the solvent showed an increase in yield across the cyclic series with *exo*:*endo* ratios remaining constant. From these results we assumed dry methanol and the hydrochloride salt as the optimal conditions for the remainder of the investigation.

3.3 Conversion vs. Yield

Throughout the investigation to this point yields quoted are from purified isolated samples of Diels-Alder adducts. At this stage it was observed that yields after purification were equivalent to the conversions calculated from integration of ^{1}H NMR signals in the crude reaction mixtures. Therefore, to save time experiments were carried out to discover if this relationship was direct and extendable to a variety of reaction conditions, thus negating the requirement for purification of the Diels-Alder adducts.

The standard catalytic procedure was carried out with a variety of cyclic and acyclic catalysts between *trans*-cinnamaldehyde **9** and cyclopentadiene **8** under our new standard reaction conditions with a reaction time of twenty-four hours. Integrations of the ^{1}H NMR signals post hydrolysis corresponding to the aldehyde peaks of products (*exo*- and *endo*-isomers) and starting material **9** in the crude reaction mixture gave the percentage conversion into products and the ratio of *exo*:*endo* isomers formed within the reaction. The crude reaction mixtures were subsequently purified with isolated yields and *exo*:*endo* ratios measured. The results are detailed below (*Table* 16).

Entry	Catalyst[a]	Structure	Conversion[b] %	*exo*:*endo*[c]	Yield[d] %	*exo*:*endo*[c]
1	none	-	7	36:64	7	34:66
2	**16**		>98	57:43	>98	57:43
3	**137**[e]		26	29:71	25	28:72
4	**136**		7	67:33	5	67:33
5	**140**		56	68:32	54	66:34
6	**141**		53	69:31	52	68:32

(*Table* 16)

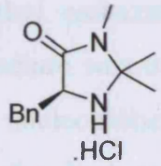
(a) Reactions were carried out in methanol at 25 °C for 24 hours with 10 mol% catalyst. (b) Conversions were calculated from ^{1}H NMR of aldehyde signals of products and starting materials in the crude reaction mixture. (c) *Exo*/*endo* ratios determined by ^{1}H NMR. (d) Yields were calculated by mass of combined purified Diels-Alder products. (e) 1.7 equiv. of HCl.

This data shows unequivocally the relationship between the ^{1}H NMR conversion of the crude reaction mixtures *vs.* those of the isolated products post-purification. In all cases percentages of products and *exo*:*endo* ratios were within experimental error suggesting ^{1}H NMR analysis of crude reaction mixtures would provide an accurate and quicker method for us to compare the activities of catalysts prepared.

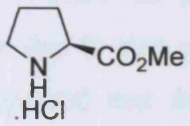
This method of analysis was employed for all subsequent catalyst screening experiments.

3.4 Reassessment

Previous work within our group showed the α-effect to increase catalytic activity of acyclic nitrogen containing compounds to approach that of commercially available heterocycles such as **16** and **12** within the Diels-Alder reaction. We initially postulated that a combination of an α-heteroatom within a five-membered heterocycle would lead to further increases in reactivity due to ring strain increasing the nucleophilicity of the reactive nitrogen centre.



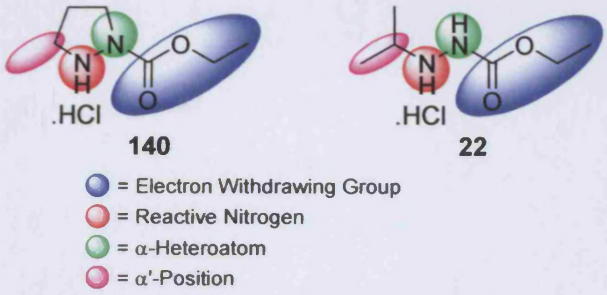
16



12

Initial results from the catalysts prepared to investigate this hypothesis showed much lower reactivity than expected. We deemed it important at this stage to investigate the structural requirements of a catalyst for greater activity which would hopefully lead to a greater understanding of processes involved in the iminium ion catalysed Diels-Alder reaction. This work was carried out through the use of a structure-activity relationship (SAR) study of the cyclic and acyclic catalysts prepared.

Examination of the best catalyst from both the cyclic and acyclic series, **141** and **22,** showed an electron withdrawing group attached directly to α-heteroatom resulted in a greater activity (*Figure* 23). However, within the acyclic series the α-heteroatom was a secondary centre, whereas the in the cyclic series (e.g. **141**) this nitrogen was tertiary. We believed this could be a contributing factor to the reduced activity within these molecules. Therefore, we postulated that if the α-nitrogen within an acyclic catalyst was tri-substituted we should observe a lowering in the activity of the catalyst. At this point it is important to note that previous work within the group indicated an α-nitrogen centre produced the best results in the acyclic series therefore we assumed it should also be the case within the cyclic series.



140 **22**

(*Figure* 23)

SAR study of the cyclic and acyclic catalyst skeleton.

The SAR also showed other subtle differences between the two catalyst architectures. Both catalysts contained the ethyl carbazate moiety; however, we presumed the lone pair of electrons of the cyclic structure was more available due to ring constraints. Therefore, this centre was deemed more nucleophilic. It now appeared that the catalysts with the lower nucleophilicity produced the best results, despite the literature statement that the rate determining step of iminium ion catalysed processes was the formation of the iminium ion, a factor greatly governed by the nucleophilicity of the attacking species. This suggested enlargement of the cyclic structure from a five- to a six-membered heterocycle could possibly display increased activity within the Diels-Alder reaction. However, examination of the literature shows six-membered catalysts to perform poorly in enamine and iminium ion catalysis compared to their five-membered analogues.[116]

Finally, examination of the carbon centre directly attached to the reactive nitrogen (the α'-position) displayed a greater substitution in our acyclic series. Work previously within the group showed a tertiary α'-centre, as seen in **23**, to catalyse reactions more efficiently than a secondary, **24**. This indicated that increased substitution at this position would subsequently increase reactivity of our cyclic catalysts although this was thought only to result in superficial increase in activity as previous work detailed only minor increases in yield from this alteration.[117]

23 **24**

With the continuing SAR studies in mind we moved on to examine the influences of these parameters in the acyclic series.

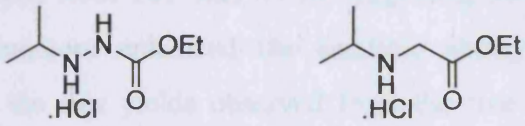
Chapter 4: Acyclic Catalyst Elaboration

4.1 Acyclic Extensions

At this stage we thought it appropriate to further investigate the SAR of our acyclic catalyst scaffold in the iminium ion catalysed Diels-Alder reaction.

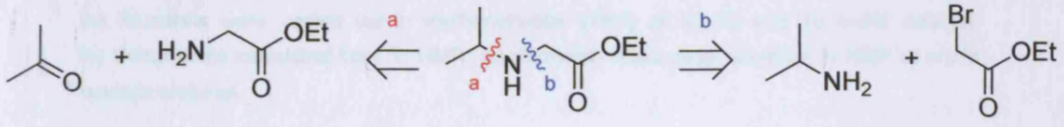
4.1.1 Proof of α-effect

It appeared from our initial catalytic studies that the five-membered cyclic systems had failed to provide us with the improved catalytic performance we had anticipated. We required confirmation of the effect of the introduction of an α-heteroatom to the reactive nitrogen centre within the acyclic catalyst series. We therefore targeted the glycine derivative **161**; replacing the α-heteroatom of **22** with a methylene unit.



22 **161**

Disconnection of **163** revealed two possible synthetic strategies (*Scheme* 37). Disconnection of bond 'a' showed a reductive amination reaction between glycine ethyl ester **162** and acetone **60**. Our chosen synthetic route, disconnection 'b' suggested an S_N2 reaction between *iso*-propylamine **164** and 2-bromo ethyl acetate **165**.

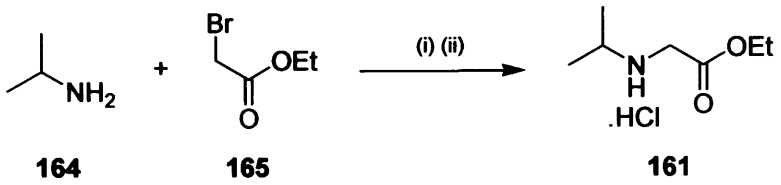


60 **162** **163** **164** **165**

(*Scheme* 37)

Treatment of 2.3 equivalents of *iso*-propylamine **164** with ethyl bromoacetate **165** in toluene at reflux for two hours produced a crystalline precipitate. The solution was made alkaline and extracted affording ethyl 2-(*iso*-propylamino)acetate, **163**, in a yield of 85% as a clear colourless liquid after distillation. The hydrochloride salt was formed by mixing the liquid

with hydrochloric acid in ether. This gave **161** in an overall yield of 83% as a colourless solid (*Scheme* 38).



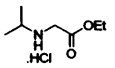
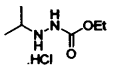
164 **165** **161**

(i) PhMe, Δ, 2 hr, 85%. (ii) 2M hydrochloric acid in ether, r.t., 5 min, 98%.

(*Scheme* 38)

4.1.2 α-Effect verification

Under the standard Diels-Alder reaction described previously **161** gave an isolated yield of 5% after forty-eight hours compared to 90% after just twenty-four hours for **22** (*Table* 17). The *exo*/*endo* ratio observed from **161** was 64:36 suggesting iminium ion catalysis. This result proved the α-heteroatom enhanced the catalytic ability of the acyclic systems significantly. Therefore, the low yields observed from the five-membered cyclic systems were most likely attributed to an alternative factor.

Entry	Catalyst[a]	Structure	Time hr	Conversion[b] %	*exo*:*endo*[c]
1	**161**		48	5	64:36
2	**22**		24	90	65:35

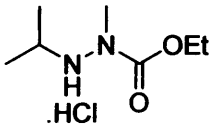
(*Table* D)

(a) Reactions were carried out in methanol/water (19:1) at 25 °C with 10 mol% catalyst. (b) Conversions calculated from ^{1}H NMR. (c) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixtures.

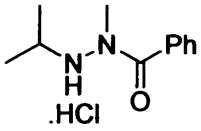
4.2 Acyclic Catalyst Modification

4.2.1 α-Heteroatom substitution

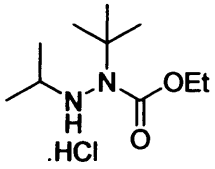
Next, we wanted to test the catalytic ability of acyclic systems incorporating a more highly substituted α-heteroatom to advance our SAR investigations. From the initial SAR studies we expected this higher substitution would decrease the catalytic ability of our systems. To test this hypothesis we targeted compounds **166**, **167** and **168**.



166

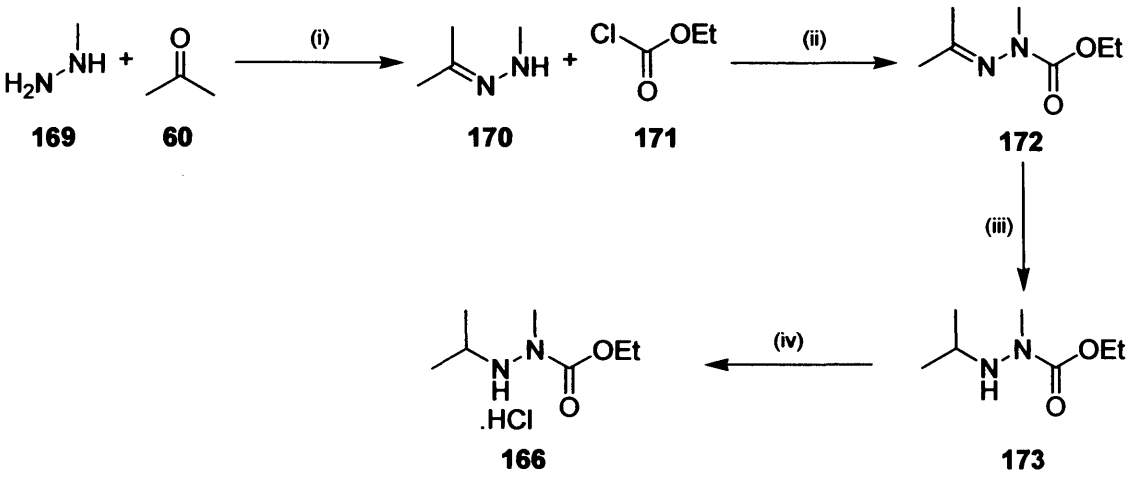


167



168

Synthesis of **166** utilised protection of the primary nitrogen centre of methylhydrazine **169** with acetone **60** forming the hydrazone **170** (*Scheme* 39).[118] **170** was isolated as a clear colourless mobile liquid in a yield of 81% after purification by distillation. Subsequent coupling with ethyl chloroformate **171** in a mixture of dichloromethane and aqueous saturated sodium hydrogen carbonate resulted in **172**. Surprisingly, this compound was unstable to chromatography with evidence for hydrazone hydrolysis. This decomposition was not observed in the synthesis of previous acyclic catalysts and was attributed to the increased substitution of the α-heteroatom. We continued the synthesis with the hydrogenation of the crude hydrazone **172** with a platinum(IV) oxide catalyst under an atmosphere of hydrogen. This provided the catalyst precursor *N*-methyl-*N'*-*iso*-propyl ethyl carbazate **173**, which, on treatment with hydrochloric acid in ether gave the required salt **166** in an overall yield of 62% for the four steps.

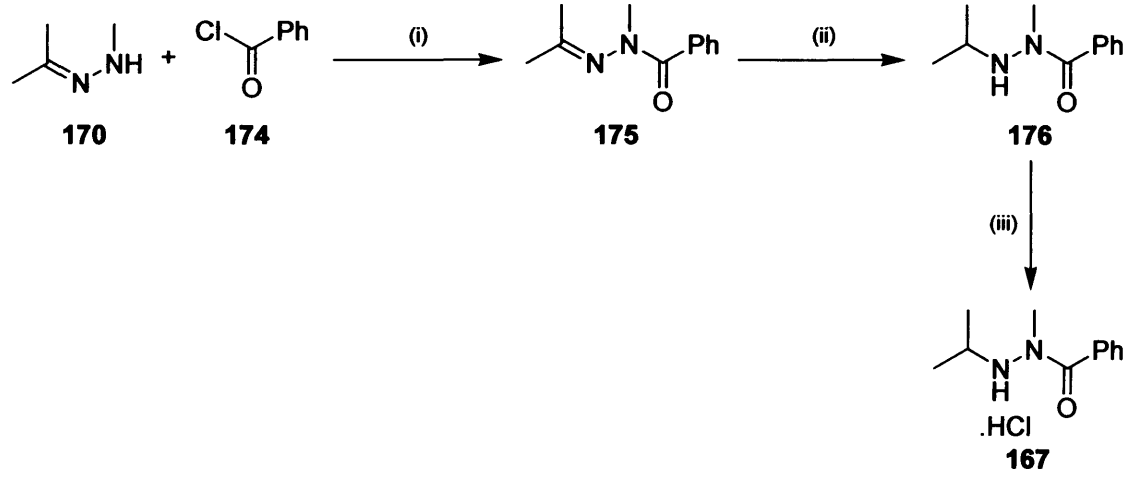


169 60 170 171 172 173 166

(i) KOH, r.t., 3 hr, 81%. (ii) $NaHCO_3$ (aq), CH_2Cl_2, 0 °C, 30 min., r.t.,16 hr., 92%. (iii) H_2(g), AcOH, EtOH, PtO_2 (2 mol%), r.t., 16 hr., 86% (crude). (iv) 2M hydrochloric acid in ether, r.t., 30 mins., 97%.

(*Scheme* 39)

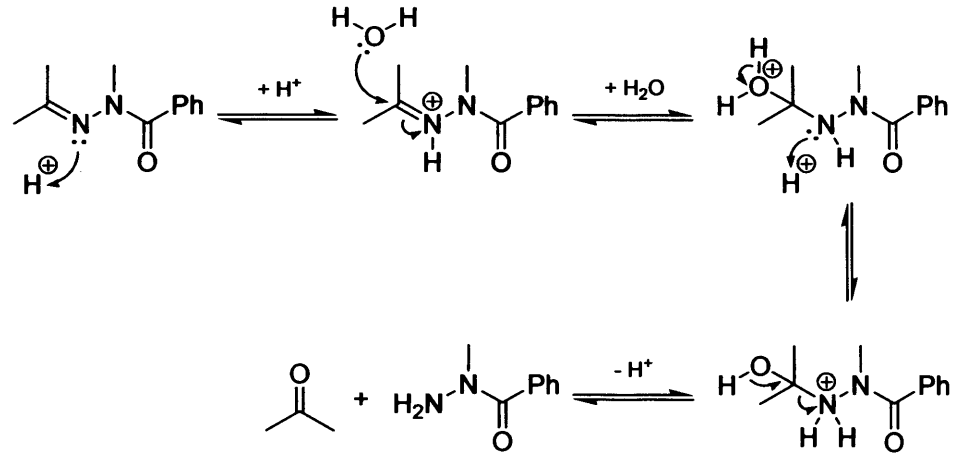
Catalyst **167** was synthesised in an analogous fashion. The common hydrazone precursor **170** was reacted with benzoyl chloride **174** at 0 °C for thirty minutes warming to room temperature (*Scheme* 40). Similar to the synthesis of **172**, we observed a low yield for **175** after purification. To increase overall yield we telescoped this step with the hydrogenation of the carbon-nitrogen double bond as carried out previously with platinum(IV) oxide in an ethanol-acetic acid mixture under an atmosphere of hydrogen forming **176**. The hydrochloride salt was formed by swirling with hydrochloric acid in ether forming **167** in an overall yield of 11%. The low yield was attributed to the labile hydrazone **175** being hydrolysed under the hydrogenation conditions (*Mechanism* 6), which required higher loadings of platinum(IV) oxide (10 mol%) to overcome the kinetics associated with the hydrolysis step.



170 174 175 176 167

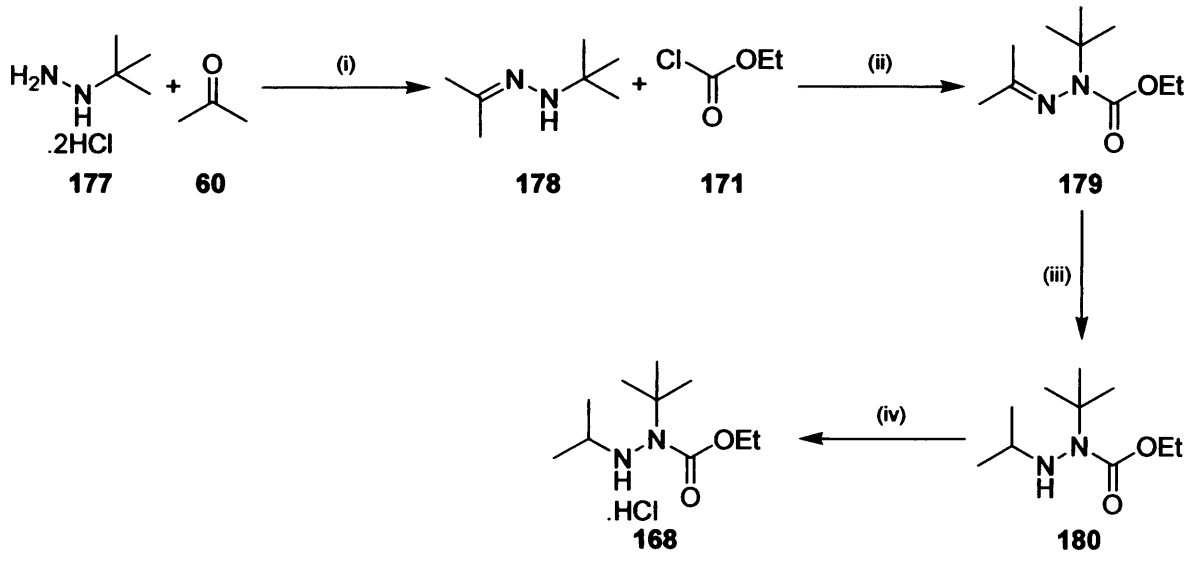
(i) $NaHCO_3$(aq), CH_2Cl_2, 0 °C, 30 min., r.t., 16 hr. (ii) H_2(g), AcOH, EtOH, PtO_2 (10 mol%). (iii) 2M hydrochloric acid in ether, r.t., 30 mins., 11% (three steps).

(*Scheme* 40)



(*Mechanism* 6)

Synthesis of **168** originated similarly with the condensation of acetone **60** with *tert*-butyl hydrazine dihydrochloride **177** forming **178** in a yield of 64%. Reaction with ethyl chloroformate **171** and subsequent hydrogenation of the hydrazone **179** formed **180**. Treatment of **180** with hydrochloric acid in ether afforded the required catalyst as its hydrochloride salt in an overall yield of 20% for the four steps (*Scheme* 41).

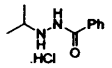
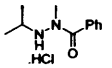
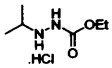
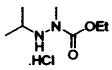
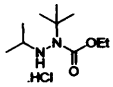
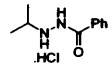
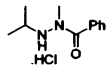
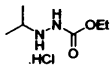
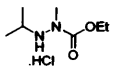
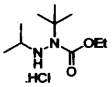


(i) KOH, r.t., 7 hr., 64%. (ii) CH_2Cl_2, $NaHCO_3$(aq), 0 °C, 30 min, r.t., 24 hr., 64%. (iii) H_2(g), AcOH, EtOH, PtO_2 (2 mol%), r.t., 24 hr., 52% (iv) 2M hydrochloric acid in ether, r.t., 10 mins., 92%.

(*Scheme* 41)

4.2.2 Catalysis: α-heteroatom substitution

With catalysts **166**, **167** and **168** synthesised, they were tested to discover the influence of α-heteroatom substitution on catalytic activity. These new structures underwent the standard reaction with *trans*-cinnamaldehyde **9** and cyclopentadiene **8** for twenty-four hours, the results of which can be seen below (*Table* 18).

Entry	Catalyst[a]	Structure	Solvent[b]	Conversion[c] %	*exo*:*endo*[d]
1	**23**		i	72	69:31
2	**167**		i	84	67:33
3	**22**		i	90	65:35
4	**166**		i	96	65:35
5	**168**		i	34	59:41
6	**23**		ii	85	65:35
7	**167**		ii	89	64:36
8	**22**		ii	90	66:34
9	**166**		ii	98	65:35
10	**168**		ii	70	65:35

(*Table* 18)

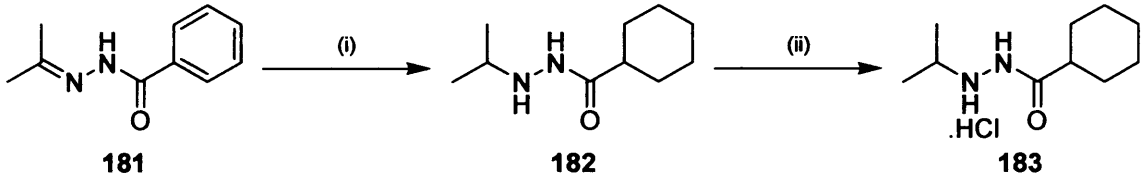
(a) Reactions were carried out at 25 °C for 24 hours with 10 mol% catalyst. (b) Solvent (i) refers to methanol/water (19:1) solvent (ii) refers to methanol. (c) Conversion determined by ^{1}H NMR of crude reaction mixtures. (d) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixtures.

It was noted from these results that a 2:1 *exo*/*endo* ratio was observed in all cases suggesting the transformations had occurred *via* iminium ion catalysis. In accordance with previous findings we observed increased catalytic ability with the use of dry methanol as opposed to methanol/water (19:1) mixtures. Our initial SAR study had led us to expect a lower yield

from increased substitution of the α-heteroatom; this did not turn out to be the case. With the incorporation of a *tert*-butyl group on the α-heteroatom **168**, a decrease in catalyst activity was observed with a significant lowering of yield with the methanol/water solvent system (*Table* 18, *entry* 5 & 10). However, substitution of the α-nitrogen with a methyl group showed our most active catalysts to date, **166** and **167**. **166** and **167** gave conversion of >90% in both solvent systems (*Table* 18, *entries* 4 & 9 and 2 & 7) with **166** giving an almost quantitative yield after the twenty-four hour period similar to that of the commercially available imidazolidinone **16**. It is important at this point to note we were now approaching quantitative yields with these catalysts and therefore to gain a full appreciation of individual catalysts reactivity we decided to reduce reaction times to six hours to acquire a greater understanding of their relative reactivities.

4.2.3 Acyclic catalyst extension

In the preparation of these catalysts we observed a surprising result during the routine synthesis of **23**. An increased hydrogenation time for the hydrazone **181** also reduced the phenyl ring in its entirety forming **182** in a 53% yield (*Scheme* 42). Hydrogenation of a benzoyl group usually requires increased temperatures and high pressures to proceed.[119] This result highlights the diverse chaos inherent in any chemical transformation. This compound was yet another example of a possible catalyst and therefore we included it in our studies as its hydrochloride salt **183**.



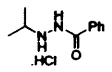
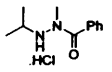
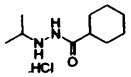
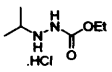
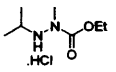
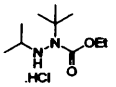
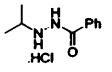
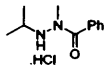
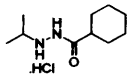
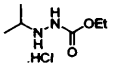
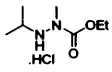
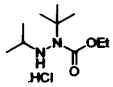
181 **182** **183**

(i) H_2(g), AcOH, EtOH, PtO_2 (2 mol%) r.t., 96 hr., 53%. (ii) 2M hydrochloric acid in ether, r.t., 10 min., 89%.

(*Scheme* 42)

4.2.4 Reduction of catalyst reaction times

Reassessment of these acyclic catalysts was carried out for a period of six hours to gain greater insight into the relative individual activities (*Table* 19).

Entry	Catalyst[a]	Structure	Solvent[b]	Conversion[c] %	*exo*:*endo*[d]
1	**23**		i	58	62:38
2	**167**		i	72	69:31
3	**183**		i	72	69:31
4	**22**		i	74	66:34
5	**166**		i	88	68:32
6	**168**		i	10	50:50
7	**23**		ii	82	68:32
8	**167**		ii	89	67:33
9	**183**		ii	86	68:32
10	**22**		ii	90	67:33
11	**166**		ii	98	68:32
12	**168**		ii	20	62:38

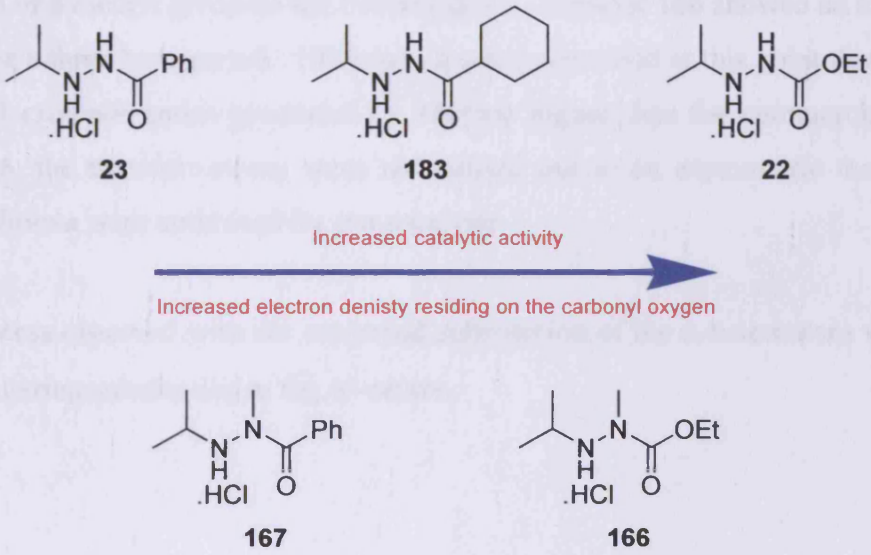
(*Table* 19)

(a) Reactions were carried out at 25 °C for 6 hours with 10 mol% catalyst. (b) Solvent (i) refers to methanol/water (19:1) solvent (ii) refers to methanol. (c) Conversions determined by ^{1}H NMR of crude reaction mixture. (d) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixture.

All cases displayed the expected *exo*:*endo* ratio indicative of iminium ion catalysis with the exception of catalyst **168** in the methanol/water solvent mixture. Here a low yield implies

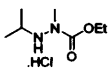
poor activity under these conditions probably due to the steric encumbrance associated with the bulky *tert*-butyl group (*Table* 19, *entry* 6 & 12). The incorporation of a methyl group on the

α-heteroatom increased catalytic activity in both the hydrazide and carbazate series (*Table* 19, *entries* 2 & 8 and 5 & 11 respectively). A second significant observation from these results was the effect of the electron-withdrawing group. In both solvent systems there was a general trend showing an increase in catalytic ability with greater electron density on the carbonyl oxygen. This was observed for both the substituted (**166** and **167**) and unsubstituted (**22**, **23** and **183**) α-heteroatom series, (*Figure* 24). At this point it was unknown whether this effect manifested itself as an alteration in the magnitude of the α-effect within the molecule, or was more closely linked to the mechanism of iminium ion formation by a contribution of the carbonyl group.



