Novel Asymmetric Catalysts for the Activation of α,β-Unsaturated Carbonyl Compounds

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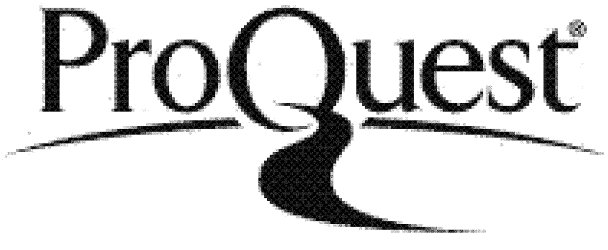
A Thesis Submitted for the Degree of Doctor of Philosophy

at

Cardiff University

2004



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Apart from consideration of the hydrogen bond, we organic chemists have really paid little attention to linkages other than the purely covalent. I believe that it will be the duty of organic chemists in the future to study the weak non-covalent interactions which are of enormous importance in the large natural macromolecules. Such studies will lead to a new blossoming of organic chemistry in the future.

Lord Alexander R. Todd.[1]

ABSTRACT

This thesis embraces two main sections – studies towards the synthesis of a family of indole-based ligands for Lewis acid catalysis and the development of new molecular scaffolds for organocatalytic transformations.

Chapter **1** describes some of the recent advances made in metal-free asymmetric catalysis and sets the work involved within this thesis into context. The rational design and synthesis of ligands for Lewis acid catalysis is presented in *Chapter* **2**. The preparation of mono- and bis-(indol-3-yl)ethane-1,2-diols is described along with our initial studies into their use in the asymmetric catalysis of the Diels-Alder reaction. *Chapter* **3** describes our investigations into the development of the first acyclic system for aminocatalysis *via* an iminium ion pathway by utilisation of the *α-effect*, which was shown to be an effective platform for the acceleration of this class of reaction. We went on to apply our new molecular scaffold to a family of chiral aminocatalysts based upon 8-phenylmenthamine, as described in *Chapter* **4**.

The catalysts described in *Chapter* **4** were proposed to affect the diastereoselective discrimination of α,β-unsaturated carbonyl compounds, owing to the postulated presence of face-face π–π interactions between the double bond of the α,β-unsaturated moiety in the resulting iminium ion, and an aromatic ring incorporated into the structure of the catalyst. Investigation into the proposed π–π stacking was achieved by the synthesis of catalysts with electron withdrawing and electron donating groups attached to the aromatic ring, followed by utilisation of this family of novel aminocatalysts to promote asymmetric Diels-Alder reactions. A trend was discovered in which the stereoselectivity of the Diels-Alder cycloaddition increased as the electron density of the aromatic ring incorporated into the structure of each catalyst increased; the enantiomeric excess of the (2*R*)-adduct formed between cyclopentadiene and *E*-cinnamaldehyde improved from 7% using a 4-trifluoromethyl substituent on the aromatic ring to 21% utilising a 4-methoxy group and 39% with a tetrahydronaphthyl-based catalyst. A hypothetical model which readily explains the stereochemical outcome of these aminocatalytic Diels-Alder cycloadditions is proposed.

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Dr Nicholas C. O. Tomkinson for his encouragement, support and guidance. His enthusiasm and knowledge helped to make my Ph.D. both enjoyable and rewarding. I would also like to thank both Dr Jens-Uwe Peters and Dr Andrew Thomas at F. Hoffmann-La Roche, Basel, for all their advice and for making my placement in Basel possible.

Thank you to the members of Lab 1.119 in Cardiff, both past and present, especially to Lisa, Claire, Eve, Ian, Dan and Niall. I also wish to thank Silja and Stephane for making my time at Roche so enjoyable. Also to Michael, Andrea, Maya and Simone for the all the good times and especially for the fondue!

Additional thanks go to all the technical staff in Cardiff, in particular to Rob Jenkins for all his help. To Dr Brigitte Horisberger and the HPLC department, Dr Andreas A. Staempfli and the mass spec. team, the NMR and IR departments at Roche; your help was much appreciated.

I would also like to say a special thank you to my family for their continued love and support, especially my mum and dad – I couldn't have achieved any of it without you. Also to David for your motivation and inspiration. You always told me I should be a doctor.....hopefully I soon will be!

To Charlotte, Joni and Fiona - *life's truest happiness is found in friendships we make along the way*, so thank you for your friendship, the fun times and all the chats; hopefully there will be many more good times ahead!

Finally, thank you to everyone from the Development Department at Evotec OAI, especially to Ian, Elaine, Rob, Amanda and Stuart for keeping me smiling throughout the writing of this thesis!

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ABBREVIATIONS

Several abbreviations have been used throughout this thesis that may not be familiar to the reader. These abbreviations are listed below:

AA	Asymmetric aminohydroxylation
Ac	Acetyl
AD	Asymmetric dihydroxylation
APcI	Atmospheric pressure chemical ionisation
Ar	Aromatic
atm	Atmosphere
ax	Axial
[bmim]PF_6	1-*n*-Butyl-3-methylimidazolium hexafluorophosphate
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
CAB	Chiral Acyloxy Borane
CAN	Cerium ammonium nitrate
Cbz	Phenylmethoxycarbonyl
CI	Chemical ionisation
COX-2	Cycloxygenase-2
cy	Cyclohexyl
d	Day(s)
d	doublet
Da	Dalton(s)
DEAD	Diethyl azodicarboxylate

dec.	Decomposed
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMTC	5,5-Dimethylthiazolidinium-4-carboxylate
DNBA	2,4-Dinitrobenzoic acid
DNPH	Dinitrophenylhydrazine
dr	Diastereomeric ratio
EDG	Electron donating group
ee	Enantiomeric excess
EI	Electron ionisation
EPSRC	Engineering and Physical Sciences Research Council
eq	Equatorial
equiv.	Equivalent(s)
Et	Ethyl
EWG	Electron withdrawing group
FMO	Frontier molecular orbital
FTIR	Fourier transform infra-red
GC	Gas chromatography
gem	Geminal
h	Hour(s)
HDA	Hetero-Diels-Alder
hfc	3-(Heptafluoropropylhydroxymethylene)-(+)-camphorate
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanal
HOMO	Highest occupied molecular orbital

HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
HX	Protonic acid
Hz	Hertz
i	*Iso*
^{i}Bu	*Iso*butyl
IPA	*Iso*propanol
^{i}Pr	*Iso*propyl
IR	Infra-red
k	Kilo
LA	Lewis acid
lit.	Literature
LUMO	Lowest unoccupied molecular orbital
m	*meta*
m	milli
m	Multiplet
M	Metal
M	Molar
MCR	Multi-component reaction
Me	Methyl
MHz	Megahertz
min	Minute(s)
mmol	Millimole(s)
mp	Melting point
MPLC	Medium pressure liquid chromatography
MS	Mass spectroscopy
MVK	Methyl vinyl ketone

n	*normal*
n	nano
Naph	Naphthyl
NMP	*N*-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
o	*ortho*
OAI	Oxford Asymmetry International
p	*para*
PCC	Pyridinium chlorochromate
PGA	Prostaglandin A
PGE	Prostaglandin E
PGE_2	Prostaglandin E_2
PGF	Prostaglandin F
Ph	Phenyl
PHAL	Phthalazine
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
psi	Pound(s) per square inch
*p*TSA	*para*-Toluenesulfonic acid
PYR	Pyrazine
q	Quartet
quant.	Quantitative
rt	Room temperature
RTIL	Room temperature ionic liquid
s	Singlet

SAMP	*S*-(-)-1-Amino-2-(methoxymethyl)pyrrolidine
SDS	Sodium dodecyl sulphate
sept.	Septuplet
SMP	(*S*)-2-Methoxymethylpyrrolidine
t	*tertiary*
t	Triplet
TBAF	Tetra *n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
tert	*tertiary*
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFPAA	Trifluoroperacetic acid
THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Toluene-4-sulfonyl
Vol.	Volume
VT-NMR	Variable temperature nuclear magnetic resonance
Å	Angstroms
Δ	Heat
μmol	Micromole(s)
σ	Sigma
*	Chiral

Chapter 1: Introduction

1.1 Asymmetric Catalysis

Asymmetric synthesis is dedicated to the preparation of chiral compounds with defined three-dimensional molecular structure (stereochemistry).[2] This is at the core of modern organic chemistry, around which, the design of intricate routes revolve. Obtaining chemically defined, enantiomerically pure compounds is of growing importance to the organic chemist, especially in the pharmaceutical industry, where the stereochemical purity of biologically active products has been one of the major driving forces in the quest for improved control over the stereochemical outcome of organic reactions. The significance of asymmetric synthesis to contemporary synthetic chemistry was highlighted by the award of the 2001 Nobel Prize in Chemistry to K. B. Sharpless, R. Noyori and W. S. Knowles in recognition for their seminal contributions to this vibrant area of science.[3]

An enantiomerically pure compound can be obtained by use of a chiral starting material, resolution of a mixture of enantiomers or introduced by either reactions of pro-chiral substrates (such as chiral reduction of a double bond or asymmetric carbon-carbon bond formation) or by converting substrates containing enantiotopic groups into enantiomerically enriched compounds by breaking the symmetry (e.g. *meso* or achiral) of the starting material (such as epoxide ring opening or allylic oxidation) (*Figure* **1**).[4] These transformations can result in the stereoselective formation of a product by use of either a stoichiometric amount of chiral reagent to create a chiral auxiliary or by utilisation of a catalytic amount of chiral substance. Asymmetric catalysis is an especially appealing aspect of asymmetric synthesis as small amounts of the catalyst can be used to control the stereochemical outcome of a reaction.

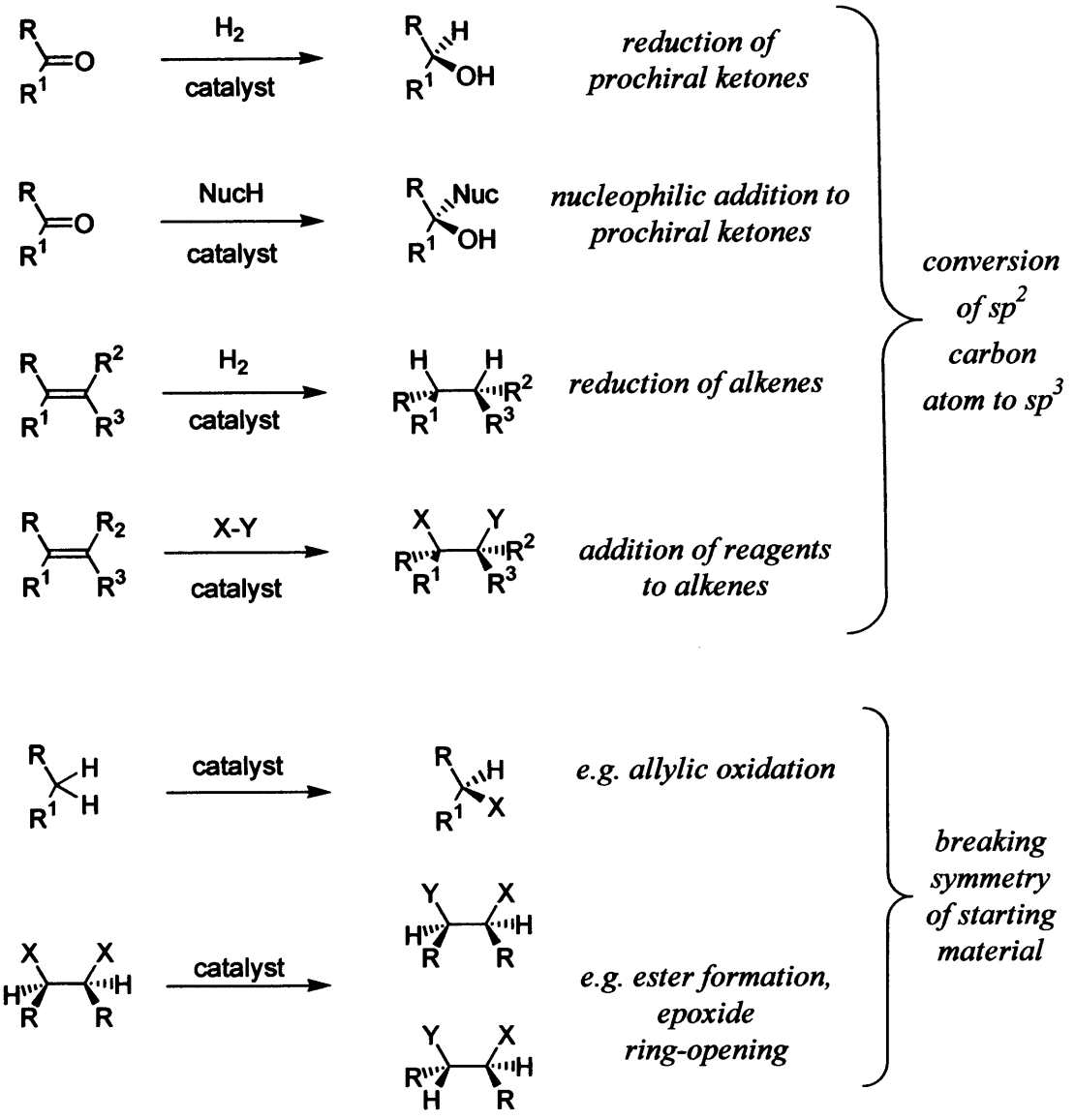


Figure **1**

1.2 Asymmetric Organocatalysis

Over the past 30 years, asymmetric catalysis has become one of the most important frontiers in synthetic organic chemistry research. During this time, remarkable advances have been made in the development of organometallic asymmetric catalysts, which have been utilised in a wealth of asymmetric processes. Surprisingly, however, relatively few asymmetric transformations have been reported which employ organic molecules as reaction catalysts, despite the widespread availability of organic chemicals in enantiopure form.

The term organocatalysis is used to define an organic compound (of relatively low molecular weight and simple structure) that is used as a catalyst for a given transformation.[5] In this

context, organic means metal-free. Within this review the use of asymmetric aminocatalysis is highlighted with particular focus on carbon-carbon bond forming reactions.

Several important processes utilise the chemistry of carbonyl compounds. These reactions are typically catalysed by metal-containing species, for example, the use of Lewis acid catalysts.[6] Recent research has shown that several carbonyl transformations can also be catalysed by amines. This concept is based on the reasoning that the reversible formation of iminium ions from carbonyl compounds and a secondary amine simulates the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis.[7] The formation of an iminium ion significantly enhances the reactivity of the carbonyl compound, resulting in the α-C-H-acidity dramatically increasing (*Figure* **2**).[8]

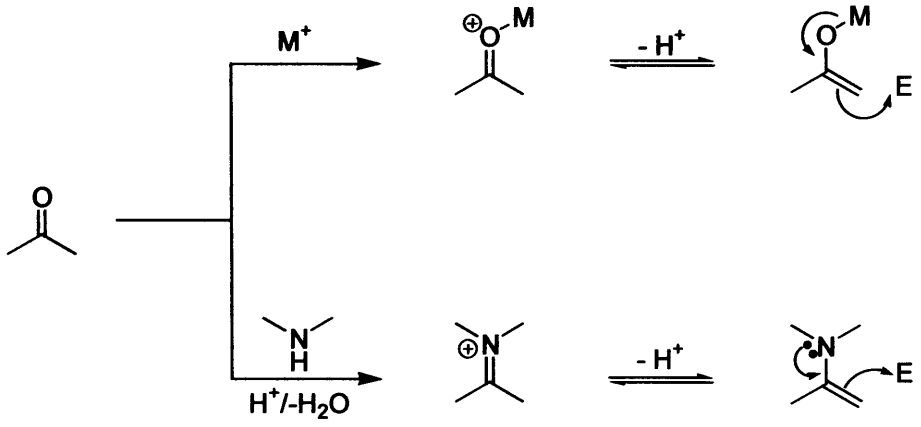


Figure **2**

The catalysis of a given reaction by an amine is known as aminocatalysis. This is a biomimetic strategy that is used by important enzymes such as Class I aldolases (enamine catalysis) and ketoacid decarboxylases (iminium ion catalysis), amongst others. There are two aminocatalytic pathways.[9] Iminium ion catalysis directly utilises the higher reactivity of the iminium ion compared to the carbonyl species and facilitates Knoevenagel-type condensation,[10] cycloaddition and nucleophilic addition reactions, as well as cleavage of the σ-bond adjacent to the α-carbon. Enamine catalysis involves catalytically generated enamine intermediates that are formed *via* deprotonation of an iminium ion. These react with various electrophiles and also undergo pericyclic reactions.

Rigorous application of aminocatalysis in asymmetric organic synthesis has only recently been investigated, with several valuable and broadly applicable transformations, including the aldol, Michael, Mannich and Diels-Alder reactions, which are all amenable to aminocatalysis.

1.3 Why Organocatalysis?

There are certainly considerable advantages to using metals in catalytic processes. They have molecular and structural diversity and a large array of reactivity patterns that can easily be tuned by the variation of ligands. But as well as the advantages that metal derivatives offer, their use also has several disadvantages, such as high price, the resulting toxicity and pollution problems, the need for waste treatment and the possibility of product contamination by the metal.[11]

In comparison, many of the problems associated with the use of metal-based catalysts can be avoided by utilising metal-free organocatalysis, the advantages of which include: (i) the reactions can usually be carried out in wet solvents under an aerobic atmosphere; (ii) the catalysts are inexpensive, with a widespread availability of organic chemicals in enantiopure form; (iii) the catalysts are often stable and robust; (iv) the leaching of a possibly toxic metal into the organic product is avoided; (v) the small organic molecules can be anchored to a solid support and reused more conveniently than organometallic analogues.[12] Thus, organocatalysis represents a remarkable synthetic alternative to established organometallic transformations to both augment and complement existing methodology.

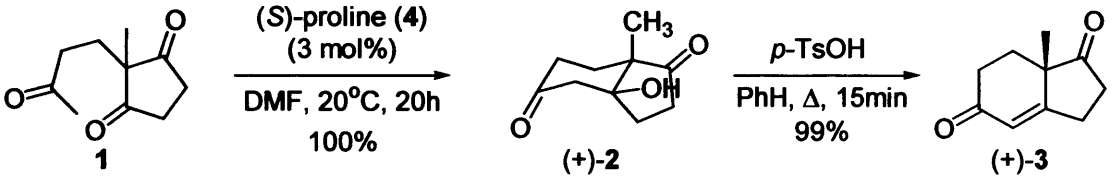
1.4 Asymmetric Aminocatalysis *via* an Enamine or Iminium Ion Intermediate

The crux of this introduction will be concerned with methods of asymmetric carbon-carbon bond forming reactions, catalysed by chiral non-racemic amines of low molecular weight, in which either an enamine or an iminium ion intermediate is involved. A discussion of catalytic systems will be provided for the classical carbon-carbon bond forming reactions – namely, the aldol, Baylis-Hillman, Diels-Alder, hetero Diels-Alder, [4+3] cycloaddition, 1,3-dipolar cycloaddition, Knoevenagel, Mannich, Michael, Mukaiyama-Michael, 1,4-conjugate addition and Robinson annulation reactions. A brief discussion of catalytic systems for the carbon-nitrogen bond forming α-amination reaction, and the carbon-oxygen bond forming α-oxyamination reaction will also be included.

1.5 Intramolecular Aldol Cyclisation

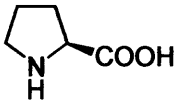
1.5.1 Early Examples of Intramolecular Aldol Cyclisations

Asymmetric enamine catalysis was first realised in the early 1970's when two groups independently reported the use of proline (**4**) as a catalyst for the intramolecular aldol reaction. Hajos and Parrish, at Hoffmann-La Roche began their research with the aim of finding a method by which compounds, such as optically active bicyclic ketone **3**, could be prepared in an asymmetric manner as an alternative to the previously utilised method of classical chemical resolution.[13] A synthesis was required that would promote the cyclisation of triketone **1** to the bicyclic ketol **2** or to its dehydration product **3** (*Scheme* **1**) in high chemical yield and with a high degree of optical purity.[14]



Scheme **1**

Initial studies used a stoichiometric amount of (*S*)-proline (**4**), with the reactions carried out in various polar protic solvents at 20°C under an inert atmosphere. The reactions were complete after stirring for 3-4 days and yielded enone **3** predominantly. An increase in the polarity of the solvent gave the product in higher optical purity, with *iso*propyl alcohol yielding product **3** in 61% ee. Use of a catalytic amount of (*S*)-proline (**4**) (10 mol%) under otherwise identical reaction conditions resulted in a comparable optical purity (57% ee).

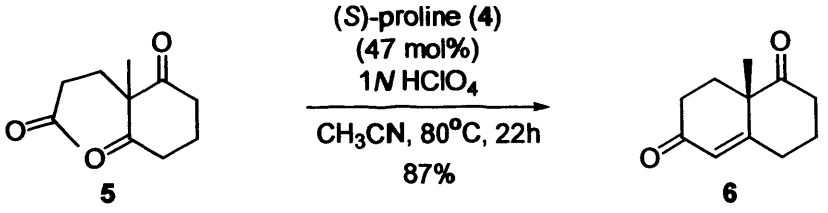


4

Figure **3**

It was assumed that hydrogen-bonding played an important role in the asymmetric cyclisation reaction, and so in an attempt to increase the optical purity of enone **3**, the reaction was carried out in polar aprotic solvents. A catalytic quantity of (*S*)-proline (**4**) (3 mol%) in *N,N*-dimethylformamide (DMF) yielded ketol (+)-**2** in quantitative yield with 93% ee. The ketol (+)-**2** was converted to the corresponding enone (+)-**3** without loss of enantiomeric excess. The Wieland-Miescher ketone **6** can also be prepared in optically pure form (after recrystallisation) by this route.

Eder, Sauer and Wiechert at Schering showed that the enone products, **3** and **6**, could be obtained directly from the triketone starting material if the cyclisation was carried out in the presence of proline (**4**) (10-200 mol%) and an acid co-catalyst (*Scheme* **2**).[15] Product **6** was obtained in an 87% yield and 84% ee. It was observed that the optical purity of the enone was strongly dependent on the substrate, amine component, solvent and the acid co-catalyst.



Scheme **2**

The asymmetric proline-catalysed intramolecular aldol reaction, also called the Hajos-Parrish-Eder-Sauer-Wiechert reaction,[16] has been applied to the asymmetric synthesis of numerous steroids and terpenoids since it was first published in the 1970's.[17] The reaction has also been studied using polymer-bound (*S*)-proline as the catalyst.[18]

1.5.2 Mechanism of the Intramolecular Aldol Cyclisation

Elucidation of the mechanism by which this catalytic intramolecular asymmetric aldol reaction took place began with the notion that an enamine intermediate was formed between the nitrogen atom of proline (**4**) and one of the carbonyl groups of the triketone (**1** or **5**). Both the secondary amine and the carboxylate functionalities of proline (**4**) were found to be critical for catalysis to occur.[19] In the examples of asymmetric intramolecular aldol reactions discussed (*Schemes* **1** and **2**), there is a desymmetrisation of the triketone starting material after reaction due to discrimination between the two enantiotopic carbonyl groups, which must be explained by any proposed mechanisms.

Agami and co-workers proposed a mechanism (*Model* **A**) in which two proline (**4**) molecules were involved.[20] Kinetic studies were carried out by Agami, who observed a non-linear effect that supported the involvement of more than one proline molecule in the enantioselectivity-determining step.[21]

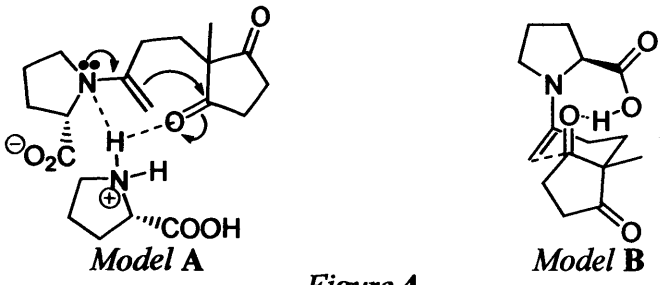


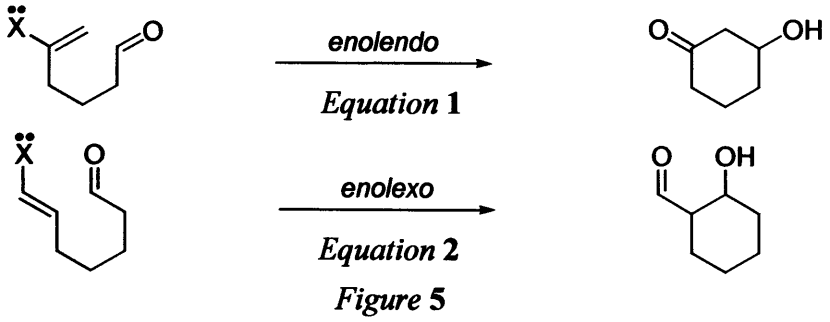
Figure **4**

Houk and co-workers recently proposed a new model (*Model* **B**, *Figure* **4**), based on quantum mechanical calculations, which readily explains the observed enantioselectivity.[22] This model involves the formation of an enamine intermediate, with a hydrogen bond between the carboxylate group of the proline moiety and one of the carbonyl groups of the cyclopenta-1,3-dione ring. This gives rise to the asymmetric induction, with the length of the hydrogen bond as one of the criteria that allows for the selection between enantiotopic carbonyl groups. In contrast to the results obtained by Agami,[21] kinetic, stereochemical and dilution experiments carried out by List, Houk and co-workers, have provided evidence for the involvement of only one proline molecule in the transition state for the proline-catalysed aldol reaction.[23]

These early examples of the use of chiral amines to catalyse asymmetric transformations have since prompted further research by many synthetic chemists around the world. As will be described below, this research has led to simple chiral organic molecules being employed as asymmetric aminocatalysts for a wide range of transformations that traditionally utilise metal salts.

1.5.3 Direct Catalytic *Enolexo* Aldol Cyclisation

The proline-catalysed Hajos-Parrish-Eder-Sauer-Wiechert reaction discussed above (*Sections* **1.5.1** and **1.5.2**) was, until 2003, the only example of a catalytic asymmetric intramolecular aldol cyclisation reaction in the literature. While this reaction has proved extremely useful in the asymmetric synthesis of numerous steroids and terpenoids, only 6-*enolendo* aldolisations (*Equation* **1**, *Figure* **5**) had been reported. Direct catalytic asymmetric *enolexo* aldolisations (*Equation* **2**, *Figure* **5**) were unknown.



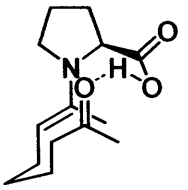
Equation **1**

Equation **2**

Figure **5**

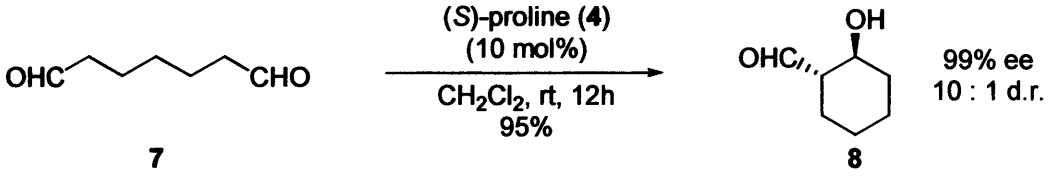
6-*Enolexo* aldol cyclisations are very common and are favoured by Baldwin rules.[24,25] By inspection of the proposed mechanism of the Hajos-Parrish-Eder-Sauer-Wiechert reaction, List and co-workers realised that in addition to the established 6-*enolendo* aldolisations *via*

Model **B** (*Figure* **4**), proline (**4**) should also catalyse the corresponding 6-*enolexo* aldolisations *via Model* **C** (*Figure* **6**).[26]



Model **C**
Figure **6**

To test their hypothesis, List and co-workers reacted various heptane-1,5-dialdehydes with a catalytic amount of (*S*)- or (*R*)-proline (**4**) in dichloromethane. The best result was obtained with heptane-1,5-dialdehyde (**7**), which gave aldol **8** in high yield and diastereoselectivity, and with excellent enantioselectivity (*Scheme* **3**).



Scheme **3**

This reaction provides β-hydroxy-cyclohexane carbonyl derivatives, with an *anti* configuration, that can potentially be used in a wide variety of target syntheses. An advantage of this aldolisation method is that both enantiomeric products can be obtained simply by using either (*S*)- or (*R*)-proline (**4**) as the catalyst.

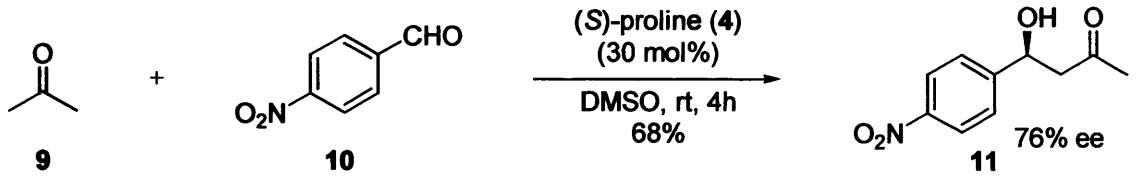
1.6 The Intermolecular Aldol Reaction

The aldol reaction is one of the most important carbon-carbon bond forming reactions utilised in organic synthesis. The classical aldol reaction is highly atom-economic, but suffers from problems in selectivity, notably chemo- and regioselectivity.[27] The development of asymmetric methodologies for this type of reaction has typically involved preformed enolate equivalents in combination with a chiral catalyst.[28] Traditionally a metal is involved in the reaction mechanism.[29] Most enzymes, however, use a fundamentally different strategy in that they catalyse a direct aldol reaction between two unmodified carbonyl compounds. Lerner and co-workers developed aldolase antibodies that catalyse the aldol reaction *via* an enamine mechanism.[30] These can be used in a wide range of direct asymmetric aldol reactions, yielding products with excellent enantioselectivities.

Both the aldolase antibody catalysed intermolecular aldol and the proline-catalysed Hajos-Parrish-Eder-Sauer-Wiechert (intramolecular aldol) reactions involve an enamine mechanism. These important studies showed the potential for enamine catalysis in asymmetric synthesis, and led to the development of the first proline-catalysed direct asymmetric aldol reaction.

1.6.1 The First Proline-Catalysed Direct Asymmetric Aldol Reaction

B. List, R. A. Lerner and C. F. Barbas III reported the first proline-catalysed aldol reaction in 2000.[31] *p*-Nitrobenzaldehyde (**10**) was reacted with an excess of acetone (**9**) to furnish β-hydroxyketone **11** in 68% yield with 76% ee (*Scheme* **4**). This reaction represented the first low molecular weight amine-catalysed direct asymmetric aldol reaction.



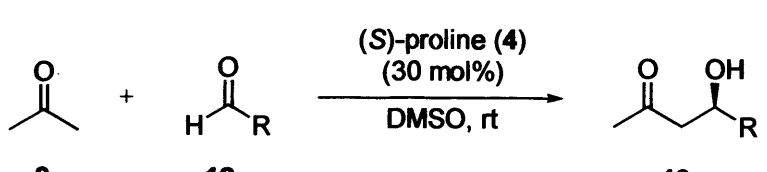
9 **10** **11**

Scheme **4**

Reaction conditions of anhydrous DMSO at room temperature were found to give optimum reaction times and enantioselectivities.

1.6.2 Scope of the Direct Asymmetric Aldol Reaction

List and co-workers tested the scope of the proline-catalysed direct asymmetric aldolisation by reacting several aromatic and aliphatic aldehydes with acetone (**9**) (*Scheme* **5**).[30,32] Aromatic aldehydes gave the aldol product with similar yields (54-94%) and optical purities (~70% ee) to the model reaction with *p*-nitrobenzaldehyde (**10**).



9 **12** **13**

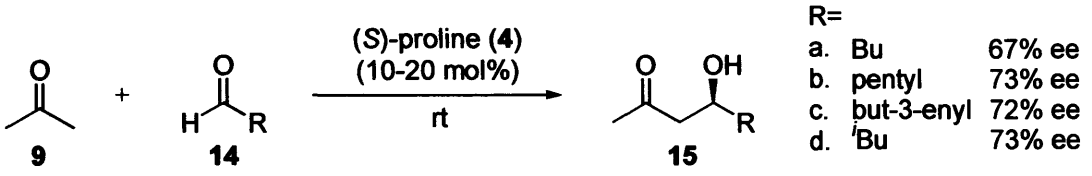
R=

a.	Ph	60% ee
b.	*p*-PhBr	65% ee
c.	*o*-PhCl	69% ee
d.	naphthyl	77% ee
e.	^{i}Pr	96% ee
f.	Cy	84% ee
g.	^{t}Bu	>99% ee

Scheme **5**

Higher enantioselectivities and yields were obtained when α-branched aldehydes, such as *iso*butyraldehyde (**12e**) (96% ee), were used and tertiary aldehydes (**12g**) gave exceptionally high ee's of >99%.

Under the standard conditions employed by List *et al*, α-unsubstituted aldehydes did not react to provide the aldol addition product. Instead these compounds furnished mainly the aldol condensation product or self-aldolisation products. The fundamental problem with the use of α-unsubstituted aldehydes is that the catalyst needs to differentiate between the α-protons of the acceptor aldehyde and the donor ketone, as deprotonation of the aldehyde may lead to undesirable self-aldolisation products. To overcome this problem the effect of solvent polarity and reaction temperature were studied.[33]



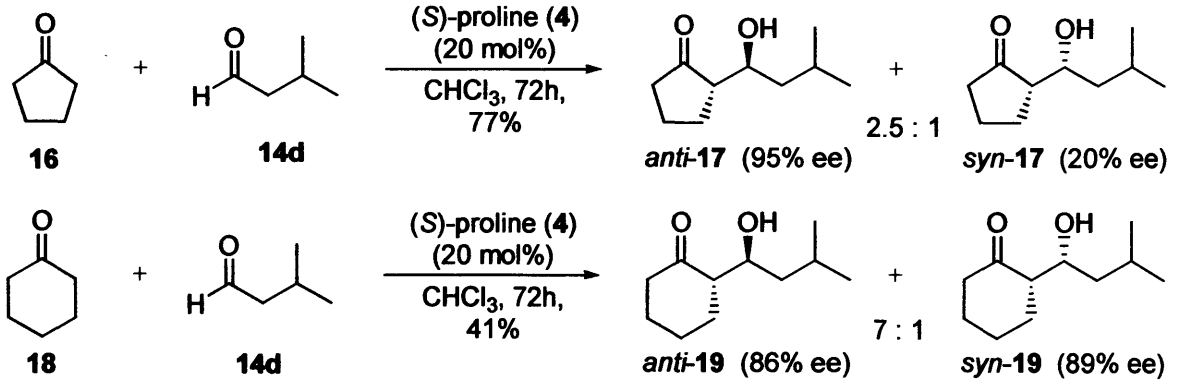
9 **14** **15**

Scheme **6**

Cooling of the reaction mixture to 0°C in DMSO did not improve yields. However, by screening solvents of varying polarity it was found that the aldol product could be obtained in acceptable yields (22–35%) and good enantioselectivities (67-73% ee) when the reactions were carried out in pure acetone or in chloroform/acetone (4:1) (*Scheme* **6**). Self aldolisation was suppressed completely, although significant amounts of the aldol condensation product were still formed (35-50%). Szöllősi and co-workers also reported the use of α-unbranched aldehydes with comparable results obtained.[34]

1.6.3 Proline-Catalysed Aldol Reactions with Other Ketones

List and co-workers found that a variety of cyclic and acyclic ketones, including butanone, cyclopentanone (**16**) and cyclohexanone (**18**), could be used as donors in the aldol reaction to yield the products with useful regio-, diastereo- and enantioselectivities (*Scheme* **7**).[33]

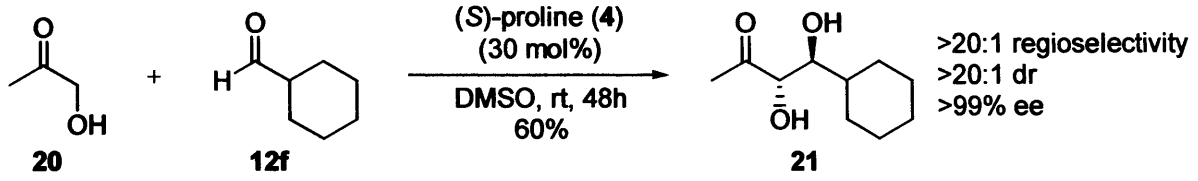


16 **14d** *anti*-**17** (95% ee) *syn*-**17** (20% ee)

18 **14d** *anti*-**19** (86% ee) *syn*-**19** (89% ee)

Scheme **7**

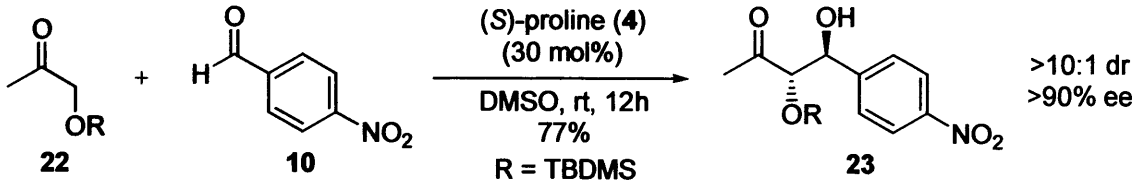
Excellent results were obtained with hydroxyacetone (**20**), which reacted with an aldehyde to furnish the corresponding *anti*-1,2-diol. These reactions were highly regio- and diastereoselective and yielded *anti*-1,2-diols with excellent enantioselectivities. The best result was obtained from the reaction between cyclohexanecarboxaldehyde (**12f**) and hydroxyacetone (**20**), which furnished *anti*-diol **21** in 60% yield, with >20:1 dr and an enantioselectivity of >99% (*Scheme* **8**).[35]



Scheme **8**

While *syn*-1,2-diols can be formed by the Sharpless asymmetric dihydroxylation (AD) of (*E*)-alkenes,[36] the diastereomeric *anti*-1,2-diols are far less accessible, mainly because (*Z*)-alkenes show reduced enantioselectivity in the Sharpless-AD reaction. The proline-catalysed asymmetric synthesis of *anti*-diols, developed by Notz and List, therefore complements the Sharpless-AD.

Li extended the proline-catalysed asymmetric aldol reaction to the use of TBDMS protected hydroxyacetone (**22**). This donor provided mono-protected 1,2-diols in good yields and regioselectivities, for example, reaction with *p*-nitrobenzaldehyde (**10**) afforded the corresponding *anti*-aldol product (**23**) in 77% yield, with a diastereomeric ratio of >10:1 and in 90% ee (*Scheme* **9**).[37]



Scheme **9**

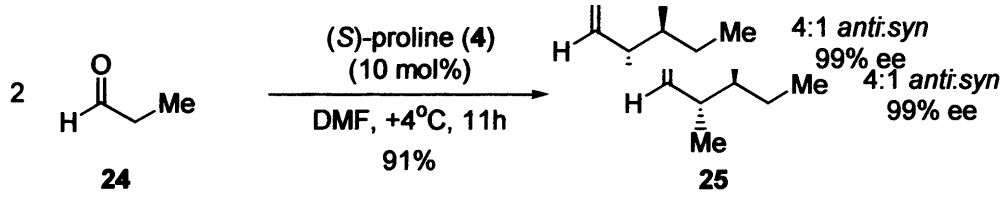
These mono-protected *anti*-1,2-diols are useful aldol products as they allow for the independent manipulation of the two hydroxyl groups in further synthetic transformations.

1.6.4 Aldehydes as Donors in the Direct Asymmetric Aldol Reaction

Until recently there were no reports in the literature of aldehydes being used as donors in the proline-catalysed direct asymmetric aldol reaction. The use of aldehydes as donors in the aldol reaction is a challenge due to the lower reactivity of the enamine intermediate generated

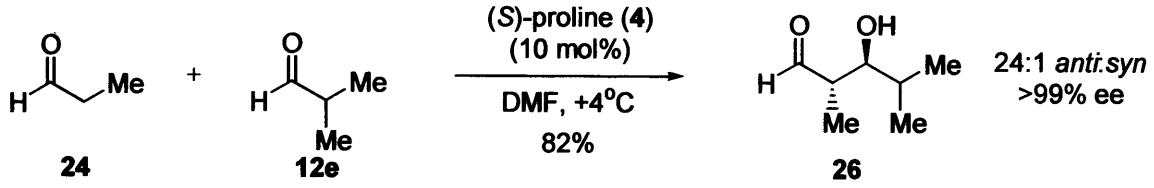
from aldehydes compared to that resulting from ketones. If two aldehydes are to be coupled then there is the additional mechanistic requirement that non-equivalent aldehydes must selectively partition into two discrete components, a nucleophilic donor and an electrophilic acceptor. In 2002, the groups of MacMillan and Jørgensen published examples, almost simultaneously, of aldol reactions that utilised aldehydes as donors.

MacMillan and colleagues demonstrated that enamine catalysis can be utilised in a highly enantioselective coupling of aldehyde substrates. In their initial investigations they exposed two equivalents of propionaldehyde (**24**) to catalytic quantities of proline (**4**) in DMF, which afforded the desired aldol adduct with *anti*-aldol selectivity and excellent enantioselectivity (*Scheme* **10**).[38] This enantioselective aldehyde coupling can be achieved in a broad range of solvents, with by-products not isolated in any significant quantities (≤4% yield).



Scheme **10**

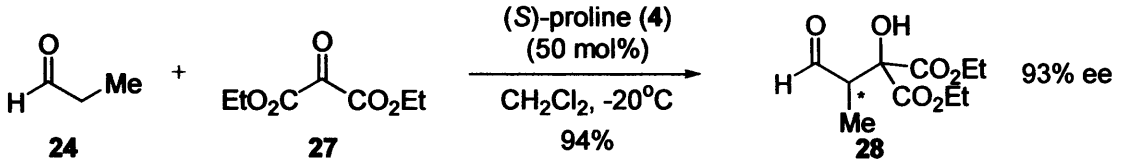
They went on to examine the capacity for proline (**4**) to catalyse asymmetric cross-aldol reactions between non-equivalent aldehydes. Syringe pump addition of propionaldehyde (**24**) to a series of aldehyde acceptors in the presence of the amine catalyst effectively suppressed homo-dimerisation of the donor aldehyde. This provided excellent yields of the cross-aldol product with a wide variety of aldehyde acceptors, including both alkyl and aromatic substituted aldehydes. Structural variation in the aldehyde donor can also be tolerated. The best result was obtained for the addition of propionaldehyde (**24**) to *iso*butyraldehyde (**12e**) furnishing cross aldol product (**26**) in excellent yield and enantioselectivity (*Scheme* **11**).



Scheme **11**

This represented the first direct enantioselective catalytic aldol reaction using aldehydes as both the aldol donor and the aldol acceptor, allowing enantioselective access to β-hydroxy-aldehydes, important synthons in natural product synthesis.

Jørgensen and co-workers performed the catalytic enantioselective direct aldol reaction of aldehyde donors to activated carbonyl compounds. The (*S*)-proline (**4**) catalysed direct aldol reaction of propionaldehyde (**24**) to diethyl ketomalonate (**27**) afforded the cross-aldol product in high yield (up to 94%) and enantioselectivity (75-93% ee) for all solvents examined.[39] The highest yield (94%) and enantioselectivity (93% ee) were obtained using 50 mol% catalyst in dichloromethane at –20°C (*Scheme* **12**), although a similar result was achieved with 20 mol% catalyst at room temperature (93% yield, 88% ee).



Scheme **12**

Both the aldehyde donor and the activated carbonyl compound were varied to give the corresponding aldol products in high yields and enantioselectivities. This method therefore represents a simple approach to the synthesis of optically active β-hydroxy-carboxylic acid derivatives.

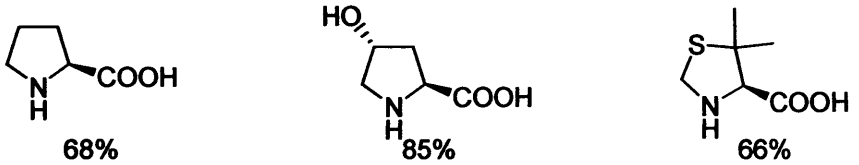
1.6.5 Structure/Activity Relationship of the Proline Catalyst

List, Lerner and Barbas III initially tested several (*L*)-amino acids as catalysts in the direct asymmetric aldol reaction.[31] These included histidine, valine, tyrosine, phenylalanine and proline (**4**), but only proline (**4**) yielded significant quantities of aldol product. Other failed reactions included the use of *N*-methylvaline (**29**) and 2-pyrrolidine carboxamide (**30**) as reaction catalysts (*Figure* **7**).

Figure **7**

These results suggest that a cyclic secondary amine as well as an acidic proton in close proximity are necessary for efficient catalysis to occur.[40] Studies using azetidine (4-membered ring) and piperidine (6-membered ring) analogues of proline (**4**) also showed that the presence of the secondary amine moiety in a 5-membered pyrrolidine ring is optimal. This result is in agreement with the known structure/activity relationships between amines and their enamine reactivity.[41]

Provided with this structure/activity relationship List performed a structure-based catalyst screen for the direct asymmetric aldol reaction.[31] Chiral amines that were structurally similar to (*S*)-proline (**4**) (*Figure* **8**) were tested by reacting *p*-nitrobenzaldehyde (**10**) in DMSO/acetone (4:1) with 20 mol% catalyst at room temperature for 4-24 h.



68% 76% ee **4** | 85% 78% ee **31** | 66% 86% ee **32**

Figure **8**

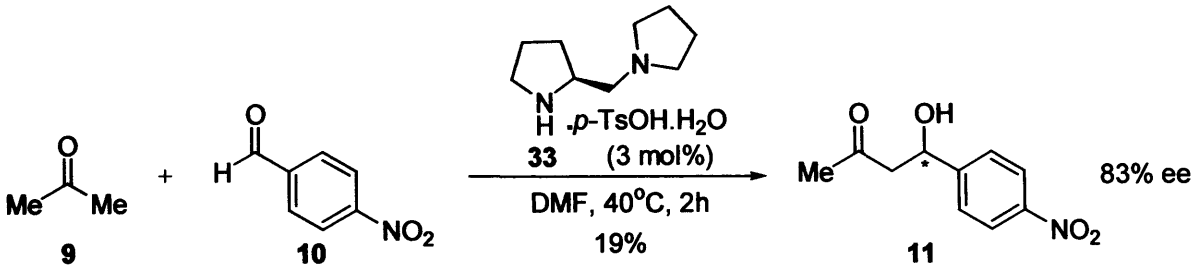
Commercially available proline-derivative **31** gave comparable enantioselectivities to proline (**4**) itself, while 5,5-dimethylthiazolidinium-4-carboxylate (DMTC) (**32**) afforded an 86% ee, representing a 10% increase in enantioselectivity compared to proline (**4**). In contrast, a DMTC catalyst with a substituent in the 2-position provided the aldol product in less than 10% yield. This result can be rationalised by the fact that formation of the assumed enamine intermediate is disturbed by both steric factors and by changes in the pK_a value of the amine functionality, caused by additional α-substituents.

Therefore substitution at the 4-position of (*S*)-proline (**4**) and 5-position of (*S*)-thiaproline (**32**) increases the enantioselectivity observed in the amine-catalysed direct asymmetric aldol reaction.

1.6.6 Other Amine Catalysts

As well as the extensive literature on the use of proline (**4**) and proline-derived catalysts for the direct asymmetric aldol reaction, other amines have also been utilised. These include the use of diamine-protonic acid salts by Yamamoto, and the use of a nicotine derivative by Janda.

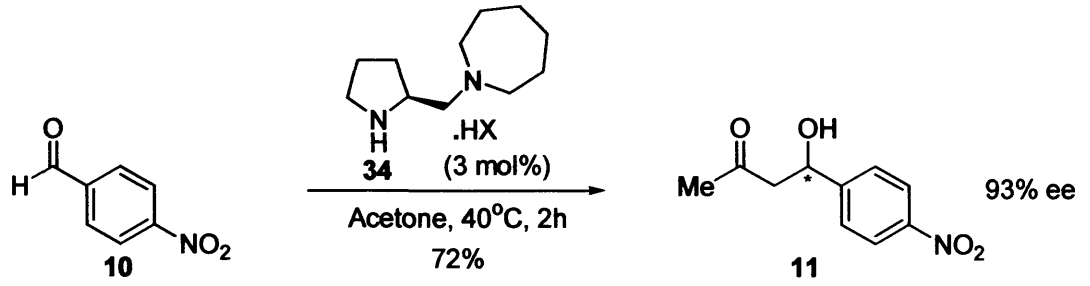
Yamamoto utilised diamine **33** as its *p*-toluenesulfonic acid monohydrate salt to catalyse an aldol reaction between acetone (**9**) and *p*-nitrobenzaldehyde (**10**). This gave aldol product **11** in a 19% yield with 83% ee (*Scheme* **13**). The use of diamine **33** or the protonic acid alone led to negligible formation of the aldol product **11** under similar reaction conditions. The most suitable diamine-acid ratio was determined to be 1:1 for effective rate acceleration.[42]



Scheme **13**

Diamine **33** was evaluated for catalysis of the aldol reaction in the presence of a series of protonic acids. In general, the rate of the aldol reaction was enhanced as the acidity of the protonic acid increased. The acid that gave the highest yield and enantioselectivity was 2,4-dinitrophenylsulfonic acid dihydrate, while acetone was shown to be the optimal solvent. This combination yielded 61% of **11** with 83% ee.

On the basis of the above results, a parallel library approach was utilised to optimise the nature of the diamine catalyst. Twelve different diamines, each with a secondary amino structure derived from (*S*)-proline (**4**), as well as three diamines derived from (*S*)-phenylalanine, were synthesised and screened with a variety of aldehydes. On the basis of these results catalyst **34**, derived from (*S*)-proline (**4**) gave the highest yield and enantioselectivity (72% yield, 93% ee) (*Scheme* **14**).[43]



Scheme **14**

Thus, the use of chiral diamine (**33**) or (**34**), with a protonic acid co-catalyst, represents an alternative to the use of proline (**4**) as a catalyst for the direct asymmetric aldol reaction.

Janda utilised nornicotine (**35**) (*Figure* **9**), a nicotine-related alkaloid that is found both endogenous in tobacco and as a minor metabolite of nicotine *in vivo*, and with a structural similarity to proline (**4**), as a catalyst for the aldol reaction between acetone (**9**) and *p*-nitrobenzaldehyde (**10**). No reaction was observed in any common organic solvents. However, by performing the reaction in aqueous phosphate buffer (*p*H 7.4, 12h), the aldol product **11** was formed in 81% yield.[44]

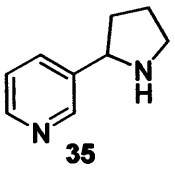


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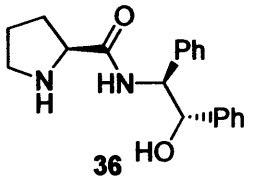
Figure **9**

Proline (**4**) and pyrrolidine (**55**) were tested to see if they could also catalyse the aldol reaction in water, but these produced little rate enhancement over the background reaction. The 2-pyridyl and 4-pyridyl analogues of nornicotine gave similar rate enhancements to nornicotine (**35**) itself, while 2-phenylpyrrolidine also showed an increased rate.

Nornicotine (**35**) represents the first example of a small molecule organic catalyst for the aldol reaction that operates exclusively in *aqua*. As maximum rate acceleration is observed near physiological *p*H, nornicotine (**35**) could also catalyse *in vivo* aldol reactions.

Wu and co-workers have investigated the use of (*S*)-pyrrolidine-2-carboxamide catalysts with a terminal hydroxyl group, for the direct aldol reactions of aromatic and aliphatic aldehydes. They initially studied the reaction of *p*-nitrobenzaldehyde (**10**) in neat acetone (**9**). The highest enantioselectivity of 69% was observed with catalyst **36** (*Figure* **10**), which afforded 89% yield of aldol product **11** when the reaction was performed at ambient temperature. Upon lowering of the reaction temperature to -25°C the enantioselectivity was increased significantly to 93% ee (66% yield).[45]



36

Figure **10**

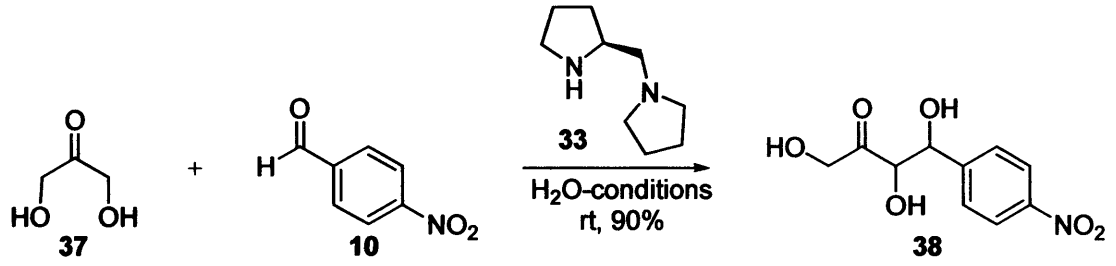
A variety of aldehydes can be utilised in the aldol reaction catalysed by **36**, affording aldol adducts in moderate to high yields with high enantioselectivities of up to >99% ee.

The above examples illustrate that amines other than proline itself have successfully been employed to catalyse the direct asymmetric aldol reaction, but all of the catalysts discussed have structural similarities. Each contains a secondary amine moiety within a 5-membered ring system and has, with the exception of nornicotine (**35**), which has not been used asymmetrically, either a hydrogen bond-donor group in close proximity to the amine or requires a protonic acid co-catalyst.

1.6.7 Use of Environmentally Friendly Reaction Systems

After publication by Dickerson and Janda of the use of nornicotine (**35**) in buffered aqueous media (see *Section* **1.6.6**) as a catalyst for the aldol reaction,[44] other examples of the use of amine catalysts in environmentally friendly reaction systems have been reported, with particular focus on the use of aqueous micelles.

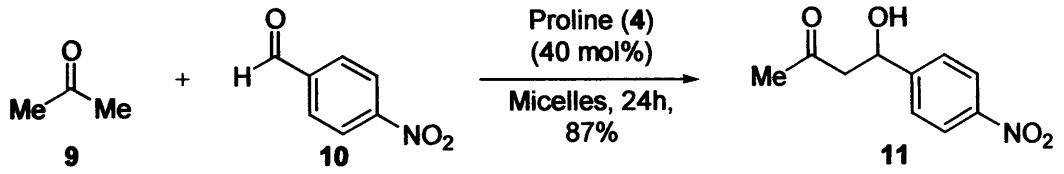
Barbas III and colleagues studied the aldol reaction with a variety of ketones and *p*-nitrobenzaldehyde (**10**), in phosphate-buffered aqueous media, with sodium dodecyl sulphate (SDS), an anionic surfactant, as an additive. Under these buffered aqueous conditions, proline (**4**) was found to be a useful catalyst for the cross aldol reaction of donors such as 2-butanone and hydroxyacetone (**20**), giving yields of up to 90%. Of particular interest was the use of unprotected dihydroxyacetone (**37**), which cannot be used in organic solvents as it dimerises under these conditions. Under buffered aqueous conditions, (*S*)-proline (**4**) only produced trace amounts of polyol **38**, while diamine **33** furnished a 90% yield (*Scheme* **15**).[46]



Scheme **15**

Several other aldehydes were utilised in this diamine catalysed cross-aldol reaction with dihydroxyacetone (**37**), producing the corresponding polyols in good yields and high regioselectivities. This method therefore provides a direct and efficient route to the formation of polyols under environmentally benign reaction conditions.

Cheng and co-workers further investigated the use of aqueous micelles as an environmentally friendly reaction system. The reaction between acetone (**9**) with *p*-nitrobenzaldehyde (**10**) was performed in phosphate-buffered aqueous media, with SDS as an additive. The aldol product **11** was obtained in 87% yield after 24 hours, a substantial increase compared to that of the corresponding reaction in organic solvents (68%) (*Scheme* **16**). This reaction is also very efficient, with the α,β-unsaturated ketone by-product formed only in trace amounts.



Scheme **16**

The effects of different surfactants on the reaction were examined, including anionic, non-ionic and cationic systems. Good yields were obtained with anionic surfactants such as SDS, but non-ionic and cationic systems did not efficiently promote the reaction and the observed yields were much lower.[47] To test the scope of this reaction several aliphatic and activated aromatic ketones were reacted with *p*-nitrobenzaldehyde (**10**). Importantly, both the diastereoselectivity and the chemical yields of these aldol reactions in micelles were much better than those of the corresponding reactions in organic solvents, thus providing an environmentally friendly reaction system in which such reactions can be performed.

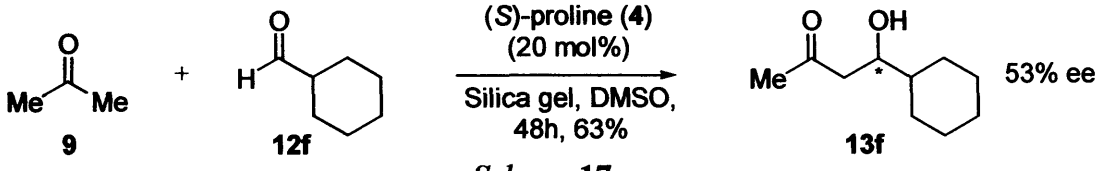
1.6.8 Recovery and Reuse of the Proline Catalyst

Recovery and reuse of chemicals has become ever more important as concerns over environmental issues increase. Several methods for the recovery of proline (**4**) have been studied, including the use of the catalyst in an ionic liquid and the employment of polymer-supported proline.

Barbas III studied two routes to catalyst recycling. The first route involved the direct recovery of the catalyst from the reaction mixture. It was noticed that (*S*)-proline (**4**) did not dissolve in chloroform to any significant extent. Therefore, the aldol reaction between acetone (**9**) and *p*-nitrobenzaldehyde (**10**) was carried out in chloroform, giving product **11** in 61% ee. While this represents a reduction in enantioselectivity compared to the analogous reaction in DMSO, (*S*)-proline (**4**) could be recovered in quantitative yield by simple filtration of the reaction mixture. Reuse of the catalyst in a second reaction showed no loss in activity, suggesting that many rounds of catalyst use and recovery should be possible.[40]

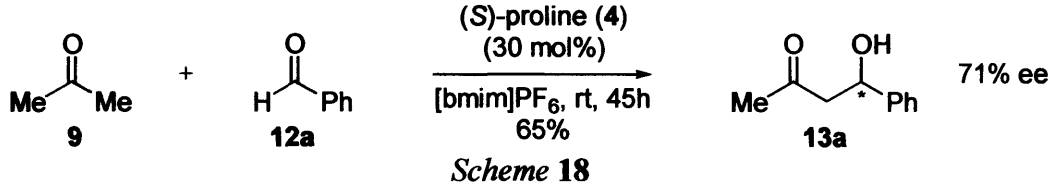
As a second route to catalyst recovery and reuse, Barbas III and co-workers studied catalyst immobilisation. (*S*)-Proline (**4**) (20 mol%) was adsorbed onto a silica gel column, and cyclohexanecarboxaldehyde (**12f**) in DMSO/acetone (4:1) was introduced into the column and incubated for 48 hours at room temperature. After washing of the column with ethyl acetate, aldol product **13f** was isolated in 63% yield with 53% ee (*Scheme* **17**). The recovered

silica gel column was then reused for a second cycle. Unfortunately this method led to significantly reduced enantiomeric excesses compared to analogous reactions carried out in an organic solvent, so is of limited use as a catalytic method for the direct asymmetric aldol reaction.[40]



Scheme **17**

The use of proline (**4**) as a catalyst for the direct asymmetric aldol reaction has also been studied in room temperature ionic liquids (RTIL). Ionic liquids are non-volatile, have insolubility in some solvents, and are able to dissolve catalysts, allowing them to be recycled easily. Loh and colleagues utilised (*S*)-proline (**4**) in imidazolium-based ionic liquids. For the aldol reaction between acetone (**9**) and benzaldehyde (**12a**), carried out in [bmim]PF_6 ionic liquid, the aldol adduct (**13a**) was obtained in 65% yield with an enantioselectivity of 71% (*Scheme* **18**).[48] This represents a significant increase compared to the 60% ee obtained in an otherwise equivalent reaction in DMSO. Indeed, all ionic liquids tested afforded comparable or better enantioselectivities than the organic solvent counterpart.

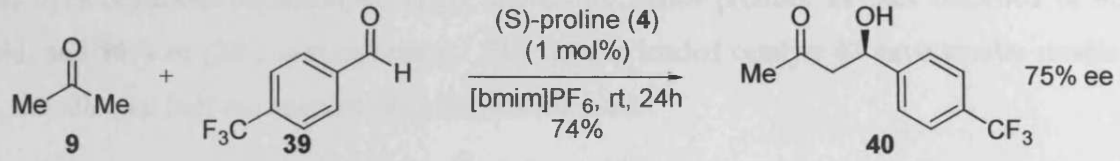


Scheme **18**

In this study, both aromatic and aliphatic aldehydes were examined, and in all cases the aldol addition product was obtained in good yield with moderate to excellent optical purity.

The recyclability of the catalyst was tested by study of the aldol reaction above (*Scheme* **18**). After the reaction was complete, the reaction mixture was extracted with diethyl ether to give the ionic liquid residue containing (*S*)-proline (**4**). This residue was then utilised for another catalytic run, and it was found that after four repeated cycles the desired aldol product **13a** could still be obtained with comparable yield and enantioselectivity.

Toma and co-workers further investigated the direct asymmetric aldol reaction in [bmim]PF_6. They found that the reaction between acetone (**9**) and *p*-trifluoromethylbenzaldehyde (**39**) could be performed with just 1 mol% catalyst loading, without any effect on the enantioselectivity for the reaction (*Scheme* **19**).

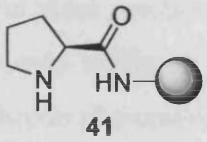


Scheme **19**

The experiments with 1 mol% (*S*)-proline (**4**) in [bmim]PF_6 were repeated several times, and a serious drop in yield was observed after the third repetition (30%), but the enantioselectivity of the reaction was maintained (75% ee) even after the eighth cycle.[49] The addition of 0.5 mol% catalyst to the reaction medium returned the yield to its original value (74%).

Therefore, the room temperature ionic liquid [bmim]PF_6 is a suitable solvent for proline-catalysed asymmetric aldol reactions. The catalyst in an ionic liquid phase can be recycled and the product yield and enantiopurity remain at a comparable level to that obtained with the fresh catalyst.

Another method for the recovery and reuse of the proline (**4**) catalyst is by binding onto a solid support. Szöllősi and co-workers prepared a resin-bound catalyst, (*S*)-Pro-MBHA (**41**), with (*S*)-proline (**4**) coupled to the resin *via* its carboxylate group (*Figure* **11**). When this polymer-bound catalyst was utilised in an aldol reaction between acetone (**9**) and 2,2-dimethylpropionaldehyde (**12g**), a 66% yield of the corresponding aldol adduct was obtained with 86% ee, significantly lower than the >99% ee obtained under similar reaction conditions with (*S*)-proline (**4**), and this was the case for all aldol reactions performed.[34]



41

Figure **11**

Even so, the immobilised catalyst could be removed from the reaction mixture by simple filtration and reused in a second and third run. In these repeated reactions the enantioselectivities were only slightly lower than for the first run.

Benaglia *et al* also prepared two polymer supported proline catalysts **42** and **43** (*Figure* **12**). Catalyst **42** (0.25-0.35 mol%) was used in the reaction of acetone (**9**) with a variety of aldehydes in DMF at room temperature. These reactions gave the corresponding aldol products in good yield (up to 80%) with ee (up to >98%) comparable to that obtained using (*S*)-proline (**4**), although in longer reaction times. For the reaction of hydroxyacetone (**20**)

with cyclohexanecarboxaldehyde (**12f**), the *anti*-1,2-diol product **21** was obtained in 45% yield, and 96% ee (20:1 *anti/syn* ratio). The double loaded catalyst **43** gave similar results to **42**, but allowed half the amount of catalyst to be used.[50]

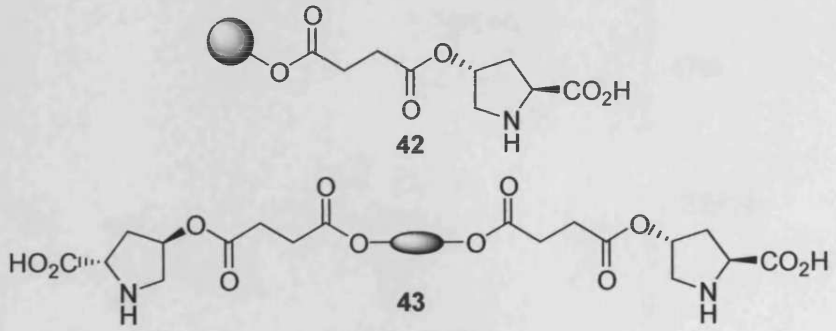


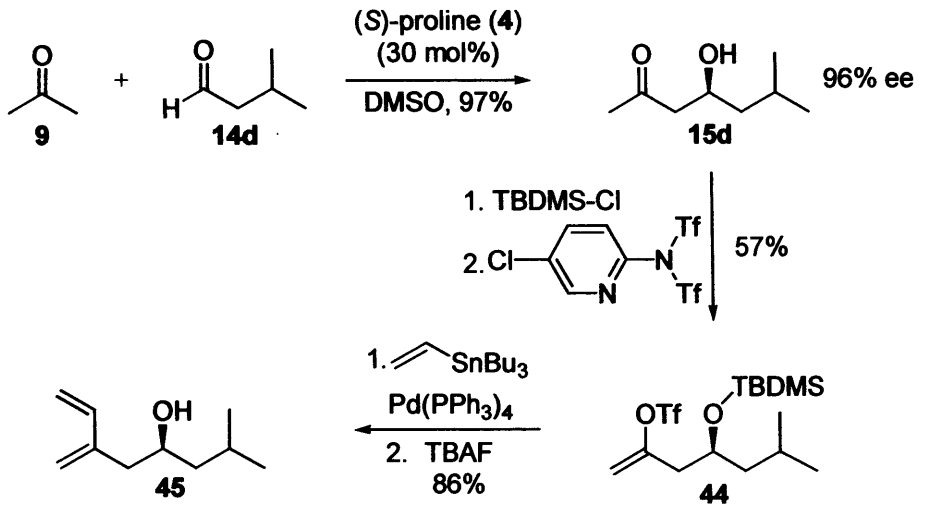
Figure **12**

Catalyst **42** could be recovered by filtration and recycled 3-4 times. The chemical yields slowly diminished with each run, but the enantioselectivities remained virtually unchanged.

These examples show that the proline-catalysed aldol reaction can be carried out in an ionic liquid, or by utilising a polymer-supported proline catalyst. These methods gave comparable results to the standard reaction conditions, and allowed the catalyst to be recycled and reused, constituting a more environmentally friendly approach to the catalytic direct asymmetric aldol reaction.

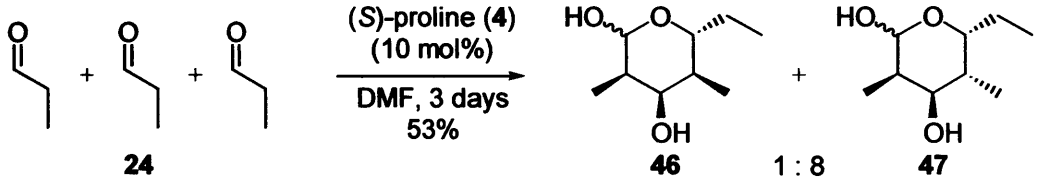
1.6.9 Applications of the Direct Asymmetric Aldol Reaction

The proline-catalysed direct asymmetric aldol reaction can easily be performed on a multi-gram scale, required for complex molecule synthesis. This was demonstrated with a short asymmetric total synthesis of the bark beetle pheromone (*S*)-ipsenol (**45**), which is required in kilogram quantities for insect traps. In this synthesis a proline-catalysed aldol reaction was carried out between acetone (**9**) and 3-methylbutyraldehyde (**14d**) to give β-hydroxyketone **15d**, which was converted in four steps to (*S*)-ipsenol (**45**) in good overall yield (*Scheme* **20**).[33]



Scheme **20**

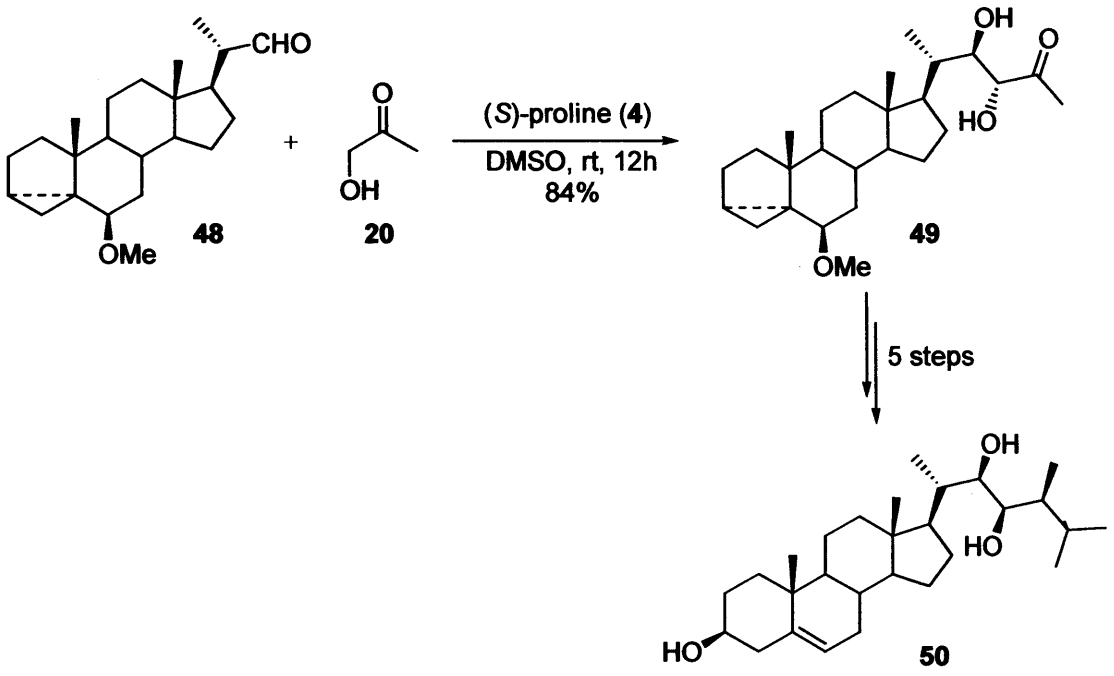
A further application of this method is in the assembly of carbohydrates and polyketides, which can be formed using a proline-catalysed asymmetric double aldol reaction involving three aldehyde components. For example, propionaldehyde (**24**) trimerisation can be carried out under proline-catalysed conditions to give trimeric products **46** and **47** in a 53% isolated yield as a 1:8 mixture of diastereoisomers with an anomeric ratio of 1:2 (α:β) (*Scheme* **21**).[51] This trimerisation reaction can be carried out on a 10g scale, with the lactol products obtained in crystalline form.



Scheme **21**

It was also possible to carry out the double aldol reaction using non-equivalent aldehydes. The product pyranoses from these reactions contain four asymmetric centres constructed under proline (**4**) catalysis with excellent diastereoselectivity and modest enantioselectivity from three aldehyde molecules. This simple one-pot procedure provided direct access to carbohydrates and polyketides that are otherwise prepared using multi-step procedures.

(*S*)-Proline (**4**) has also been used in the stereoselective construction of the side chain of brassinolide. A direct aldol reaction was performed between hydroxyacetone (**20**) and aldehyde **48**, to yield *anti*-1,2-diol **49** in an 84% yield with a diastereomeric ratio of 5:1 *anti*/*syn*. The aldol product **49** was then converted in five steps to triol **50**, a known precursor of brassinolide (*Scheme* **22**).[52]



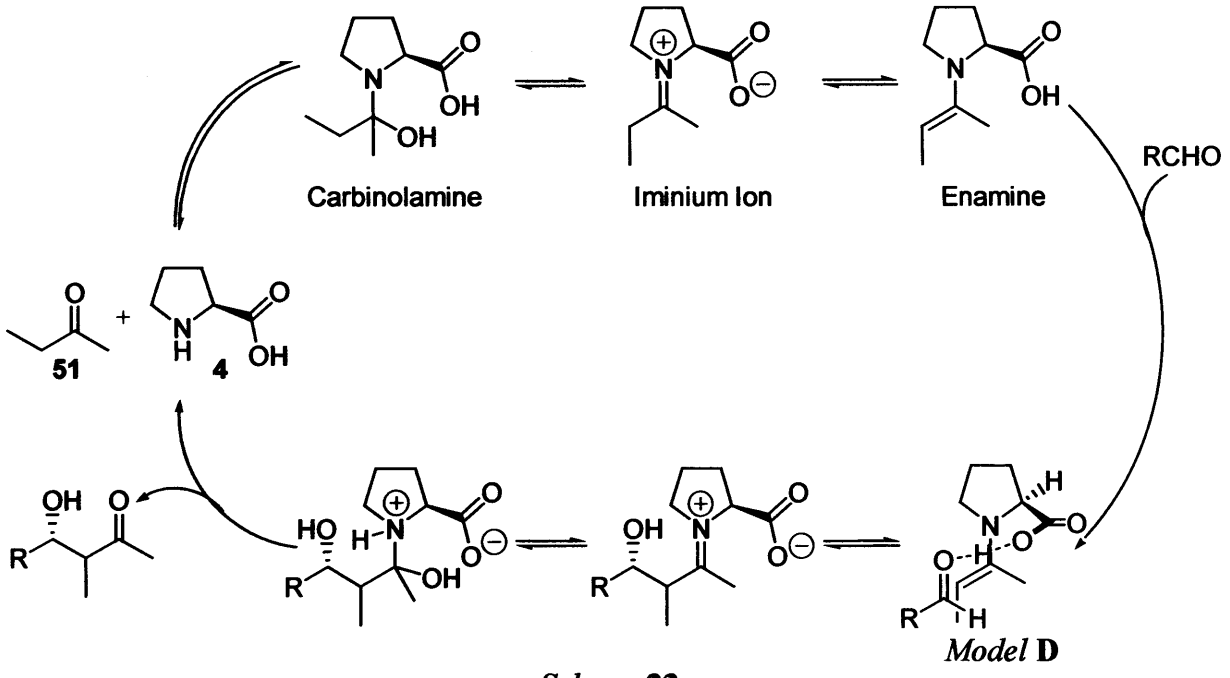
Scheme **22**

The above examples illustrate that the synthesis of complex molecules from simple starting materials is within the realm of organocatalysis involving the naturally occurring amino acid proline (**4**).

1.6.10 Mechanism of the Proline-Catalysed Aldol Reaction

It is proposed that the proline-catalysed intermolecular aldol reaction follows an enamine mechanism that is closely related to that of the Hajos-Parrish-Eder-Sauer-Wiechert reaction (*Section* **1.5**) as well as that used by natural class-I aldolases. According to this proposal, proline (**4**) functions as a *micro-aldolase* with the secondary amine group acting as a nucleophilic enamine catalyst and the carboxylic acid moiety as a general Brønsted co-catalyst.[9]

In the postulated mechanism for this reaction, condensation of the secondary amino group of proline (**4**) with a carbonyl substrate leads to the formation of a nucleophilic enamine intermediate. The adjacent carboxylic acid group of the enamine intermediate then directs the approach of the electrophile by formation of a specific hydrogen bond in the transition state structure (*Model* **D**). This provides both pre-organisation of the substrates and stabilisation of the transition state. After reaction, the resulting iminium ion is hydrolysed to release the product and the proline (**4**) catalyst, which can proceed to repeat the cycle. The chirality of proline (**4**) is therefore relayed into the product.[2]



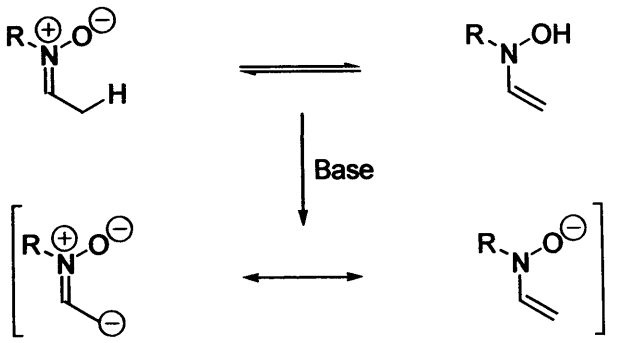
Scheme **23**

This proposed multi-step reaction mechanism (*Scheme* **23**) has been confirmed using density functional theory calculations.[53] The validity of the transition state (*Model* **D**) has been demonstrated by using density functional theory to predict the stereoselectivities of proline-catalysed aldol reactions, followed by experimental verification.[54]

The use of chiral amines to catalyse the asymmetric aldol reaction has received extensive attention from synthetic chemists. Proline (**4**) *and proline-derived compounds have been found to catalyse such reactions with excellent enantiocontrol via an enamine activation pathway.*

1.7 A Nitrone-Aldol Reaction

Nitrones can react with carbonyl compounds in an aldol-type reaction to form functionalised β-hydroxynitrones. Nitrones with an α-proton can be in equilibrium with their *N*-hydroxylenamine tautomer (*Scheme* **24**), which can be initiated by deprotonation with a base. A nucleophilic carbon atom is generated that can add to carbonyl compounds forming a new carbon-carbon bond. This reaction is therefore the nitrone analogue of the aldol reaction; the nitrone-aldol reaction.

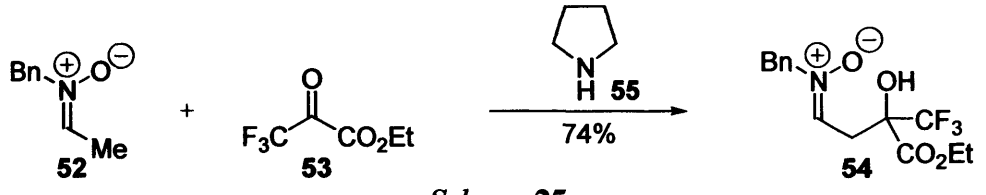


Scheme **24**

This fundamental reaction of nitrones was first documented in 2002 by Jørgensen and co-workers, who have also developed an amine-catalysed asymmetric version.

1.7.1 Amine-Catalysed Nitrone-Aldol Reactions

Jørgensen carried out a nitrone-aldol reaction between *N*-benzyl-*C*-methylnitrone (**52**) and ethyl-1,1,1-trifluorpyruvate (**53**) to give addition product **54**. With the absence of a catalyst a 63% yield of **54** was obtained in 24 hours. The use of Brønsted and Lewis acids as catalysts did not improve the reaction rate significantly, and often resulted in decomposition of the desired products. But, addition of a catalytic amount of pyrrolidine (**55**) did increase the reaction efficiency, affording a 74% yield of **54** in just 4 hours (*Scheme* **25**).[55]



52 **53** **54**

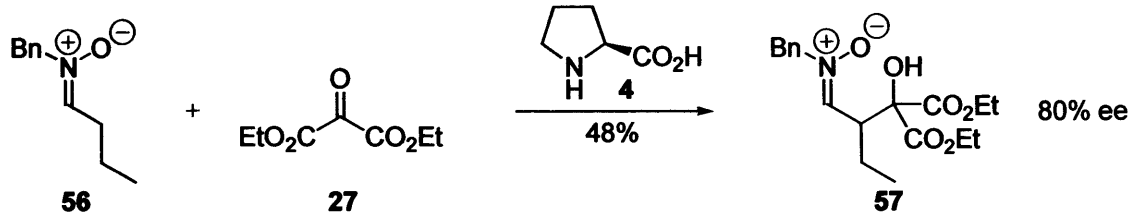
Scheme **25**

With the use of pyrrolidine (**55**) as a catalyst this reaction could also be performed with carbonyl compounds other than the highly activated **53**. Notably, in the absence of a catalyst only highly activated **53** could be employed. A series of different ketones were utilised with good yields obtained throughout.

1.7.2 An Asymmetric Nitrone-Aldol Reaction

Having established that secondary amines successfully catalyse an aldol-type reaction of nitrones to carbonyl compounds, Jørgensen went on to develop an asymmetric version using chiral secondary amines. Proline (**4**) was found to give the highest levels of enantiocontrol in the reaction of nitrone **52** with carbonyl compound **53**, to afford adduct **54** in 50% yield with

30% ee. It was found that an increased enantioselectivity was obtained for the use of α-substituted nitrones, such as **56**, in reactions with diethyl ketomalonate (**27**). The use of proline (**4**) to catalyse this reaction furnished the product β-hydroxynitrone **57** in 48% yield with 80% ee (*Scheme* **26**).[55]

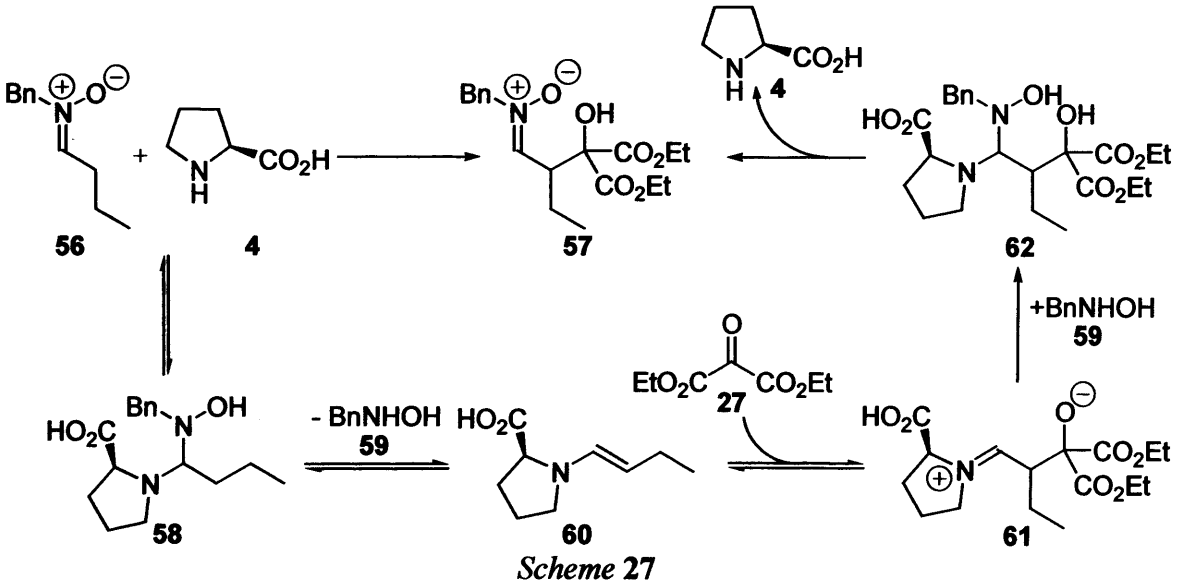


Scheme **26**

Aldehydes can also be employed in these reactions, but the initially formed β-hydroxynitrone eliminates water to give the corresponding α,β-unsaturated compound.

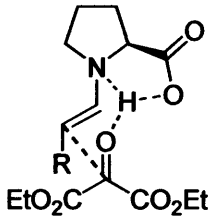
1.7.3 Mechanism of the Proline-Catalysed Nitrone-Aldol Reaction

Kinetic measurements, intermediate and product analysis, and the absolute configuration of the optically active β-hydroxynitrone product have shown that the proline-catalysed nitrone-aldol reaction proceeds *via* an enamine intermediate. In the proposed reaction mechanism, the nitrone **56** reacts with the proline (**4**) catalyst to form aminal **58**, which after elimination of hydroxylamine **59** forms chiral enamine **60**. This enamine reacts with the carbonyl compound **27** to form a zwitterionic aldol product **61**, which reacts with the hydroxylamine **59** to form a second aminal **62**. Elimination of the proline (**4**) catalyst yields the optically active β-hydroxynitrone **57** (*Scheme* **27**).[55]



Scheme **27**

The formation of the new stereocentre is determined by the approach of the activated carbonyl compound to the enamine intermediate. It has been proposed that this approach is directed by the interaction between the incoming carbonyl oxygen atom and the proton of the carboxylic acid of (*S*)-proline (**4**) (*Figure* **13**). This is supported by the fact that no enantioselectivity is observed if proline methyl ester is employed as the reaction catalyst.



Model **E**

Figure **13**

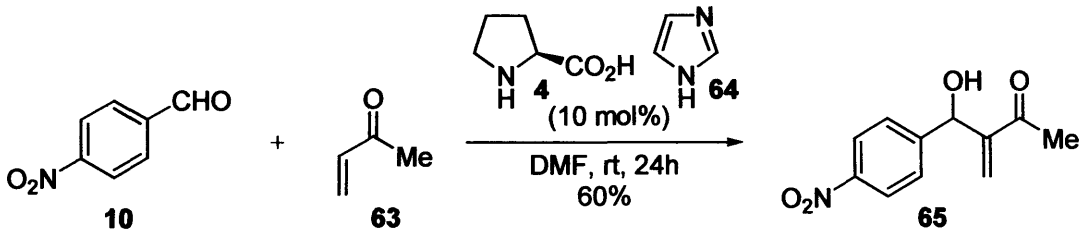
This proline-catalysed nitrone-aldol reaction further illustrates the value of organocatalysis. While Brønsted and Lewis acids were inefficient as reaction catalysts, proline (**4**) *was found to enhance the rate of reaction and furnish products with high enantioselectivities.*

1.8 The Baylis-Hillman Reaction

Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of strong Lewis bases in 1972.[56] The Baylis-Hillman reaction is a convenient process for the preparation of β-hydroxy-α-methylene -ketones, -nitriles or -esters in one step from the reaction of α,β-unsaturated ketones, acrylonitriles or acrylic esters, respectively, with aldehydes. The mechanism of this reaction is multi-step, so any of the reaction components can be used to influence the stereochemistry of the newly formed stereogenic carbon atom, but few asymmetric versions of the Baylis-Hillman reaction have been reported.[57]

1.8.1 Use of Proline as a Co-Catalyst for the Baylis-Hillman Reaction

Shi and co-workers reacted methyl vinyl ketone (MVK) (**63**) with *p*-nitrobenzaldehyde (**10**) and a weak Lewis base, imidazole (**64**), in the presence of catalytic amounts of (*S*)-proline (**4**), which afforded a good yield (60%) of product **65** (*Scheme* **28**).[58]



Scheme **28**

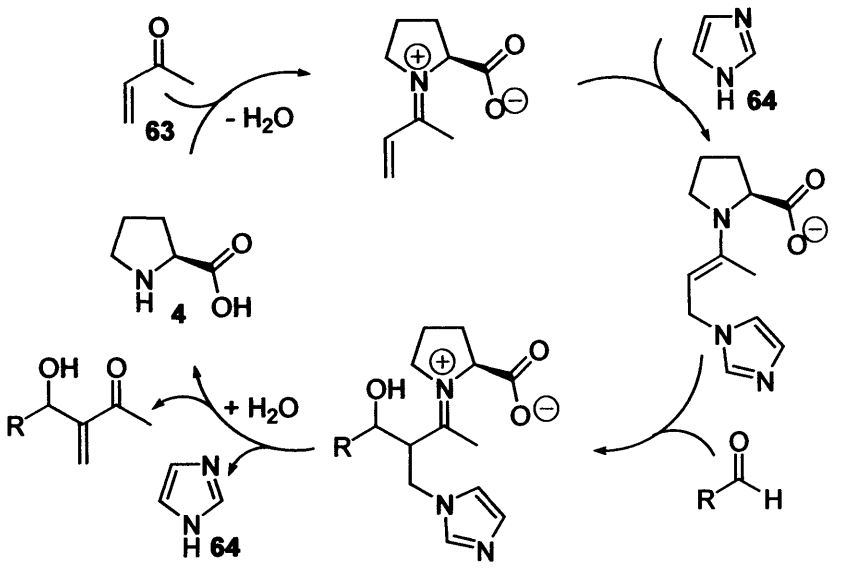
Increasing the amount of imidazole (**64**) and (*S*)-proline (**4**) to 30 mol% gave product **65** in excellent yield (91%) under the same conditions. Notably, use of either imidazole (**64**) or (*S*)-proline (**4**) alone gave no reaction.

Other amino acids, such as (*L*)-phenylalanine and glycine were tested as co-catalysts in this reaction, but only low yields (20-30%) were achieved. The use of benzimidazole or triethylamine as the Lewis base also furnished lower yields under the same reaction conditions.

Several arylaldehydes were reacted with methyl vinyl ketone (**63**) in the (*S*)-proline (**4**) and imidazole (**64**) co-catalysed Baylis-Hillman reaction, with the corresponding adducts obtained in moderate to excellent yield (30-90%). In all cases the adducts were obtained with low enantioselectivity (5-10% ee).

1.8.2 Mechanism of the Organocatalytic Baylis-Hillman Reaction

Based on the mechanism for the proline-catalysed aldol reaction (*Section* **1.6.10**), a mechanism for the (*S*)-proline (**4**) and imidazole (**64**) co-catalysed Baylis-Hillman reaction has been postulated.[58] Proline (**4**) reacts with MVK (**63**) to form an iminium ion, facilitating the conjugate addition of imidazole (**64**). The resulting enamine reacts with the aldehyde component in an aldol reaction. The Baylis-Hillman product is then formed *via* elimination of water and hydrolysis of the iminium ion to release the proline (**4**) catalyst (*Scheme* **29**).



Scheme **29**

This example of the use of proline (**4**) *as a co-catalyst for the Baylis-Hillman reaction gave essentially no asymmetric induction, but demonstrates the potential for chiral amines to catalyse such transformations, and future investigations may lead to a highly enantioselective organocatalytic Baylis-Hillman reaction.*

1.9 The Diels-Alder Reaction

The Diels-Alder reaction is one of the most important methods of carbon-carbon bond construction in synthetic organic chemistry,[59] enabling, in one step, the rapid preparation of cyclic compounds containing an unsaturated six-membered ring from the reaction of a conjugated diene with a double or triple bond (the *dienophile*). Almost eighty years after its discovery in 1928,[60] organic chemists still utilise and continue to develop this elegant tool.

Since the Diels-Alder reaction creates a molecule with up to four contiguous stereogenic centres, control of absolute stereochemistry and regiochemistry is particularly attractive. There are three basic strategies for the enantioselective control of the desired product in these cycloadditions: the use of a chirally modified diene, a chirally modified dienophile or a chiral catalyst.[61] It wasn't until the 1970's that the first highly stereoselective version of the Diels-Alder reaction was reported by Corey and co-workers.[62] Since then, there have been many impressive chiral auxiliaries and catalysts designed to investigate the scope and limitations of asymmetric [4+2] cycloadditions.[62,63]

1.9.1 The First Highly Enantioselective Organocatalytic Diels-Alder Reaction

D. W. C. MacMillan reported the first highly enantioselective organocatalytic Diels-Alder reaction in 2000.[7] It was hypothesised that the reversible formation of an iminium ion from an α,β-unsaturated carbonyl compound and an amine should activate it to reaction *via* lowering of the LUMO (lowest unoccupied molecular orbital) (*Figure* **14**).

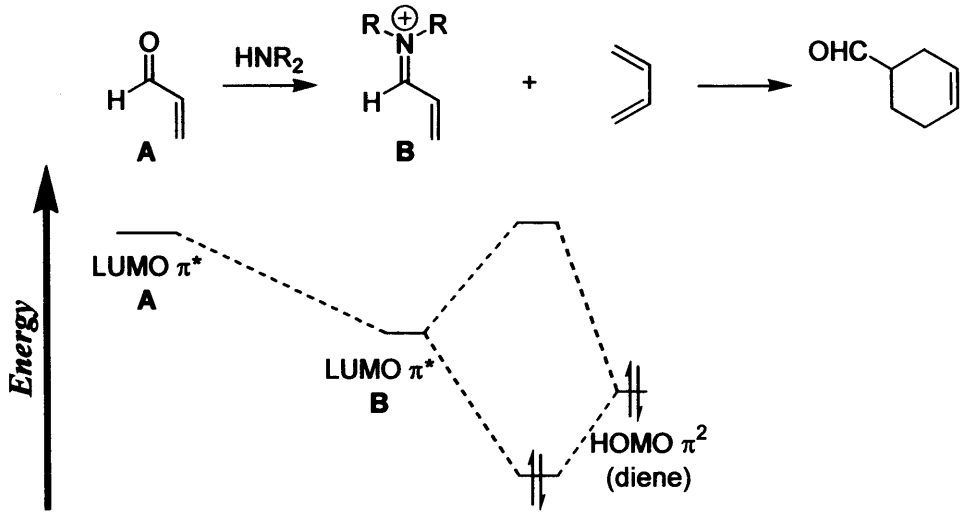
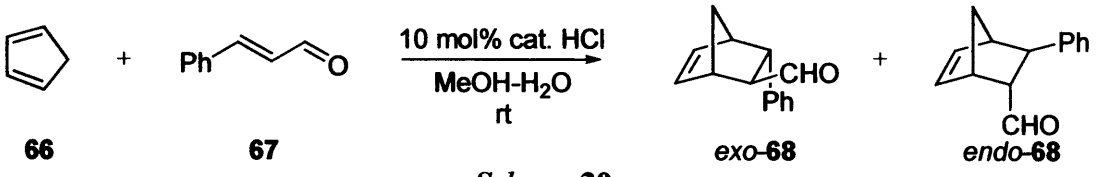


Figure **14**

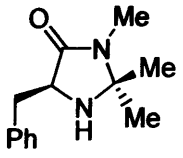
Initially a variety of chiral amines were investigated to test their capacity to enantioselectively catalyse the Diels-Alder reaction between cyclopentadiene (**66**) and (*E*)-cinnamaldehyde (**67**), (*Scheme* **30**).



66 **67** *exo*-**68** *endo*-**68**

Scheme **30**

Amines tested included (*S*)-proline methyl ester and (*S*)-abrine (*N*-methyltryptophan) methyl ester. These provided the Diels-Alder adduct (**68**) in excellent yields (>80%) with moderate stereoselectivity (≈2.5:1 *exo*:*endo*, 48-59% ee). The highest levels of enantioselectivity (93% ee) were given by chiral imidazolidinone **69** (*Figure* **15**), which provided control of the iminium ion geometry through the use of steric constraints on the catalyst architecture.

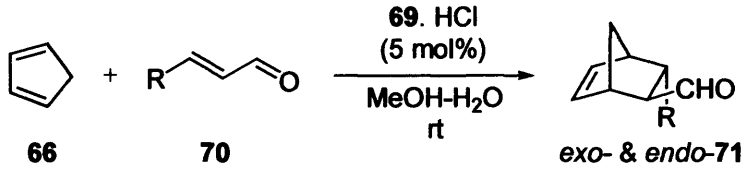


69

Figure **15**

1.9.2 Scope of the Organocatalytic Diels-Alder Reaction

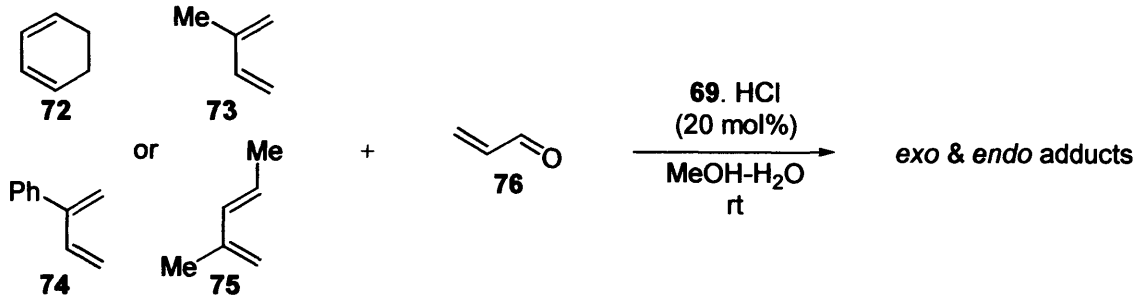
The scope of the organocatalytic Diels-Alder reaction was tested by reacting cyclopentadiene (**66**) with both aromatic and aliphatic α,β-unsaturated aldehydes (*Scheme* **31**). An increase in the steric bulk of the R group (Me, Pr, ^{i}Pr) was possible without loss of yield or enantioselectivity (>75% yield, *exo* >84% ee). Aromatic groups on the dienophile were also utilised.[7]



R =	Yield	*exo*:*endo*	% ee
a Me	75	1:1	86
b Pr	92	1:1	86
c ^{i}Pr	81	1:1	84
d Furyl	89	1:1	91

Scheme **31**

The amine-catalysed Diels-Alder cycloaddition was also general with respect to diene structure. A wide range of diene reactivity could be accommodated without loss in stereocontrol, allowing access to a number of cyclohexenyl building blocks incorporating acetoxy, alkyl, formyl and aryl substituents with high levels of regio- and enantioselectivity (72-89% yield, 5:1 – 11:1 *exo*:*endo*, 83-90% ee) (*Scheme* **32**).[7]

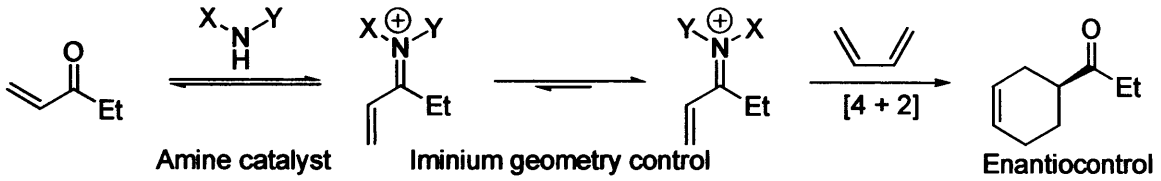


Scheme **32**

All of the above reactions were carried out under an aerobic atmosphere using wet solvents. The addition of 5% water to the reaction solvent gave both increased yields and enantioselectivities. It has been proposed that this addition of water facilitates the catalytic turnover.

1.9.3 Use of α,β-Unsaturated Ketones

Lewis acid coordination is traditionally a non-selective process with ketone dienophiles and often leads to poor levels of enantiocontrol. This has prevented the use of simple ketone dienophiles in asymmetric catalytic Diels-Alder reactions. In order for an amine catalyst to induce enantioselectivity, a selective π-bond must result when the iminium ion is formed (*Scheme* **33**).



Scheme **33**

MacMillan utilised a series of chiral imidazolidinones (**69**, **79-82**) to catalyse a Diels-Alder reaction between cyclopentadiene (**66**) and 4-hexen-3-one (**77**). It was found that the previously identified catalyst **69** (*Section* **1.9.1**) gave a low yield (20%) of the Diels-Alder adduct with no enantiocontrol (0% ee). Therefore substituents in the C2 and C5 positions were varied to try to improve the enantioselectivity (*Figure* **16**). It was found that a benzyl group in the C2 position gave optimum results, while aromatic and heteroaromatic groups in the C5 position (Catalysts **80**, **81**, **82**) improved the enantioselectivity. Imidazolidinone **82**, with a furyl-derived side chain, gave excellent yields and afforded superior levels of enantiocontrol (89% yield, 90% ee).[64]

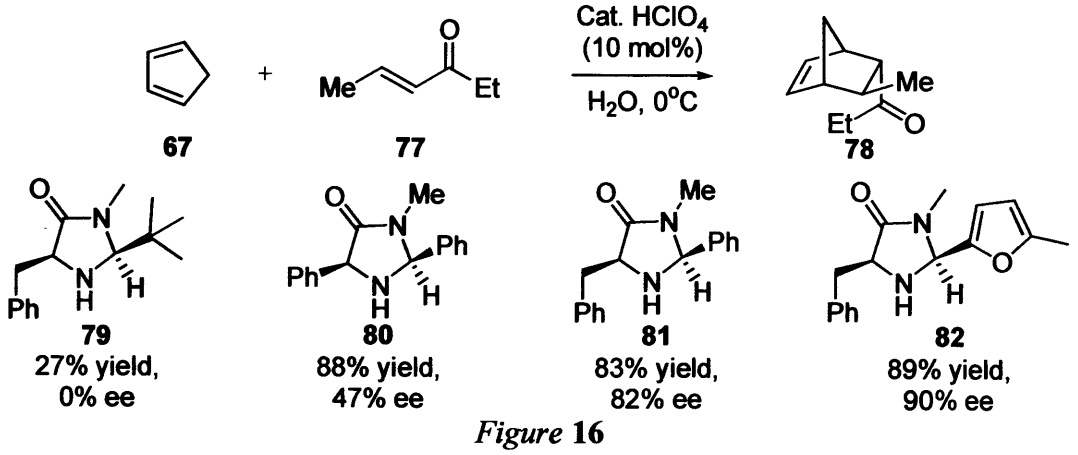


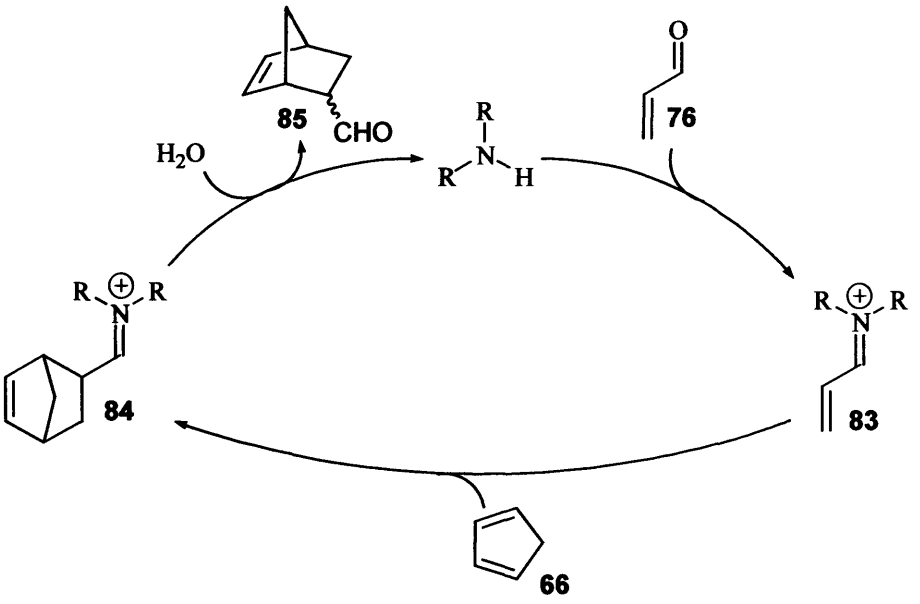
Figure **16**

It was found that imidazolidinone **82** catalysed the Diels-Alder reaction with a wide variety of dienes and ketone dienophiles without loss of reaction efficiency or enantiocontrol. This represents the first highly enantioselective catalytic Diels-Alder reaction with simple ketone dienophiles.

This method is also environmentally friendly as the above Diels-Alder reactions were all carried out in aqueous or ethanolic solvents, and the amine catalyst **82** could be recovered in 91% yield after column chromatography for reuse in further catalytic runs.

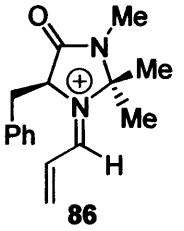
1.9.4 Mechanism of the Imidazolidinone-Catalysed Diels-Alder Reaction

In the mechanism of the organocatalytic Diels-Alder reaction, the α,β-unsaturated carbonyl compound reacts with the enantiopure amine catalyst to form an iminium ion, **83**. This activates the carbonyl compound to a [4+2] cycloaddition reaction with the diene reaction partner, leading to iminium ion **84**. Hydrolysis affords the enantioenriched cycloaddition product **85** and the chiral amine catalyst, which can proceed to repeat the cycle (*Scheme* **34**).



Scheme **34**

The iminium ion intermediate **86** shows two significant stereocontrol elements. Firstly, the (*E*)-iminium ion is formed to avoid non-bonding interactions between the substrate olefin and the C5 substituents, and secondly, the benzyl group in the C2 position effectively shields the *re* face of the dienophile, leaving the *si* face exposed for cycloaddition to take place (*Figure* **17**). This iminium ion structure was confirmed using molecular modelling calculations.[7,64]



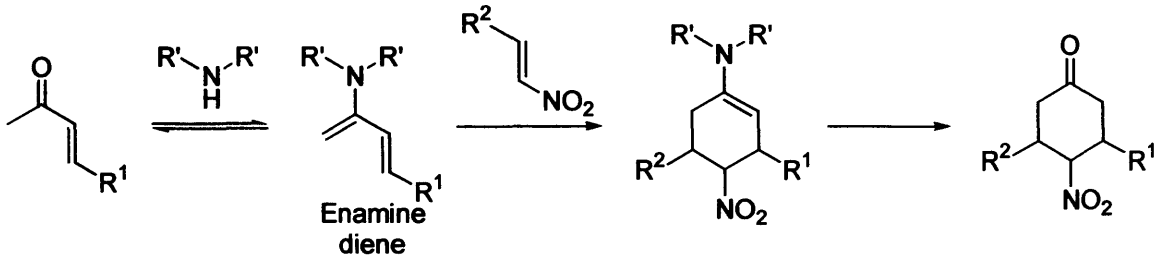
86

Figure **17**

These imidazolidinone-based catalysts achieved high levels of organisational control with simple aldehydes and ketones, most probably due to the geometrical constraints that accompany the formation of the iminium π-bond.

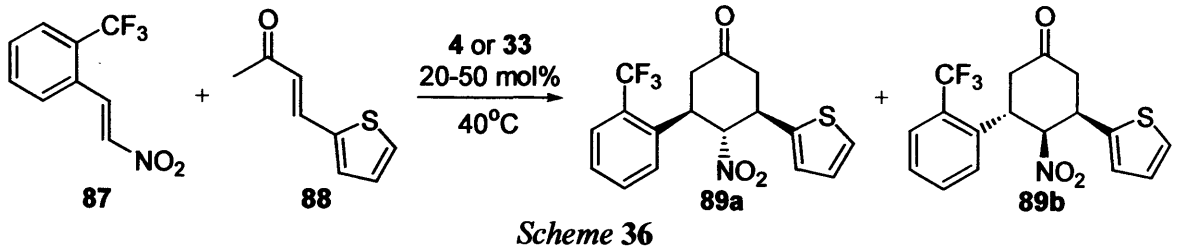
1.9.5 Amine-Catalysed Diels-Alder Reaction *via* an Enamine Pathway

The above examples of amine-catalysed Diels-Alder reactions (*Sections* **1.9.1-1.9.4**) involve the activation of the α,β-unsaturated carbonyl compound *via* formation of an iminium ion. An alternative strategy involves the *in situ* formation of an enamine from the α,β-unsaturated carbonyl compound. This enamine can then act as the diene in a [4+2] cycloaddition reaction with an alkene, providing an efficient single-step route to the synthesis of cyclohexanone derivatives (*Scheme* **35**).



Scheme **35**

Barbas III and co-workers utilised proline (**4**) and diamine (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**33**) as catalysts for a Diels-Alder reaction between nitro olefin **87** and α,β-unsaturated ketone **88** to provide cyclohexanone derivative **89**. Use of proline (**4**) in methanol gave a 75% yield of adduct **89** with a 3.6:1 ratio of **a**:**b**, while diamine **33** under neat conditions gave an 85% yield of adduct **89** with a 3:1 ratio of **a**:**b** (*Scheme* **36**). A variety of solvents, including water, could be utilised without loss of selectivity.[65]



87 **88** **89a** **89b**

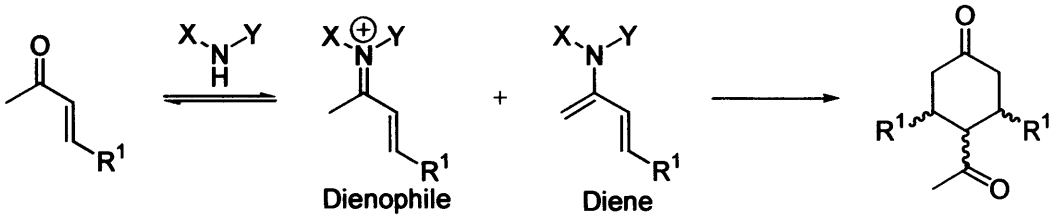
Scheme **36**

Both proline (**4**) and diamine **33** catalysed the Diels-Alder reaction with a variety of nitro olefins and α,β-unsaturated ketones, affording good yields of the corresponding adduct (32-75%). All of the reactions performed yielded adducts with moderate enantioselectivities (up

to 38% ee). These reactions demonstrated that an enamine can be generated *in situ* and reacted with nitro olefin dienes under amine-catalysed conditions.

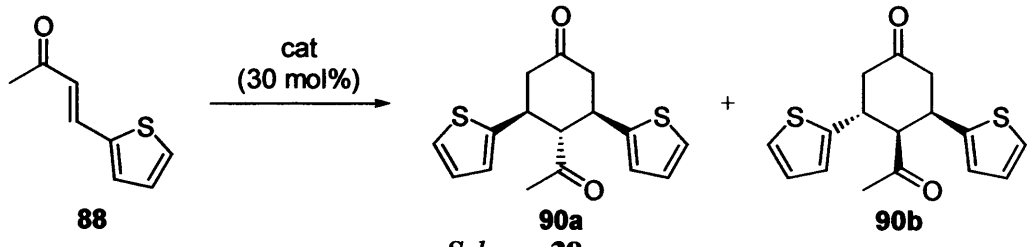
1.9.6 Combining Iminium and Enamine Pathways

When an α,β-unsaturated carbonyl compound reacts with a secondary amine either an iminium ion dienophile (*Sections* **1.9.1-1.9.4**) or an enamine diene can be formed (*Section* **1.9.5**). Barbas III showed that these two pathways can be combined, such that cyclohexanone derivatives can be formed in a single-step *via* a [4+2] cycloaddition reaction between an iminium ion dienophile and an enamine diene (*Scheme* **37**).



Scheme **37**

Proline (**4**), diamine (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**33**) and pyrrolidine (**55**), under a variety of reaction conditions, were tested as amine catalysts for a direct self Diels-Alder reaction of α,β-unsaturated ketone (**88**) to afford cyclohexanone derivatives **90a** and **90b** (*Scheme* **38**).[66]



88 **90a** **90b**

Scheme **38**

Pyrrolidine (**55**) was found to give both increased yields and selectivities compared to diamine **33** and proline (**4**), with a 70% yield and 6:1 ratio of **90a**:**90b** when the reaction was carried out in water. Although proline (**4**) afforded a lower yield (52%) and diastereoselectivity (4.5:1), this catalyst did provide adduct **90b** with modest enantioselectivity (23% ee) when the reaction was performed in methanol.

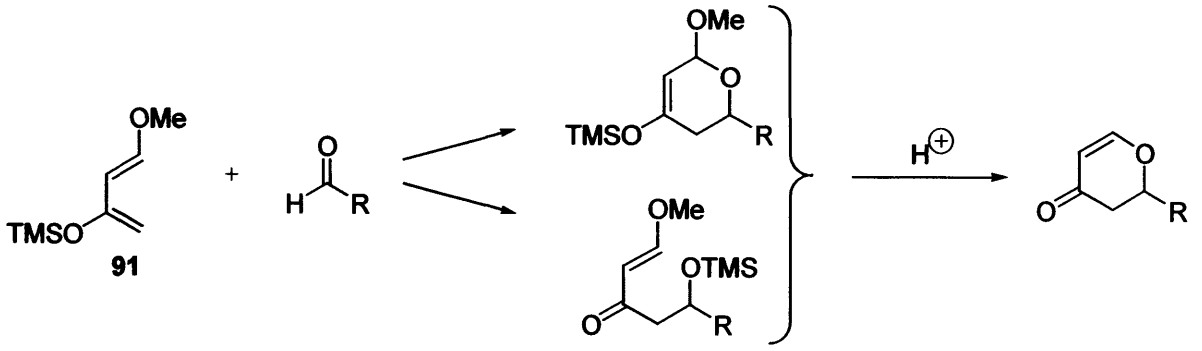
It was shown that a variety of α,β-unsaturated ketones could be utilised in this transformation with yields of the cyclohexanone derivatives ranging from 47-80%. Performing these amine-catalysed self Diels-Alder reactions in water provided the *exo*-isomer as the major product,

and this procedure was scalable, allowing gram quantities of cyclohexanone derivatives to be prepared under very mild conditions.

The above examples illustrate that the Diels-Alder reaction can be catalysed by small chiral amines, either via an iminium ion mechanism, which lowers the LUMO of the α,β-unsaturated carbonyl compound, or by an enamine-based activation strategy. These two strategies can also be combined allowing for the direct self Diels-Alder reactions of α,β-unsaturated ketones. These examples further exemplify the use of amines as organocatalysts for important synthetic transformations.

1.10 The Hetero-Diels-Alder Reaction

The hetero-Diels-Alder (HDA) reaction provides the opportunity to incorporate a heteroatom into the six membered ring of the Diels-Alder product. Most commonly, the catalytic asymmetric version of this reaction involves the cycloaddition between an aldehyde and a reactive diene (typically with one or two oxygen atoms attached, for example Danishefsky's diene **91**). The products can be formed by either a direct cycloaddition or *via* a two-step aldol-Michael sequence (*Scheme* **39**).

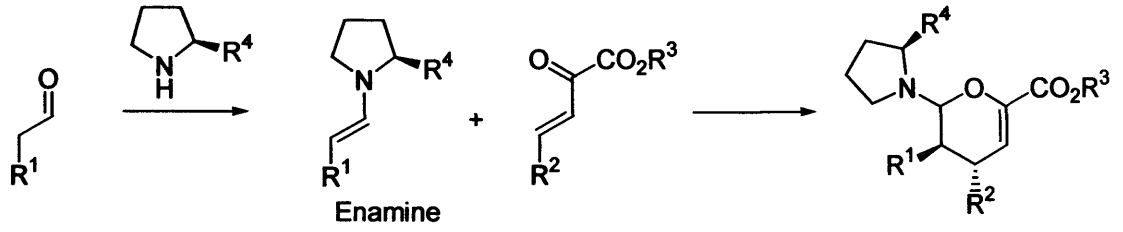


Scheme **39**

This reaction provides the ability to incorporate various heteroatoms at any of the six possible positions in the diene and dienophile components of the reaction, with many examples reported since the discovery of the Diels-Alder reaction.[67] Alder documented one of the first examples of a hetero-Diels-Alder reaction in 1943 when he discovered, by chance, that an imine could react with appropriate dienes in a [4+2] cycloaddition.[68]

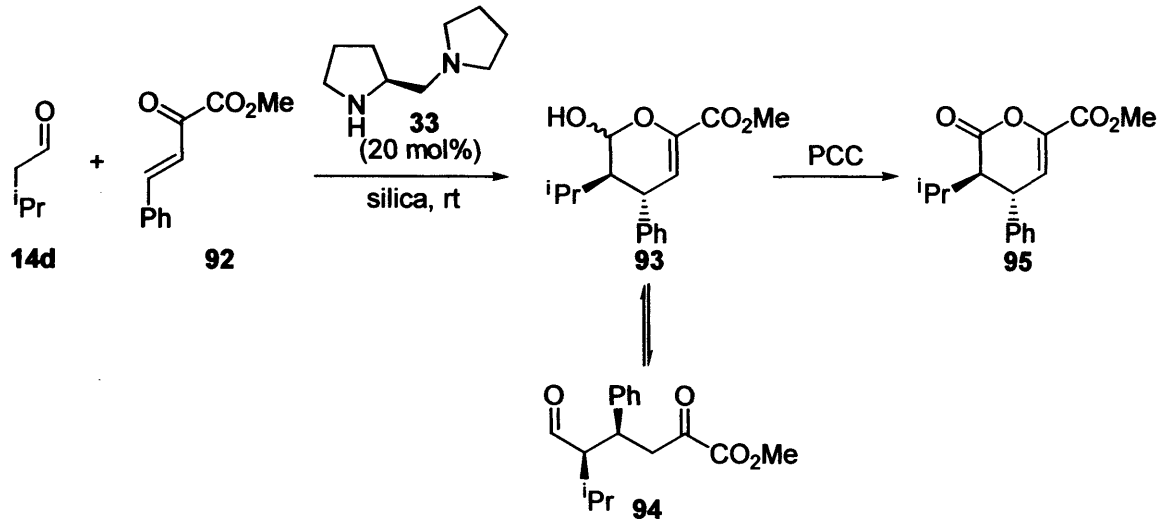
1.10.1 An Organocatalytic Enantioselective Hetero-Diels-Alder Reaction

Jørgensen and colleagues reported the first organocatalytic inverse-electron-demand hetero-Diels-Alder reaction in 2003. They hypothesised that reaction between an aldehyde and a chiral pyrrolidinone would generate a chiral enamine, which would then act as an electron-rich alkene and undergo an enantioselective hetero-Diels-Alder reaction (*Scheme* **40**).



Scheme **40**

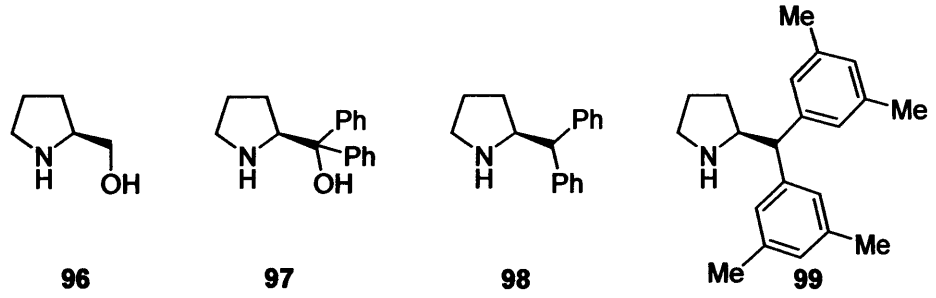
To examine this theory, *iso*valeraldehyde (**14d**) was reacted with diamine (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine (**33**) to form an enamine *in situ*. This was reacted with electron-poor enone **92** to yield a mixture of two anomers of hemiacetal **93** and the aldehyde **94** in a 69% yield and 51% ee (*Scheme* **41**). Oxidation of this mixture with pyridinium chlorochromate (PCC) provided lactone **95** as a single diastereoisomer. Catalytic turnover was accomplished by addition of silica, as this facilitates the hydrolysis step of the catalytic cycle.[69]



Scheme **41**

To improve both the yield and enantioselectivity several pyrrolidine-based catalysts were employed (*Figure* **18**). While prolinol (**96**) gave a similar yield and selectivity to diamine **33**, diphenylprolinol (**97**) promoted a highly selective hetero-Diels-Alder reaction (97% ee), but the increased steric bulk at the C2 position led to a low yield (6%). Dehydroxylated catalyst

98 gave a higher yield (46%), but also a slight decrease in enantioselectivity (88% ee). Catalyst **99** was found to be optimal, giving a similar enantioselectivity (87% ee), with a significant increase in yield (87%) at a lower catalyst loading (10 mol%).



96 **97** **98** **99**

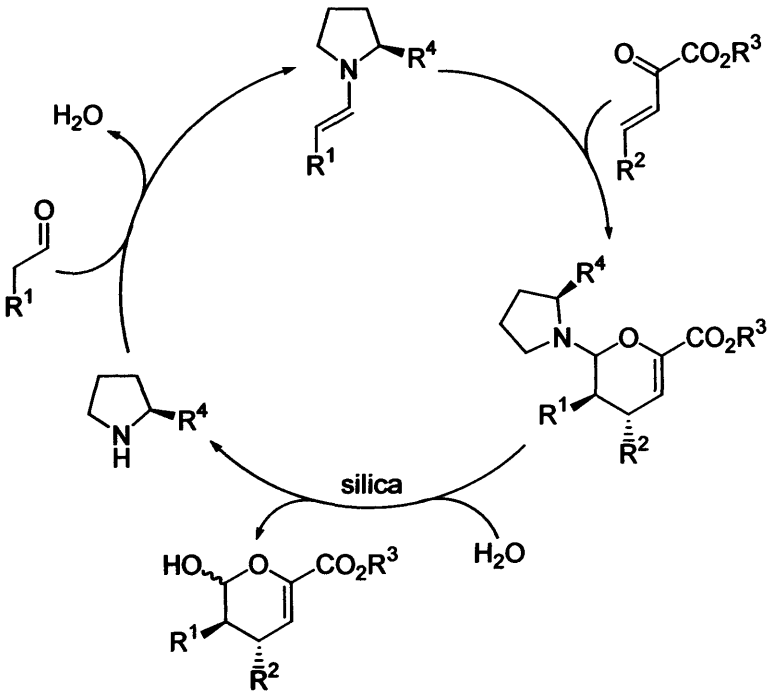
Figure **18**

A higher yield could be obtained by mixing the reagents and catalyst at -15°C and allowing the reaction to warm to room temperature. A variety of solvents could be used, with little effect on the enantioselectivity (89-92% ee for all solvents employed), while dichloromethane afforded the highest yield (93%).

The scope of the enantioselective organocatalytic hetero-Diels-Alder reaction was demonstrated by employing a variety of aldehydes and enones. It was found that enones with aromatic or aliphatic substituents in the γ-position underwent the hetero-Diels-Alder reaction to afford adducts with excellent diastereoselectivities and enantioselectivities. The reaction was also general with respect to the aldehyde component.

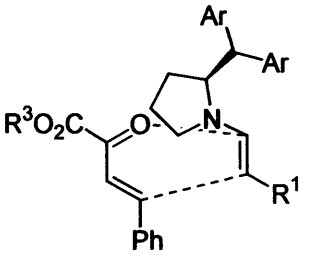
1.10.2 Mechanism of the Amine-Catalysed Hetero-Diels-Alder Reaction

In the proposed reaction mechanism of the aminocatalytic hetero-Diels-Alder reaction, an enamine is generated *in situ* from an aldehyde and the chiral amine catalyst. This enamine acts as an electron-rich alkene and undergoes a stereoselective hetero-Diels-Alder reaction with the enone. The HDA adduct is obtained, after hydrolysis, with the amine catalyst regenerated to continue through another catalytic cycle (*Scheme* **42**).[69]



Scheme **42**

The proposed transition state (*Model* **F**) is consistent with the observed absolute and relative stereochemistry of the products obtained from the organocatalytic hetero-Diels-Alder reaction. The electronic properties of the enamine governs the regioselectivity, while the 2,2-diarylmethyl substituent on the pyrrolidine ring of catalyst **99** shields the *si*-face of the enamine, so directing the addition of the enone to the *re*-face of the alkene fragment in an *endo*-selective manner (*Figure* **19**).



Model **F**
Figure **19**

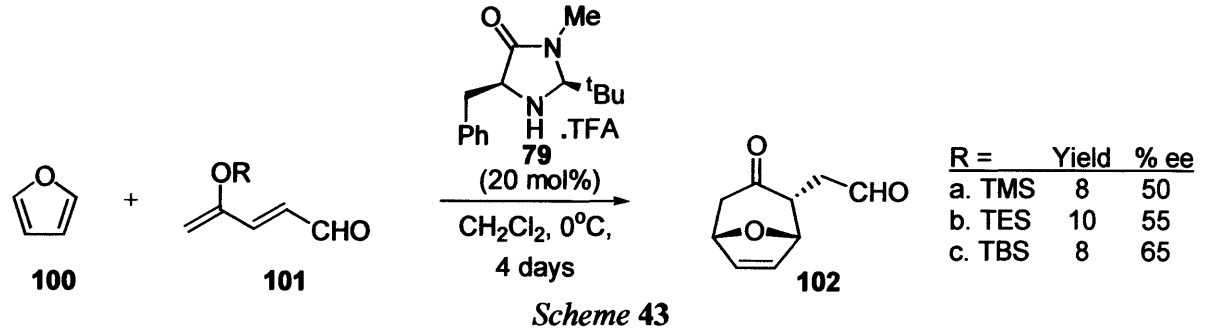
This represents the first example of a hetero-Diels-Alder reaction catalysed by a simple amine molecule. Proline-derived catalysts were employed to furnish the hetero-Diels-Alder adducts in high yields with excellent enantioselectivities, further illustrating the versatility of small organic molecules as reaction catalysts.

1.11 [4+3] Cycloaddition Reactions

The [4+3] cycloaddition of allylic cations with dienes represents a powerful approach to the synthesis of seven-membered rings. Many approaches to the generation of allylic cations and their subsequent cycloadditions have been published, but it is only recently that asymmetric [4+3] cycloaddition reactions have appeared in the literature, with most of the systems used to date based on a chiral auxiliary approach.[70]

1.11.1 An Asymmetric Organocatalytic [4+3] Cycloaddition Reaction

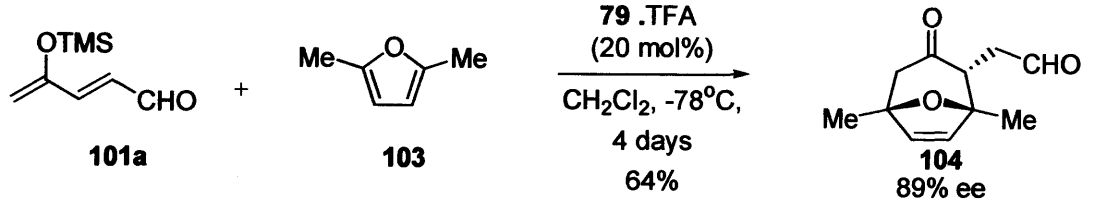
Harmata and co-workers hypothesised that the generation of chiral unsaturated iminium ions, such as the intermediates formed in the asymmetric Diels-Alder reaction (see *Section* **1.9**), should also be amenable to the catalysis of [4+3] cycloaddition reactions. Therefore, furan (**100**) was reacted with several silyloxypentadienals (**101a-c**) in the presence of chiral imidazolidinone **79**. In each case the [4+3] cycloadduct **102** was formed with *endo* selectivity, and good enantioselectivity but with low yield (*Scheme* **43**).[71]



R =	Yield	% ee
a. TMS	8	50
b. TES	10	55
c. TBS	8	65

Scheme **43**

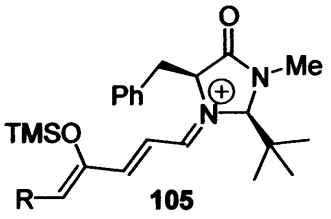
2,5-Disubstituted furans were also utilised in the [4+3] cycloaddition reaction with trialkylsilyloxypentadienals. The reaction of 2,5-dimethylfuran (**103**) with **101a** afforded adduct **104** in good yield (64%) as a single diastereoisomer with 89% ee (*Scheme* **44**). For all the dimethylfurans reacted, low to good yields of the corresponding cycloadduct were obtained (18-74%) with high enantiomeric excesses (80-90% ee).



Scheme **44**

1.11.2 Iminium Ion Intermediate of the [4+3] Cycloaddition Reaction

At present, no proof of mechanism has been reported for the asymmetric organocatalytic [4+3] cycloaddition reaction, but in accord with proposals by MacMillan (*Section* **1.9.4**) it has been assumed by Harmata that iminium ion **105** is formed (*Figure* **20**).[71]



105

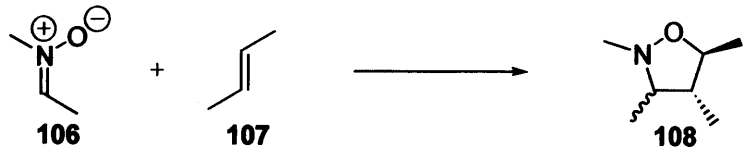
Figure **20**

The benzyl group in the C5 position blocks the top face of the iminium ion, while the trialkyl-silyloxy-group forces attack of the diene from one side predominantly. It has been suggested that these two factors lead to the observed selectivity, although further studies are required to determine the stereochemical and mechanistic features of this [4+3] cycloaddition reaction.

This represents the first example of asymmetric organocatalysis of the [4+3] cycloaddition reaction. Although further research and optimisation are required, this example illustrates another application of low molecular weight chiral amines as reaction catalysts.

1.12 1,3-Dipolar Cycloaddition Reactions

The 1,3-dipolar cycloaddition reaction can be used for the general construction of five-membered heterocycles *via* the addition of a 1,3-dipolar species to a multiple bond (the *dipolarophile*). The 1,3-dipolar species can consist of carbon, nitrogen and oxygen atoms in various combinations. The 1,3-dipolar cycloaddition of nitrones with alkenes has received considerable attention in asymmetric synthesis.[72] In contrast to most other 1,3-dipoles, nitrones are often stable compounds and do not typically require *in situ* formation, thus accounting for their success in synthetic applications. In the 1,3-dipolar cycloaddition reaction of a nitrone (**106**) with an alkene (**107**), up to three new contiguous asymmetric centres can be formed in the product isoxazolidine **108** (*Scheme* **45**), and this is a useful synthon in the preparation of biologically important compounds.



106 **107** **108**

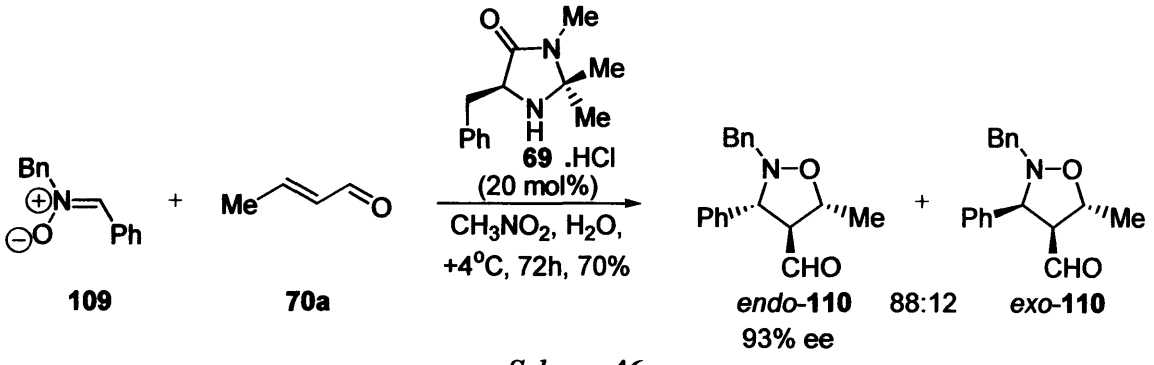
Scheme **45**

1,3-Dipolar cycloaddition reactions can be divided into two major groups: the normal electron-demand reactions and the inverse electron demand reactions. Many examples within the literature are of diastereoselective reactions that involve the use of chiral alkenes or nitrones, but over the past ten years catalytic enantioselective versions have been reported.

1.12.1 An Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition

Chiral imidazolidinones can be used to catalyse an enantioselective organocatalytic 1,3-dipolar cycloaddition reaction between a nitrone and an α,β-unsaturated carbonyl compound. These amine catalysts react reversibly with the α,β-unsaturated carbonyl compound by iminium ion formation, lowering the LUMO of the alkene, so activating it to reaction with the nitrone species.

MacMillan performed a [3+2] cycloaddition reaction of *N*-benzylidenebenzylamine *N*-oxide (**109**) with (*E*)-crotonaldehyde (**70a**) to afford isoxazolidine **110** (*Scheme* **46**). This reaction was successful using a variety of chiral imidazolidinone catalysts, with the phenylalanine-derived imidazolidinone **69** providing the highest levels of enantiocontrol (93% ee).[73]



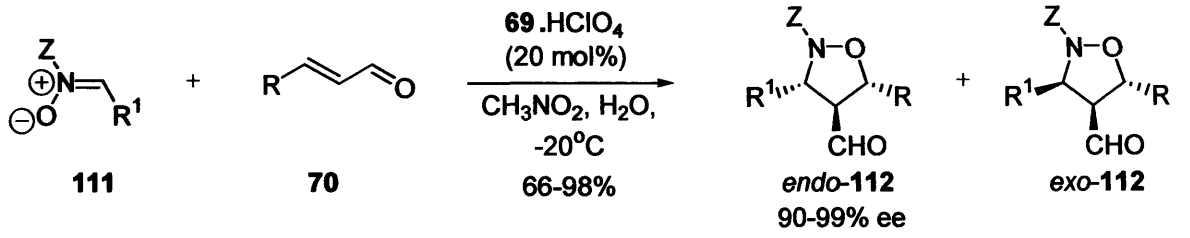
Scheme **46**

An increase in reaction efficiency was accomplished using the perchloric acid salt of catalyst **69** (98% yield, 100h), and optimal stereochemical control was achieved by lowering the reaction temperature to –10°C.