(*Figure* 24)

To realise the potential of catalyst **166** it was re-subjected to the Diels-Alder reaction for three hours along side the commercially available imidazolidinone **16** and the cyclic catalyst **140** (*Table* 20).

Entry	Catalyst[a]	Structure	Time hr	Conversion[b] %	exo:*endo*[c]
1	**16**		3	63	58:42
2	**140**		3	11	71:29
3	**166**		3	86	65:35

(*Table* 20)

(a) Reactions were carried out at 25 °C for 3 hours in methanol with 10 mol% catalyst. (b) Conversions determined by ^{1}H NMR of crude reaction mixture. (c) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixture.

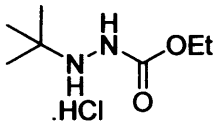
These combined results indicated increased catalytic activity within the acyclic series with the incorporation of a methyl group on the α-heteroatom. Catalyst **166** showed an excellent yield of 86% in just a three hour period. However, it was understood at this point that even though the yield and *exo*:*endo* ratios generated by **166** are higher than the commercially available compound **16**, the transformations were not carried out in an asymmetric manner and the reaction conditions were optimised for our catalysts.

With the success observed with the increased substitution of the α-heteroatom we turned our attention to altering substitution at the α′-centre.

4.3 α'-Substitution

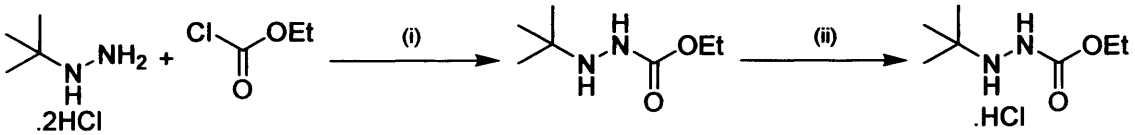
4.3.1 Design and synthesis of alternatives

With the increase in catalytic activity of the more highly substituted α-heteroatom within the acyclic catalysts series we looked at further substitution of the α'-centre in a continuation of our SAR studies. To this end we prepared the catalyst **184**.



184

Synthesis of **184** commenced from commercially available *tert*-butyl hydrazine dihydrochloride **177**. This was reacted with ethyl chloroformate **171** at 0 °C warming to room temperature after thirty minutes forming the desired catalyst precursor **185** albeit in a low yield of 10% (Scheme 43). Although a particularly poor yield we were able to obtain sufficient quantities of **185** for our needs after careful purification by chromatography. The hydrochloride salt, **185**, was formed from hydrochloric acid in ether in a good yield of 92%.



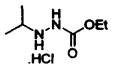
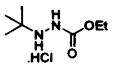
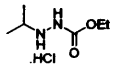
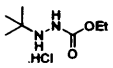
177 **171** **185** **184**

(i) CH_2Cl_2, $NaHCO_3$(aq) , 0 °C, 30 min., r.t., 24 hr., 10%. (ii) 2M hydrochloric acid in ether, r.t., 10 min., 92%.

(*Scheme* 43)

4.3.2 Catalysis: α'-centre substitution

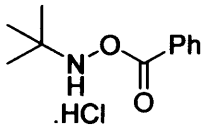
Catalyst **184** was subjected to our standard Diels-Alder reaction and compared to catalyst **22** (*Table* 21).

Entry	Catalyst[a]	Structure	Solvent[b]	Conversion[c] %	*exo*:*endo*[d]
1	**22**		i	90	65:35
2	**184**		i	22	65:35
3	**22**		ii	90	66:34
4	**184**		ii	35	66:34

(*Table* 21)

(a) Reactions were carried out at 25 °C for 24 hours with 10 mol% catalyst. (b) Solvent (i) refers to methanol/water (19:1) solvent. (ii) refers to methanol. (c) Conversions determined by ^{1}H NMR of crude reaction mixture. (d) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixture.

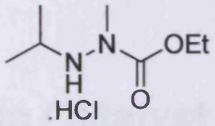
Increase in the steric bulk around the reactive nitrogen centre resulted in a significantly lower conversion within the Diels-Alder reaction. This is consistent with the findings of others within the group whereby *N*-*tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride **186** was inert, or very slow, to reaction with aldehydes at room temperature and required warming to 50 °C in order to bring about iminium ion formation.[120]



186

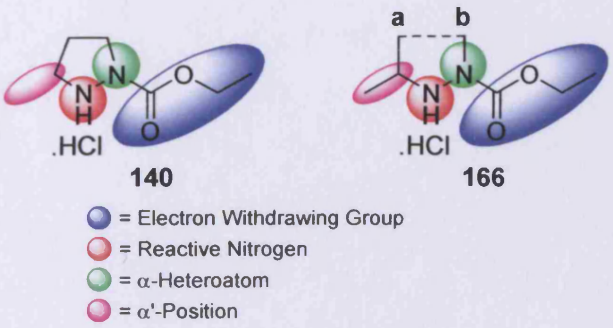
4.4 Reassessment

Investigations into the structure surrounding the acyclic series of catalysts had produced a variety of mixed results. In all cases, these results had provided essential information for the ongoing SAR studies of these molecules. The initial SAR between the five-membered heterocyclic catalysts and existing acyclic systems led us to investigate additional substitution on the acyclic skeleton helping to identify key functional groups for catalyst activity. In doing so we realised the acyclic catalyst **166** whose reactivity surpassed previous catalysts within the group.



166

Even though this work provided us with information regarding the acyclic series we still failed to understand the low reactivity observed from the five-membered heterocyclic catalyst series. The acyclic work provided evidence that an increase in steric bulk surrounding the reactive centre had, to a point, increased reactivity. If carbon **a** and **b** of **166** were connected this molecule would closely resemble that of **140**. Therefore we postulated the most highly contributing factors in the poor activity of **140** over **166** were the substitution of the α′-position and the bond angle of the reactive nitrogen centre itself. With this in mind we turned our attention towards further modifications in the cyclic series, the key driving force being to design and prepare a bench-mark catalyst for asymmetric iminium ion accelerated processes.



140 **166**

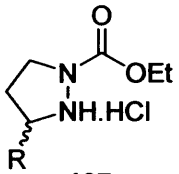
Chapter 5: Cyclic Catalyst Reinvestigation

5.1 Cycle Functionalisation

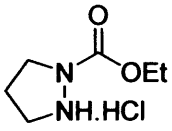
5.1.1 Cyclic substitution

With the excellent results observed from the modified acyclic catalysts, we decided to alter the five-membered cyclic catalysts based on observations in the acyclic series in an attempt to increase their activity. The SAR studies carried out had shown evidence that increased steric bulk at the α'-position generally gave greater conversion in the Diels-Alder reaction.[121] Commercially availably compounds utilised in the iminium ion catalysed Diels-Alder reaction, such as the imidazolidinone **16**, also exhibited greater substitution in this position. Addition of an alkyl group in this position could possibly increase the catalytic activity of our five-membered heterocyclic systems, perhaps through destabilisation of the iminium ion. To test this we targeted **187**, which was based on our best cyclic catalyst to date, **140**.

16

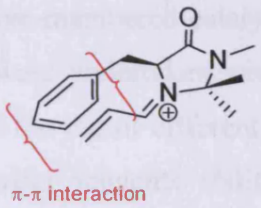


187



140

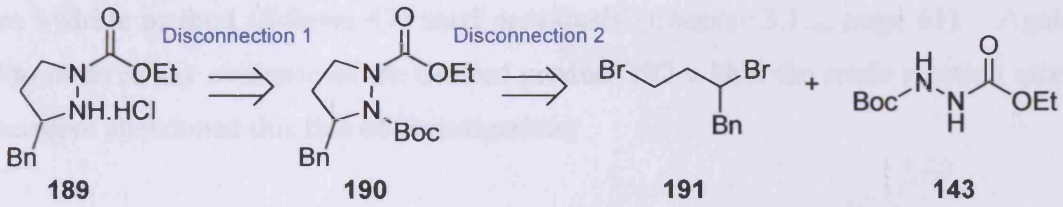
A literature review indicated the most effective group for this position was the benzyl functionality. The imidazolidinone of MacMillan **16** was a prime example of this as it had already been shown to produce excellent enantioselectivities within the Diels-Alder reaction (*See Chapter* 1). The asymmetric induction was thought to be enhanced by π-π interactions between the phenyl ring of the catalyst and the carbon-carbon double bond of the iminium ion **188** (*Figure* 25).[8] It was proposed that this interaction served to lower the energy of the intermediate and to block attack of the diene from one side of the molecule. We postulated that if we could introduce this benzyl subunit into the five-membered cyclic scaffold we could increase catalytic activity and provide a handle for asymmetric induction within our catalyst architecture.



188

(*Figure* 25)

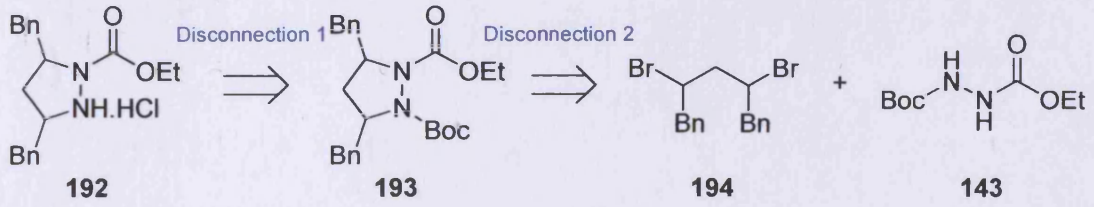
Our initial synthetic strategy to this catalyst series could allow for the incorporation of such a substituent (*Scheme* 44). However, this synthesis would require regiochemical control within disconnection 2. We thought there to be insufficient differentiation between the two nitrogen centres of the bis-substituted hydrazine **143** to allow for the required regiodiscrimination, and hence selective formation of **190**. In addition, separation of product isomers was thought to be too time consuming at this stage of the project.



189 **190** **191** **143**

(*Scheme* 44)

This was solved though the proposal of a C_2-symmetric dibrominated intermediate **194** (*Scheme* 45). This negated the issue of the regiochemical control within the cyclisation step, and led to a simpler synthesis of the target material **192** *via* deprotection of **193**.

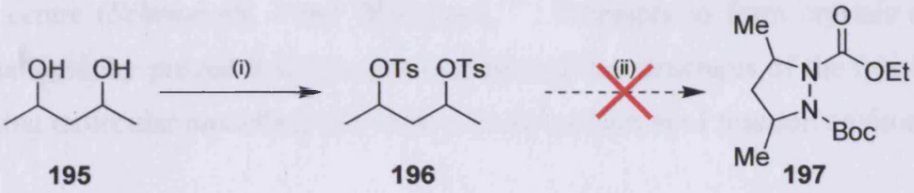


192 **193** **194** **143**

(*Scheme* 45)

Suitable dibrominated materials were not commercially available; therefore, we adopted an alternative synthetic strategy. We took a racemic mixture of 2,4-pentanediol **195** and reacted it with tosyl chloride in pyridine at 0 °C to give the bis-tosyl derivative **196** in 82% yield (*Scheme* 46).[122] We subsequently attempted to employ the phase-transfer conditions used

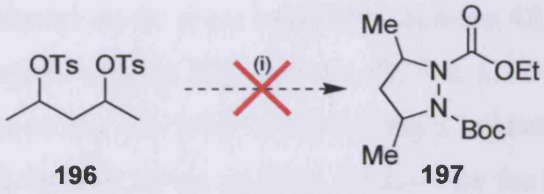
previously for the synthesis of the five-membered catalysts to form our desired ring. Many attempts at the preparation of **197** were undertaken with a range of reaction conditions to induce the cyclisation. This included the use of different concentrations of sodium hydroxide together with alternative phase-transfer reagents (NEt_4Br, NEt_4I). However, the target compound remained elusive with no evidence of its formation in any significant amount.



(i) TsCl, pyridine, 0 °C, 1 hr., r.t., 15 hr., 82%. (ii) **143**, NEt_4Br, PhMe, NaOH (aq 50% w/w), Δ, 2 hr., (no reaction).

(*Scheme* 46)

Together with this phase-transfer approach to cyclisation we also investigated the use of the sodium hydride method (*Scheme* 47) used previously (*Chapter* 3.1.2, *page* 61). Again, we failed to observe any evidence of the desired product **197** within the crude reaction mixtures. We therefore abandoned this line of investigation.



(i) **143**, NaH, DMF, Δ, 3hr.

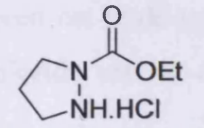
(*Scheme* 47)

5.1.2 Heterocyclic ring expansion

Our initial SAR studies had shown evidence for more effective catalysis of the Diels-Alder reaction with what appeared to be a less nucleophilic catalyst; **140** *vs.* **166**. This can be seen by measurement of the bond angle between the α′-carbon, the reactive nitrogen centre and the α-nitrogen centre (*Scheme* 48, **I** and **IV** *below*).[123] Attempts to form crystals suitable for X-ray crystallography proved fruitless so we examined the structures of the free base of our catalysts using molecular modelling to obtain a crude indication of reaction environment.

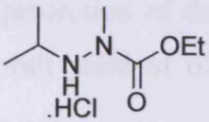
As expected, the bond angle of **140** (*Scheme* 48, **I**) was smaller than **166** (*Scheme* 48, **IV**); 104° *vs.* 116° respectively. We postulated that an increase in this bond angle within a cyclic structure could possibly produce a catalyst with activities approaching that of **166**. We believed it was necessary to investigate a cyclic architecture as the ultimate goal of this project was to produce a bench-mark asymmetric catalyst. The rigid structure of a cyclic system would reduce the number of possible conformations that the iminium ion could adopt which we believed was the key to the success of the imidazolidinone **16** described earlier.

Modelling of the six-membered cyclic homologue **198** (*Scheme* 48, **II**) showed a bond angle approaching that of our acyclic catalyst **166** (*Scheme* 48, **IV**); 111° *vs.* 116°. More over, this angle was almost the same as that observed in MacMillan's imidazolidinone **16** (*Scheme* 48, **III**). Therefore we targeted **198** and **199** as possible catalysts for the Diels-Alder reaction.



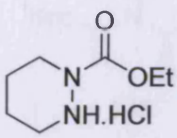
Low catalytic activity

140



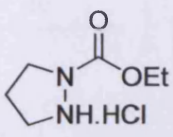
High catalytic activity

166

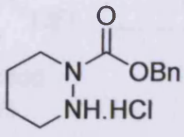


198

Analogous to

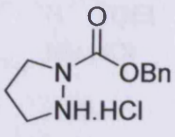


140

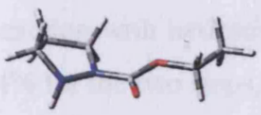
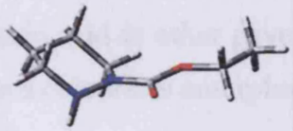
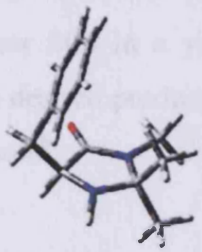
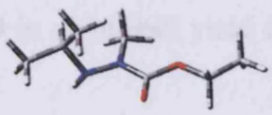
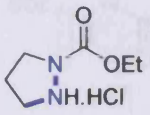
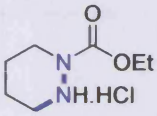
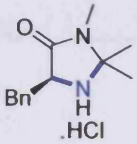
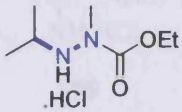


199

Analogous to



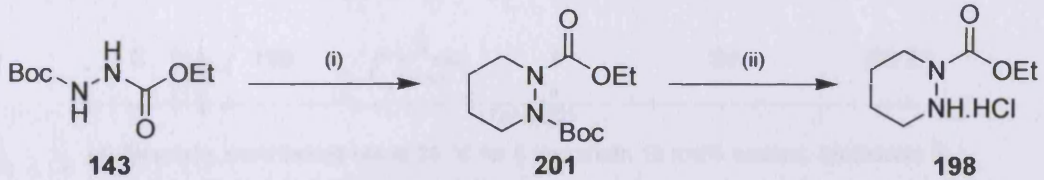
141

I	II	III	IV
			
 **140** Bond angle 104°	 **198** Bond angle 111°	 **16** Bond angle 110°	 **166** Bond angle 116°

(*Scheme* 48)

5.1.3 Six-membered heterocyclic catalyst synthesis

Synthesis of **198** was carried out in an analogous fashion to the five-membered analogue **140**. Phase-transfer conditions with tetraethylammonium bromide allowed for the cyclisation of the *N*-*tert*-butyl ester ethyl carbazate **143** with dibromobutane **200** in a yield of 79% after purification (*Scheme* 49). The synthesis of **201** resulted in a faster, cleaner reaction without the incessant need for monitoring by TLC that was necessary in the synthesis of the five-membered catalysts. This was attributed to the formation of a more thermodynamically stable six-membered cyclic structure. Reaction mixtures still displayed signs of degradation after extended reaction times (greater than ninety minutes); however, completion was reached within forty-five minutes even on scale-up. Deprotection of the nitrogen gave the desired catalyst **198** as its hydrochloride salt in an overall yield of 62% for the two steps, as a colourless amorphous solid.

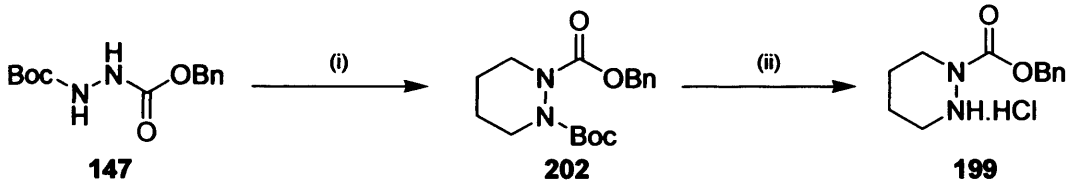


143 **201** **198**

(i) 1,4-Dibromobutane **200**, NEt_4Br, PhMe, NaOH (aq. 50% w/w), Δ, 45 min., 79%. (ii) 2M hydrochloric acid in ether, r.t., 24 hr., 78%.

(*Scheme* 49)

N'-tert-butyl ester benzyl carbazate **147** underwent a similar phase-transfer reaction with dibromobutane **200** to form the catalyst precursor **202** in a yield of 52% (*Scheme* 50). Reaction with hydrochloric acid in ether gave the desired product **199** in an overall yield of 44% for the two steps, as a colourless amorphous solid.



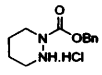
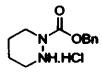
147 **202** **199**

(i) 1,4-Dibromobutane **200**, NEt_4Br, PhMe, NaOH (aq. 50% w/w), Δ, 1 hr., 52%. (ii) 2M hydrochloric acid in ether, r.t., 22 hr., 85%.

(*Scheme* 50)

5.1.4 Catalysis: Advanced investigations

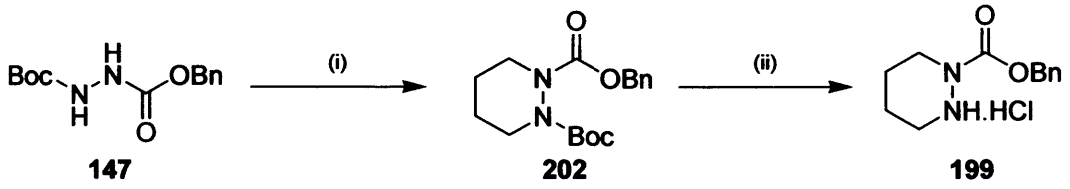
Catalysts **198** and **199** were submitted to the standard Diels-Alder reaction conditions for six hours (*Table* 22).

Entry	Catalyst[a]	Structure	Solvent[b]	Conversion[c] %	*exo*:*endo*[d]
1	**16**		i	86	60:40
2	**198**		i	96	67:33
3	**199**		i	96	69:31
4	**16**		ii	87	61:39
5	**198**		ii	99	68:32
6	**199**		ii	94	68:32

(*Table* 22)

(a) Reactions were carried out at 25 °C for 6 hours with 10 mol% catalyst. (b) Solvent (i) refers to methanol/water (19:1) solvent (ii) refers to methanol. (c) Conversions determined by ^1H NMR of crude reaction mixture. (d) *Exo*/*endo* ratios determined by ^1H NMR of crude reaction mixture.

N'-tert-butyl ester benzyl carbazate **147** underwent a similar phase-transfer reaction with dibromobutane **200** to form the catalyst precursor **202** in a yield of 52% (*Scheme* 50). Reaction with hydrochloric acid in ether gave the desired product **199** in an overall yield of 44% for the two steps, as a colourless amorphous solid.



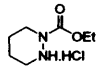
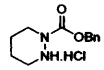
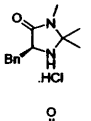
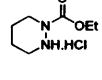
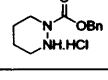
147 **202** **199**

(i) 1,4-Dibromobutane **200**, NEt_4Br, PhMe, NaOH (aq. 50% w/w), Δ, 1 hr., 52%. (ii) 2M hydrochloric acid in ether, r.t., 22 hr., 85%.

(*Scheme* 50)

5.1.4 Catalysis: Advanced investigations

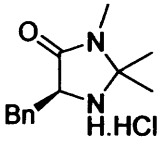
Catalysts **198** and **199** were submitted to the standard Diels-Alder reaction conditions for six hours (*Table* 22).

Entry	Catalyst[a]	Structure	Solvent[b]	Conversion[c] %	*exo*:*endo*[d]
1	**16**		i	86	60:40
2	**198**		i	96	67:33
3	**199**		i	96	69:31
4	**16**		ii	87	61:39
5	**198**		ii	99	68:32
6	**199**		ii	94	68:32

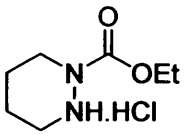
(*Table* 22)

(a) Reactions were carried out at 25 °C for 6 hours with 10 mol% catalyst. (b) Solvent (i) refers to methanol/water (19:1) solvent (ii) refers to methanol. (c) Conversions determined by ^{1}H NMR of crude reaction mixture. (d) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixture.

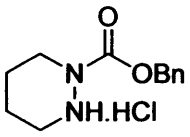
The results showed excellent conversions with both six-membered catalysts in methanol/water (19:1) and dry methanol. We obtained a near quantitative yield from catalyst **198** (*Table* 22, *entry* 5) in six hours similar to that seen from **166**. *Exo*:*endo* ratios were in favour of the *exo*-isomer as we had come to expect from the iminium ion catalysed Diels-Alder reaction. Both six-membered cyclic catalysts exhibited faster reaction rates when compared to the commercially available imidazolidinone **16** (*Table* 22, *entries* 2 & 5 and 3 & 6 *vs.* 1 & 4).



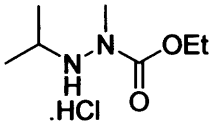
16



198



199



166

5.1.5 Catalyst performance limits

With quantitative results observed after six hours we wanted to examine the performance limit of **198** within the Diels-Alder reaction. Reaction times and catalyst loadings were reduced to three hours with a range of catalyst loading (1-10 mol%) (*Table* 23).

These results showed the limits of catalyst **198**. Interestingly, the rate of formation of products within the two different solvent systems was almost identical. From these results we could extrapolate showing near quantitative yields after four hours at 10 mol% catalyst loading in methanol.

With these results we had completed one of our initial targets for this project; to decrease reaction times and catalyst loadings within the Diels-Alder reaction through the incorporation of the α-effect within a cyclic structure. However, why the six-membered heterocyclic catalysts, with their suggested lower nucleophilicity, had produced greater catalytic activity than their five-membered analogues was unclear at this point.

Entry	Loading[a]	Solvent[b]	Conversion[c] %	*exo*:*endo*[d]
1	1 mol%	i	13	69:31
2	2 mol%	i	28	68:32
3	5 mol%	i	58	69:31
4	10 mol%	i	89	68:32
5	1 mol%	ii	14	70:30
6	2 mol%	ii	26	69:31
7	5 mol%	ii	50	68:32
8	10 mol%	ii	89	68:32

(*Table* 23)

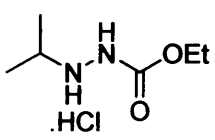
(a) Reactions were carried out at 25 °C for 3 hours with catalyst **198** at the designated loading. (b) Solvent (i) refers to methanol/water (19:1) solvent (ii) refers to methanol. (c) Conversion determined by ^{1}H NMR of crude reaction mixtures. (d) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixtures.

5.2 Catalyst Reclamation

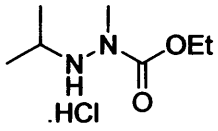
We required confirmation of the stability of the catalyst under the Diels-Alder reaction conditions. It was thought possible that the five-membered catalysts could, in theory, be more active than the six-membered systems with the low conversions observed due to their decomposition under the reaction conditions. Proving the integrity of catalysts after completion of the reaction would validate previous results and show conversions found to be a correct indication of individual catalyst activity. This also served as evidence for the ability of the catalysts to be recycled and reused.

5.2.1 Catalyst cross-section

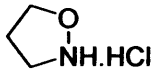
We included a variety of catalysts synthesised to date from both the cyclic and acyclic series. This formed a cross-section of all catalysts prepared and our chosen standard, **16**, for which to test the integrity of architectural motifs under the catalytic reaction conditions. The catalysts chosen were:



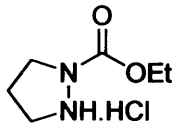
22



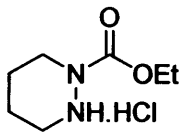
166



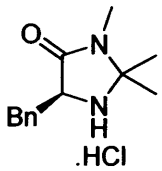
136



140



198

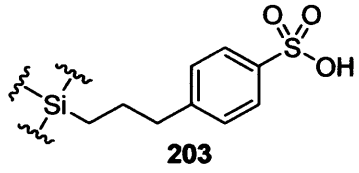


16

5.2.2 Reclamation procedure

The recovery of the catalysts was carried out with Varian Mega Bond Elut® SCX columns. These columns are used throughout industry for both chromatography and solid phase extractions. They contain solid phase sulfonic acids **203** (*Figure* 26) which sequester basic compounds allowing for their separation from mixtures. Subsequent washing of these columns with a basic solution (usually ammonia dissolved in methanol) liberates the captured molecules, in our case, the catalysts. The selected catalysts were subjected to the standard Diels-Alder reaction conditions for a period of twenty-four hours. After this time the volatiles were removed under reduced pressure and the crude reaction mixtures were diluted with methanol. This was then passed through the Varian Mega Bond Elut® SCX columns which

were subsequently washed with methanol to remove impurities. A solution of ammonia dissolved in methanol was then passed through the column removing the sequestered catalyst. Volatiles were removed from these washings under reduced pressure and the resulting mixtures were reacidified with hydrochloric acid dissolved in ether. Attempts to recover the catalyst after the hydrolysis step, which was always performed on the crude reaction mixture of the Diels-Alder reaction to hydrolyse any acetals formed on the reaction, proved ineffective. This was thought most likely due to the strongly acidic conditions employed leading to the decomposition of catalysts.



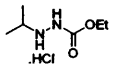
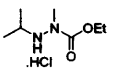
203

(*Figure* 26)

Molecular structure of Varian Mega Bond Elut® SCX columns.

5.2.3 Reclamation results

The samples were recharacterised with resulting data matching that of the initial catalysts. Having proved the integrity of samples we calculated their retrieval percentages (*Table* 24).

Entry	Catalyst	Structure[a]	Mass in mg	Mass out mg	Recovery %
1	**22**		34.8	31.0	89
2	**166**		37.5	35.3	94
3	**136**		20.9	18.5	89
4	**140**		34.4	29.4	85
5	**198**		37.1	34.1	92
6	**16**		48.6	44.2	91

(*Table* 24)

(a) Reactions were carried out at 25 °C for 24 hours in methanol with 10 mol% catalyst.

Excellent recovery percentages were observed for all catalysts. This was evidence for the stability of the catalysts under the Diels-Alder reaction conditions employed. Therefore, the poor conversions within the Diels-Alder reaction from the five-membered cyclic catalysts

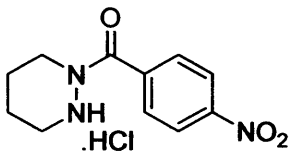
could be attributed to their structural characteristics and not their decomposition within the reaction mixture. These recovery results also showed the possibility for the catalysts to be recovered and recycled before hydrolysis of the reaction mixtures.

5.3 Electron Withdrawing Group Effects

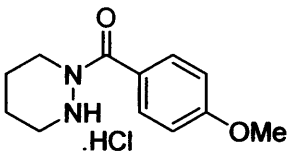
5.3.1 Target compounds

Previous SAR observations of the acyclic systems had suggested that the electron withdrawing group attached to the α-heteroatom could influence catalytic activity (*Section* 4.2.4, *page* 83). We decided to investigate this further by examining a series of compounds containing a variety of electron withdrawing groups. From the work within the acyclic series it was seen that catalysts based on benzoic hydrazide closely mimicked the activity of carbamic esters based structures (*Section* 4.2.2, *page* 81, *table* 18, *entries* 1 & 3). Due to this we included a series of substituted benzoic hydrazides restrained within a cyclic structure. This series comprised of non-substituted **204**, the *p*-nitro **205** and the *p*-methoxy **206** benzoic hydrazides. This gave us a range of electron-withdrawing, -donating and neutral aromatic compounds. In addition to these we included a semicarbazide **207**, a thiosemicarbazide **208** together with **209** the thionated product of our most active catalyst to date.

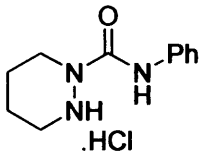
204



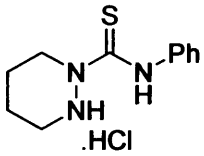
205



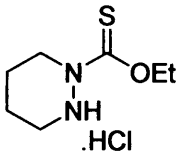
206



207



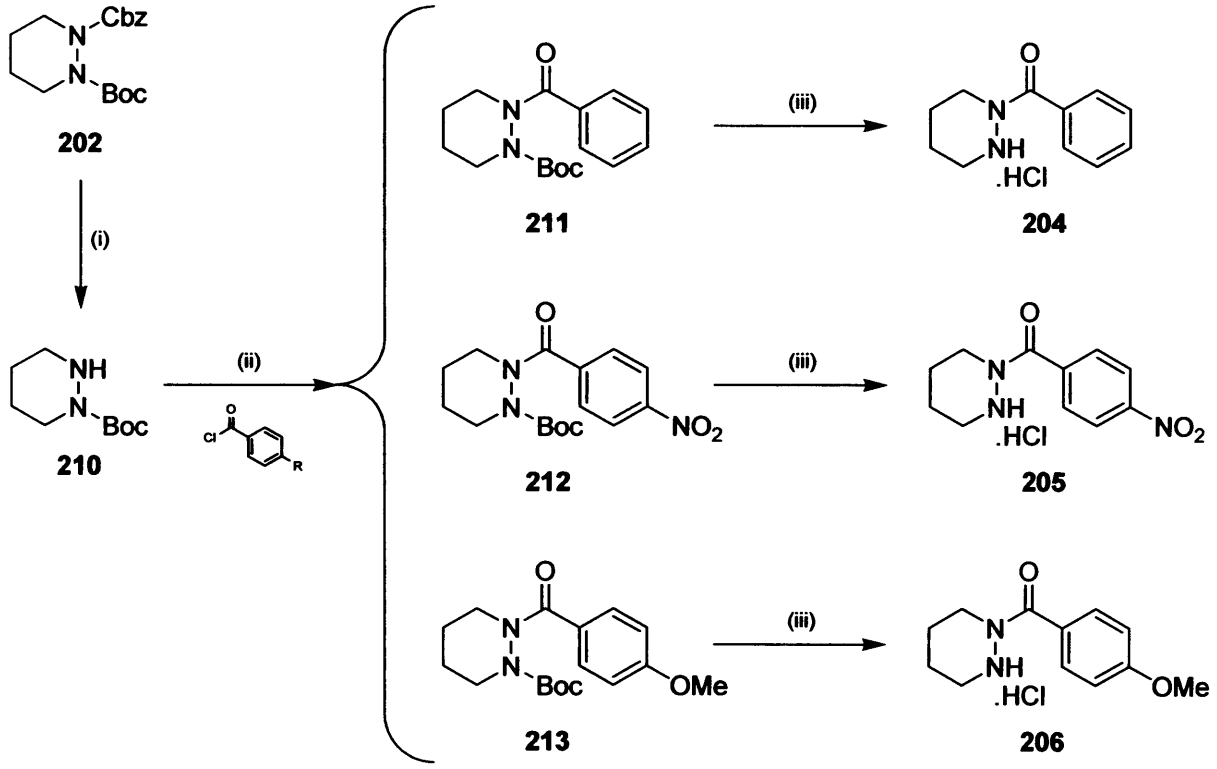
208



209

5.3.2 Catalyst syntheses

Catalysts **204, 205** and **206** were synthesised from a previously prepared intermediate **202** (*Scheme* 51). Deprotection of the carbobenzyloxy moiety of **202** by hydrogenation with palladium on carbon under an atmosphere of hydrogen resulted in *tert*-butyl piperazine-1-carboxylate **210** in a yield of 89% after chromatography. This was subsequently reacted with a series of substituted benzoyl chlorides forming the 1,2-bis-substituted piperazines, **211, 212** and **213,** in yields of 67-94% after purification. Dissolving these compounds in hydrochloric acid in methanol deprotected the nitrogen centre resulting in the target catalysts **204, 205** and **206,** in overall yields from **202** of 59-79%.

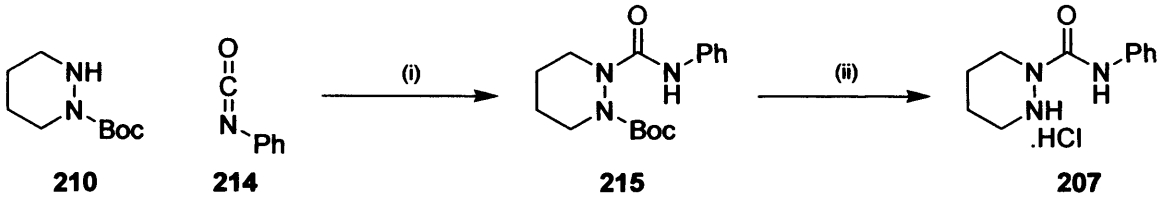


(i) Pd/C (1 mol%), H_2(g), EtOH, r.t., 24 hr., 89%. (ii) CH_2Cl_2, $NaHCO_3$(aq), r.t., 18-24 hr., **211** 82%, **212** 94%, **213** 67%. (iii) 2.2M hydrochloric acid in methanol, r.t., 24 hr., **204** 96%, **205** 94%, **206** 96%.

(*Scheme* 51)

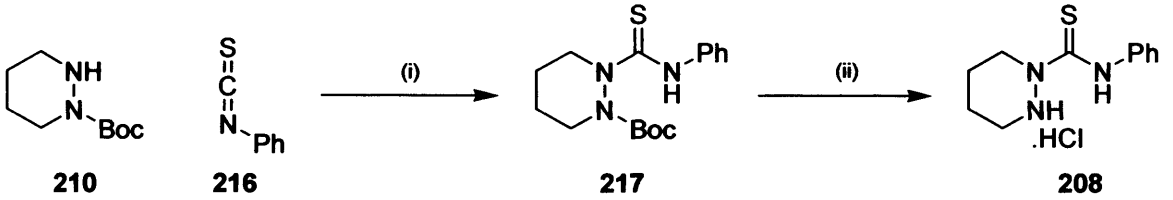
Catalysts **207** and **208** were formed from the same intermediate **210** (*Scheme* 52). Compound **210** was reacted with phenyl isocyanate **214** and phenyl isothiocyanate **215** in dichloromethane at room temperature. Catalyst precursors **215** and **217** were formed within four hours in yields of 89% and 79% respectively. Removal of the Boc protection group was

carried out in an analogous fashion to previous examples with hydrochloric acid in methanol forming the hydrochloride salts **207** and **208** in overall yields of 85% and 65% from precursor **210**.



210 **214** **215** **207**

(i) CH_2Cl_2, r.t., 3 hr., 89%. (ii) 2.2M hydrochloric acid in methanol, r.t., 20 hr., 96%.

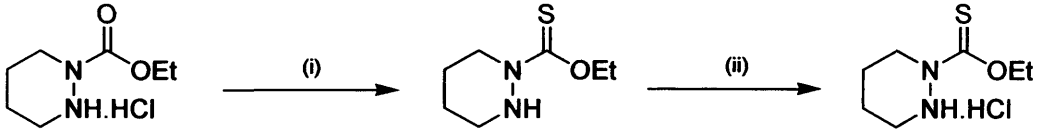


210 **216** **217** **208**

(i) CH_2Cl_2, r.t., 4 hr.,79%. (ii) 2.2M hydrochloric acid in methanol, r.t., 24 hr., 82%.

(*Scheme* 52)

Catalyst **209** was synthesised by the thionation of compound **198** with Lawesson's reagent in toluene at reflux for four hours (*Scheme* 53). This formed **218**, in a yield of 84% after purification, as an extremely viscous oil proving exceedingly difficult to manipulate. Formation of its hydrochloride salt with hydrochloric acid in methanol gave **209** as a colourless amorphous solid which was much easier to handle in an overall yield of 74% for the two steps.



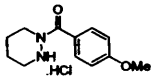
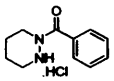
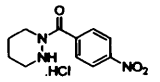
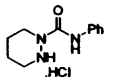
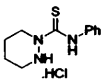
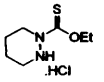
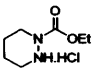
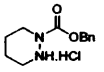
198 **218** **209**

(i) $NaHCO_3$ (aq), then Lawesson's reagent, PhMe, Δ, 4 hr., 84%. (ii) 2.2M hydrochloric acid in methanol, r.t., 5 min., 88%.

(*Scheme* 53)

5.3.2 Catalyst testing

With secure synthetic approaches to the six target compounds we submitted them to the Diels-Alder reaction for twenty-four hours in methanol. The results can be seen below (*Table* 25).

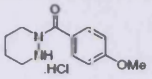
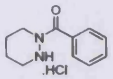
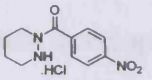
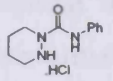
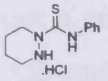
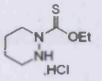
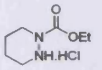
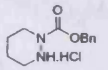
Entry	Catalyst[a]	Structure	Time hr	Conversion[b] %	*exo*:*endo*[c]
1	**206**		24	90	65:35
2	**204**		24	86	67:33
3	**205**		24	81	65:35
4	**207**		24	22	43:57
5	**208**		24	27	32:68
6	**209**		24	76	67:33
7	**198**		24	>99	68:32
8	**199**		24	>99	68:32

(*Table* 25)

(a) Reactions were carried out at 25 °C in methanol with 10 mol% catalyst. (b) Conversions determined by ^{1}H NMR of crude reaction mixture. (c) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixture.

The results showed the impact the alternative electron withdrawing groups could have on the catalytic activity of the cyclic architecture. The semicarbazide **207** and thiosemicarbazide **208** catalysts gave poor conversions and both favoured the *endo*-isomer (*Table* 25, *entries* 4 & 5). The thionated catalyst **209** produced a good conversion, however, this was much lower than its oxygen analogue **198** (*Table* 25, *entries* 6 *vs.* 7). The benzoic hydrazide based systems, **204**, **205** and **206**, produced good conversions with *exo*:*endo* ratios of 2:1 favouring *exo*-selectivity. Increasing the electron density on the carbonyl also appeared to increase the relative conversions (*Table* 25, *entries* 3, 2 & 1).

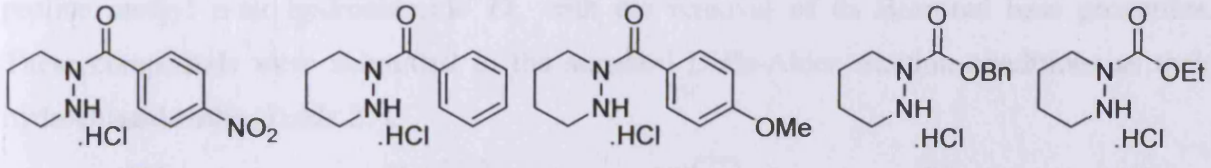
Catalysts were reaching almost quantitative conversions within these reactions; therefore, they were resubmitted to the Diels-Alder reaction with a reduced time of six hours to further examine their activities (*Table* 26).

Entry	Catalyst[a]	Structure	Time hr	Conversion[b] %	*exo*:*endo*[c]
1	**206**		6	67	66:34
2	**204**		6	59	64:36
3	**205**		6	32	62:38
4	**207**		6	17	50:50
5	**208**		6	15	32:68
6	**209**		6	35	69:31
7	**198**		6	99	68:32
8	**199**		6	94	68:32

(*Table* 26)

(a) Reactions were carried out at 25 °C in methanol with 10 mol% catalyst. (b) Conversions determined by ^{1}H NMR of crude reaction mixture. (c) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixture.

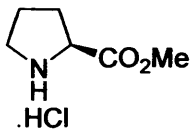
The relative order of activity within the series remained constant with the reduced reaction times. Again, the semicarbazide **207** and thiosemicarbazide **208** catalysts gave poor yields favouring the *endo*-isomer (Table 26, entries 4 & 5). Examination of the other catalysts within this six-membered heterocyclic series displayed a prominent pattern in activities. The more electron rich the carbonyl of the electron withdrawing group the greater the conversion to products within the Diels-Alder reaction (*Table* 25, *entries* 1-3, 7 & 8). This finding was in keeping with the observed trends within the acyclic series, however, it did not explain the reduced activity within the semicarbazide and thiosemicarbazide catalysts, **207** and **208**.



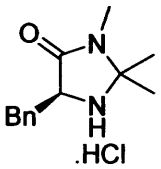
5.4 Development of Commercially Available Catalysts

5.4.1 Catalyst analysis

Throughout this work we had been developing a SAR study of the cyclic and acyclic catalyst architectures. As detailed throughout the work, the main catalysts employed within the literature for the Diels-Alder transformation are proline methyl ester **12** and MacMillan's imidazolidinone **16**. We carried out a critical examination of these structures, based on the information gathered from our SAR studies, for features believed to enhance their activity towards iminium ion catalysed processes.

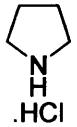


12

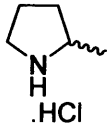


16

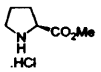
Initially we investigated **12** due to it containing less functionality compared to **16**. The proposed mechanisms of a variety of enamine catalysed processes have been published and are well accepted within the chemical community, examples of which include intramolecular proton transfers (*Section* 1.5.1, *figure* 8, *page* 21). We therefore postulated that iminium ion formation, which forms the initial step in the formation of an enamine, could also benefit from a localised proton source within the catalyst structure. An example of this can be seen in the ester functionality of **12**. To investigate the requirement of this ester moiety within the catalyst we examined two five-membered heterocycles as prospective catalysts; pyrrolidine hydrochloride **219** and 2-methyl pyrrolidine hydrochloride **220**, both as their hydrochloride salts. 2-Methyl pyrrolidine was included to crudely simulate the sterics of the 2-position of proline methyl ester hydrochloride **12**, with the removal of its Brønsted base properties. These compounds were submitted to the standard Diels-Alder reaction conditions as their hydrochloride salts (*Table* 27).



219



220

Entry	Catalyst[a]	Structure	Conversion[b] %	*exo*:*endo*[c]
1	**219**		trace	n.d.
2	**220**		trace	n.d.
3	**12**		62	70:30

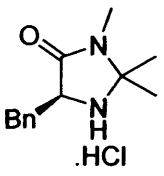
(*Table* 27)

(a) Reactions were carried out at 25 °C for 6 hours with 10 mol% catalyst. (b) Conversions determined by ^{1}H NMR of crude reaction mixture. (c) *Exo*/*endo* ratios determined by ^{1}H NMR of crude reaction mixture.

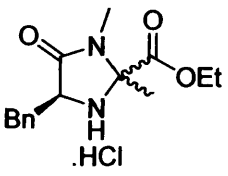
Both pyrrolidine hydrochloride **219** and 2-methyl pyrrolidine hydrochloride **220** failed to give any measurable quantity of Diels-Alder products under the reaction conditions. This suggested the incorporation of Brønsted base in the β–position to the reactive nitrogen centre could increase reactivity within this particular iminium ion catalysed process. We therefore concluded this carbonyl must be crucial for catalyst activity.

Interestingly, MacMillan's oxazolidinone **16** contains a carbonyl group β– to the reactive nitrogen centre, however, its location and the constraint within the cyclic structure precludes its direct participation in iminium ion formation.

We was speculated that the presence of a Brønsted base increased catalytic activity by acting as a proton shuttle within the iminium ion formation step of the Diels-Alder catalytic cycle. We wanted to examine the effect of the incorporation of a more accessible carbonyl moiety within the imidazolidinone structure to see if it would increase the catalytic activity of this commercially available compound. Compound **221** was initially targeted for this investigation.



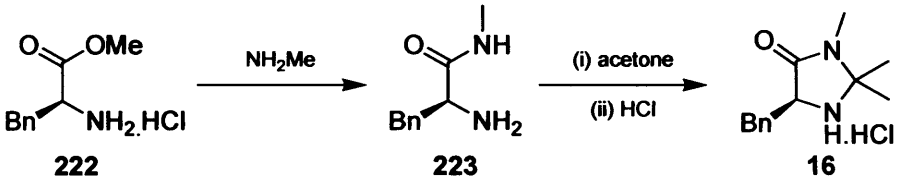
16



221

5.4.2 Catalyst modification

Synthesis of **221** was attempted in an analogous manner to the literature preparation of the imidazolidinone **16** (*Scheme* 54).[7]

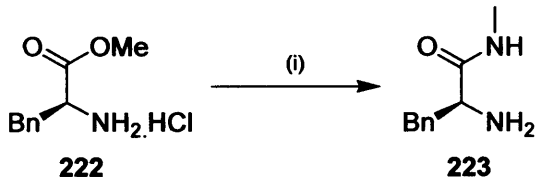


222 **223** **16**

Overall yield of 59%.

(*Scheme* 54)

(*S*)-Phenylalanine methyl ester hydrochloride **222** was stirred in a solution of methylamine in ethanol for sixteen hours at room temperature (*Scheme* 55). The volatiles were removed under reduced pressure and the resulting crude mixture was treated with aqueous sodium hydrogen carbonate. Extraction of the aqueous phase afforded **223** as a colourless solid in a yield of 71%, with no purification required.

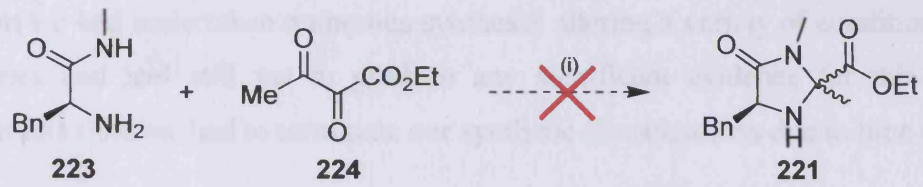


222 **223**

(i) NH_2Me in ethanol, r.t., 16 hr., 71%.

(*Scheme* 55)

Synthesis of **221** was attempted with the reaction of **223** with ethyl pyruvate **224** (*Scheme* 56) under analogous conditions to the formation of **16,** which we had carried out previously. However, substitution of acetone for ethyl pyruvate **224** failed to result in the desired product, **221**. Numerous attempts were made to access the target **221** under a variety of reaction conditions. Extended reaction times produced an intractable mixture of compounds while lower temperatures returned only starting materials. Alternative solvents gave similar results. Dichloromethane, tetrahydrofuran and *iso*-propanol failed to return the desired product. Attempts to azeotrope the water produced within the reaction with a Dean-Stark apparatus also failed to drive the reaction forward.

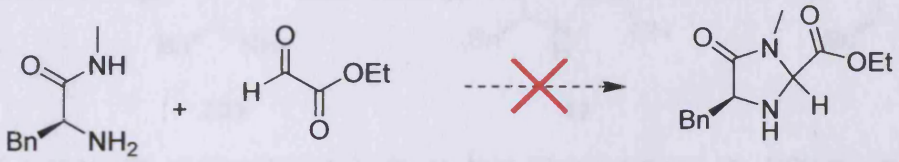


223 224 221

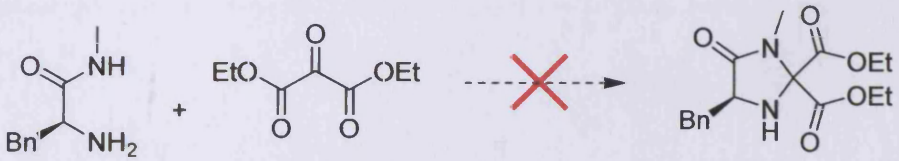
(i) Solvent, *p*TSA, Δ, 1-24 hr.

(*Scheme* 56)

Simultaneously, we examined the use of the alternative electrophiles ethyl glyoxalate **225** and diethyl ketomalonate **227** (prepared in two steps from diethylmalonate) (*Scheme* 56). Similar results to ethyl pyruvate **224** were obtained with no definitive evidence for desired products **226** and **228**.



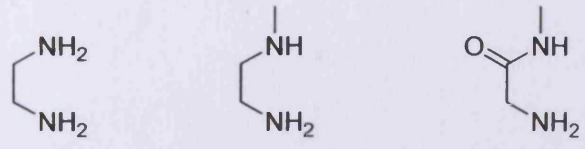
223 225 226



223 227 228

(*Scheme* 56)

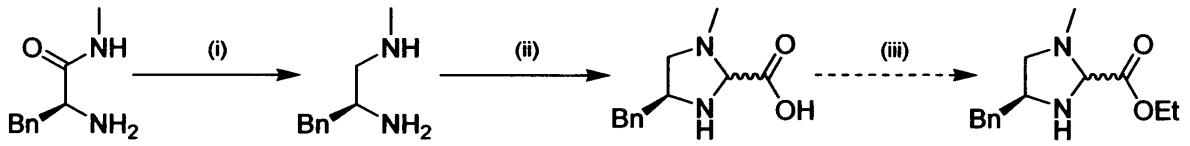
Subsequent to failed attempts to synthesise compounds **221**, **226** and **228**, we removed surplus substitution from **223** in an attempt to discover conditions for the cyclisation. We examined 1,2-ethanediamine **229**, *N*-methyl-1,2-ethanediamine **230** and 2-amino-*N*-methylacetamide **231**. Frustratingly, again no evidence for the desired products was found.



229 230 231

To this point we had undertaken numerous syntheses altering a variety of conditions, solvents and substrates and had still yet to produce any significant evidence for this cyclisation reaction. At this time we had to terminate our synthetic investigations due to time constraints.

Future synthetic strategies towards **221** could utilise the methodology of Jørgensen in his synthesis of **42**.[30] Jørgensen reduced the amide of **232** with lithium aluminium hydride and condensed the resulting diamine **233** with glyoxylic acid forming **42** (Scheme 57). It is entirely feasible that esterification of **42** would lead to **234** which could be used as its hydrochloride salt to examine this theory.



232 **233** **42** **234**

(i) $LiAlH_4$, THF, Δ, 16 hr., 92%. (ii) Glyoxylic acid, CH_2Cl_2, r.t., 15 hr. (iii) (prospective) H_2SO_4, EtOH, then 2M hydrochloric acid in ether.

(*Scheme* 57)

Chapter 6: Catalytic Cycle Investigation

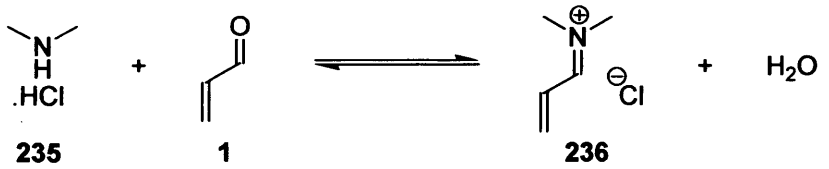
6.1 Stepwise Analysis of the Iminium Ion Catalysed Diels-Alder Reaction

Throughout this work, an ongoing investigation into the formation of iminium ions through theoretical calculations had been carried out in an associated project with Dr. James Platts and Gareth Evans. Separately, we have undertaken initial studies towards the proposed catalytic cycle for the iminium ion catalysed Diels-Alder reaction. A summary of our findings to date can be found below.

6.1.1 Theoretical Calculations

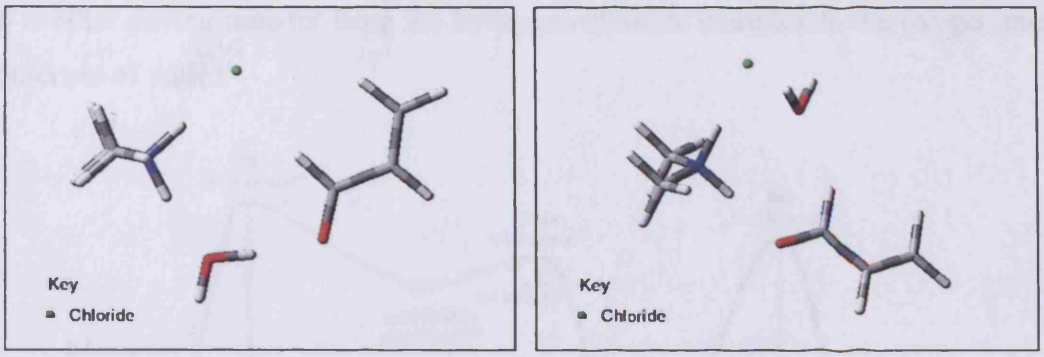
Theoretical calculations by Evans were directed at establishing a model for the formation of the active iminium ion. The aim of this ongoing study was to ultimately develop a predictive scale for amine reactivity to direct future synthetic studies.

Initially, a realistic model of the formation of an iminium ion was created. This was between dimethylamine hydrochloride **235**, acrolein **1** and a single molecule of water enclosed within a spherical dielectric approximation of methanol solvation (*Scheme* 58). Optimisation of this model was carried out from various positions which formed a number of stable conformations of very similar energy with negligible barriers to inter-conversion. Two such starting conformations are shown below, which differ in energy by only 2.9 kJ mol^{-1} (*Figure* 27).



235 **1** **236**

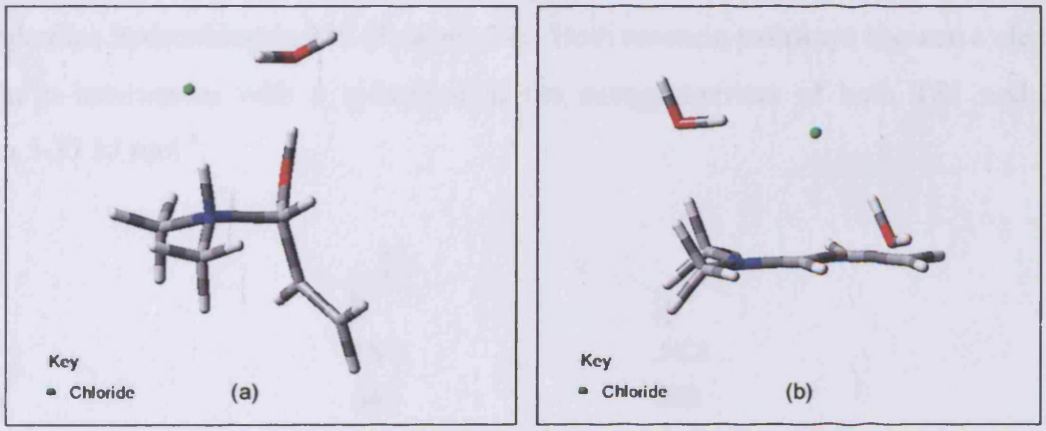
(*Scheme* 58)



Two possible reaction geometries.

(*Figure* 27)

Evans found a second stable structure, higher in energy than the reactant complex by 10 kJ mol^{-1} (*Figure* 28, **a**). In this aminol species, the first nitrogen-carbon bond of the iminium ion had formed and a proton had been transferred from the amine to the hydroxyl group (*Figure* 28, **a**). A third low energy minimum, corresponding to the iminium ion product was located at 40 kJ mol^{-1} above the reactants (*Figure* 28, **b**).

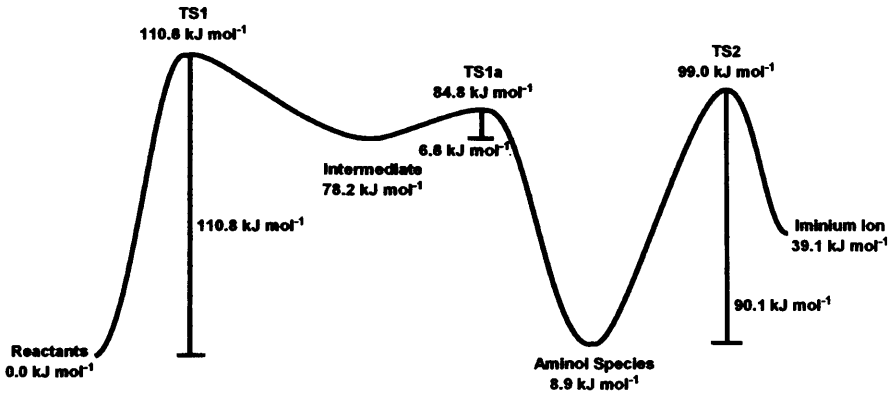


(**a**) Optimised geometry of aminol and (**b**) iminium ion product.

(*Figure* 28)

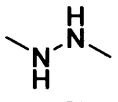
Evans located transition states connecting these three minima using the QST3 approach in Gaussian '03, specifying reactants and product along with an estimation of the transition states obtained from relaxed potential energy surface (PES) scans. Two transition states were found between the initial reactants and the aminol species (*Scheme* 59). TS1 links the free reactants with the aminol species. The sizable energy barrier of 110.8 kJ mol^{-1} was associated with a proton transfer from the amine to the chloride. TS2 was found to be the elimination of water from the iminium ion with a proton transfer from the amine to the oxygen with an associated energy barrier of 90.1 kJ mol^{-1}. The third transition state, TS1a, was essentially negligible when compared to TS1 and TS2. Its energy barrier was only 7 kJ mol^{-1} and was

linked to another proton transfer from the hydrogen chloride complex to the oxygen mediated by the molecule of water.