1.12.2 Scope of the Amine-Catalysed 1,3-Dipolar Cycloaddition

The scope of the 1,3-dipolar cycloaddition reaction was investigated by reacting α,β-unsaturated aldehydes with various nitrones. It was found that the reaction was quite general with respect to the nitrone structure (**111**). Variation in the *N*-alkyl group (Z = Me, Bn, allyl) was possible without loss in enantioselectivity (94-99% ee), and a variety of aromatic

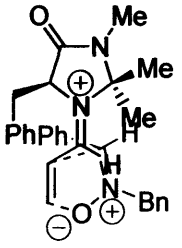
substituents on the dipole (R^1 = Ph, *p*-PhCl, *p*-PhOMe, 2-naphthyl) could also be tolerated (91-95% ee). Structural variation of the dipolarophile (**70**) was also achieved (R = Me, H), which provided high levels of reaction efficiency and stereocontrol (*Scheme* **47**).[73]



111 **70**

Scheme **47**

The *endo*-(4*S*)-isoxazolidine adduct **112** was formed as the major isomer in the above examples. This result is consistent with the iminium ion intermediate **86** proposed by MacMillan to explain the stereochemical outcome of imidazolidinone-catalysed Diels-Alder reactions (See *Section* **1.9.4**). The reaction of the imidazolidinone catalyst **69** with an α,β-unsaturated aldehyde generates an (*E*)-iminium ion (*Model* **G**). The presence of a benzyl group on the catalyst structure promotes the cycloaddition of the dipole from the *si*-face of the dipolarophile, and cycloaddition through an *endo* pathway effectively alleviates non-bonding interactions between the nitrone phenyl group and the neopentyl methyl substituent on the catalyst framework (*Figure* **21**).[73]



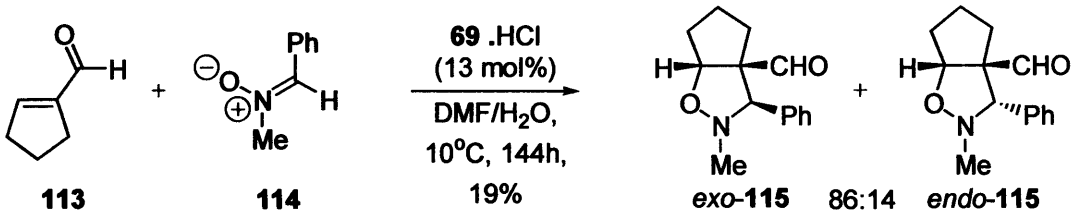
Model **G**

Figure **21**

This use of chiral amines to catalyse 1,3-dipolar cycloadditions is synthetically important as it has been shown that α,β-unsaturated carbonyl compounds are poor substrates for metal-catalysed nitrone cycloadditions. This is due to the preferential co-ordination of the Lewis acid to the nitrone oxygen rather than to the carbonyl oxygen atom. Therefore, the use of an amine catalyst enables α,β-unsaturated aldehydes to be used as substrates in [3+2] cycloaddition reactions involving nitrones.

1.12.3 Use of Cyclic Dipolarophiles

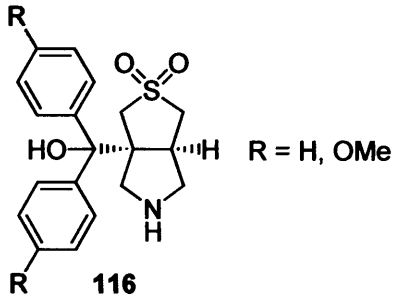
Karlsson utilised chiral imidazolidinone **69** to catalyse a 1,3-dipolar cycloaddition of acyclic nitrone **114** with cyclopentenecarboxaldehyde (**113**). But the fused bicyclic isoxazolidine **115** product was formed in both low yield and enantiomeric excess (*Scheme* **48**).[74]



113 **114** *exo*-**115** 86:14 *endo*-**115**
5% ee

Scheme **48**

To increase both the reaction efficiency and the stereochemical control, other chiral amine catalysts were investigated. Firstly, highly functionalised bicyclic pyrrolidines **116** (*Figure* **22**) were tested as it was hypothesised that the increased rigidity and steric bulk in the catalyst structure would lead to a higher enantioselectivity.



116

Figure **22**

Use of bicyclic pyrrolidine **116** gave reasonable yields (59-61%) of isoxazolidine **115** with good enantiomeric excess (67-70%), with the highest optical purities obtained when wet dimethylformamide was used as the solvent.

To further improve the yield and enantioselectivity some proline-based catalysts were tested. While diphenylprolinol (**97**) was inefficient as a reaction catalyst, diamines **33** and **117** (*Figure* **23**) gave isoxazolidine **115** with both very high diastereoselectivity and excellent enantioselectivity (85-91% ee), although with low yield (26-44%).

33 **117**

Figure **23**

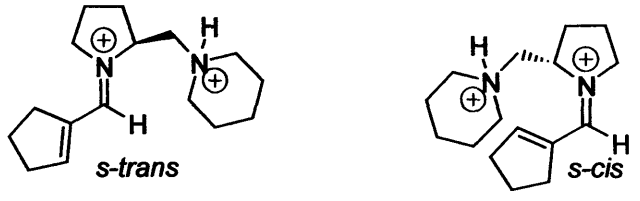
The yield of isoxazolidine **115** obtained could be increased slightly (49%) by use of the dihydrochloride salt of diamine **117**, while use of an excess of the nitrone component (2 equivalents) lead to a significant increase in yield (70%). The catalyst loading could also be lowered to 1 mol% while maintaining the high diastereo- and enantioselectivities.[74]

Variation in the structure of both the aldehyde and the nitrone components was possible. The diastereoselectivity remained high throughout, but a considerable variation in the enantiomeric excess was observed. The structure of the aldehyde was found to be important for achieving a successful reaction, with lower yields obtained as the steric bulk of the aldehyde increased.[75]

These examples illustrate that cyclic dipolarophiles can be employed effectively in the 1,3-dipolar cycloaddition reaction, furnishing fused bicyclic isoxazolidines with both high diastereo- and enantioselectivity.

1.12.4 Iminium Ion Intermediate of the Aminocatalytic 1,3-Dipolar Cycloaddition

The iminium ion intermediate of the aminocatalytic 1,3-dipolar cycloaddition reaction is believed to be either *Model* **H** or *Model* **I** (*Figure* **24**). Either a (*Z*)- or an (*E*)-iminium ion can result from reaction between the aldehyde component and the catalyst, and the π-system can adopt either an *s-cis* or an *s-trans* conformation. Attack of the nitrone from the sterically least hindered side of either *Model* **H** or *Model* **I** would lead to the major enantiomer observed in the above experiments.



(*E*)-Iminium Isomer (*Z*)-Iminium Isomer

Model **H** *Model* **I**

Figure **24**

With *Model* **I**, the piperidine ring effectively shields the rear face of the alkene, and so the nitrone must approach from the top face, explaining the observed selectivity. With *Model* **H**, the nitrone can approach from either face of the alkene, so a low enantioselectivity would be expected. Although *Model* **I** best explains the observed results, further studies are required to prove the structure of the iminium ion intermediate.

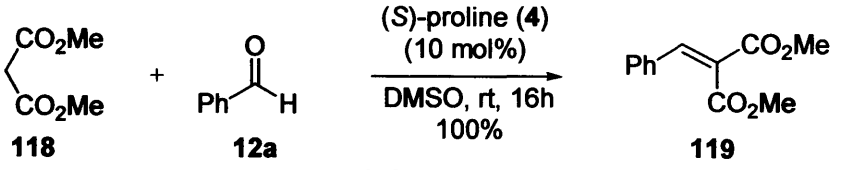
These studies further establish LUMO-lowering organocatalysis as a broadly useful concept for asymmetric catalysis. Moreover, this work further illustrates that chiral amine compounds can be employed as asymmetric catalysts for a range of transformations that traditionally utilise metal salts.

1.13 Knoevenagel Condensation Reactions

The Knoevenagel condensation involves the reaction of an aldehyde or a ketone with a compound containing an active methylene group and is an important method for the preparation of substituted alkenes.[10] This reaction has been widely studied under a variety of conditions, solvents and catalysts, with a base or a Lewis acid typically employed as the reaction catalyst.

1.13.1 Proline-Catalysed Knoevenagel Condensation

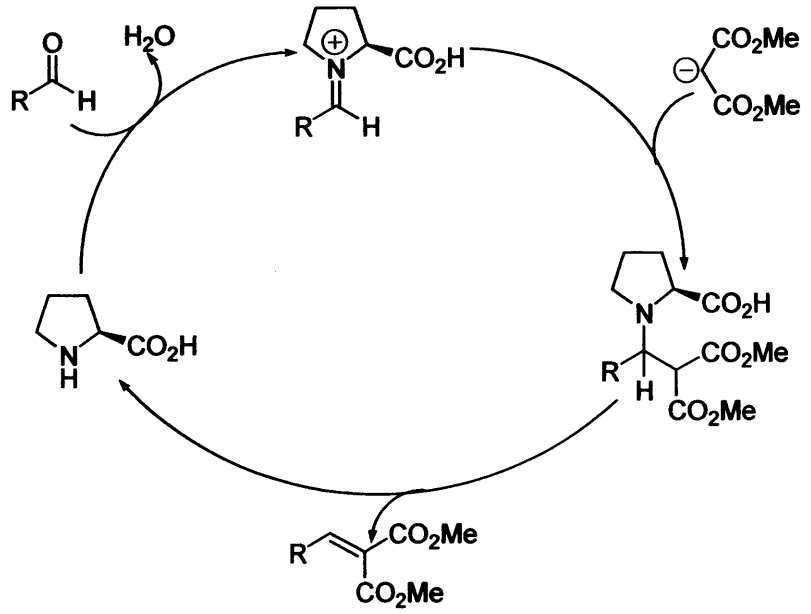
Cardillo has utilised (*S*)-proline (**4**) as a catalyst in the Knoevenagel reaction between dimethylmalonate (**118**) and a variety of aldehydes, for example benzaldehyde (**12a**), to form arylidene product **119** in quantitative yield. This reaction was performed under very mild reaction conditions. Very good yields were obtained with both aliphatic (72-97%) and aromatic aldehydes (66-100%), furnishing alkylidene and arylidene malonates respectively.[76]



Scheme **49**

The condensation of ethyl cyanoacetate with aromatic aldehydes also provided the corresponding arylidene product in almost quantitative yield.

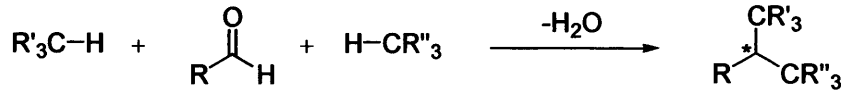
The proposed mechanism for this reaction is based on results obtained by Knoevenagel,[77] who showed that the condensation of an aldehyde and an amine takes place to form an iminium ion. This iminium ion then reacts with the activated methylene compound to form the alkylidene or arylidene product (*Scheme* **50**).



Scheme **50**

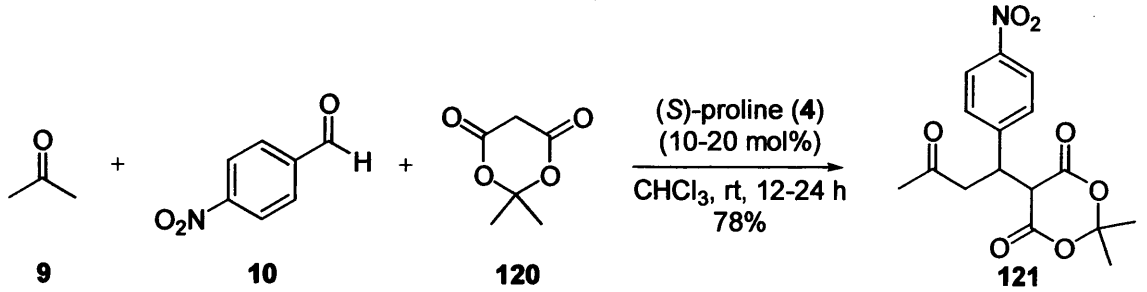
1.13.2 Proline-Catalysed Domino Knoevenagel-Hetero-Diels-Alder Reaction

In this multi-component reaction (MCR), two C-H bond containing compounds condense with an aldehyde to generate two new carbon-carbon bonds (*Scheme* **51**). Unsymmetrical variants, in which two different C-H-containing compounds combine with an aldehyde are much less studied than symmetrical versions, but are useful for the construction of tertiary stereogenic centres.



Scheme **51**

List has studied the Knoevenagel-hetero-Diels-Alder domino reaction of unmodified ketones with aldehydes and Meldrum's acid (**120**) catalysed by proline (**4**). The proline-catalysed reaction of *p*-nitrobenzaldehyde (**10**), Meldrum's acid (**120**) and acetone (**9**) readily furnished keto ester **121** in 78% yield (*Scheme* **52**).[78]



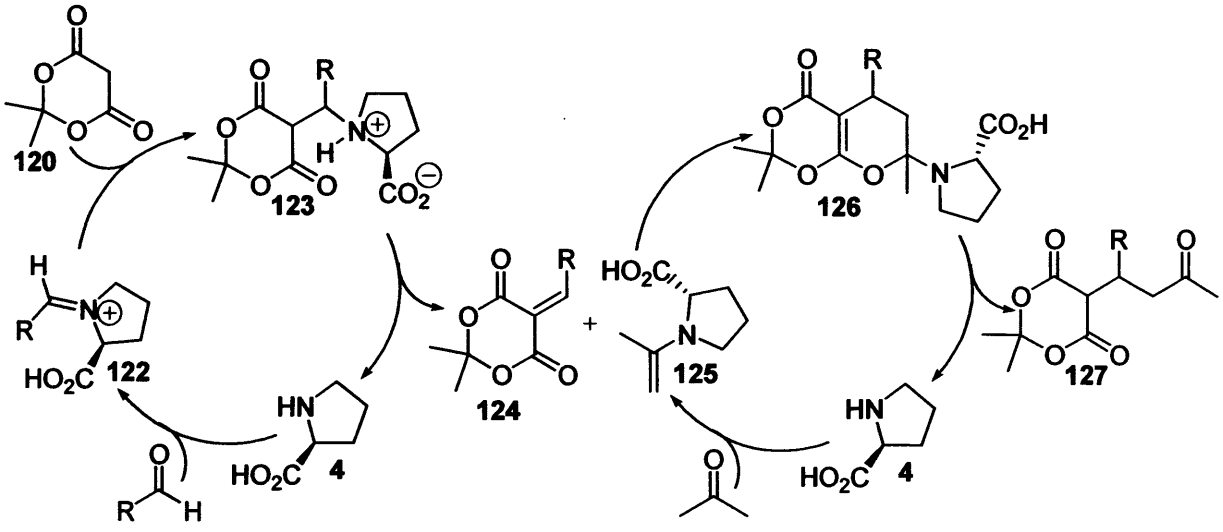
9 **10** **120** **121**

Scheme **52**

Other aldehydes, including α-branched and unbranched and cyclic aldehydes were used to afford the corresponding keto ester in good yields (51-83%). Cyclic ketones can also be employed, furnishing the corresponding products as single diastereoisomers.

Unfortunately, the enantioselectivities of these reactions were generally low, with the keto ester products obtained in <5% ee. Although the α-chirality of proline does not lead to any significant asymmetric induction within this reaction, the carboxylate group seems essential for catalysis to occur as pyrrolidine (**55**) was found to be ineffective.

It has been proposed that this three-component reaction involves a domino Knoevenagel-hetero-Diels-Alder process. In this sequence, proline (**4**) utilises both iminium- and enamine-catalysis. The initial Knoevenagel condensation proceeds *via* iminium ion **122** and ammonium ion **123** to give alkene **124**. In the hetero-Diels-Alder step, proline (**4**) forms an enamine **125** with the ketone, and the resulting dienophile reacts with the hetero-diene **124** generated from the Knoevenagel condensation. This gives adduct **126**, which upon hydrolysis yields the final product **127** while regenerating the proline catalyst (*Scheme* **53**).



Scheme **53**

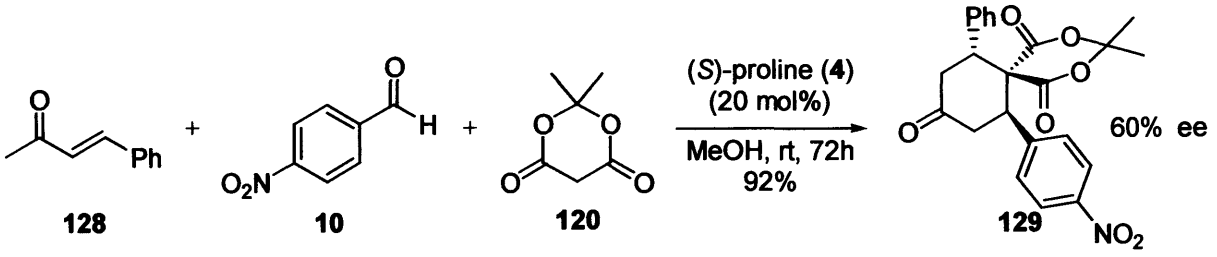
This reaction allows the rapid construction of complex carbon-scaffolds with two new carbon-carbon bonds generated from three commercially available components. The products are valuable precursors to highly functionalised 1,5-dicarbonyl compounds.

1.13.3 Amine-Catalysed Domino Knoevenagel-Diels-Alder Reaction

In this three-component reaction, an aldehyde reacts with Meldrum's acid (**120**) in a Knoevenagel condensation to provide an alkylidene derivative, which then undergoes a

concerted [4+2] cycloaddition with a diene enamine, generated *in situ* from an enone and an amine catalyst, to form a substituted spiro[5,5]undecan-1,5,9-trione. A quaternary centre is generated and three new carbon-carbon bonds are formed. Spirocyclic ketones are important intermediates in the synthesis of natural products and in medicinal chemistry.

The three-component reaction of α,β-unsaturated ketone **128**, *p*-nitrobenzaldehyde (**10**) and Meldrum's acid (**120**) in the presence of a catalytic amount of (*S*)-proline (**4**) furnished adduct **129** as a single diastereoisomer in 92% yield with 60% ee (*Scheme* **54**).[79]



Scheme **54**

The optical purity was significantly increased by using proline-derived catalyst, dimethyl thiazolidinium-4-carboxylate (**32**), which furnished spirotrione **129** in 88% yield with 86% ee. A variety of aldehydes and enones were employed in this reaction, with the corresponding products formed in high yield (80-99%) and enantioselectivity (84-99% ee) throughout.

The intermediate alkylidene **130**, generated *via* Knoevenagel condensation of *p*-nitrobenzaldehyde (**10**) with Meldrum's acid (**120**), and the enamine diene **131**, formed by condensation of the proline (**4**) catalyst with the enone **128**, are shown in *Figure* **25**. These two species undergo a [4+2] cycloaddition to form the spirotrione **129**. It was proposed that a H-bond between the carboxylate group of the proline (**4**) moiety and one of the carbonyl groups of the alkylidene **130** induces the enantioselectivity observed in the product.

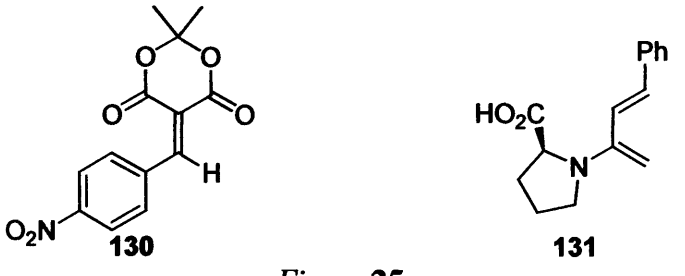


Figure **25**

These Knoevenagel-type condensation reactions add to the increasing number of efficient organocatalytic transformations catalysed by small-molecule amines, further illustrating the use of organocatalysis as a viable alternative to traditional metal-based catalysts.

1.14 The Mannich Reaction

Many natural products, including proteins and nucleic acids and most biologically active compounds, contain nitrogen. Methods for the synthesis of nitrogenous compounds are therefore at the frontiers of synthetic organic chemistry. The Mannich reaction is such an example. In this transformation, three components, a ketone, an aldehyde and an amine react to form a β-amino-ketone. Both *direct* variants, which use unmodified ketone donors, and *indirect* variants that utilise preformed enolate equivalents have been described.[80] In addition, the imine intermediate may be preformed or its amine and aldehyde precursors used directly (*Figure* **26**).

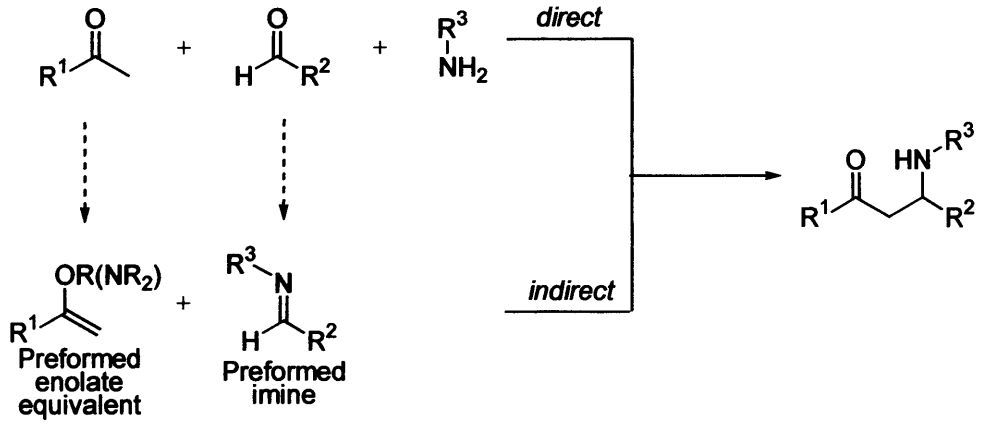
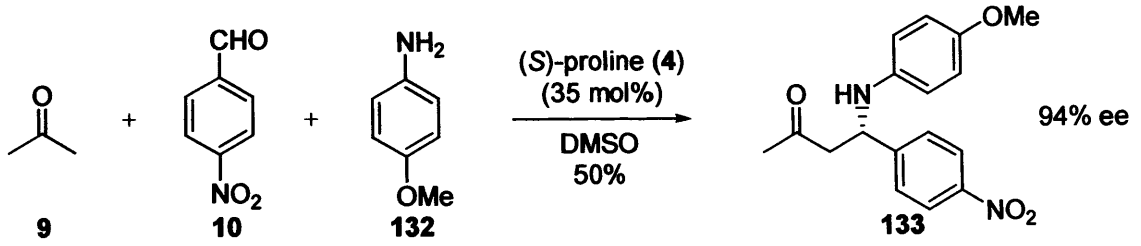


Figure **26**

Several asymmetric Mannich-type reactions have been reported in recent years. However, catalytic enantioselective variants are rare and typically involve pre-formation of both the imine and enol equivalents.

1.14.1 Direct Catalytic Asymmetric Three-Component Mannich Reaction

If the imine is not preformed and so exists in equilibrium with the free aldehyde, aldol and Mannich reactions compete. List hypothesised that Mannich reactions, catalysed by a chiral aminocatalyst, could be performed directly because the nucleophilic addition of the proline enamine should be faster to an imine than to an aldehyde. This concept worked extremely well. A three-component Mannich reaction, catalysed by proline (**4**), between *p*-nitrobenzaldehyde (**10**), *p*-anisidine (**132**) and acetone (**9**) afforded the corresponding Mannich product **133** in 50% yield with 94% ee (*Scheme* **55**).[81] The corresponding aldol product was also formed under these conditions, but in much lower yield.



9 10 132 133

Scheme **55**

Both α-substituted and α-unsubstituted aldehydes gave the corresponding β-amino-ketones in good to excellent yields and with enantioselectivities up to 94%. The reactions of α-unsubstituted aldehydes were performed in pure acetone (**9**), and after completion, proline (**4**) could be recovered from the reaction mixture in almost quantitative yield by filtration.

A desirable feature of the amine component is that the substituent on the nitrogen must be easily removed to allow for further manipulations. Yields and enantioselectivities were optimal with *p*-anisidine (**132**), which introduces the *p*-methoxyphenyl (PMP) group into the product. The PMP group can easily be removed under oxidative conditions, thus *p*-anisidine (**132**) acts as a synthetic ammonia equivalent in these reactions.

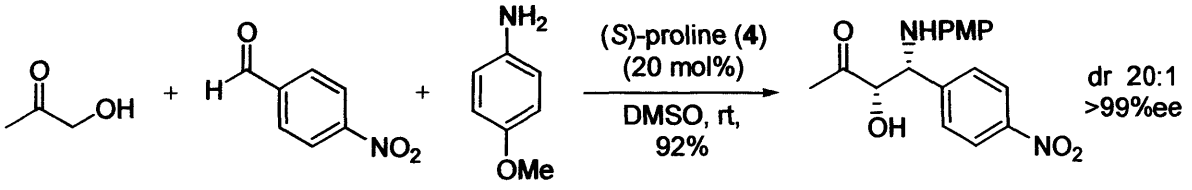
Performing the reactions under high pressure induced by water freezing can increase both the yield and optical purity of the β-amino-ketone.[82] Both high pressure and low temperature were found to be essential for the success of the asymmetric proline-catalysed Mannich reaction. The increased pressure both accelerated the reaction and suppressed side reactions, while the decrease in temperature gave rise to higher enantiomeric excess.

1.14.2 Synthesis of Highly Enantioselective 1,2-Amino Alcohols

A variety of ketones could be employed in the three-component Mannich reaction with excellent results obtained. Butanone, methoxyacetone and hydroxyacetone (**20**) all furnished the desired products in high yield (92-96%) with excellent enantiomeric excess (up to >99%). Excellent diastereoselectivities were also observed, and essentially no aldol products were formed with these three ketones.[83]

Use of hydroxyacetone (**20**) as the donor furnished *syn*-1,2-amino alcohols in good yields with high chemo-, regio-, diastereo- and enantioselectivities. These Mannich reactions can be considered as a regiospecific alternative to the Sharpless asymmetric aminohydroxylation reaction (AA). Use of aromatic aldehydes provided the corresponding products in good to

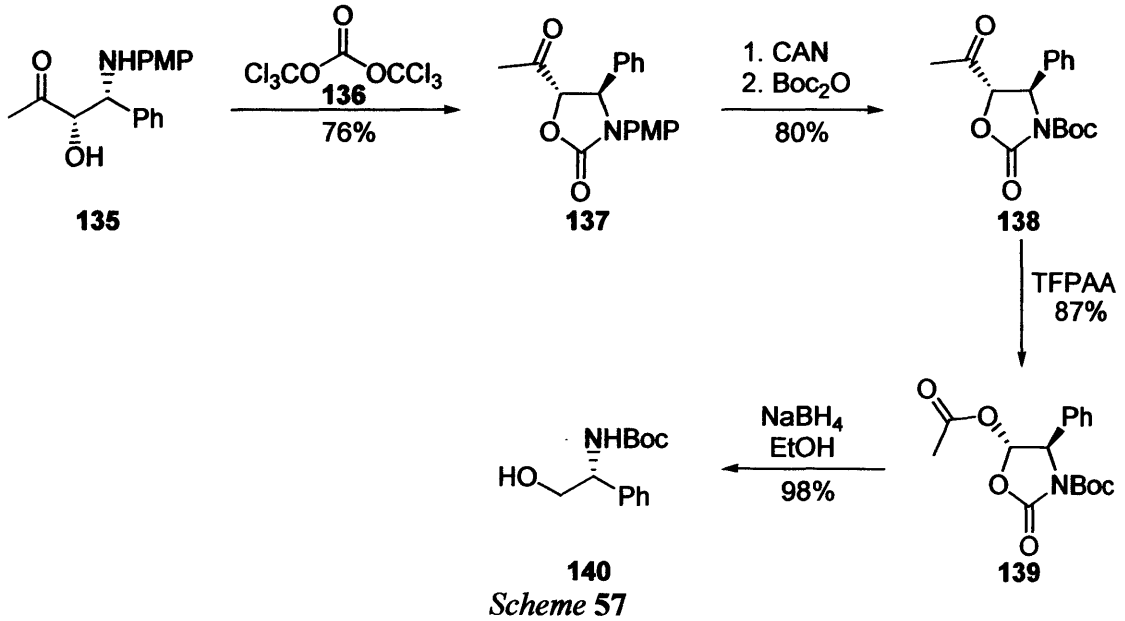
excellent yields and enantioselectivities, for instance, use of *p*-nitrobenzaldehyde (**10**) gave the corresponding *syn*-1,2-amino alcohol **134** in 92% yield with >99% ee (*Scheme* **56**).



20 **10** **132** **134**

Scheme **56**

Enantiomerically enriched *syn*-1,2-amino alcohols are valuable products as α-amino acid derivatives can be synthesised from them in four steps. Yields up to 64% of the α-amino acid derivative were obtained with no racemisation observed during the synthesis (*Scheme* **57**).[83]



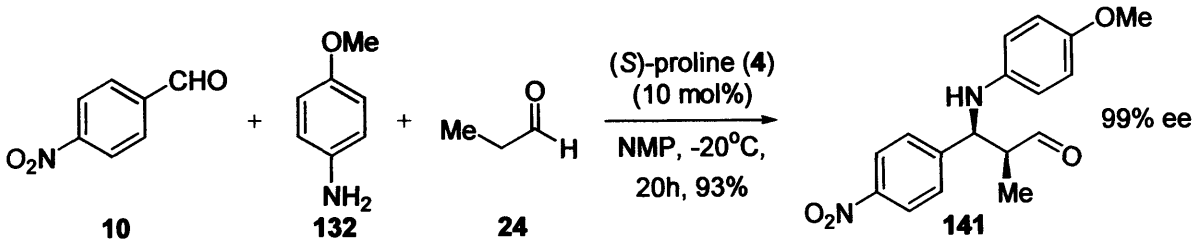
135 **137** **138** **139** **140**

Scheme **57**

1.14.3 Aldehydes as Donors in the Proline-Catalysed Mannich Reaction

Hayashi developed a direct and enantioselective, one-pot, three-component cross-Mannich reaction of two different aldehydes. In this reaction one aldehyde is employed as the Mannich donor with the other aldehyde utilised as a component of the Mannich acceptor to afford a β-amino aldehyde.

A cross-Mannich reaction was performed with propionaldehyde (**24**) as the Mannich donor and *p*-nitrobenzaldehyde (**10**) as a component of the Mannich acceptor under proline-catalysed reaction conditions. At –20°C the *syn*-isomer **141** was generated selectively with excellent enantioselectivity (*Scheme* **58**).[84]



10 132 24 141

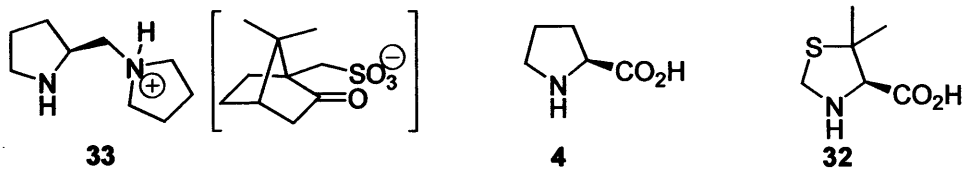
Scheme **58**

At higher temperatures (>0°C) a competing cross-aldol reaction between the two aldehyde components significantly reduced the yield of Mannich adduct obtained. These side-reactions were suppressed at lower temperatures (<0°C) to afford the β-amino aldehyde in excellent yield and enantioselectivity.

A variety of aromatic aldehydes were employed as the Mannich acceptor with high *syn*-diastereo- and enantioselectivities obtained throughout. The Mannich donor could also be varied, with excellent yields and selectivities achieved. A self-Mannich reaction of propionaldehyde (**24**) was also accomplished to afford the *syn*-adduct in good yield and high enantioselectivity.

1.14.4 Alternative Amine Catalysts

Barbas III has studied the three-component Mannich reaction of acetone (**9**), an aldehyde and an amine component in the presence of an aminocatalyst. The catalysts employed were diamine **33** as a protonic acid salt, (*S*)-proline (**4**) and sulfur-containing proline derivative DMTC (**32**) (*Figure* **27**).

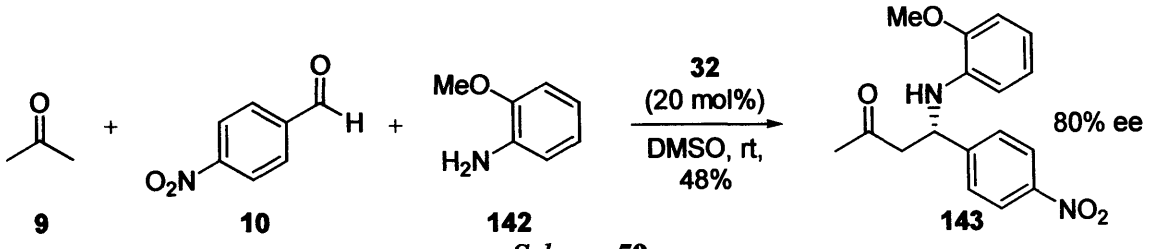


33 **4** **32**

Figure **27**

To test the utility of these organocatalysts, acetone (**9**) was added to an aldimine, preformed from an aromatic aldehyde and *o*-anisidine (**142**). Each of the catalysts employed afforded similar yields of the β-amino-ketone product, although with varying degrees of enantioselectivity. For all reactions performed higher enantiomeric excesses were obtained with DMTC (**32**) as the reaction catalyst. For example, the β-amino-ketone **143** obtained from *p*-nitrobenzaldehyde (**10**) was formed with 80% ee when DMTC (**32**) was employed as

the aminocatalyst (*Scheme* **59**), compared to 55% ee with diamine **33** and 40% ee with (*S*)-proline (**4**).[85]

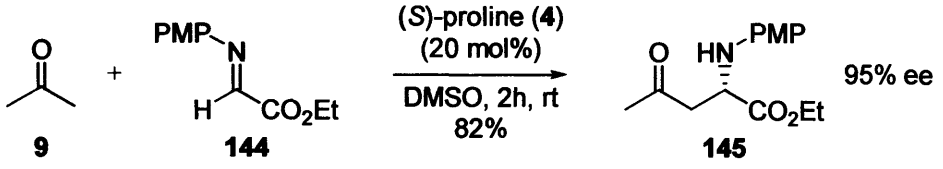


Scheme **59**

Both aromatic and non-aromatic aldehydes were utilised in a one-pot three-component Mannich reaction between acetone (**9**) and *p*-nitrobenzaldehyde (**10**) using DMTC (**32**) as the reaction catalyst. Good yields (38-58%) and high enantiomeric excesses (up to 89% ee) of the β-amino ketone adduct were obtained. The DMTC (**32**) catalyst thus represents a useful alternative to proline (**4**) as an aminocatalyst for the asymmetric catalytic Mannich reaction as it is non-toxic, relatively inexpensive and readily available in both enantiomeric forms.

1.14.5 Highly Enantioselective Synthesis of Amino Acid Derivatives

The amine-catalysed asymmetric Mannich reaction can be used to synthesise α-amino acid derivatives, using an α-imino glycoxylate as the acceptor. Barbas III reacted *N*-PMP-protected α-imino glycoxylate **144** with acetone (**9**) in the presence of proline (**4**). This generated the corresponding α-amino acid derivative **145** as the only product in excellent yield and enantioselectivity (*Scheme* **60**).[86]

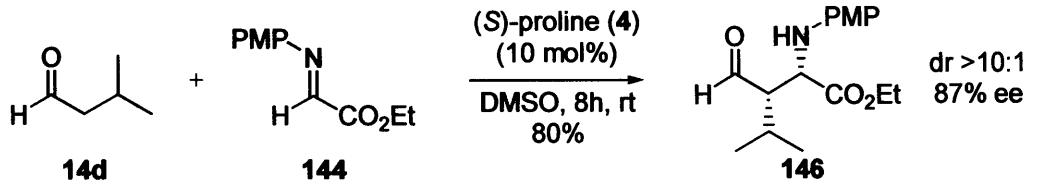


Scheme **60**

This protocol was applied to a variety of unmodified ketone donors. In all cases the corresponding α-amino acid derivative was obtained in high yield (62-86%) with excellent regio- and diastereoselectivities and in most examples enantiomeric excesses of >95% were achieved.

The use of unmodified aldehyde donors was also investigated. The proline-catalysed Mannich reaction of *iso*valeraldehyde (**14d**) with *N*-PMP-protected α-imino glycoxylate **144**

generated the α-amino acid derivative **146** in high yield with excellent diastereo- and enantioselectivities (*Scheme* **61**).[87]

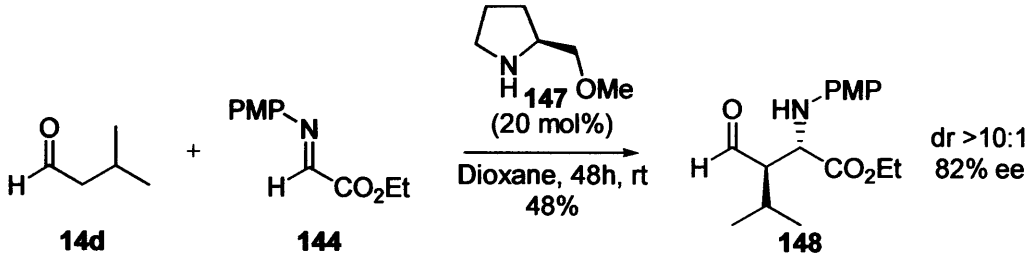


14d **144** **146**

Scheme **61**

A number of aliphatic aldehydes were reacted under these reaction conditions to afford α-amino acid derivatives. In each example good yields and excellent enantioselectivities were obtained. Higher diastereoselectivities were achieved as the steric bulk of the substituents on the aldehyde donor increased, with the *syn*-diastereoisomer formed preferentially in each case. These transformations can also be carried out as three-component one-pot operations.[88] Yields are slightly reduced in this process, but enantiomeric excesses are analogous to those obtained when using preformed *N*-PMP-protected α-imino glycoxylates.

In order to obtain α-amino acid derivatives with a *anti*-diastereoselectivity it was necessary to employ a different aminocatalyst. (*S*)-2-Methoxymethylpyrrolidine (SMP) (**147**) provided functionalised amino acid derivatives from unmodified aldehyde donors with high *anti*-selectivity and excellent enantioselectivities (up to 92%) (*Scheme* **62**).[89]

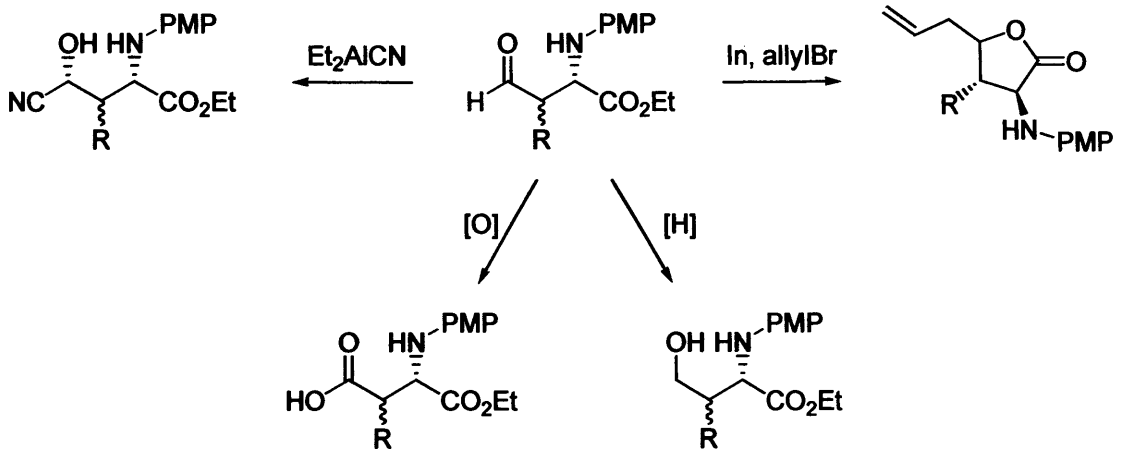


14d **144** **148**

Scheme **62**

The α-amino acid derivatives generated in these reactions can undergo a variety of further transformations (*Scheme* **63**). The aldehyde functionality can be oxidised to a carboxylic acid to generate a β-amino acid,[87] or can be reduced to an alcohol generating a γ-amino alcohol.[88] A hydrocyanation reaction can also be performed to generate a new carbon-carbon bond. This reaction can be carried out in the same pot as the Mannich reaction without the need for prior isolation or purification, providing cyanohydrin-functionalised α-amino acid derivatives bearing three contiguous stereogenic centres in high optical purity.[90] Further functionalisation can also be achieved by carrying out a one-pot Mannich-allylation reaction. This provides

cyclic-γ-allyl substituted α-amino acid derivatives in good yields and high enantioselectivities.[91]

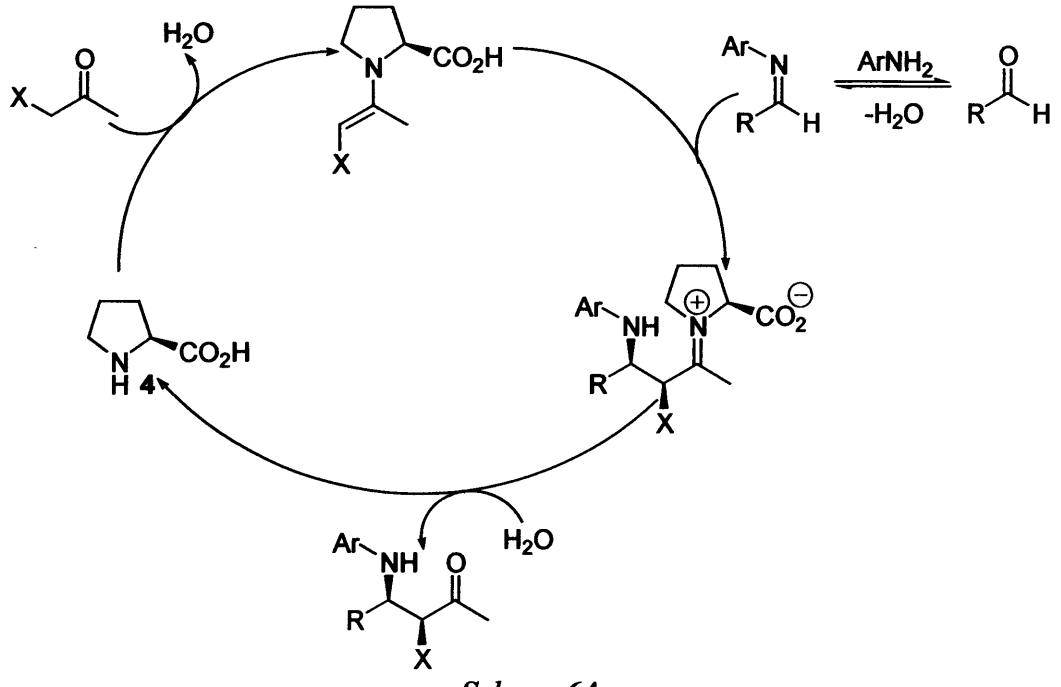


Scheme **63**

Therefore the α-amino acid derivatives generated by the Mannich reaction can be efficiently used in a variety of further chemical modifications to provide synthetically valuable synthons.

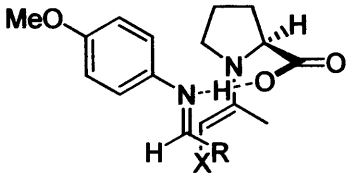
1.14.6 Mechanism of the Amine-Catalysed Asymmetric Mannich Reaction

In the proposed mechanism for the proline-catalysed three-component Mannich reaction, the ketone reacts with proline (**4**) to form an enamine. In a second pre-equilibrium the aldehyde and aniline components generate an imine. The enamine and imine species react and after hydrolysis generate the enantiomerically enriched Mannich product (*Scheme* **64**).[83]



Scheme **64**

The Mannich products are formed *via si*-facial attack on the imine component. Both the proline enamine transition state and the imine are assumed to be of *E*-configuration. The *si*-face of the imine is selectively attacked by the enamine to allow for the protonation of its lone pair and compensation of the negative charge formed during the Mannich reaction. Attack to the imine *re*-face would result in unfavourable steric interactions between the pyrrolidine ring and the aromatic moiety. The proposed transition state (*Model* **J**) is shown in *Figure* **28**.

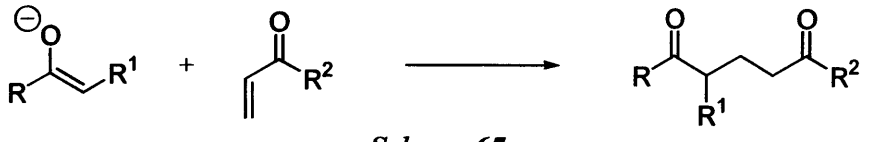


Model **J**
Figure **28**

The development of the amine-catalysed direct three-component Mannich reaction constitutes a significant advancement over previous asymmetric Mannich reaction technologies. The reaction is broad in scope allowing for the synthesis of β-amino carbonyl compounds in high enantio-, diastereo-, regio- and chemoselectivities, which can then undergo a variety of further chemical modifications to yield synthetically useful synthons. This further illustrates the extensive variety of asymmetric chemical transformations that can be promoted by simple amine catalysts.

1.15 The Michael Reaction

The Michael reaction is a powerful and efficient method for the formation of carbon-carbon bonds, enabling the construction of enantioenriched, highly functionalised 1,5-dicarbonyl compounds.[92] This reaction involves the conjugate addition of a nucleophilic enolate ion donor to the β-carbon of an electron deficient alkene (*Scheme* **65**). Conjugated aldehydes, esters, nitriles, amides and nitro compounds can all act as the electrophilic acceptor component in the Michael reaction. Similarly, a variety of donors can be used, including β-diketones, β-keto esters, malonic esters, β-keto nitriles and nitro compounds.[93]



Scheme **65**

Studies concerning the Michael reaction have played an important role in the development of modern synthetic organic chemistry.[94] Much research has been carried out into the development of asymmetric variants of this reaction, providing for the preparation of Michael adducts with high enantiomeric purity.[95] The Michael reaction has, for the most part, been dominated by the application of metal-containing asymmetric catalysts, especially chiral Lewis acids.

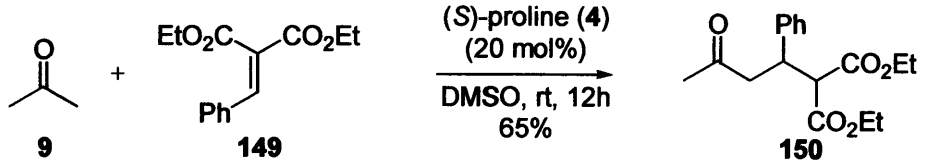
Aminocatalysis of the Michael reaction is also possible, with catalysis able to proceed *via* two different pathways. Firstly, an unmodified ketone donor can be activated as an enamine, or an acceptor α,β-unsaturated carbonyl species can be activated as an iminium ion (*Figure* **29**).

Figure **29**

1.15.1 Aminocatalytic Asymmetric Michael Reactions *via* an Enamine Pathway

The stoichiometric use of enamines as nucleophiles in the Michael reaction was established by Stork,[96] and several variants, including asymmetric versions,[97] have been described in the literature. Michael reactions of preformed enamines with nitro olefins have been thoroughly studied by Seebach,[98,99] but enamine *catalysis* has only recently been exploited.

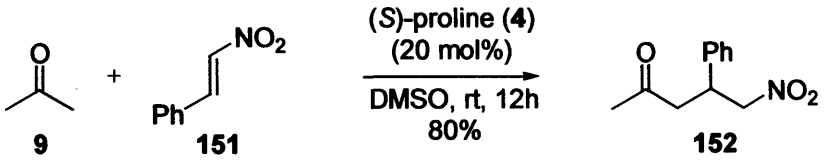
Barbas III studied the Michael addition of acetone (**9**) to various Michael acceptors catalysed by (*S*)-proline (**4**). Use of the alkylidene malonate acceptor **149** afforded a 65% isolated yield of the Michael adduct **150** (*Scheme* **66**).[40]



9 **149** **150**

Scheme **66**

Similar results were obtained with β-nitro olefin **151**, which provided the acetone addition product **152** in 80% yield (*Scheme* **67**). Mild conditions were employed, allowing for the simple construction of Michael adducts.



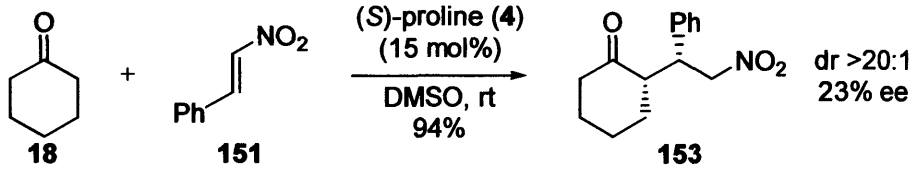
9 151 152

Scheme **67**

These examples represent the first organocatalytic intermolecular Michael additions. Unfortunately, the products obtained were racemic, but this work has led to further research that has provided enantioselective versions.

1.15.2 Enantioselective Michael Addition of Unmodified Ketones to Nitro-Olefins

List performed the proline-catalysed Michael addition of unmodified ketones to Michael acceptors. α,β-Unsaturated ketones, esters and amides gave the Michael adduct in only low yield and enantioselectivity upon reaction with acetone (**9**) in the presence of a catalytic amount of proline (**4**). However, if a more reactive nitro-olefin acceptor was subjected to the same conditions excellent yields of the corresponding adduct were obtained. For example β-nitrostyrene (**151**) was reacted with cyclohexanone (**18**) to give adduct **153** in 94 % yield. An excellent diastereoselectivity was observed, although only a modest enantioselectivity (23% ee) was achieved.[100]



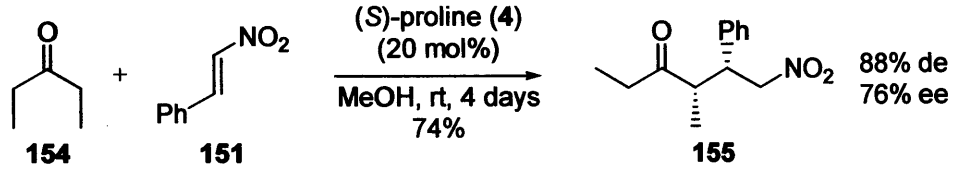
18 151 153

Scheme **68**

Enders further investigated the proline-catalysed asymmetric Michael addition under a variety of reaction conditions. It was found that use of methanol as the reaction solvent improved the solubility of the proline (**4**) catalyst and led to increased diastereo- and enantioselectivities. By performing the above reaction between cyclohexanone (**18**) and β-nitrostyrene (**151**) in methanol, the enantioselectivity of Michael adduct **153** was significantly increased to 57% ee.[101]

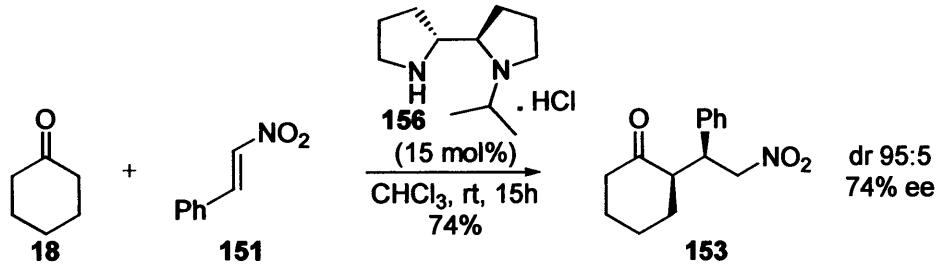
Enders studied the scope of the Michael addition by performing reactions between various ketones and β-nitrostyrene (**151**) under the above proline-catalysed conditions. These conjugate additions furnished the corresponding γ-nitro ketone adducts with *syn*-diastereoselectivity. The highest enantioselectivity was achieved for the addition of 3-

pentanone (**154**) to β-nitrostyrene (**151**) with Michael adduct **155** obtained in 76% ee (*Scheme* **69**).



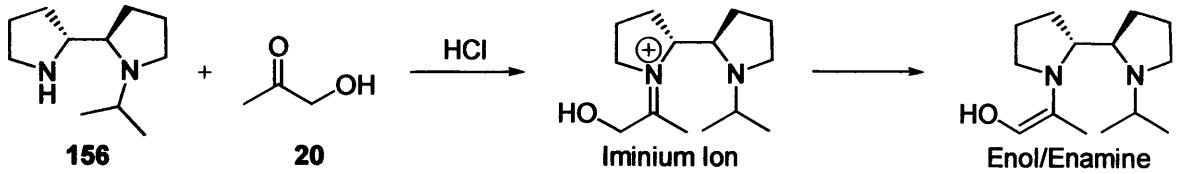
Scheme **69**

Alexakis also studied the Michael addition of unmodified ketones to nitro-olefins. Diamine **156** was employed as the reaction catalyst for the addition of various ketones to β-nitrostyrene (**151**). The β-nitro ketone adducts were obtained with *syn*-diastereoselectivity from both cyclic and acyclic ketone donors. Use of acetone (**9**) yielded adduct **152** in a modest 25% ee, while cyclohexanone (**18**) afforded γ-nitro ketone **153** with an enantioselectivity of 74% (*Scheme* **70**).[102]



Scheme **70**

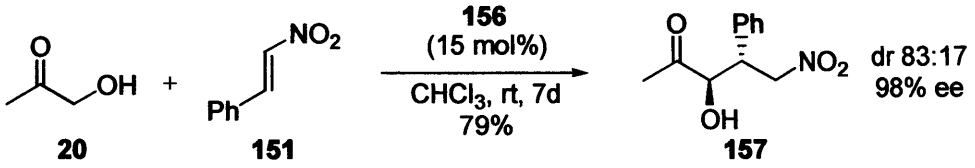
The use of non-symmetrical ketone donors was also examined, but this was found to introduce regioselectivity problems. In the mechanistic cycle, an iminium ion is initially formed between the ketone and the amine catalyst. Deprotonation of an α-hydrogen atom yields the intermediate enamine. In order to control the regiochemistry Alexakis employed α-alkoxycarbonyl compounds, as the difference in acidity between the α and α' protons leads exclusively to the enol/enamine intermediate (*Scheme* **71**).[103]



Scheme **71**

The Michael addition of α-methoxyacetone to β-nitrostyrene (**151**) provided the desired product with good selectivity (69% ee, *anti/syn* 17:83), while use of hydroxyacetone (**20**)

afforded adduct **157** in good yield with excellent enantiocontrol (98% ee), and interestingly, the opposite diastereoisomer predominated (*Scheme* **72**).



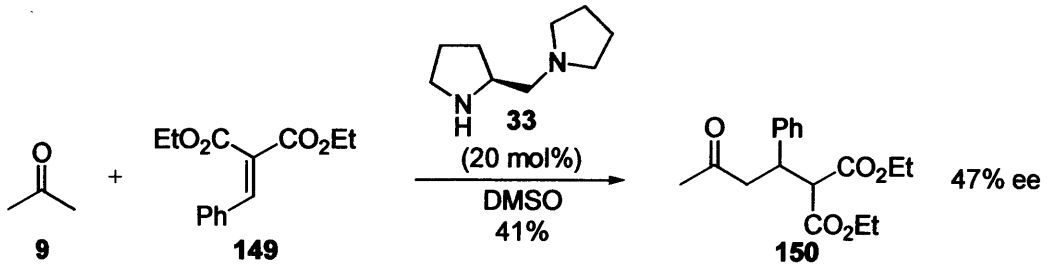
Scheme **72**

The scope of this organocatalytic Michael addition was tested by reacting hydroxyacetone (**20**) with a variety of β-arylnitro-olefins. High yields (65-85%) of the γ-nitro ketone adduct were achieved throughout and all reactions were *anti*-diastereoselective and highly enantioselective (97-99% ee).

The γ-nitro ketone adducts, generated from the Michael addition of unmodified ketones to β-nitro-olefins, are useful precursors to other functionalities that can be derived from the venerable nitro group.

1.15.3 Michael Addition of Unmodified Ketones to Alkylidene Malonates

The enantioselective addition of unmodified ketones to alkylidene malonates was further investigated by Barbas III. A Michael addition of acetone (**9**) to diethyl benzalmalonate (**149**) was studied with a variety of aminocatalysts. DMTC (**32**) did not catalyse the Michael addition at all, while proline-catalysed conditions did afford the Michael adduct **150** but with no enantiomeric excess. Two substituted pyrrolidines yielded the Michael adduct **150** with moderate enantioselectivity (up to 51% ee) although in very low yield (<10%), but the optimal catalyst was found to be diamine **33** which afforded adduct **150** in 41% yield with an optical purity of 47% ee (*Scheme* **73**).[104]



Scheme **73**

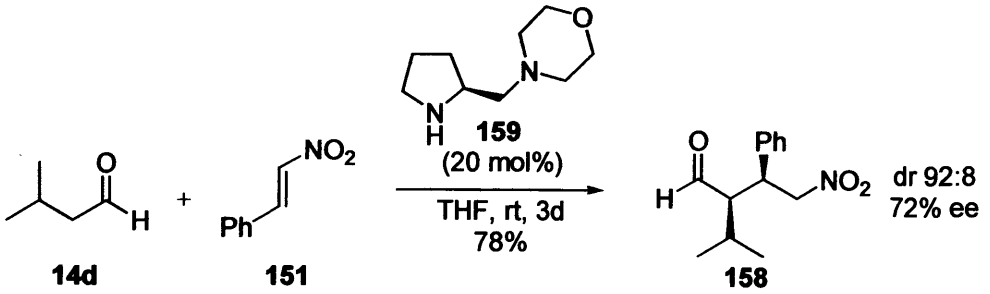
To further improve both the yield and enantioselectivity, a diverse range of solvents were screened. Use of tetrahydrofuran (THF) provided adduct **150** with improved yield and enantioselectivity (59% ee).

This reaction was found to be general with respect to the ketone component, with both acyclic and cyclic ketones affording the corresponding Michael adduct in good enantioselectivity (up to 65%). Several malonates were also employed in the diamine-catalysed Michael reaction. It was found that a modest enhancement in enantioselectivity was achieved as the size of the alkyl group of the ester functionality was increased. Both alkylidene and arylidene malonates were employed. Arylidene malonates provided good selectivities, with *ortho* substituted aromatics furnishing the best results. With alkylidene malonates only low yields and selectivities were attained.

These examples illustrate that ketones can be used as donors in the amine-catalysed Michael reaction without the need for prior modification.

1.15.4 Use of Unmodified Aldehyde Donors

Barbas III further added to the scope of the aminocatalytic Michael reaction by employing unmodified aldehydes as donors. The reaction of *iso*valeraldehyde (**14d**) with β-nitrostyrene (**151**) was explored with several aminocatalysts. Proline (**4**) afforded adduct **158** in very low yield (<5%) with 25% ee, so several diamines were screened in order to determine the optimal catalyst. A significant improvement in both the yield and enantioselectivity was observed with diamine **33** (80% yield, 75% ee) but only a 4:1 diastereomeric ratio was achieved. The most favourable catalyst was morpholine-derivative **159** which gave adduct **158** in a 78% isolated yield and 72% ee with a significant improvement in the diastereoselectivity (92:8 *syn/anti*) (*Scheme* **74**).[105]



14d **151** **158**

Scheme **74**

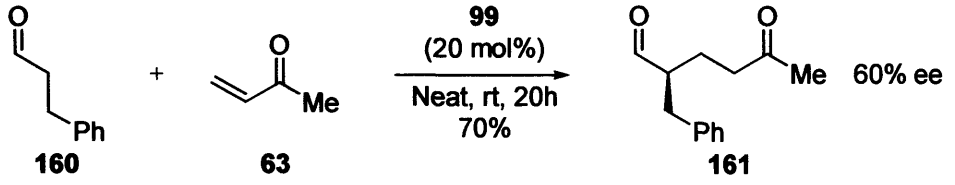
A series of aldehydes and β-nitro-olefins were examined using (*S*)-2-(morpholinomethyl)-pyrrolidine (**159**) as the catalyst. Higher enantioselection was achieved by increasing the steric bulk of the substituent on the aldehyde donor, and by using a β-nitro-olefin with an *ortho*-substituted aromatic component.

Similar results were achieved with diamine **156** which furnished γ-nitro aldehyde **158** in excellent yield and diastereoselectivity (95:5) with good enantiomeric excess (68%).[103]

This methodology provides a simple and convenient method for the synthesis of optically active 2,3-disubstituted γ-nitro aldehydes in one step. These useful synthons can be further converted into a wide array of building blocks such as 1,4-amino alcohols or amino acids, and can be used in the synthesis of substituted chiral pyrrolidines.

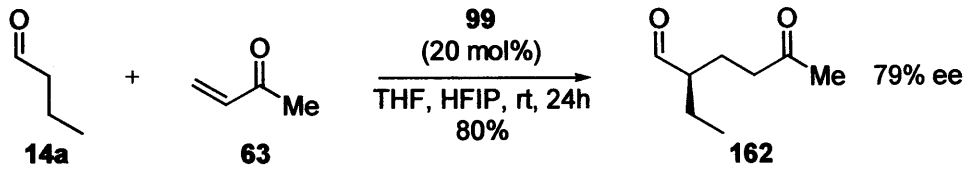
1.15.5 Aminocatalytic Michael Additions to Vinyl Ketone Acceptors

Jørgensen developed an organocatalytic direct enantioselective Michael addition of simple aldehydes to vinyl ketones. The proline-catalysed reaction of 3-phenylpropanal (**160**) to methyl vinyl ketone (**63**) afforded a 15% conversion to adduct **161** with low enantioselectivity (20% ee). Consequently, a series of chiral amines, each based on the pyrrolidine skeleton, were screened as catalysts for this asymmetric Michael addition. The highest conversion was achieved with (*S*)-prolinol (**96**) as the catalyst (90% yield), however, the Michael-addition adduct **161** was formed with low selectivity (15% ee). The highest enantiomeric excess was obtained when diphenylprolinol (**97**) was employed (74% ee), but unfortunately only a low conversion was achieved (15%). In terms of reaction time, yield and enantioselectivity (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**99**) gave optimal results (*Scheme* **75**).[106]



Scheme **75**

Other aldehydes were also utilised in the enantioselective Michael addition, but when these reactions were performed under neat conditions several by-products were generated. For example, the addition of butanal (**14a**) to MVK (**63**), catalysed by pyrrolidine-derivative **99**, furnished adduct **162** in high yield (87%) with good enantiomeric excess (77%), but several by-products, which were difficult to remove from the desired product, were also formed under neat conditions. After examining a variety of reaction conditions, the solvent combination of choice for this transformation was determined to be tetrahydrofuran with 1,1,1,3,3,3-hexafluoro-2-propanal (1:1 THF/HFIP) as this gave a very clean reaction, affording the Michael-addition adduct in high yield (80%) and enantioselectivity (79%) (*Scheme* **76**).



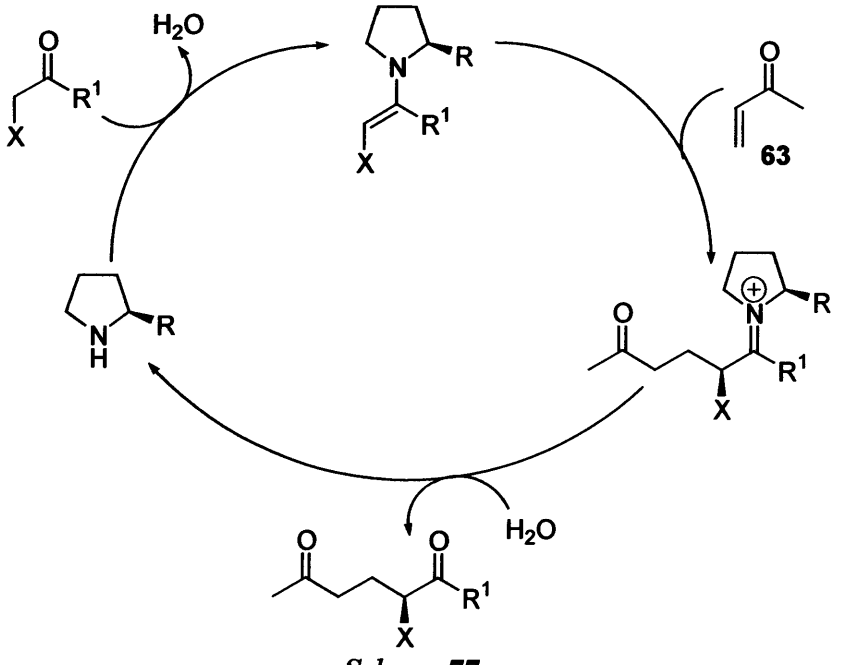
Scheme 76

The scope of this reaction was examined by utilising a variety of unmodified aldehyde donors and vinyl ketone acceptors under THF/HFIP reaction conditions. The corresponding Michael adducts were obtained in very good yields (72-93%), with good to very good enantiomeric purities (54-82%) throughout.

The optically active substituted 5-keto aldehydes, formed *via* a direct Michael addition of unmodified aldehydes to vinyl ketones, can undergo various synthetic transformations and are useful starting materials for further synthesis, including the preparation of optically active terpenoids and γ-lactones.

1.15.6 Mechanism of Aminocatalytic Michael Additions *via* an Enamine Pathway

In the proposed mechanism for the aminocatalytic direct enantioselective Michael addition, the aldehyde/ketone donor reacts with the aminocatalyst to form an enamine. This enamine undergoes a conjugate addition with the Michael acceptor to afford, after hydrolysis, the enantiomerically enriched Michael adduct, while regenerating the aminocatalyst allowing it to continue through another cycle (*Scheme* 77).



Scheme 77

The proposed transition state for the proline-catalysed Michael reaction readily explains the observed selectivity, and is in accordance with Seebach's model.[107] An intermolecular hydrogen bond between the enamine intermediate and the Michael acceptor directs its approach, and so transfers the chirality of the proline (**4**) catalyst to the resulting adduct (*Figure* **30**).[101]

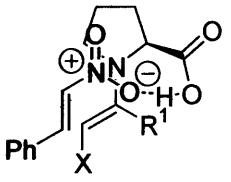


Figure **30**

The proposed transition state for pyrrolidine-derived catalysts is different, as in this case the approach of the Michael acceptor is determined by steric factors. For example, one face of the enamine intermediate that is generated with diamine catalyst **156** is less accessible due to the presence of the *N-iso*propyl-pyrrolidine group. Therefore, approach to the sterically less hindered face predominates. A second factor controlling the stereochemical outcome of the reaction is the enamine geometry. This too is governed by steric factors, with different conformers predominating for ketone donors compared to aldehyde donors (*Figure* **31**).[102]

Aldehyde Donors: Ketone Donors:

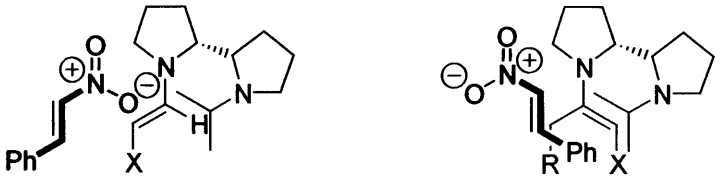


Figure **31**

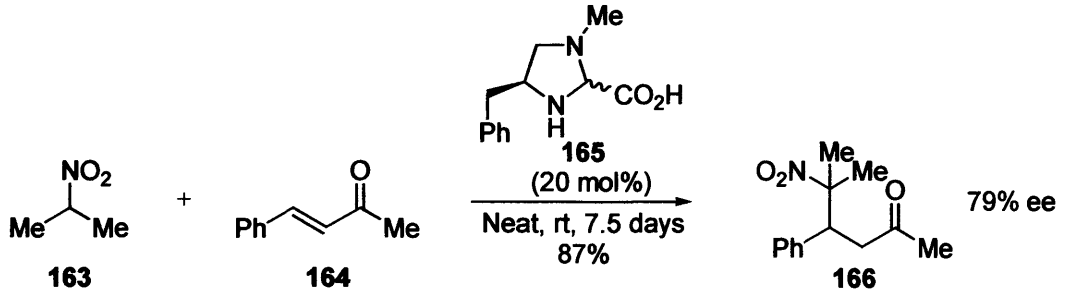
Therefore, the absolute configuration of the resulting Michael-addition adduct is inverted between aldehyde and ketone donors when catalysed by diamine **156**.