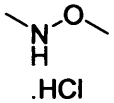


(*Scheme* 59)

Evans applied the same method to two α-nucleophiles; *N,N'*-dimethylhydrazine hydrochloride **237** and *N,O*-dimethylhydroxylamine hydrochloride **238** which gave similar PES to that of dimethylamine hydrochloride **235** (*Scheme* 59). Both reaction pathways showed a clear effect from the α-heteroatom with a reduction in the energy barriers of both TS1 and TS2 of between 5-35 kJ mol^{-1}.



237



238

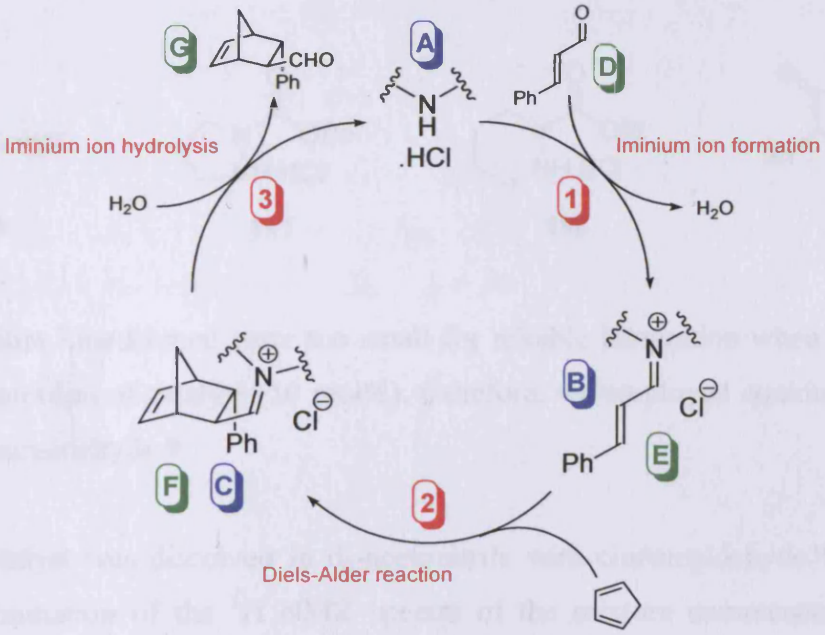
These theoretical investigations revealed the importance of water within reactions where the catalyst did not possess an accessible β-carbonyl to the reactive nitrogen centre to help facilitate iminium ion formation. This provided evidence for the previous suggestion, within the experimental work, that the carbonyl group is intimately involved in iminium ion formation possibly as a proton shuttle. Work is currently ongoing in this investigation.

6.1.2 Catalytic Cycle Analysis

During the evolution of the catalyst scaffolds and our investigations into the SAR of the catalysts we also sought to develop a better understanding of the catalytic cycle. Although the mechanistic rationale provided by MacMillan to explain his observed reactivities was compelling, there was still no absolute proof of the reaction pathway.

With this in mind we also carried out a series of preliminary studies to investigate the individual steps of the reaction and the catalytic cycle as a whole. It was hoped that this would complement and augment the on-going theoretical calculations as well as provide a method for further catalysts design.

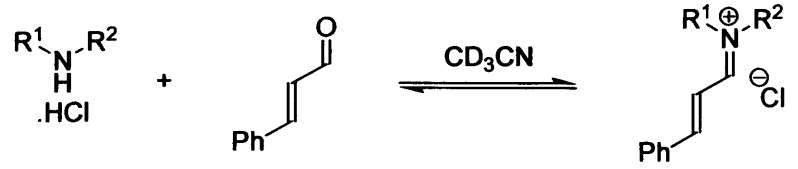
Examination of the proposed iminium ion catalysed Diels-Alder reaction showed three main steps (Mechanism 7); initial iminium ion formation **1**, the carbon-carbon bond forming event **2**, and the hydrolysis of the pro-Diels-Alder adduct regenerating the catalyst **3**. These three steps link three discrete intermediates for the amine, **A**, **B** and **C**, and four discrete possibilities for the α,β-unsaturated carbonyl, **D-G**. Our initial idea was to examine each of the steps within the catalytic cycle (steps **1-3**) to obtain inroads to a full mechanistic understanding of the reaction process through NMR and UV techniques.



(*Mechanism 7*)

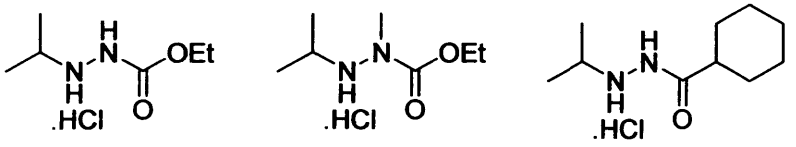
6.1.2.1 Step 1: Iminium Ion Formation

Initially we investigated the formation of the iminium ion between an amine catalyst **3** and cinnamaldehyde **9** (*Scheme* 60). It has previously been reported that this was the rate determining step of the catalytic cycle.[24] If this was correct, it would be advantageous to discover the time taken to reach the equilibrium between the free catalyst **3** and the iminium ion **239**, and also the position of this equilibrium. This was carried out initially through ^{1}H NMR studies of catalysts (shown below) with cinnamaldehyde **9**. Throughout this work we employed deuterated acetonitrile as opposed to methanol so as to remove the possibility of forming the dimethyl acetal of cinnamaldehyde upon reaction with the solvent.



3 **9** **239**

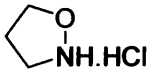
(*Scheme* 60)



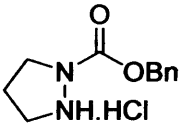
22

166

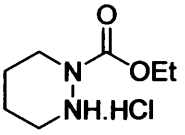
183



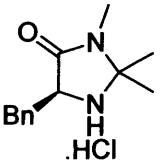
136



141



198



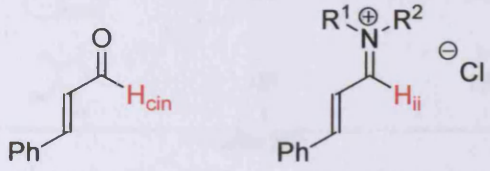
16

Levels of iminium ions formed were too small for reliable integration when working at our standard concentration of catalyst (10 mol%); therefore, we employed equimolar amounts of amine and cinnamaldehyde **9**.

The desired catalyst was dissolved in d_3-acetonitrile with cinnamaldehyde **9** added in one aliquot. Determination of the ^{1}H NMR spectra of the mixture commenced immediately. Acquisition of the ^{1}H NMR spectra was repeated after thirty minutes, two hours and twenty-

four hours. It was found that the ^{1}H NMR spectra for each catalyst/iminium ion mixture was the same regardless of the time it was left to react. This led us to believe that equilibria of the systems tested were reached within the time taken to acquire a ^{1}H NMR spectra, *c.a.* 7 minutes. This was deemed important as the formation of the iminium ion was assumed to be the rate determining step for this reaction with literature examples of this reaction allowing the catalyst and α,β-unsaturated carbonyl compound to stir for five minutes prior to the addition of the diene.

Equilibrium positions for the formation of iminium ions were calculated from the integration of the aldehyde proton signal of cinnamaldehyde **9** compared to that of the equivalent proton within the iminium ion (*Figure* 29).

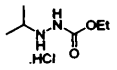
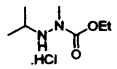
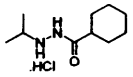


9 **239**

(*Figure* 29)

H_{cin} appeared at δ9.68 in the ^{1}H NMR spectra, whereas H_{ii} for the catalysts listed above (*page* 116) appeared between δ9.00-9.93. Analysis of the position of H_{ii} in the chemical shift will be dealt with in the next section (*Section* 6.1.2.2, *page* 119). The results of the equilibrium positions and chemical shift of the iminium ions can be seen below (*Table* 28).

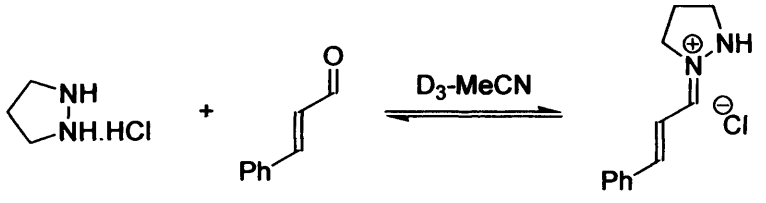
The results obtained from these initial studies failed to provide any significant indication that the position of the equilibrium between the free catalyst and iminium ion was related to the observed conversions within the Diels-Alder reaction. The solvent systems for the reaction conversions and equilibria positions were different, however, it was believed that the relative activities of the catalysts would remain constant.

Entry	Catalyst	Structure	Conversion[a] %	Equilibrium Position[b] % iminium ion	Chemical Shift of iminium ion[b] δ
1	136		3	62	9.08
2	22		90	46	9.12
3	166		98	21	n.d.
4	183		86	12	9.02
5	141		28	20	9.00
6	198		99	59	9.93
7	16		98	13	9.30

(*Table* 28)

(a) Conversion under our standard reaction conditions; carried out in methanol at 25 °C for 6 hours with 10 mol% catalyst. (b) Determined by ^{1}H NMR in CD_3CN.

Initial studies into the use of ultra-violet (UV) spectrometry to follow the Diels-Alder reaction were undertaken. Here, **137** was reacted with cinnamaldehyde **9** in equimolar quantities in acetonitrile (*Scheme* 61). The UV spectra displayed two peaks; one with a maximal absorption of 282 nm which corresponded to cinnamaldehyde **9**, the second at 342 nm related to the iminium ion **240**. Low concentrations were required due to the high extinction coefficients of the reactants, *c.f.* 0.15 mM *vs.* 0.95 M used for catalytic runs. At this time we were unable to quantify alternative catalysts as conditions for the UV analysis did not reflect closely enough those within the Diels-Alder test reactions. However, it was believed that UV analysis of the Diels-Alder reaction would be the most effective way investigating the catalytic cycle. This work is continuing within the group.



137 **9** **240**

(*Scheme* 61)

6.1.2.2 Step 2: Diels Alder Reaction

In order to study the second step of the proposed Diels-Alder catalytic cycle, the carbon-carbon bond forming event itself, we tried to form and isolate the pure iminium ion of a series of cyclic and acyclic catalysts. These reactions were carried out with equimolar amounts of amine catalyst and cinnamaldehyde **9** and in a variety of solvents. These solvents consisted of acetonitrile and dichloromethane both of which were left to stand over 3 Å molecular sieves. Trimethyl orthoformate was also employed as a dehydrating agent to drive the reaction to completion as was toluene with a Dean-Stark apparatus. Reactions were also carried out neat.

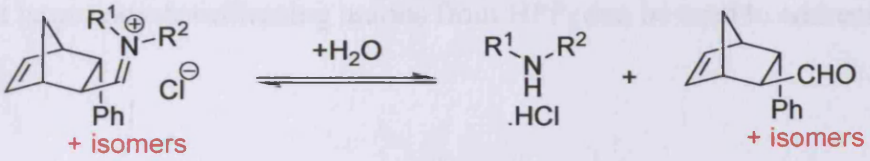
High levels of the desired iminium ions appeared in reaction mixtures, however, all attempts to produce 100% iminium ion in solution failed. Also, all methods to isolate iminium ions resulted in intractable mixtures of compounds. This is probably due to the high reactivity to moisture frustrating our work. It is currently thought that the use of alternative acid salt, such as HPF_6, to increase the size of the counter anion could be employed to form pure iminium ions, and recent work within our laboratories has shown this to be the case.

Following on from the ^1H NMR work carried out in the examination of step **1** the position of the chemical shift of proton H_{ii} (*Figure* 29, *page* 117) within the iminium ion was compared to the Diels-Alder conversion of the associated catalyst. This was carried out to discover if there was a correlation between the chemical shift of the protons within the iminium ion and the observed conversion. The theory behind this was that the chemical shift, and therefore the degree of deshielding within the molecule could have an effect on the LUMO of the carbon-carbon double bond, which facilitates the Diels-Alder reaction. Unfortunately, no correlation was found, however, investigation into the energy levels of the LUMO's within various iminium ions related to the overall conversion from reaction is being carried out in the associated theoretical project carried out by Evans.

Following from initial studies of step **1**, we postulated that UV spectroscopy could also be employed to examine the Diels-Alder reaction itself, step **2**. This was thought to be able to be carried out by the measurement of the consumption of iminium ion **B** and the formation of the Diels-Alder product (note that the UV spectrum of the Diels-Alder iminium ion **C** has not been observed (*Section* 6.1.2.3, *page* 120)). Again, this work would be carried out in acetonitrile as opposed to methanol so as not to form the dimethyl acetals in the reaction mixture.

6.1.2.3 Step 3: Iminium Ion Hydrolysis

The final step of the reactions catalytic cycle was proposed to be the hydrolysis of the iminium ion of the Diels-Alder adduct **241** with regeneration of the catalyst **3** (*Scheme* 62). Similar experiments to those utilised in the formation of the iminium ion were employed with the use of the Diels-Alder adduct **10** and a range of catalysts produced to date. However, no evidence for the presence of **241** was found at any time. This could be due to (a) the hydrolysis of **241** being faster than any technique we have employed to examine it, and/or (b) the equilibrium of this reaction lies predominantly towards the Diels-Alder products **10** and free amine **3**, or (c) the proposed mechanism is incorrect.

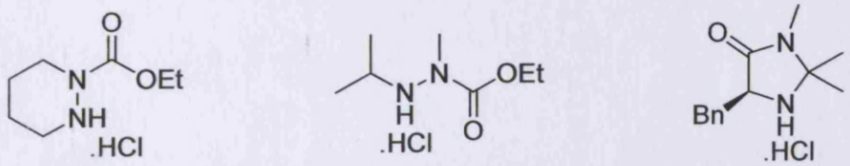


241 **3** **10**

(*Scheme* 62)

6.1.2.4 Overall Reaction analysis

The overall iminium ion catalysed Diels-Alder reaction was studied through the use of NMR spectroscopy. **198**, **166** and **16** were subjected to our standard Diels-Alder reaction conditions with samples being removed at regular intervals. These samples were independently hydrolysed and the conversions measured from the ^{1}H NMR spectra. The conversions as a percentage were plotted against time (*Appendix* II).



198 **166** **16**

The plots of conversion *versus* time show the reaction profile for each of the catalysts tested. However, due to time constraints, further analysis has yet to be carried out on the data.

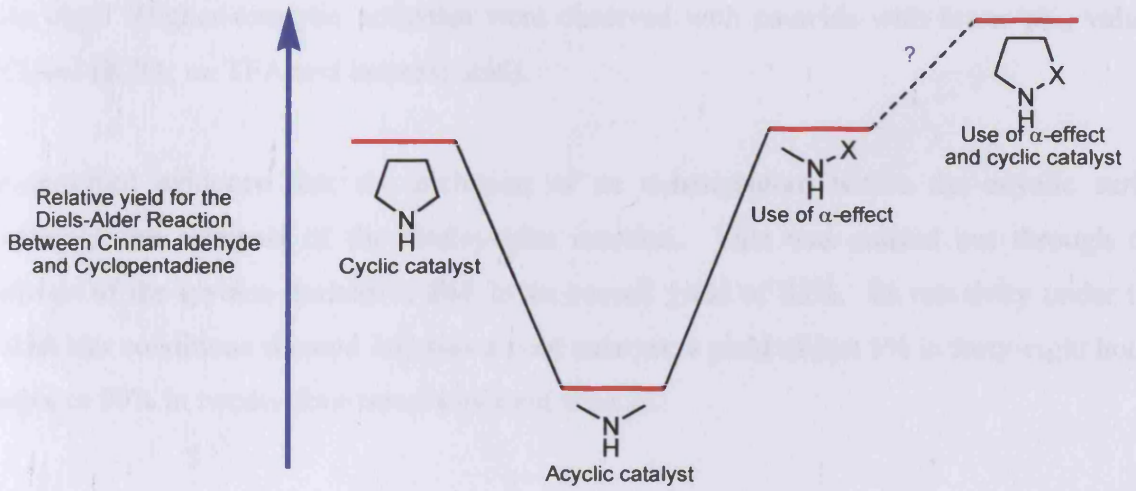
6.1.3 Catalytic Cycle Investigation - Summary

Although these studies were frustrating and led to no concrete results on determining the catalytic cycle reaction pathway some positive conclusions can be made. Firstly, it appears that ^{1}H NMR is not appropriate to establish the kinetics of iminium ion formation. Faster techniques such as UV spectroscopy may well provide in roads into establishing reaction kinetics with cinnamaldehyde **9** and the derived iminium ion showing discrete peaks in the UV trace. Although in our investigations it was necessary to use substantially lower concentrations of reactants than those adopted in the catalytic cycle use of more specialised equipment would circumvent this problem. Attempts to isolate iminium ion were confounded using the chloride counter anion, however, work carried out within our group more recently has shown that larger non-coordinating anions from HPF_6 can be used to address this issue.

Chapter 7: Conclusions

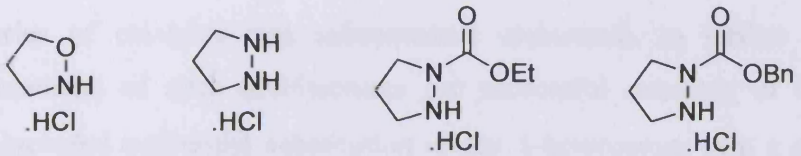
The work herein stands as an independent investigation into use of the α-effect within a heterocyclic skeleton directed towards the iminium catalysed Diels-Alder reaction. We completed a detailed exploration into the structural requirements of a catalyst for effective acceleration of the reaction through continuing SAR studies. These SAR studies provided an important overview of the area of research allowing for the feedback of information into subsequent catalyst design.

Previous work within the group had shown that the incorporation of an α-heteroatom within an acyclic architecture had, through use of the α-effect, increased catalytic activity within the iminium ion catalysed Diels-Alder reaction. It was initially thought that a more nucleophilic nitrogen centre within the catalyst would increase the overall rate of this reaction. Therefore, we had postulated that the inclusion of an α-heteroatom within a five-membered cyclic structure would increase the nucleophilicity of the reactive nitrogen centre further to produce a more active catalyst (*Figure* 30).



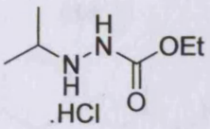
(*Figure* 30)

To this end, we synthesised a series of five-membered cyclic catalysts containing either an α-oxygen, **136**, α-nitrogen, **137**, and with the inclusion of an *exo*-electron withdrawing group, **140** and **141**, in overall yields of 15-71%.

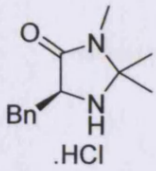


136 **137** **140** **141**

These catalysts were studied in the Diels-Alder reaction between cinnamaldehyde **9** and cyclopentadiene **8** with conditions taken from the literature.[7] *Exo*:*endo* ratios for these catalysts were roughly 2:1 which is indicative of an iminium ion catalysed process. The exception was **137** which returned a reverse selectivity of 1:2. Poor yields were observed throughout with the highest being 36% from **140**. This was compared to 90% for the acyclic catalyst **22** prepared previously within the group, and 98% for the commercially available imidazolidinone **16**.



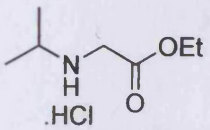
22



16

Reaction conditions were optimised for these five-membered cyclic catalysts with the use of dry methanol as the solvent increasing yields across the series with a best yield of 56% from **140**. Studies on the acid co-catalysts revealed that the hydrochloride salt was most active for those tried. Higher catalytic activities were observed with co-acids with lower pK_a values (HCl and $HClO_4$ *vs.* TFA and benzoic acid).

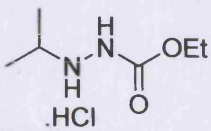
We provided evidence that the inclusion of an α-heteroatom within the acyclic series accelerated the catalysis of the Diels-Alder reaction. This was carried out through the synthesis of the glycine derivative **161** in an overall yield of 83%. Its reactivity under the Diels-Alder conditions showed **161** was a poor catalyst; a yield of just 5% in forty-eight hours relative to 90% in twenty-four hours observed with **22**.



161

48 hours, 5%

vs.

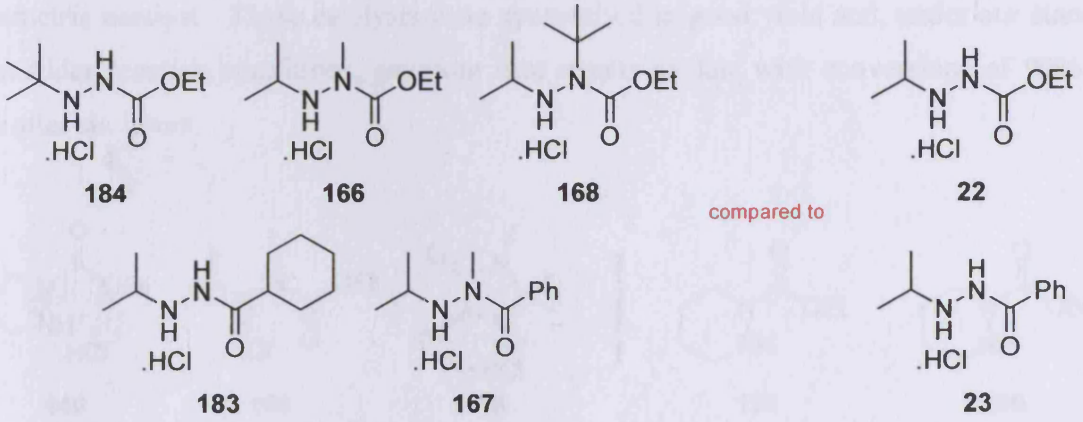


22

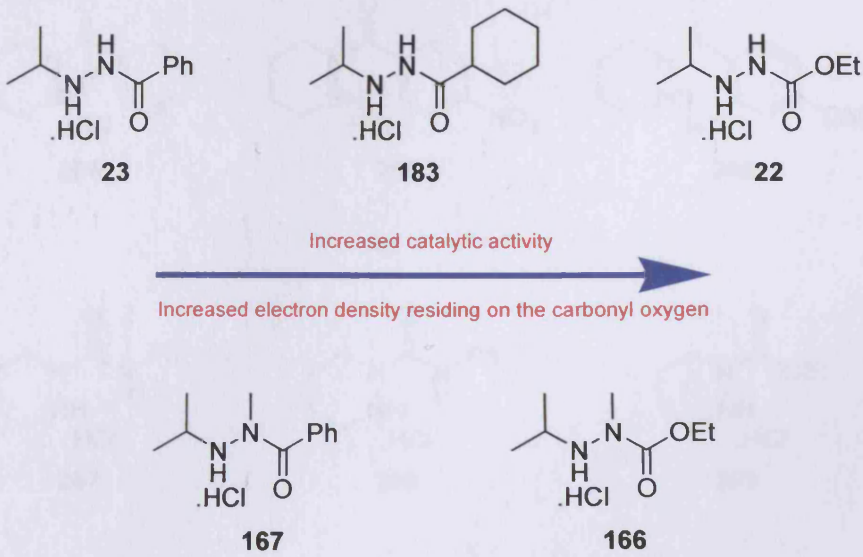
24 hours, 90%

The acyclic series of catalysts was subsequently elaborated, to further investigate the structural requirements of such architectures for successful catalysis of the Diels-Alder reaction. This included additional substitution of the α-heteroatom with a methyl group in **166** and **168**, and a *tert*-butyl group in **168**, whose activities were compared to catalysts **22**

and **23**. Alternative substitution of the α′-position was also investigated with the synthesis of **184** containing a *tert*-butyl group attached to the reactive nitrogen centre. The series included an extension of the original series with the synthesis of **183**.

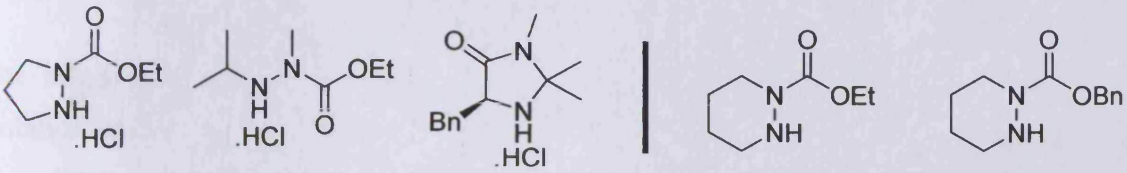


Incorporation of a *tert*-butyl group in either position (**184** and **168**) produced poor catalysts. This was attributed to the steric bulk of the catalyst reducing the nucleophilicity of the reactive nitrogen centre. However, inclusion of a methyl group on the α-heteroatom (**166** and **167**) increased the rate of reaction and produced the most active acyclic catalyst to date. **166** gave a yield of 86% after three hours at 10 mol% catalyst loading. We postulated this to be due to the inductive effect of the methyl group increasing the α-effect within the catalyst. These results displayed the first evidence for the observed increase in reactivity across a series containing varying degrees of electron density on the carbonyl functionality of the catalyst (*Figure* 31).



(*Figure* 31)

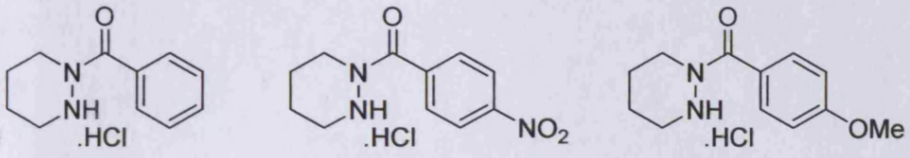
MM2 calculations of **140**, **166** and **16** showed the bond angle of the reactive nitrogen centre to be largest for **166**. We targeted **198** and **199** as in these catalysts this angle was closer to that observed in the acyclic catalyst **166**. We believed that this would produce a more active catalyst with the cyclic architecture providing a firm base for development of a future asymmetric catalyst. These catalysts were synthesised in good yield and, under our standard Diels-Alder reaction conditions, gave our best results to date with conversions of 99% and 94% after six hours.



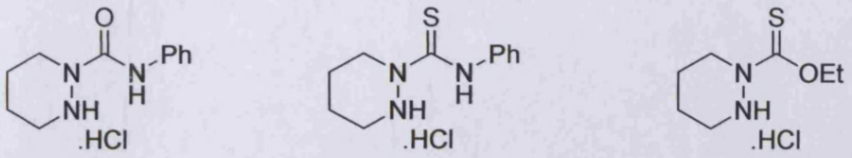
140 **166** **16** **198** **199**

6 hours, 99% 6 hours, 94%

Evidence from the acyclic series showed increased rates of reaction from catalysts with greater electron density based on the carbonyl of the electron withdrawing group (*Figure* 31, *above*). A series of six-membered heterocyclic catalysts containing a selection of electron withdrawing groups was synthesised to examine this further. This series consisted of the electron deficient and rich aromatics derived from benzoic hydrazide, **204**, **205** and **206**, the semicarbazide and thiosemicarbazide, **207** and **208**, and the thionated carbazate **209**.



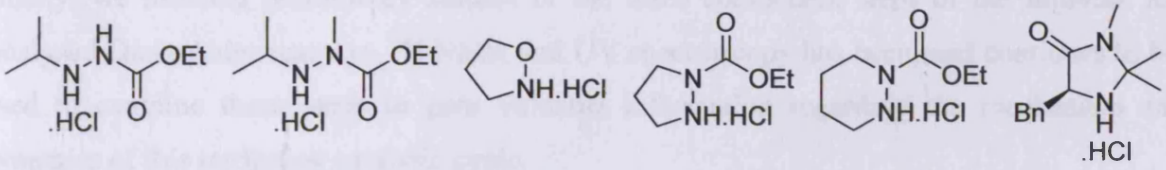
204 **205** **206**



207 **208** **209**

Within the benzoic hydrazide series the *p*-methoxyphenyl catalyst, **206**, with its electron rich aromatic group catalysed the Diels-Alder reaction to a greater extent than the non-substituted phenyl system **204**, which in turn was more active than the electron deficient *p*-nitro derivative **205**. These results adhered to the initial observations regarding electron density on the carbonyl within the acyclic series. However, the semicarbazide **207** and thiosemicarbazide **208** catalysts failed to produce efficient catalysis of the Diels-Alder reaction. Also **207** showed a lowering in the *exo*:*endo* ratio to 1:1 with a reversal in selectivity in the case of **208**.

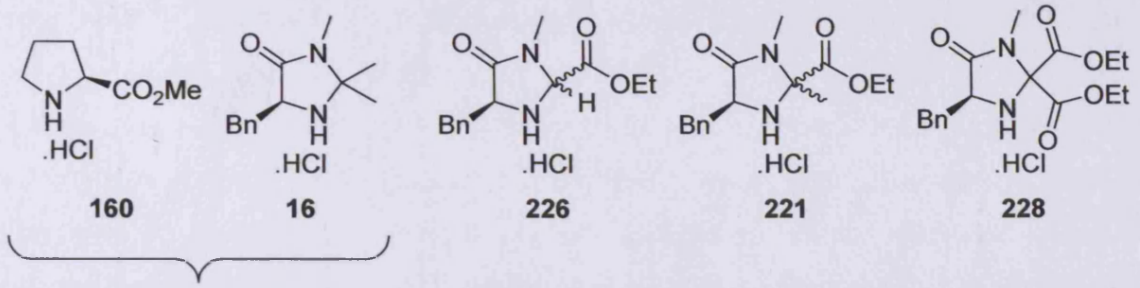
The integrity of the catalysts within the Diels-Alder reaction was investigated by their isolation after reaction using Varian Mega Bond Elut® SCX solid phase extraction columns. The variety of catalysts tested consisted of a cross section of all catalysts prepared (*Shown below*). Recovery was 85-94% after a twenty-four hour period. All attempts to isolate catalysts after the hydrolysis step proved inconclusive indicating degradation of the catalysts under the highly acidic conditions employed.