These examples show that small chiral amines can successfully catalyse the direct enantioselective Michael reaction via an enamine pathway. Both unmodified aldehyde and ketone donors can be employed with a range of Michael acceptors, allowing simple access to a variety of optically active Michael-addition adducts that are useful synthons for further synthetic manipulations.

1.15.7 Aminocatalytic Asymmetric Michael Reactions *via* an Iminium Pathway

Proline (**4**) was first used as a catalyst for the Michael reaction by Yamaguchi,[108] but only low yields of the Michael-addition adduct were observed, so further investigations were centred around the use of metal salts of proline.[109] It was postulated that iminium ion intermediates were involved in the mechanism of this Michael reaction.

Jørgensen further investigated the Michael addition reaction *via* an iminium ion mechanism. The reaction of 2-nitropropane (**163**) with benzylidene acetone (**164**) was studied with a variety of chiral amine catalysts. In concordance with the results obtained by Yamaguchi, (*S*)-proline (**4**) was found to be a poor catalyst for this Michael addition. The imidazolidinone catalyst developed by MacMillan (**69**) also gave no conversion to the desired Michael adduct **166** under the reaction conditions employed, whereas imidazoline **165**, prepared from phenylalanine, was an excellent catalyst for this transformation affording Michael adduct **166** in high yield with 79% enantiomeric excess (*Scheme* **78**).[110]



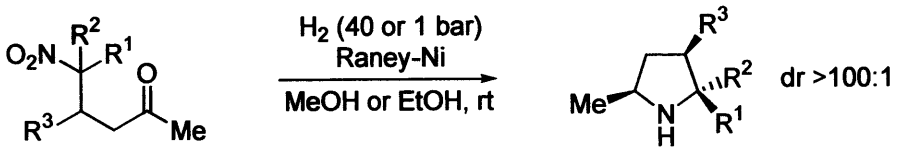
Scheme **78**

The preparative utility of this organocatalysed reaction was demonstrated by performing the reaction on a kilogram scale. Recovery and reuse of the imidazoline catalyst **165** was possible without any decrease in catalytic activity or enantioselectivity.

The imidazoline-catalysed Michael reaction was general with respect to both the nitroalkane and the α,β-unsaturated enone components. Both cyclic and acyclic nitroalkanes were employed to generate Michael-addition adducts in good yields (52-100%) with similar enantioselectivities (58-79% ee) for all the reactions studied. This reaction is therefore tolerant to changes in both nitroalkane, and α,β-unsaturated enone structure. Alkyl, aromatic and heteroaromatic substituents in the β-position were all tolerated to afford the corresponding Michael adducts with good enantioselectivities throughout (52-86% ee). It was found that bulkier alkyl substituents, such as an *iso*propyl group, on either the carbonyl group or in the β-position led to very low conversions, although good enantioselectivities were

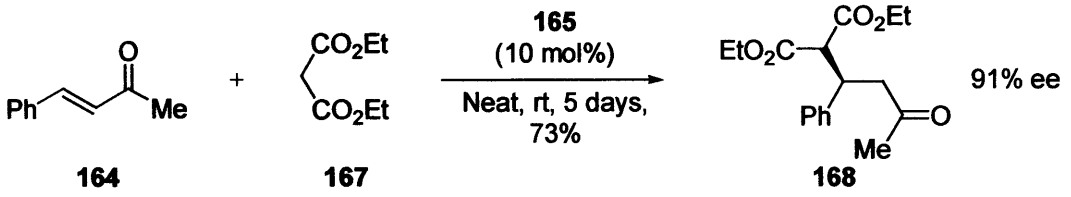
maintained. Cyclic α,β-unsaturated enones were also employed to give the corresponding adduct in good yield (84%), but with a reduced enantiomeric excess (49% ee).

The products generated in the imidazoline-catalysed Michael reaction can be readily converted into optically active pyrrolidines *via* reductive amination. The corresponding pyrrolidines were obtained as a single diastereoisomer with the enantioselectivity from the Michael reaction maintained (*Scheme* **79**).



Scheme **79**

Jørgensen went on to investigate the Michael addition of malonates to acyclic α,β-unsaturated enones using imidazoline catalyst **165**. The addition of diethyl malonate (**167**) to benzylidene acetone (**164**) afforded the Michael adduct **168** in high yield and enantioselectivity (91% ee) (*Scheme* **80**).[111]



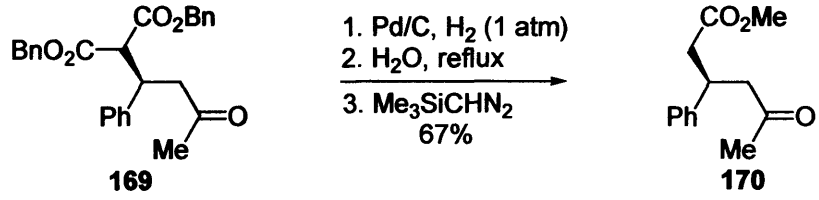
164 **167** **168**

Scheme **80**

A series of malonates were tested in this Michael addition reaction. It was found that the ester functionality had a large influence on both the yield and the asymmetric induction. The reaction rate was decreased considerably with more sterically hindered malonates leading to a low yield of the corresponding Michael adduct. Medium-sized malonates all reacted to furnish adducts in excellent yields and enantioselectivities, for example, use of dibenzyl malonate afforded the Michael adduct in 93% yield and >99% ee.

The scope of the imidazoline-catalysed Michael addition was further examined by reacting a variety of α,β-unsaturated enones with dibenzyl malonate. Aromatic and heteroaromatic enones reacted to give the corresponding Michael adducts in high yields (75-99%) and enantioselectivities (86-99% ee), with the exception of the *N,N*-dimethylaniline derivative (58% yield, 77% ee). Alkyl-substituted enones were found to react quite slowly and so low yields resulted, however, high enantiomeric excesses were still achieved (88-91%).

The Michael adducts generated in the addition of malonates to α,β-unsaturated enones can easily undergo further chemical modifications, such as a one-pot decarboxylation-transesterification procedure to yield the corresponding optically active δ-ketoester (*Scheme* **81**).



169 **170**

Scheme **81**

1.15.8 Iminium Ion Intermediate of the Organocatalytic Michael Reaction

The proposed iminium ion intermediate formed during the organocatalytic Michael reaction is shown in *Figure* **32**. It was postulated that this intermediate is favoured due to an attractive π–π interaction between the benzyl group and the α,β-unsaturated function.[110]

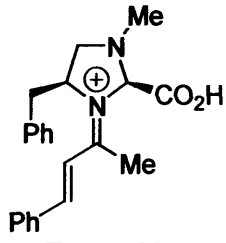


Figure **32**

The benzyl group of the imidazoline catalyst **165** shields the *re*-face of the enone, leaving the *si*-face open for attack. This accounts for the stereochemistry observed in the aminocatalytic Michael reactions *via* an iminium pathway.

The above examples show that aminocatalysed Michael additions can proceed via an enamine or an iminium pathway to afford adducts with high enantiomeric excesses. A variety of Michael donors and acceptors can be used to afford an array of optically active Michael adducts that can readily undergo further synthetic transformations. This organocatalytic approach compares favourably to Lewis acid catalysed Michael additions in terms of handling, yield and enantioselectivity, further illustrating the importance of aminocatalysis.

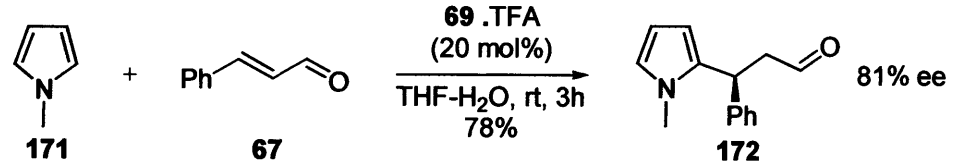
1.16 Other 1,4-Conjugate Addition Reactions

As well as the Michael reaction, small chiral amines can be used to catalyse other 1,4-conjugate additions. For example, alkylation reactions involving the addition of an aromatic or heteroaromatic donor to an α,β-unsaturated acceptor component are applicable to aminocatalysis. Traditionally these alkylation reactions are promoted using a Lewis acid, such as $AlCl_3$, with this reaction commonly known as the Friedel-Crafts alkylation.[112] This is a powerful method for the formation of carbon-carbon bonds,[113] but relatively few asymmetric catalytic protocols have been reported,[114] despite the widespread availability of electron-rich aromatics and the chemical utility of the resulting products.

1.16.1 Asymmetric Aminocatalytic Pyrrole Alkylations

The asymmetric alkylation of pyrroles is not amenable to Lewis acid catalysis. This is because electron-rich aromatics undergo acid-catalysed 1,2-carbonyl additions preferentially with α,β-unsaturated aldehydes rather than 1,4-conjugate additions.[115] MacMillan postulated that the α,β-unsaturated iminium ion arising from imidazolidinone catalyst **69** would be inert to 1,2-addition on the basis of steric constraints imposed by the catalyst framework, and so promote the non-conventional and less sterically demanding 1,4-addition.

To test this hypothesis, MacMillan performed the alkylation of *N*-methyl pyrrole (**171**) with (*E*)-cinnamaldehyde (**67**) catalysed by imidazolidinone **69**. This furnished β-pyrrolyl carbonyl compound **172** in good yield with excellent enantiopurity (*Scheme* **82**). The product arising from the 1,2-iminium addition was not observed in this reaction, in accord with the mechanistic postulation.[116]



171 **67** **172**

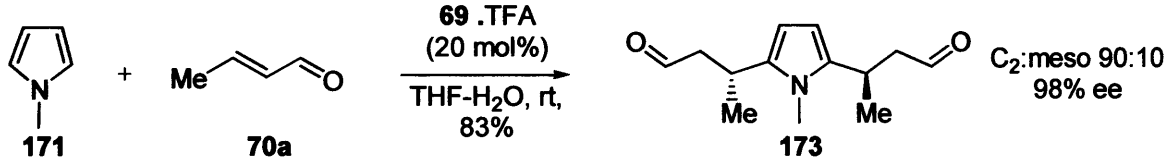
Scheme **82**

Optimal enantiocontrol was achieved in this reaction at a temperature of –30°C, affording substituted pyrrole **172** in 93% ee.

The amine-catalysed pyrrole alkylation was found to be general with respect to both the α,β-unsaturated carbonyl species and the pyrrole component. Significant variation in the β-

position of the α,β-unsaturated carbonyl compound was possible without loss in yield or enantioselectivity. Electron-deficient aldehydes that do not readily participate in iminium ion formation were also accommodated. Additionally, variation in the pyrrole architecture was achieved. A range of *N*-alkyl substituents were tolerated as well as substituents in both the C2 and C3 positions, with excellent levels of enantiocontrol maintained throughout.

The utility of the aminocatalysed pyrrole alkylation was further demonstrated by reacting *N*-methyl pyrrole (**171**) with excess (*E*)-crotonaldehyde (**70a**). Catalyst-controlled alkylation at both the C2 and C5 positions of the aromatic nucleophile allowed enantioselective access to C_2-symmetric pyrrole adducts (*Scheme* **83**).



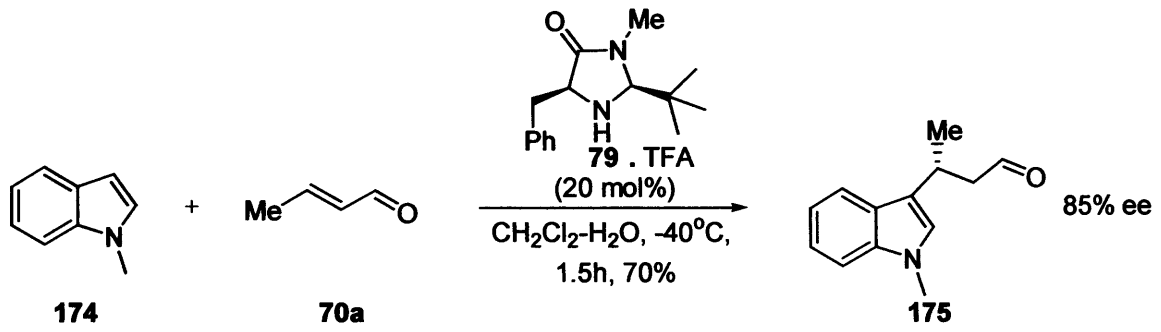
Scheme **83**

The β-pyrrolyl carbonyl compounds generated in these organocatalytic pyrrole alkylation reactions are useful synthons as they can be utilised in the construction of a variety of biomedical agents.[117]

1.16.2 Enantioselective Organocatalytic Indole Alkylations

Having established the capacity of iminium catalysis to mediate the enantioselective coupling of pyrroles and α,β-unsaturated aldehydes, MacMillan went on to extend this alkylation strategy to indole nucleophiles. Although there are structural similarities between them, the pyrrole π-system is known to be significantly more activated toward electrophilic substitution than the indole framework,[118] as was demonstrated by the low rate of reaction for the addition of *N*-methylindole (**174**) to (*E*)-crotonaldehyde (**70a**) catalysed by imidazolidinone **69**. In order to overcome this limitation in indole reactivity, and to enable less electron-rich heteroaromatic compounds to undergo alkylation, other imidazolidinone catalysts were tested for their ability to catalyse this indole alkylation.

The enantioselective alkylation of *N*-methylindole (**174**) with (*E*)-crotonaldehyde (**70a**) using the *tert*-butyl-benzyl imidazolidinone catalyst **79** provided benzylic substituted indole **175** with high levels of enantioselectivity and reaction efficiency (*Scheme* **84**).[119]

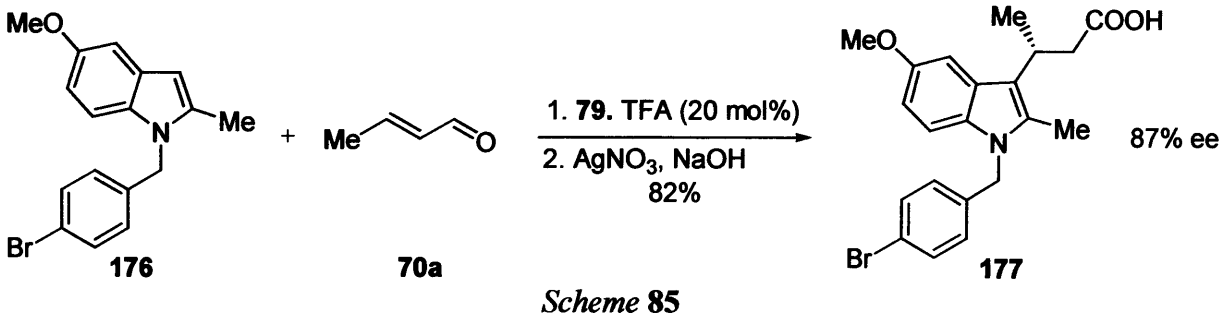


Scheme **84**

Optimal enantiocontrol was achieved in this reaction at a temperature of –83°C with catalyst **79**, affording substituted indole **175** in 92% ee. The rate of reaction was significantly enhanced, without compromising the enantioselectivity, by use of dichloromethane containing *iso*propanol (15% w/w) instead of water.

The scope of this alkylation reaction, with respect to the α,β-unsaturated aldehyde substrate and the indole architecture, was also studied. The reaction is tolerant to increased steric bulk in the β-position of the aldehyde component. Electron-deficient carbonyl compounds and aldehydes that led to the formation of stabilised iminium ions were accommodated without loss in enantiocontrol or reaction efficiency. The amine-catalysed conjugate addition was also general with respect to the indole component. Variation in the *N*-alkyl substituent was possible while maintaining high yields and enantiomeric excesses. Substitution at the indole C4 position was allowed as well as use of electron deficient 6-chloro substituted indoles. Such halogenated indole adducts are valuable synthons for use in organometallic coupling reactions such as the Buchwald-Hartwig,[120] or Stille reactions.[121]

The utility of this asymmetric organocatalytic alkylation was demonstrated by the synthesis of indolobutyric acid (**177**), a COX-2 inhibitor. The aminocatalytic alkylation of indole **176** with (*E*)-crotonaldehyde (**70a**), followed by oxidation of the formyl moiety, provided COX-2 inhibitor (**177**) in high yield and enantiopurity over the two synthetic steps (*Scheme* **85**).



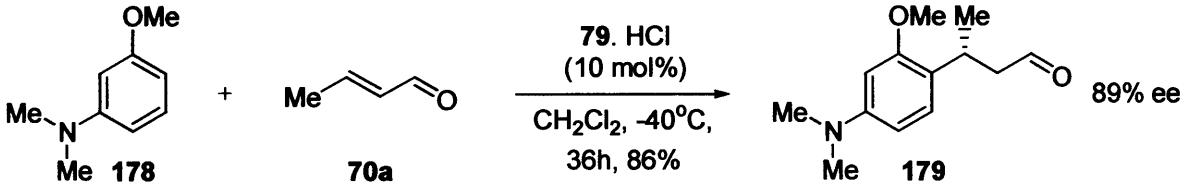
Scheme **85**

This simple procedure shows that complex, enantioenriched drug-like molecules can readily be accessed using this organocatalytic protocol. With over 3000 isolated natural products and 40 medicinal agents that incorporate the indole framework,[117a] the enantioselective indole alkylation methodology is thus extremely valuable in medicinal chemistry and complex target synthesis.

1.16.3 Asymmetric Organocatalytic 1,4-Additions of Electron-Rich Benzenes

While catalytic access to the enantioenriched benzylic architecture had previously been accomplished using hydrogenation,[122] or metallobenzene addition technologies,[123] MacMillan aimed to further enhance his iminium activated alkylation strategy in the development of an organocatalytic approach to such enantioenriched benzylic structures.

To this end, the organocatalytic alkylation of electron-rich aniline rings was investigated using imidazolidinone **79**. This catalyst successfully promoted the 1,4-conjugate addition of *N,N*-dimethyl-3-anisidine (**178**) to (*E*)-crotonaldehyde (**70a**) to generate aniline adduct **179** with a high level of enantioselectivity (*Scheme* **86**).[124]



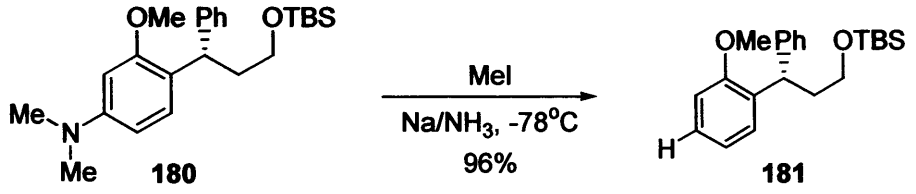
Scheme **86**

Variation in the β-substituent on the aldehyde component was possible without loss in yield or enantiocontrol. There was also a broad scope in the electronic nature of the α,β-unsaturated aldehyde substrate as electron-deficient carbonyl compounds, and aldehydes that led to the formation of stabilised iminium ions were accommodated. In addition, a variety of aromatic β-substituents were employed to construct bis-benzylic structures, a motif that is commonly found among drug candidates.[125]

Significant structural changes in the aniline component were also realised. The reaction was general with respect to the nature of the nitrogen substituents, with the 1-phenyl-pyrrolidine and indoline rings significantly more reactive than *N,N*-dimethyl aniline (**178**). A variety of heteroatom substituents were also incorporated on the aniline ring at both the *ortho* and *meta* positions without loss in reaction efficiency or enantiocontrol. Use of electron-deficient

anilines provided halogenated benzene adducts, valuable synthons for use in organometallic technologies such as Stille[126] and Suzuki[127] coupling reactions.

MacMillan went on to develop a method for the direct deamination of *N,N*-dialkyl aniline rings. This was achieved *via* treatment of aniline **180** with methyl iodide followed by exposure of the resulting quaternary amine to reductive conditions to provide the parent aromatic system **181** in excellent yield (*Scheme* **87**).



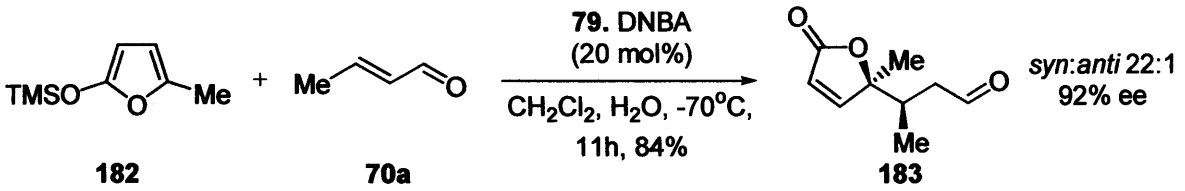
Scheme **87**

Importantly, this operationally simple protocol effectively enables dialkylanilines to be employed as benzene surrogates in this organocatalytic alkylation strategy. With over 5000 isolated natural products and therapeutic agents such as Paxil,[128] Zoloft,[125a] and Detrol,[125b] which incorporate a benzylic carbon stereocentre, catalytic access to enantioenriched benzylic architecture is thus extremely valuable.

1.16.4 Enantioselective Organocatalytic Mukaiyama-Michael Additions

The Mukaiyama-Michael reaction involves the 1,4-conjugate addition of silyl enol ethers to electron deficient alkenes. This reaction is not amenable to Lewis acid catalysis as these promote 1,2-addition (the Mukaiyama-Aldol reaction) in preference to 1,4-addition (the Mukaiyama-Michael reaction). MacMillan found that these limitations could be overcome when using chiral imidazolidinone **79** to activate an α,β-unsaturated carbonyl compound. Silyloxy-furans can undergo a 1,4-conjugate addition with the resulting iminium ion to generate an enantioenriched γ-butenolide architecture.

MacMillan first examined the enantioselective organocatalytic butenolide synthesis by performing the imidazolidinone-catalysed conjugate addition of silyloxy-furan (**182**) to (*E*)-crotonaldehyde (**70a**). Excellent levels of *syn*-diastereoselectivity and enantiocontrol were achieved, although with poor reaction efficiency (31% yield). It was assumed that imidazolidinone turnover was being inhibited by loss of water from the catalytic cycle due to formation of $(TMS)_2O$. Hence the reaction was repeated with an excess of water (2 equivalents), which provided optimal reaction efficiency (*Scheme* **88**).[129]

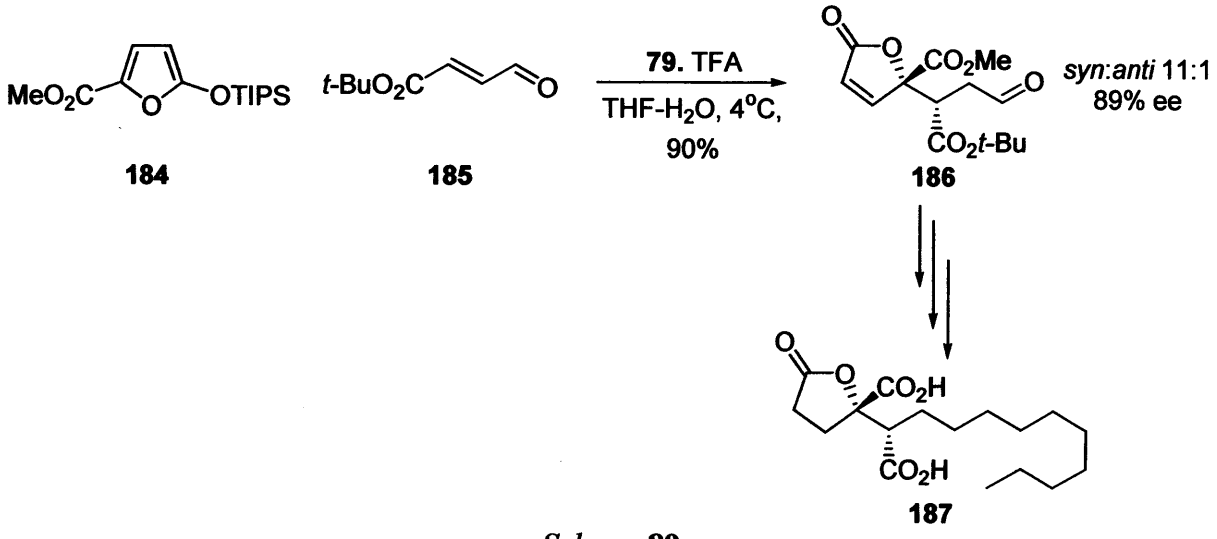


Scheme **88**

A broad variety of β-substituents on the carbonyl species can be accommodated in the organocatalytic Mukaiyama-Michael addition, with no adverse affect on the yield or selectivity. Moreover, variation in the electronic nature of the aldehyde component had little influence on the stereochemical outcome of the reaction. Importantly, the products arising from the 1,2-iminium addition were not observed with any of the aldehydes examined.

Significant variation in the silyloxy-furan system was also realised. The reaction was tolerant to a series of substituents at the furanyl 5-position, and to the presence of alkyl substituents in the C3 position of the furan ring. Under the reaction conditions employed the *syn*-diastereoisomer was formed preferentially, but importantly, *via* selection of an appropriate co-catalyst and solvent the *anti*-diastereoisomer can be generated instead.

The utility of the enantioselective organocatalytic silyloxy-furan additions to form butenolide products was demonstrated in a four-step synthesis of spiculisporic acid (**187**), a *Penicillium spiculisporum* fermentation adduct[130] that is used commercially as a biosurfactant for metal decontamination processes[131] and in fine polymer production.[132] The stereochemical core of spiculisporic acid (**186**) was generated *via* an organocatalytic Mukaiyama-Michael protocol, and elaboration of this to spiculisporic acid (**187**) was accomplished in 54% overall yield using a three-step procedure (*Scheme* **89**).[129]



Scheme **89**

As shown above, the enantioselective organocatalytic Mukaiyama-Michael reaction provides access to asymmetric γ-butenolides, a structure present in over 13,000 natural products. This methodology is therefore valuable to synthetic organic chemists to facilitate the construction of complex architectures.

1.16.5 Iminium Ion Intermediate of the 1,4-Conjugate Addition Reactions

The proposed iminium ion intermediate formed during the organocatalytic 1,4-conjugate addition reaction is shown in *Figure* **33**. Both the benzyl group and the *tert*-butyl substituent shield the *si*-face of the α,β-unsaturated iminium ion, forcing the aromatic nucleophile to attack the *re*-face, leading to the observed enantioselectivity.[119]

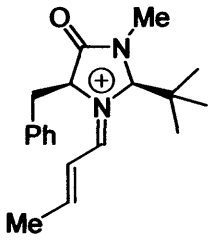


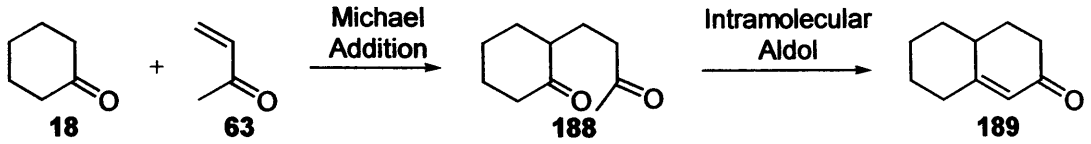
Figure **33**

As the *re*-face of the α,β-unsaturated iminium ion is unhindered an increased rate of reaction was observed compared to the use of catalyst **69** with a geminal dimethyl group in the C5 position.

These examples of enantioselective 1,4-conjugate additions further establish LUMO-lowering organocatalysis as a broadly useful concept for asymmetric synthesis. These reactions allow the construction of alkylated aromatic species that are useful synthons for a variety of applications in medicinal chemistry and target orientated synthesis.

1.17 The Robinson Annulation Reaction

The Robinson annulation reaction comprises a Michael addition of a cyclic ketone to an α,β-unsaturated carbonyl compound, followed by an intramolecular aldol cyclisation to furnish a bicyclic enone (*Scheme* **90**). This method of carbon-carbon bond formation generates a synthetically useful fused bicyclic ring system. High regioselectivity is often achieved in these reactions by the use of preformed enolates. The aldol cyclisation step can also be carried out in the presence of a chiral auxiliary to yield the product in high enantiomeric excess.[133]



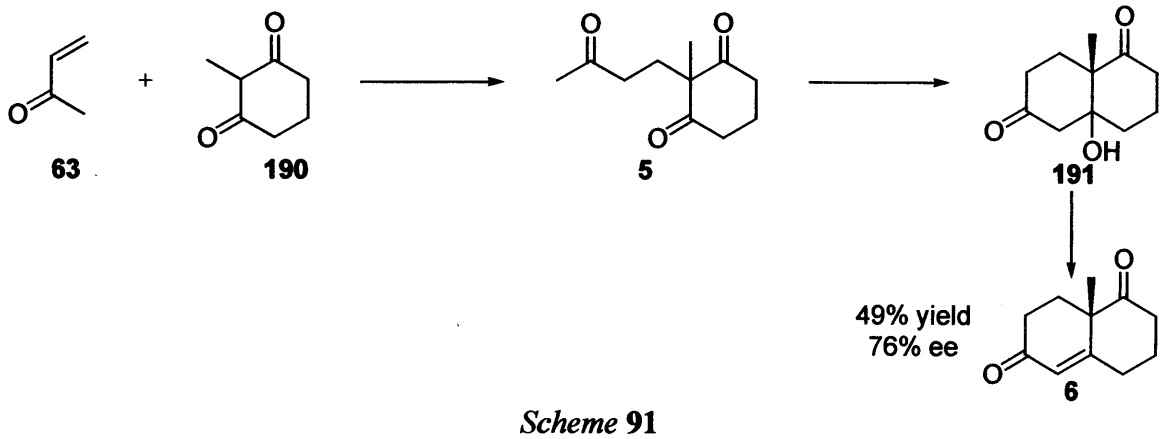
Scheme **90**

Organocatalytic Michael reactions have been achieved to yield the corresponding adduct with high levels of enantiocontrol (*Section* **1.15**). Aminocatalysed asymmetric intramolecular aldol condensations are also known (*Section* **1.5**). Therefore the Robinson annulation reaction should be amenable to aminocatalysis *via* the combination of these strategies.

1.17.1 Proline-Catalysed Asymmetric Robinson Annulation Reaction

Hajos, Parrish, Eder, Sauer and Wiechert were 30 years ahead of their time when they carried out the original studies into the proline-catalysed intramolecular aldol condensation in the early 1970's.[17] But recent advances have been made. Barbas III reported a protocol in which an antibody aldolase catalysed both steps of the Robinson annulation reaction *via* an enamine mechanism.[134] Provided with this success and the ability of proline (**4**) to catalyse the intramolecular aldol cyclisation, Barbas III went on to examine the potential for (*S*)-proline (**4**) to catalyse both steps of the Robinson annulation reaction.

Studies were aimed towards the one-pot synthesis of the Wieland-Miescher ketone (**6**) from methyl vinyl ketone (**63**) and 2-methylcyclohexane-1,3-dione (**190**). (*S*)-Proline (**4**) was found to catalyse the entire annulation sequence to provide ketone **6** with an overall yield and enantiomeric purity similar to that of the two-step procedure (*Scheme* **91**).[135]



Scheme **91**

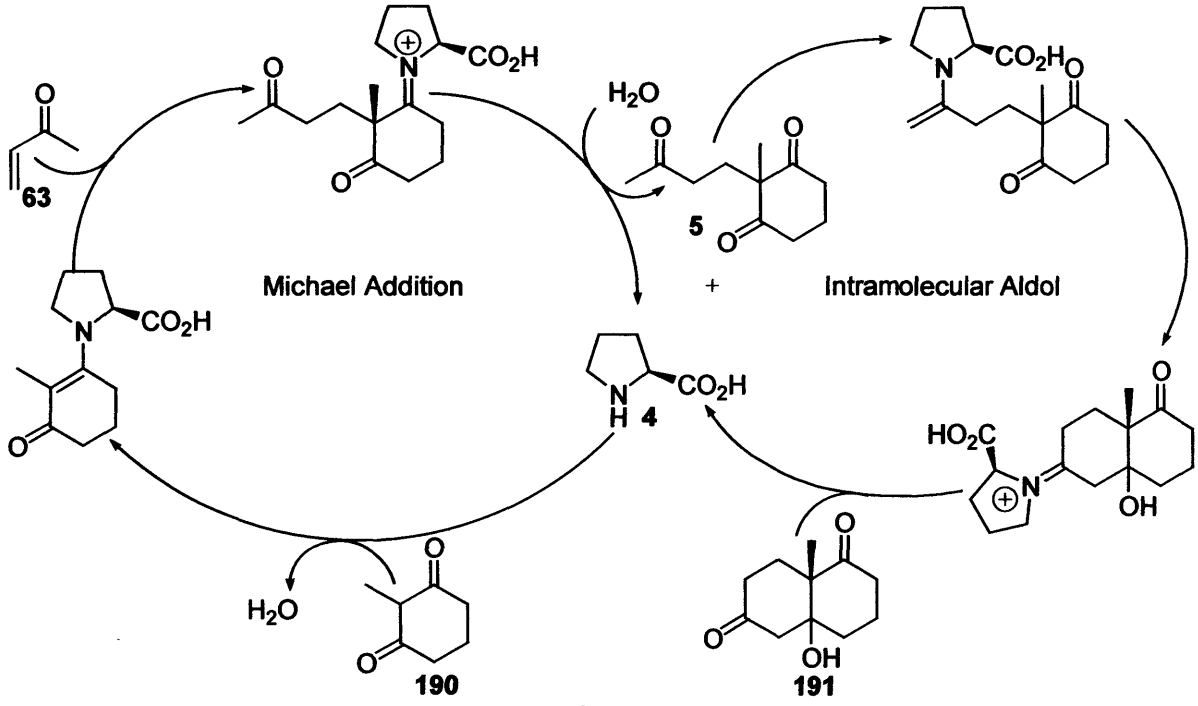
Several commercially available proline-like derivatives were also tested for their ability to catalyse this reaction sequence, as well as 16 commercially available chiral amines. Only those bearing a cyclic secondary amine demonstrated reactivity in this screen, with the best

results obtained from the use of pyrrolidine-type systems. A carboxylate functionality was also found to be necessary for catalysis of the dehydration step.

1.17.2 Mechanism of the Organocatalytic Robinson Annulation Reaction

Presumably the proline-catalysed Robinson annulation reaction takes place *via* a mechanism that is a combination of that for the organocatalytic Michael addition (*Section* **1.15.6**) with the mechanistic cycle of the aminocatalysed intramolecular aldol cyclisation (*Section* **1.5.2**).

As such, an activated enamine would be formed between the proline (**4**) catalyst and diketone **190**. This would then undergo a 1,4-conjugate addition with methyl vinyl ketone (**63**), which after hydrolysis would yield Michael adduct **5**. Generation of a second enamine with the proline (**4**) catalyst would then promote an intramolecular aldol cyclisation, which after hydrolysis of the resulting iminium species, would yield ketol product **191** (*Scheme* **92**). Subsequent dehydration of ketol **191** would furnish bicyclic enone **6**.



Scheme **92**

This mechanism is only a postulation based on the catalytic cycles discussed in *Sections* **1.15.6** and **1.5.2**. No information regarding the mechanism for this one-pot organocatalytic Robinson annulation reaction has yet been reported.

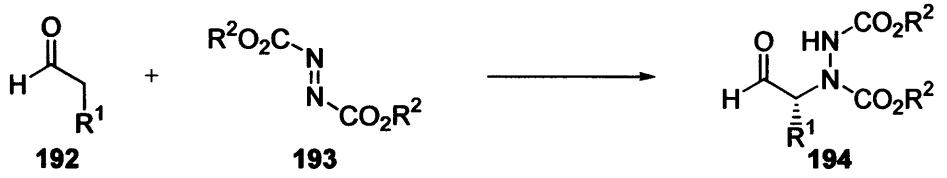
This organocatalytic Robinson annulation reaction provides a straightforward procedure for the synthesis of bicyclic enones in one-pot. Such ketones, in enantiopure form, are useful

synthons for the construction of a variety of biologically active compounds. This organocatalytic Robinson annulation reaction further exemplifies the success of small chiral amines as catalysts for a broad range of chemical transformations.

1.18 The α-Amination of Carbonyl Compounds

The biological importance of enantiomerically pure natural and non-natural α-amino acids, α-amino aldehydes and α-amino alcohols has led to a wealth of research into stereoselective methods for their synthesis.[136] Catalytic asymmetric approaches have focused on both carbon-carbon and carbon-nitrogen bond forming reactions. As seen in *Section* **1.14** the Mannich Reaction is an example of a C-C bond forming reaction that has been successfully used to synthesise optically pure nitrogenous compounds.

An α-amination involves the reaction of an aldehyde or ketone with an electrophilic nitrogen source, such as an azodicarboxylate (**193**), to form a new carbon-nitrogen bond, and thus generate a stereogenic carbon centre attached to a nitrogen atom (*Scheme* **93**). This method provides a simple synthetic approach to optically active α-amino carbonyl compounds (**194**).



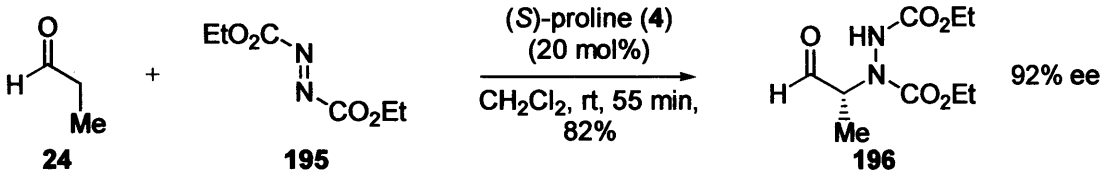
Scheme **93**

The electrophilic α-amination of carbonyl compounds has increasingly been used in the synthesis of nitrogenous compounds.[137] Several asymmetric versions have been reported, for example, the reaction of chiral auxiliary preformed enolates/enolethers with azodicarboxylates has been used to furnish α-amino acid derivatives with high stereoselectivities.[138] Catalytic enantioselective versions have also been developed, including the metal-catalysed reactions of enolsilanes with azodicarboxylates.[139] In addition to these indirect variants that require the use of preformed enolate equivalents, a catalytic direct asymmetric α-amination of 2-keto esters with azodicarboxylates has been reported that uses chiral copper(II)-bisoxazoline complexes as reaction catalysts.[140]

Aminocatalysis of the α-amination reaction is also possible.[141] This involves a reaction between the carbonyl component and the amine catalyst to generate an enamine, which is then activated to undergo reaction with the azodicarboxylate species.

1.18.1 Direct Organocatalytic Asymmetric α-Amination of Aldehydes

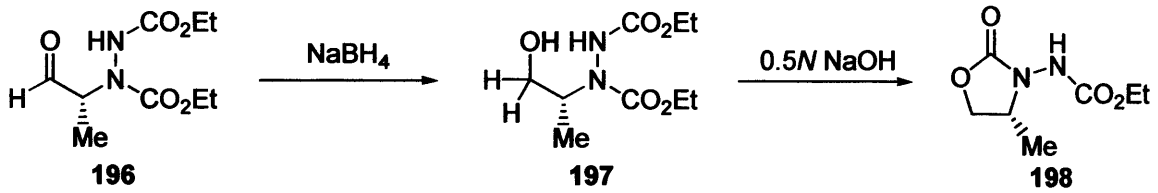
Jørgensen reported the first organocatalysed α-amination of aldehydes with azodicarboxylates to generate optically active α-amino aldehydes. The (*S*)-proline (**4**) catalysed direct enantioselective α-amination reaction was first examined with propionaldehyde (**24**) and diethyl azodicarboxylate (DEAD) (**195**). This reaction was found to proceed in high yield to afford the α-hydrazino aldehyde **196** in 92% ee (*Scheme* **94**).[142]



Scheme **94**

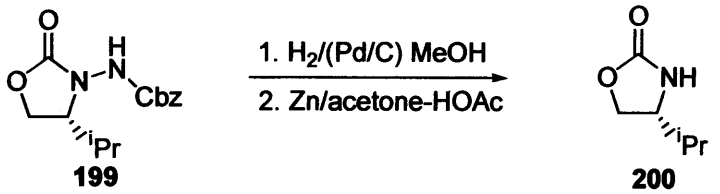
Even with a catalyst loading of 2 mol% a highly enantioselective reaction was maintained (84% ee). The reaction could also be performed under neat reaction conditions to afford adduct **196** in 77% ee with full conversion after 2 minutes at ambient temperature.

The scope of this reaction was expanded by reacting various aldehydes with DEAD (**195**) to afford the corresponding α-aminated aldehydes in high yields and enantioselectivities in the presence of (*S*)-proline (10 mol%) as the catalyst. The *in situ* reduction of the resulting adducts was performed to yield valuable α-aminated alcohols (**197**), which were then converted into *N*-amino oxazolidinones (**198**) (*Scheme* **95**).



Scheme **95**

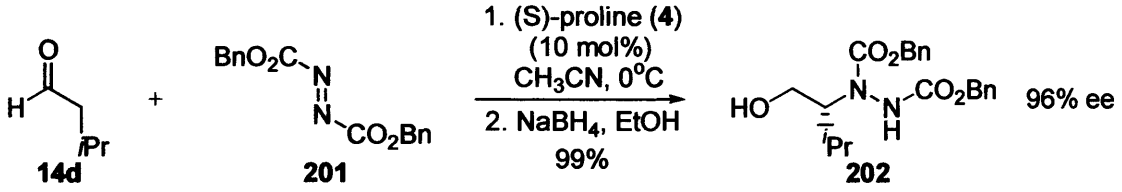
If dibenzyl azodicarboxylate (**201**) was used as the nitrogen source, *N*-Cbz protected *N*-amino oxazolidinone **199** resulted. This could be converted to the corresponding oxazolidinone **200** by removal of the *N*-protecting group and cleavage of the N-N bond (*Scheme* **96**).



Scheme **96**

This methodology therefore provides a novel route for the synthesis of 4-substituted 2-oxazolidinones, including various Evans auxiliaries in both enantiomeric forms.

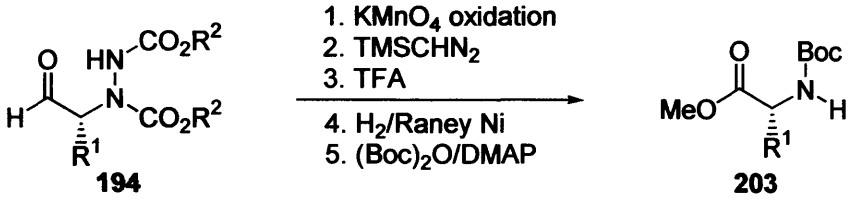
List, almost simultaneously with Jørgensen, also published the direct proline-catalysed α-amination reaction of aldehydes. List found that optimal results were obtained when the α-amination reaction was carried out in acetonitrile at 0°C. Under these conditions a variety of aldehydes, including *iso*valeraldehyde (**14d**), were reacted with dibenzyl azodicarboxylate (**201**) to generate an α-aminated aldehyde, which was reduced *in situ* to the corresponding α-amino alcohol, e.g. **202** (*Scheme* **97**). High yields (93-99%) and enantioselectivities (>95% ee) were achieved throughout.[143]



14d **201** **202**

Scheme **97**

An important aspect of the direct α-amination reaction is that it allows simple and attractive access to optically active non-proteogenic α-amino acids (**203**). These are formed from the α-aminated aldehyde adducts (**194**) *via* a five step protocol, with the enantiomeric excess obtained in the α-amination step maintained throughout this synthesis (*Scheme* **98**).[141]



194 **203**

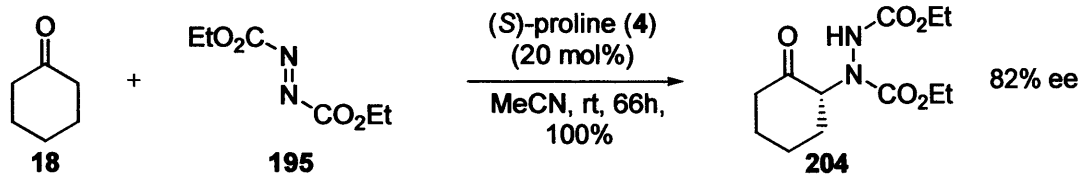
Scheme **98**

The α-hydrazino aldehydes, formed by the direct proline-catalysed α-amination of aldehydes can therefore be used to synthesise a variety of optically active compounds, such as α-amino alcohols and α-amino acids. These are all key chiral elements in many natural products as well as in medicinal chemistry.

1.18.2 Direct Proline-Catalysed Asymmetric α-Amination of Ketones

Jørgensen further expanded the scope of the organocatalytic α-amination reaction to include ketone donors. For instance, the (*S*)-proline (**4**) catalysed direct enantioselective α-amination

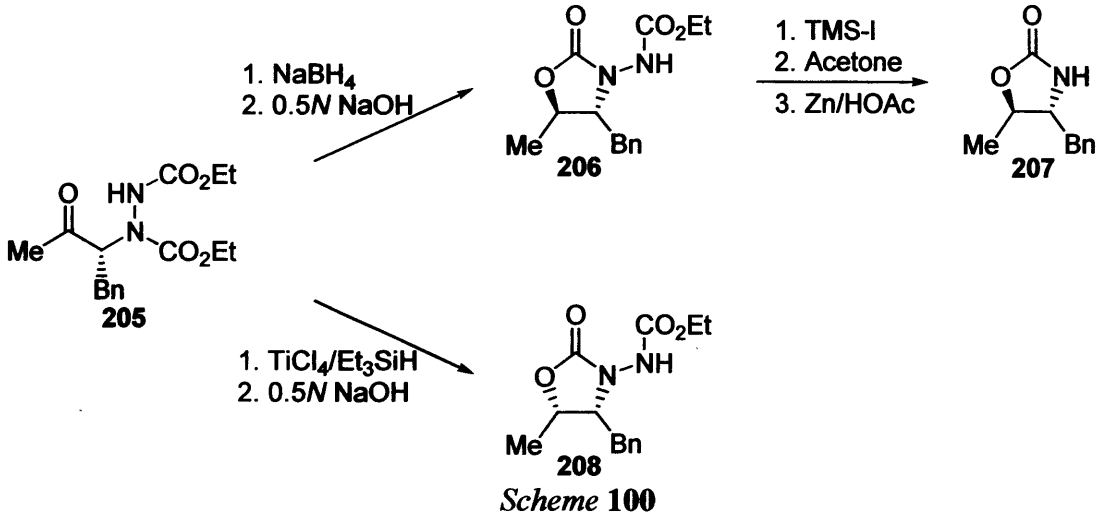
reaction of cyclohexanone (**18**) by DEAD (**195**) was found to proceed in high yield to afford the α-hydrazino ketone **204** in 82% ee (*Scheme* **99**).[144]



Scheme **99**

The direct α-amination of various non-symmetrical ketones by DEAD (**195**) in the presence of (*S*)-proline (**4**) yielded the corresponding α-hydrazino ketones with excellent enantioselectivities. The reaction was also highly regioselective as the amination occurred at the most highly substituted carbon atom.

Several valuable optically active products can be formed from the α-aminated ketone adducts, for example, reduction of the carbonyl functionality of **205** with sodium borohydride yields the corresponding *syn*-α-amino alcohol, which upon treatment with sodium hydroxide forms the *N*-amino oxazolidinone **206**. Further reactions can then provide oxazolidinone **207**. The *anti*-α-amino alcohol **208** can also be obtained by reduction of **205** with triethylsilane and titanium tetrachloride (*Scheme* **100**).



Scheme **100**

The α-hydrazino ketones, formed by the direct proline-catalysed α-amination of ketones, thus offers a new and simple approach to *syn*- and *anti*-α-amino alcohols, which are highly valuable chiral fragments in many different compounds and very useful as chiral starting materials.[136]

1.18.3 Enamine Transition State of the Proline-Catalysed α-Amination Reaction

Both List and Jørgensen proposed transition states to rationalise the stereochemical outcome observed in the proline-catalysed α-amination reaction of aldehydes and ketones. List proposed chair-like enamine transition state *Model* **K** (*Figure* **34**), based on the transition state of the Hajos-Parrish-Eder-Sauer-Wiechert reaction calculated by Houk.[145] This model is consistent with the proposed models for the intermolecular aldol (*Model* **D**, *Section* **1.6.10**) and Mannich reactions (*Model* **J**, *Section* **1.14.6**).[143] Jørgensen on the other hand predicted boat-like *Model* **L** (*Figure* **34**) as the lowest energy conformation for the transition state.[142]

Model **K** *Model* **L**

Figure **34**

It is worth noting that the enamine transition state proposed by List (*Model* **K**) lacks the hydrogen bond to the proline (**4**) nitrogen. Houk and co-workers have recently shown through a series of calculations that this N-H hydrogen bond does not lower the transition state energy in the corresponding aldol reaction.[22a] While both transition models lead to identical products directed by the hydrogen bond from the carboxylate group of proline (**4**), each transition state should possess a unique energy and so one should be favoured, however, the operative transition state has yet to be determined.

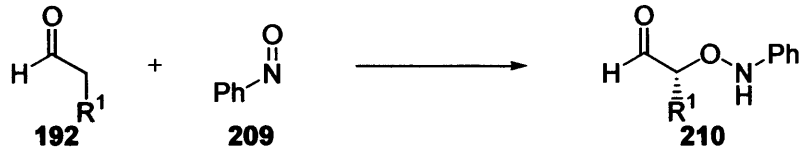
The proline-catalysed α-amination of aldehydes and ketones is thus an efficient method for the formation of carbon-nitrogen bonds, allowing the synthesis of α-amino acids, α-amino aldehydes/ketones and α-amino alcohols. Such optically active compounds are key chiral fragments in many natural products and are very useful as chiral precursors in medicinal chemistry.

1.19 The α-Oxidation of Carbonyl Compounds

The α-oxycarbonyl moiety is abundant among natural products and is a versatile functional intermediate. Consequently many methods have been developed for its preparation,[146] for example, the α-oxycarbonyl species can be formed from chiral natural sources such as amino acids,[147] sugars,[148] and chiral α-hydroxy acids.[149] Diastereoselective reactions such as

nucleophilic addition to chiral glycoxal derivatives,[150] or alkylation of chiral hydrazones,[146] can also be applied. In addition, the Sharpless asymmetric dihydroxylation of silyl enol ethers can be used.[36b] Furthermore, asymmetric hydrocyanation,[151] and enzymatic resolution,[152] have been employed as a key step in the synthesis of α-oxycarbonyl compounds, but most of these preparations require multiple manipulations. The only direct chemical method for the α-hydroxylation of aldehydes, leading to α-hydroxyaldehydes in high enantiomeric purity, was provided by the oxidation of preformed enolates from aldehydes derivatised with chiral auxiliaries.[153,154] Therefore the development of new methodologies for the direct catalytic asymmetric α-hydroxylation of aldehydes was an important target in organic synthesis.

An α-oxidation involves the reaction of an aldehyde with an electrophilic oxygen source, such as a nitrosobenzene (**209**), to form a new carbon-oxygen bond, and thus generate a stereogenic carbon centre attached to an oxygen atom (*Scheme* **101**). This method provides a simple synthetic approach to optically active α-oxycarbonyl compounds (**210**).



Scheme **101**

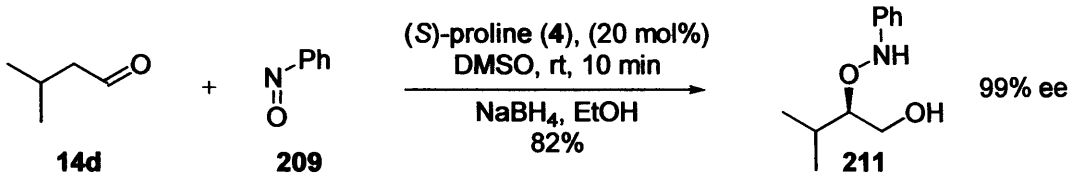
Aminocatalysis of the α-oxidation reaction is possible. This involves a reaction between an aldehyde component and the amine catalyst to generate an enamine, which is then activated to undergo reaction with the electrophilic oxygen atom of the nitroso species.

1.19.1 Direct Organocatalytic Enantioselective α-Oxidation of Aldehydes

Almost simultaneously, Zhong, MacMillan and Hayashi independently reported the direct catalytic enantioselective α-aminoxylation of aldehydes using nitrosobenzene (**209**) as the oxygen source and (*S*)-proline (**4**) as the catalyst. This method allowed the synthesis of versatile α-aminoxylated aldehydes in high yields and enantioselectivities.

Each report was remarkably similar with only minor differences in the reaction conditions employed. Zhong initially looked at the α-aminoxylation reaction using *iso*valeraldehyde (**14d**) as the donor. The superior reactivity of nitrosobenzene (**209**), compared to the aldehyde itself, as the acceptor meant that the self-aldolisation reaction of the aldehyde was minimised. The proline-catalysed reaction in DMSO was complete in just ten minutes at

ambient temperature to afford, after reduction, 2-aminoxy alcohol **211** in good yield and excellent enantioselectivity (*Scheme* **102**).[155]

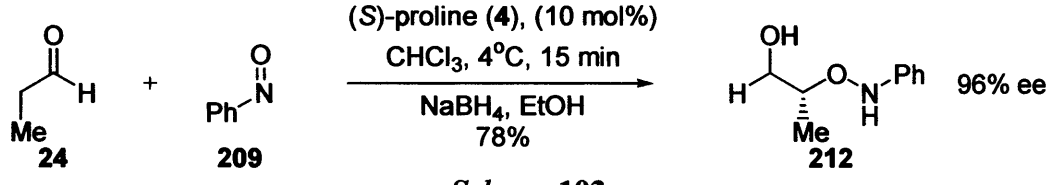


14d + **209** → **211**

Scheme **102**

The scope of this reaction was explored by reacting a series of aliphatic aldehydes with nitrosobenzene (**209**). After *in situ* reduction, these reactions afforded *O*-regioselective products with excellent enantioselectivities (94-99% ee) in good overall yields (54-85%).

MacMillan studied the proline-catalysed α-aminoxylation reaction of propionaldehyde (**24**) with nitrosobenzene (**209**) to furnish 2-aminoxy alcohol **212**. The optimum yield (78%) and enantioselectivity (96% ee) were achieved when the reaction was performed in chloroform at 4°C (*Scheme* **103**).[156]



24 + **209** → **212**

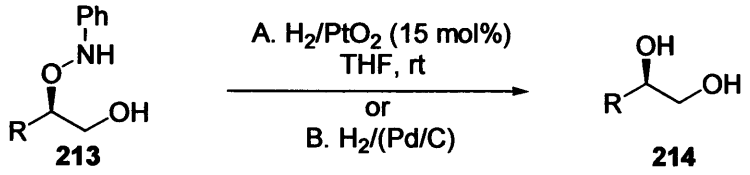
Scheme **103**

Catalyst loadings as low as 0.5 mol% could be utilised without significant loss in enantiocontrol. Use of 2 mol% was found to be optimal as this provided high reaction efficiency and enantioselectivity while maintaining expedient reaction times (88% yield, 97% ee, 2h).

The α-aminoxylation reaction of propionaldehyde (**24**) with nitrosobenzene (**209**) was also investigated by Hayashi, who found superior results were attained when the reaction was performed in acetonitrile at -20°C. Under these proline-catalysed conditions (10 mol%), a quantitative yield of 2-aminoxy alcohol **212** was furnished in 24 hours with 98% enantiomeric excess.[157]

Both MacMillan and Hayashi found considerable variation in the steric demand of the aldehyde component was possible without loss in reaction efficiency or enantiocontrol. Notably, electron-rich π-systems, which are typically prone to oxidative degradation, could be employed under these mild reaction conditions.

The 2-aminoxy alcohol products formed by the α-aminoxylation of aldehydes with nitrosobenzene (**209**), followed by *in situ* reduction, are useful synthons for further chemical transformations. One such protocol involves the synthesis of the corresponding chiral 1,2-diol by cleavage of the oxygen-nitrogen bond. This catalytic hydrogenation can be carried out using either Adams' catalyst (PtO_2),[155] or palladium on carbon (Pd/C),[156] to furnish terminal diol **214** without any loss in optical purity (*Scheme* **104**).

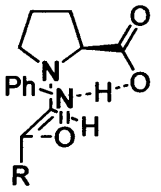


Scheme **104**

This organocatalytic protocol therefore acts as a dihydroxylation surrogate allowing the synthesis of terminal 1,2-diols. Enantioselective routes to optically active 1,2-diols are of considerable interest as this structural moiety is found in biologically active natural products and synthetic pharmaceuticals.[158] Since proline (**4**) is commercially available in both enantiopure forms, this one-pot procedure allows the synthesis of *R*- or *S*- configured 1,2-diols with excellent enantioselectivities for use as building blocks in natural product synthesis.[158a]

1.19.2 Enamine Transition State of the Proline-Catalysed α-Oxidation Reaction

Zhong proposed that the catalytic α-oxidation of aldehydes proceeds *via* an enamine mechanism and that the stereochemical outcome of the reaction can be rationalised by the formation of chair-like transition state *Model* **M** (*Figure* **35**).[155] This model is in accord with the model proposed for the aminocatalytic intermolecular Aldol reaction (*Model* **D**, *Section* **1.6.10**).



Model **M**
Figure **35**

In this postulated model, the *si*-face of the *E*-enamine, formed from the aldehyde and (*S*)-proline (**4**), approaches the less-hindered oxygen atom of nitrosobenzene (**209**) to provide a chiral α-aminoxy aldehyde with *R*-configuration, in accord with the observed stereocontrol.

The proline-catalysed α-oxidation of aldehydes is therefore an efficient method for the formation of carbon-oxygen bonds, allowing the synthesis of chiral α-aminoxy aldehydes, 2-aminoxy alcohols and terminal 1,2–diols. Such optically active compounds are versatile intermediates in natural product synthesis. This further illustrates the scope of small chiral amines as catalysts for a variety of synthetic transformations.

1.20 Summary

While the unique reactivity of enamines and iminium ions has long been used in organic synthesis, most of these reactions use stoichiometric quantities of the amine. Until recently, amines had rarely been used catalytically despite the fact that they are readily available in enantiomerically pure form from several sources, including the chiral pool.[9] As discussed in this introduction, small chiral amines can be employed as catalysts for a wide variety of chemical transformations, *via* both enamine and iminium activation pathways.

Carbon-carbon bond forming reactions, such as the aldol, Mannich, Michael and Diels-Alder reaction are all amenable to aminocatalysis. In addition, the C-N bond forming α-amination reaction and the C-O bond forming α-oxyamination reaction are promoted by chiral amine catalysts. These transformations proceed with high levels of reaction efficiency and excellent enantiocontrol. Thus, organocatalysis represents a remarkable synthetic alternative to established organometallic transformations.

Although a significant amount of research has been conducted within the area of aminocatalysis over the past few years, additional investigations are required to further advance this methodology. For instance, aminocatalysis of the Baylis-Hillman reaction has provided adducts with essentially no asymmetric induction, however, future studies may provide a highly enantioselective version. Furthermore, the discovery of new aminocatalysed reactions may result.

The fact that there are some areas which still require further research to develop the ideal catalyst means that there will be many more exciting discoveries to come, hopefully facilitated by the constant improvement of technologies and information available in the modern chemical community.

Chapter 2: Results and Discussion

2.1 Introduction

Over recent years, significant advances have been made in the field of catalytic asymmetric synthesis.[4,6,159] The design of these systems has stretched the imagination of the chemist and has led to numerous commercially viable catalytic systems, such as the asymmetric dihydroxylation and allylic epoxidation of Sharpless,[36,160] the Salen Mn(III) catalysts of Jacobsen,[161] and the asymmetric transfer hydrogenation catalysts developed by Noyori,[162] to highlight a few very high profile contributions.

Whilst important advances have been made in the development of chiral Lewis acid catalysts, the ultimate goal of discovering a single catalyst that can affect a wide range of processes with high levels of enantioselectivity remains to be achieved. Chapter two of this thesis will be concerned with the design and synthesis of a first generation Lewis acid that can discriminate between the prochiral faces of α,β-unsaturated carbonyl compounds, which, if successful, would provide useful insight into solving this universal problem.

2.1.1 α,β-Unsaturated Carbonyl Compounds

α,β-Unsaturated carbonyl compounds are useful tools to the contemporary organic chemist. There are a range of transformations that can be carried out on these pro-chiral substrates, including the Ene reaction,[163] Baylis-Hillman reaction,[164] Sakurai reaction,[165] and cycloadditions ([3+2][166] or [4+2][167]), to highlight just a few. Achieving stereoselective transformations with α,β-unsaturated aldehydes, ketones and acrylates is an ongoing and fascinating challenge in this field.

At this point it is pertinent to mention the conformational aspects of α,β-unsaturated carbonyl systems. In a recent article[168] the conformational preferences of this functional group was addressed and it was shown that the *s-trans* conformation is preferred for aldehydes such as acrolein (**76**). However, for acids and acrylates, such as acrylic acid (**215**) and methyl acrylate (**216**), the preference is for an *s-cis* conformation (although this preference is not strong) (*Figure* **36**).

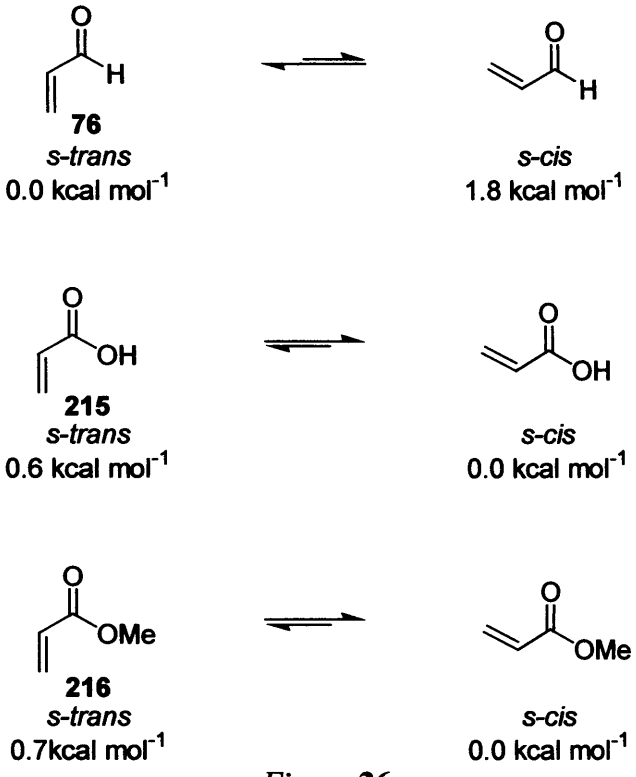


Figure **36**

It is well accepted that carbonyl groups can interact with a Lewis acid *via* a sigma (σ) interaction between the lone pair located on the carbonyl oxygen atom and the metal of the Lewis acid.[169] Upon interaction of an α,β-unsaturated carbonyl compound with a homochiral Lewis acid there are eight possible conformations that the resulting complex can adopt (two *s-trans-anti*, two *s-trans-syn* and their *s-cis* counterparts) (*Figure* **37**). Complexed acrylates can adopt 16 conformations. Design of a Lewis acid that could selectively adopt one of these conformations when complexed is a challenging problem, which if solved would have a significant impact on the chemical community.

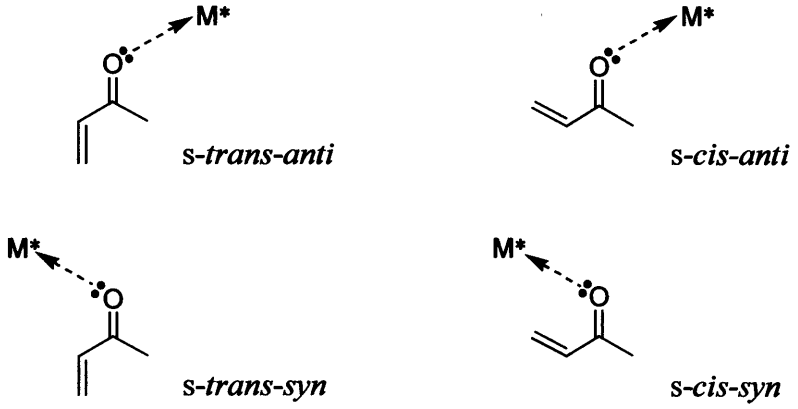
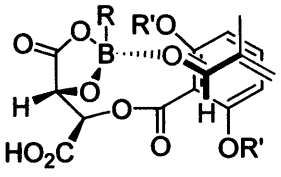


Figure **37**

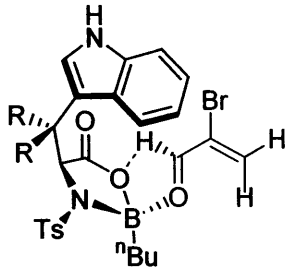
2.1.2 Previous Catalytic Systems

In previous years, elegant catalytic systems have been introduced by Yamamoto,[170] Corey[171] and Hawkins,[172] to emphasise a few of the more prominent examples. The authors constructed Lewis acid catalysts that promoted selective complexation of the α,β-unsaturated carbonyl substrate. Furthermore, the systems of Yamamoto and Corey were found to have multi-reaction applicability.

The CAB (Chiral Acyloxy Borane) catalysts,[173] introduced by Yamamoto, and Corey's chiral oxazaborolidine derived systems,[171] were utilised in the catalytic asymmetric reactions of α,β-unsaturated aldehydes. The efficacy of these catalysts was explained by invoking an attractive face-face π-π interaction with the substrate, as depicted in *Figure* **38**.



Methacrolein complexed to Yamamoto's CAB catalyst.



Bromoacrolein complexed to Corey's oxazaborolidine catalyst.

Figure **38**

The CAB catalysts have been employed in Diels-Alder[174] and hetero-Diels-Alder[175] cycloadditions, as well as in aldol[176] and allylation[177] reactions. This versatility, combined with the stability in air of the substituted boron analogues (R = phenyl or alkyl, derived from the corresponding phenyl- or alkylboronic acid), provides a family of catalysts ideal for many applications. The tryptophan derived system has been used to catalyse Diels-Alder cycloadditions,[171] Mukaiyama-aldol and aldol-dihydropyrone annulation reactions.[178] Use of either catalyst led to the formation of products with commendable stereoselectivities.