22 **166** **136** **140** **198** **16**

Recovered catalysts

Literature investigations detailed the use of α-amino esters, such as proline methyl ester, to catalyse the Diels-Alder reaction at reasonable rates. Studies suggested the ester function was paramount for catalysis to occur. This α-amino carbonyl can be observed in the commercially available imidazolidinone **16**, however, its constraints within the cyclic architecture suggested its direct participation within the catalytic reaction would be minimal. Therefore, synthesis of targets **226**, **221** and **228** was attempted to increase the reactivity by providing a Brønsted base in closer spatial proximity to the reactive nitrogen centre. Initial attempts at the synthesis of these and analogous molecules were unsuccessful despite a variety reaction of conditions, electrophiles and nucleophiles being employed.



160 **16** **226** **221** **228**

commercially available

Theoretical studies of the formation of iminium ions carried out by Platts and Evans have indicated that the incorporation of water within the reaction media increased reactivity for catalysts which did not contain an accessible proton donor/acceptor, such as a β-carbonyl. Here, the molecule of water was determined to facilitate the transfer of a proton within the initial stages of iminium ion formation. This supported our experimental evidence that showed catalysts containing an accessible β-carbonyl preformed better in dry methanol as opposed to the water/methanol (19:1) mixtures observed within the literature.

Finally, we initiated preliminary studies of the three component steps of the iminium ion catalysed Diels-Alder reaction. ^{1}H NMR and UV spectroscopy has been, and continues to be, used to examine these steps to gain valuable information regarding the mechanism and dynamics of this intriguing catalytic cycle.

Chapter 8: Experimental

Reagents were obtained from Aldrich, Lancaster and Fluka chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[124] Dichloromethane was dried by refluxing over, and distilling from calcium hydride. Ethanol was dried by refluxing over magnesium, followed by distillation. Toluene was dried over sodium wire for twenty-four hours prior to use. Anhydrous diethyl ether was obtained by distillation from sodium benzophenone ketyl. Light petrol refers to petroleum ether 40-60 °C.

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

TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}. Product spots were viewed either by the quenching of UV fluorescence, or by staining with a solution of 2 % aqueous potassium permanganate. Chromatography refers to flash column chromatography using head pressure by means of compressed air according to the procedure of Still,[125] using Merck Kieselgel 60 H silica or Matrix silica 60.

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

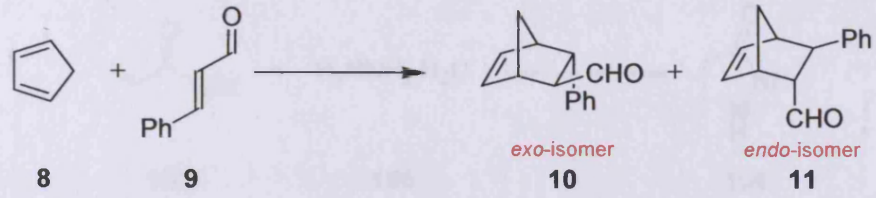
Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1600 series FTIR instrument either as a thin film, a nujol mull or dissolved in dichloromethane between sodium chloride plates. All absorptions are quoted in wave numbers (cm^{-1}).

^{1}H NMR spectra (δ_H) were recorded using an Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 500 (500MHz), with ^{13}C NMR spectra (δ_C) recorded at 100 MHz or 125 MHz respectively. Chemical shifts (δ_H and δ_C) were recorded in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 ($CHCl_3$) for ^{1}H NMR and 77.30 ($CHCl_3$), centre line, for ^{13}C NMR. The abbreviations s, d, t,

q, sept., m, and br, denote singlet, doublet, triplet, quartet, septet, multiplet and broadened resonances, respectively; all coupling constants were recorded in hertz (Hz).

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

Typical experimental procedure for catalytic runs

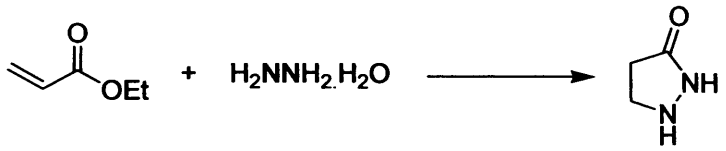


exo-isomer endo-isomer

8 **9** **10** **11**

trans-Cinnamaldehyde **9** (252 mg, 1.9 mmol, 0.24 mL, 1.0 eq) was added to a solution of catalyst (10 mol%, 0.19 mmol) in methanol (2.0 mL) at 25 °C and the resulting mixture was stirred for 5 minutes to initiate iminium ion formation. Freshly cracked cyclopentadiene **8** (323 mg, 4.9 mmol, 0.38 mL, 2.5 eq) was added in a single aliquot and stirring was continued for 24 hours. The volatiles were removed under reduced pressure and the resulting organics were hydrolysed in a chloroform (2 mL), water (1 mL) trifluoroacetic acid (1 mL) mixture over night. Saturated sodium hydrogen carbonate solution (18 mL) was added to neutralise the solution and the aqueous phase was extracted with dichloromethane (2x20 mL). The combined organics were washed with water (10 mL) and dried (Na_2SO_4) prior to the removal of the volatiles under reduced pressure. ^{1}H NMR of the crude reaction mixture was used to establish the conversion to the products and *exo*:*endo* ratios through the integration of aldehyde peaks at: δ_H (400 MHz, $CDCl_3$) 9.80 (*exo*) 9.65 (cinnamaldehyde) 9.53 (*endo*). The products were then purified by flash column chromatography eluting with 10% ethyl acetate in light petrol resulting in a mixture of the *exo*- and *endo*- isomers of 3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **10** and **11** as a pale yellow oil. ^{1}H NMR, ^{13}C NMR and IR data were consistent with previously reported literature values;[126] υ_{max} (liquid film)/cm^{-1} 1718, 1601, 1497; *exo*-isomer **10** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.85 (1H, d, J = 2.0, C<u>H</u>O) 7.4-7.0 (5H, m, Ar-<u>H</u>) 6.27 (1H, dd, J = 5.6 3.6, C<u>H</u>=CH) 6.01 (1H, dd, J = 5.6 3.6, CH=C<u>H</u>) 3.66 (1H, dd, J = 5.0 3.4, C<u>H</u>Ph) 3.25-3.05 (2H, m, C<u>H</u>CH$_2$) 2.55-2.45 (1H, m, C<u>H</u>CHO) 1.65-1.45 (2H, m, C<u>H</u>$_2$); *endo*-isomer **11** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.53 (1H, d, J = 2.1, C<u>H</u>O) 7.4-7.0 (5H, m, Ar-<u>H</u>) 6.36 (1H, dd, J = 5.6 3.6, C<u>H</u>=CH) 6.10 (1H, dd, J = 5.6 3.6, CH=C<u>H</u>) 3.26 (1H, m, C<u>H</u>Ph) 3.05 (1H, m, C<u>H</u>CH$_2$) 3.01 (1H, m, C<u>H</u>CH$_2$) 2.91 (1H, m, C<u>H</u>CHO) 1.46-1.49 (2H, m, C<u>H</u>$_2$); *m/z* (EI) $[M]^+$ 198 (10%) 132 (89) 131 (100) 103 (52) 77 (21) 66 (54).

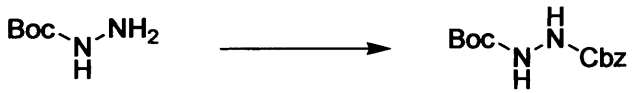
Pyrazolidin-3-one 154[112]



155 156 154

Ethyl acrylate **155** (12.50 g, 125 mmol, 13.50 mL) was added drop wise to a stirred solution of hydrazine hydrate **156** (7.00 g, 140 mmol, 6.70 mL), in ethanol (75 mL). The mixture was stirred at room temperature for 1 hour and subsequently brought to reflux for 4 hours. After stirring for a further 48 hours at ambient temperature the volatiles were removed under reduced pressure. The crude mixture was purified by chromatography eluting with methanol/light petrol (1:19) obtaining the *title compound* **154** (2.37 g, 22%) as an extremely viscous orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.58 (2H, s br, NH) 3.42 (2H, t, J = 7.8, CH_2CO) 2.43 (2H, t, J = 7.8, CH_2NH); Further characterisation was not carried out due to decomposition of the target molecule.

N'-tert-butyl ester benzyl carbazate 147[110]

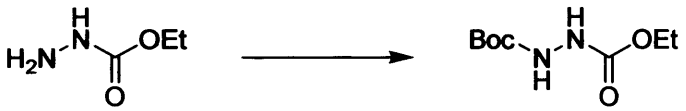


146 147

Benzylchloroformate (5.69 g, 33.4 mmol, 4.80 mL) was added to a vigorously stirred solution of *tert*-butyl carbazate **146** (4.41 g, 33.4 mmol), in a biphasic solution of chloroform (62 mL) and aqueous sodium hydroxide (1.8 M, 1.49 g, 37 mmol, 21 mL). The resulting solution was stirred at room temperature for 24 hours. The organic layer was separated and washed with water (10 mL) and a citric acid solution (10 mL, 10 % w/w). The resultant liquor was dried ($MgSO_4$) and the volatiles were removed affording **147** (8.08 g, 91%) as a white solid with no further purification required; mp (chloroform/light petrol) 71-73 °C [lit.[110] mp 79-80 °C]; ν_{max} (nujol)/cm^{-1} 3268, 2924, 1755, 1703, 1515, 1463, 1377; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26 (5H, s, Ar-H) 6.76 (1H, s br, NH) 6.45 (1H, s br, NH) 5.07 (2H, s, CH_2) 1.38

(9H, s, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.7 (C) 155.7 (C) 135.6 (C) 128.5 (CH) 128.4 (CH) 128.3(CH) 81.9 (C) 67.8 (CH_2) 28.14 (CH_3); *m/z* (APcI) $[M+H\text{-Boc}]^+$ 167.5 (46) 91.8 (100); HRMS (ES) (found 267.1268 $[M+H]^+$; $C_{13}H_{19}N_2O_4$ requires 267.1267).

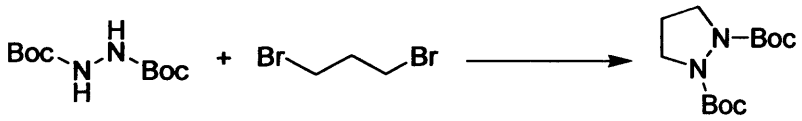
N'-tert-butyl ester ethyl carbazate 143



142 **143**

Di-*tert*-butyl dicarbonate (10.47 g, 48 mmol), in THF (90 mL), was cooled to 0 °C. Ethyl carbazate **142** (5.00 g, 48 mmol) was added. The resulting solution was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature for a further 24 hours. Removal of the volatiles under reduced pressure afforded the *title compound* **143** (9.40 g, 96%) as a white amorphous solid with no further purification required; mp (THF) 98-99 °C [lit.[127] mp 92-93 °C]; ν_{max} (nujol)/cm^{-1} 3282, 2926, 2852, 1740, 1712; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.54 (1H, s br, N<u>H</u>) 6.39 (1H, s br, N<u>H</u>) 3.95 (2H, q, J = 7.1, C<u>H</u>$_2$) 1.36 (9H, s, C(C<u>H</u>$_3$)$_3$) 1.20 (3H, t, J = 7.1, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.9 (C) 155.8 (C) 81.7 (C) 62.1 (CH_2) 28.1 (CH_3) 14.4 (CH_3); *m/z* (APcI) $[M+H]^+$ 205 (10%) 149 (100); HRMS (ES) (found 205.1183 $[M+H]^+$; $C_8H_{16}N_2O_2$ requires 205.1183).

Di-*tert*-butyl pyrazolidine-1,2-dicarboxylate 152 (Sodium hydride method)[110]

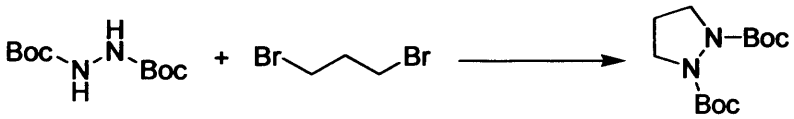


151 **145** **152**

A solution of di-*tert*-butyl hydrazodiformate **151** (5.00 g, 21.5 mmol) in DMF (50 mL) was added dropwise to a stirred suspension of sodium hydride (1.13 g, 47.3 mmol) in DMF (50 mL) at room temperature. After stirring for 30 minutes 1,3-dibromopropane **145** (4.3 g,

21.5 mmol, 2.16 mL) was added dropwise to the reaction mixture and the resulting solution was allowed to stir for 16 hours. The reaction was quenched with water (10 mL). The DMF and water was removed by distillation under reduced pressure. The crude material was dissolved in ethyl acetate (50 mL), washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by chromatography eluting with acetone/light petrol (1:9) resulting in the *title compound* **152** (3.27 g, 56%) as a clear colourless oil; ν_{max} (nujol)/cm^{-1} 2928, 2853, 1704, 1489, 1422, 1156; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.79-3.86 (2H, m, CHHN) 3.11-3.19 (2H, m, CHHN) 1.91-1.98 (2H, m, CH_2CH_2N) 1.41 (18H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1 (C), 81.1 (C), 46.3 (CH_2), 28.2 (CH_3), 25.7 (CH_2); *m/z* (APcI) $[M+H]^+$ 273.7 (10%) 217.7 (10) 117.8 (100); HRMS (ES) (found 273.1812 $[M+H]^+$; $C_{13}H_{24}N_2O_4$ requires 273.1809).

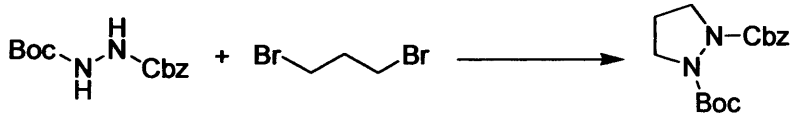
Di-*tert*-butyl pyrazolidine-1,2-dicarboxylate 152 (Phase-transfer method)[110]



151 **145** **152**

Di-*tert*-butyl hydrazodiformate **151** (5.00 g, 21.5 mmol) was stirred in a solution of toluene (50 mL), sodium hydroxide (25 mL, 50% w/w) and tetraethylammonium bromide (650 mg, 3.10 mmol). 1,3-Dibromopropane **145** (6.50 g, 32.3 mmol, 3.27 mL) was added and the reaction was brought to reflux for 90 minutes. Ethyl acetate (50 mL) was added and the mixture was washed with saturated sodium hydrogen carbonate (70 mL), water (50 mL) and brine (30 mL). The organics were separated, dried ($MgSO_4$) and the volatiles were removed under reduced pressure. The crude product was purified by chromatography eluting with acetone/light petrol (1:9) resulting in the *title compound* **152** (4.33 g, 74%) as a clear colourless oil; spectroscopic data was consistent with previously reported values.

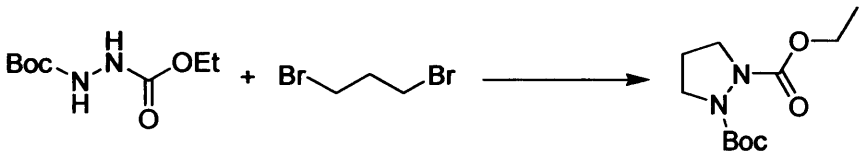
tert-Butyl benzyl pyrazolidine-1,2-dicarboxylate 148[110]



147 145 148

N'-tert-Butyl ester benzyl carbazate **147** (5.00 g, 18.8 mmol) was stirred in a solution of toluene (50 mL), sodium hydroxide (25 mL, 50% w/w) and tetraethylammonium bromide (650 mg, 3.10 mmol). 1,3-Dibromopropane **147** (5.69 g, 28.2 mmol, 2.90 mL) was added and the solution was brought to reflux for 80 minutes. Ethyl acetate (50 mL) was added and the mixture was subsequently washed with saturated sodium hydrogen carbonate solution (70 mL), water (50 mL) and brine (30 mL). The organics were separated, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The reaction mixture was purified by chromatography eluting with acetone/light petrol (1:9) which resulted in the *title compound* **148** (4.54 g, 79%) as a clear colourless oil; ν_{max} (nujol)/cm^{-1} 2933, 1710, 1459, 1379, 1087; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.25-7.38 (5H, m, Ar-H) 5.10-5.28 (2H, m, OCH_2Ar) 3.87-3.96 (2H, m, CHHN) 3.16-3.35 (2H, m, CHHN) 1.98-2.08 (2H, m, CH_2CH_2N) 1.37 (9H, s, CH_3); ^{13}C NMR (60 MHz, $CDCl_3$) δ_C 156.8 (C) 156.3 (C) 136.2 (C) 128.5 (CH) 127.9 (CH) 127.0 (CH) 81.6 (C) 67.8 (CH_2) 46.7 (CH_2) 46.3 (CH_2) 28.1 (CH_3) 25.7 (CH_2); *m/z* (APcI) $[M+H]^+$ 307.3 (100%); HRMS (ES) (found 307.1649 $[M+H]^+$; $C_{16}H_{22}N_2O_4$ requires 307.1652).

tert-Butyl benzyl pyrazolidine-1,2-dicarboxylate 144

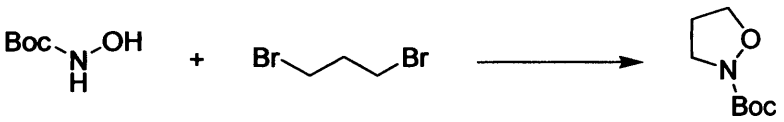


143 145 144

N'-tert-Butyl ester ethyl carbazate **143** (2.00 g, 9.8 mmol) was stirred in a solution of toluene (20 mL), sodium hydroxide (10 mL, 50% w/w) and tetraethylammonium bromide (290 mg, 1.24 mmol). 1,3-Dibromopropane **145** (3.07 g, 14.7 mmol, 1.55 mL) was added to the slurry,

which was subsequently brought to reflux for 90 minutes. Ethyl acetate (15 mL) was added and the mixture which was washed with saturated sodium hydrogen carbonate solution (20 mL), water (15 mL) and brine (15 mL). The organics were separated, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The crude reaction mixture was purified by chromatography eluting with acetone/light petrol (1:9) resulting in the *title compound* **144** (1.94 g, 81%) as a clear colourless oil; ν_{max} (nujol)/cm^{-1} 2979, 1730, 1700, 1484, 1453, 1426, 1108; ^1H NMR (400 MHz, $CDCl_3$) δ_H 4.03-4.22 (2H, m, $C\underline{H}_2N$) 3.85 (2H, q, J = 7.1, $C\underline{H}_2CH_3$) 3.10-3.26 (2H, m, $C\underline{H}_2N$) 1.98 (2H, p, J = 7.0, $C\underline{H}_2CH_2N$) 1.42 (9H, s, CH_3) 1.23 (3H, t, J = 7.1, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.4 (C) 158.2 (C) 82.1 (C) 59.7 (CH_2) 51.2 (CH_2) 51.9 (CH_2) 34.1 (CH_2) 29.7 (CH_3) 14.2 (CH_3); *m/z* (APcI) $[M+H]^+$ 245.7 (16%) 189.6 (100) 145.6 (71); HRMS (ES) (found 262.1759 $[M+NH_4]^+$; $C_{11}H_{24}N_3O_4$ requires 262.1761).

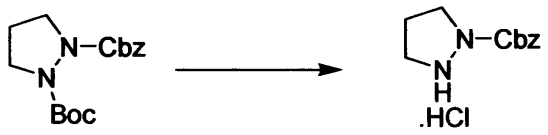
tert-Butyl isoxazolidine-2-carboxylate 150



149 **145** **150**

tert-Butyl *N*-hydroxycarbamate **149** (2.00 g, 15.0 mmol) was stirred in a solution of toluene (20 mL), sodium hydroxide (10 mL, 50% w/w) and tetraethylammonium bromide (453 mg, 2.16 mmol). 1,3-Dibromopropane **145** (4.71 g, 22.5 mmol, 2.37 mL) was added to the slurry, which was subsequently brought to reflux for 90 minutes. Ethyl acetate (15 mL) was added to dilute and the mixture which was then washed with saturated sodium hydrogen carbonate solution (20 mL), water (15 mL) and brine (15 mL). The organics were separated, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The crude product was purified by chromatography eluting with acetone in light petrol (1:9) resulting in the *title compound* **150** (441 mg, 17%) as a clear colourless oil; ν_{max} (nujol)/cm^{-1} 2979, 1734, 1709; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.84 (2H, t, J = 7.2, $CH_2C\underline{H}_2ON$) 3.55 (2H, t, J = 7.2, $C\underline{H}_2N$) 2.16 (2H, p, J = 7.2, $C\underline{H}_2CH_2N$) 1.43 (9H, s, $C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.7 (C), 81.8 (C), 68.4 (CH_2), 46.8 (CH_2), 28.2(CH_3) 27.9 (CH_2); *m/z* (APcI) $[M+H]^+$ 174.7 (8%) 118.7 (100); HRMS (ES) (found 174.1128 $[M+H]^+$; $C_{18}H_{16}NO_3$ requires 174.1125).

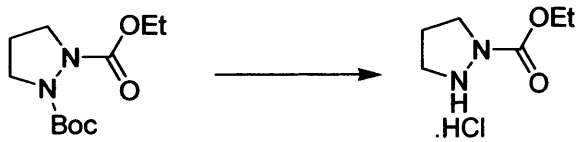
Benzyl pyrazolidine-1-carboxylate hydrochloride 141[110]



148 **141**

tert-Butyl benzyl pyrazolidine-1,2-dicarboxylate **148** (100 mg, 0.33 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 0.85 mL, 1.65 mmol) was added and the reaction left to stand for 24 hours or until all starting material was consumed by TLC. The volume of ether was reduces and the precipitate was filtered and washed with cold ether. The volatiles were removed under reduced pressure resulting in the *title compound* **141** as a colourless solid (74 mg, 94%); mp (ether/chloroform) 150–151 °C; ν_{max} (nujol)/cm^{-1} 2927, 2854, 1721; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30-7.51 (5H, m, Ar-H) 5.22 (2H, s, CH_2Ar) 3.64 (2H, t, J = 6.9, CH_2N) 3.42 (2H, t, J = 6.9, CH_2N) 2.51 (2H, s br, NH_2) 2.20 (2H, p, J = 6.9, CH_2CH_2N); ^{13}C NMR (125 MHz, d_6-DMSO) δ_C 154.7 (C) 136.0 (C) 128.9 (CH) 128.7 (CH) 128.4 (CH) 68.3 (CH_2) 46.6 (CH_2) 46.4 (CH_2) 24.6 (CH_2); *m/z* (APcI) $[M+H-HCl]^+$ 207.7 (81%); HRMS (ES) (found 207.1126 $[M+H-HCl]^+$; $C_{11}H_{15}N_2O_2$ requires 207.1128).

Ethyl pyrazolidine-1-carboxylate hydrochloride 140



144 **140**

tert-Butyl benzyl pyrazolidine-1,2-dicarboxylate **144** (100 mg, 0.40 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 1.0 mL, 2.00 mmol) was added and the reaction left to stand for 24 hours or until all starting material was consumed by TLC. The volume of ether was reduced and the precipitate was filtered and washed with cold ether. The volatiles were removed under reduced pressure resulting in the *title compound* **140** as a colourless solid (74 mg, 87%); mp (ether/chloroform) 129–130 °C; ν_{max} (nujol)/cm^{-1}

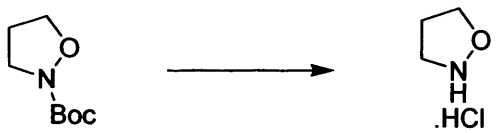
2921, 1712, 1460, 1377, 1300, 1215, 1157, 1122, 1090, 1032; ^{1}H NMR (400 MHz, CD_3OD) δ_H 4.30 (2H, q, J = 7.1, $C\underline{H}_2CH_3$) 3.74 (2H, t, J = 7.0, $C\underline{H}_2N$) 3.60 (2H, t, J = 7.0, $C\underline{H}_2N$) 2.37 (2H, p, J = 7.0, $C\underline{H}_2CH_2N$) 1.34 (3H, t, J = 7.1, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 153.8 (C) 63.8 (CH_2) 46.3 (CH_2) 45.4 (CH_2) 24.4 (CH_2) 14.4 (CH_3); *m/z* (ES) $[M+H-HCl]^+$ 145.0 (100%) 116.9 (43); HRMS (ES) (found 145.0973 $[M+H-HCl]^+$; $C_6H_{13}N_2O_2$ requires 145.0972).

Pyrazolidine hydrochloride 137[110]

152 **137**

Di-*tert*-butyl pyrazolidine-1,2-dicarboxylate **152** (200 mg, 0.73 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 1.85 mL, 3.67 mmol) was added and the resulting solution was left to stand for 24 hours or until the starting material was consumed by TLC. The volume of liquor was reduced and the precipitate was filtered and washed with cold ether resulting in the *title compound* **137** as a colourless solid (94.6 mg, 96%); mp (ether/chloroform) 77-78 °C [lit.[110] mp 54-56 °C]; Found: C, 26.44; H, 7.25; N, 18.97; Cl, 41.05. $C_3H_9N_2Cl$ requires C, 33.19; H, 8.36; N, 25.80; Cl, 32.65%; ν_{max} (nujol)/cm^{-1} 3395, 2922, 2852, 1461, 1377; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 8.89 (3H, s br, $N\underline{H}_2$) 3.12 (4H, t, J = 7.2, $C\underline{H}_2N$) 2.04 (2H, p, J = 7.2, $C\underline{H}_2CH_2N$); ^{13}C NMR (100MHz, d_6-DMSO) δ_C 45.8 (CH_2) 25.4 (CH_2).

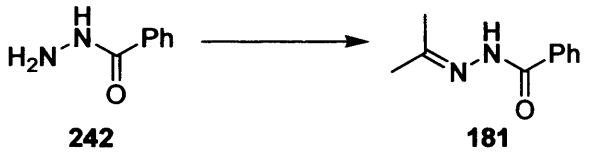
Isoxazolidine hydrochloride 136



150 **136**

tert-Butyl isoxazolidine-2-carboxylate **150** (112 mg, 0.65 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 3.24 mmol, 1.62 mL) was added and the resulting solution allowed to stand for 24 hours or until the starting material was consumed by TLC. The volume of liquor was reduced and the precipitate was filtered and washed with cold ether affording the *title compound* **136** as a colourless solid (63 mg, 89%); mp (ether/chloroform) 111-112 °C; ν_{max} (nujol)/cm^{-1} 3386, 2923, 2853, 1459, 1377, 1003; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 12.48 (2H, s br, NH$_2$) 4.19 (2H, t, J = 7.1, CH$_2$O) 3.49 (2H, t, J = 7.1, CH$_2$N) 2.41 (2H, p, J = 7.1, CH$_2$CH$_2$N); ^{13}C NMR (125 MHz, d_6-DMSO) δ_C 70.9 (CH_2) 45.5 (CH_2) 27.9 (CH_2).

N'-(Propan-2-ylidene)benzoic hydrazide 181[121]



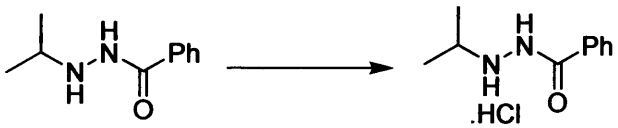
Benzoic hydrazide **242** (5.00 g, 36.7 mmol) was stirred in an excess of acetone **60** (22 mL, 0.3 mmol), containing acetic acid (40 μL, 0.7 mmol), for 48 hours at ambient temperature. Water (30 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were dried (Na_2SO_4) and reduced *in vacuo* to afford the *title compound* **181** (5.57 g, 86%) as a colourless solid; mp (petrol/ether) 141–143 °C [lit.[121] mp 142-143 °C]; ν_{max} (nujol)/cm^{-1} 3221, 1655, 1578, 1578, 1531, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.70 (1H, s, NH) 7.79 (2H, d, J = 7.1, Ar-H) 7.52 (1H, t, J = 7.1, Ar-H) 7.44 (2H, t, J = 7.1, Ar-H) 2.15 (3H, s, CH$_3$) 1.97 (3H, s, CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 164.6 (C) 156.9 (C) 134.1 (C) 132.1 (CH) 129.0 (CH) 127.6 (CH) 26.0 (CH_3) 17.3 (CH_3); *m/z* (EI) $[M]^+$ 176 (8%), 161 (50), 105 (100); HRMS (EI) (found 176.0950 $[M]^+$; $C_{10}H_{12}N_2O$ requires 176.0950).

N'-iso-Propylbenzoic hydrazide 243[121]

181 243

Platinum(IV) oxide (68 mg, 0.3 mmol) was placed in a nitrogen flushed flask with ethanol (12 mL) and acetic acid (6 mL). *N'*-(Propan-2-ylidene)benzoic hydrazide **181** (2.50 g, 14.2 mmol) was added, the flask was charged with hydrogen and stirred for 48 hours at ambient temperature. The reaction mixture was filtered over Celite and the filtrate was neutralised with saturated sodium bicarbonate solution (180 mL). The volatiles were removed under reduced pressure and the aqueous phase was extracted with diethyl ether (5x50 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure to give the *title compound* **243** (2.18 g, 86%) as a colourless powder; mp (petrol/ether) 110–112 °C [lit.[128] mp 115-117 °C]; ν_{max} (nujol)/cm^{-1} 3289, 1640, 1537, 725, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (1H, s, NH) 7.69 (2H, d, J = 7.7, Ar-H) 7.46 (1H, t, J = 7.7, Ar-H) 7.38 (2H, t, J = 7.7, Ar-H) 4.81 (1H, s, NH) 3.18 (1H, sept., J = 6.2, NCH$(CH_3)_2$) 1.05 (6H, d, J = 6.2, NCH$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.5 (C) 132.9 (C) 131.9 (CH) 128.7 (CH) 126.9 (CH) 51.4 (CH) 20.9 (CH_3); *m/z* (EI) $[M]^+$ 178 (3%), 163 (9), 122 (13), 105 (100); HRMS (EI) (found 178.1105 $[M]^+$; $C_{10}H_{14}N_2O$ requires 178.1106).

N'-iso-propylbenzoic hydrazide hydrochloride 23

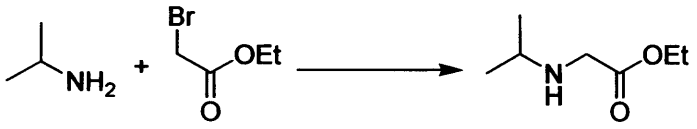


243 23

N'-iso-propylbenzoic hydrazide **243** (500 mg, 2.81 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 512 mg, 14.0 mmol, 7.02 mL) was added and the resultant solution was left for 15 minutes. The volume of liquor as reduced and the

resulting precipitate was filtered and washed with cold ether to give the *title compound* **23** (553 mg, 92%) as a colourless powder; mp 215-218 °C; ν_{max} (nujol film)/cm^{-1} 3408, 2923, 2853, 2645, 1678, 1600, 1549, 1527, 1463, 1377; ^{1}H NMR (400 MHz, CD_3OD) δ_H 8.00 (2H, d, J = 7.5, Ar-H) 7.45 (1H, t, J = 7.4, Ar-H) 7.31 (2H, m, Ar-H) 3.94 (1H, sept., J = 6.6, NCH(CH$_3$)$_2$) 1.41 (6H, d, J = 6.6, NCH(CH$_3$)$_2$); ^{13}C NMR (125 MHz, CD_3OD) δ_C 166.8 (C) 133.5 (C) 128.7 (CH) 128.6 (CH) 128.5 (CH) 56.0 (CH) 18.0 (CH_3); *m/z* (APcI) [M+H-HCl]$^+$ 179 (100%).

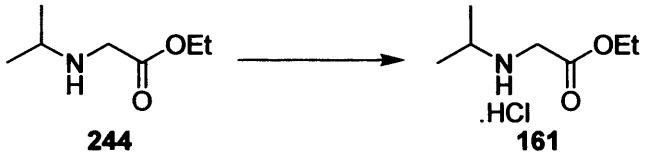
Ethyl 2-(*iso*-propylamino)acetate 163[129]



164 **165** **163**

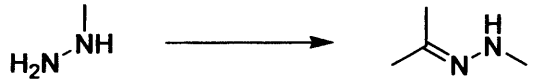
A solution of *iso*-propylamine **164** (13.6 g, 230 mmol, 19.6 mL) in toluene (100 mL) was treated with ethyl bromoacetate **165** (16.7 g, 100 mmol, 11.1 mL) at ambient temperature. The solution was refluxed for 2 hours and subsequently stirred at room temperature for 16 hours during which time a crystalline precipitate was formed. The solution was made alkaline with sodium hydroxide (20 mL, 50% w/w) dissolving the precipitate. The organic layer was separated and washed with water (20 mL), brine (20 mL), and dried ($MgSO_4$). The volatiles were removed *in vacuo* and the product purified by distillation (5 mbar, 73-75 °C) [lit.[129] b.pt. 30 °C at 2.00 Torr] affording the *title compound* **163** (12.3 g, 85%) as a clear colourless liquid; ν_{max} (film)/cm^{-1} 3335, 2966, 1740, 1466, 1379, 1347, 1098, 1028; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.12 (2H, q, J = 7.2, OCH$_2$CH$_3$) 3.34 (2H, s, NHCH$_2$CO) 2.73 (1H, sept., J = 6.3, CH(CH$_3$)$_2$) 1.52 (1H, s br, NH) 1.21 (3H, t, J = 7.2, OCH$_2$CH$_3$) 0.99 (6H, d, J = 6.3, CH(CH$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.7 (C) 60.8 (CH_2) 48.7 (CH) 48.3 (CH_2) 22.7 (CH_3) 14.2 (CH_3); *m/z* (APcI) [M+H]$^+$ 146 (100%); HRMS (ES) (found 146.1177 [M+H]$^+$; $C_7H_{15}N_1O_2$ requires 146.1176).

Ethyl 2-(*iso*-propylamino)acetate hydrochloride 161



Ethyl 2-(*iso*-propylamino)acetate **163** (150 mg, 1.03 mmol) was dissolved in ether (0.2 mL). Hydrochloric acid in ether (2 M, 189 mg, 5.17 mmol, 2.60 mL) was added and the resultant solution was swirled for 5 minutes. The volume of liquor as reduced and the resulting precipitate was filtered and washed with cold ether. The volatiles were removed under reduced pressure to give the *title compound* **161** (183 mg, 98%) as a colourless amorphous solid; mp 111-112 °C; ν_{max} (nujol)/cm^{-1} 3330, 2926, 2853, 1757, 1590, 1463, 1377; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.77 (2H, s br, N$\underline{H}_2$) 4.21 (2H, q, J = 7.1, OC$\underline{H}_2$CH$_3$) 3.76 (2H, s, NC$\underline{H}_2$C(O)O) 3.50-3.59 (1H, m, NC$\underline{H}$(CH$_3$)$_2$) 1.44 (6H, d, J = 6.7, NCH(C$\underline{H}_3$)$_2$) 1.24 (3H, t, J = 7.1, OCH$_2$C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$). δ_C 166.0 (C) 62.5 (CH_2) 50.8 (CH) 44.2 (CH_2) 18.9 (CH_3) 14.0 (CH_3); *m/z* (APcI) [M+H-HCl]$^+$ 146 (100%); HRMS (ES) (found 146.1177 [M+H-HCl]$^+$; $C_7H_{15}NO_2$ requires 146.1176).

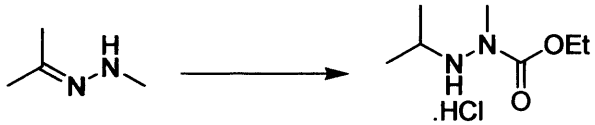
2-Methyl-1-(propan-2-ylidene)hydrazine 170



Methyl hydrazine **169** (13.6 g, 295 mmol, 15.7 mL) was added drop wise to acetone **60** (23.7 g, 409 mmol, 30 mL) maintaining the reaction temperature below 35 °C. The solution was stirred for 1 hour after which the top layer was removed and allowed to stand over potassium hydroxide (5 g) for a further 1 hour. The upper liquid was decanted from the lower aqueous phase and allowed to stand over two successive portions of potassium hydroxide (2x2.5 g) for 30 minutes each. Purification was by distillation (1 atm., 110 °C) [lit.[118] b.pt. 116-118 °C] under nitrogen affording the *title compound* **170** (17.85 g, 70%); ν_{max} (liquid film)/cm^{-1} 3394, 3262, 2911, 1711, 1631; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.28 (1H, s br, N$\underline{H}$)

2.76 (3H, s, NHC<u>H</u>$_3$) 1.88 (3H, s, N=CC<u>H</u>$_3$ *trans*) 1.68 (3H, s, N=C-C<u>H</u>$_3$ *cis*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 146.4 (C) 37.9 (CH_3) 25.0 (CH_3) 15.5 (CH_3); *m/z* (APcI) $[M+H]^+$ 87 (100%); HRMS (EI) (found 86.0841 $[M]^+$; $C_4H_{10}N_2$ requires 86.0838).

N-Methyl-*N'*-*iso*-propyl ethyl carbazate hydrochloride 166

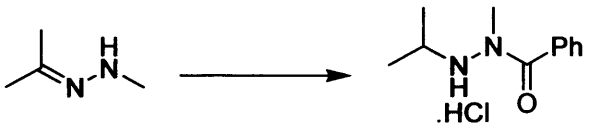


170 **166**

Ethyl chloroformate **171** (1.26 g, 1.10 mL, 11.6 mmol) was added dropwise to a stirred solution of *N-iso*-propylidene-*N'*-methyl-hydrazine **170** (1.00 g, 11.6 mmol) in a mixture of CH_2Cl_2 (10 mL) and saturated sodium bicarbonate solution (10 mL) at 0 °C. After addition the reaction mixture was allowed to warm to ambient temperature and stirred for 18 hours. The organics were separated and the aqueous layer extracted with CH_2Cl_2 (2x20 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The organics were added to a nitrogen flushed flask, charged with platinum(IV) oxide (52.7 mg, 232 μmol) in ethanol (20 mL) and acetic acid (10 mL). The atmosphere was replaced with hydrogen and the reaction stirred for 16 hours at ambient temperature. The mixture was filtered over Celite and the filtrate was neutralised with saturated sodium bicarbonate solution (300 mL). The single phase solution was extracted with diethyl ether (3x50 mL) and the combined organics were washed with brine (30 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure to give a clear oil. Purification was by chromatography eluting with ether/light petrol (1:1). The solvent volume was decreased under reduced pressure and hydrochloric acid in ether (1 M, 58.0 mmol, 58 mL) was added to the solution with swirling for 30 minutes at ambient temperature. The precipitate was filtered under nitrogen affording the *title compound* **166** (808 mg, 35%) as a colourless powder; mp 85-86 °C; ν_{max} (nujol)/cm^{-1} 3399, 2921, 2852, 1729, 1562, 1503, 1462, 1378, 1332, 1312, 1202, 1122, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.31 (2H, q, J = 7.2, OC<u>H</u>$_2$CH$_3$) 5.48 (1H, sept., J = 6.6, NC<u>H</u>(CH$_3$)$_2$) 3.46 (3H, s, NC<u>H</u>$_3$) 1.50 (6H, d, J = 6.6, NCH(C<u>H</u>$_3$)$_2$) 1.36 (3H, t, J = 7.2, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 154.2 (C) 64.1 (CH_2) 54.6 (CH) 35.9 (CH_3)

17.8 (CH_3) 14.3 (CH_3); *m/z* (ES) $[M+H-HCl]^+$ 161 (90%) 119 (60) 118 (100); HRMS (ES) (found 161.1286 $[M+H-HCl]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

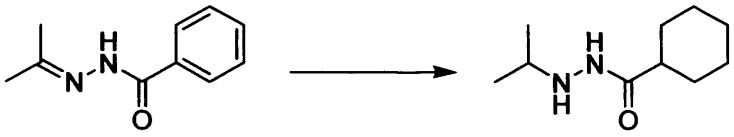
N-Methyl-*N'*-*iso*-propyl benzoic hydrazide hydrochloride 167



170 **167**

Benzoyl chloride **174** (817 mg, 5.8 mmol, 0.65 mL) was added dropwise to a stirred solution of *N-iso*-propylidene-*N'*-methyl-hydrazine **170** (500 mg, 5.8 mmol) in a mixture of CH_2Cl_2 (5 mL) and saturated sodium bicarbonate solution (5 mL) at 0 °C. After addition, the reaction mixture was allowed to warm to ambient temperature and stirred for 18 hours. The organics were separated and the aqueous layer extracted with CH_2Cl_2 (2x10 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The organics were added to a nitrogen flushed flask charged with platinum(IV) oxide (66 mg, 0.29 mmol, 5 mol%) in ethanol (12 mL) and acetic acid (6 mL). The atmosphere was replaced with hydrogen and the reaction stirred for 16 hours at ambient temperature. The reaction mixture was filtered over Celite and the filtrate was neutralised with saturated sodium bicarbonate solution (180 mL). The single phase solution was extracted with diethyl ether (3x50 mL) and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure resulting in a clear oil. Purification was by chromatography eluting with diethyl ether/light petrol (1:1). The volume of elutent was reduced and hydrochloric acid in ether (1 M, 13.0 mmol, 13 mL) was added to the solution with swirling for 30 minutes at ambient temperature. The precipitate was filtered under nitrogen affording the *title compound* **167** (150 mg, 11%) as a colourless solid; mp 145-146 °C; ν_{max} (nujol)/cm^{-1} 3408, 2923, 1638, 1460, 1377, 1333, 1122, 1077; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.51 (2H, d, J = 8.0, Ar-H) 7.49 (1H, t, J = 7.1, Ar-H) 7.42 (2H, m, Ar-H) 3.94 (1H, sept., J = 6.6 NCH$(CH_3)_2$) 3.61 (3H, s, NCH_3) 1.51 (6H, d, J = 6.6, NCH$(CH_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.8 (C) 132.3 (C) 130.7 (CH) 128.9 (CH) 128.2 (CH) 53.7 (CH_3) 38.6 (CH) 18.0 (CH_3); *m/z* (ES) $[M+H-HCl]^+$ 193 (100%); HRMS (ES) (found 193.1336 $[M+H-HCl]^+$; $C_{11}H_{17}N_2O$ requires 193.1335).

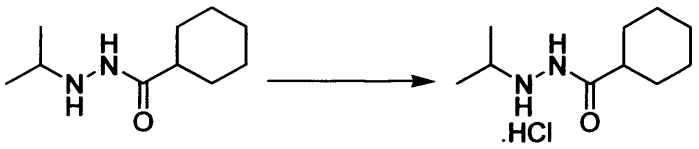
N'-iso-Propylcyclohexanecarbohydrazide 182



181 182

Platinum(IV) oxide (108 mg, 0.48 mmol) was placed in a nitrogen flushed flask with ethanol (50 mL) and acetic acid (25 mL). *N'*-(Propan-2-ylidene)benzoic hydrazide **181** (4.20 g, 23.8 mmol) was added, the flask was charged with hydrogen and stirred for 96 hours at ambient temperature. The reaction mixture was filtered over Celite and the filtrate was neutralised with saturated sodium bicarbonate solution (450 mL) which caused the product to precipitate. The suspension was extracted with diethyl ether (5x100 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and the volatiles were removed *in vacuo* affording the *title compound* **182** (2.31 g, 53%) as a colourless amorphous solid; mp (ether/chloroform) 120-124 °C [lit.[130] mp 122-123 °C]; ν_{max} (nujol)/cm^{-1} 3397, 2926, 1708, 1549, 1525, 1462, 1377, 1336, 1173, 1110; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.94 (1H, s br, NH) 4.61 (1H, s br, NH) 3.02-3.11 (1H, m, $NCH(CH_3)_2$) 2.03-2.09 (1H, m, Cy) 1.70-1.91 (4H, m, Cy) 1.66-1.69 (1H, m, Cy) 1.42-1.48 (2H, m, Cy) 1.22-1.29 (3H, m, Cy) 1.03 (6H, d, J = 6.4, $NCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.9 (C) 51.5 (CH) 44.2 (CH) 38.2 (CH_2) 29.8 (CH_2) 26.0 (CH_2) 21.1 (CH_3); *m/z* (APcI) $[M+H]^+$ 185 (95%) 143 (100); HRMS (ES) (found 185.1645 $[M+H]^+$; $C_{10}H_{21}N_2O$ requires 185.1648).

N'-iso-Propylcyclohexanecarbohydrazide hydrochloride 183

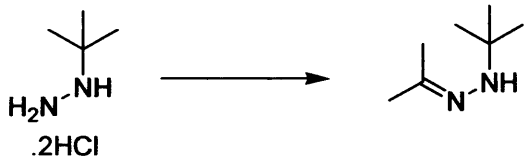


182 183

N'-iso-Propylcyclohexanecarbohydrazide **182** (500 mg, 2.72 mmol) was dissolved in the minimum volume of dry ether prior to the addition of hydrochloric acid in ether (1 M,

13.6 mmol, 13.6 mL) and the solution was swirled for 10 minutes. The volume of liquor was reduced and the precipitate was filtered and washed with cold ether affording the *title compound* **183** (533 mg, 89%) as a colourless solid; mp 193-194 °C; ν_{max} (nujol)/cm^{-1} 3330, 2923, 1707, 1548, 1525, 1461, 1377, 1336, 1259, 1192, 1174, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.30 (1H, s, NH) 3.81 (1H, sept., J = 6.6, NCH(CH$_3$)$_2$) 2.60-2.50 (1H, m, OCCH) 1.89-1.20 (10H, m, Cy) 1.43 (6H, d, J = 6.6 Hz, NCH(CH$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.2 (C) 55.6 (CH) 42.3 (CH) 29.0 (CH_2) 25.5 (CH_2) 25.2 (CH_2) 17.8 (CH_3); *m/z* (APcI) [M+H-HCl]$^+$ 185 (100%); HRMS (ES) (found 185.1653 [M+H-HCl]$^+$; $C_{10}H_{21}N_2O$ requires 185.1648).

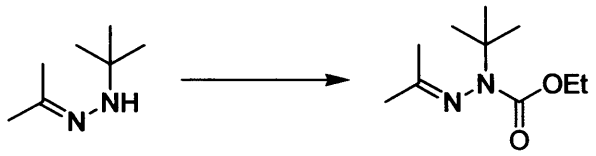
2-*tert*-Butyl-1-(propan-2-ylidene)hydrazine 178



177 **178**

tert-Butylhydrazine dihydrochloride **177** (10.0 g, 80 mmol) was added to acetone **60** (4.66 g, 80 mmol, 5.90 mL) maintaining the temperature under 35 °C. Potassium hydroxide (5 g) was added the mixture stirred for 1 hour. The liquid portion was decanted from the solid residue and allowed to stand over two successive portions of potassium hydroxide (5 g) for 1 hour each. The clear colourless liquid was purified by distillation (4 mbar, 40-41 °C) affording the *title compound* **178** (6.60 g, 64%); ν_{max} (liquid film)/cm^{-1} 3418, 3265, 2972, 1705, 1441, 1385, 1361, 1279, 1237, 1116; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.98 (1H, s br, NH) 1.70 (3H, s, N=C(CH$_3$)(CH$_3$)) 1.49 (3H, s, N=C(CH$_3$)(CH$_3$)) 0.95 (9H, s, NHC(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.2 (C) 53.0 (C) 28.6 (CH_3) 25.5 (CH_3) 15.3 (CH_3); *m/z* (APcI) [M+H]$^+$ 129 (100%). HRMS (ES) (found 129.1312 [M+H]$^+$; $C_7H_{17}N_2$ requires 129.1313).

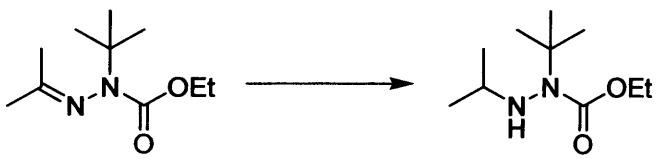
N-tert-Butyl-*N'*-(propan-2-ylidene) ethyl carbazate 179



178 179

To a suspension of *N-tert*-butyl-*N'-iso*-propylidene-hydrazine **178** (1.00 g, 7.80 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added saturated sodium bicarbonate solution (10 mL). Ethyl chloroformate **171** (1.02 g, 9.36 mmol, 0.90 mL) was added dropwise to the suspension and stirring was continued at 0 °C for 30 minutes and at ambient temperature for 16 hours. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2x5 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed *in vacuo* to give a yellow oil. Purification by chromatography eluting with ether/light petrol (1:1) afforded the *title compound* **179** (662 mg, 64%) as a colourless oil; ν_{max} (liquid film)/cm^{-1} 2975, 2923, 1698, 1652, 1482, 1456, 1393, 1367, 1304, 1257, 1224, 1170, 1086; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.91 (2H, q, J = 7.1, OC$\underline{H}_2$CH$_3$) 1.91 (3H, s, N=C(C$\underline{H}_3$)(CH$_3$)) 1.71 (3H, s, N=C(CH$_3$)(C$\underline{H}_3$)) 1.21 (9H, s, NC(C$\underline{H}_3$)$_3$) 1.04 (3H, t, J = 7.1, OCH$_2$C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.0 (C) 153.6 (C) 60.8 (CH_2) 58.3 (C) 28.2 (CH_3) 24.5 (CH_3) 19.5 (CH_3) 14.6 (CH_3); *m/z* (APcI) $[M+H]^+$ 201 (100%); HRMS (ES) (found 201.1597 $[M+H]^+$; $C_{10}H_{21}N_2O_2$ requires 201.1598).

N-tert-Butyl-*N'-iso*-propyl ethyl carbazate 180

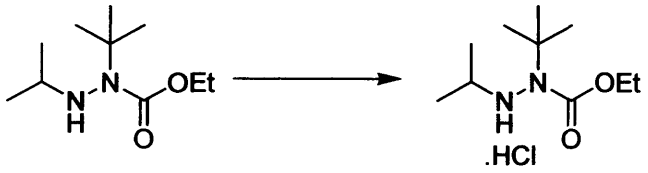


179 180

Platinum(IV) oxide (28 mg, 0.12 mmol, 5 mol%) was placed in a nitrogen flushed flask with ethanol (6 mL) and acetic acid (3 mL). *N-tert*-Butyl-*N'*-(propan-2-ylidene) ethyl carbazate **179** (500 mg, 2.50 mmol) was added, the flask was charged with hydrogen and stirring was

continued for 24 hours at ambient temperature. The reaction mixture was filtered over Celite and the filtrate was neutralised with saturated sodium bicarbonate solution (25 mL) which caused the product to precipitate. The suspension was extracted with diethyl ether (5x15 mL) and the combined organic extracts were washed with brine (8 mL), dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **180** (467 mg, 93%) as a clear colourless oil; ν_{max} (liquid film)/cm^{-1} 3314, 2971, 1702, 1467, 1396, 1367, 1308, 1250, 1223, 1168, 1081; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.09 (2H, q, J = 7.1, OC<u>H</u>$_2$CH$_3$) 3.80 (1H, s br, N<u>H</u>) 3.01 (1H, sept., J = 6.4, NC<u>H</u>(CH$_3$)$_2$) 1.28 (9H, s, NC(C<u>H</u>$_3$)$_3$) 1.22 (3H, t, J = 7.1, OCH$_2$C<u>H</u>$_3$) 0.92 (6H, d, J = 6.4, NCH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.3 (C) 61.2 (CH_2) 58.9 (C) 50.6 (CH) 29.0 (CH_3) 21.3 (CH_3) 20.8 (CH_3) 14.5 (CH_3); *m/z* (APcI) $[M+H]^+$ 203 (100%); HRMS (ES) (found 203.1756 $[M+H]^+$; $C_{10}H_{23}N_2O_2$ requires 203.1754).

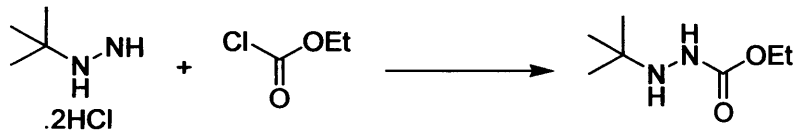
N-tert-Butyl-*N'-iso*-propyl ethyl carbazate hydrochloride 168



180 **168**

N-tert-Butyl-*N'-iso*-propyl ethyl carbazate **180** (250 mg, 1.24 mmol) was diluted with dry ether (500 µL) prior to the addition of ethereal hydrochloride (1 M, 6.19 mmol, 3.10 mL) and the solution was swirled for 10 minutes. The volume of liquor was reduced and the precipitate was filtered and washed with cold ether affording the *title compound* **168** (272 mg, 92%) as a colourless solid; mp 115-117 °C; ν_{max} (nujol)/cm^{-1} 2924, 2853, 1732, 1541, 1464, 1376, 1290; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.50 (2H, s br, N<u>H</u>$_2$) 4.26 (2H, q, J = 7.1, OC<u>H</u>$_2$CH$_3$) 3.69 (1H, sept., J = 6.6, NC<u>H</u>(CH$_3$)$_2$) 1.61 (9H, s, NC(C<u>H</u>$_3$)$_3$) 1.46 (6H, s br, NCH(C<u>H</u>$_3$)$_2$) 1.32 (3H, t, J = 7.1, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.0 (C) 64.4 (CH_2) 62.3 (C) 57.6 (CH) 29.0 (CH_3) 18.5 (CH_3) 14.3 (CH_3); *m/z* (APcI) $[M+H]^+$ 203 (100%); HRMS (ES) (found 203.1753 $[M+H-HCl]^+$; $C_{10}H_{23}N_2O_2$ requires 203.1754).

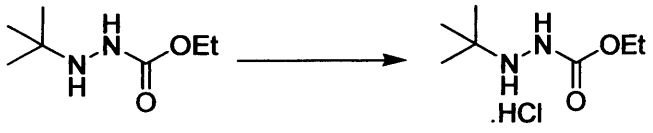
N'-tert-Butyl ethyl carbazate 185



177 **171** **185**

tert-Butylhydrazine dihydrochloride **177** (5.00 g, 40.1 mmol) was cooled to 0 °C in a biphasic solution of CH_2Cl_2 (50 mL) and saturated aqueous sodium bicarbonate (50 mL). Ethyl chloroformate **171** (4.35 g, 3.84 mmol, 40.1 mmol) was added dropwise to the suspension and stirring was continued at 0 °C for 30 minutes and at ambient temperature for 18 hours. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2x20 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed *in vacuo* to give a colourless oil. Purification by chromatography eluting with ether/light petrol (1:1) afforded the *title compound* **185** (662 mg, 10%) as a colourless oil; ν_{max} (liquid film)/cm^{-1} 3302, 2973, 1713, 1538, 1475, 1445, 1364, 1335; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.97 (1H, s br, NH) 4.10 (2H, q, J = 6.8, $OC\underline{H}_2CH_3$) 1.20 (3H, t, J = 6.8, $OCH_2C\underline{H}_3$) 1.02 (9H, s, $NC(C\underline{H}_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.1 (C) 61.4 (CH_2) 54.9 (C) 27.0 (CH_3) 14.6 (CH_3); *m/z* (APcI) $[M+H]^+$ 161 (100%); HRMS (ES) (found 161.1285 $[M+H]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

N'-tert-Butyl ethyl carbazate hydrochloride 184

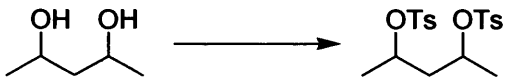


185 **184**

N'-tert-butyl ethyl carbazate **185** (200 mg, 1.25 mmol) was diluted with ether (400 μL) prior to the addition of ethereal hydrochloride (2 M, 6.25 mmol, 3.1 mL) and the solution was swirled for 10 minutes. The volume of liquor was reduced and the precipitate was filtered and washed with cold ether affording the *title compound* **184** (226 mg, 92%) as a colourless solid; mp (ether/chloroform) 157-158 °C; ν_{max} (nujol)/cm^{-1} 3238, 2924, 2684, 1714, 1531, 1463,

1376, 1275, 1176; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 10.77 (2H, s br, $N\underline{H}_2$) 9.38 (1H, s, $N\underline{H}$) 4.23 (2H, q, J = 6.9, $OC\underline{H}_2CH_3$) 1.41 (9H, s, $NC(C\underline{H}_3)_3$) 1.26 (3H, t, J = 6.9, $OCH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 156.3 (C) 63.9 (CH_2) 63.3 (C) 24.8 (CH_3) 14.3 (CH_3); *m/z* (APcI) $[M+H-HCl]^+$ 161 (100%); HRMS (ES) (found 161.1284 $[M+H-HCl]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

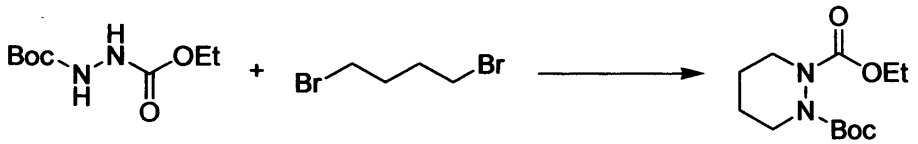
2,4-pentane di-4-methylbenzenesulfonate 196[122]



195 **196**

4-Methylbenzene-1-sulfonyl chloride (458 mg, 2.40 mmol) was added gradually to a stirred solution of racemic 2,4-dihydroxy pentane **195** (100 mg, 0.96 mmol) in pyridine (4 mL) at 0 °C. After 1 hour the mixture was allowed to warm to ambient temperature and stirred for a further 15 hours. The reaction was poured into water (4 mL) the resulting solution extracted with ether (7x3 mL). The combined organics we washed with aqueous hydrochloric acid (7x3 mL), saturated sodium hydrogen carbonate (6 mL) and brine (6 mL) and then dried ($MgSO_4$). The volatiles were removed under reduced pressure and the crude product was purified by chromatography eluting with ether providing the *title compound* **196** (324 mg, 82%) as a colourless powder; mp (ether/petrol) 136-137 °C [lit.[131] mp 135.5-136 °C]; ^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.68 (4H, d, J = 8.1, Ar-$\underline{H}$) 7.25 (4H, d, J = 8.1, Ar-$\underline{H}$) 4.64 (2H, tq, J = 6.1 6.1, $CH_3C\underline{H}(O)CH_2$) 2.36 (6H, s, Ar-$C\underline{H}_3$) 1.82 (2H, t, J = 6.1, $C\underline{H}_2$) 1.17 (6H, d, J = 6.1, $C(O)HC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.6 (C) 133.2 (C) 130.6 (CH) 128.3 (CH) 77.2 (CH) 43.9 (CH_2) 21.8 (CH_3) 21.5 (CH_3). Spectroscopic data agreed with literature values.