Hawkins designed a catalytic system for the stereoselective reaction of α,β-unsaturated acrylates. This catalyst utilised the concept of dual point binding in order to hold the substrates rigidly in a single conformation, thus leading to a single transition state being observed during the Diels-Alder reaction (*Figure* **39**).[172]

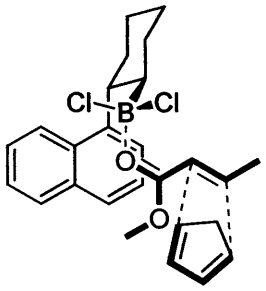


Figure **39**

In this proposed transition state the acrylate is fixed in an *s-trans* conformation and is lying parallel to, and at a distance of 3.172Å from, the aromatic ring. In this conformation, attack to the lower face of the dienophile is shielded by the edge of the naphthalene ring. Use of this catalyst led to enantiomeric excesses of up to 99.5% being observed in the Diels-Alder cycloaddition reaction with cyclopentadiene.

2.1.3 Fundamental Contribution?

In the cases highlighted above, (*Section* **2.1.2**), the stereochemical outcome was explained by invoking π–π interactions, however, the exact nature of the 'π-stacking effect' is still a subject of some debate in the synthetic organic and computational arenas. The design of processes which harness their full potential will not be possible until we are able to fully understand the origins of these interactions.

At the commencement of this project our aim was to design and synthesise a series of ligands that would enable us to investigate and ultimately understand the nature of face-face π–π interactions and the subtleties associated with their existence, and to use these ligands as catalysts in a series of asymmetric transformations.

2.2 Design Concept

The challenge ahead was the rational design of a ligand that was non-substrate specific and non-reaction specific. Our design involved the introduction of two points of interaction between the Lewis acid and the carbonyl compound; namely, a sigma interaction between the lone pair located on the carbonyl oxygen atom and the metal of the Lewis acid, and an attractive face-face π–π interaction between the double bond of the α,β-unsaturated carbonyl compound and an aromatic ring incorporated into the structure of the Lewis acid (*Figure* **40**).

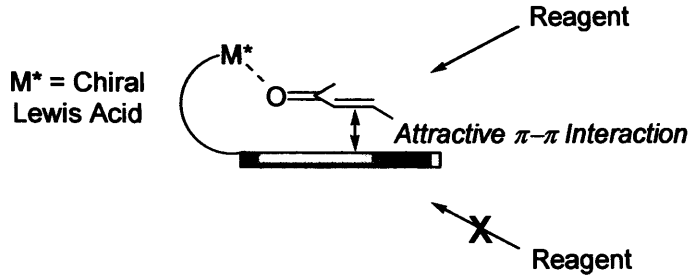


Figure **40**

π-Stacking is a concept that has attracted increasing interest from organic chemists in recent years.[179] The name signifies an attractive, non-covalent π-π interaction between a multiple bond (typically C=O or C=C) and an aromatic ring. To achieve this, the unsaturated bond must lie parallel to and between 3.0-3.5Å from the aromatic ring (*Figure* **41**).

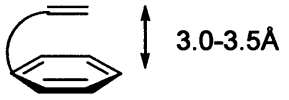
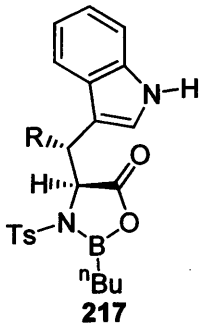


Figure **41**

π-Stacking effects can enhance selectivity in asymmetric C-C bond forming reactions and many chiral auxiliaries and catalysts have been designed with this interaction in mind.[180]

2.2.1 Ligand Design Features

Face-face π–π interactions are often observed in nature and play a critical role in the determination of the tertiary structure of many proteins as well as in small molecule drug-receptor interactions. In biological systems, enzymes are catalysts, and thus some of the features of enzymes can be incorporated into the design of catalysts. One such example of this is seen in the tryptophan derived oxazaborolidine catalyst **217** (*Figure* **42**).[171]



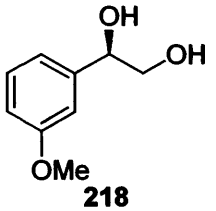
217

Figure **42**

When employed in a Diels-Alder cycloaddition reaction between bromoacrolein and cyclopentadiene (**66**), catalyst **217** afforded the corresponding adduct with an unprecedented

>200:1 enantioselectivity. The presence of the indolyl moiety was found to significantly enhance the observed selectivity. Replacement of this π-basic subunit with a naphthyl group gave an enantioselection of 7:1, while a phenyl, cyclohexyl or *iso*propyl group gave only 2:1 selectivity combined with a reversal in the facial selectivity.

We therefore sought to incorporate an indole moiety into the design of our initial target ligand. Complexation to the Lewis acidic metal was envisaged *via* the incorporation of a diol subunit into the catalyst design. Such a functionality is present in the styrene derived ligand **218** reported by Jones (*Figure* **43**).[181]



218

Figure **43**

This ligand was used in the catalysis of a Diels-Alder reaction between cyclopentadiene (**66**) and methacrolein (**252**), and led to the corresponding adduct **248** with 30% enantiomeric excess.

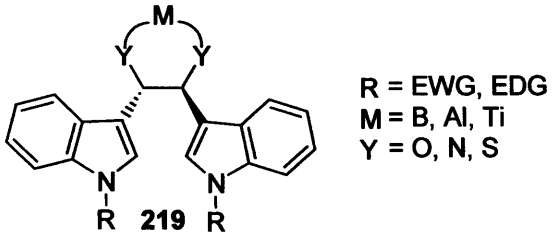
A possible problem associated with the catalyst arising from ligand **218** is that the α,β-unsaturated carbonyl reagent can approach from the side of the metal where no aromatic functionality is present. Such an approach would result in the aromatic ring not being involved in the diastereofacial discrimination of the ensuing cycloaddition reaction.

Therefore, in the design of our first target ligand we attempted to rationally overcome this problem by using a C_2-symmetrical ligand, in order that the Lewis base has the opportunity to interact with the aromatic functionality from whichever side it approaches the catalyst. One face of the carbonyl compound should thus be blocked by the presence of the aromatic ring, leading to diastereofacial discrimination.

2.2.2 Generic Ligand Structure

Compounds of generic structure **219** should be able to form complexes with α,β-unsaturated carbonyl compounds (*Figure* **44**). There are many possible permutations of metal (M), donor (Y) and the electronic nature of the ring (R) that can arise from this and related structures,

providing a family of Lewis acids whose properties could be systematically studied in Lewis acid catalysed processes.



219

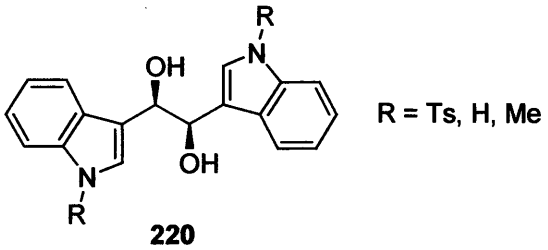
Figure **44**

Design features of these ligands worth noting include: (i) the use of electronic rather than steric interactions for the diastereofacial discrimination, which should mean that the ligand will not be substrate specific as is often the inherent problem with previously reported systems; (ii) the ability to modify the electronic nature of the aromatic ring by altering the substituent R attached to the indole nitrogen atoms; (iii) the possibility of altering the Lewis acidity of the metal M by changing the donor Y, as well as the metal M.

The novelty of this family of ligands is that the diastereofacial discrimination that is proposed relies on electronic rather than steric interactions. The main thrust was to probe into a subtle modification of the electronics of the aromatic ring (by attachment of electron withdrawing or donating groups) and investigate the effect on the strength of the proposed π–π interactions and hence the effect on selectivity observed in catalytic asymmetric transformations.

2.3 Proposed Ligand Design

Our initial target ligand was compound **220** (*Figure* **45**). Notable features are the C_2-symmetrical design that incorporates two indolyl subunits along with a diol functionality to chelate to the Lewis acidic metal.



220

Figure **45**

We proposed to synthesise this ligand with a variety of groups attached to the nitrogen atom of each indole moiety. Initially we aimed to synthesise the bis[1-(toluene-4-sulfonyl)indole]-, bis(indole)- and bis(*N*-methylindole)- diols, (**220**, R = Ts, H, Me, respectively), as this should

provide us with "electron deficient", "electron neutral" and "electron rich" aromatic systems. This subtle modification of the electronics of the aromatic ring should allow us to probe the nature of the proposed non-covalent interactions through experimental evidence, to provide valuable guidance into catalyst design and architecture.

Retrosynthetic analysis of target ligand **220** led to three feasible routes (*Figure* **46**).

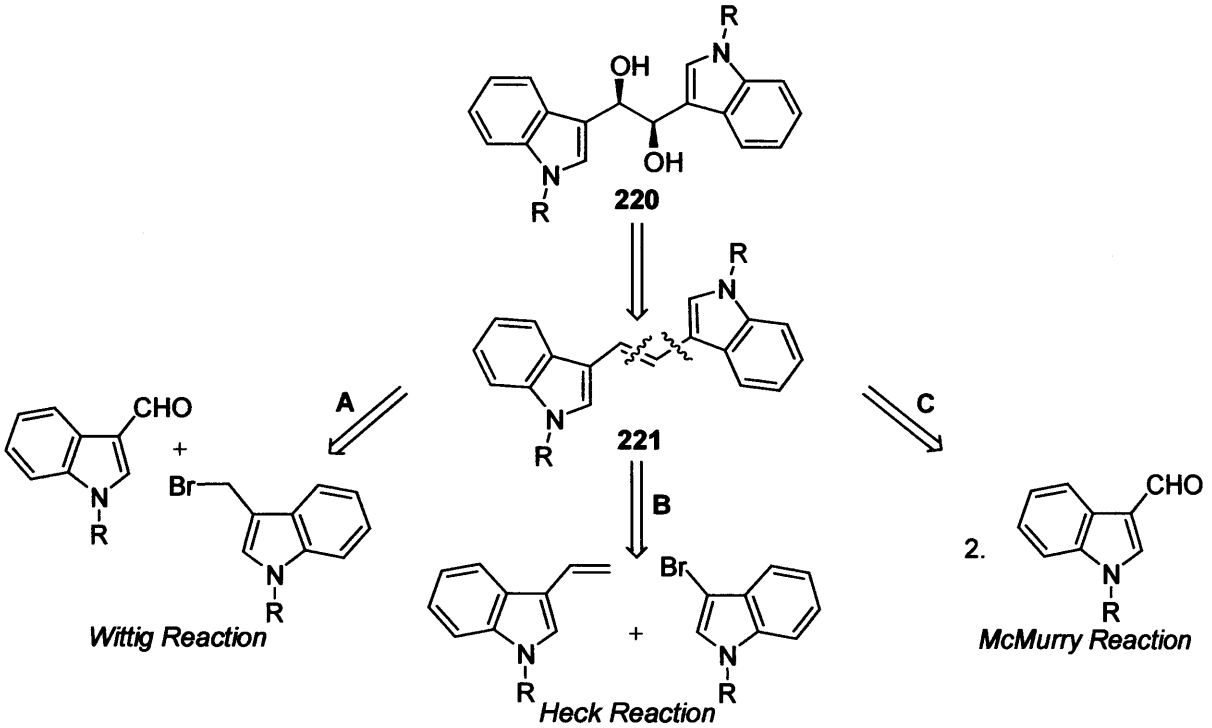
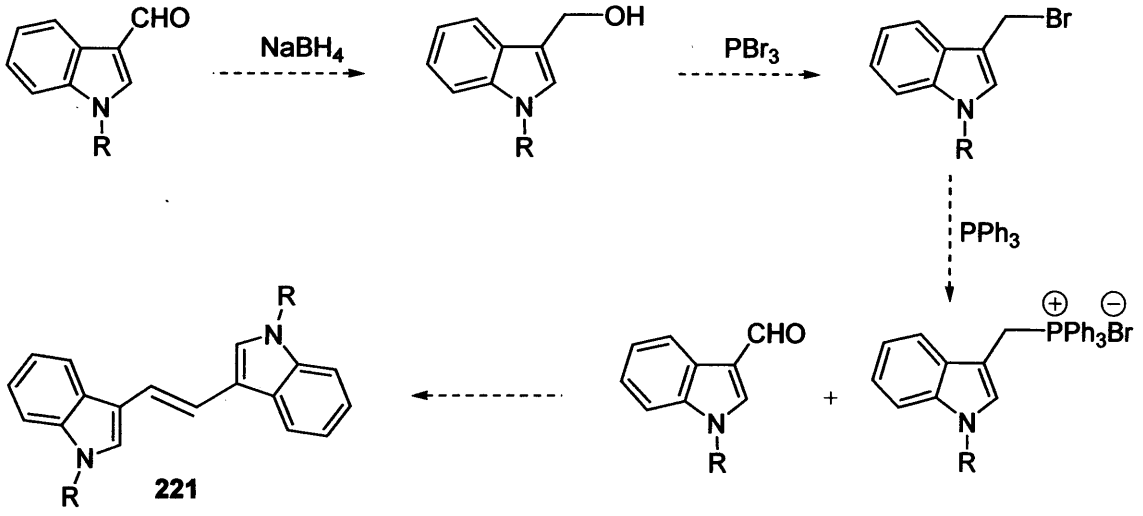


Figure **46**

2.3.1 Analysis of Route A

A general synthetic route using pathway **A** is shown in *Scheme* **105**.



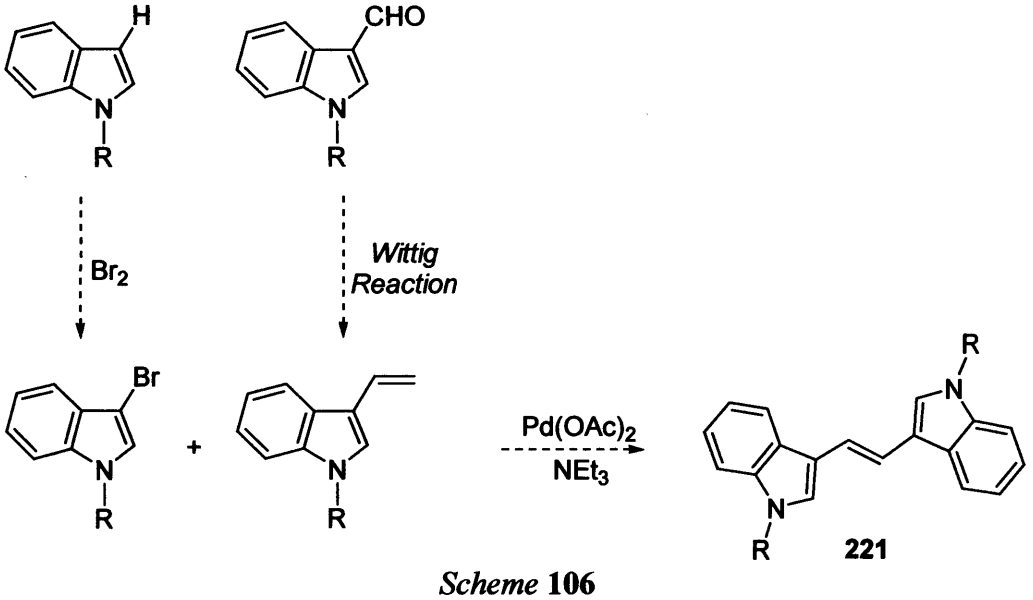
Scheme **105**

This pathway would involve the formation of an indole phosphonium salt, which could then partake in a Wittig reaction with the indole-3-carboxaldehyde. This phosphonium salt could be generated from the indole-3-carboxaldehyde, *via* reduction to the alcohol and subsequent replacement of the hydroxyl group with a bromine atom. Reaction with triphenylphosphine would then generate the required phosphonium salt. Although a three step procedure is required to form the phosphonium salt, the reactions involved have considerable literature precedent. The main drawback to this route was that the Wittig reaction often generates a mixture of *cis*- and *trans*-alkene products. The *trans*-alkene, upon dihydroxylation, should furnish the required C_2-symmetric chiral diol, whereas the *cis*-alkene would afford a *meso*-diol that could not be utilised as a ligand in asymmetric catalysis.

2.3.2 Analysis of Route B

Over recent years, palladium-catalysed cross-coupling reactions have been extensively studied.[182] The Heck reaction allows for the coupling of an alkyl, aryl or vinyl group to an alkene. This process takes place *via* a catalytic cycle involving the formation of a palladium(II) complex with the aryl, alkyl or vinyl species (*Oxidative Addition*). Addition of this complex to the alkene (*Olefin Insertion*), followed by a β-elimination, releases the substituted alkene product. The palladium(0) catalyst is regenerated by reaction with a base, such as triethylamine.

The potential for the use of a palladium-catalysed Heck coupling in the synthesis of compound **221** is illustrated in *Scheme* **106**.

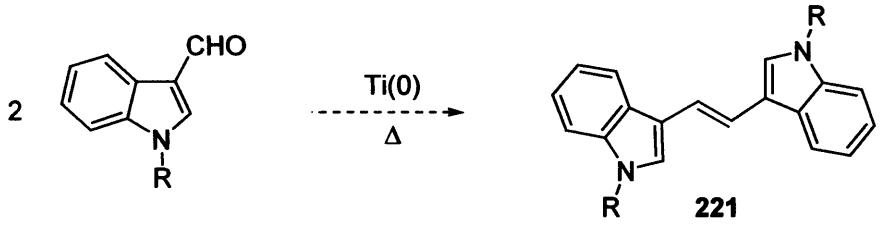


Scheme **106**

Pursuance of pathway **B** would entail the synthesis of the two indole species required for the Heck coupling reaction. There is literature precedent for the bromination of an indole in the 3-position as well as for the formation of 3-vinylindoles. Less synthetic steps are required to generate compound **221** by this route compared to route **A**, and the synthesis is also convergent, rather than linear. Disadvantages associated with this method involve the use of the palladium catalyst, including its cost, as well as possible contamination of the product by the metal and the disposal of contaminated waste.

2.3.3 Analysis of Route C

Another prospective synthesis of compound **221** involved the reductive coupling of two aldehydes (*Scheme* **107**), using the McMurry reaction,[183] (this process is also applicable for ketones). This reaction permits the reductive dimerisation of aldehydes/ketones to yield an alkene by reaction with low-valent titanium as a reducing agent.

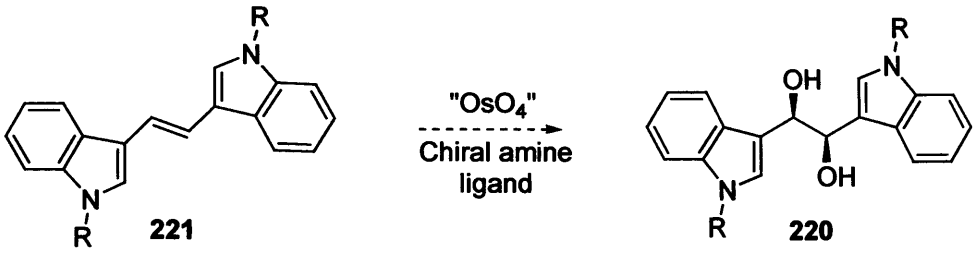


Scheme **107**

Employment of this protocol would involve the use of two equivalents of the indole-3-carboxaldehyde, with only one synthetic step required to generate compound **221**. This represents a significant advantage over routes **A** and **B**. The low-valent titanium species has to be freshly prepared *in situ* from titanium tetrachloride (or titanium trichloride), by reaction with, for example, lithium aluminium hydride, an alkali metal, magnesium or zinc. This method therefore involves the use of metal species and so has similar disadvantages to those discussed previously for the use of palladium (*Section* **2.3.2**).

2.3.4 Asymmetric Dihydroxylation

If successful, each of the above pathways (*Sections* **2.3.1 – 2.3.3**) would furnish alkene **221**. Asymmetric dihydroxylation, following the protocol of Sharpless,[36] would then be required in order to generate the target ligand **220** (*Scheme* **108**).



Scheme **108**

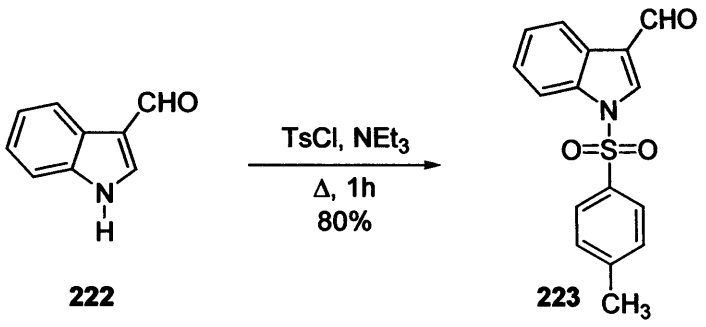
The Sharpless asymmetric dihydroxylation involves the use of a chiral amine ligand, which binds to osmium tetroxide, leading to both an enhanced rate of reaction and a selective addition to one face of the alkene. This generates diol products with high levels of enantioselectivity, for example, mono-, 1,1-di- and *trans*-disubstituted alkenes typically give diols with 90-99% ee. The best chiral amines are based on two alkaloids, dihydroquinidine (DHQD), which produces one enantiomer of the diol product, and dihydroquinine (DHQ), which gives the other. Although these amines are not enantiomers, to all intents and purposes they behave as such in the dihydroxylation reaction. Both DHQD and DHQ are obtained from natural sources and are readily available. The active catalyst used in the Sharpless asymmetric dihydroxylation (AD) is a dimer of either DHQD or DHQ joined (at the hydroxyl group of the alkaloid) by a spacer group. Two of the most common spacer groups are phthalazine (PHAL) and pyrazine (PYR).

2.4 Ligand Synthesis

Each of the protocols discussed above (*Sections* **2.3.1** – **2.3.3**) represented viable routes for the synthesis of alkene **221**, each of which had advantages and disadvantages associated with them. We decided to investigate each of these methods for the synthesis of our first ligand, an "electron deficient" diol incorporating two tosyl-protected indole moieties (**221**, R = Ts), so that the most suitable synthesis for our substrate could be determined. The "electron neutral" (**221**, R = H) and "electron rich" (**221**, R = Me) systems would then be synthesised using the optimal synthetic procedure.

2.4.1 Route A – A Wittig Approach

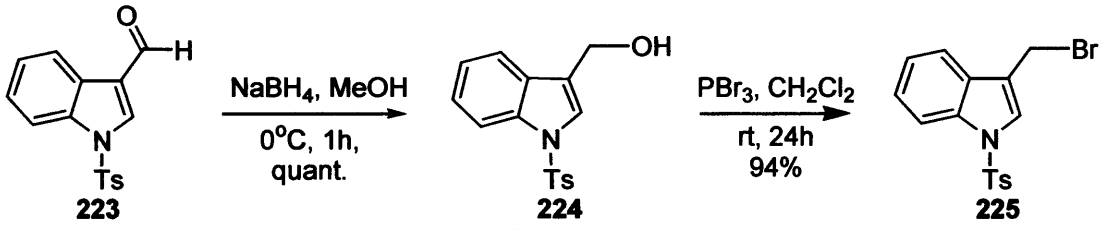
Commercially available indole-3-carboxaldehyde (**222**) was stirred in triethylamine, before addition of toluene-4-sulfonylchloride. Heating the reaction mixture at reflux for one hour gave the desired tosyl-protected indole-3-carboxaldehyde **223** (*Scheme* **109**).[184]



222 223

Scheme **109**

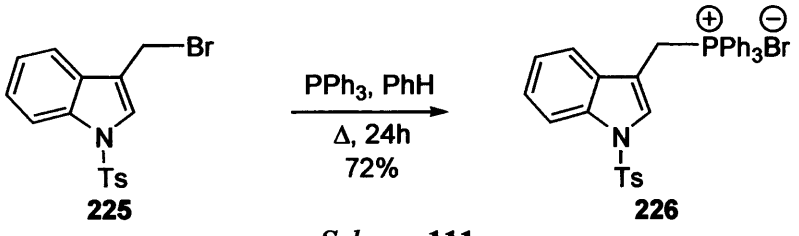
Purification by filtration through a plug of silica gave the desired product **223** in an 80% yield. Subsequent reduction of the carbonyl moiety, followed by substitution of the resulting hydroxyl group with a bromine atom gave 3-bromomethyl-1-(toluene-4-sulfonyl)-1*H*-indole (**225**). This was achieved by reacting compound **223** with one equivalent of sodium borohydride in methanol at 0°C. Treatment of the reaction mixture with 2M HCl, followed by aqueous work-up and removal of the solvent gave the alcohol **224** in a quantitative yield without the need for purification. This was reacted with phosphorus tribromide in dichloromethane for 24 hours at ambient temperature to afford the desired product **225** in 94% yield (*Scheme* **110**).



223 224 225

Scheme **110**

The indole phosphonium salt **226** was generated by reacting bromo-compound **225** with triphenylphosphine in benzene. The reaction mixture was heated to reflux for 24 hours, and after cooling to room temperature, the desired product **226** was collected by filtration. This gave an isolated yield of 72% without any purification required (*Scheme* **111**).

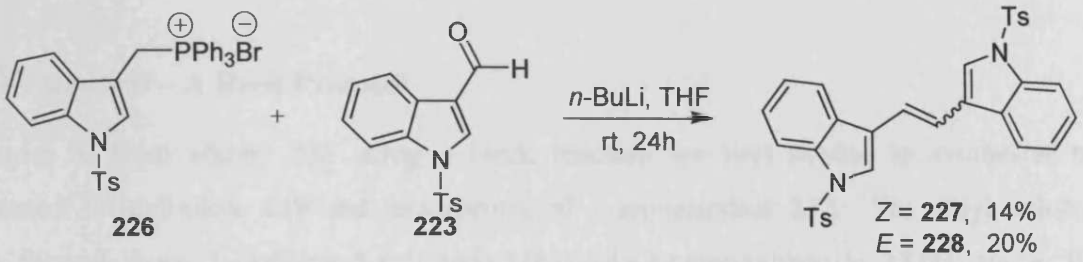


225 226

Scheme **111**

Having synthesised the phosphonium salt **226**, we were then in a position to perform a Wittig reaction. This involved the formation of a phosphonium ylide, which could be reacted with

tosyl-protected indole-3-carboxaldehyde **223** to form an alkene. This was accomplished by reacting the phosphonium salt **226** with one equivalent of *n*-butyllithium at 0°C to generate the phosphonium ylide, which was added to a solution of aldehyde **223** in tetrahydrofuran. Stirring at ambient temperature for 24 hours gave a mixture of the *cis*-alkene **227** and the desired *trans*-alkene **228** (*Scheme* **112**).



Scheme **112**

Separation and purification of the two compounds was achieved by column chromatography on silica gel. Determining which of the two compounds was the desired *trans*-alkene **228** was not straightforward. ^{1}H NMR could not be used to distinguish between the two isomers because, for each compound the two alkene protons were visible only as a singlet (integration = 2), due the fact that the compounds were symmetrical, as indeed we had designed them to be!

X-ray crystallographic analysis was therefore utilised to determine the stereochemistry (*Figure* **47**). This clearly showed that the minor product, alkene **227**, had a *cis*-configuration.

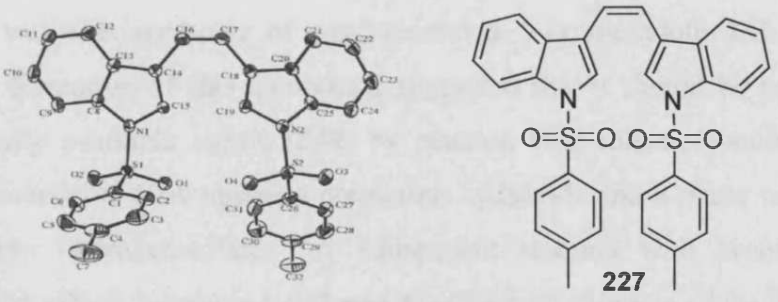


Figure **47** – X-ray structure of compound **227**

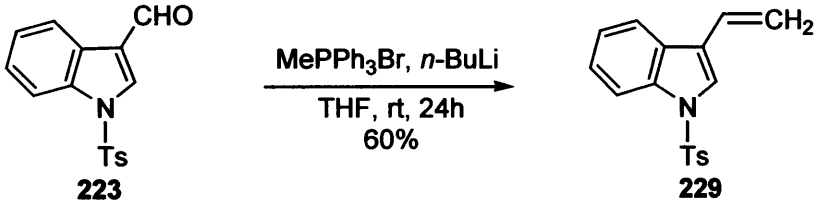
Hence, we were able to determine that the major product, compound **228**, was the desired *trans*-alkene. We had therefore successfully synthesised target alkene **228** *via* a five step procedure, with an overall yield of 11%.

Route A had enabled us to synthesise the desired C_2-symmetrical alkene **228**. *The first four steps proceeded with an overall yield of 54%, but the Wittig reaction resulted in a 60:40*

mixture of the trans- and cis-alkenes, with only a 20% isolated yield of the desired product **228**, *giving an overall yield of 11%. Further optimisation may have increased this yield, but this route was not ideal due to the formation of a mixture of products in the Wittig reaction. Consequently, we decided to investigate another possible route to the synthesis of alkene* **228**; *namely via the Heck protocol (Route* **B** – see *Section* **2.3.2**).

2.4.2 Route B – A Heck Protocol

In order to form alkene **228** using a Heck reaction we first needed to synthesise tosyl-protected 3-vinylindole **229** and tosyl-protected 3-bromoindole **232**. The vinyl indole **229** was formed from 1-(toluene-4-sulfonyl)-1*H*-indole-3-carboxaldehyde (**223**) *via* a Wittig reaction. This was achieved by treatment of methyltriphenylphosphonium bromide with *n*-butyllithium at 0°C in tetrahydrofuran to generate the corresponding phosphonium ylide. Aldehyde **223** was added dropwise and the resulting solution was stirred at ambient temperature for 24 hours (*Scheme* **113**). Compound **229** was furnished in a 60% yield after purification by flash chromatography.



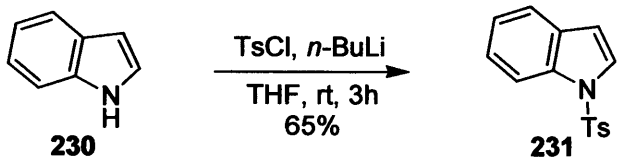
223 **229**

Scheme **113**

Our next target was the synthesis of tosyl-protected 3-bromoindole **232**. A literature procedure for the formation of this compound suggested that it should be possible to tosyl protect commercially available indole (**230**) by reaction with toluene-4-sulfonylchloride in toluene, in the presence of 50% aqueous potassium hydroxide and a phase transfer catalyst; tetrabutylammonium hydrogensulfate. A subsequent reaction with bromine in carbon tetrachloride should afford 3-bromo-1-(toluene-4-sulfonyl)-1*H*-indole (**232**).[185] In practice, we were unable to form 1-(toluene-4-sulfonyl)-1*H*-indole (**231**) using this literature procedure and after 24 hours at room temperature both starting materials remained in the reaction mixture.

We reasoned that potassium hydroxide may not be a strong enough base to carry out the deprotonation of indole (**230**). We therefore performed the tosyl-protection reaction between indole (**230**) and toluene-4-sulfonylchloride under a variety of reaction conditions. None of

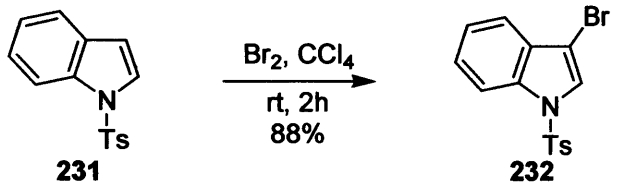
the desired product was observed when the reagents were stirred in an excess of triethylamine at ambient temperature. Heating the reaction mixture to reflux temperature afforded no improvement. After much experimentation we found that it was possible to perform this reaction by employing *n*-butyllithium as the base. This was accomplished by addition of the base into a solution of indole (**230**) in tetrahydrofuran, followed by the addition of toluene-4-sulfonylchloride. Stirring for three hours at ambient temperature, followed by trituration of the crude product with diethyl ether, furnished tosyl-protected indole **231** in a 65% isolated yield (*Scheme* **114**).



230 **231**

Scheme **114**

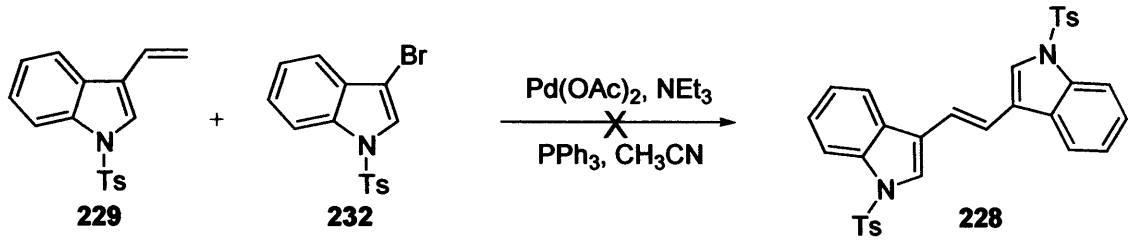
The next step was to brominate compound **231** in the 3-position, which was achieved by following the procedure reported by Widdowson *et al.*[185] Bromine was added dropwise into a solution of tosyl-protected indole **231** in carbon tetrachloride and the resulting mixture was stirred for 2 hours. Quenching with saturated aqueous sodium bicarbonate solution, followed by an aqueous work-up afforded the crude product, which was recrystallised from absolute ethanol to give the desired brominated indole **232** in an 88% yield (*Scheme* **115**).



231 **232**

Scheme **115**

We were then in a position to carry out a Heck cross-coupling reaction between tosyl-protected 3-vinylindole **229** and tosyl-protected 3-bromoindole **232** (*Scheme* **116**). We employed palladium(II) acetate as the catalyst in the presence of triethylamine. A phosphine donor, triphenylphosphine, was also utilised as it has been suggested that this aids the formation of the active palladium(0) species.[186]



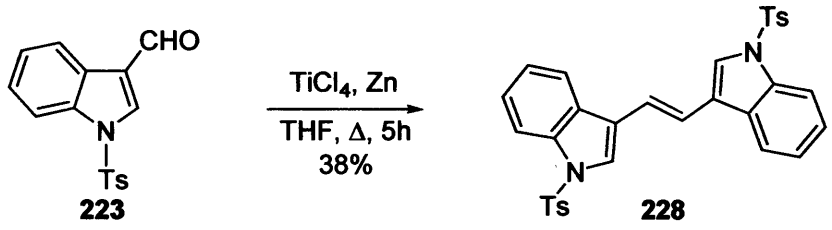
Scheme **116**

None of the desired product was observed when this reaction was carried out at ambient temperature and an increase to 50°C offered no improvement. Performing the reaction in the presence of a more bulky phosphine donor ligand, tri(*tert*-butyl)phosphine, also gave none of the desired product.

Further attempts to synthesise alkene **228** using a palladium-catalysed Heck coupling reaction were abandoned as investigations using a McMurry reaction (Route **C** – see *Section* **2.3.3**) had proved more successful.

2.4.3 Route C – The McMurry Route

To synthesise alkene **228** using a McMurry reaction we needed to react two equivalents of tosyl-protected indole-3-carboxaldehyde **223** in the presence of low valent titanium. This was prepared from titanium tetrachloride using zinc as a reducing agent, and the mixture was heated to reflux in tetrahydrofuran before addition of aldehyde **223**.[187] Stirring at this temperature for a further five hours afforded the desired *trans*-alkene **228** (*Scheme* **117**).



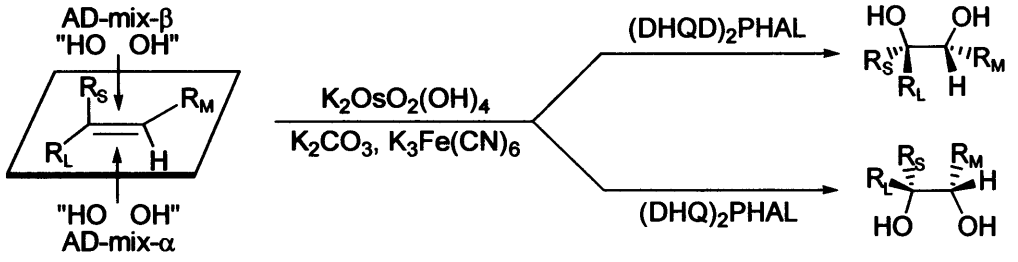
Scheme **117**

Purification by column chromatography gave a 38% isolated yield of 1,2-bis-(1-(toluene-4-sulfonyl)-1*H*-indol-3-yl)ethene (**228**), with the *trans*-isomer formed exclusively.

The McMurry protocol thus provided the desired trans-alkene **228** *in two synthetic steps from commercially available indole-3-carboxaldehyde* **222** *in a 30% overall yield. This was a significant improvement compared to the synthesis via a Wittig reaction (11% over 5 steps –*

see Section **2.4.1***). This method proved both convenient and reliable, allowing access to gram quantities of alkene* **228**.

Introduction of asymmetry into the system was achieved using a Sharpless asymmetric dihydroxylation.[36] Enantioselective alkene dihydroxylation constitutes an appealing strategy for the synthesis of optically active organic compounds. The oxidising agent, osmium tetroxide, can be formed *in situ* from potassium osmate dihydrate, potassium carbonate and potassium ferricyanide. A premix of these three reagents, along with the chiral amine ligand is commercially available. The composition containing $(DHQD)_2PHAL$ is termed the AD-mix-β, while the mixture containing $(DHQ)_2PHAL$ is called the AD-mix-α (*Figure* **48**). Methanesulfonamide may also used in this reaction as an aid for the hydrolysis of the intermediate osmate esters, accelerating the progress of the reaction.



(R_L = largest substituent; R_M = medium-sized substituent; R_S = smallest substituent).

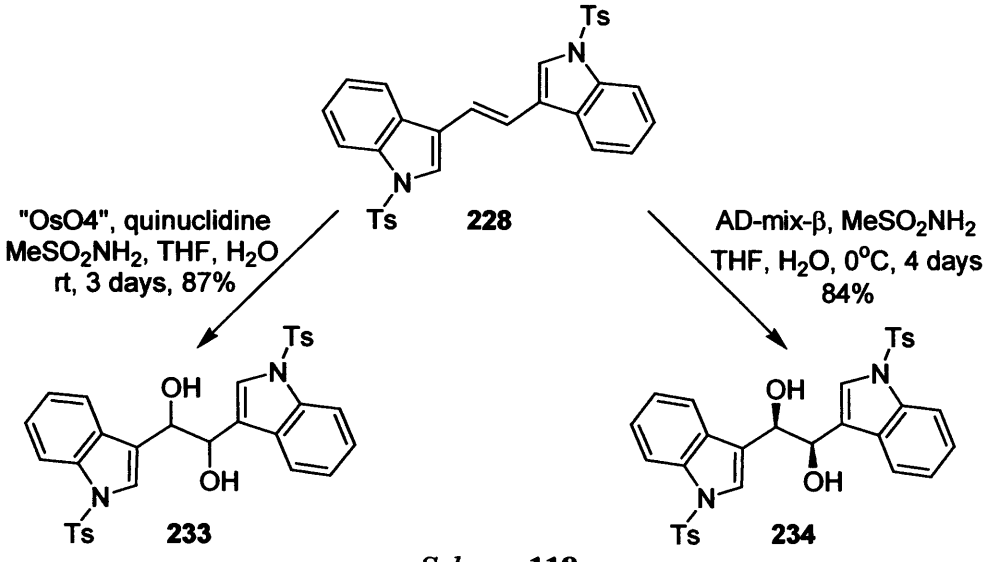
Figure **48**

When bound to the $(DHQD)_2PHAL$ chiral amine ligand, osmium tetroxide is postulated to approach the alkene from the top face, leading to a chiral diol product. The amine ligand enhances the rate of the oxidation reaction, which means that the background reaction of unbound osmium tetroxide (which would lead to a racemic product) is not competitive with the enantioselective process.

In the standard Sharpless procedure a two-phase solvent system of *t*-butanol and water are used.[36] But when these conditions were applied to the dihydroxylation of alkene **228** it was found that no reaction occurred. We determined that alkene **228** was insoluble in this solvent system, so the reaction was carried out again using tetrahydrofuran and water, a solvent system that alkene **228** does dissolve in!

Treatment of a solution of **228** in tetrahydrofuran/water (1:1) at 0°C with the AD-mix-β and methanesulfonamide, followed by stirring at 0°C for four days gave the corresponding diol **234** in 84% yield. This synthesis was also carried out to generate a sample of the racemic diol

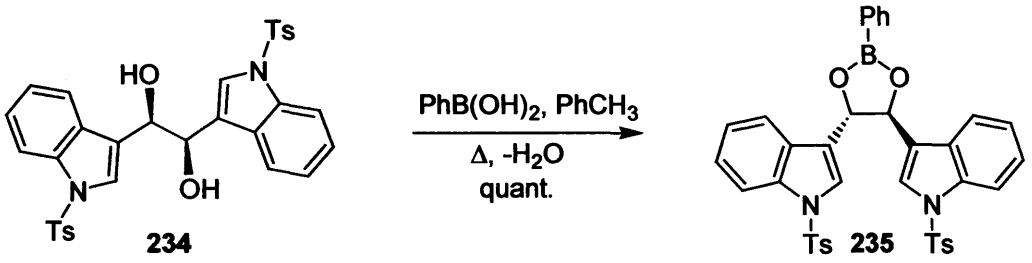
233 using quinuclidine,[188] a non-chiral amine ligand, enabling the determination of the enantiomeric excess of diol **234** (*Scheme* **118**). This was achieved by chiral HPLC analysis using a Chiralpak AD column (See *Chapter* **5**, pages 212-213 and *Appendix* **A1**, page 265 for details). Analysis of diol **234** showed an enantiopurity of >97%, which was confirmed by performing ^{1}H NMR titrations with a europium chiral shift reagent, Eu(hfc)$_3$ (See *Chapter* **5**, page 214 and *Appendix* **A2**, pages 266-268 for details).



Scheme **118**

We had therefore successfully synthesised our first target ligand with an electron-withdrawing tosyl group attached to each of the indole nitrogen atoms. This was achieved *via* a three-step protocol involving a tosyl-protection, a McMurry reaction and a Sharpless asymmetric dihydroxylation. This generated chiral diol **234** in a 26% overall yield with >97% ee. The absolute stereochemistry of the asymmetric centre of **234** was assumed to be *S,S* in accordance with the proposed addition of osmium tetroxide to the top face of the alkene when chiral ligand (DHQD)$_2$PHAL is utilised.[36]

As the ultimate aim of this project was to use diol **234** as a ligand in a Lewis acid catalysed process, we decided to investigate the complexation of **234** to a Lewis acid. This was achieved by the addition of one equivalent of phenyl boronic acid to a solution of **234** in toluene, with azeotropic removal of water (*Scheme* **119**).



Scheme **119**

The formation of boronate ester **235** demonstrated the ability of ligand **234** to bind to a Lewis acid, enabling us to move on to examine the utility of ligand **234** in Lewis acid catalysed processes.

In summary, we had developed a short synthesis (3 steps) to target diol **234** *starting from commercially available indole-3-carboxaldehyde* **222**, *in 26% overall yield. The enantiopurity of* **234** *was determined using chiral HPLC, which showed this to be >97%. Complexation of the diol to phenyl boronic acid occurred readily, to produce the boronate ester* **235**, *suggesting that this ligand could be used in Lewis acid catalysed processes.*

2.5 Asymmetric Catalysis

Attainment of ligand **234** allowed us to begin an investigation into its use in Lewis acid catalysed processes. Although we desired our catalysts to be versatile in respect to both the type of asymmetric carbon-carbon bond forming reaction and the choice of α,β-unsaturated carbonyl substrate, exploiting both of these variables could create complexity and complicate the answering of fundamental questions.

It was decided to commence the catalytic investigations by probing into just one type of asymmetric C-C bond forming reaction. The selection of a suitable reaction was rather straightforward. We chose the Diels-Alder reaction due to the vast literature precedent and the synthetic importance of this powerful [4+2] cycloaddition reaction. This would be a fantastic area for us to test our hypotheses and ascertain any rationale in the nature of the proposed π–π interactions, without the need to compete with the excellent Diels-Alder catalysts that already exist.

2.5.1 The Diels-Alder Reaction

The Diels-Alder reaction is one of the most compelling methods of C-C bond construction in synthetic organic chemistry,[59] enabling in one step, the rapid preparation of cyclic compounds containing a six-membered cyclohexene ring. Almost eighty years after its discovery in 1928,[60] organic chemists still utilise and continue to develop this elegant tool. Contemporary advances include intramolecular [4+2] cycloadditions, hetero-Diels-Alder reactions and pressure- or Lewis acid-accelerated reactions.[189] Its application not only leads to a strong increase in molecular complexity (molecular size, topology, stereochemistry, functionality and appendages), but also can result in structures that lend themselves to additional amplification of complexity by the use of other powerful synthetic reactions on the cyclic products.[190]

It is pertinent to mention that the Diels-Alder reaction can be classified into one of three types of [π2s + π4s] cycloaddition reactions: (i) the normal HOMO diene-controlled reaction using an electron rich diene and an electron deficient dienophile; (ii) the neutral Diels-Alder reaction; and (iii) the inverse demand or LUMO diene-controlled counterpart.[189] If a concerted reaction is assumed, both a *cis*-addition (suprafacial mode) and a preferred *endo* orientation can be expected, except for the use of α,β-unsaturated aldehydes with an α-substituent, which consistently give an *exo*-adduct.[191]

Since the Diels-Alder reaction creates a molecule with up to four contiguous stereogenic centres, control of absolute stereochemistry and regiochemistry is particularly attractive. There are three basic strategies for the enantioselective control of the desired product in these cycloadditions: the use of a chirally modified diene, a chirally modified dienophile or a chiral catalyst.[61] An enantioselective Diels-Alder catalyst can incorporate a chiral Lewis Acid-carbonyl complex, which serves to not only lower the LUMO energy of the carbonyl substrate (*Figure* **49**), but also provides a chiral environment that engenders facial selectivity.

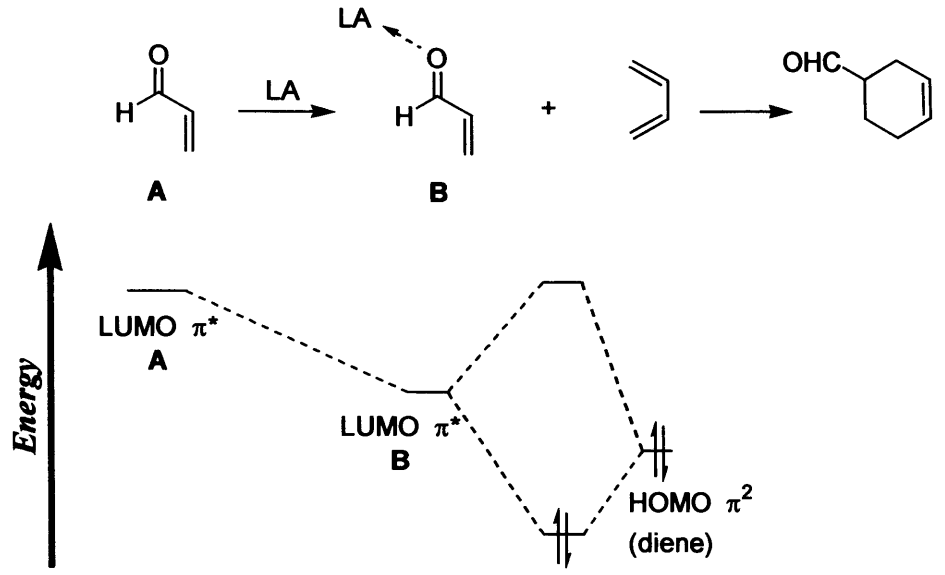
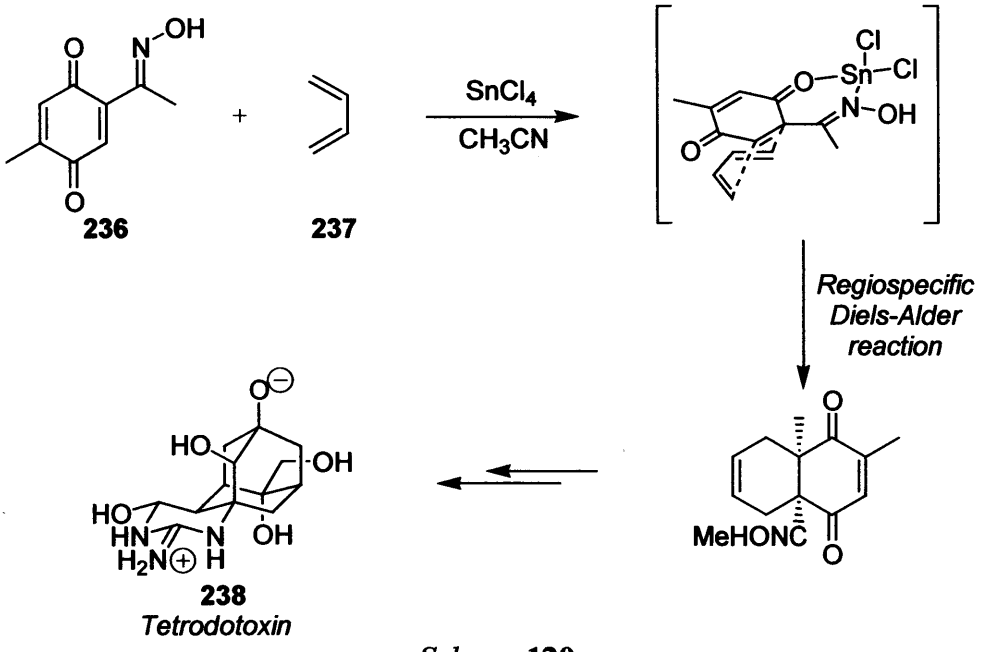


Figure **49**

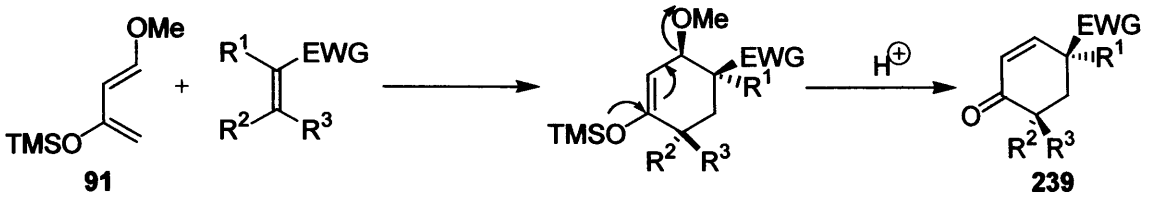
Regiocontrol by the exploitation of Lewis acids has been widely reported in the literature, with an early example provided by the total synthesis of tetrodotoxin (**238**), where Kishi and co-workers[192] showed that the use of tin tetrachloride was essential for the chemoselective engagement of butadiene (**237**) with the oxime-bound dienophile **236** (*Scheme* **120**).



Scheme **120**

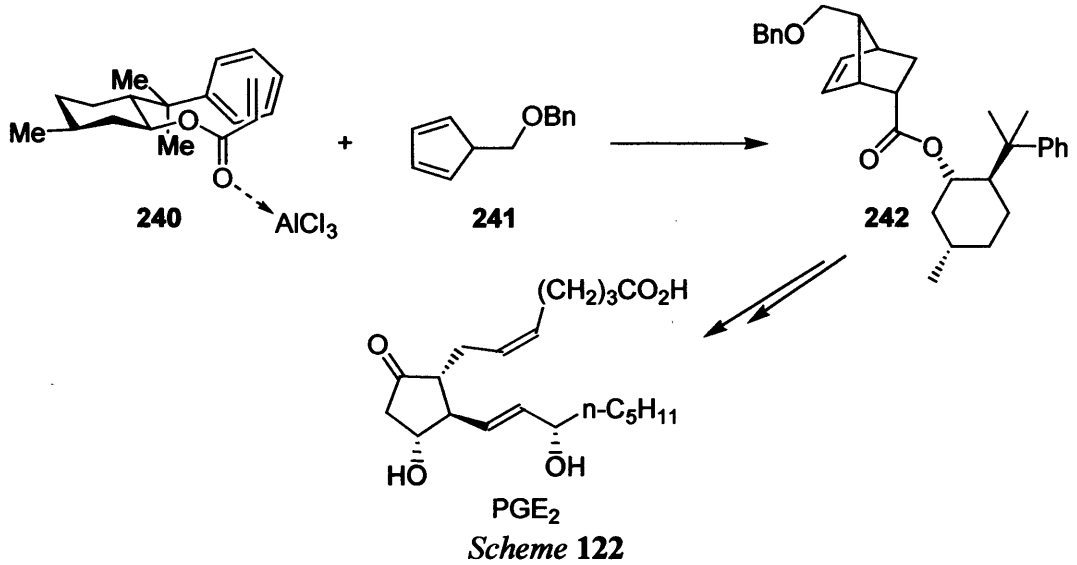
Danishefsky's widely applicable diene system,[193] is another example of a method that introduces excellent regioselectivity in the Diels-Alder cycloaddition. The power of the diene **91** rests in the synergistic effects of the two incorporated oxygen groups, which provide mutually reinforcing electronic contributions to the diene system such that regiospecific

formation of a lone *endo*-adduct **239** results upon reaction with most dienophiles (*Scheme* **121**).



Scheme **121**

It wasn't until the 1970's that the first highly stereoselective version of the Diels-Alder reaction was reported by Corey and co-workers.[62] An enantioselective synthesis of biologically important prostaglandins was achieved utilising, in one of the key transformations, the dextrorotatory acrylate ester of 8-phenyl menthol **240** as a chiral ketene equivalent. This was used in an aluminium trichloride catalysed Diels-Alder reaction with the achiral diene **241** (*Scheme* **122**).[194] The *endo*-adduct **242** was formed with commendable yield and 97:3 diastereoselectivity, which may be rationalised by the preference of the carbonyl and vinyl subunits of the acrylate to adopt an s-*trans* conformation owing to strong steric repulsions which discourage the adoption of the s-*cis* form. Additionally, the phenyl ring of the 8-phenyl menthol chiral auxiliary served to π-shield the rear face of the substrate, forcing the diene to add preferentially to the top face.



Scheme **122**

Since this first stereoselective Diels-Alder reaction there have been many impressive chiral auxiliaries and catalysts designed to investigate the scope and limitations of asymmetric [4+2] cycloadditions. Some examples include Evans' oxazolidinone chiral auxiliary **243**,[195] Corey's chiral diazaaluminolidine **244**,[196] and oxazaborolidine based catalysts **217**,[171b] Yamamoto's

chiral acyloxy borane catalysts **245**,[170] Hawkins' aromatic alkyldichloroborane systems **246**,[172b] Wulff's aluminium/biaryl complex catalysts **247**,[197] and MacMillan's chiral amine ligand **69**[7] (*Figure* **50**). (See *Section* **2.1.2** for a more detailed discussion of some of these systems).

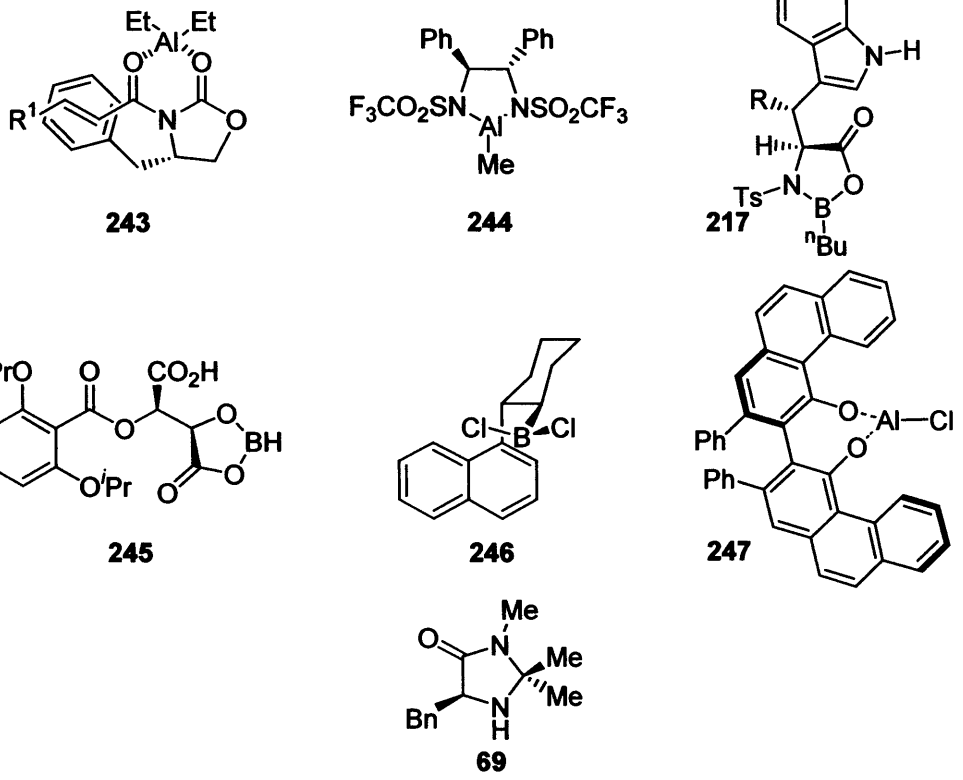
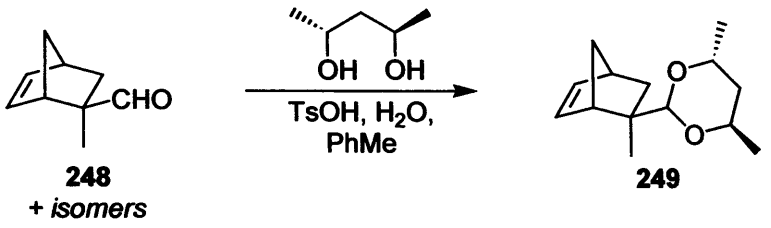


Figure **50**

The extensive investigations into developing the scope of the Diels-Alder reaction and improving the stereoselectivities of the adducts formed are catalogued in various reviews.[63,190] The broad knowledge of this powerful reaction, gained over the last eighty years, is an eloquent testimony to the investigative skills and intellectual prowess of many synthetic chemists.

2.5.2 Analysis of the Diels-Alder Products

There are several methods available for the determination of the enantiomeric excess of both the *endo*- and *exo*-isomers of the Diels-Alder adducts **248** between, for example, methacrolein (**252**) and cyclopentadiene (**66**). These methods include direct determination of the ee using ^{1}H NMR techniques in the presence of the chiral shift reagent europium *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate],[198] or the indirect ee determination *via* the formation of diastereomeric acetals **249**, followed by GC analysis (*Scheme* **123**).[191c]

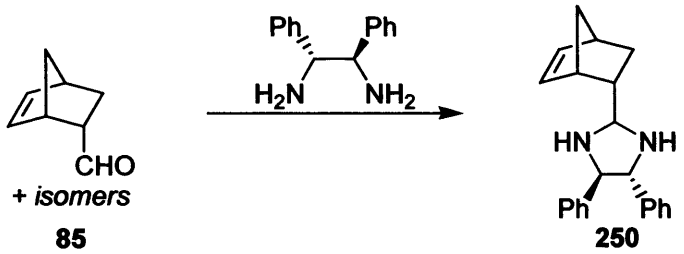


248
+ isomers

249

Scheme **123**

The above methods both require a stoichiometric amount of either the external chiral ligand or the chiral reagent, which proves to be expensive. These methods are also time/labour intensive, requiring aqueous work-ups and purification by column chromatography. Another option for the determination of optical purity was *via* formation of the corresponding aminals **250** with (*R,R*)-1,2-diphenylethylene diamine, followed by ^{13}C NMR analysis, as reported by Alexakis (*Scheme* **124**).[199] But the cost of the diamine and the NMR machine time required led us to disregard this idea.



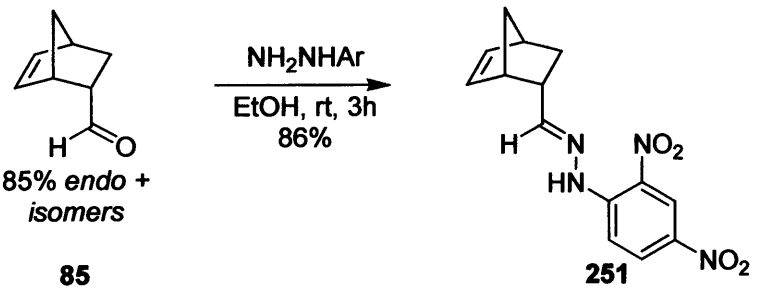
+ isomers

85

250

Scheme **124**

An alternative derivatisation method for the Diels-Alder adducts, derived from cyclopentadiene (**66**) and a series of electron deficient dienophiles, is by HPLC analysis of their 2,4-dinitrophenylhydrazones. Recent work within our research laboratory showed that racemic adduct **85** (85% *endo*-diastereoisomer), formed from acrolein (**76**) and cyclopentadiene (**66**), can be converted into a suitable candidate for HPLC analysis, **251**, by treatment with a slight excess of 2,4-dinitrophenylhydrazine in an ethanolic solution (*Scheme* **125**). After stirring at room temperature for three hours, the orange solution is subjected to an aqueous work-up and filtered through silica.[200]



85% endo + isomers

85

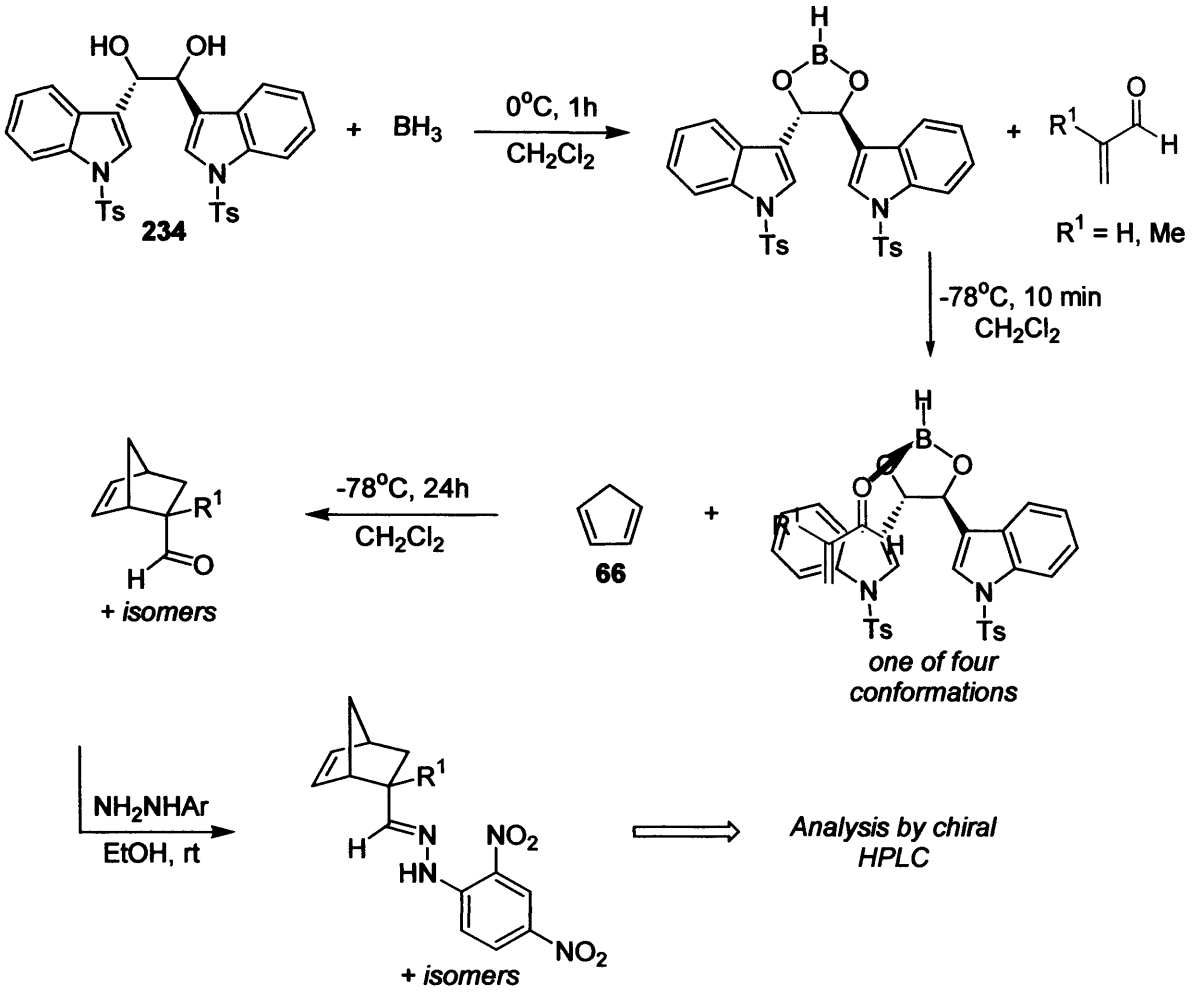
251

Scheme **125**

Direct analysis of the reaction mixture provided both the *endo/exo* ratio and the enantiomeric excess for Diels-Alder adduct **251** using chiral HPLC (see *Chapter* **5**, pages 216-218 and *Appendix* **A3**, pages 269-270 for details). Moreover, this method can be used to determine the enantiopurity of adducts arising from the cycloaddition between cyclopentadiene (**66**) and acrolein (**76**), bromoacrolein, methacrolein (**252**) or methyl vinyl ketone (**63**), thus constituting an efficient, cheap and reliable method for ee determination.[201]

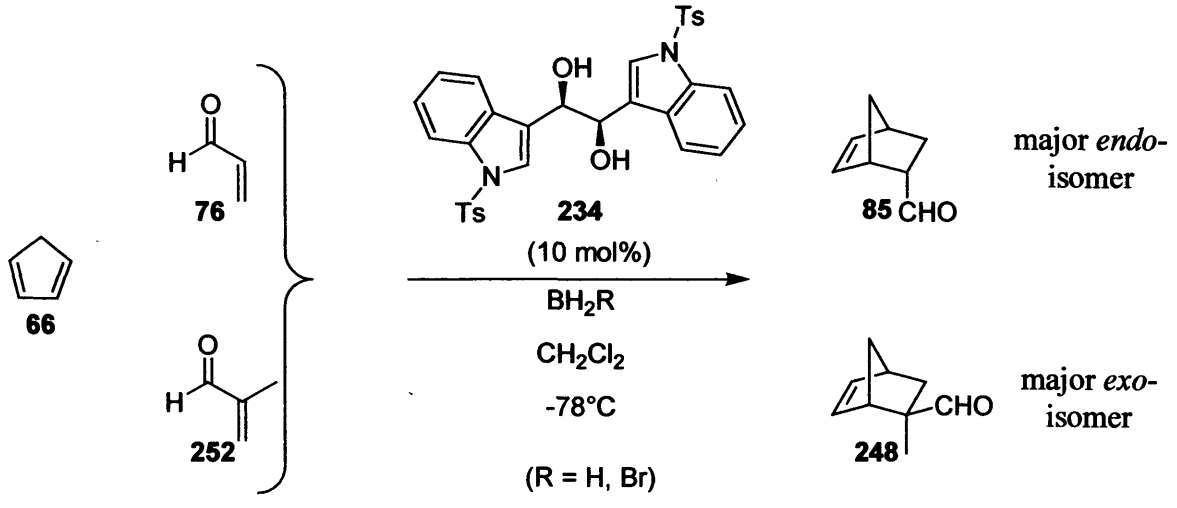
2.5.3 Catalysis – Initial Investigations

We were now able to embark upon an investigation into the use of ligand **234** in the Lewis acid catalysed Diels-Alder reaction. Mimicking the conditions reported in the modern literature,[172a,202] 10 mol% of ligand **234** was stirred in anhydrous dichloromethane at 0°C under an inert atmosphere, and one equivalent of the Lewis acid (a 1.0 molar solution in tetrahydrofuran) was added (*Scheme* **126**). After stirring for one hour at this temperature, it was assumed that complexation had occurred and the reaction temperature was lowered to -78°C, followed by addition of the dienophile and cyclopentadiene (**66**) (cracked from dicyclopentadiene immediately prior to the addition). After stirring overnight at -78°C, the reaction mixture was quenched by the addition of ethanol, and treated with 2,4-dinitrophenylhydrazine. The crude reaction mixture was analysed by ^{1}H NMR to gain a representative diastereomeric ratio, followed by purification by column chromatography. The purified material was again analysed by ^{1}H NMR and weighed for an accurate yield measurement, followed by chiral HPLC analysis to determine any asymmetric induction observed.