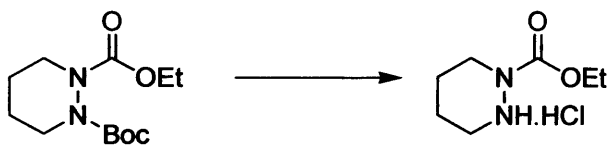
tert-Butyl ethyl piperazine-1,2-dicarboxylate 201



143 200 201

N'-tert-Butyl ester ethyl carbazate **143** (2.00 g, 9.80 mmol) was added to a stirred solution of toluene (40 mL) containing tetraethylammonium bromide (230 mg, 1.63 mmol) and 1,4-dibromobutane **200** (3.17 g, 14.7 mmol, 1.75 mL). Aqueous sodium hydroxide (20 mL, 50% w/w) was added at ambient temperate and the reaction brought to reflux for 45 minutes or until the *N'-tert*-butyl ester ethyl carbazate was consumed. The reaction was cooled and diluted with ethyl acetate (50 mL) and washed with aqueous saturated sodium hydrogen carbonate. The organic layer was separated, washed with water (10 mL) and brine (10 mL) and subsequently dried ($MgSO_4$). The volatiles were removed under reduced pressure. The crude mixture was purified by chromatography eluting with ether/light petrol (1:1) affording the *title compound* **201** (2.00 g, 79%) as a light yellow oil; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 4.17 (2H, m br, $OC\underline{H}_2CH_3$) 4.07 (2H, m br, C<u>H</u>HN) 2.88 (2H, m br, CH<u>H</u>N) 1.63 (4H, m br, $CH_2C\underline{H}_2C\underline{H}_2CH_2$) 1.46 (8H, s, $(C\underline{H}_3)_3$) 1.27 (3H, t, J = 7.0, $C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.2 (C) 159.9 (C) 80.4 (C) 59.7 (CH_2) 47.2 (CH_2) 46.5 (CH_2) 29.1 (CH_3) 21.7 (CH_2) 14.1 (CH_3); *m/z* (ES) $[M+H]^+$ 253.0 (68%) 231.1 (21) 185.0 (79) 157.0 (100); HRMS (ES) (found 259.1581 $[M+H]^+$; $C_{12}H_{23}N_2O_4$ requires 259.1580).

Ethyl piperazine-1-carboxylate hydrochloride 198

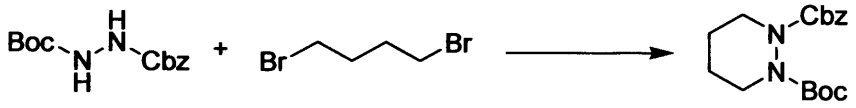


201 198

tert-Butyl ethyl piperazine-1,2-dicarboxylate **201** (500 mg, 1.97 mmol) was dissolved in dry ether (1.0 mL) prior to the addition of hydrochloric acid in ether (1 M, 10 mL). The reaction

was left to stand at ambient temperature for 24 hours or until the starting material was consumed by TLC. The volume of liquor was reduced and the precipitate filtered and washed with cold ether affording the *title compound* **198** (294 mg, 78%) as a colourless solid; mp 147.5–148 °C; ν_{max} (nujol)/cm^{-1} 3460, 2962, 2253, 1734, 1560, 1468, 1382, 1261; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 4.32 (2H, q, J = 7.1, OC$\underline{H}_2$CH$_3$) 3.92 (2H, t, J = 5.6, C$\underline{H}_2$NCO) 3.45 (2H, t, J = 5.8, C$\underline{H}_2$NH$_2$) 2.08-2.19 (2H, m, C$\underline{H}_2$CH$_2$NCO) 1.69-1.78 (2H, m, C$\underline{H}_2$CH$_2$NH$_2$)1.36 (3H, t, J = 7.1, CH$_2$C$\underline{H}_3$); ^{13}C NMR (125 MHz, d_6-DMSO) δ_C 153.2 (C) 62.7 (CH_2) 46.0 (CH_2) 45.7 (CH_2) 24.0 (CH_2) 14.6 (CH_2) 14.3 (CH_3); *m/z* (ES) [M+H-HCl]$^+$ 159.1 (90%) 131.0 (28) 113.0 (100); HRMS (ES) (found 159.1129 [M+H]$^+$; $C_7H_{15}N_2O_2$ requires 159.1128).

tert-Butyl benzyl piperazine-1,2-dicarboxylate 202



147 **200** **202**

N'-tert-Butyl ester benzyl carbazate **147** (2.00 g, 7.51 mmol) was added to a stirred solution of toluene (40 mL) containing tetraethylammonium bromide (260 mg, 1.44 mmol) and 1,4-dibromobutane **200** (2.43 g, 11.3 mmol, 1.35 mL). Aqueous sodium hydroxide (20 mL, 50% w/w) was added at ambient temperate and the reaction brought to reflux for 60 minutes or until the *N'-tert*-butyl ester benzyl carbazate had been consumed. The reaction was cooled and diluted with ethyl acetate (50 mL) and washed with aqueous saturated sodium hydrogen carbonate (20 mL). The organic layer was separated, washed with water (15 mL) and brine (15 mL) and subsequently dried ($MgSO_4$). The volatiles were removed under reduced pressure. The mixture was purified by chromatography eluting with ether/light petrol (1:1) affording the *title compound* **202** (1.26 g, 52%) as a colourless solid; mp 73-74 °C; ν_{max} (nujol)/cm^{-1} 2928, 2855, 1712, 1683, 1453, 1425, 1369, 1288, 1261, 1201, 1164, 1134, 1080, 1058; ^{1}H NMR (400MHz, d_6-DMSO) δ_H 7.29-7.39 (5H, m, Ar-$\underline{H}$) 5.05-5.29 (2H, m, C$\underline{H}_2$Ar) 4.00-4.22 (2H, m, C$\underline{H}$HN) 2.81-3.12 (2H, m, CH$\underline{H}$N) 1.54-1.72 (4H, m, CH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$) 1.28-1.54 (9H, m, C(C$\underline{H}_3$)$_3$); ^{13}C NMR (125MHz, $CDCl_3$) δ_C 154.8 (C) 154.0 (C) 136.4 (C) 128.4 (CH) 128.0 (CH) 127.9 (CH) 81.2 (C) 67.5 (CH_2) 44.8 (CH_2) 40.4 (CH_2) 28.1 (CH_3)

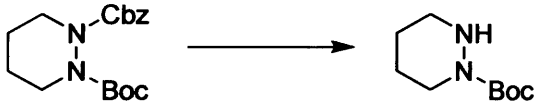
23.8 (CH_2) 23.6 (CH_2); *m/z* (ES) $[M+Na]^+$ 343 (20%) 265 (31) 221 (78); HRMS (ES) (found 321.1803 $[M+H]^+$; $C_{17}H_{25}N_2O_4$ requires 321.1809).

Benzyl piperazine-1-carboxylate hydrochloride 199

202 **199**

tert-Butyl benzyl piperazine-1,2-dicarboxylate **202** (1.00 g, 3.12 mmol) was dissolved in dry ether (0.5 mL) prior to the addition of hydrochloric acid in ether (1 M, 15.6 mmol). The reaction was left to stand at ambient temperature for 22 hours until the starting material was consumed. The volume of liquor was reduced and the precipitate filtered and washed with cold ether affording the *title compound* **199** (682 mg, 85%) as a colourless solid; mp (ether/chloroform) 146-147 °C; ν_{max} (nujol)/cm^{-1} 3340, 2920, 1736, 1558, 1461, 1377; ^1H NMR (400 MHz, d_6-DMSO) δ_H 11.92 (2H, s br, $N\underline{H}_2$) 7.23-7.39 (5H, m, Ar-$\underline{H}$) 5.52 (2H, s, $C\underline{H}_2Ar$) 3.78-3.86 (2H, m, $C\underline{H}_2N$) 3.38-3.42 (2H, m, $C\underline{H}_2N$) 1.95-2.08 (2H, m, $CH_2CH_2C\underline{H}_2CH_2$) 1.56-1.65 (2H, m, $CH_2C\underline{H}_2CH_2CH_2$); ^{13}C NMR (100 MHz, d_6-DMSO) δ_C 159.1 (C) 141.2 (C) 129.4 (CH) 128.1 (CH) 127.4 (CH) 66.8 (CH_2) 52.4 (CH_2) 49.1 (CH_2) 23.4 (CH_2) 20.8 (CH_2); *m/z* (ES) $[M+H-HCl]^+$ 221 (100%); HRMS (ES) (found 221.1285 $[M+H-HCl]^+$; $C_{12}H_{17}N_2O_2$ requires 221.1285).

tert-Butyl piperazine-1-carboxylate 210[132]

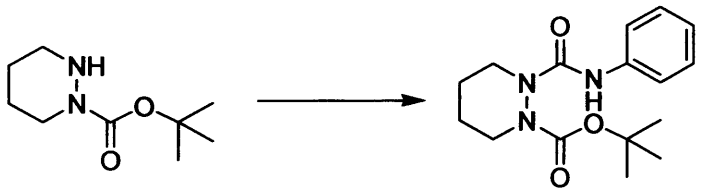


202 **210**

Palladium (10% on activated carbon, 16 mg, 15.6 μmol) was placed in a nitrogen flushed flask with ethanol (5 mL). *tert*-Butyl benzyl piperazine-1,2-dicarboxylate **202** (500 mg,

1.56 mmol) was added, the flask was charged with hydrogen and stirred for 24 hours or until the starting material was consumed. The reaction mixture was filtered over Celite and the volatiles were removed from the filtrate under reduced pressure. The crude product was purified by chromatography eluting with ether affording the *title compound* **210** (258 mg, 89%) as a clear colourless oil; ν_{max} (CH_2Cl_2)/cm^{-1} 3054, 2985, 1695, 1420, 1400, 1265, 1159, 1125, 1054; ^1H NMR (400 MHz, d_6-DMSO) δ_H 4.61 (1H, s br, NH) 3.45 (2H, t, J = 5.5, CH_2NCO) 2.81 (2H, t, J = 5.4, CH_2NH) 1.57-1.62 (2H, m, CH_2CH_2N) 1.46-1.52 (2H, m, CH_2CH_2N) 1.41 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.1 (C) 80.2 (C) 52.1 (CH_2) 49.5 (CH_2) 39.1 (CH_3) 23.1 (CH_2) 21.8 (CH_2); *m/z* (APcI) $[M+H]^+$ 187 (23%) 87 (100); HRMS (ES) (found 187.1366 $[M+H]^+$; $C_9H_{19}N_2O_2$ requires 187.1368).

tert-Butyl 2-(phenylcarbamoyl)piperazine-1-carboxylate 215

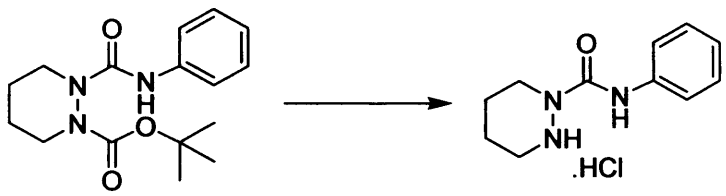


210 **215**

tert-Butyl piperazine-1-carboxylate **210** (200 mg, 1.08 mmol) was dissolved in CH_2Cl_2 (5 mL) at ambient temperature. Phenyl isocyanate **214** (128 mg, 1.08 mmol, 113 μL) was added dropwise with stirring which continued for 3 hours. The volatiles were removed under reduced pressure and the crude product was purified by chromatography eluting with ether followed by recrystallisation with chloroform/petrol (6:1) resulting in the *title compound* **215** (292 mg, 89%) as a colourless solid; mp (chloroform/petrol) 131-132 °C; ν_{max} (nujol)/cm^{-1} 3339, 2923, 2853, 1733, 1702, 1668, 1593, 1533, 1452, 1376; 1303, 1255, 1227, 1155; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.36 (2H, d, J = 8.2, Ar-H) 7.23 (2H, dd, J = 8.2 7.1, Ar-H) 6.97 (1H, t, J = 7.1, Ar-H) 4.34-4.39 (1H, m, NCHH) 4.02-4.12 (1H, m, NCHH) 2.89-2.96 (1H, m, NCHH) 2.72-2.81 (1H, m, NCHH) 1.51-1.69 (4H, m, $NCH_2CH_2CH_2CH_2N$) 1.41 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 156.0 (C) 153.8 (C) 138.6 (C) 128.9 (CH) 123.0 (CH) 119.2 (CH) 82.7 (C) 47.0 (CH_2) 41.8 (CH_2) 28.15 (CH_3) 23.3 (CH_2) 23.0 (CH_2); *m/z*

(ES) $[M+Na]^+$ 328 (11%) 306 (10) 250 (21) 206 (46); HRMS (ES) (found 306.1809 $[M+H]^+$; $C_{16}H_{24}N_3O_3$ requires 306.1812).

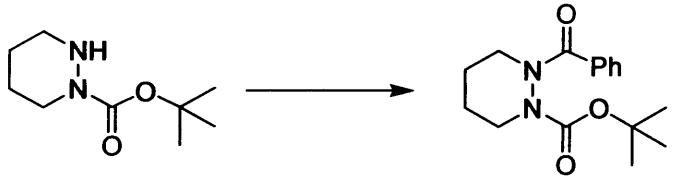
N-Phenylpiperazine-1-carboxamide hydrochloride 207



215 **207**

tert-Butyl 2-(phenylcarbamoyl)piperazine-1-carboxylate **215** (558 mg, 1.83 mmol) was dissolved in hydrochloride acid in methanol (2.35 M, 9.15 mmol, 3.90 mL) and left under an inert atmosphere at ambient temperature for 20 hours until the starting material was consumed by TLC. The volatiles were removed under reduced pressure resulting in the *title compound* **207** (426 mg, 96%) as a colourless solid; mp 162-163 °C; ν_{max} (nujol)/cm^{-1} 3423, 3181, 2916, 1708, 1600, 1540, 1461, 1378, 1302, 1243, 1205, 1097, 1076; ^1H NMR (400 MHz, d_6-DMSO) δ_H 7.55 (2H, d, J = 7.7, Ar-H) 7.3 (2H, m, Ar-H) 7.03 (1H, t, J = 7.3, Ar-H) 3.78-3.92 (2H, m, NCH_2) 3.09-3.19 (2H, m, NCH_2) 1.75-1.82 (2H, m, NCH_2CH_2) 1.74-1.63 (2H, m, NCH_2CH_2); ^{13}C NMR (125 MHz, d_6-DMSO) δ_C 155.2 (C) 138.8 (C) 128.7 (CH) 123.0 (CH) 119.7 (CH) 46.2 (CH_2) 45.5 (CH_2) 22.3 (CH_2) 20.87 (CH_2); *m/z* (ES) $[M+H-HCl]^+$ 206 (100%).

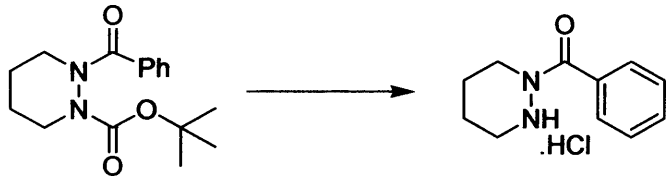
tert-Butyl 2-benzoylpiperazine-1-carboxylate 211



210 **211**

tert-Butyl piperazine-1-carboxylate **210** (300 mg, 1.61 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and stirred with saturated aqueous sodium hydrogen carbonate (1.5 mL). Benzoyl chloride **174** (453 mg, 3.23 mmol, 374 μL) was added drop wise over 10 minutes and the biphasic solution was stirred vigorously for 17 hours at ambient temperature. The organics were separated and the aqueous layer was extracted with CH_2Cl_2 (2x1 mL). The combined organics were dried (Na_2SO_4) and the volatiles were removed under reduced pressure. The crude product was purified by chromatography eluting with ether/light petrol (1:1) resulting the *title compound* **211** (382 mg, 82%) as a colourless powder; mp (ether/petrol) 117-118 °C; ν_{max} (nujol)/cm^{-1} 2924, 2855, 1699, 1655, 1458, 1377, 1283, 1208, 1156, 1079, 1045; ^{1}H NMR (400MHz, $CDCl_3$) δ_H 7.45-7.67 (2H, m, Ar-H) 7.25-7.43 (3H, m, Ar-H) 4.48-4.58 (1H, m, NCHH) 4.05-4.17 (1H, m, NCHH) 2.83-2.97 (1H, m, NCHH) 2.70-2.81 (1H, m, NCHH) 1.60-1.88 (4H, m, $CH_2CH_2CH_2CH_2$) 1.25 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 154.61(C) 159.82 (C) 134.3 (C) 130.2 (CH) 127.7 (CH) 127.4 (CH) 82.1 (C) 46.7 (CH_2) 42.5 (CH_2) 28.0 (CH_3) 23.6 (CH_2) 23.1 (CH_2); *m/z* (ES) $[M+Na]^+$ 313 (19%) 235 (22) 191 (100); HRMS (ES) (found 291.1702 $[M+H]^+$; $C_{16}H_{23}N_2O_3$ requires 291.1703).

Phenyl(piperazin-1-yl)methanone hydrochloride 204

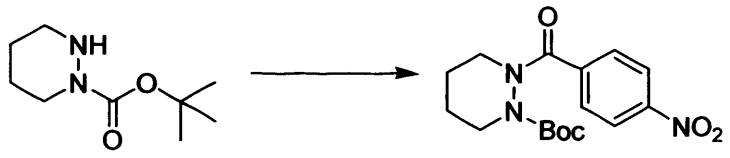


211 **204**

tert-Butyl 2-benzoylpiperazine-1-carboxylate **211** (200 mg, 0.69 mmol) was dissolved in hydrochloric acid in methanol (1.65 M, 3.45 mmol, 2.10 mL) and stood under an inert atmosphere 19 hours until the starting material was consumed by TLC. The volatiles were removed under reduced pressure affording the *title compound* **204** (150 mg, 96%) as a colourless solid; mp 164-166 °C; ν_{max} (nujol)/cm^{-1} 3336, 2844, 1697, 1589, 1461, 1378, 1321, 1287, 1179, 1075, 1041; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 7.61-7.79 (5H, m, Ar-H) 3.81-3.88 (2H, m, NCH_2) 3.10-3.13 (2H, m, NCH_2) 1.95 (2H, s br, NH_2) 1.76-1.81 (4H, m, $CH_2CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.6 (C) 135.2 (C) 132.3 (CH) 131.9

(CH) 131.2 (CH) 49.9 (CH_2) 48.7 (CH_2) 26.3 (CH_2) 25.1 (CH_2); *m/z* (APcI) $[M+H]^+$ 191 (18%) 137 (100).

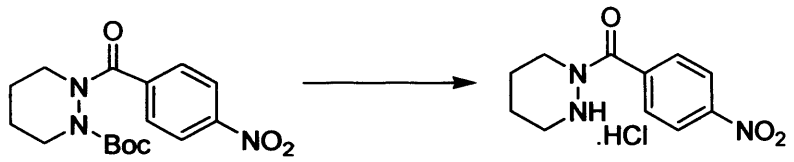
tert-Butyl 2-(4-nitro)benzoylpiperazine-1-carboxylate 212[132]



210 **212**

tert-Butyl piperazine-1-carboxylate **210** (200 mg, 1.08 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and stirred over saturated aqueous sodium hydrogen carbonate (1.0 mL). 4-nitrobenzoyl chloride (399 mg, 2.16 mmol) was added in one portion and the biphasic solution was stirred vigorously at ambient temperature for 18 hours. The organics were separated and the aqueous layer was extracted with CH_2Cl_2 (2x1 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed under reduced pressure. The crude product was purified by chromatography eluting with ether resulting in the *title compound* **212** (339 mg, 94%) as a light cream solid; mp (chloroform/petrol) 98-99 °C; ν_{max} (nujol)/cm^{-1} 2924, 1720, 1660, 1599, 1520, 1459, 1370, 1349, 1312, 1281; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.15 (2H, d, J = 7.7, Ar-H) 7.61 (2H, d, J = 7.7, Ar-H) 4.46-4.51 (1H, m, NCHH) 3.82-4.10 (1H, m, NCHH) 2.84-2.91 (2H, m, NCH_2) 1.77-1.82 (2H, m, $CH_2CH_2CH_2CH_2$) 1.66-1.72 (2H, m, $CH_2CH_2CH_2CH_2$) 1.29 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2 (C) 148.6 (C) 131.1 (C) 128.1 (C) 124.2 (CH) 123.0 (CH) 82.8 (C) 48.2 (CH_2) 44.6 (CH_2) 28.0 (CH_3) 23.4 (CH_2) 22.6 (CH_2); *m/z* (ES) $[M+Na]^+$ 358 (23%) 336 (18) 280 (78) 236 (100); HRMS (EI) (found 336.1551 $[M+H]^+$; $C_{16}H_{22}N_3O_5$ requires 336.1554).

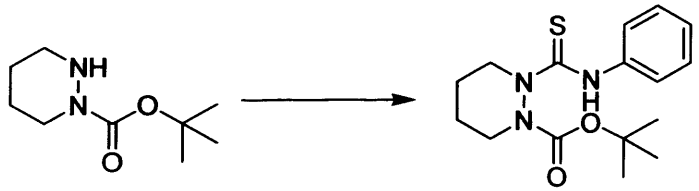
(4-Nitrophenyl)(piperazin-1-yl)methanone hydrochloride 205



212 205

tert-Butyl 2-(4-nitro)benzoylpiperazine-1-carboxylate **212** (100 mg, 299 μmol) was dissolved in hydrochloric acid in methanol (1.62 M, 1.49 mmol, 1.0 mL) and left at ambient temperature for 23 hours until the starting material was consumed. The volatiles were removed under reduced pressure resulting in the *title compound* **205** (73 mg, 94%) as a colourless solid; mp 159-160 °C; ν_{max} (nujol)/cm^{-1} 3409, 2932, 2855, 1652, 1597, 1525, 1466, 1446, 1404, 1384, 1357, 1321; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 8.48 (2H, d, J = 7.6, Ar-H) 8.26 (2H, d, J = 7.6, Ar-H) 3.20-3.28 (2H, m, NCH$_2$) 2.67-2.73 (2H, m, NCH$_2$) 1.62-1.71 (4H, m, CH$_2$CH$_2$CH$_2$CH$_2$); ^{13}C NMR (100 MHz, d_6-DMSO) δ_C 174 (C) 153.1 (C) 141.8 (C) 129.4 (CH) 128.1 (CH) 51.8 (CH_2) 48.2 (CH_2) 23.7 (CH_2) 21.4 (CH_2); *m/z* (ES) $[M+H-HCl]^+$ 236.2 (100%) 167 (54).

tert-Butyl 2-(phenylthiocarbamoyl)piperazine-1-carboxylate 217

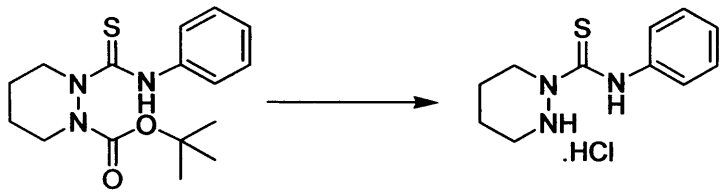


210 217

tert-Butyl piperazine-1-carboxylate **210** (125 mg, 670 μmol) was dissolved in CH_2Cl_2 (1.0 mL) at ambient temperature. Phenyl isothiocyanate **216** (109 mg, 803 μmol) was added dropwise with stirring which continued for 4 hours. The volatiles were removed under reduced pressure and the crude product was purified by chromatography eluting with ether, resulting in the *title compound* **217** (171 mg, 79%) as a colourless solid; mp (chloroform/petrol) 124-125 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3295, 2942, 2857, 1724, 1595, 1515,

1451, 1370, 1271, 1251, 1155, 1063, 1028; ^{1}H NMR (400MHz, $CDCl_3$) δ_H 8.26 (1H, s br, NH) 7.39 (2H, d, J = 7.7, Ar-H) 7.30 (2H, m, Ar-H) 7.16 (1H, t, J = 7.4, Ar-H) 5.41-5.47 (1H, m, NCHH) 4.08-4.13 (1H, m, NCHH) 2.90-2.98 (2H, m, CH_2N) 1.65-1.85 (4H, m, $CH_2CH_2CH_2CH_2$) 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 179.6 (C) 154.9 (C) 138.7 (C) 128.7 (CH) 126.11 (CH) 125.6 (CH) 83.24 (C) 47.1 (CH_2) 46.6 (CH_2) 28.2 (CH_3) 23.2 (CH_2) 22.6 (CH_2); *m/z* (ES) $[M+H]^+$ 322 (12%) 266 (23) 222 (37); HRMS (ES) (found 322.1581 $[M+H]^+$; $C_{16}H_{24}N_3O_2S$ requires 322.1584).

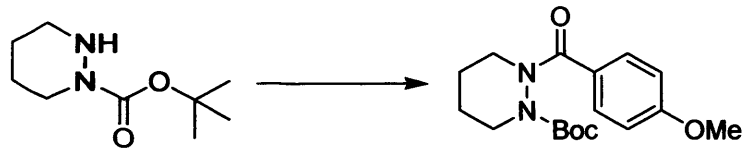
N-Phenylpiperazine-1-carbothioamide hydrochloride 208



217 **208**

tert-Butyl 2-(phenylthiocarbamoyl)piperazine-1-carboxylate **217** (100 mg, 312 μmol) was dissolved in hydrochloric acid in methanol (1.62 M, 1.49 mmol, 1 mL) and left at ambient temperature for 24 hours until the starting material was consumed. The volume of methanol was reduced and the precipitate was filtered and washed with ether (0.5 mL). The volatiles were removed under reduced pressure resulting in the *title compound* **208** (66.8 mg, 82%) as a colourless solid; mp (chloroform/petrol) 120-121 °C; ν_{max} (nujol)/cm^{-1} 3336, 2925, 2852, 1589, 1519, 1461, 1377, 1284, 1250, 1226, 1188, 1131, 1071, 1022; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 7.03 (2H, m, Ar-H) 6.73 (1H, t, J = 7.3, Ar-H) 6.48 (2H, d, J = 7.7, Ar-H) 3.52-3.57 (2H, m, NCH_2) 2.74-2.79 (2H, m, NCH_2) 1.64-1.78 (4H, m, $CH_2CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, d_6-DMSO) δ_C 158.1 (C) 136.9 (C) 131.4 (CH) 125.7 (CH) 122.6 (CH) 53.4 (CH_2) 50.1 (CH_2) 23.4 (CH_2) 24.5 (CH_2); *m/z* (ES) $[M+H-HCl]^+$ 222 (26%) 190 (40) 167 (100); HRMS (ES) (found 222.1058 $[M+H-HCl]^+$; $C_{11}H_{16}N_3S$ requires 222.1059).

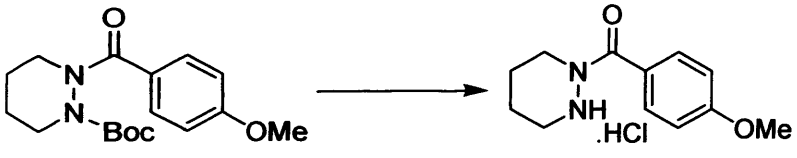
tert-Butyl 2-(4-methoxy)benzoylpiperazine-1-carboxylate 213[132]



210 **213**

4-Methoxybenzoyl chloride (220 mg, 1.29 mmol) was dissolved in a biphasic mixture of CH_2Cl_2 (6.0 mL) and saturated aqueous sodium hydrogen carbonate (6.0 mL) and was cooled to 0 °C. *tert*-Butyl piperazine-1-carboxylate **210** (200 mg, 1.08 mmol) was added drop wise and the mixture stirred at 0 °C for 30 minutes and the allowed to warm to ambient temperature and stirred for a further 19 hours. The organics were separated and the aqueous layer was extracted with CH_2Cl_2 (2x3 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed under reduced pressure. The crude product was purified by flash column chromatography eluting with ether/petrol (1:1) resulting in the *title compound* **213** (231 mg, 67%) as a clear colourless oil; ν_{max} (CH_2Cl_2)/cm^{-1} 3055, 2983, 2949, 1711, 1651, 1512, 1455, 1395, 1303, 1265; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 (2H, d, J = 8.2, Ar-H) 6.78 (2H, d, J = 8.2, Ar-H) 4.44-4.50 (1H, m, NCHH) 4.08-4.13 (1H, m, NCHH) 3.79 (3H, s, OCH_3) 2.68-2.98 (2H, m, NCH_2) 1.61-1.71 (4H, m, $CH_2CH_2CH_2CH_2$) 1.22 (9H, s br, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 170.4 (C) 161.2 (C) 153.6 (C) 129.6 (CH) 126.7 (C) 113.0 (CH) 81.9 (C) 55.3 (CH_3) 46.6 (CH_2) 42.7 (CH_2) 28.0 (CH_3) 23.5 (CH_2) 23.2 (CH_2); *m/z* (ES) $[M+H]^+$ 321 (13%) 265 (23) 221 (59); HRMS (ES) (found 321.1809 $[M+H]^+$; $C_{17}H_{25}N_2O_4$ requires 321.1809).