Scheme **126**

Each of the dienophiles were subjected, in duplicate, to these conditions (*Scheme* **127**).



Scheme **127**

The results of this initial study are tabulated below (*Table* **1**).

Table 1[a]: **Results of Initial Diels-Alder Cycloaddition Experiments**

Entry	Dienophile	Lewis acid	Isolated Yield (%)	*Endo* / *Exo*	Enantiomeric Excess (% ee)
1	**76**	BH_3	92	86 : 14	0.5
2	**76**	BH_2Br	49	88 : 12	2.0
3	**252**	BH_3	68	10 : 90	11.6
4	**252**	BH_2Br	72	7 : 93	12.2

(a) All Diels-Alder reactions were carried out in duplicate and values quoted in the table are an average of the results. Ligand **234** (10 mol%), with either BH_3.THF or $BH_2Br.SMe_2$, was used as the catalytic system with dichloromethane as the reaction solvent. The reactions were carried out at -78°C for 24 hours. All enantiomeric excesses were determined by HPLC analysis of the purified material, diastereomeric ratios were obtained from the ^1H NMR of the pure adduct and yields were determined by weight of isolated product.

The preliminary findings were slightly disappointing since the enantiomeric excesses were not competitive, but we had established a solid starting point upon which to build. The low enantiomeric excesses established for the adducts formed from the cycloaddition between cyclopentadiene (**66**) and acrolein (**85**) (*entries* **1** and **2**) were unsurprising as this substrate is generally avoided in the literature! Slight asymmetric inductions were observed in products of the cycloaddition between cyclopentadiene (**66**) and methacrolein (**252**) (*entry* **3**; 12% ee). Bromoborane was found to be slightly more effective than borane in terms of both yield and enantioselectivity (*entries* **3** and **4**).

We went on to probe into the effect the metal of the Lewis acid had on the selectivities of the Diels-Alder adduct formed. Having already utilised boron-based Lewis acids (*Table* **1**), we went on to employ two aluminium-based Lewis acids; diethylaluminium chloride and dimethylaluminium chloride. Once again the Diels-Alder reaction was performed between cyclopentadiene (**66**) and either acrolein (**85**) or methacrolein (**252**). The results are tabulated below (*Table* **2**).

Table 2[a]: **Results of the Study Using Aluminium-Based Lewis Acids**

Entry	Dienophile	Lewis acid	Isolated Yield (%)	*Endo* / *Exo*	Enantiomeric Excess (% ee)
1	**76**	Me_2AlCl	32	85 : 15	0.7
2	**76**	Et_2AlCl	78	90 : 10	2.7
3	**252**	Me_2AlCl	14	9 : 91	3.3
4	**252**	Et_2AlCl	18	11 : 89	10.3

(a) All Diels-Alder reactions were carried out in duplicate and values quoted in the table are an average of the results. Ligand **234** (10 mol%), with either Et_2AlCl or Me_2AlCl, was used as the catalytic system with dichloromethane as the reaction solvent. The reactions were carried out at -78°C for 24 hours. All enantiomeric excesses were determined by HPLC analysis of the purified material, diastereomeric ratios were obtained from the ^1H NMR of the pure adduct and yields were determined by weight of isolated product.

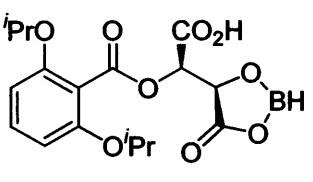
Once again, low enantiomeric excesses were observed for the use of acrolein (**76**) as the dienophile (*entries* **1** and **2**). For the use of methacrolein (**252**), we were able to deduce that diethylaluminium chloride is more effective than dimethylaluminium chloride (*entries* **3** and **4**) in terms of both yield and the enantioselectivity of the Diels-Alder adduct formed.

If we compare the results of *Table* **1** and *Table* **2**, we can see that both boron- and aluminium-based Lewis acids gave the Diels-Alder adduct with very low enantioselectivity when using acrolein (**76**). For this substrate the best result was achieved with diethylaluminium chloride (*Table* **2**, *entry* **2**; 78% yield, 2.7% ee). Similar levels of enantiocontrol resulted for the adduct formed from methacrolein (**252**) when employing borane, bromoborane or diethylaluminium chloride. In terms of both yield and enantioselectivity, the best result was achieved with bromoborane (*Table* **1**, *entry* **4**; 72% yield, 12.2 % ee).

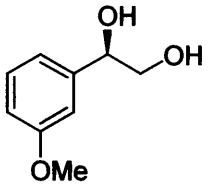
We had therefore established that diol **234** *can be used as a ligand in the Lewis acid catalysed Diels-Alder reaction. Small enantioselectivities were observed for the cycloaddition reactions between cyclopentadiene (***66***) and methacrolein (***252***), giving us hope that electronic modifications to our ligand structure would lead to improved enantiocontrol.*

2.5.4 A Possible Model For Complexation

The HPLC peaks corresponding to the (*S*)- and (*R*)- *exo*-Diels-Alder adducts **248**, resulting from the cycloaddition between cyclopentadiene (**66**) and methacrolein (**252**), were determined within our research laboratory.[200b] The peaks were correlated with the known absolute configurations of these adducts from the Diels-Alder reactions catalysed by tartaric acid derivative **245**,[174a] and the styrene derivative **218**,[181] reported by Yamamoto and Jones respectively (*Figure* **51**).



245

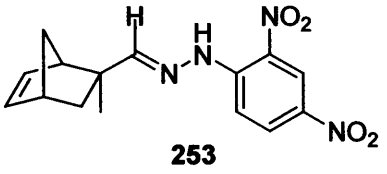


218

Figure **51**

Ligands **245** and **218** were utilised in the Diels-Alder cycloaddition of cyclopentadiene (**66**) and methacrolein (**252**), under the catalytic conditions reported in the corresponding publications. This was followed by direct addition of 2,4-dinitrophenylhydrazine to the reaction mixture. In each case, it was established that the HPLC peak at 104.5 minutes corresponded to the (*R*)-isomer, and the peak at 113.2 minutes related to the (*S*)-isomer, of *exo*-Diels-Alder adduct **248**. Each of the catalytic reactions gave identical selectivities to those reported, proving that there was no compromise to the stereoselectivities of the original Diels-Alder adducts during the formation of the 2,4-dinitrophenylhydrazine derivatives.

Armed with this information, we could be confident in stating that during the catalysis of the cycloaddition between methacrolein (**252**) and cyclopentadiene (**66**), catalysed by ligand **234** and a Lewis acid, the corresponding adduct **248** was formed with up to 12% ee with the *exo*-(*S*)-isomer preferentially formed (*Figure* **52**).

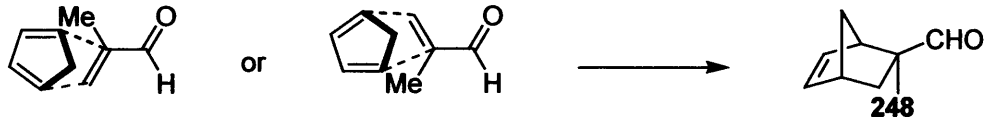


253

Figure **52**

Conformation of the absolute configuration of the major isomer formed enabled the postulation of a working model to explain how the diastereoselective complexation of methacrolein (**252**) within our catalytic system occurred.

It was decided that to form an excess of the (*S*)-Diels-Alder adduct **248**, cyclopentadiene (**66**) must have preferentially reacted with the *si*-face of methacrolein (**252**) (*Scheme* **128**).



248

Addition of **66** to *si* face of **252** in *s-trans* conformation

Addition of **66** to *si* face of **252** in *s-cis* conformation

exo-(*S*)-enantiomer formed

Scheme **128**

To correlate this information with the possible transition states proposed for the complexes formed between ligand **234** and methacrolein (**252**), the following structures needed to be considered (*Figure* **53**).

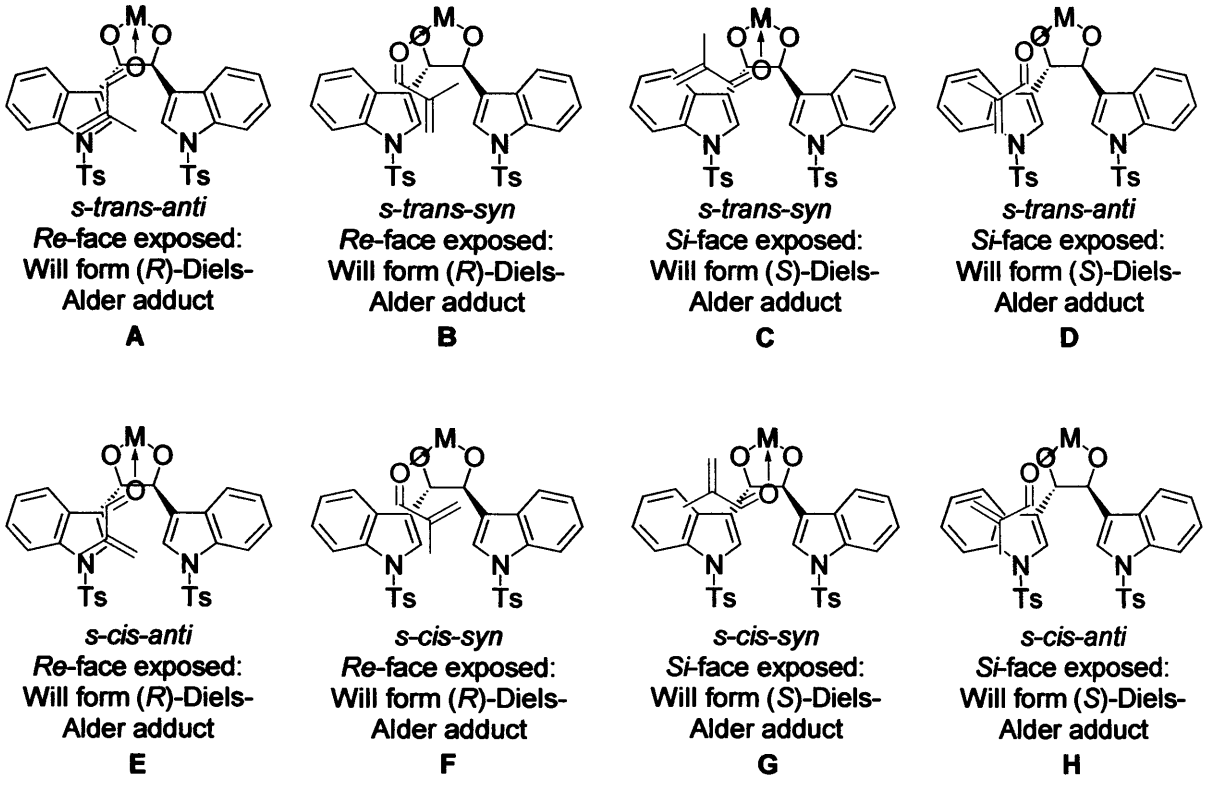
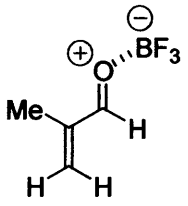


Figure **53**

From the diagrams shown above (*Figure* **53**), it is evident that certain conformations may be disfavoured owing to steric effects; namely **A**, **B**, **C**, **E**, **F** and **G**, thus leaving conformations **D** and **H** as the possible reactive conformations for methacrolein (**152**) complexed to diol **234**.

It is generally accepted that complexation of an α,β-unsaturated carbonyl compound to a Lewis acid dramatically stabilizes the *s-trans* conformation relative to the *s-cis*, by either electronic or steric effects.[203,204] Indeed, Corey and co-workers isolated a 1:1 crystalline complex of BF_3 and methacrolein (**252**), and from the ^1H NMR data and nOe studies, it was apparent that even in solution, the *s-trans* structure of the complex predominated (*Figure* **54**).[205]



s-trans-anti
Figure **54**

In view of this information, it is plausible to suggest that a suitable model for the complexation of methacrolein (**252**) with ligand **234** would be diagram **D** (c.f. *Figure* **53**),

where methacrolein (**252**) adopts an *s-trans-anti* conformation, which would lead to the observed (*S*)-enantiomer of the Diels-Alder product **248**. This model is consistent with our original proposal that π-stacking could occur between the C=C of the substrate and the aromatic ring incorporated into the structure of the ligand (*Figure* **55**).

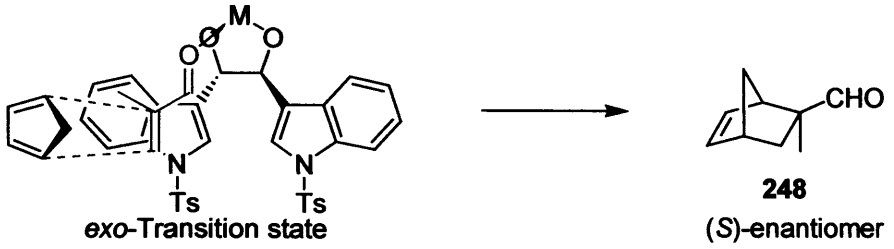


Figure **55**

However, the fact that ligand **234** affords only low enantiomeric excesses of Diels-Alder adduct **248**, suggests that other transition states also exist and elimination of this problem needs careful consideration. It is also of great importance to appreciate that the thermodynamically favoured ground state geometry of a complex may not be the same as the reactive geometry (c.f. the Curtin-Hammett principal).[206]

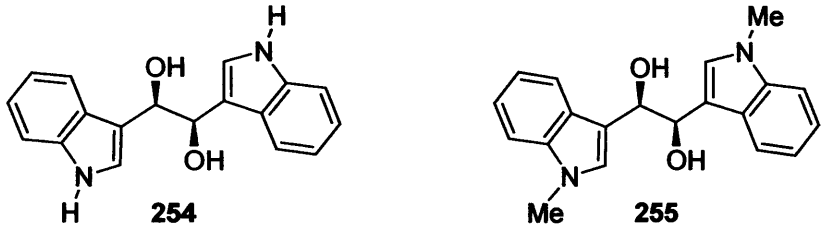
We had therefore determined a suitable model for the complexation of methacrolein (**252**) *to diol* **234**, *which readily explained the stereoselectivities observed in a Diels-Alder cycloaddition reaction with cyclopentadiene* (**66**). *This model was consistent with the proposal that π-stacking could occur between the C=C of the substrate and the aromatic ring incorporated into the structure of the ligand.*

Our next goal was to investigate the nature of the proposed π–π interactions. Diol **234** incorporates two indole moieties with an electron-withdrawing tosyl group attached to each of the nitrogen atoms. If ligand **234** does indeed interact with the dienophile *via* the proposed π–π interactions, then we would expect the enantioselectivities observed in the Lewis acid catalysed Diels-Alder reaction to increase as the electron density of the indole subunits is increased. Therefore the bis(indole) and bis(*N*-methylindole) analogues of diol **234** may lead to higher observed enantiomeric excesses. As such we considered it necessary at this stage to synthesise these analogues, so as to allow us to both probe the proposed π–π interactions, and to hopefully lead to higher levels of enantiocontrol in the Diels-Alder reaction!

2.6 Investigation into the Modulation of Electronics

There has to date, been the lack of a rigorous study into the nature of face-face π–π interactions of enones with aromatic systems. Hunter states that the magnitude of the interaction is the sum of the π-electron repulsions (interaction between the net charges on the atoms) and the interactions between the net charges and the π-electrons.[207] It could be expected that for the desired interaction to arise, an electron rich aromatic ring would be necessary to bring about the maximum interaction with an electron deficient unsaturated carbonyl compound. The aim was to delve deeper into this concept and probe the nature of these non-covalent interactions through experimental evidence, to provide valuable guidance into ligand design and architecture.

Gaining access to ligands **254** and **255** (*Figure* **56**) would create the opportunity for comparisons between the "electron poor" electronic system **234** and these more "electron rich" systems, in the diastereofacial discrimination of α,β-unsaturated carbonyl compounds. Our aim was to ascertain if modulation of the electronic nature of the aromatic ring would alter the selectivities observed during asymmetric catalytic reactions. Obtaining diols **254** and **255**, with the nitrogen atom of the indole moieties protonated or methylated, would allow an investigation into what, if any, effect, the change in electron density on the aromatic group has on the proposed non-covalent interactions with enones.



254 **255**

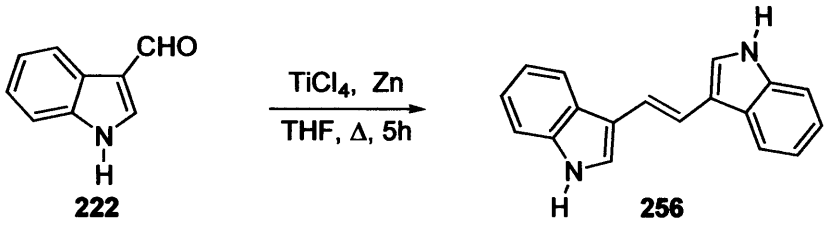
Figure **56**

Synthesis of ligands **254** and **255** was envisaged *via* an analogous synthetic pathway to that employed in the synthesis of diol **234**, involving a McMurry reaction to generate a C_2-symmetric alkene, followed by a Sharpless asymmetric dihydroxylation to incorporate the chiral diol functionality.

2.6.1 Synthesis of an "Electron Neutral" Diol

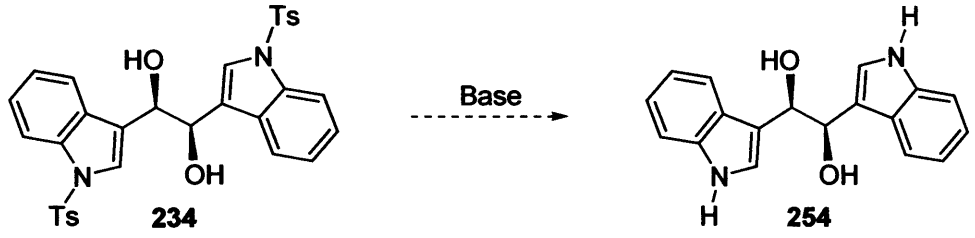
A low valent titanium species was generated *in situ* by reacting titanium tetrachloride with zinc in refluxing tetrahydrofuran. Two equivalents of indole-3-carboxaldehyde (**222**) were

added at reflux temperature, and heating was continued for five hours to generate 1,2-bis-(1*H*-indol-3-yl)-ethene (**256**) (*Scheme* **129**).[187]



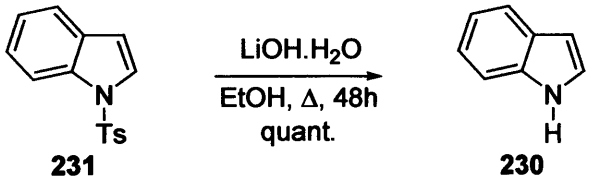
Scheme **129**

A brown solid was isolated after the reaction, which was shown by ^{1}H NMR to contain no starting material, but a complex mixture of products had resulted. Some of the desired alkene **256** had been formed, but this proved difficult to separate from the by-products using column chromatography on silica gel. This may have been due to hydrogen-bonding between the desired compound and the silica. Addition of triethylamine to the chromatography solvent system did not aid in the purification of **256**, and all attempts to attain pure alkene **256** by this method proved unsuccessful. Consequently, we felt that the McMurry protocol may not be ideal for the synthesis of **256**. As a result, we went on to investigate another possible route to the synthesis of diol **254** (*Scheme* **130**).



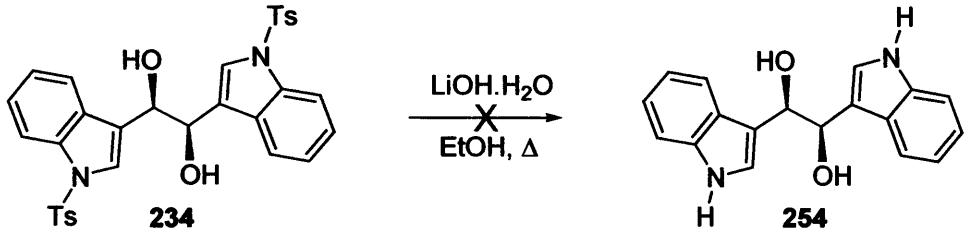
Scheme **130**

We hoped that we would be able to acquire diol **254** from the already synthesised chiral diol **234**, by removal of the tosyl-protecting groups. We needed to perform a series of reactions in order to determine suitable reaction conditions for this transformation. However, we did not want to use chiral diol **234** for this method development, so we decided to perform an initial study using tosyl-protected indole **231** (*Scheme* **131**).



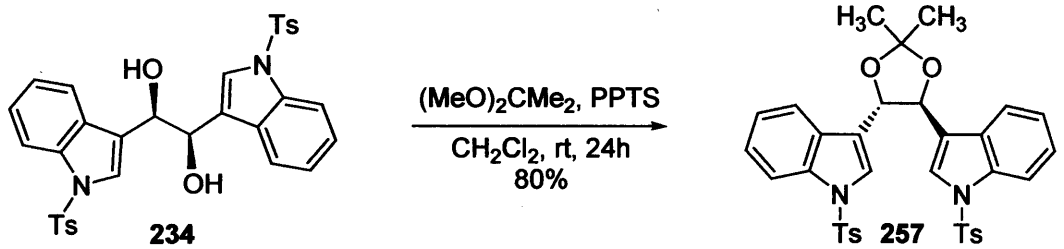
Scheme **131**

To this end, we reacted a solution of **231** in ethanol with sodium hydroxide. After heating at reflux temperature for two days, a mixture of starting material and product was isolated. Further endeavours to achieve this deprotection included the use of potassium *tert*-butoxide and lithium hydroxide monohydrate in refluxing *tert*-butanol and ethanol, respectively. Modifications were made to the number of equivalents of base employed and the reaction temperature, and we found that optimal conditions for this transformation were the use of two equivalents of lithium hydroxide monohydrate. This was stirred in refluxing ethanol for two days, affording indole (**230**) in a quantitative yield, without the need for purification. Having determined suitable reaction conditions for the tosyl deprotection of an indole species, we went on to apply this to the formation of diol **254** (*Scheme* **132**).



Scheme **132**

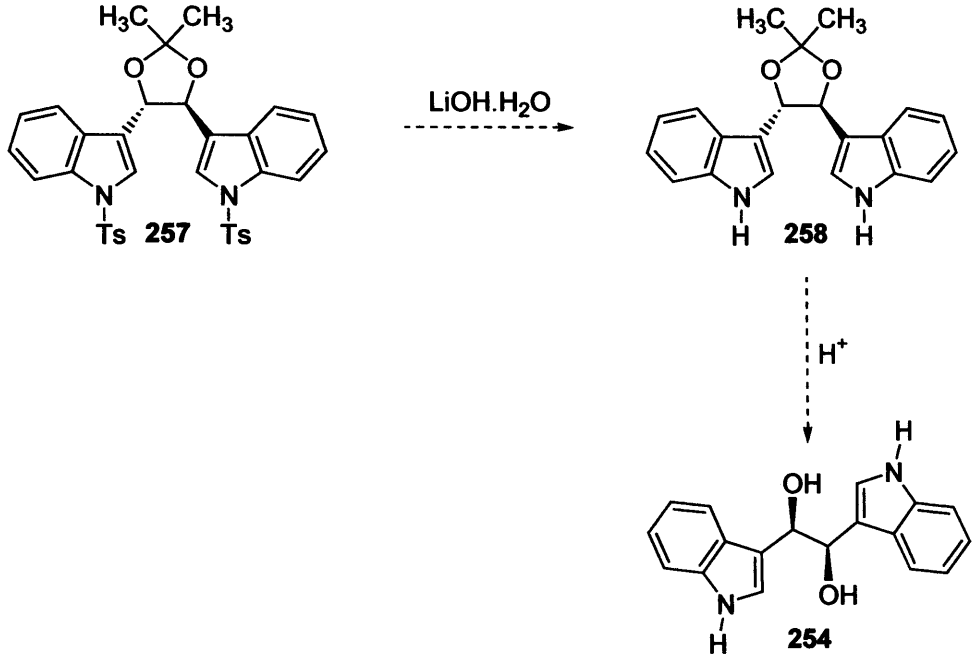
This reaction produced a mixture of products that could not easily be purified. Intriguingly, two aldehyde species were present after reaction, suggesting that the carbon-carbon bond between the two hydroxyl groups had been cleaved. We believe that these two aldehydes were indole-3-carboxaldehyde (**222**) and tosyl-protected indole-3-carboxaldehyde **223**. If so, we were achieving a degree of tosyl deprotection, but additional reactions were also taking place under the reaction conditions employed. We therefore decided to protect the diol functionality of **234** with the aim of facilitating the removal of the tosyl-group, whilst minimising further reactions around the diol functionality (*Scheme* **133**).



Scheme **133**

Protection of the diol functionality was achieved by reacting diol **234** with 2,2-dimethyoxypropane in the presence of a catalytic amount of pyridinium *para*-toluenesulfonate (PPTS). Stirring in dichloromethane for 24 hours at ambient temperature, followed by purification by column chromatography, gave acetal **257** with an 80% isolated yield. Once

the diol functionality had been protected as an acid labile acetal, we were in a position to perform the tosyl deprotection reaction under the basic conditions applied previously. If successful, we would then need to hydrolyse the resulting acetal under acidic conditions to provide our target diol **254** (*Scheme* **134**).



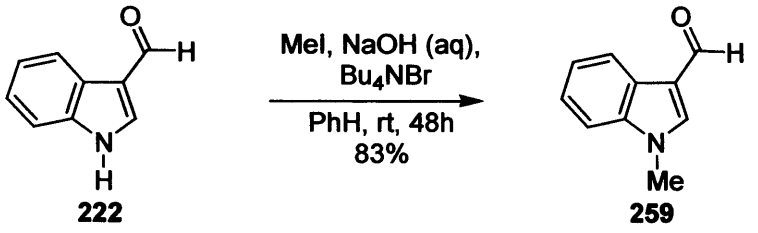
Scheme **134**

Acetal **257** was stirred in ethanol before addition of lithium hydroxide monohydrate. After heating at reflux temperature for 48 hours, a complex mixture of products was obtained and isolation of any of the desired product **258** was not achieved. Once again an aldehyde was generated during the reaction, suggesting that the basic conditions employed were promoting undesirable side reactions.

The synthesis of diol **254** was therefore proving elusive. In order to probe and investigate the proposed π–π interactions it was essential that we generate a ligand with a more "electron rich" aromatic system than that of diol **234**. Rather than continue to explore methods for the synthesis of diol **254**, we decided to suspend these investigations until we had first synthesised *N*-methylated diol **255**. We realised that if the synthesis of diol **255** also proved difficult, then our chosen ligand design would not allow us to realise our aim of investigating the proposed non-covalent interactions. For this reason we moved on to examine the synthesis of diol **255**.

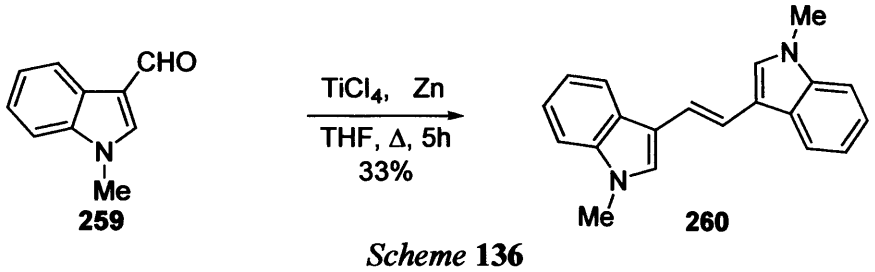
2.6.2 Synthesis of an "Electron Rich" Diol

We conceived that we could synthesise diol **255** using a McMurry reaction followed by a Sharpless asymmetric dihydroxylation, as indeed we had for tosyl-protected diol **234**. Firstly we needed to acquire *N*-methylindole-3-carboxaldehyde (**259**). This was accomplished by reacting a solution of indole-3-carboxaldehyde (**222**) in benzene with methyl iodide and aqueous sodium hydroxide, in the presence of a phase transfer catalyst, tetrabutylammonium bromide, for 48 hours at ambient temperature (*Scheme* **135**).[208]



Scheme **135**

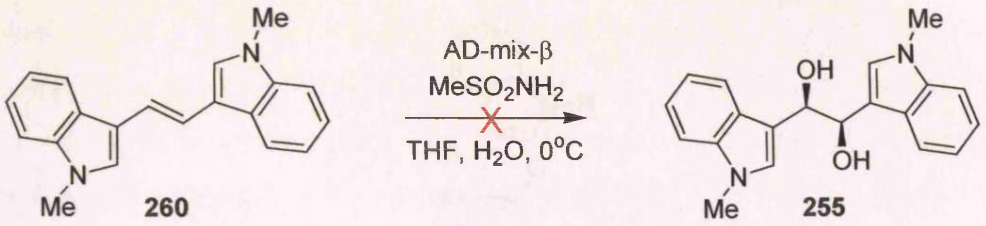
After column chromatography the desired product **259** was isolated in an 83% yield. Two equivalents of compound **259** were then coupled together under the McMurry reaction conditions employed previously (see *Section* **2.4.3**). This furnished the C_2-symmetrical alkene **260** with 33% isolated yield after purification by column chromatography (*Scheme* **136**).[187]



Scheme **136**

We observed alkene **260** to be light sensitive as it decomposed unless stored under conditions where light was excluded. All reactions involving compound **260** were also carried out under darkness.

Having successfully synthesised alkene **260**, we then needed to incorporate the asymmetric diol functionality into the molecule. We attempted this using AD-mix-β, under congruent conditions to those applied to the formation of ligand **234** (see *Section* **2.4.3**) (*Scheme* **137**).[36]



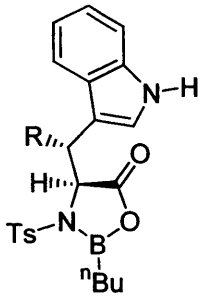
Scheme **137**

After stirring at 0°C for four days, some alkene **260** remained in the reaction mixture. None of the desired diol **255** was observed, and the major product isolated was *N*-methylindole-3-carboxaldehyde (**259**). Performing this oxidation under non-chiral conditions, using a quinuclidine ligand,[188] afforded an equivalent mixture. We were curious as to whether the osmium tetroxide was responsible for the generation of aldehyde **259**, so we stirred alkene **260** under otherwise identical reaction conditions, but without the presence of the oxidising agent. Once again, aldehyde **259** predominated in the reaction mixture. This suggested that under the reaction conditions employed the carbon-carbon double bond of alkene **260** was being cleaved. The reaction performed with the exclusion of any oxidising agent rules out the possibility that diol **255** is formed first, and that it is this compound that decomposes.

Therefore our attempts to synthesise ligands **254** *and* **255** *had proved unsuccessful, since there appeared to be stability issues with the electron-rich bis-indolyl systems. Our inability to form these "electron rich" diols meant that we were unable to investigate the proposed π–π interactions using our chosen family of ligands* **220**. *It was apparent at this stage that we needed to rethink our design strategy, in order to achieve our ultimate goal.*

2.7 An Alternative Ligand Design

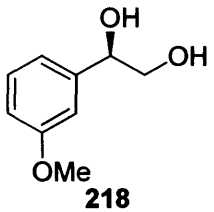
A look back at the design features that we originally wanted to incorporate into our ligand (*Section* **2.2.1**), revealed to us that we had elected to incorporate the indolyl subunit due to its presence in the natural amino acid, tryptophan. Tryptophan is the amino acid that is most often observed in nature to interact *via* π–π interactions. The indolyl moiety is also present in oxazaborolidine catalyst **217**, utilised with immense success by Corey, to catalyse the Diels-Alder reaction (*Figure* **57**).[171]



217

Figure **57**

Additionally, we had chosen to incorporate a diol subunit into the catalyst structure to facilitate the complexation of our ligand to a Lewis acid. Such a functionality is present in the styrene derived ligand **218** reported by Jones, which was utilised in Lewis acid catalysed Diels-Alder reactions (*Figure* **58**).[181]

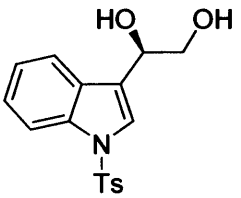


218

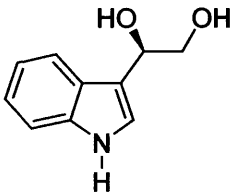
Figure **58**

Our final design feature involved the generation of a C_2-symmetrical ligand. We rationalised that a problem associated with ligand **218** was that the α,β-unsaturated carbonyl reagent could potentially approach from the side of the metal where no aromatic functionality was present, reducing the possibility of the proposed face-face π–π interaction.

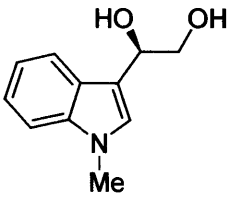
On reflection, we decided that the use of a C_2-symmetrical ligand was not essential. After all, Jones had achieved an enantiomeric excess of 30% using ligand **218** in a Lewis acid catalysed Diels-Alder reaction between cyclopentadiene (**66**) and methacrolein (**252**). An indole-derived version of ligand **218** should partake more readily in π–π interactions. Therefore, we could expect to achieve a higher enantiomeric excess using an electron-rich indole system compared to ligand **218**, if indeed π–π interactions are transpiring. As a consequence, we decided to synthesise ligands **261**, **262**, and **263** (*Figure* **59**).



261



262



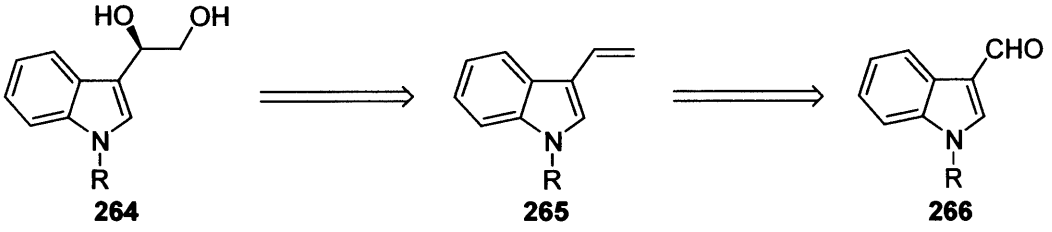
263

Figure **59**

Our revised design still incorporated an indolyl aromatic group along with a chiral diol functionality. Once again we aimed to adjust the electronics of the aromatic ring by varying the group bonded to the indole nitrogen atom. Thus, our initial target was the synthesis of "electron deficient" diol **261**, "electron neutral" ligand **262** and "electron rich" system **263**. This subtle modification of the electronics of the aromatic ring should allow us to investigate the effect on the strength of the proposed π-π interactions and hence the effect on selectivity observed in catalytic asymmetric transformations.

2.7.1 Retrosynthetic Analysis

Retrosynthetic analysis of our revised ligand structure led us to a synthesis from the corresponding 3-vinylindole **265**. We already knew that this alkene could be synthesised from the indole-3-carboxaldehyde **266** using a Wittig reaction (see *Section* **2.4.2**). Hence, we believed that the synthesis of ligands **261**, **262** and **263** should be possible *via* a two-step Wittig reaction – Sharpless asymmetric dihydroxylation procedure, from the appropriate indole-3-carboxaldehyde **266** (*Figure* **60**).



264 **265** **266**

Figure **60**

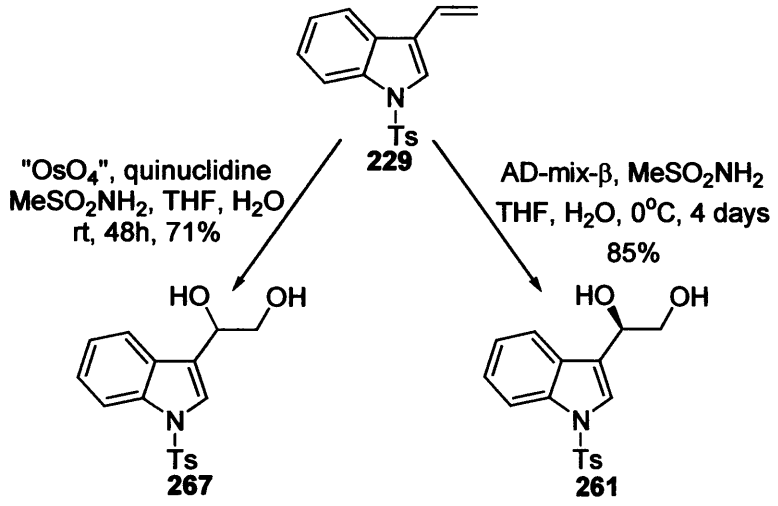
2.8 Ligand Synthesis

Thus, we moved on to synthesise this new family of ligands. Once again we initially explored the formation of "electron deficient" diol **261**, before pursuing investigations that should hopefully lead to more "electron rich" versions.

2.8.1 Synthesis of an "Electron Deficient" Ligand

Our first target was the synthesis of ligand **261**, with an electron withdrawing tosyl group bound to the indole nitrogen atom. We had already synthesised the corresponding tosyl-protected 3-vinyl indole **229** (see *Section* **2.4.2**), we therefore needed to perform a Sharpless asymmetric dihydroxylation in order to incorporate both the diol functionality and the asymmetry into the molecule.

The Sharpless asymmetric dihydroxylation was carried out by treating a solution of **229** in tetrahydrofuran/water (1:1) at 0°C with the AD-mix-β and methanesulfonamide, followed by stirring at 0°C for four days.[36] This gave the corresponding diol **261** in 85% yield. The synthesis was also carried out to generate a sample of the racemic diol **267** using quinuclidine,[188] a non-chiral amine ligand, enabling the determination of the enantiomeric excess of diol **261** (*Scheme* **138**). This was achieved by chiral HPLC analysis using a Chiralcel OD column (See *Chapter* **5**, pages 221-223 and *Appendix* **A4**, page 271 for details). Analysis of diol **261** showed an enantiopurity of 73%. Recrystallisation from ethanol/water (80:20) increased this to 81% ee.



Scheme **138**

The absolute stereochemistry of the asymmetric centre of **261** was assumed to be *S* in accordance with the proposed addition of osmium tetroxide to the top face of the alkene when chiral ligand $(DHQD)_2PHAL$ is utilised.[36]

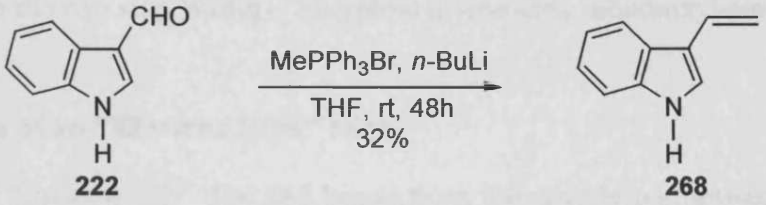
In summary, we had successfully synthesised diol **261** *via a three step procedure from commercially available indole-3-carboxaldehyde* (**222**). *This synthesis began with a tosyl protection, followed by a Wittig reaction with the ylide derived from methyltriphenylphosphonium bromide, and concluded with a Sharpless asymmetric dihydroxylation. This protocol furnished ligand* **260** *in a 41% overall yield. The optical purity of diol* **261**, *even after one recrystallisation, was 81% ee.*

In order to utilise compound **261** as a ligand in Lewis acid catalysed asymmetric transformations, it was essential that this enantiopurity be higher. However, at this stage we felt it was pertinent to ensure that synthesis of "electron rich" diols **262** and **263** was

achievable, before spending time optimising the Sharpless asymmetric dihydroxylation of alkene **229**.

2.8.2 Formation of an "Electron Neutral" System

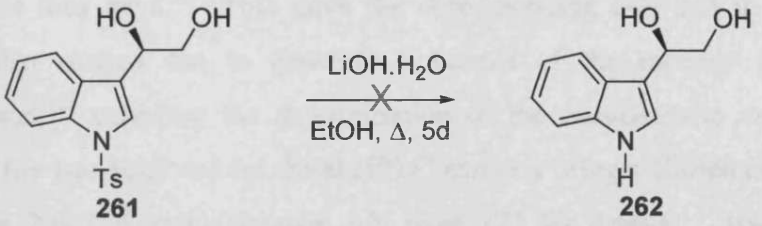
Synthesis of diol **262** began from commercially available indole-3-carboxaldehyde (**222**). This was achieved by treatment of methyltriphenylphosphonium bromide with *n*-butyllithium at 0°C in tetrahydrofuran to generate the corresponding phosphonium ylide. Aldehyde **222** was added dropwise, and the resulting solution was stirred at ambient temperature for 48 hours (*Scheme* **139**).



Scheme **139**

After purification by column chromatography, compound **268** was furnished in a 32% isolated yield. We were then able to perform a Sharpless asymmetric dihydroxylation on 3-vinylindole (**268**) under comparable conditions to those employed previously (see *Section* **2.8.1**). After stirring for three days at 0°C, no starting material remained in the reaction mixture. Upon isolation we found that the major product was indole-3-carboxaldehyde (**222**). This indicated that either the vinyl group of **268** was being cleaved under these oxidative reaction conditions, or that diol **262** was initially being formed, but was unstable.

We went on to explore the possibility of acquiring diol **262** from the already synthesised chiral diol **261**, by removal of the tosyl-protecting group using the conditions employed in the tosyl-deprotection of compound **231** (see *Section* **2.6.1**). To this end, we reacted a solution of **261** in ethanol with lithium hydroxide monohydrate, and the reaction was heated to reflux temperature for five days (*Scheme* **140**).

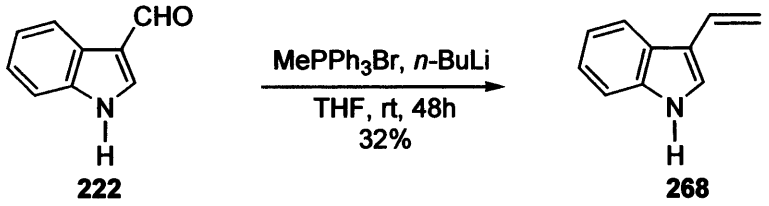


Scheme **140**

achievable, before spending time optimising the Sharpless asymmetric dihydroxylation of alkene **229**.

2.8.2 Formation of an "Electron Neutral" System

Synthesis of diol **262** began from commercially available indole-3-carboxaldehyde (**222**). This was achieved by treatment of methyltriphenylphosphonium bromide with *n*-butyllithium at 0°C in tetrahydrofuran to generate the corresponding phosphonium ylide. Aldehyde **222** was added dropwise, and the resulting solution was stirred at ambient temperature for 48 hours (*Scheme* **139**).

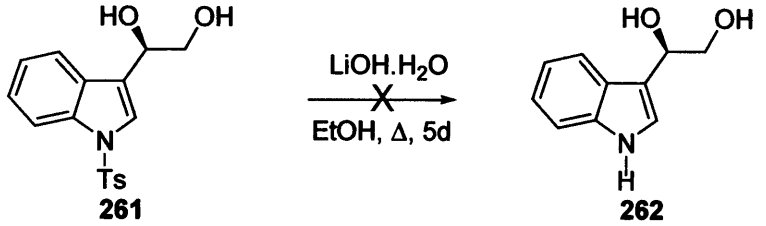


222 **268**

Scheme **139**

After purification by column chromatography, compound **268** was furnished in a 32% isolated yield. We were then able to perform a Sharpless asymmetric dihydroxylation on 3-vinylindole (**268**) under comparable conditions to those employed previously (see *Section* **2.8.1**). After stirring for three days at 0°C, no starting material remained in the reaction mixture. Upon isolation we found that the major product was indole-3-carboxaldehyde (**222**). This indicated that either the vinyl group of **268** was being cleaved under these oxidative reaction conditions, or that diol **262** was initially being formed, but was unstable.

We went on to explore the possibility of acquiring diol **262** from the already synthesised chiral diol **261**, by removal of the tosyl-protecting group using the conditions employed in the tosyl-deprotection of compound **231** (see *Section* **2.6.1**). To this end, we reacted a solution of **261** in ethanol with lithium hydroxide monohydrate, and the reaction was heated to reflux temperature for five days (*Scheme* **140**).



261 **262**

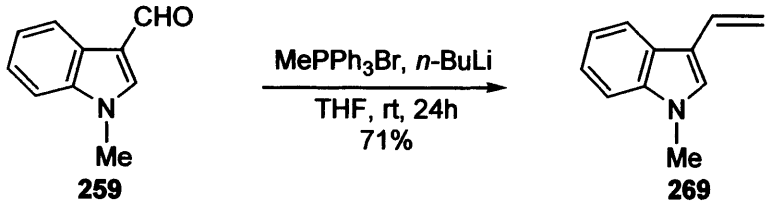
Scheme **140**

Neither the starting material **261**, nor the desired product **262** were present upon isolation of the crude reaction mixture. Enigmatically, two aldehyde species were present after reaction, suggesting that the carbon-carbon bond between the two hydroxyl groups had been cleaved. We believe that these two aldehydes were indole-3-carboxaldehyde (**222**) and tosyl-protected indole-3-carboxaldehyde **223**. If so, we were achieving a degree of tosyl deprotection, but additional reactions were also occurring under the reaction conditions employed.

Essentially we had now encountered the same problems that had mired the synthesis of the electron-rich bis-indolyl systems **254** and **255** (see *Section* **2.6**). Before exploring alternative methods for the formation of diol **262**, we decided to first attempt the synthesis of "electron rich" diol **263** *via* the two step Wittig – Sharpless asymmetric dihydroxylation protocol.

2.8.3 Synthesis of an "Electron Rich" Diol

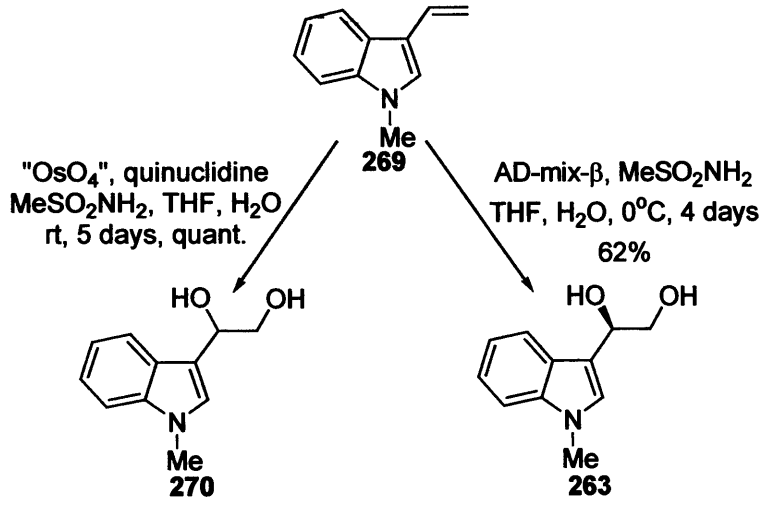
The synthesis of "electron rich" diol **263** began from the already synthesised *N*-methylindole-3-carboxaldehyde **259** (see *Section* **2.6.2**). A Wittig reaction was carried out between aldehyde **259** and the ylide arising from methyltriphenylphosphonium bromide, in an identical manner to that exercised for the synthesis of 3-vinylindole (**268**) (see *Section* **2.8.2**). Stirring of the reaction mixture for 24 hours at ambient temperature furnished *N*-methyl-3-vinylindole **269** (*Scheme* **141**).



259 **269**

Scheme **141**

Alkene **269** was isolated in 71% yield after purification by column chromatography. Sharpless asymmetric dihydroxylation was carried out by treating a solution of **269** in tetrahydrofuran/water (1:1) at 0°C with the AD-mix-β and methanesulfonamide, followed by stirring at 0°C for four days.[36] This gave the corresponding diol **263** in 62% yield. The synthesis was also carried out to generate a sample of the racemic diol **270** using a quinuclidine ligand,[188] enabling the determination of the enantiomeric excess of diol **263** (*Scheme* **142**). This was achieved by chiral HPLC analysis using a Chiralcel OD column (See *Chapter* **5**, pages 224-226 and *Appendix* **A5**, page 272 for details). Analysis of diol **263** showed an enantiopurity of 55%.



Scheme **142**

The absolute stereochemistry of the major isomer of **263** was assumed to be *S* in accordance with the proposed addition of osmium tetroxide to the top face of the alkene when chiral ligand $(DHQD)_2PHAL$ is utilised.[36]

We had therefore accomplished the synthesis of diol **263** *via a three step procedure from commercially available indole-3-carboxaldehyde* (**222**). *This synthesis began with a methylation of the indole nitrogen atom, followed by a Wittig reaction with the ylide derived from methyltriphenylphosphonium bromide, and concluded with a Sharpless asymmetric dihydroxylation. This protocol furnished ligand* **263** *in a 37% overall yield, with an optical purity of 55%.*

We had now attained "electron deficient" diol **261** and the "electron rich" version **263**, with 81% and 55% enantiomeric excess, respectively. Rather than trying to obtain these ligands with complete enantiomeric purity, we decided to first find out if they could indeed be employed as ligands in the Lewis acid catalysed Diels-Alder reaction. With this goal in mind we designed an experiment in which we would spike samples of enantiomerically enriched diol **261** with racemic version **267**, thus providing us with three samples of diol **261**, with 75%, 50% and 25% ee, respectively. These three samples would all be employed in asymmetric catalysis, and the enantioselectivities achieved in the Diels-Alder reaction should allow us to plot a graph of ligand enantiomeric excess *versus* asymmetric induction observed. This should provide an indication of the approximate level of asymmetric induction that would be achievable if we were able to obtain optically pure diol **261** and an indication as to whether non-linear effects were occurring within the reaction. If this proved successful, we would go on to spike a sample of enantiomerically enriched diol **263** with racemic version

270, giving access to a sample with 50% ee. This should allow a direct comparison between the "electron deficient" ligand **261** and the "electron rich" version **263**.

2.9 Asymmetric Catalysis Using Our Design-Modified Ligands

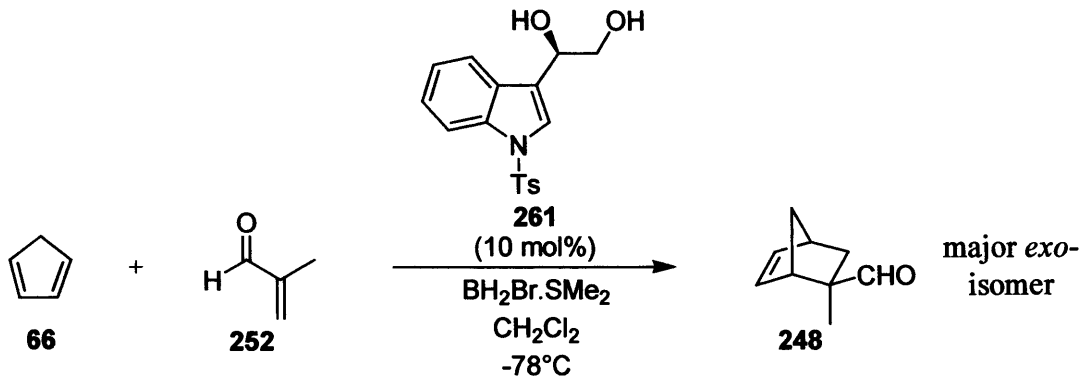
We were now able to begin an investigation into the use of ligands **261** and **263** in Lewis acid catalysed processes. Once again, it was decided to commence our catalytic investigations by probing into just one type of asymmetric C-C bond forming reaction, the Diels-Alder reaction (see *Section* **2.5.1**). This would hopefully allow us to test our hypotheses and ascertain any rationale in the nature of the proposed π–π interactions.

The enantiomeric excess of both the *endo*- and *exo*-isomers of the Diels-Alder adduct would again be determined by chiral HPLC analysis of their 2,4-dinitrophenylhydrazones. This is a direct method for the analysis of the reaction mixture, providing both the *endo/exo* ratio and the enantiomeric excess for the Diels-Alder adduct (see *Section* **2.5.2**).[201]

Our catalytic investigations with ligand **234** showed us that the use of bromoborane or diethylaluminium chloride gave improved enantioselectivity in the resulting Diels-Alder adduct. We therefore opted to utilise these two Lewis acids in the following catalytic runs. We also learned that achieving diastereofacial discrimination between the two faces of an α,β-unsaturated system appeared more difficult with acrolein (**76**), compared to methacrolein (**252**) (see *Section* **2.5.3**). Consequently we decided to analyse ligands **261** and **263** in the Lewis acid catalysed Diels-Alder reaction between cyclopentadiene (**66**) and methacrolein (**252**), mimicking the conditions reported in the modern literature.[172a,202]

2.9.1 Asymmetric Catalysis of the Diels-Alder Reaction

We embarked upon an investigation into the use of ligand **261** in a Lewis acid catalysed Diels-Alder reaction between cyclopentadiene (**66**) and methacrolein (**252**), using the Lewis acid, bromoborane (*Scheme* **143**).



Scheme **143**

The results of this study are tabulated below (*Table* **3**).

Table **3**[a]: **Results of the Study Using a Bromoborane Lewis Acid**

Entry	% ee of Diol **261**[b]	Isolated Yield (%)	*Endo* / *Exo*	Enantiomeric Excess (% ee)
1	25	62	12 : 88	6.1
2	51	27	15 : 85	5.0
3	75	40	17 : 83	5.2

(a) All Diels-Alder reactions were carried out in duplicate and values quoted in the table are an average of the results. Ligand **261** (10 mol%) with $BH_2Br.SMe_2$, was used as the catalytic system with dichloromethane as the reaction solvent. The reactions were carried out at -78°C for 48 hours. All enantiomeric excesses were determined by HPLC analysis of the purified material, diastereomeric ratios were obtained from the ^1H NMR of the pure adduct and yields were determined by weight of isolated product.
(b) Determined by chiral HPLC analysis using a Chiralcel OD column (see *Chapter* **5**, pages 224-226 and *Appendix* **A6**, page 273).

The results of these catalytic reactions were somewhat disappointing. Each of the three runs afforded Diels-Alder adduct **248** with low enantiomeric excess. If we assumed a linear relationship between the optical purity of the ligand **261** and the asymmetric induction observed in the Diels-Alder reaction, we could expect to achieve an enantiomeric excess of approximately 6% if we were able to synthesise enantiomerically pure diol **261**. On the positive side, our original hypothesis that a C_2-symmetric diol should lead to higher enantiocontrol seemed to be correct (C_2-symmetric ligand **234** afforded adduct **248** with 12% ee under equivalent reaction conditions, see *Section* **2.5.3**); albeit rather low.

We went on to analyse the use of an aluminium-based Lewis acid, diethylaluminium chloride, to determine if its use, along with ligand **261**, would lead to higher enantioselection in the Diels-Alder reaction. The results of this study are outlined below (*Table* **4**).

Table 4[a]: **Results of the Study Using an Aluminium-Based Lewis Acid**

Entry	% ee of Diol **261**[b]	Isolated Yield (%)	*Endo* / *Exo*	Enantiomeric Excess (% ee)
1	25	17	11 : 89	8.4
2	51	18	13 : 87	8.8
3	75	14	12 : 88	8.8

(a) All Diels-Alder reactions were carried out in duplicate and values quoted in the table are an average of the results. Ligand **261** (10 mol%) with Et_2AlCl, was used as the catalytic system with dichloromethane as the reaction solvent. The reactions were carried out at -78°C for 48 hours. All enantiomeric excesses were determined by HPLC analysis of the purified material, diastereomeric ratios were obtained from the ^1H NMR of the pure adduct and yields were determined by weight of isolated product.
(b) Determined by chiral HPLC analysis using a Chiralcel OD column (see *Chapter* **5**, pages 224-226 and *Appendix* **A6**, page 273).

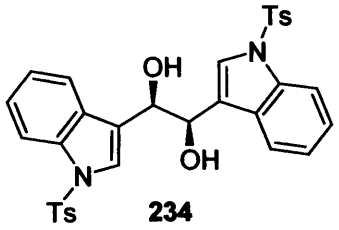
Once again, each of the three reactions provided adduct **248** with comparable enantiomeric excess, suggesting that optically pure diol **261** would also deliver a similar result. Encouragingly, a slightly higher enantiomeric excess was achieved when employing diethylaluminium chloride (~9% ee) compared to the use of bromoborane (~6% ee). But, overall these results were very disappointing due to the poor yields of adduct **248** achieved, combined with the low enantiomeric excesses.

We decided not to attempt to synthesise optically pure ligand **261**, as these results suggested that such a ligand would not increase the asymmetric induction observed in the catalytic Diels-Alder reaction by very much, if even at all. Moreover, we found that the "electron rich" diol **263** was unstable, and so would require fresh preparation from *N*-methyl-3-vinylindole **269** before it could be employed as a ligand in the Diels-Alder reaction. Such a ligand is certainly not ideal, and this, in combination with the problems we had encountered in the synthesis of this family of ligands in enantiomerically pure form, as well as the low enantioselectivities observed for the use of ligand **261** in the Lewis acid catalysed Diels-Alder reaction, made us think again about the future of this study.

2.10 Conclusions

During the course of these investigations we successfully synthesised bis-indolyl diol **234** (*Figure* **61**), and went on to use this as a ligand in the Lewis acid catalysed Diels-Alder reaction. In association with bromoborane, catalysis of the cycloaddition between cyclopentadiene (**66**) and methacrolein (**252**) led to the formation of adduct **248** in 72% yield

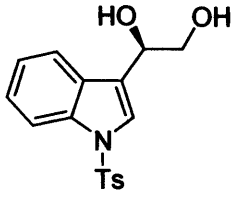
with 12% enantiomeric excess. Encouraged by this result we attempted to synthesise the "electron rich" versions, **254** and **255**. Unfortunately, our attempts were mired by stability issues with these "electron rich" indole systems.



234

Figure **61**

Modification of the ligand design ensued, and we were able to synthesise diol **261**, albeit with an enantioselectivity of only 81% (*Figure* **62**). We performed catalytic runs using samples of ligand **261** with differing levels of optical purity. Ligand **261** (75% optical purity) yielded Diels-Alder adduct **248** in 40% yield with 6% ee, using bromoborane as the Lewis acid. Extrapolation of the results obtained indicated that an optically pure sample of diol **261** would furnish the Diels-Alder adduct **248** with similar enantioselectivity (~6%). Stability issues were again encountered with more "electron rich" versions of this ligand.



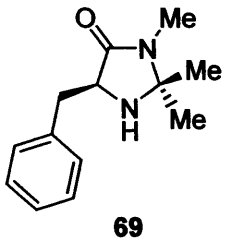
261

Figure **62**

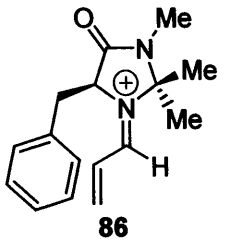
These catalytic results seemed to support our hypothesis that C_2-symmetrical diol **234** should lead to higher levels of enantiocontrol in the Lewis acid catalysed Diels-Alder reaction, than the non-symmetrical version **261**, under congruent reaction conditions.

2.11 The Future

During the course of our investigations into the synthesis of bis-indolyl ligand family **220**, and the mono-indolyl version **264**, work was published by MacMillan on the use of metal-free imidazolidinone catalyst **69** to promote the Diels-Alder reaction, achieving high levels of enantiocontrol (*Figure* **63**).[7]



69



86

Figure **63**

An iminium ion **86** is formed upon interaction of imidazolidinone **69** with an α,β-unsaturated carbonyl compound (*Figure* **63**). It has been hypothesised that π-shielding of the top face of the α,β-unsaturated species by the benzyl group leads to the high levels of facial selectivity observed (see *Chapter* **1**, *Section* **1.9** for a more detailed discussion).

There are many advantages associated with the use of metal-free asymmetric catalysis, compared to Lewis acid catalysis. For example, a Lewis acid catalysed Diels-Alder reaction must be carried out under an inert atmosphere at –78°C. In comparison, a metal-free analogue can be performed at ambient temperature in wet solvent under an aerobic atmosphere. Use of a metal-derived catalyst has further disadvantages, including high price, the resulting toxicity and pollution problems, the need for waste treatment and the possibility of product contamination by the metal. In comparison, many of these problems can be avoided by utilising metal-free organocatalysis.[11] Therefore, organocatalysis represents a remarkable synthetic alternative to established organometallic transformations to both augment and complement existing methodology.

At the onset of this project our aim was to design and synthesise a first generation Lewis acid that could discriminate between the prochiral faces of α,β-unsaturated carbonyl compounds, and to use this ligand to investigate and probe the nature of face-face π–π interactions and the subtleties associated with their existence. On reflection, we realised that this objective could also be achieved using a metal-free organocatalyst, allowing us to perform our catalytic experiments under more favourable reaction conditions. Thus, for the remainder of this project we decided to focus our attentions on metal-free organocatalysis, with the aim to design and synthesise a novel chiral aminocatalyst for use in a series of asymmetric transformations, that should enable us to investigate these non-covalent interactions.

Chapter 3: Results and Discussion

3.1 Introduction

Over the past 30 years, enantioselective catalysis has become one of the most important frontiers in exploratory synthetic research.[209] During this time, remarkable advances have been made in the development of organometallic asymmetric catalysts that have in turn provided a wealth of enantioselective processes. Surprisingly, however, relatively few asymmetric transformations have been reported that employ organic molecules as reaction catalysts, despite the widespread availability of organic chemicals in enantiopure form and the accordant potential for academic, industrial, environmental and economic benefit.[5]

Enantioselective organocatalysis, in which the reaction is mediated by a catalytic amount of a chiral organic molecule, is emerging as a powerful tool in organic synthesis. The interest in this field has increased spectacularly in the last few years and more reactions are expected in the near future. Currently the scope of reactions that have been applied to organocatalysis is restricted, and additional investigations are required to further advance this methodology. Chapter three of this thesis will be concerned with the design and synthesis of a new class of compound for the activation of α,β-unsaturated carbonyl compounds, that should provide a novel molecular scaffold capable of performing organocatalytic transformations.

3.1.1 Aminocatalysis

Several important processes utilise the chemistry of carbonyl compounds. These reactions are typically catalysed by metal-containing species, and can be catalysed by Lewis or Brønsted acids and bases. Recent research has shown that several carbonyl transformations can also be catalysed by secondary amines. This concept is based on electronic similarities between a protonated (or Lewis acid activated) carbonyl group and an iminium ion (*Figure* **64**).[7]

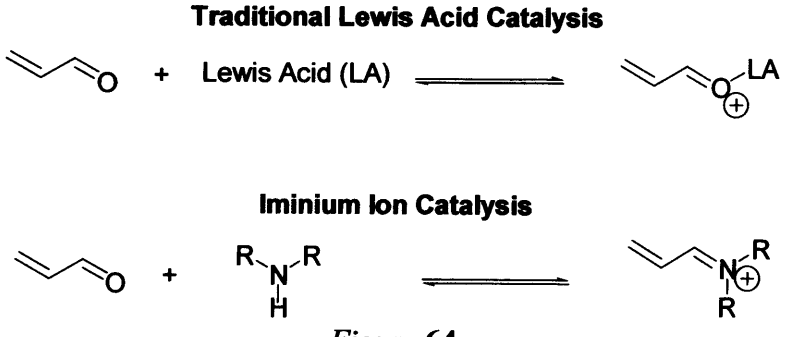


Figure **64**

The unique reactivity of iminium ions and enamines has long been employed in organic synthesis, however, most of these reactions use stoichiometric amounts of the amine. Until recently, amines had rarely been used catalytically despite their ready availability in enantiomerically pure form from several sources, including the chiral pool.[9]

The catalysis of a given reaction by an amine is known as aminocatalysis. This can be viewed as a biomimetic strategy that is exemplified by important enzymes such as Class I aldolases (enamine catalysis) and ketoacid decarboxylases (iminium ion catalysis), among others. There are two aminocatalytic pathways.[9] Iminium ion catalysis directly utilises the higher reactivity of the iminium ion compared to the carbonyl species and facilitates Knoevenagel-type condensation,[10] cycloaddition and nucleophilic addition reactions, as well as cleavage of the σ-carbon-carbon bond adjacent to the α-carbon. Enamine catalysis involves catalytically generated enamine intermediates that are formed *via* deprotonation of an iminium ion. These react with various electrophiles and also undergo pericyclic reactions (*Figure* **65**).

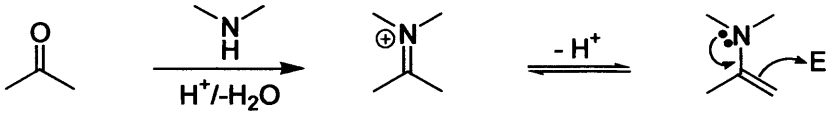


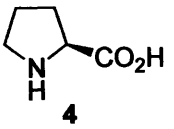
Figure **65**

Rigorous application of secondary amine catalysts in asymmetric organic synthesis has only recently been investigated, with several valuable and broadly applicable transformations acquiescent to aminocatalysis.

3.1.2 Previous Catalytic Systems

In recent years, chiral secondary amines have been introduced by List and MacMillan, among others, as effective catalysts for enantioselective aldol condensations,[31] Mannich reactions,[81] Diels-Alder cycloadditions,[7] Michael reactions,[100] and alkylations,[116] leading to remarkable levels of asymmetric induction.

Asymmetric enamine catalysis was first realised in the early 1970's when two groups independently reported the use of proline (**4**), (*Figure* **66**), as a catalyst for intramolecular aldol cyclisations.[13-15] This research showed the potential for aminocatalysis in asymmetric synthesis, leading to the development of several aminocatalysed asymmetric transformations.[32]

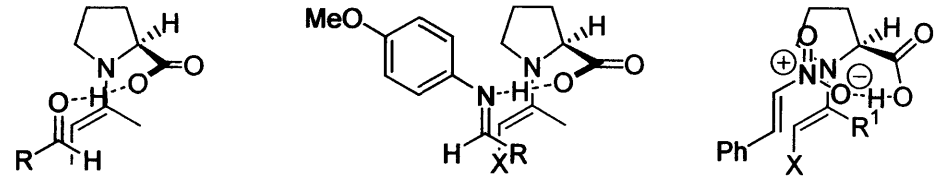


4

Figure **66**

There are several reasons for the importance of proline (**4**) in asymmetric catalysis. It is an abundant chiral molecule that is inexpensive and available in both enantiomeric forms. It is also bifunctional, with a carboxylic acid and an amine portion. These two functional groups can both act as acid or base, and can facilitate chemical transformations in concert, similar to enzymatic catalysis. Whilst these criteria apply to all amino acids, proline (**4**) is a secondary, cyclic, pyrrolidine-based amino acid. Proline's unique nucleophilic reactivity is primarily a consequence of this pyrrolidine portion, which forms iminium ions and enamines with carbonyl compounds more readily than most other amines, including cyclic ones such as piperidine.[41] This enables proline (**4**) to be an effective aminocatalyst, thus facilitating iminium- and enamine-based transformations.[9] The carboxylate moiety further contributes to this by acting as a general Brønsted co-catalyst.

Proline (**4**) has been employed in the asymmetric catalysis of intra- and intermolecular aldol condensations,[31] as well as in Mannich[81] and Michael[100] reactions. Its effectiveness is due to the formation of an enamine intermediate upon reaction with a carbonyl substrate. The adjacent carboxylic acid group is then proposed to direct the approach of an incoming electrophile by formation of a specific hydrogen bond in the transition state structure. This provides both pre-organisation of the substrates and stabilisation of the transition state, leading to the formation of products with commendable stereoselectivity.[32] Proposed transition states for the intramolecular aldol condensation, Mannich and Michael reactions are shown in *Figure* **67**. (For a more detailed discussion of these systems see *Chapter* **1**, *Sections* **1.6**, **1.14** and **1.15**, respectively).

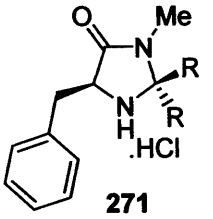


Aldol Condensation *Mannich Reaction* *Michael Reaction*

Figure **67**

The imidazolidinone catalyst **271**, (*Figure* **68**), introduced by MacMillan, has been utilised as an aminocatalyst for Diels-Alder,[7] [4+3][71] and [3+2][73] cycloadditions as well as in conjugate

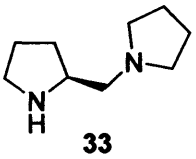
additions,[116,119] furnishing products with high levels of enantioselectivity (See *Chapter* **1**, *Sections* **1.9**, **1.11**, **1.12** and **1.16**, respectively, for further details). An iminium ion is formed upon interaction of catalyst **271** with an α,β-unsaturated carbonyl compound. It has been hypothesised that π-shielding of the top face of the α,β-unsaturated species by the benzyl group leads to the high levels of facial selectivity observed.



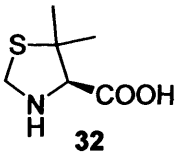
271

Figure **68**

In addition to proline (**4**) and imidazolidinone **271**, several other small chiral amines have been reported for their use in organocatalysis, including diamine **33**, first reported by Yamamoto, which has been used as a catalyst for the asymmetric aldol condensation[42] and Hetero-Diels-Alder reaction.[69] Furthermore, several derivatives of proline (**4**) have been employed in aminocatalytic transformations, including 5,5-dimethylthiazolium-4-carboxylate (**32**), and (*S*)-2-methoxymethylpyrrolidine (**147**) (*Figure* **69**).



33



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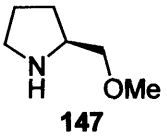


147

Figure **69**

3.1.3 Fundamental Contribution?

Examination of those compounds reported to be efficient as aminocatalysts shows them all to possess structural similarities. Each contains a secondary amine moiety within a five-membered ring system, and have either a hydrogen bond donor group in close proximity to the amine, or require a protonic acid co-catalyst. It has been suggested that in order to gain effective catalytic turnover within these reactions it is necessary to have a highly nucleophilic nitrogen atom to accelerate the formation of the active iminium ion, which is thought to be the rate determining step of the catalytic cycle.[119]

It is well established that the nucleophilicity of a heteroatom can be greatly increased by the addition of an adjacent heteroatom. Known as the α-effect,[210] and rationalised by frontier molecular orbital theory,[211] it has been used to explain the reactivity of a number of systems

and has previously been exploited to accelerate synthetic transformations.[212] Our aim was to depart from the constraints inherent to the five-membered ring systems by taking advantage of the α-effect, and develop effective acyclic amine catalysts capable of high catalytic turnover. This should present the opportunity to greatly diversify the previously reported catalyst structures, providing the ability to design and investigate other systems that should allow us to probe this exciting and fundamental area of research.

It is invariably the case that the systems recently reported in the literature provide products with remarkable levels of enantiomeric excess and excellent yields, however, the levels of catalyst loading and long reaction times frequently required fall short of contemporary standards. Therefore, an understanding of catalyst structure and its relationship to reaction rate may provide the means to address this short fall.

3.2 Design Concept

We therefore embarked upon an investigation to discover if the α-effect could be used to promote catalytic activity. The design and synthesis of a suitable acyclic catalyst structure to enable high catalytic turnover would then be pursued.

3.2.1 The α-Effect

An enhancement in nucleophilicity is observed when the atom adjacent to a nucleophilic site bears a lone pair of electrons. Examples of such nucleophiles include NH_2NH_2, HO_2^- and $Me_2C{=}NO^-$. This is known as the *alpha effect*.[210]

The enhanced reactivity of α-nucleophiles was first reported in 1947, but it wasn't until 1962 that Edwards and Pearson gave the phenomenon its name.[213] They stated the α-effect to be a positive deviation of an α nucleophile (a nucleophile possessing a non-bonding pair of electrons on an atom α to the nucleophilic site) from a Brønsted-type plot of log *k versus* the pK_a of the nucleophile (*k* being the rate constant of the nucleophilic attack).

The origins of this phenomenon are of some debate, although several possible explanations have been offered.[214] One such example is that the ground state of the nucleophile is destabilised by repulsion between the adjacent pairs of electrons.[215] Another is that the transition state is stabilised by the extra pair of electrons,[216] and a third is that the adjacent electron pair reduces solvation of the nucleophile.[217]

Here, we will focus on just one of these possible explanations, namely ground state destabilisation. Pair-pair repulsion is often invoked as the source of the α-effect, and the theoretical basis for this destabilisation is schematically depicted in *Figure* **70**. A linear combination of the atomic orbitals results in a new set of two molecular orbitals. The out-of-phase combination is raised to a larger extent than that by which the in-phase combination is lowered, thus leading to an overall destabilisation of the system. The enhanced nucleophilicity in this case can arise from two different sources (i) an increase in the overall energy of the ground state and (ii) an increase in the energy of the HOMO itself. According to the Frontier Molecular Orbital (FMO) Theory, the latter can lead to a rate enhancement since it diminishes the energy gap between the HOMO of the nucleophile and the LUMO of the substrate.[218]

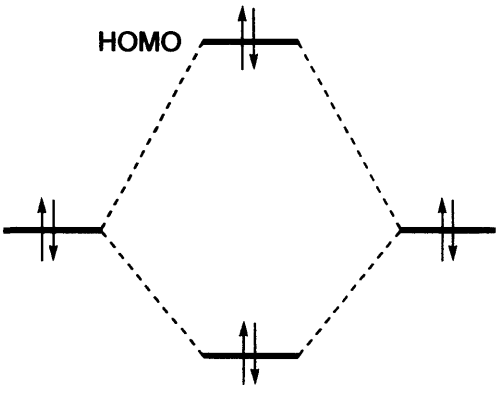


Figure **70**

While this explanation provides a convenient basis for understanding the α-effect, it is pertinent to remember that it is generally believed that there are several origins of this phenomenon. As long as the nature of these individual effects and the exact conditions under which they are operative are not recognised, then it is difficult to prove or disprove theories regarding the origin of these effects.

3.3 Proof of Concept

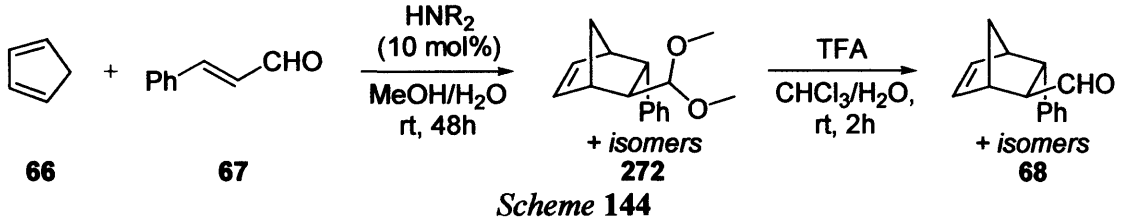
Each of the aminocatalysts reported to date has a structure based on a five-membered nitrogen-containing ring system. We believed that such systems are effective in the formation of the active iminium ion species due to the high nucleophilicity associated with a nitrogen atom in a five-membered ring. We hypothesised that such an increase in the nucleophilicity of a secondary amine could also be achieved by exploiting the α-effect. In order to establish if this was indeed the case, we needed to conduct a series of experiments in order to compare

the aminocatalytic reactivity of a pyrrolidine-type system, a linear secondary amine as well as a linear secondary amine with an α-heteroatom.

Firstly, a suitable reaction with which to test such systems needed to be determined. We elected to perform Diels-Alder cycloadditions, due to the experience we had already gained in performing and analysing such reactions (See *Chapter* **2**, *Section* **2.5**), although ultimately we aspired to utilise any catalyst that we designed in a variety of aminocatalytic processes.

3.3.1 Commercially Available Amines

We were now in a position to embark upon an investigation into the potential for the use of the α-effect as a platform for iminium ion catalysis. Mimicking the conditions reported in the literature,[7] 10 mol% of each amine (as its HCl salt) was stirred in methanol/water (19:1) at ambient temperature, and one equivalent of *E*-cinnamaldehyde (**67**) was added. After stirring for 15 minutes, cyclopentadiene (**66**) (3 equivalents) was added, and the reaction mixture was stirred for 48 hours. An aqueous work-up furnished the resulting adduct as the dimethyl acetal **272**, and subsequent hydrolysis with trifluoroacetic acid in chloroform/water for two hours at ambient temperature afforded the corresponding aldehyde **68** (*Scheme* **144**).



66 **67** **272** **68**

Scheme **144**

We examined six commercially available secondary amines for their ability to catalyse the Diels-Alder reaction. We opted to analyse proline methyl ester (**273**), containing a pyrrolidine ring system, as this would provide us with an indication of the level of reactivity that is achievable with cyclic amine systems. In addition, the use of dimethylamine (**274**) would enable us to determine if the presence of an α-heteroatom does indeed lead to an increase in aminocatalytic reactivity, by comparison of these results with those attained when using hydrazines **275** and **276**, and hydroxylamines **277** and **278** (*Figure* **71**). A reaction was also performed in the absence of a catalyst so that we could check for a background reaction under the conditions applied. Additionally, triethylamine hydrochloride was examined, allowing us to ascertain if the protonic acid co-catalyst leads to a rate enhancement, since the tertiary amine would not itself be able to catalyse the Diels-Alder reaction.

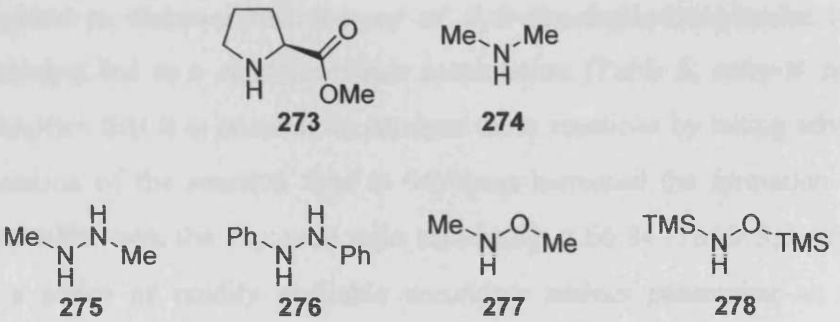


Figure **71**

The initial results for the catalysis of the Diels-Alder reaction between *E*-cinnamaldehyde (**67**) and cyclopentadiene (**66**) are outlined in *Table* **5**.[219]

Table **5**[a]: Catalysis of the Diels-Alder reaction by commercially available amines

Entry	Catalyst	Time	% Yield	*Exo* : *Endo*[b]
1	None	48	7	36 : 64
2[c]	NEt_3	48	7	37 : 63
3[c]	**273**	48	85	71 : 29
4[c]	**274**	48	22	62 : 28
5[d]	**275**	48	37	35 : 65
6[d]	**275**	96	48	32 : 68
7[c]	**276**	48	17	62 : 38
8[c]	**277**	48	65	66 : 34
9[c]	**277**	96	73	66 : 34
10[c]	**278**	48	23	34 : 66

(a) All reactions were carried out in methanol/water (19:1) at room temperature with 10 mol% catalyst. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture. (c) Catalyst used as its hydrochloride salt. (d) Catalyst used as a bis-hydrochloride salt.

In the absence of any catalyst, or in the presence of only the protonic acid co-catalyst, the reaction proceeded to just 7% completion inside 48 hours with the *endo* isomer predominating (*Table* **5**, *entries* **1** and **2**). Observations made by MacMillan suggest that the *exo* isomer of **68** predominates when iminium ion catalysis is occurring,[7] as was indeed observed with proline methyl ester (**273**), a catalyst that led to an 85% yield of the Diels-Alder adduct (*Table* **5**, *entry* **3**). The use of dimethylamine hydrochloride (**274**) as the catalyst afforded a 22% yield of adduct **68**, with the *exo* isomer favoured (*Table* **5**, *entry* **4**), suggesting that iminium ion catalysis was occurring, albeit sluggishly.

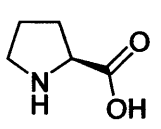
We were delighted to discover that the use of *N,O*-dimethylhydroxylamine hydrochloride (**277**) as the catalyst led to a significant rate acceleration (*Table* **5**, *entry* **8**, 65% yield, 48 hours). This implies that it is possible to catalyse these reactions by taking advantage of the α-effect. Extension of the reaction time to 96 hours increased the formation of the Diels-Alder adduct to 80%, with the *exo*:*endo* ratio remaining at 66:34 (*Table* **5**, *entry* **9**). Further evaluation of a series of readily available secondary amines possessing an α-heteroatom showed similar trends to be observed (*Table* **5**, *entries* **5, 6, 7** and **10**).

Therefore, a rate acceleration was observed when using N,O-dimethylhydroxylamine hydrochloride (**277**) *as the reaction catalyst compared to the use of dimethylamine* (**274**). *This suggested that the α-effect might well prove to be an effective handle with which to promote catalytic activity, and represented a novel acyclic scaffold capable of catalysing this type of organocatalytic transformation.*

The catalytic activity observed for the use of *N,O*-dimethylhydroxylamine hydrochloride (**277**) was not as profound as with proline methyl ester (**273**). In order to further increase the reactivity of this system we went on to prepare a disubstituted hydrazide which we hoped would provide a similar rate acceleration to that observed with pyrrolidine-based systems.

3.4 Proposed Catalytic Design

Analysis of the structures of proline (**4**), proline methyl ester (**273**), as well as imidazolidinone catalyst **69**, shows them all to contain an electron withdrawing carbonyl functionality in a β-position from the nucleophilic amino group (*Figure* **72**).



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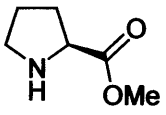
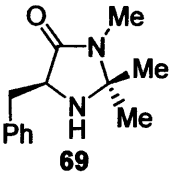


273

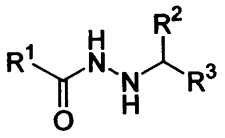


69

Figure **72**

Each of the above amines are proficient as aminocatalysts. Our objective was to generate a non-cyclic catalyst that would impart similar levels of aminocatalytic reactivity to these pyrrolidine-based systems. We therefore decided to mimic the characteristics of these systems by incorporating a carbonyl functionality into the structure of our linear secondary amine, in anticipation that this would provide the desired rate enhancement. To this end, we

designed a disubstituted hydrazide with an electron withdrawing carbonyl functionality in a position β to the nucleophilic amine (i.e. attached to the α-heteroatom) (*Figure* **73**).



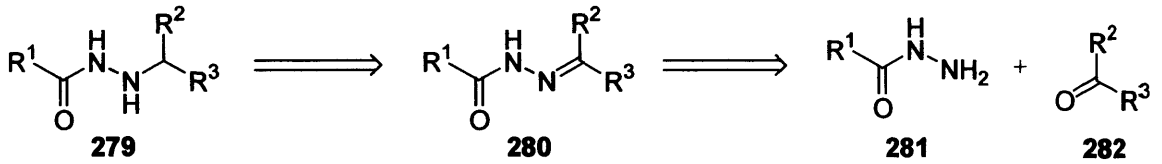
279

Figure **73**

Generic structure **279** would provide us with the opportunity to vary the nature of the carbonyl functionality (by variation of group R^1) so as to maximise catalytic activity. Groups R^2 and R^3 could also be varied, allowing both α-branched and α-unbranched amine systems to be investigated. Additionally, chirality could be incorporated into the molecule *via* the R^2 and R^3 positions, enabling this type of catalyst to be employed in asymmetric organocatalytic transformations.

3.4.1 Retrosynthetic Analysis of Generic Catalyst Structure

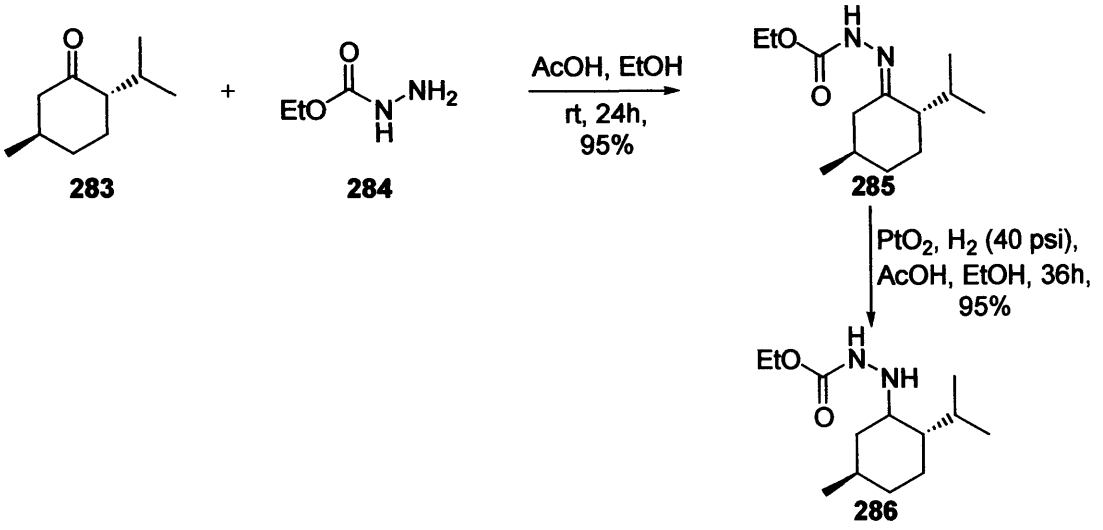
Analysis of disubstituted hydrazide **279** revealed that synthesis could be achieved from the corresponding hydrazine **281** and carbonyl compound **282** *via* a reductive amination protocol (*Figure* **74**).



279 **280** **281** **282**

Figure **74**

There is literature precedent for the use of a reductive amination to generate a system akin to **279**. For instance, Corey reported the use of such a procedure towards the synthesis of chiral hindered amines.[220] The method employed involved the condensation of (-)-menthone (**283**) with ethyl carbazate (**284**) in ethanol and acetic acid, which generated the corresponding hydrazone **285**. A subsequent hydrogenation using Adam's catalyst was applied, affording hydrazine **286** in a 90% yield for the two synthetic steps (*Scheme* **145**).



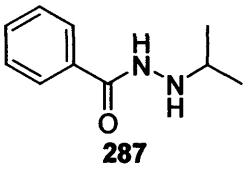
283 284 285 286

Scheme **145**

Utilisation of a reductive amination strategy should thus provide a rapid and efficient method for the synthesis of hydrazides with generic structure **279**.

3.5 Synthesis of Benzoic Hydrazide Derived Catalyst

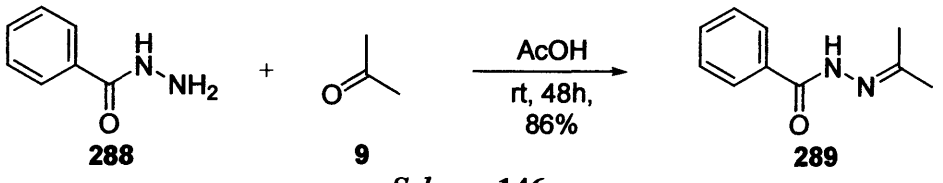
Our initial target was hydrazide **287** with a phenyl group in the R^1 position, and an α-branched group attached to the nucleophilic nitrogen atom ($R^2 = R^3 = Me$) (*Figure* **75**).



287

Figure **75**

Synthesis of **287** was achieved by stirring benzoic hydrazide (**288**) in an excess of acetone (**9**), in the presence of a catalytic amount of acetic acid. After stirring at room temperature for 48 hours, hydrazone **289** was furnished after aqueous work-up in an 86% yield, without any further purification required (*Scheme* **146**).

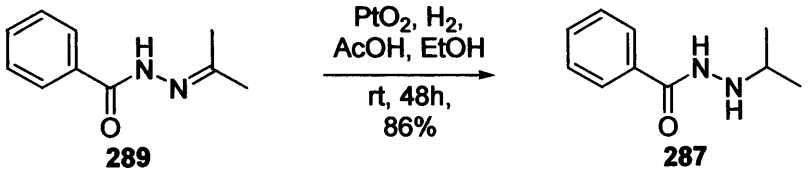


288 **9** **289**

Scheme **146**

Hydrazone **289** was then added to a solution of Adam's catalyst (PtO_2) in ethanol and acetic acid. The reaction flask was charged with hydrogen, and stirring was continued for 48 hours

at ambient temperature, before filtration through Celite®. Neutralisation with saturated aqueous sodium bicarbonate, followed by evaporation of the organic phase, afforded the desired hydrazide **287** in an 86% yield (*Scheme* **147**).[219] Further purification was not necessary.



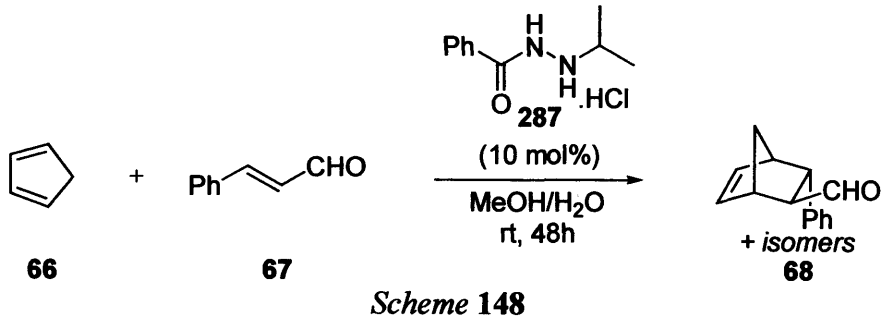
289 **287**

Scheme **147**

Synthesis of aminocatalyst **287** *was therefore achieved via a two step procedure, involving a condensation reaction followed by reduction of the resulting hydrazone* **289** *using Adam's catalyst. This furnished* **287** *in a 74% overall yield from commercially available benzoic hydrazide* (**288**).

3.6 Catalysis: Initial Investigations

We were then in a position to evaluate the ability of secondary hydrazide **287** to catalyse Diels-Alder cycloadditions.[219] We initially evaluated the reaction between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**), allowing us to compare the catalytic reactivity of hydrazide **287** and the commercially available amines previously utilised (See *Table* **5**, *Section* **3.3.1** for details) (*Scheme* **148**).



66 **67** **68**

Scheme **148**

The result of this study is tabulated below (*Table* **6**).

Table **6**[a]: Result of Initial Diels-Alder Cycloaddition Experiment

Entry	Product	% Yield	*Exo* : *Endo*[b]
1	**67**	93	67 : 33

(a) Reaction was carried out in methanol/water (19:1) at room temperature for 48h with 10 mol% catalyst **287** as a HCl salt. (b) The *exo*/*endo* ratio was obtained from the ^{1}H NMR of the crude reaction mixture.

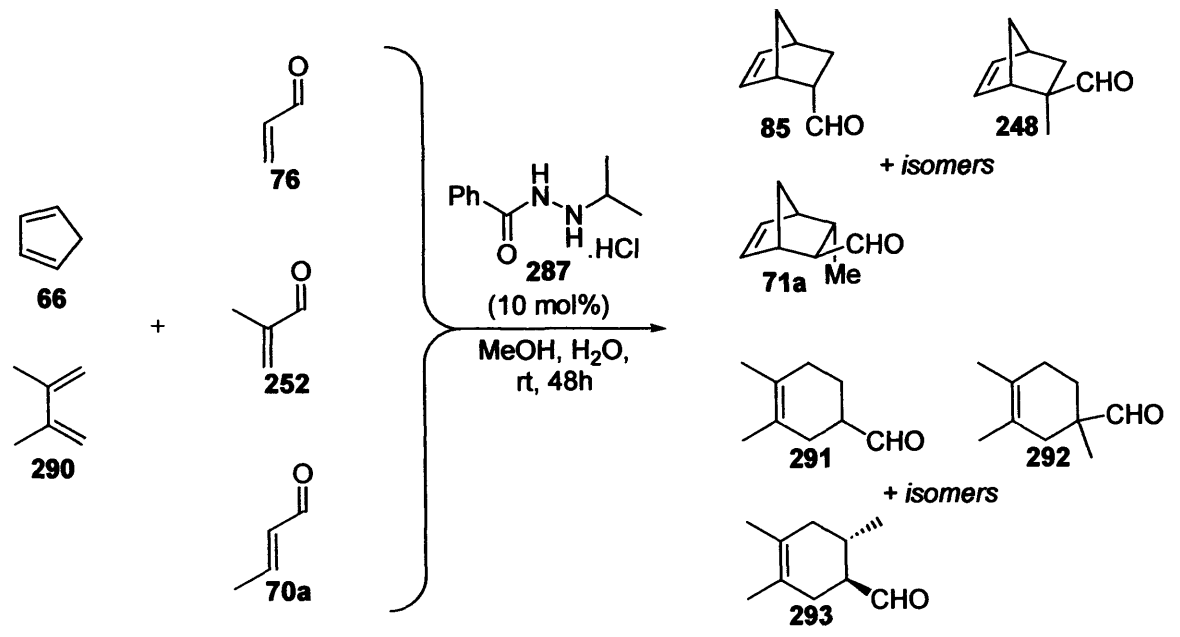
Introduction of the electron withdrawing group onto the α-heteroatom greatly increased the reactivity of our system, with the Diels-Alder reaction going to completion when catalysed by the hydrochloride salt of **287**. A similar *exo*:*endo* ratio of adduct **67** was obtained to that observed previously for the use of iminium ion catalysis. This suggested that the use of iminium ion catalysis for the acceleration of Diels-Alder reactions will reverse the selectivity often observed and provide a viable alternative to the Lewis acid catalysed process which tends to favour the *endo* isomer.[221]

Hydrazide **287**, *(as a protonic acid salt), therefore provided a rate acceleration comparable to that given by proline methyl ester* (**273**), *when employed as a catalyst for a Diels-Alder cycloaddition between cyclopentadiene* (**66**) *and E-cinnamaldehyde* (**67**). *With the basic reaction conditions established and proof that the α-effect was indeed a suitable platform with which to promote such organocatalytic processes, our catalytic investigations could begin.*

In order to accommodate the high throughput work, a Radley's® reaction station was purchased.[222] This allows the chemist to simultaneously run twelve reactions under an inert atmosphere, with the knowledge that each reaction has been subjected to exactly the same external conditions, creating the opportunity for more accurate comparisons.

3.6.1 Investigating the Generality of Our Catalyst

We desired our catalyst to be non-substrate specific, so in order to test the generality of our system, and to prove that we had indeed discovered a novel molecular scaffold for iminium ion catalysis, we carried out a series of reactions using hydrazide **287** as the catalyst, with acrolein (**76**), methacrolein (**252**) and crotonaldehyde (**70a**) as the dienophiles and cyclopentadiene (**66**) and 2,3-dimethylbuta-1,3-diene (**290**) as the dienes (*Scheme* **149**).



Scheme **149**

The results of this investigation are shown below (*Table* **7**).

Table **7**[a]: Variation of the Diene and Dienophile Components

Entry	Product	% Yield	*Exo* : *Endo*[b]
1	**85**	98	41 : 59
2	**248**	98	83 : 17
3	**71a**	98	54 : 46
4	**291**	97	-
5	**292**	98	-
6	**293**	89	-

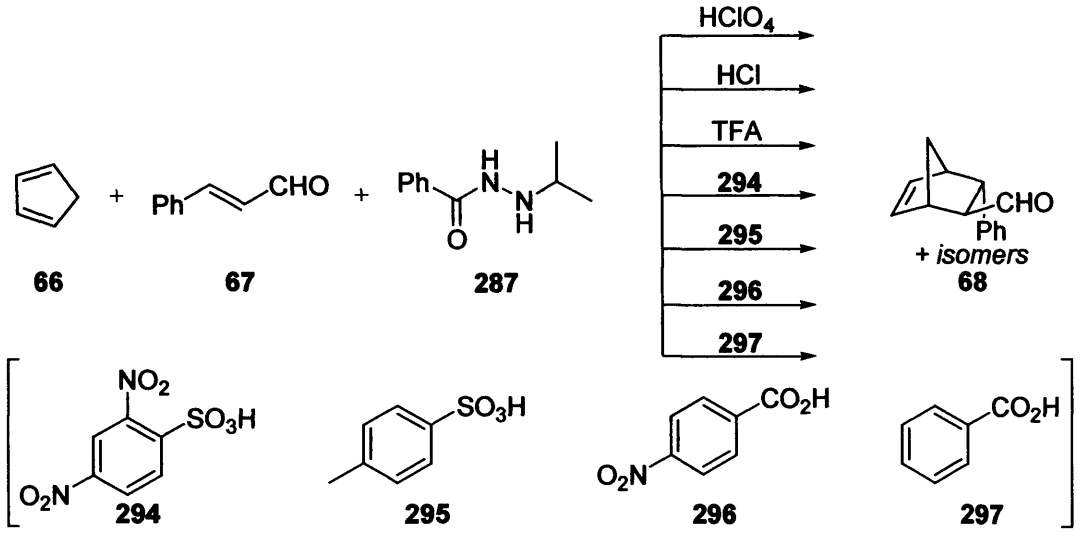
(a) All reactions were carried out in methanol/water (19:1) at room temperature for 48 hours with 10 mol% catalyst **287** as a HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture.

An excellent yield of the Diels-Alder adduct was attained from each of the cycloaddition reactions performed. The use of methacrolein (**252**) as the dienophile and cyclopentadiene (**66**) as the diene, afforded adduct **248** with the *exo*-isomer predominating (*Table* **7**, *entry* **2**). The reaction of cyclopentadiene with acrolein (**85**) showed a small preference for the *endo*-isomer (*Table* **7**, *entry* **1**), while with crotonaldehyde (**70a**) *exo* selectivity was observed (*Table* **7**, *entry* **3**). These results confirmed that catalytic reactivity can be greatly enhanced by taking advantage of the α-effect, suggesting that we had indeed discovered a novel molecular scaffold with which to promote aminocatalytic transformations. In addition, this

class of catalyst appeared to be general for the Diels-Alder reaction of α,β-unsaturated aldehydes with both cyclic and acyclic dienes.

3.6.2 Investigation into the Protonic Acid Co-Catalyst

To probe the effect of the selected protonic acid co-catalyst on the yield and selectivity of the Diels-Alder reaction, a set of experiments were carried out using *E*-cinnamaldehyde (**67**) as the standard dienophile, with cyclopentadiene (**66**) consistently employed as the diene and hydrazide **287** as the aminocatalyst. Each reaction was performed at ambient temperature in a methanol/water (19:1) solvent system (*Scheme* **150**). The results are shown below (*Table* **8**).



Scheme **150**

Table **8**[a]: Results of the Study into the Use of Various Protonic Acids

Entry	Protonic Acid	Time	% Yield	*Exo* : *Endo*[b]
1	$HClO_4$	48	95	64 : 36
2	**$HClO_4$**	**24**	**86**	**65 : 35**
3	HCl	48	93	65 : 35
4	HCl	24	64	62 : 38
5	TFA	48	81	67 : 33
6	**294**	48	82	65 : 35
7	**295**	48	74	64 : 36
8	**296**	48	21	67 : 33
9	**297**	48	10	53 : 47

(a) All reactions were carried out in methanol/water (19:1) at room temperature with 10 mol% catalyst **287**. (b) All *exo*/*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture.

These results showed that the rate of reaction was enhanced as the pK_a of the protonic acid was increased. This indicated that iminium ion formation is the rate determining step of the catalytic cycle, which can be rationalised since a stronger acid should more readily protonate the carbonyl substrate, thus enabling a more rapid formation of the iminium ion species.

Similar *exo/endo* ratios were observed with all of the protonic acids employed. The Diels-Alder reaction went to completion in 48 hours when using either perchloric acid or hydrochloric acid (*Table* **8**, *entries* **1** and **3**). Moreover, use of perchloric acid led to an 86% yield of adduct **68** in just 24 hours (*Table* **8**, *entry* **2**).

3.6.3 Choice of Solvent

We went on to repeat the catalytic Diels-Alder reaction between *E*-cinnamaldehyde (**67**) and cyclopentadiene (**66**) in a variety of solvent systems. Two polar protic solvents; methanol and ethanol, were studied along with the polar aprotic solvents; acetonitrile, dimethylformamide (DMF) and dimethylsulfoxide (DMSO). In addition, two apolar aprotic solvents; dichloromethane and toluene, were examined allowing us to monitor the effect that solvent had on both the yield and the selectivity of the aminocatalysed Diels-Alder reaction. The results of these experiments are tabulated below (*Table* **9**).

Table **9**[a]: Results of the Study Into the Use of a Variety of Solvents

Entry	Solvent	% Yield	*Exo* : *Endo*[b]
1	**MeOH**	**93**	**65 : 35**
2	EtOH	90	64 : 36
3	**CH_3CN**	**95**	**60 : 40**
4	DMF	44	59 : 41
5	DMSO	46	63 : 37
6	CH_2Cl_2	30	56 : 44
7	$PhCH_3$	6	57 : 43
8	H_2O	7	67 : 33

(a) All reactions were carried out in solvent/water (19:1) at room temperature for 48 hours with 10 mol% catalyst **287** as its HCl salt. (b) All *exo/endo* ratios were obtained from the ^1H NMR of the crude reaction mixture.

These results clearly showed that solubility issues resulted if the Diels-Alder reaction was carried out in aqueous solution (*Table* **9**, *entry* **8**). Therefore, use of an organic solvent was

necessary for catalytic activity. With apolar aprotic solvents low yields of adduct **68** resulted. An improvement was observed with DMF and DMSO, and full conversions were seen when the reactions were performed in the polar protic solvents as well as with acetonitrile. This suggested that a polar solvent was necessary for effective catalyst turnover. The presence of a polar solvent could possibly aid the stabilisation of the charged iminium ion intermediates that are formed during the catalytic cycle, so promoting catalytic activity.

We decided to continue our investigations using the two solvents that afforded the best results; namely methanol and acetonitrile (*Table* **9**, *entries* **1** and **3**). Further optimisation of the solvent system was examined by varying the water content, whilst performing the cycloaddition reactions under congruent conditions to those applied previously. The results of this study are outlined below (*Table* **10**).

Table **10**[a]: Results of the Study into Solvent/Water Ratio

Entry	Solvent	% Water Content	% Yield	*Exo* : *Endo*[b]
1	**MeOH**	**0**	**93**	**65 : 35**
2	MeOH	5	62	66 : 34
3	MeOH	10	55	64 : 36
4	MeOH	20	51	67 : 33
5	MeOH	50	25	62: 38
6	CH_3CN	0	87	57 : 43
7	CH_3CN	5	73	60 : 40
8	CH_3CN	10	57	61 : 39
9	CH_3CN	20	48	61 : 39
10	CH_3CN	50	19	59 : 41

(a) All reactions were carried out at room temperature for 24 hours with 10 mol% catalyst **287** as its HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture.

It was immediately apparent on examination of these results that higher yields were achieved as the water content was reduced. This was exemplified by the use of anhydrous methanol (*Table* **10**, *entry* **1**), which led to a significantly higher yield of adduct **68** compared to the result obtained when the reaction was performed in the presence of 5% water (*Table* **10**, *entry* **2**). Upon consideration of these observations, it was evident that the optimum result in terms of both yield and selectivity was achieved when anhydrous methanol was used as the solvent.

Performing the Diels-Alder cycloaddition in this solvent system provided adduct **68** in 93% yield in just 24 hours.

The results of our investigations (*See Sections* **3.6.2** *and* **3.6.3**) *led us to adopt the following standard conditions for the remainder of our studies: use of the catalyst as its perchloric acid salt, in anhydrous methanol as the organic medium, with the Diels-Alder cycloaddition carried out at room temperature over 24 hours.*

3.6.4 Examination of the Catalyst Loading

In any catalytic investigation, it is essential to determine the optimum catalyst loading. Expense is a valid consideration in the design of a catalyst and the lower the amount of catalyst employed, the more cost effective and appealing the process. We embarked upon an investigation into this matter, and performed Diels-Alder reactions between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**), catalysed by hydrazide **287** as its perchloric acid salt. Each reaction was performed in anhydrous methanol for 24 hours at ambient temperature. The loading of catalyst **287** was varied as tabulated below (*Table* **11**).

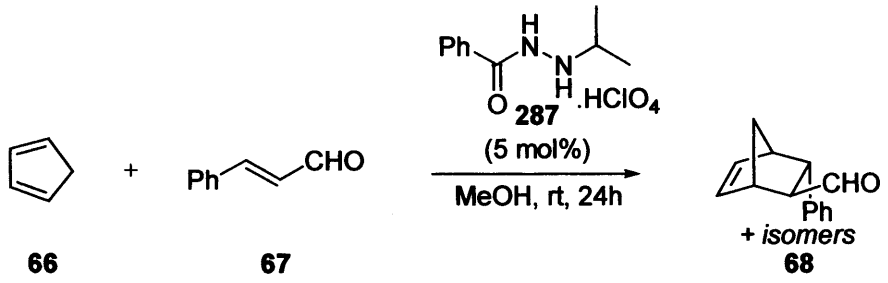
Table **11**[a]: Results of the Study into Catalyst Loading

Entry	Loading (mol%)	% Yield	*Exo* : *Endo*[b]
1	10	98	68 : 32
2	**5**	**97**	**66 : 34**
3	1	26	65 : 35

(a) All reactions were carried out in anhydrous methanol at room temperature for 24 hours with the catalyst **287** as its $HClO_4$ salt. (b) All *exo*/*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture.

This investigation revealed that lowering the catalyst loading of **287** from the standard 10 mol%, to 1 mol% had no adverse effect on the observed selectivity (*Table* **11**, *entries* **1** and **3**). A catalyst loading of 1 mol% provided adduct **68** in 26% yield after 24 hours. This result compares favourably to the literature precedent where catalyst loadings of 20 mol% are typically required for effective catalyst turnover.[7] In terms of both the amount of catalyst needed and the reaction time required for complete reaction, the optimal result was achieved with a catalyst loading of 5 mol%, which enabled the reaction to go to completion inside 24 hours (*Table* **11**, *entry* **2**).

From the above investigations (Tables **8**, **9**, **10** *and* **11**) *we were able to establish optimal reaction conditions for the aminocatalysed Diels-Alder reactions with hydrazide* **287**. *Use of 5 mol% of catalyst* **287**, *as its $HClO_4$ salt, catalysed the Diels-Alder reaction between cyclopentadiene* (**66**) *and E-cinnamaldehyde* (**67**) *to complete conversion in 24 hours when performed in anhydrous methanol at ambient temperature (Scheme* **151**).



Scheme **151**

Having determined optimal reaction conditions, we went on to investigate how changes in the catalyst structure, (for example the use of an α-unbranched hydrazide), affected the aminocatalytic Diels-Alder cycloaddition.

3.7 Variation of the Catalyst Structure

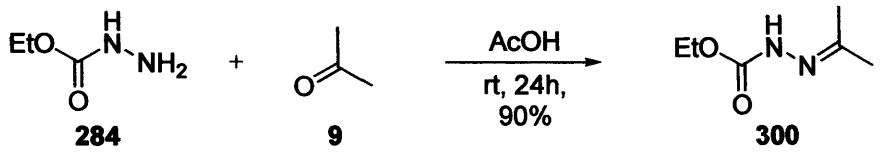
Variations were made to the structure of the catalyst, enabling us to monitor the effect these changes had on catalytic turnover. We chose to prepare catalyst **298** containing a carbamate functionality so that the nature of the electron withdrawing group attached to the α-heteroatom could be studied. Additionally, catalyst **299** with an α-unbranched group attached to the nucleophilic nitrogen atom was prepared, allowing us to determine how changes in steric encumbrance around the nucleophilic site affected the catalytic activity (*Figure* **76**).

298 **299**

Figure **76**

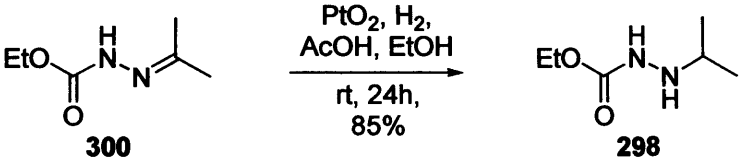
3.7.1 Preparation of Ethyl Carbazate Derived Catalyst

The condensation of ethyl carbazate (**284**) with acetone (**9**) under acid catalysed reaction conditions provided, after stirring at ambient temperature for 24 hours, hydrazone **300**. Upon isolation, a 90% yield of the desired product was furnished (*Scheme* **152**).[219]



Scheme **152**

A subsequent reduction to the corresponding hydrazine **298** was achieved using Adam's catalyst in an analogous procedure to that described previously (*Section* **3.5**). This afforded the desired product in an 85% isolated yield (*Scheme* **153**).

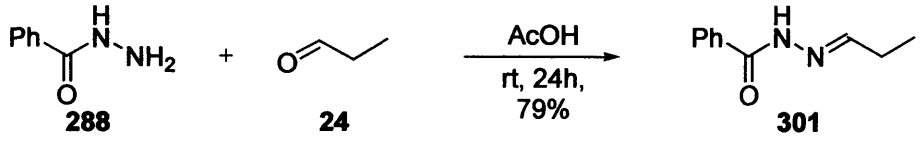


Scheme **153**

Aminocatalyst **298** *was therefore synthesised via a two step reductive amination protocol, furnishing* **298** *in a 77% overall yield from commercially available ethyl carbazate* (**284**). *This represents a simple, fast and reliable synthesis for the preparation of such systems.*

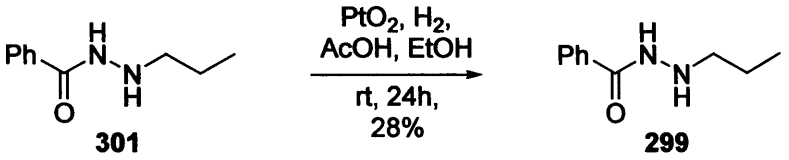
3.7.2 Synthesis of an α-Unbranched Catalyst

We went on to prepare an α-unbranched analogue of hydrazide **287**. Benzoic hydrazide (**288**) was reacted in an excess of propionaldehyde (**24**), in the presence of a catalytic amount of acetic acid. This afforded hydrazone **301** in 79% yield (*Scheme* **154**).



Scheme **154**

Purification of hydrazone **301** was not required, hence hydrogenation to the desired hydrazine **299** was performed. Hydrazone **301** was added to a suspension of Adam's catalyst in ethanol and acetic acid. The flask was charged with hydrogen, and stirring was continued for 24 hours at ambient temperature (*Scheme* **155**).



Scheme **155**

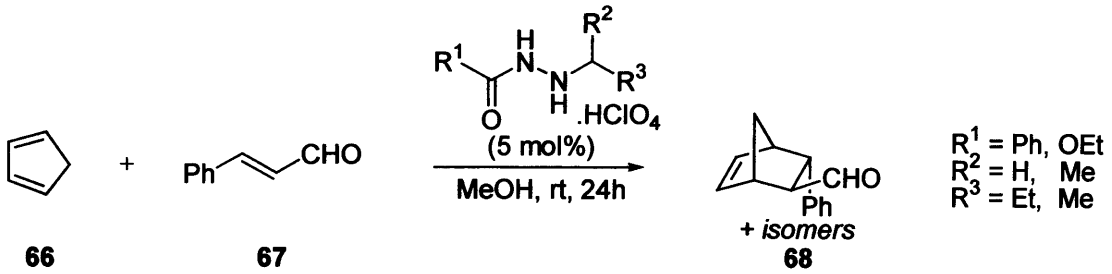
The crude reaction material was purified by column chromatography to afford the desired hydrazide **299** in 28% yield.

Preparation of the α-unbranched hydrazide **299** *was thus achieved from commercially available benzoic hydrazide* (**288**), *via a condensation with propionaldehyde* (**24**), *followed by reduction using Adam's catalyst. This provided a 22% yield of the desired product* **299** *over the two synthetic steps. This process was not as clean compared to the previous condensations performed with acetone* (**9**), *hence purification by column chromatography was required.*

Having successfully synthesised catalysts **298** and **299**, we were ready to embark upon an investigation into the nature of the electron withdrawing group on the α-heteroatom, and how this affected both the catalytic turnover and the selectivity resulting from an iminium ion catalysed transformation. Investigations into the effects resulting from changes in steric density around the nucleophilic nitrogen atom would also be performed.

3.7.3 Diels-Alder Aminocatalysis With Modified Catalysts

We went on to probe the influence of catalyst structure on the outcome of an aminocatalytic Diels-Alder reaction. Each catalyst was employed in the cycloaddition of *E*-cinnamaldehyde (**67**) and cyclopentadiene (**66**) under our optimised reaction conditions (See *Section* **3.6**). This allowed for a direct comparison between hydrazides **287**, **298** and **299** (*Scheme* **156**).



66 **67** **68**

Scheme **156**

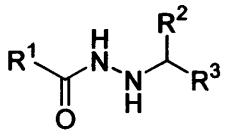
The results of this catalytic investigation are tabulated below (*Table* **12**).

Table **12**[a]: Results of the Study into Catalyst Structure

Entry	Catalyst	% Yield	*Exo* : *Endo*[b]
1	**287**	97	66 : 34
2	**298**	96	63 : 37
3	**299**	93	65 :35

(a) All reactions were carried out in anhydrous methanol at room temperature for 24 hours with 5 mol% catalyst as its $HClO_4$ salt. (b) All *exo*/*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture.

Each hydrazide catalyst provided Diels-Alder adduct **68** with similar *exo*/*endo* ratios, and the *exo* isomer was formed predominately in each case. This suggested that iminium ion catalysis was transpiring with each of the catalysts employed. In addition, each hydrazide catalyst promoted the Diels-Alder reaction to completion within 24 hours at room temperature. These results indicated that alterations to the steric environment of the nucleophilic site had little effect on the yield or selectivity of the aminocatalytic Diels-Alder reaction. Moreover, no detrimental effect was observed upon variation of the electron withdrawing group attached to the α-heteroatom. Thus, the catalyst is tolerant to structural modifications, which bodes well for future development of an asymmetric version based on generic structure **279** (*Figure* **77**).



279

Figure **77**

We had therefore established the ability of catalysts with generic structure **279** *to promote Diels-Alder cycloadditions. Ultimately we aspired to design a catalyst that was able to promote a variety of asymmetric transformations. The above results suggested that modifications to the catalyst structure should be possible, enabling us to incorporate asymmetry into the system.*

Before moving on to investigate asymmetric versions of aminocatalyst **279**, we first wanted to establish if catalysts with such a generic structure were suitable for use in organocatalytic transformations other than the Diels-Alder reaction.

3.8 Aminocatalytic Conjugate Addition Reactions

We were interested to see if catalyst **287** could catalyse the conjugate addition of an aromatic or heteroaromatic donor to an α,β-unsaturated acceptor component. Traditionally, these alkylation reactions are promoted using a Lewis acid, such as $AlCl_3$, commonly known as the Friedel-Crafts reaction.[112] This represents a powerful method for the formation of carbon-carbon bonds,[113] but relatively few asymmetric versions have been reported,[114] despite the widespread availability of electron-rich aromatics and the chemical utility of the resulting products.

The asymmetric alkylation of pyrroles,[116] indoles[119] and electron rich benzenes[124] has been reported by MacMillan using imidazolidinone catalysts **69** and **79** (*Figure* **78**). These aminocatalysts led to the formation of conjugate addition products with high levels of enantioselectivity.

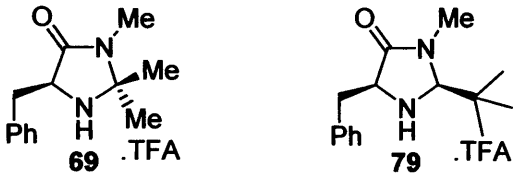


Figure **78**

The observed selectivity can be explained by the formation of an active iminium ion intermediate between the imidazolidinone catalyst and the carbonyl component. The *si*-face of the resulting α,β-unsaturated species is shielded by the aromatic ring, which forces the nucleophile to attack from the *re*-face (lower face), leading to the observed enantioselectivity (*Figure* **79**).[119]

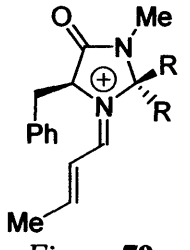
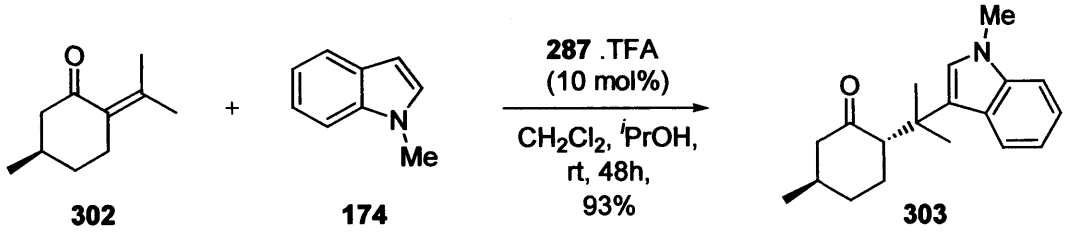


Figure **79**

For a more detailed discussion of aminocatalytic conjugate addition reactions see *Chapter* **1**, *Section* **1.16**.

3.8.1 Organocatalytic Indole Alkylation

In order to test the ability of our hydrazide catalysts to promote reactions other than Diels-Alder cycloadditions, we decided to perform an aminocatalytic indole alkylation reaction. To this end, we reacted *N*-methylindole (**174**) with *R*-(+)-pulegone (**302**) in the presence of 10 mol% hydrazide **287** as its trifluoroacetic acid salt. Stirring this mixture in a solvent system of dichloromethane and *iso*propanol (85:15) at ambient temperature for 48 hours furnished adduct **303** as a single diastereoisomer (*Scheme* **157**).



302 **174** **303**

Scheme **157**

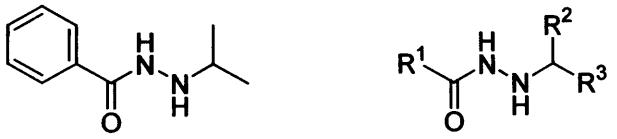
Purification by column chromatography provided adduct **303** in 93% isolated yield. This result demonstrated the ability of catalyst **287** to promote conjugate addition reactions, suggesting that compounds with generic structure **279** may be suitable as aminocatalysts for a variety of chemical transformations.

Although an isolated example, this still represents a significant result for this class of transformation. It is the first example of an aminocatalytic conjugate addition to an α,β-unsaturated ketone and also represents the first example of an addition to a hindered disubstituted carbon atom, which could be extended to the formation of chiral quaternary centres, arguably the most significant challenge for catalytic asymmetric synthesis. The reaction also formed the new chiral centre on the cyclohexane ring with complete stereoselectively, providing the thermodynamically more stable diastereoisomer (**303**) as the only isolatable product in an excellent 93% isolated yield.

The α-effect was once again shown to be a suitable platform with which to promote catalytic reactivity. We had successfully utilised secondary hydrazides with generic structure **279** *to catalyse both Diels-Alder cycloadditions and an indole alkylation, showing the potential for such systems to be employed in a multitude of aminocatalytic processes, operating via an iminium ion activation pathway. With a suitable molecular scaffold determined, we were then in a position to investigate the formation of chiral versions of catalyst* **279**, *which should enable us to study asymmetric aminocatalytic transformations.*

3.9 Conclusions

In summary, we had established that the α-effect was a suitable platform for the acceleration of aminocatalytic transformations. Hydrazide **287** (*Figure* **80**) provided a similar level of reactivity to pyrrolidine-based proline methyl ester (**273**), when employed in the catalysis of Diels-Alder cycloaddition reactions. Catalyst **287** was found to be non-substrate specific with respect to α,β-unsaturated aldehydes, and allowed cycloadditions to be performed with both cyclic and acyclic dienes.



287 **279**

Figure **80**

Optimal results were achieved when using catalyst **287** as its perchloric acid salt, with a catalyst loading of 5 mol%. Use of this catalytic system for a Diels-Alder cycloaddition between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**), in anhydrous methanol, gave complete conversion to adduct **68** in 24 hours.

Modifications were made to the catalyst structure, providing hydrazides **298** and **299**. Use of these compounds in Diels-Alder catalysis demonstrated that our catalytic system was tolerant to changes in the nature of the electron withdrawing group attached to the α-heteroatom, as well as to modifications to the steric density around the nucleophilic nitrogen atom. This bodes well for the future development of a chiral analogue of secondary hydrazide **279** (*Figure* **80**).

Having established the ability of hydrazide **287** to catalyse Diels-Alder cycloadditions, we went on to examine another aminocatalytic transformation; namely a conjugate addition of *N*-methylindole (**174**) to *R*-(+)-pulegone (**302**). Complete conversion to adduct **303** was observed in 48 hours at ambient temperature, with a single diastereoisomer of **303** formed. This result suggests that secondary hydrazides with generic structure **279** may be capable of catalysing a variety of chemical transformations involving α,β-unsaturated carbonyl components.

3.10 The Future

We were then in a position to design and synthesise an asymmetric hydrazide, which would hopefully be suitable as a catalyst for enantioselective aminocatalytic transformations. Incorporated into the design of such a system would be an aromatic functionality that should provide a second point of interaction between the catalyst and the α,β-unsaturated carbonyl moiety, in the form of an attractive face-face π–π interaction. Modifications to the electronics of this aromatic functionality should enable us to investigate and probe the nature of these non-covalent interactions and the subtleties associated with their existence.

Chapter 4: Results and Discussion

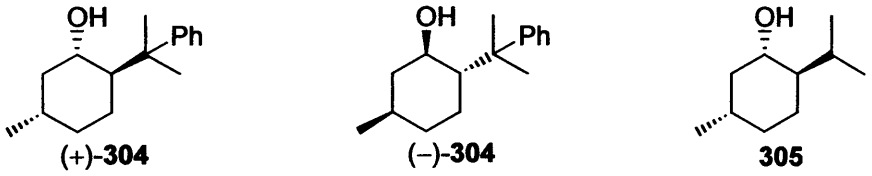
4.1 Introduction

Having established that the α-effect was indeed a suitable platform with which to promote aminocatalytic transformations (see *Chapter* **3**), we were then in a position to design and synthesise an asymmetric hydrazide, which would hopefully be amenable as a catalyst for a range of enantioselective aminocatalytic transformations. We aspired to incorporate into the design of this system a second point of interaction between the catalyst and the α,β-unsaturated carbonyl moiety, in the form of an attractive face-face π–π interaction. This would be achieved *via* the incorporation of an aromatic functionality into the catalyst structure. Modifications to the electronics of this aromatic group should enable us to investigate and probe the nature of these non-covalent interactions and the subtleties associated with their existence, which was indeed our primary aim at the onset of this project.

A suitable molecular scaffold to promote catalytic activity, as well as enable a study into the existence of π–π interactions needed to be determined. Chapter four of this thesis will be concerned with the design and synthesis of a suitable family of asymmetric aminocatalysts that can discriminate between the prochiral faces of α,β-unsaturated carbonyl compounds. The use of this catalyst family in asymmetric organocatalysis will be discussed along with our investigations into the nature of π–π interactions.

4.1.1 8-Phenyl Menthol

Since its introduction in 1975 by Corey and Ensley,[62] 8-phenyl menthol (**304**) has found widespread use as a chiral auxiliary in organic synthesis. Auxiliary **304** has provided dramatically superior levels of diastereomeric discrimination when compared to other commonly used chiral auxiliaries, such as menthol (**305**) (*Figure* **81**).

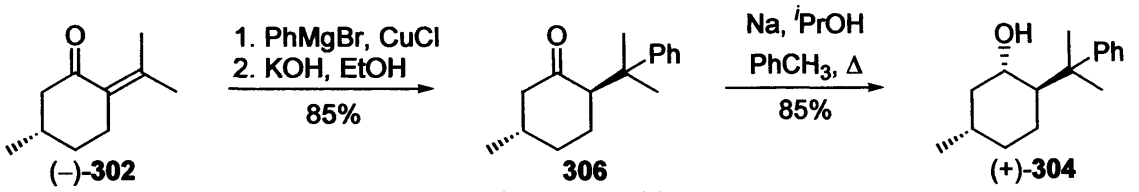


(+)-**304** (−)-**304** **305**

Figure **81**

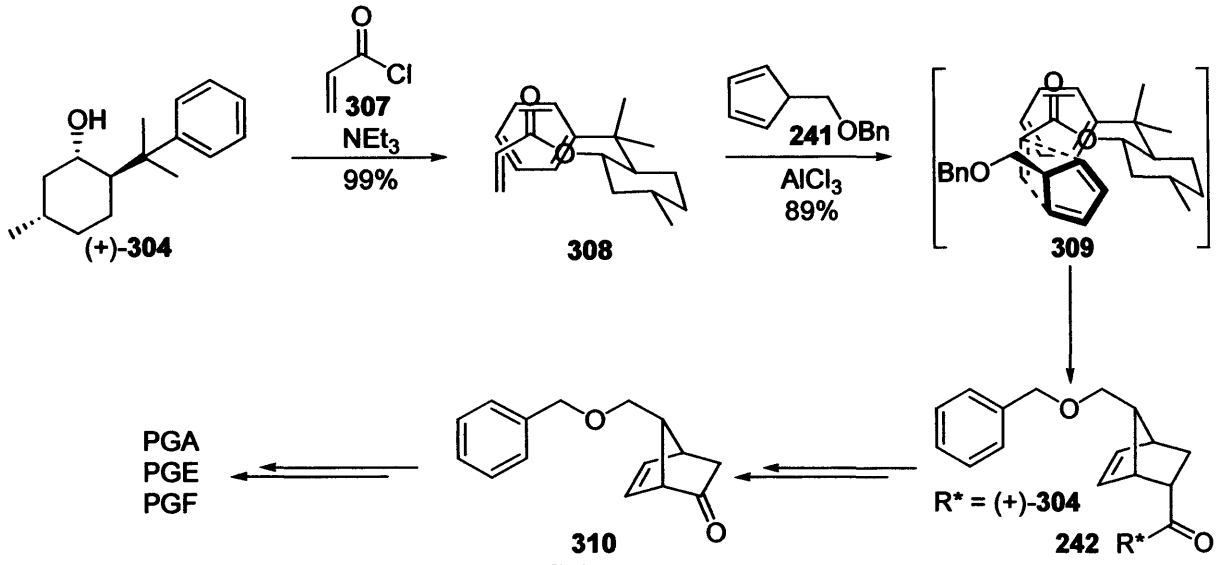
Corey designed 8-phenyl menthol (**304**) as a chiral auxiliary for use in the synthesis of a key prostaglandin intermediate, in order to circumvent the need for classical chemical resolution.[62]

Synthesis of chiral auxiliary **304** was achieved from (-)-pulegone (**302**), *via* alkylation, equilibration and reduction to give (+)-**304** in a 72% overall yield (*Scheme* **158**).[223]



Scheme **158**

Treatment of (+)-8-phenyl menthol (**304**) with acryloyl chloride (**307**) gave acrylate **308** in 99% yield. A Diels-Alder cycloaddition between acrylate **308** and 5-benzyloxymethyl-cyclopentadiene (**241**) furnished adduct **242** in 89% yield and 97% diastereomeric excess (*Scheme* **159**). Adduct **242** was then converted to intermediate **310**, *en route* to the formation of prostaglandins PGA, PGE and PGF.[62]

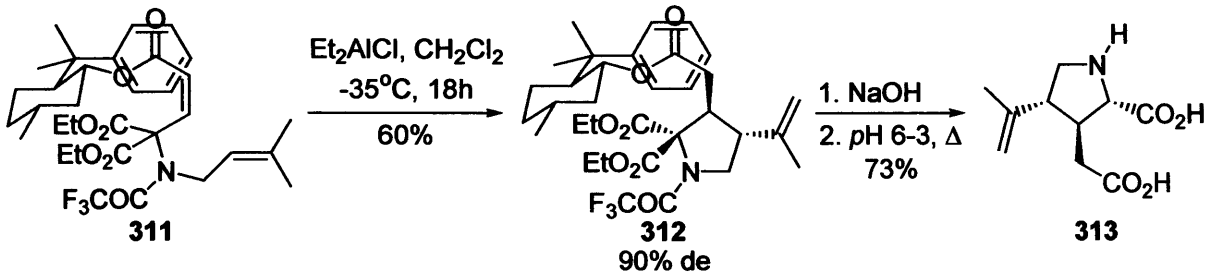


Scheme **159**

Unfortunately, the use of (+)-8-phenyl menthol (**304**) as a general chiral auxiliary has been restricted by the prohibitive cost of (-)-pulegone (**302**). However, its enantiomer (-)-8 phenyl menthol (**304**), which can be formed from (+)-pulegone (**302**), has become one of the most powerful and widely used chiral auxiliaries in organic synthesis.[179b]

(-)-8-Phenyl menthol (**304**) has been used as a chiral auxiliary for several chemical transformations including the ene reaction,[224] conjugate additions,[225] and cycloadditions ([3+2][226] and [4+2][62]). The use of (-)-8-phenyl menthol (**304**) was first exploited in the early 1980's, when Oppolzer used this chiral auxiliary to promote stereoselective direct intramolecular ene reactions. Treatment of the *Z*-dienyl ester **311**, derived from (-)-8-phenyl

menthol (**304**), with diethyl aluminium chloride or dimethyl aluminium chloride led to intramolecular ene cyclisation product **312** in a 60% yield with 90% diastereomeric excess. Subsequent conversion to the naturally occurring α-allokainic acid (**313**) was achieved *via* a two-step saponification and decarboxylation protocol (*Scheme* **160**).[227]



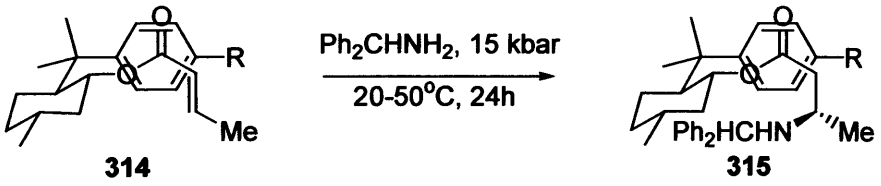
Scheme **160**

Treatment of the *E*-isomer of **311** under analogous reaction conditions provided enantiomeric α-allokainic acid (**313**) in 70% ee, effectively circumventing utilisation of the more costly (+)-8-phenyl menthol (**304**) chiral auxiliary.

It has been postulated that the high levels of stereocontrol observed for the use of 8-phenyl menthol (**304**) as a chiral auxiliary result from an attractive π–π interaction between the aromatic portion and the acrylate group (*Figure* **82**). This π-shielding of the rear face of the acrylate unit forces reactive attack solely to the top face, leading to the observed stereoselectivity.

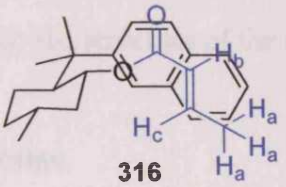
Figure **82**

The conjugate addition of amines to 8-aryl menthol crotonates was studied by d'Angelo.[228] Structural modifications were made to the aryl group, which provided valuable insight into the requirements for effective stereocontrol and therefore π-stacking interactions.



Scheme **161**

Higher stereoselectivity was observed in the conjugate addition to the 2-naphthyl menthol ester (>99% de) compared to the corresponding phenyl (R = H; 50% de), 4-*tert*-butylphenyl (R = *t*-Bu; 75% de), or 4-phenoxyphenyl (R = PhO; 95% de) menthol esters. The presence of the larger aromatic architecture presumably leads to better overlap of the entire alkene portion with the aromatic rings of the naphthyl-containing chiral auxiliary, providing an enhanced level of stereocontrol (*Figure* **83**).



316

Figure **83**

This hypothesis was supported by NMR studies performed on the 8-aryl menthol crotonates. The alkene protons (H_b and H_c) were shifted upfield in the phenyl and naphthyl menthol crotonates **316**, whereas the crotonate methyl protons (H_a) were only shifted upfield significantly in the 2-naphthyl menthol crotonate.[228] This suggests that only the vinylic protons of the crotonate unit are shielded by the phenyl group of the 8-phenyl menthol crotonate, whereas all protons in the crotonate moiety (including the methyl group) are shielded by the naphthyl substituent of the 2-naphthyl menthol crotonate.