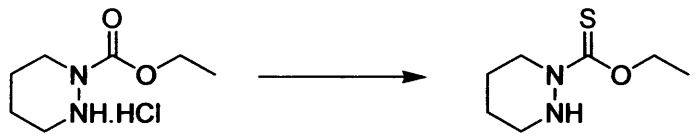
(4-Methoxyphenyl)(piperazin-1-yl)methanone hydrochloride 206



213 **206**

tert-Butyl 2-(4-methoxy)benzoylpiperazine-1-carboxylate **213** (300 mg, 940 μmol) was dissolved in hydrochloric acid in methanol (1.65 M, 4.69 mmol, 2.84 mL) and left to stand under an inert atmosphere at ambient temperature for 21 hours until the starting material was consumed. The volume of methanol was reduced and the precipitate filtered and washed with ether (1 mL). The volatiles were removed under reduced pressure resulting in the *title compound* **206** (231 mg, 96%) as a light cream solid; mp 138-139 °C; ν_{max} (nujol)/cm^{-1} 3360, 2922, 1725, 1606, 1536, 1512, 1461, 1376, 1277, 1255, 1167, 1106, 1033; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 7.96 (2H, d, J = 7.8, Ar-H) 7.05 (2H, d, J = 7.8, Ar-H) 3.86 (3H, s, CH_3) 3.28-3.32 (2H, m, NCH_2) 2.69-2.73 (2H, m, NCH_2) 2.5 (2H, s br, NH_2) 1.58-1.72 (2H, m, $CH_2CH_2CH_2CH_2$); ^{13}C NMR (125 MHz, d_6-DMSO) δ_C 176.1 (C) 166.2 (C) 131.1 (CH) 130.4 (C) 116.5 (CH) 58.5 (CH_3) 52.4 (CH_2) 49.4 (CH_2) 23.8 (CH_2) 21.1 (CH_2); *m/z* (ES) [M+H-HCl]$^+$ 221 (100%) 167 (46).

O-Ethyl piperazine-1-carbothioate 218

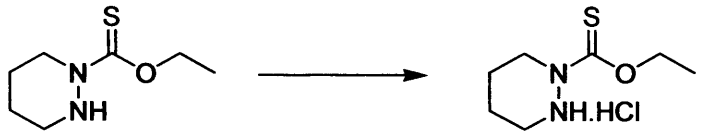


198 **218**

Ethyl piperazine-1-carboxylate hydrochloride **198** (600 mg, 3.08 mmol) was dissolved in CH_2Cl_2 (10 mL) and washed with saturated aqueous sodium hydrogen carbonate (3 mL). The organics were separated and the aqueous layer extracted with CH_2Cl_2 (2x2 mL). The combined organics were dried (Na_2SO_4) and the volatiles were removed under reduced pressure resulting in the free base of **198** as a light oil which was subsequently added in one portion to a stirred solution of Lawesson's reagent (649 mg, 1.60 mmol) in dry toluene (60 mL) and refluxed for 4 hours. The reaction mixture was allowed to cool to ambient temperature and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography eluting with ether/petrol (1:1) resulting in the *title compound* **218** (451 mg, 84%) as a viscous clear oil; ν_{max} (CH_2Cl_2)/cm^{-1} 3220, 3053, 2954, 1665, 1596, 1517, 1428, 1364, 1265, 1209, 1129, 1053; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 6.76 (1H, s br, NH) 4.43 (2H, q, J = 7.1, OCH_2CH_3) 3.77 (2H, t, J = 5.4, CH_2N) 2.92 (2H, t,

J = 5.3, C$\underline{H_2}$N) 1.71-1.78 (2H, m, C$\underline{H_2}$CH$_2$N) 1.51-1.57 (2H, m, C$\underline{H_2}$CH$_2$N) 1.28 (3H, t, J = 7.1, CH$_2$C$\underline{H_3}$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 151.4 (C) 67.6 (CH$_2$) 47.6 (CH$_2$) 45.6 (CH$_2$) 24.7 (CH$_2$) 24.0 (CH$_2$) 14.5 (CH$_3$); *m/z* (APcI) [M+H]$^+$ 175 (100%); HRMS (ES) (found 175.0901 [M+H]$^+$; $C_7H_{15}N_2OS$ requires 175.0900).

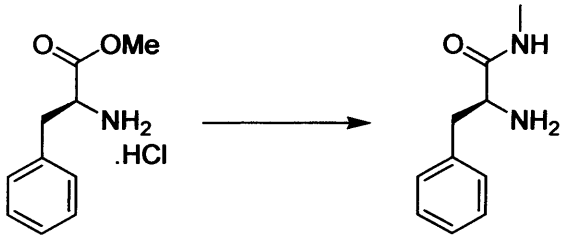
O-Ethyl piperazine-1-carbothioate hydrochloride 209



218 **209**

O-Ethyl piperazine-1-carbothioate **218** (400 mg, 2.30 mmol) was dissolved in hydrochloric acid in methanol (2.35 M, 11.5 mmol, 4.89 mL) and swirled under an inert atmosphere for 15 minutes. The volume of methanol was reduced and the precipitate was filtered and washed with ether (2 mL). The volatiles were removed under reduced pressure affording the *title compound* **209** (392 mg, 88%) as a light cream solid; mp 105-106 °C; ν_{max} (nujol)/cm^{-1} 3399, 2922, 2852, 1714, 1595, 1570, 1458, 1376, 1258, 1124, 1072, 1032; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 4.62 (2H, q, J = 7.1, OC$\underline{H_2}$CH$_3$) 3.92-3.97 (2H, m, C$\underline{H_2}$N) 3.22-3.26 (2H, m, C$\underline{H_2}$N) 1.96-2.01 (2H, m, C$\underline{H_2}$CH$_2$N) 1.83-1.88 (2H, m, C$\underline{H_2}$CH$_2$N) 1.29 (3H, t, J = 7.1, OCH$_2$C$\underline{H_3}$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 153.4 (C) 69.8 (CH$_2$) 56.4 (CH$_2$) 54.1 (CH$_2$) 28.5 (CH$_2$) 25.1 (CH$_2$) 19.8 (CH$_3$); *m/z* (APcI) [M+H-HCl]$^+$ 175 (100%); HRMS (ES) (found 175.0902 [M+H-HCl]$^+$; $C_7H_{15}N_2OS$ requires 175.0900).

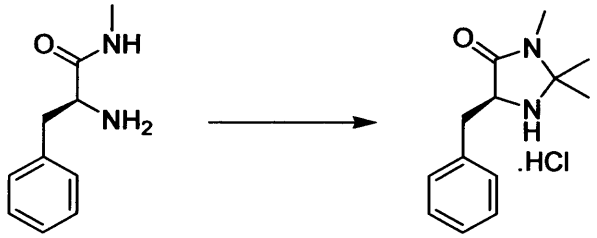
(*S*)-2-amino-*N*-methyl-3-phenylpropanamide 223[7]



222 **223**

Phenylalanine methyl ester hydrochloride **222** (1.0 g, 4.64 mmol) was dissolved in dry ethanol (0.5 mL) prior to the addition of ethanolic ammonia (576 mg, 18.5 mmol). The reaction was stirred at room temperature for 16 hours until the starting material was consumed by TLC. The volatiles were removed under reduced pressure resulting in a colourless solid which was dissolved in ether (100 mL) and subsequently washed with aqueous sodium hydrogen carbonate (10 mL). The aqueous layer was back extracted with ether (30 mL) and the combined organics were washed with brine (15 mL) and dried ($MgSO_4$). The volatiles were removed under reduced pressure affording the *title compound* **223** (594 mg, 71%) as a colourless solid requiring no further purification; spectroscopic data was consistent with the literature; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H 7.11-1.28 (5H, m, Ar-H) 3.54 (1H, dd, J = 4.0 9.5, CHHAr) 3.22 (1H, dd, J = 4.0 13.7 CHHAr) 2.75 (3H, d, J = 5.0 CH_3) 2.60 (1H, dd, J = 9.5 13.7, CH) 1.20 (2H, s br, NH_2).

(*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one 16[7]



223 **16**

(*S*)-2-amino-*N*-methyl-3-phenylpropanamide **223** (500 mg, 2.81 mmol) was dissolved in methanol (10 mL) containing acetone **60** (816 mg, 14.0 mmol, 1.03 mL) and *p*TSA (5 mg, 29 μmol). The resulting solution was refluxed for 24 hours and the volatiles were removed under reduced pressure after cooling to ambient temperature. The resulting compound was subjected to hydrochloric acid in methanol for 15 minutes. The volatiles were removed under reduced pressure resulting in the *title compound* **16** (585mg, 82%) as a colourless solid; spectroscopic data was in accordance to literature precedent.[7]

Appendices

Appendix 1: Solvent Purification Methods

Acetonitrile

Acetonitrile was dried by refluxing over, and distilling from calcium hydride.

Cyclopentadiene

Cyclopentadiene was cracked from dicyclopentadiene immediately prior to addition. The fraction boiling at 44°C was collected.

Dichloromethane

Dichloromethane was dried by refluxing over, and distilling from calcium hydride.

Diethyl Ether

Diethyl ether was obtained by distillation from sodium benzophenone ketyl.

Ethyl Acetate

Ethyl acetate was obtained by pre-drying with anhydrous magnesium sulfate followed by fresh distillation from calcium hydride.

Methanol

Methanol was dried by refluxing over magnesium, followed by distillation.

Tetrahydrofuran

Tetrahydrofuran was obtained dry by distillation from sodium-benzophenone ketyl under nitrogen.

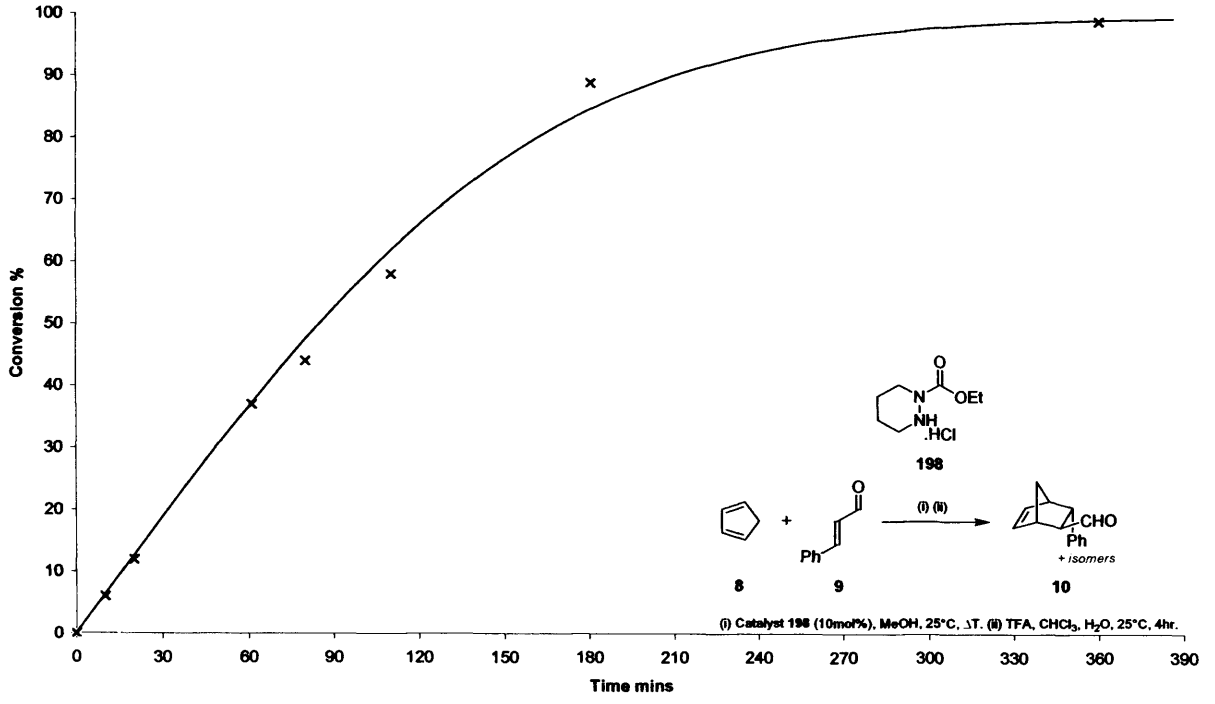
Triethylamine

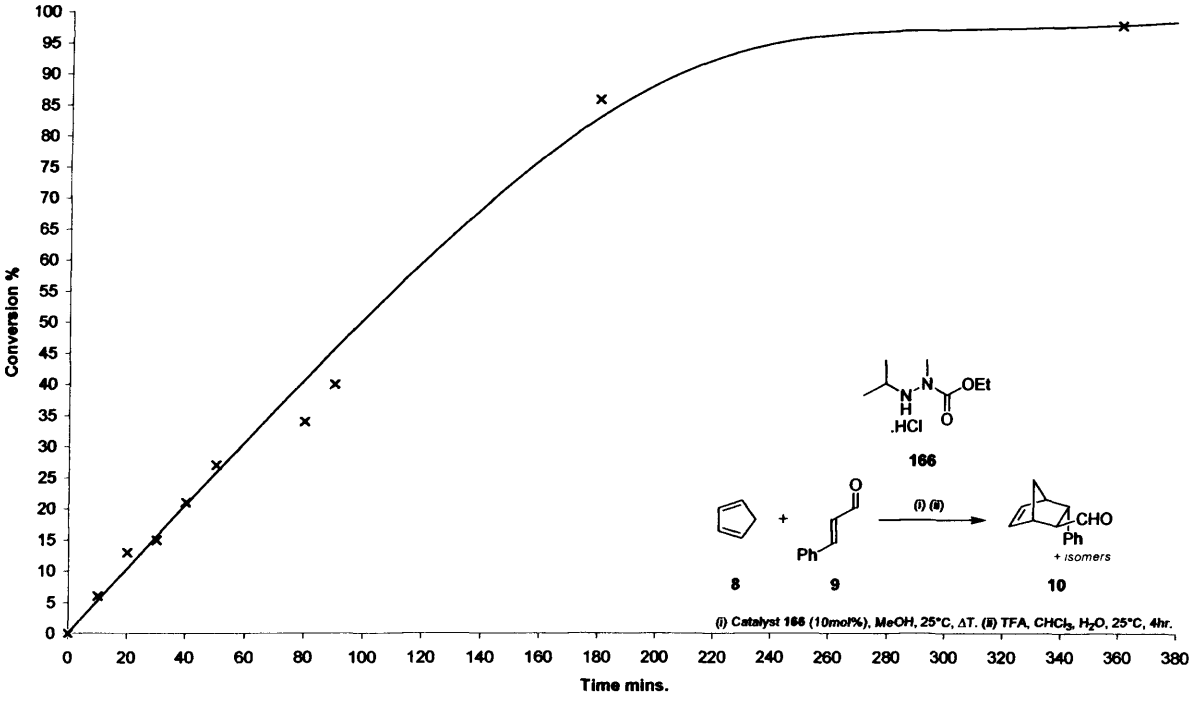
Triethylamine was purified by distillation over calcium hydride. The fraction boiling at 76°C was collected.

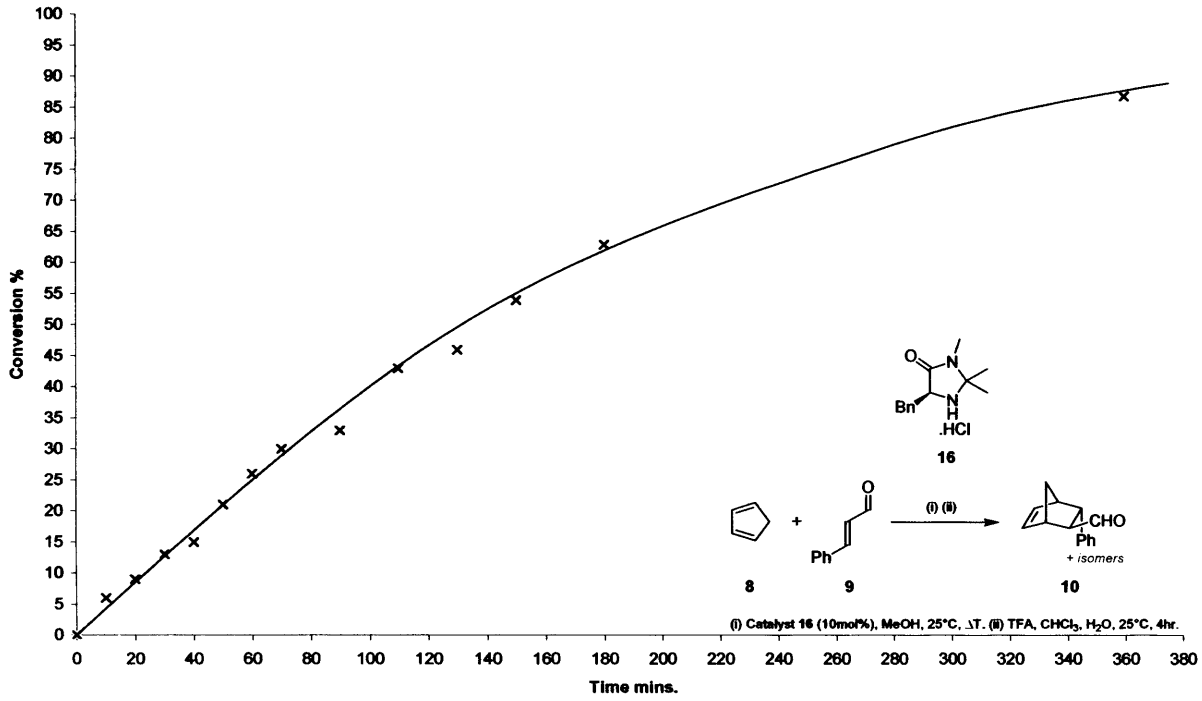
Toluene

Toluene was dried by standing over sodium wire for 24 hours prior to use.

Appendix 2: Catalysis Reaction Profiles






Conversion %
Time mins.
16
8
9
10
+ isomers
(i) Catalyst 16 (10mol%), MeOH, 25°C, ΔT. (ii) TFA, CHCl3, H2O, 25°C, 4hr.

References

1 Movassaghi, M.; Jacobsen, E. N. *Nature* **2002**, *298*, 1904.

2 Craig, D. P.; Mellor, D. P.; Gleiter, R.; Gygax, R.; Sutter, D. H.; Flygare, W. H. Top. Curr. Chem. 1976, 1.

3 (a) Pracejus. H. Justus *Liebigs Ann. Chem.* **1960**, *634*, 9. (b) Hajos, Z. G.; Parrish, D. R. J. *J. Org. Chem.* **1974**, *39*, 1615.

4 Dalko, P. I.; Miosan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.

5 Fubini, B.; Aréan, L. O. *Chem. Soc. Rev.* **1999**, *28*, 373.

6 For examples see individual sections.

7 Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

8 Alan, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

9 Park, J. K.; Sreekanth, P.; Kim, B. M. *Adv. Synth. Catal.* **2004**, *346*, 49.

10 Benaglia, M.; Celentano, G.; Cinquini, M.; Puglisi, A.; Cozzi, F. *Adv. Synth. Catal.* **2002**, *344*, 149.

11 Selkala, S. A.; Tois, J.; Pihko, P. M.; Koskinen, A. M. P. *Adv. Synth. Catal.* **2002**, *344*, 941.

12 Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.

13 Cavill, J. L.; Peters, J.-U.; Tomkinson, N. C. O. *Chem. Commun.* **2003**, 728.

14 Kim, K. H.; Lee, S.; Lee, D.-W.; Ko, D.-H.; Ha, D.-C. *Tetrahedron Lett.* **2005**, *46*, 5991.

15 Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504.

16 Lemay, M.; Ogilvie, W. *Org. Lett.* **2005**, *7*, 4141.

17 Jen, W. S.; Wiener, J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

18 Puglisi, A.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Eur. J. Org. Chem.* **2004**, *3*, 567.

19 Karlsson, S.; Hoegberg, H.-E. *Eur. J. Org. Chem.* **2003**, *13*, 2782.

20 Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

21 Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.

22 Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

23 Monte Carlo simulation, MM3 force-field; Macromodel v6.5.

24 Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.

25 Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

26 Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

27 Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5482.

28 Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051.

29 Masahiko, Y.; Tai, S.; Yoshihiro, I.; Masahiro, H. *Tetrahedron Lett.* **1994** ,*35*, 8233.

30 Halland, N.; Hazell, R. G.; Jorgensen, K. A. J. Org. Chem. **2002**, *67*, 8331.

31 Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661.

32 Hechavarria, F. M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958.

33 Woon, J.; Hechavarria, F. M. T.; List, B. Angew. Chem., Int. Ed. **2004**, *43*, 6660.

34 Yang, J. W.; Hechavarria, F. M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108.

[35] Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036.

[36] Ouellet, S. G; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

[37] In *Organic Chemistry*, Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., Oxford, **2001**, ch. 14, pp. 353.

[38] Sakthivel, K.; Notz, W.; Bui, T.; Barbas, III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.

[39] Enders, D.; Huettl, M. R. M. *Synlett* **2005**, 991.

[40] Sunden, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877.

[41] Ramachary, D., B.; Ramakumar, K.; Kishor, M. *Tetrahedron Lett.* **2005**, *46*, 7037.

[42] Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496.

[43] Hajos, Z. G.; Parrish, D. R.; Oliveto, E. P. *Tetrahedron* **1968**, *24*, 2039.

[44] Within the literature this reaction has been referred to using a combination of these names but all refer to the same transformation.

[45] For a review of Hajos-Parrish-Eder-Sauer-Wiechert reactions see: Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412.

[46] Kondo, K.; Yamano, T.; Takemoto, K. *Makremol. Chem.* **1985**, *186*, 1781.

[47] For a review see: Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357.

[48] Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.

[49] Rajagopal, D.; Moni, M. S.; Subramanian, S.; Swaminathan, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1631.

[50] List, B.; Lerner, R. A.; Barbas, III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[51] List, B.; Hoang, L.; Martin, H. J. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5839.

[52] Storer, R. I.; MacMillan, D. W. C. *Tetrahedron* **2004**, *60*, 7705.

[53] Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds. German Patent DE 2102623, July 29, **1971**.

[54] Shulmana, H.; Keinan, E.; *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1745.

[55] Mase, N.; Tanaka, F.; Barbas, III, C. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420.

[56] Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, 58, 8167.

[57] Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, 125, 2475.

[58] Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, 43, 6722.

[59] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.

[60] Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147.

[61] Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, III, C. F. *Tetrahedron Lett.* **2001**, *42*, 4441.

[62] List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

[63] Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, III, C. F. *Org. Lett.* **2004**, *6*, 2527.

[64] Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 3086.

[65] Rasalkar, M. S.; Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M. *J. Mol. Catal. A: Chem.* **2005**, *235*, 267.

[66] Bui, T.; Barbas, III, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951.

[67] Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, P. *Tetrahedron* **1985**, *41*, 1693.

[68] Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287.

[69] Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto. H. *J. Am. Chem. Soc.* **1994**, *116*, 10520.

[70] List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

[71] List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.

[72] Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, III, C. F. III. *J. Org. Chem.* **2003**, *68*, 9624.

[73] Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987.

[74] Electrostatic interactions have been observed in noncatalytic asymmetric Mannich-type reactions with preformed SMP enamines.

[75] Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, III, C. F. *Adv. Synth. Catal.* **2004**, *346*, 1131.

[76] Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243.

[77] Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677.

[78] Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476.

[79] Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.

[80] Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359.

[81] Steiner, D. D.; Mase, N.; Barbas, III, C. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706.

[82] Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219.

[83] Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *126*, 4108.

[84] Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.

[85] List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.

[86] Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jørgensen, K. A. *J. Am. Chem Soc.* **2002**, *124*, 6254.

[87] Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W, C, *J. Am. Chem. Soc.* **2003**, *125*, 10808.

[88] Engqvist, M.; Casas, J.; Sunden, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2053.

[89] Wang, W.; Wang, J.; Li, H.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 7235.

[90] Bogevig, A.; Sunden, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109.

[91] Iwamura, H.; Wells, D. H. Jr.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem Soc.* **2004**, *126*, 16312.

[92] Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317.

[93] Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

[94] Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Chem. Commun.* **1990**, 1412.

[95] Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.

[96] Wabnitz, T. C.; Saaby, S.; Jørgensen, K. A. *Org. Biomol. Chem.* **2004**, 828.

[97] In *Comprehensive Asymmetric Catalysis*, Vol. I-III: Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg. **1999**.

[98] Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

[99] (a) Grekov, A. P.; Veselov, V. Y. *Russ. Chem. Rev.* **1978**, *16*, 87. (b) Fina, N. J.; Edwards, J. O. *Int. J. Chem. Kinet.* **1973**, *5*, 1.

[100] Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16.

[101] Buncel, E.; Hoz, S. *Tetrahedron Lett.* **1983**, *24*, 4777.

[102] (a) Laloi-Diard, M.; Verchere, J.; Gosselin, P.; Terrier, F. *Tetrahedron Lett.* **1984**, *25*, 1267. (b) Hoz, S. *J. Org. Chem.* **1982**, *47*, 3545.

[103] For other explanations, see (a) Um, I.-H.; Buncel, E. *J. Org. Chem.* **2000**, *65*, 577. (b) Herschlag, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1990**, *112*, 1951. (c) Hudson, R. F.; Hansell, D. P.; Wolfe, S.; Mitchell, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1406.

[104] Hoz, S.; Buncel, E. *Isr. J. Chem.* **1985**, *26*, 313, and references therein.

[105] (a) Kice, J. L.; Legan, E. *J. Am. Chem. Soc.* **1973**, *95*, 3912. (b) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 3248.

[106] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

[107] Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223.

[108] Jones, C. L. *Ph.D. Thesis, Cardiff University*, **2003**.

[109] Wilkinson, D. E.; Thomas, IV, B. E.; Limburg, D. C.; Holmes, A.; Sauer, H.; Ross, D. T.; Soni, R.; Chen, Y.; Guo, H.; Howorth, P.; Valentine, H.; Spicer, D.; Fuller, M.; Steiner, J. P.; Hamilton, G. S.; Wu, Y.-Q. *Bioorg. Med. Chem.* **2004**, *11*, 4815.

[110] Boros, E. E.; Bouvier, F.; Randhawa, S.; Rabinowitz, M. H. *J. Heterocycl. Chem.* **2001**, *28*, 613.

[111] Dutta, A. S.; Morley, J. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1712.

[112] Perri, S. T.; Slater, S. C.; Toske, S. G.; White, J. D. *J. Org. Chem.* **1990**, *55*, 6037.

[113] Ege, S. N. *Chem. Commun.* **1968**, 759.

[114] Ege, S. N.; Butler, W. M.; Bergers, A.; Biesman, B. S.; Boerma, J. E.; Corondan, V. I.; Locke, K. D.; Meshinchi, S.; Ponas, S. H.; Spitzer, J. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1111.

[115] For examples of catalysts **12** and **16** see *Chapter* 1.

[116] See *Chapter* 1.7, *page* 46.

[117] 93 % *vs.* 97 % for secondary and tertiary centres in this position relatively. Cavill, J. *Ph.D. Thesis, Cardiff University*, **2003**.

[118] Gillis, B.T.; Schimmel, K. F. *J. Org. Chem.* **1967**, *32*, 2865.

[119] In *Organic Chemistry*, Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., Oxford, **2001**, ch. 24, pp. 623.

[120] Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O.. *Org. Lett.* **2005**, *7*, 5729.

[121] Cavill, J. *Ph.D. Thesis, Cardiff University*, **2003**.

[122] Bakos, J.; Tóth, I.; Heil, B.; Markó, L. *J. Organomet. Chem.* **1985**, *279*, 23.

[123] Using B3LYP/6-31+G(d,p) in Molden for the calculations.

[124] Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. In *Purification of Laboratory Chemicals*, 2nd Ed; Pergamon Press; Oxford. **1980**.

[125] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[126] Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J.Am. Chem. Soc.* **1998**, *120*, 6920.

[127] Wieczerzak, E.; Kozlowska, J.; Lankiewicz, L.; Grzonka, Z. *Pol. J. Chem.* **2002**, *76*, 1693.

[128] Gillis, B. T.; Kadunce, R. E. *J. Org. Chem.* **1967**, *32*, 91.

[129] Grande, M.; Trigo, G.; Soellhuber, M. *J. Heterocyclic Chem.* **1986**, *23*, 929.

[130] Hoffmann-LaRoche and Co. *Chem. Abstr.* **1962**, *56*, 2350.

[131] Eliel, E. L.; Hutchins, R. O. *J. Am. Chem. Soc.* **1969**, *91*, 2703.

[132] Toyaa, T.; Yamaguchib, K.; Endo, Y. *Bioorg. Med. Chem.* **2002**, *10*, 953.