4.1.2 Fundamental Contribution?

π–π Interactions were invoked to explain the stereochemical outcome of reactions using the chiral auxiliary, 8-phenyl menthol (**304**), however, the exact nature of the 'π-stacking effect' is still a subject of some debate in the synthetic organic and computational arenas. The design of processes which harness their full potential will not be possible until the origins of these non-covalent interactions are fully understood.

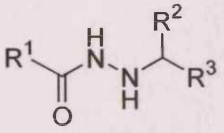
At the onset of this project our aim was to investigate and ultimately understand the nature of face-face π–π interactions and the subtleties associated with their existence. We therefore sought to design and synthesise a chiral aminocatalyst for use in a series of asymmetric transformations, that would enable us to investigate these non-covalent interactions. The α-effect would be used as a platform with which to promote catalysis, using the information ascertained in *Chapter* **3** as a basis for the catalytic design.

4.2 Design Concept

The challenge ahead was the rational design of an aminocatalyst that was non-substrate specific and non-reaction specific. The formation of an iminium ion would result from the reaction of the aminocatalyst with an α,β-unsaturated carbonyl compound. We aspired to incorporate a second point of interaction into the catalytic system, in the form of an attractive face-face π–π interaction between the double bond of the α,β-unsaturated carbonyl reagent and an aromatic ring incorporated into the structure of the aminocatalyst.

4.2.1 Proposed Aminocatalyst Design

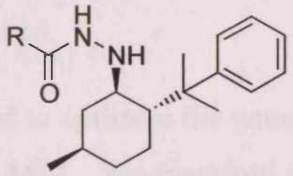
Generic structure **279** (*Figure* **84**) has been identified as a suitable molecular scaffold with which to promote a variety of aminocatalytic transformations involving α,β-unsaturated carbonyl compounds (see *Chapter* **3**).



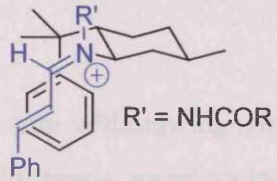
279

Figure **84**

Our next aim was to incorporate asymmetry into the structure of **279** to enable the study of enantioselective aminocatalytic processes. We sought to integrate some of the features of the 8-phenyl menthol chiral auxiliary (**304**), which has provided high levels of diastereomeric control in a range of chemical transformations, into the design of our catalyst. Thus, we aimed to synthesise 8-phenyl menthamine **317** (*Figure* **85**), containing a hydrazine subunit with an electron withdrawing carbonyl group attached to the α-heteroatom.



317



318

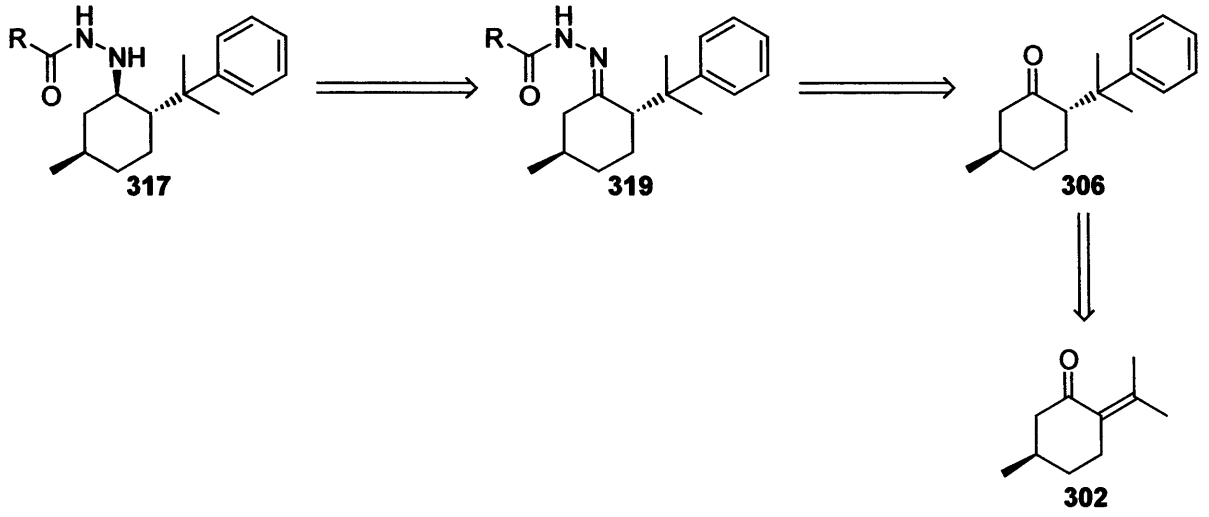
Figure **85**

Reaction of 8-phenyl menthamine **317** with an α,β-unsaturated carbonyl compound should provide iminium ion **318** (*Figure* **85**), with the possibility of an attractive face-face π–π interaction between the aromatic portion and the α,β-unsaturated moiety. Subtle modifications to the electronics of the aromatic ring of **317** should enable an investigation into

the effect on the strength of the proposed π–π interactions and hence on the selectivity observed in catalytic asymmetric transformations.

4.2.2 Retrosynthetic Analysis of 8-Phenyl Menthamine

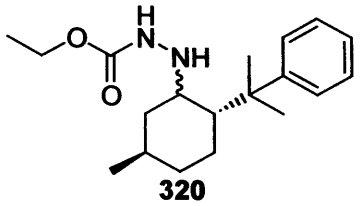
Retrosynthetic analysis of our proposed aminocatalyst, 8-phenyl menthamine **317**, shows a prospective synthesis from commercially available (*R*)-(+)-pulegone (**302**) (*Scheme* **162**).



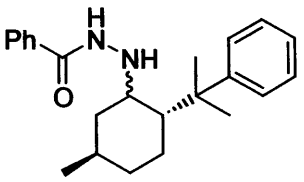
Scheme **162**

Conjugate addition, with subsequent equilibration, following the procedure of Ort,[223] should provide 8-phenyl menthone (**306**) from commercially available (*R*)-(+)-pulegone (**302**). Modifications to the aromatic group should be achievable by using a variety of nucleophiles in the conjugate addition step. Reaction of 8-phenyl menthone (**306**) with a mono-substituted hydrazine should provide hydrazone **319**, which could be converted to hydrazide **317** *via* a subsequent hydrogenation step. The use of a range of mono-substituted hydrazines in this reductive amination sequence should enable the nature of the electron withdrawing carbonyl group (R) to be varied.

We initially wished to optimise the nature of the electron withdrawing carbonyl substituent R (see **317**, *Scheme* **162**). We therefore decided to synthesise menthamines **320** and **321**, by employing ethyl carbazate (**284**) and benzoic hydrazide (**288**) respectively, in the reductive amination step (*Figure* **86**).



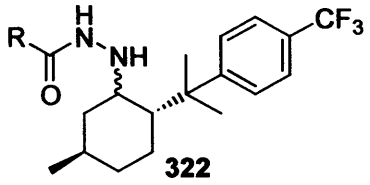
320



321

Figure **86**

Once the optimal carbonyl substituent had been determined, modifications to the nature of the aromatic functionality would ensue. We planned to synthesise the 4-trifluoromethylphenyl (**322**), 4-methoxyphenyl (**323**), 2-naphthyl (**324**) and 3-indolyl (**325**) menthamines (*Figure* **87**), which should enable an investigation into the effect on the strength of the proposed π–π interactions.



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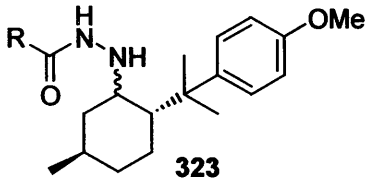

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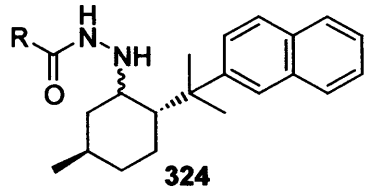

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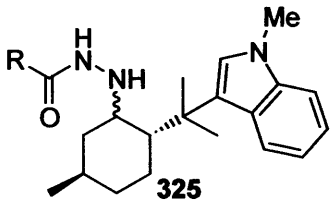
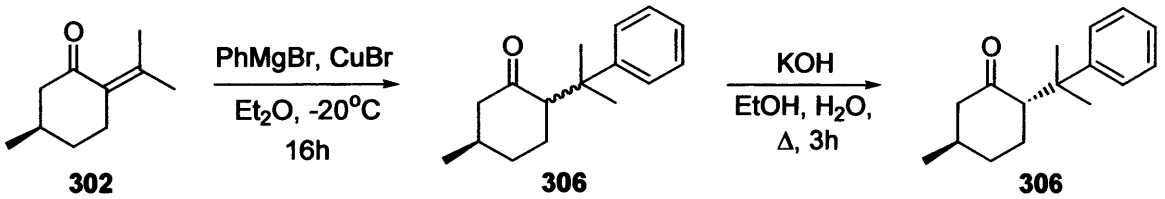


325

Figure **87**

4.3 Synthesis of 8-Phenyl Menthamine Derivative

Synthesis of aminocatalyst **320** was achieved from (*R*)-(+)-pulegone (**302**), which was reacted with phenylmagnesium bromide in the presence of copper bromide, in diethyl ether at –20°C (*Scheme* **163**). Stirring was continued at this temperature overnight under an inert atmosphere, which provided crude 8-phenyl menthone (**306**) as a mixture of diastereoisomers; 55:45 *trans*/*cis* (*Scheme* **163**).[223]



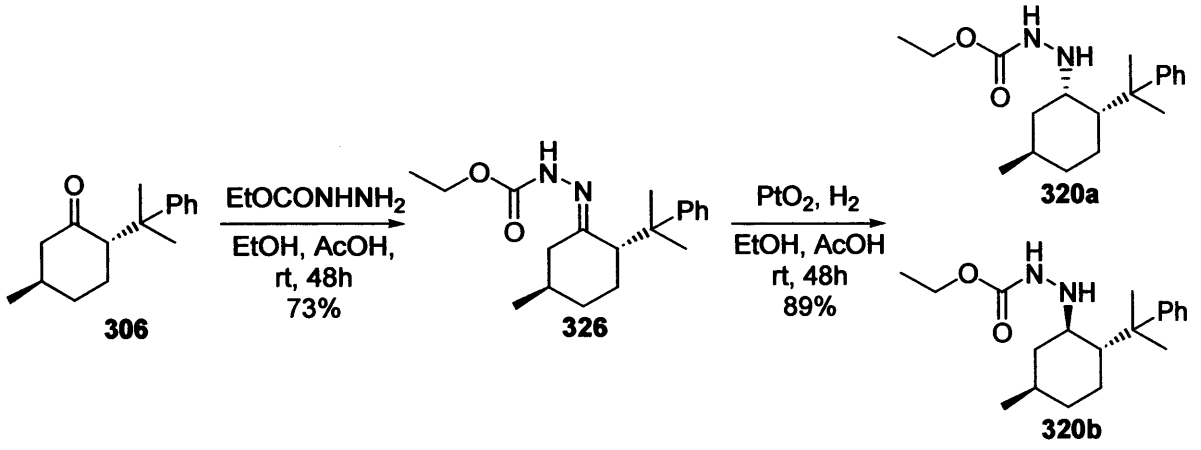
302 **306** 55:45 *trans*/*cis* **306**

Scheme **163**

Equilibration to the desired *trans*-**306** isomer was achieved by reacting the crude product with potassium hydroxide in aqueous ethanol at reflux temperature for 3 hours. The crude product

obtained after reaction comprised an 85:15 mixture of *trans/cis* isomers. Separation and purification of the desired *trans*-isomer was achieved by column chromatography to give a 71% isolated yield of *trans*-**306** over the two synthetic steps.

8-Phenyl menthone (**306**) was then reacted with ethyl carbazate (**284**) in a mixture of ethanol and acetic acid. Stirring of this solution at room temperature for 48 hours provided hydrazone **326** in 73% yield after purification by column chromatography on silica gel (*Scheme* **164**).[220]



Scheme **164**

Hydrogenation of hydrazone **326**, using Adam's catalyst in a solution of ethanol and acetic acid, provided hydrazines **320a** and **320b** in a ratio of 80:20. Separation of these two diastereoisomers was achieved by column chromatography, which afforded hydrazine **320a** in 72% yield, and hydrazine **320b** in 17% isolated yield. Both diastereoisomers were suitable as asymmetric aminocatalysts, as each contained a hydrazide functionality within a chiral environment, thus, both **320a** and **320b** were tested for their ability to promote enantioselective processes (see later).

The relative stereochemistry of each of the diastereoisomers was determined using ^{1}H NMR coupling constants. For hydrazine **320a** the proton, H, alpha to the amino group is in an equatorial position and will couple to the three hydrogen atoms, H (*Figure* **88**). Thus, one equatorial-equatorial (~3-6 Hz), and two equatorial-axial couplings (~3 Hz) result. As such, the ^{1}H NMR peak corresponding to proton H in **320a** should be a double-double-doublet, with three small coupling constants.

320a **320b**

Figure **88**

The proton, H, alpha to the hydrazine functionality in **320b** lies in an axial position (*Figure* **88**), and will couple to the three hydrogen atoms H. Therefore, two axial-axial couplings (~10 Hz) and one axial-equatorial coupling (~3 Hz) result, hence the ^{1}H NMR peak corresponding to proton H in **320b** should be a double-double-doublet, with two large and one small coupling constant. Analysis of the ^{1}H NMR spectrum of each diastereoisomer therefore allowed us to confidently assign the relative stereochemistry to each of the product hydrazines.

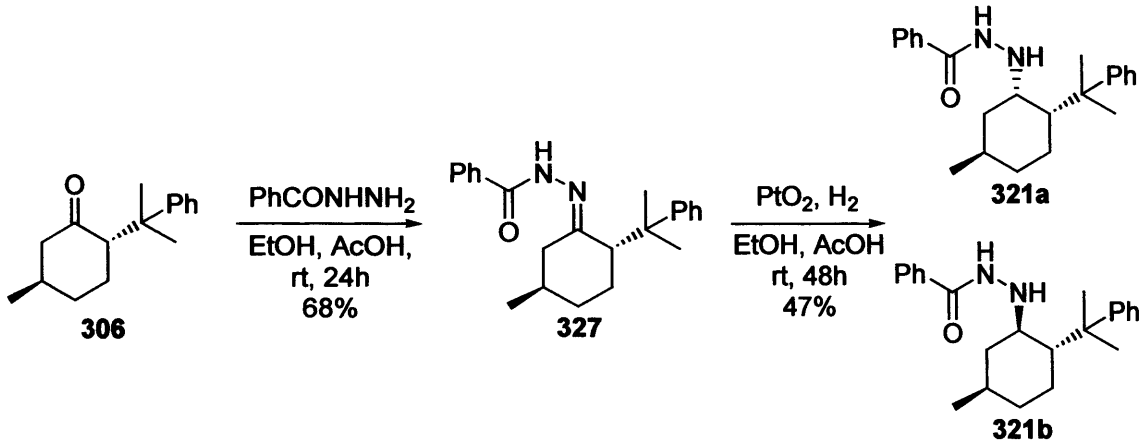
We had therefore successfully synthesised two aminocatalysts based on the structure of 8-phenyl menthamine. Catalysts **320a** *and* **320b** *were generated from the reaction of 8-phenyl menthone* (**306**) *with ethyl carbazate* (**284**)*, followed by hydrogenation with Adam's catalyst. This furnished catalysts* **320a** *and* **320b** *in 37% and 9% yield, respectively, over the four synthetic steps. The relative stereochemistry of each diastereoisomer was assigned by analysis of the ^{1}H NMR coupling constants of each compound.*

4.4 Investigation into the Nature of the Carbonyl Functionality

Our previous studies into the use of the α-effect as a platform for aminocatalytic transformations determined that generic structure **279** was a suitable molecular scaffold from which to design effective aminocatalysts (see *Chapter* **3**). An electron withdrawing carbonyl functionality attached to the α-heteroatom was found to be necessary for effective catalytic turnover. Catalysts **320a** and **320b**, synthesised above (*Section* **4.3**), contained a carbamate functionality derived from ethyl carbazate (**284**). In order to ascertain the effect of this carbonyl function on the catalytic abilities of our system, we elected to synthesise hydrazine **321** containing an amide unit derived from benzoic hydrazide (**288**). This should allow for a direct comparison between catalysts **320** and **321**, enabling us to determine the effect of the carbonyl moiety on catalytic turnover.

Synthesis of menthamine **321** was achieved by an analogous route to that employed for the generation of hydrazines **320a** and **320b** (see *Schemes* **163** & **164**). 8-Phenyl menthone (**306**)

was reacted with benzoic hydrazide (**288**), which provided hydrazone **327** in 68% yield after purification, and subsequent reduction to the corresponding hydrazine was performed using Adam's catalyst (*Scheme* **165**).



Scheme **165**

After the hydrogenation step a mixture of hydrazines **321a** and **321b** resulted. Separation and purification was once again achieved by column chromatography, which provided **321a** in 28% yield and hydrazine **321b** in 19% yield. The relative stereochemistry of hydrazines **321a** and **321b** was assigned using data from the ^{1}H NMR spectra of each compound. Both hydrazine products **321a** and **321b** contained a secondary hydrazine unit attached to an 8-phenyl menthamine backbone, and thus each compound was employed as an aminocatalyst (see later).

The synthesis of two aminocatalysts derived from benzoic hydrazide (**288**) *was therefore achieved. This furnished catalysts* **321a** *and* **321b** *in 14% and 9% yield, respectively, over the four synthetic steps from commercially available (R)-(+)-pulegone* (**302**). *The relative stereochemistry of each diastereoisomer was assigned using ^{1}H NMR coupling constants.*

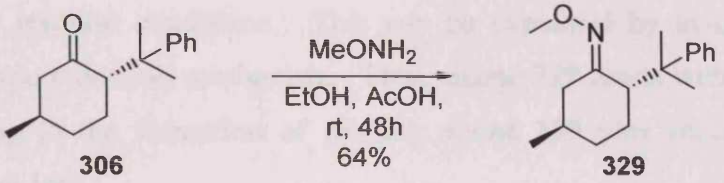
4.5 Investigation into the Nature of the α-Heteroatom

The four 8-phenyl menthamine catalysts, **320a**, **320b**, **321a** and **321b**, synthesised thus far all contained a nitrogen atom alpha to the catalytic site. We wanted to see how replacing the α-nitrogen atom with an α-oxygen atom affected the catalytic activity of these 8-phenyl menthamine aminocatalysts. We therefore embarked upon an investigation into the synthesis of methoxylamine-derived catalyst **328** (*Figure* **89**).

328

Figure **89**

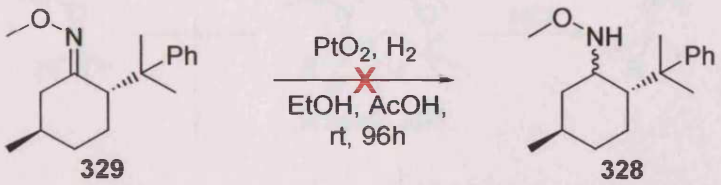
Our attempts to synthesise **328** began from 8-phenyl menthone (**306**), which was reacted with methoxylamine hydrochloride under acidic conditions. This procedure afforded oxime **329** in 64% yield after isolation from the reaction mixture and purification by column chromatography (*Scheme* **166**).



306 **329**

Scheme **166**

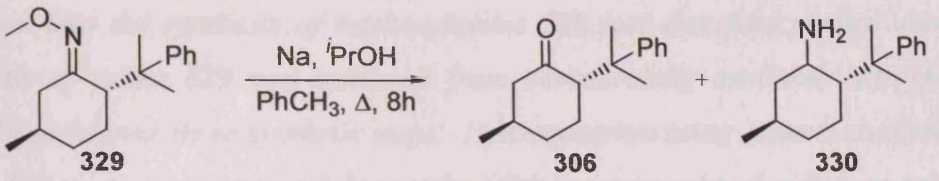
Formation of oxime **329** allowed an investigation into methods for its reduction to methoxylamine **328**. An initial reaction was carried out using Adam's catalyst under congruent reaction conditions to those applied to the synthesis of hydrazines **320** and **321** (*Scheme* **167**).



329 **328**

Scheme **167**

Only starting material was isolated after stirring oxime **329** under a hydrogen atmosphere in a mixture of ethanol and acetic acid for four days at ambient temperature. We therefore sought an alternative method for the reduction of compound **329**. To this end, a solution of oxime **329** in *iso*propanol was added dropwise to a suspension of sodium metal in toluene at reflux temperature. Heating was maintained for 8 hours prior to isolation of the products. The desired methoxylamine **328** was not present after reaction, and instead we found that 8-phenyl menthone (**306**) and primary amine **330** had been generated under the reaction conditions applied (*Scheme* **168**).

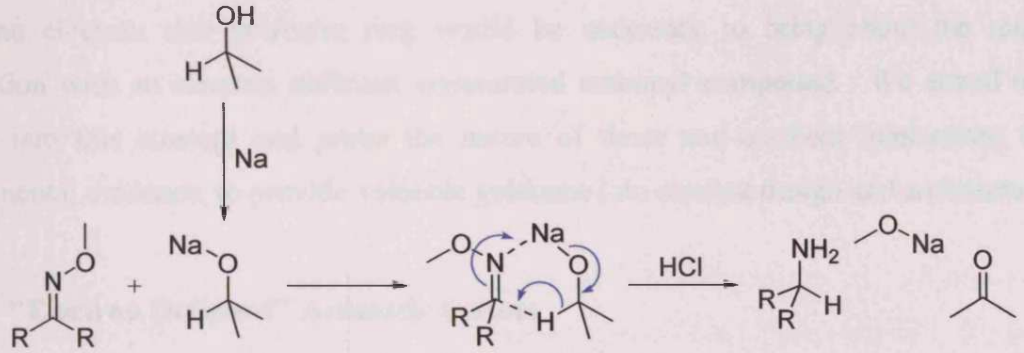


329 306 330

Scheme **168**

The formation of 8-phenyl menthone (**306**) may be rationalised due to the generation of sodium hydroxide under the reaction conditions, which when reacted with oxime **329** leads to the synthesis of 8-phenyl menthone (**306**).

In order to form primary amine **330**, the carbon-nitrogen bond of oxime **329** must have been cleaved under the reaction conditions. This can be explained by invoking a Meerwein-Ponndorf-Verley type reduction mechanism. Thus, oxime **329** reacts with the sodium salt of *iso*propanol leading to the formation of primary amine **330** plus sodium methoxide and acetone (**9**) (*Scheme* **169**).



Scheme **169**

The synthesis of methoxylamine **328** was therefore proving elusive, which led us to re-evaluate how necessary the formation of **328** was. Looking back at the results obtained from the use of commercially available amines as catalysts for the Diels-Alder reaction between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**) (see *Section* **3.3.1**), revealed to us that a lower yield of adduct **68** (65%) resulted from the use of *N,O*-dimethylhydroxylamine hydrochloride (**277**) as the catalyst, compared to use of hydrazine **287** derived from benzoic hydrazide (93%). Thus, a nitrogen atom alpha to the reactive site provided more efficient catalytic turnover compared to the presence of an α-oxygen atom. Furthermore, the primary aim of this project was to investigate π–π interactions, and as such, optimising the nature of the α-heteroatom was not considered to be an important aspect of the catalytic design. We therefore decided to halt our investigations into the synthesis of methoxylamine **328**, and concentrate on the formation of hydrazines that would enable us to achieve our ultimate goal.

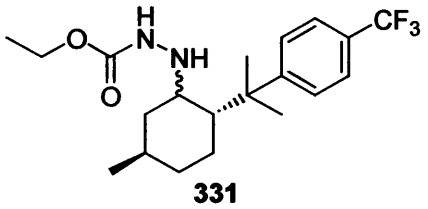
Investigations into the synthesis of methoxylamine **328** *had therefore proved unsuccessful. The synthesis of oxime* **329** *was achieved from commercially available (R)-(+)-pulegone* (**302**) *in 45% yield over three synthetic steps. Hydrogenation using Adam's catalyst returned only oxime* **329** *starting material, while reaction with isopropanol and sodium metal led to the formation of primary amine* **330** *and regeneration of 8-phenyl menthone* **306**. *Further studies towards the preparation of* **328** *were put on hold in order that the preparation of catalysts that would enable an investigation into π–π interactions could be instigated.*

4.6 Investigation into the Modulation of Electronics

There has, as yet, been the lack of a rigorous investigation into the nature of face-face π–π interactions. Hunter states that the magnitude of the interaction is the sum of the π-electron repulsions (interaction between the net charges on the atoms) and the interactions between the net charges and the π-electrons.[207] It could be expected that for the desired interaction to arise, an electron rich aromatic ring would be necessary to bring about the maximum interaction with an electron deficient unsaturated carbonyl compound. We aimed to delve deeper into this concept and probe the nature of these non-covalent interactions through experimental evidence, to provide valuable guidance into catalyst design and architecture.

4.6.1 "Electron Deficient" Aromatic System

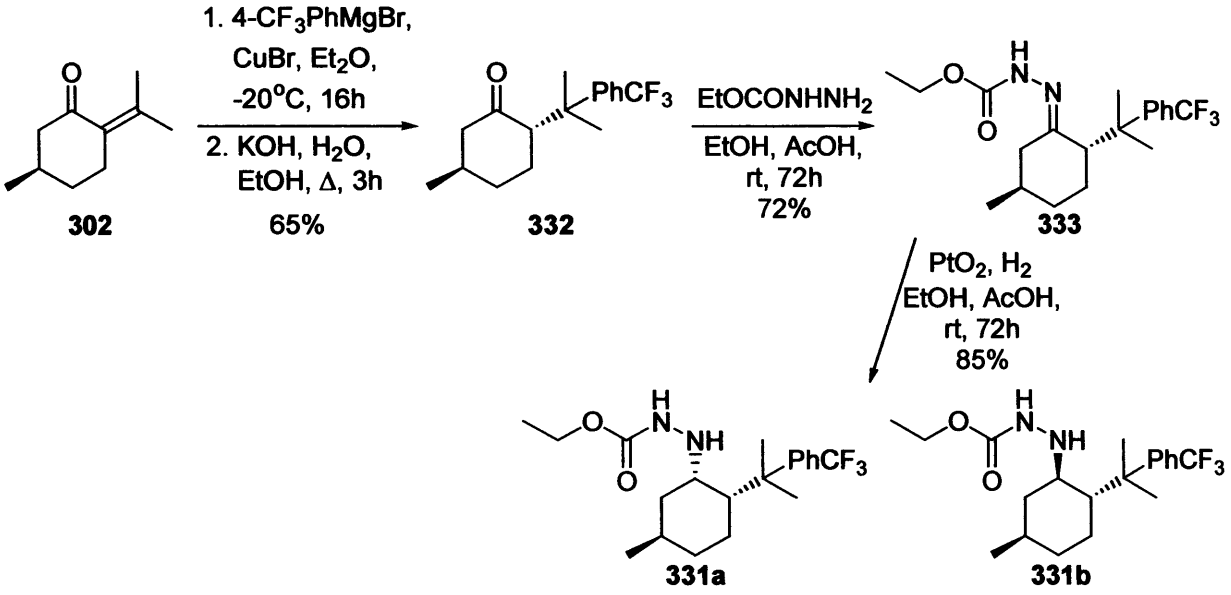
Gaining access to catalyst **331** (*Figure* **90**) would create an opportunity for comparisons between this "electron poor" system and the unsubstituted catalyst **320** in the diastereofacial discrimination of α,β-unsaturated carbonyl compounds. The aim was to ascertain if modulation of the electronic nature of the aromatic ring would alter the selectivities observed during asymmetric catalytic reactions.



331

Figure **90**

The preparation of **331** was achieved congruent to the synthesis of hydrazides **320** and **321**. 8-(4-Trifluoromethylphenyl) menthone (**332**) was prepared by the conjugate addition of trifluoromethylphenylmagnesium bromide to (*R*)-(+)-pulegone (**302**) in the presence of copper bromide. The crude product was equilibrated to the desired *trans*-isomer by reaction with potassium hydroxide in refluxing aqueous ethanol. Purification by column chromatography afforded **332** diastereomerically pure in 65% yield (*Scheme* **170**).



Scheme **170**

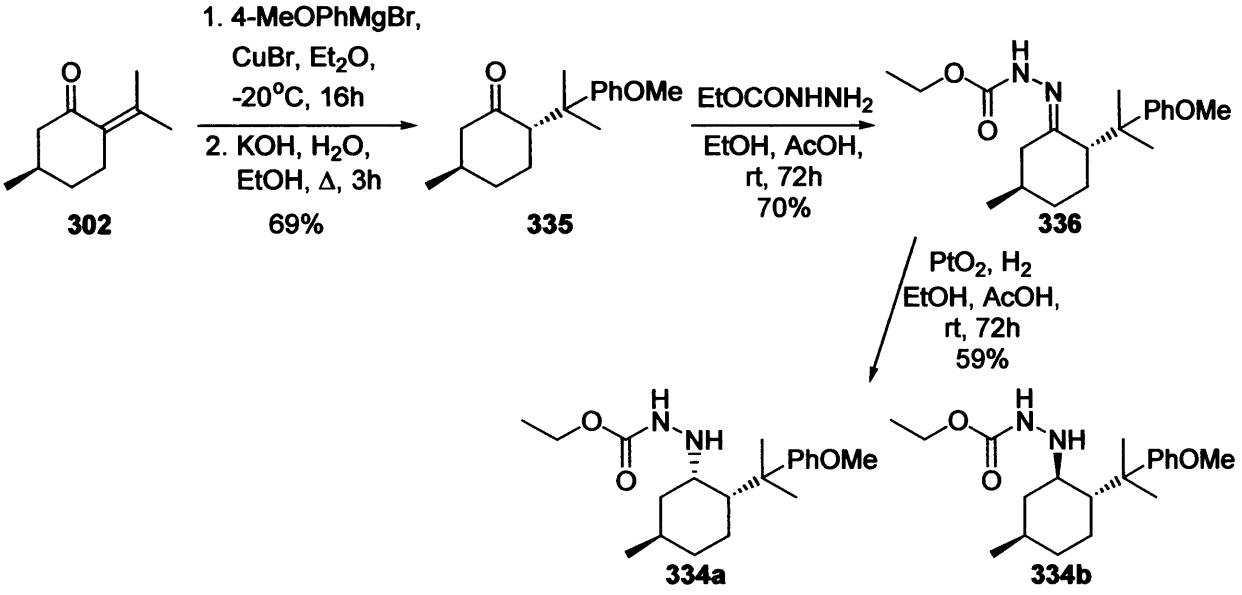
Compound **332** was then reacted with ethyl carbazate (**284**) in a solution of ethanol and acetic acid to generate, after stirring for 3 days at ambient temperature, hydrazone **333**. A 72% yield of **333** was afforded after purification by column chromatography. Hydrogenation to the corresponding hydrazine **331** was then performed under analogous conditions to those employed for the preparation of hydrazines **320** and **321**. This produced a mixture of two diastereoisomers, **331a** and **331b**. Separation of these isomers was not achieved by column chromatography on silica gel and the use of medium pressure liquid chromatography (MPLC) on a silica column afforded no improvement. Preparative chiral HPLC was therefore employed to enable separation of the diastereomeric products (See *Chapter* **5**, pages 240-241 for details). This provided complete separation to give isomer **331a** in 51% yield and hydrazine **331b** in 34% yield. The relative stereochemistry of each diastereoisomer was again assigned using ^{1}H NMR coupling constants.

Thus, hydrazines **331a** *and* **331b** *were prepared in 24% and 16% overall yields respectively. These two "electron deficient" 8-phenyl menthamine derivatives could now be used in our*

catalytic investigations to enable us to observe the effect on the stereochemical outcome of an aminocatalytic reaction.

4.6.2 "Electron Rich" Aromatic System

As a direct comparison to "electron poor" catalyst **331**, it was deemed necessary to construct a catalyst containing an "electron rich" aromatic ring. We embarked upon an investigation into the synthesis of catalyst **334** *via* an analogous route to that employed in the synthesis of hydrazine **320** (*Scheme* **171**).



302 **335** **336** **334a** **334b**

Scheme **171**

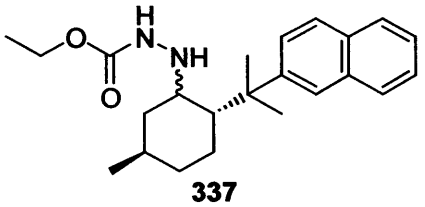
As with the previous routes, a conjugate addition of the Grignard reagent to (*R*)-(+)-pulegone (**302**), followed by equilibration, was carried out to generate 8-aryl menthone **335** in 69% yield for the two steps. A reductive amination protocol was then employed to form the desired hydrazine **334**. Separation of the two diastereomeric products was achieved by column chromatography to give isomer **334a** in 15% yield and isomer **334b** in 14% yield over the four synthetic steps. Once more we were able to determine the relative stereochemistry of each product from analysis of the ^{1}H NMR spectra of the two diastereoisomers.

Synthesis of "electron rich" aromatic systems **334a** *and* **334b**, *based on the 8-phenyl menthamine molecular scaffold was therefore achieved. The formation of these catalysts meant that we could now make comparisons between "electron poor" and "electron rich" aromatic systems in the diastereofacial discrimination of α,β-unsaturated carbonyl compounds, which was the main focus of this study.*

4.6.3 Design of a Catalyst With a Larger Aromatic Architecture

D'Angelo carried out conjugate addition reactions in which 8-aryl menthol chiral auxiliaries were employed to effect diastereofacial discrimination. These investigations showed that higher selectivities were obtained when utilising a naphthyl-based catalyst compared to the use of 8-phenyl menthol (**304**).[228] The presence of the larger aromatic architecture was postulated to lead to better overlap of the double bond of the reagent with the aromatic rings of the naphthyl-containing chiral auxiliary, providing an enhanced level of stereocontrol. We therefore decided it was necessary to synthesise an 8-aryl menthamine catalyst that incorporated a larger aromatic portion.

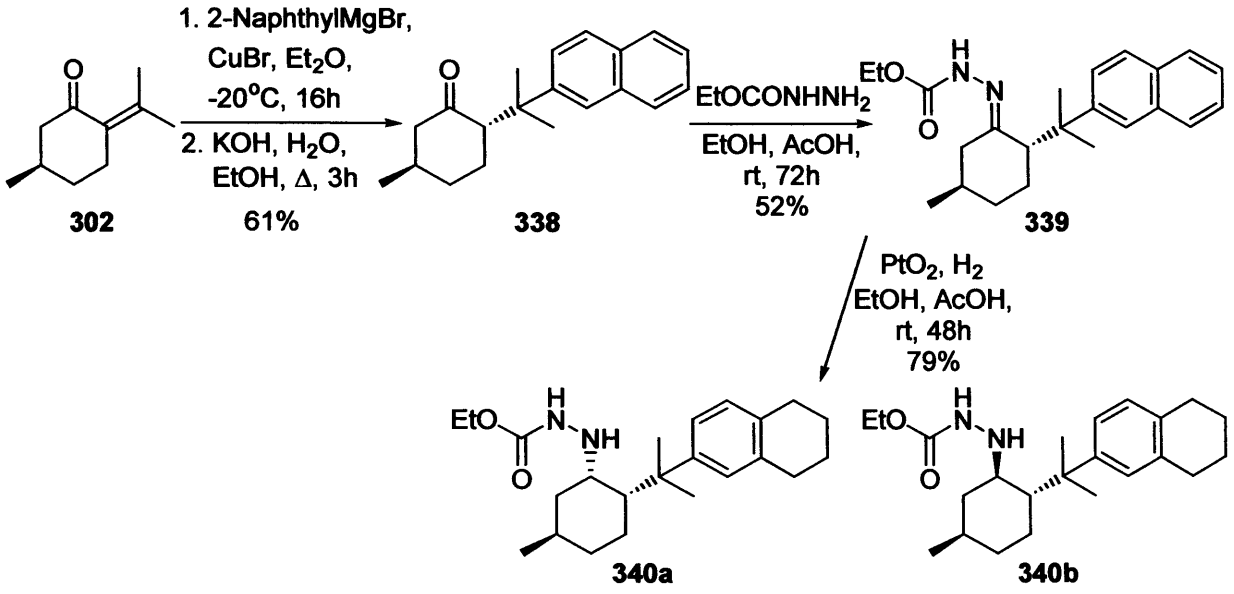
We thus began an investigation into the synthesis of hydrazine **337**, containing a 2-naphthyl moiety (*Figure* **91**), and assumed that the synthetic route would be very similar to that of catalyst **320**.



337

Figure **91**

Formation of 8-(2-naphthyl)menthone (**338**) was achieved from (*R*)-(+)-pulegone (**302**) *via* a conjugate addition and equilibration sequence. This afforded menthone **338** in 61% yield after purification by column chromatography, which was then reacted with ethyl carbazate (**284**) to generate hydrazone **339**. After column chromatography, hydrazone **339** was added to a suspension of Adam's catalyst in acetic acid and ethanol. The flask was charged with hydrogen and stirred at room temperature for 72 hours. After the reaction was complete we expected to isolate the desired product **337**, but to our surprise, we had in fact synthesised the tetrahydronaphthyl hydrazine **340** (*Scheme* **172**).



Scheme **172**

Therefore, reduction of the naphthyl group to the corresponding tetrahydronaphthyl species had taken place under the reaction conditions employed. The two diastereoisomers of **340** were separated using column chromatography, which afforded **340a** in 51% yield and **340b** in 28% yield. Although the synthesis of hydrazines **340a** and **340b** was serendipitous, these diastereomeric compounds were still suitable for use as aminocatalysts. We assigned the relative stereochemistry of each diastereoisomer by the use of ^{1}H NMR data.

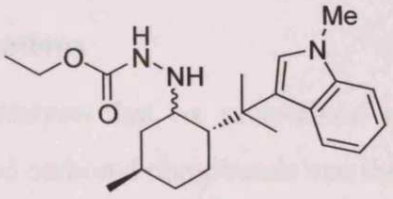
We went on to further investigate the reduction of hydrazone **339** in an attempt to obtain the 8-naphthalen-2-yl menthamine **337**. Hydrazone **339** was subjected to a variety of reductive reaction conditions, including the use of palladium on charcoal as the hydrogenation catalyst, but predominantly starting material was returned after work-up of the reaction mixture.

Further studies into the synthesis of the naphthyl-containing 8-aryl menthamine catalyst **337** were not continued as we had instead set our sights upon the formation of an alternative structure, an indole-based system, which should allow a comparison into the effect of a larger aromatic system on the stereochemical outcome of an aminocatalytic transformation.

In summary, we had rather fortuitously obtained hydrazines **340a** *and* **340b**, *with a tetrahydronaphthyl unit incorporated into their structure. These two species were obtained in 16% and 5% overall yield respectively. Synthesis of the desired naphthyl containing 8-aryl menthamine* **337** *was not achieved from hydrazone* **339** *by the methods of reduction employed. Further studies into the preparation of hydrazine* **337** *were halted as we had focused our attentions on the synthesis of an alternative indole-based catalytic structure.*

4.6.4 An Indole-Based Catalytic System

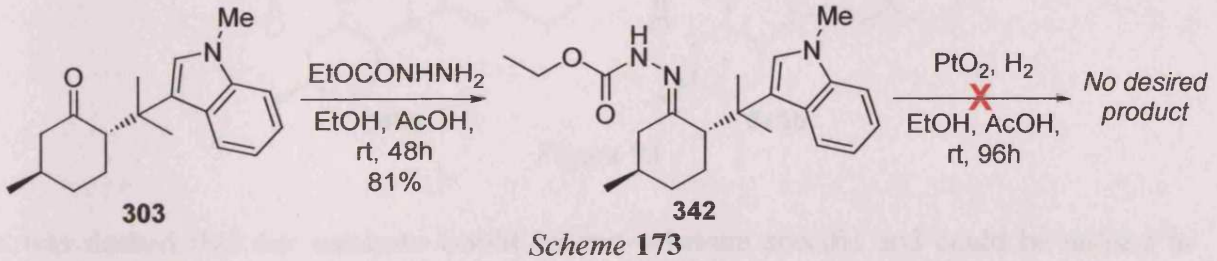
Face-face π–π interactions are often observed in nature and play a critical role in the determination of the tertiary structure of many proteins as well as in small molecule drug-receptor interactions. The indole-containing amino acid tryptophan is often observed to interact *via* π–π interactions, and this indole subunit was incorporated by Corey into the structure of his oxazaborolidine catalyst **217**, which provided unprecedented levels of enantioselectivity when employed as a catalyst for Diels-Alder cycloadditions (see *Chapter* **2**, *Section* **2.2.1** for further details). We therefore sought to integrate an indole moiety into our catalyst structure in the hope that this would lead to higher levels of enantioselectivity in aminocatalytic transformations. Thus we began investigations into the synthesis of hydrazine **341** (*Figure* **92**).



341

Figure **92**

Synthesis of hydrazine **341** was envisaged from 8-(*N*-methylindol-3yl) menthone (**303**), which was generated *via* the conjugate addition of *N*-methylindole (**174**) to (*R*)-(+)-pulegone (**302**) under aminocatalytic reaction conditions (see *Chapter* **3**, *Section* **3.8.1** for more details). Menthone **303** was reacted with ethyl carbazate (**284**) in a solution of ethanol and acetic acid at room temperature for 48 hours. This provided, after purification by column chromatography, hydrazone **342** in 81% yield. Reduction to the corresponding hydrazine **341** was then attempted under the reaction conditions applied previously for the synthesis of hydrazine **320**, but we found that use of Adam's catalyst returned only hydrazone **342** starting material after reaction.



303 **342**

Scheme **173**

Once again, problems were encountered at the hydrogenation step of our synthetic route. Although we wished to obtain a catalyst containing a larger aromatic architecture, this was not

necessary for our initial investigations into the nature of face-face π–π interactions. We had already synthesised "electron rich" hydrazine **334**, "electron neutral" catalysts **320** and **321**, "electron deficient" system **331**, as well as tetrahydronaphthyl-based catalyst **340**. We therefore decided to move on to examine the use of these hydrazines in aminocatalytic transformations prior to continuing investigations that should lead to either naphthyl-based catalyst **337** or indolyl-system **341**.

In conclusion, the synthesis of the desired indolyl-based 8-aryl menthamine **341** *was not achieved from hydrazone* **342** *under hydrogenation reaction conditions using Adam's catalyst. Further studies into the preparation of hydrazine* **341** *were put on hold while we initiated our aminocatalytic investigations.*

4.7 Aminocatalytic Investigations

The synthesis of a family of catalysts that we rationalised could discriminate between the prochiral faces of α,β-unsaturated carbonyl compounds was therefore achieved (*Figure* **93**).

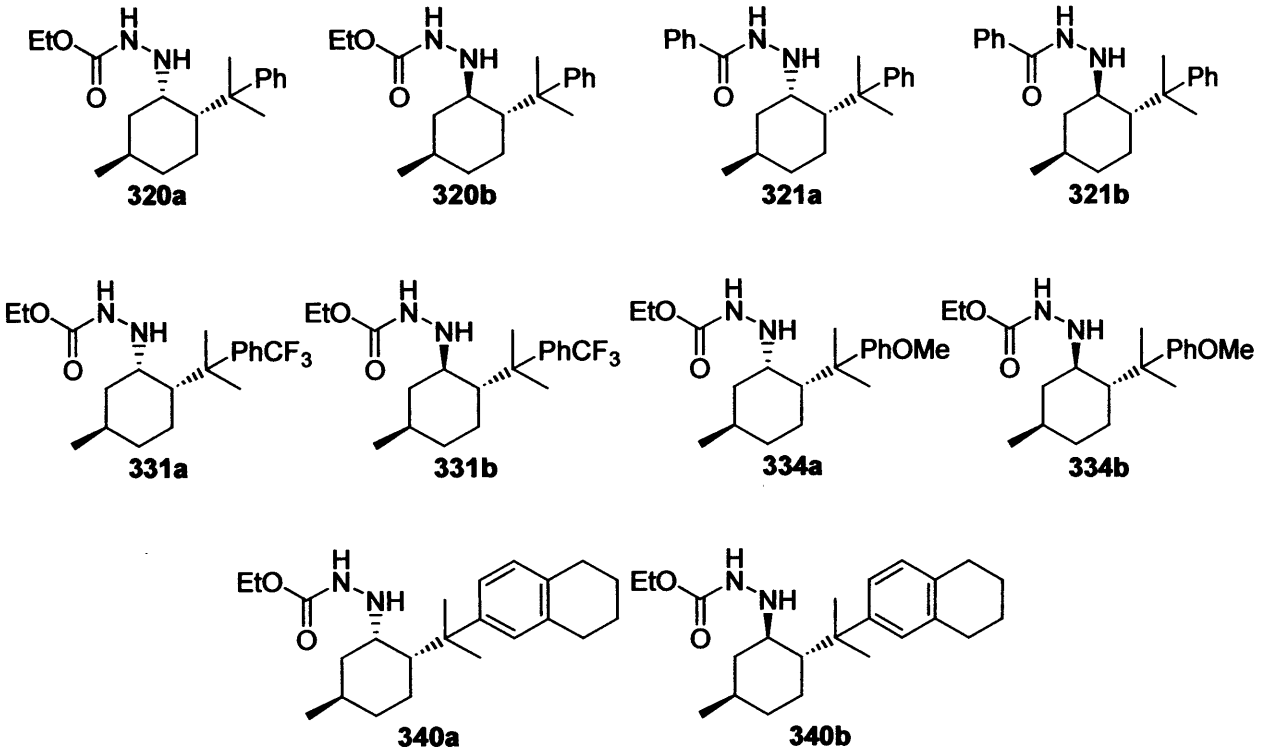


Figure **93**

It was desired that our catalysts would be non-substrate specific and could be utilised in asymmetric carbon-carbon bond forming reactions such as the Diels-Alder, Michael and Baylis-Hillman reactions. This was postulated to be possible by the exploitation of non-

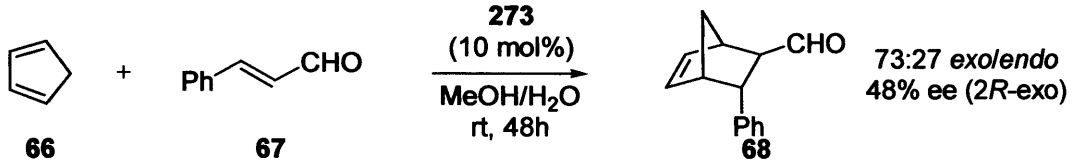
covalent, π-stacking effects rather than steric blocking, and the aim was to probe into the nature of these interactions and their involvement in catalysis by subtle modulation of the electronics of the aromatic ring incorporated into the structure of each catalyst. It was hoped that this project would create more awareness of the subtleties involved in asymmetric catalysis utilising π-stacking effects.

Attainment of the above family of catalysts (*Figure* **93**) allowed us to begin an investigation into their use in aminocatalytic processes. Although we desired our catalysts to be versatile with respect to both the type of carbon-carbon bond forming reaction and the choice of α,β-unsaturated carbonyl substrate, exploiting both of these parameters would create complexity in the optimisation of reaction conditions and the answering of fundamental questions. We therefore decided to commence the catalytic investigation by probing just one type of asymmetric C-C bond forming reaction. Due to the knowledge gained during our previous investigations into the catalysis of Diels-Alder cycloadditions (see *Chapter* **2**, *Section* **2.5** & *Chapter* **3**, *Section* **3.6**), we elected to concentrate our attentions on this reaction, which should provide an opportunity to test our hypotheses and ascertain any rationale in the nature of the proposed π–π interactions occurring, without the need to compete with the excellent Diels-Alder catalysts that already exist.

4.7.1 Analysis of the Diels-Alder Products

In preparation for the commencement of high-throughput catalytic optimisation, we embarked upon an investigation into a simple, cheap, rapid and versatile method for evaluation of the selectivity of each Diels-Alder product formed. There are several methods available for the determination of the enantiomeric excess of both the *endo*- and *exo*-isomers of the Diels-Alder adducts. These methods include direct determination of the ee using ^{1}H NMR techniques in the presence of the chiral shift reagent Eu(hfc)$_3$,[198] or the indirect ee determination *via* the formation of diastereomeric acetals, followed by GC analysis.[191c] But each of these methods require the use of a stoichiometric amount of either the external chiral ligand or the chiral reagent, which proves to be expensive. These methods are also time/labour intensive, requiring aqueous work-ups and purification by column chromatography (See *Chapter* **2**, *Section* **2.5.2** for further details on these methods). We therefore sought an alternative derivatisation method that would provide a simple, cheap and reliable means for determination of the enantiomeric excess of the Diels-Alder adducts.

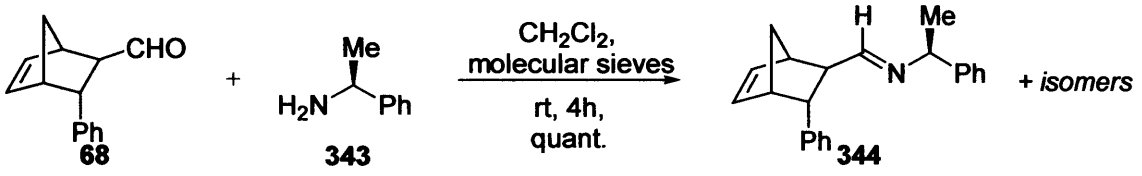
In order to evaluate the accuracy of each method employed for the determination of enantiopurity, we needed to correlate our results to those achieved in a known literature example. Thus, a Diels-Alder cycloaddition between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**) was performed utilising (*S*)-proline methyl ester (**273**) as the aminocatalyst, under analogous reaction conditions to those employed by MacMillan (*Scheme* **174**).[7] From the literature precedent we expected to obtain a 73:27 ratio of *exo*/*endo* isomers (**68**), with the *exo*-adduct formed in 48% ee (the 2*R* isomer predominating).



66 **67** **68**

Scheme **174**

We began our investigations by reacting adduct **68** with *S*-(-)-α-methylbenzylamine (**343**) in dichloromethane containing 4Å molecular sieves. The solution was stirred at ambient temperature for 4 hours, filtered and reduced *in vacuo*. This afforded a quantitative yield of chiral imine **344** (*Scheme* **175**).

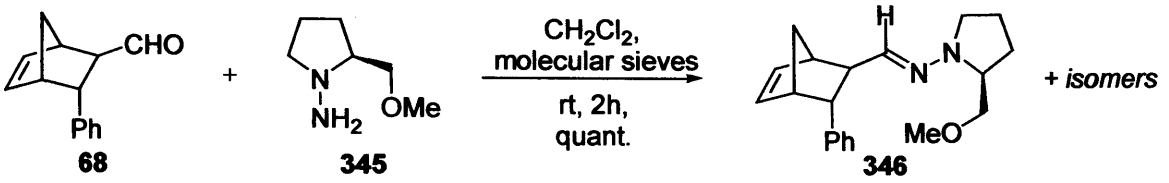


68 **343** **344**

Scheme **175**

The formation of these diastereomeric imines **344** from adduct **68** enabled NMR analysis to be used to determine both the *exo*/*endo* ratio as well as the enantiomeric excess resulting from the Diels-Alder cycloaddition. ^{1}H NMR data, analysing protons H-5 and H-6, showed that Diels-Alder adduct **68** had been formed with an *exo*/*endo* ratio of 71:29. This method showed an enantiomeric excess for the *exo*-isomers of 38%. More accurate results were achieved by analysis of the ^{13}C NMR data, although long scan experiments with an increased relaxation time were required. From carbons C-5 and C-6, it was determined that a 74:26 *exo*/*endo* ratio of **68** had resulted with the *exo*-isomers formed in 45% ee.

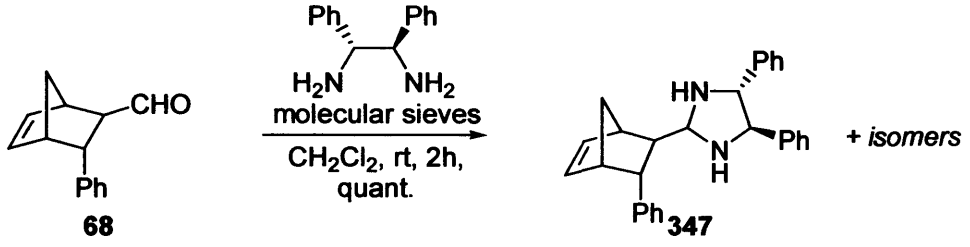
An alternative method was also investigated. This involved the reaction of Diels-Alder adduct **68** with *S*-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) (**345**) under comparable reaction conditions as those applied to the preparation of chiral imine **344**. This provided a quantitative yield of chiral hydrazone **346** (*Scheme* **176**).



Scheme **176**

The resulting diastereomeric hydrazones **346** were then analysed by NMR. No significant splitting of peaks was observed in the ^{1}H NMR, and thus ^{13}C NMR data was used to ascertain the stereochemical composition of Diels-Alder adduct **68**. Analysis of the imine carbon peak, as well as atoms C-5 and C-6, showed that adduct **68** had been formed with an *exo*/*endo* ratio of 73:27, with a 45% ee for the *exo*-isomer. Once again, long scan ^{13}C NMR experiments were required, with the relaxation time increased, to provide accurate results.

Another option for the determination of optical purity was *via* formation of the corresponding aminals with (*R,R*)-1,2-diphenylethylene diamine, followed by ^{13}C NMR analysis, as reported by Alexakis.[199] This enabled formation of aminal **347** in quantitative yield from Diels-Alder adduct **68**, by reaction under analogous conditions to those employed for the synthesis of chiral imine **344** (*Scheme* **177**).



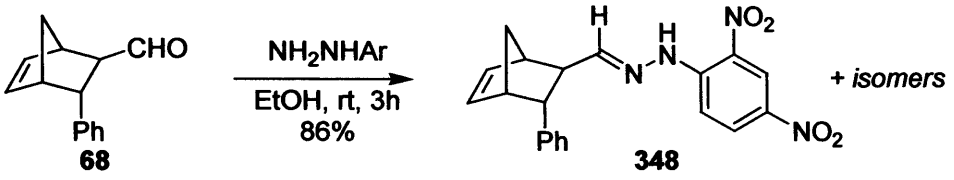
Scheme **177**

The ^{1}H and ^{13}C NMR peaks for the diastereomeric products of aminal **347** were not well separated and thus, determination of the stereochemical outcome of the Diels-Alder reaction between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**) was not possible using this derivatisation method.

In summary, we had found that reasonably accurate stereochemical data could be obtained from conversion of adduct **68** into imine **344**, by reaction with *S*-(-)-α-methylbenzylamine (**343**), or by derivatisation with SAMP (**345**) to form hydrazone **346**. ^{13}C NMR Analysis of each of these derivatives provided an *exo*/*endo* ratio and enantiomeric excess concordant with the literature values.[7] Both of these methods involved a simple and rapid derivatisation to afford the product in quantitative yield without any purification necessary. Unfortunately, the

NMR machine time required for analysis of these derivatives (**344** or **346**) was extensive, and not viable for use with the number of catalytic experiments we wished to perform.

We therefore sought an alternative derivatisation method that would allow analysis of the Diels-Alder adducts using chiral HPLC. We found that treatment of adduct **68** with a slight excess of 2,4-dinitrophenylhydrazine in an ethanolic solution provided 2,4-dinitrophenylhydrazone **348**, following the procedure reported recently by members of our research laboratory (*Scheme* **178**).[200]



Scheme **178**

Direct analysis of the reaction mixture provided both the *exo/endo* ratio (73:27) and the enantiomeric excess (47% ee) for Diels-Alder adduct **348** using chiral HPLC (see *Chapter* **5**, pages 253-254 and *Appendix* **A7**, page 274 for details), thus constituting an efficient, cheap and reliable method for ee determination.[201] This procedure proved to be reproducible and was practical for use with high throughput catalytic optimisation.

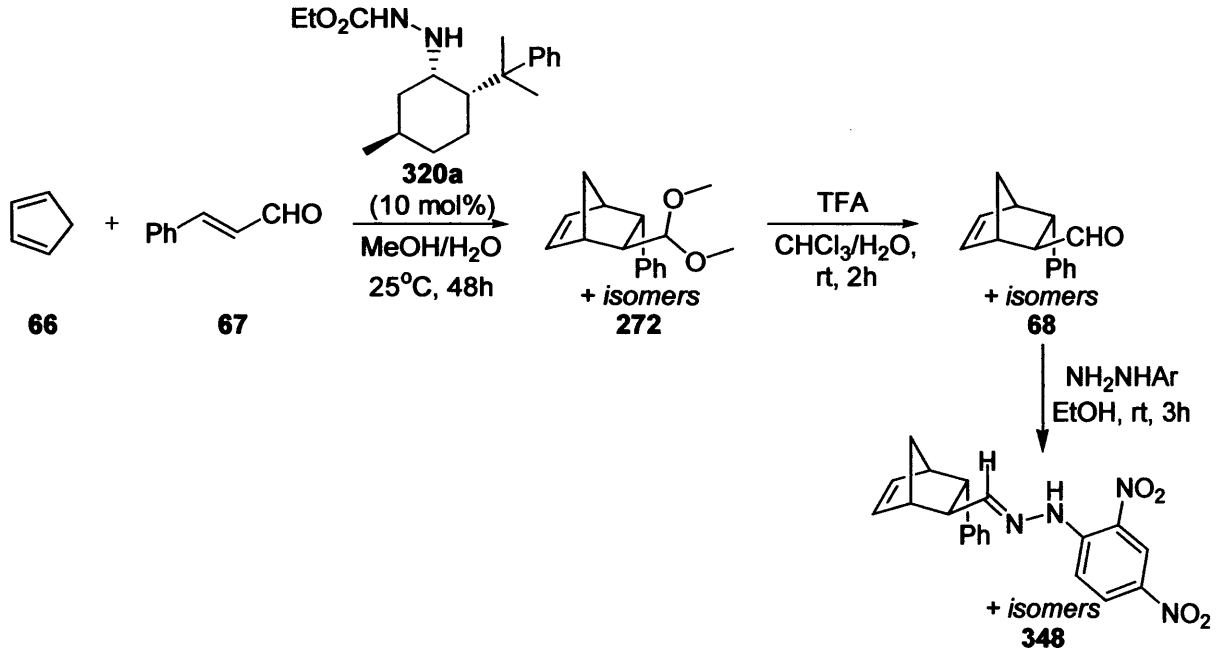
Thus, a simple, cheap, rapid and versatile method for evaluation of the selectivity of the Diels-Alder adducts **68**, *by chiral HPLC analysis, had been determined. Hence, an investigation into the use of our aminocatalysts to promote Diels-Alder cycloadditions could commence with the ultimate aim of probing into the nature and subtleties involved in the frequently inferred, yet little understood, face-face* π–π *interactions.*

4.7.2 Catalysis – Initial Investigations

Prior to the investigative asymmetric Diels-Alder studies, we first probed into the optimum catalytic reaction conditions required for our catalysts. Mimicking the conditions reported in the literature,[7] 10 mol% of amine **320a** (as its HCl salt) was stirred in methanol/water (19:1) at 25°C, and one equivalent of *E*-cinnamaldehyde (**67**) was added. After stirring for 15 minutes, cyclopentadiene (**66**) (3 equivalents) was added, and the reaction mixture was stirred for 48 hours. An aqueous work-up furnished the resulting adduct as dimethyl acetal **272**, and subsequent reaction with trifluoroacetic acid in chloroform/water for two hours at ambient temperature afforded the corresponding aldehyde **68** (*Scheme* **179**). The crude reaction

mixture was analysed by ^{1}H NMR to gain a representative diastereomeric ratio, before reacting with 2,4-dinitrophenylhydrazine. This generated hydrazone **348**, which was purified by column chromatography. The purified material was again analysed by ^{1}H NMR and weighed for an accurate yield measurement, followed by chiral HPLC analysis to determine the enantiomeric excess.

Full recovery of the aminocatalyst was achieved after reaction by neutralisation of the aqueous layer with 2M sodium hydroxide solution, followed by extraction with diethyl ether and concentration of the combined organic extracts.



Scheme **179**

We initially evaluated the reaction between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**), allowing us to assess the catalytic ability of hydrazide **320a** under standard reaction conditions.[7] The result of this study is shown below (*Table* **13**).

Table **13**[a]: Results of the Initial Diels-Alder Cycloaddition Experiment

Entry	Catalyst	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	None	7	36 : 64	-
2	NEt_3	7	37 : 63	-
3	**320a**	42	66 : 34	27 (2*S*)

(a) All reactions were carried out in methanol/water (19:1) at 25°C for 48h with 10 mol% catalyst as a HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture. (c) Enantiomeric excess was determined by chiral HPLC of the product as its 2,4-DNPH derivative.

In the absence of any catalyst, or in the presence of only the protonic acid co-catalyst, the reaction proceeded to just 7% completion inside 48 hours with the *endo* isomer predominating (*entries* **1** and **2**). Use of the hydrochloride salt of **320a** afforded an acceptable yield of Diels-Alder adduct **68** in 48 hours at 25°C (*entry* **3**). The *exo* isomer was formed preferentially, in accord with observations made by MacMillan suggesting that the *exo* isomer of **68** predominates when iminium ion catalysis is occurring.[7] This indicated that hydrazide **320a**, and related structures, can be used to promote aminocatalytic transformations, and thus could provide a viable alternative to the Lewis acid catalysed process which tends to favour the *endo* isomer.[221] The *exo* isomer was formed with a moderate enantiomeric excess of 27%, with the (2*S*)-enantiomer as the major product. Although the level of enantioselection achieved was not competitive with previously established catalytic systems, this result constituted a solid starting point upon which to build. It was hoped that optimisation of the reaction conditions would improve this result, and thus provide a basis with which to test our hypotheses.

Hydrazide **320a**, *(as a protonic acid salt), therefore provided a moderate level of enantioselection when employed as a catalyst for a Diels-Alder cycloaddition between cyclopentadiene* (**66**) *and E-cinnamaldehyde* (**67**). *With the basic reaction conditions established and proof that hydrazide* **320a** *could indeed be utilised to promote aminocatalytic processes, our catalytic investigations could begin.*

4.7.3 Investigating Variables – Choice of Solvent

We went on to repeat the catalytic Diels-Alder reaction between *E*-cinnamaldehyde (**67**) and cyclopentadiene (**66**) in a variety of solvent systems. Four polar protic solvents; methanol, ethanol, *iso*propanol and ethylene glycol were studied along with the polar aprotic solvents; acetonitrile, dimethylformamide (DMF), dimethylsulfoxide (DMSO) and tetrahydrofuran (THF). In addition, two apolar aprotic solvents; dichloromethane and toluene, were examined allowing us to monitor the effect that solvent has on both the yield and the selectivity of the aminocatalysed Diels-Alder reaction. The results of these experiments are tabulated below (*Table* **14**).

Table **14**[a]: Results of the Study Into the Use of a Variety of Solvents

Entry	Solvent	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	None	27	58 : 42	14 (2*S*)
2	**MeOH**	**42**	**66 : 34**	**27** (2*S*)
3	EtOH	32	65 :35	22 (2*S*)
4	IPA	10	56 : 44	15 (2*S*)
5	$HOCH_2CH_2OH$	32	53 : 47	19 (2*S*)
6	**CH_3CN**	**58**	**66 : 34**	**33** (2*S*)
7	DMF	3	64 : 36	-
8	DMSO	6	65 : 35	-
9	THF	2	57 : 43	-
10	CH_2Cl_2	3	60 : 40	-
11	$PhCH_3$	2	60 : 40	-
12	H_2O	4	51 : 49	-

(a) All reactions were carried out in solvent/water (19:1) at 25°C for 48 hours with 10 mol% catalyst **320a** as its HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative.

These results clearly showed that solubility issues resulted if the Diels-Alder reaction was carried out in aqueous solution (*entry* **12**). An improvement was observed under neat reaction conditions, although only a low level of enantioselection was observed (*entry* **1**). In each of the catalytic runs performed in organic solvent, the *exo* isomer was formed preferentially, indicating that iminium ion catalysis was prevailing. With the apolar aprotic solvents, low yields of adduct **68** resulted (*entries* **10** & **11**), and thus evaluation of the enantiomeric excess was not performed for these catalytic runs, which was also true for the use of the polar aprotic solvents DMF, DMSO and THF (*entries* **7**, **8** & **9**). Improved results were achieved with the polar protic solvents as well as with acetonitrile. This suggested that a polar solvent is necessary for effective catalyst turnover, which can be accounted for as a polar solvent presumably aids stabilisation of the charged iminium ion intermediates that are formed during the catalytic cycle.

Aminocatalysis of the Diels-Alder reaction between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**) by the hydrochloride salt of **320a** afforded adduct **68** in good yield and moderate enantioselectivity when carried out in an aqueous acetonitrile medium (*entry* **6**). Of

the polar protic solvents that were evaluated, methanol was found to provide the best result in terms of both yield and enantioselection (*entry* **2**).

We decided to continue our investigations using the two solvents that afforded the best results; namely methanol and acetonitrile (*Table* **14**, *entries* **2** and **6**). Further optimisation of the solvent system was examined by varying the water content, whilst performing the cycloaddition reactions under congruent conditions to those applied previously. The results of this study are outlined below (*Table* **15**).

Table **15**[a]: Results of the Study into Solvent/Water Ratio

Entry	Solvent	% Water Content	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	**MeOH**	**0**	**60**	**65 : 35**	**27** (2*S*)
2	MeOH	5	42	66 : 34	27 (2*S*)
3	MeOH	10	36	68 : 32	21 (2*S*)
4	CH_3CN	0	14	61 : 39	24 (2*S*)
5	CH_3CN	1	39	64 : 36	21 (2*S*)
6	CH_3CN	3	55	64 : 36	23 (2*S*)
7	**CH_3CN**	**5**	**58**	**66 : 34**	**33** (2*S*)
8	CH_3CN	10	42	65 : 35	24 (2*S*)

(a) All reactions were carried out at 25°C for 48 hours with 10 mol% catalyst **320a** as its HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative.

Variation in the water content of the organic reaction medium had little effect on the level of enantioselection observed in these aminocatalytic Diels-Alder cycloadditions. On further inspection of these results it was apparent that higher yields were achieved as the water content of methanol was reduced. This was exemplified by the use of anhydrous methanol (*entry* **1**), which led to a significantly higher yield of adduct **68** compared to the result obtained when the reaction was performed in the presence of 5% water (*entry* **2**). In contrast, the presence of a small amount of water appeared to be necessary for effective catalytic turnover when acetonitrile was used as the reaction medium. This result can be explained by the fact that water is necessary for hydrolysis of the iminium ion after reaction to regenerate the catalyst. Methanol is able to effect this step in the catalytic cycle (forming the dimethyl acetal), circumventing the need to add water to the solvent system, but acetonitrile cannot

perform this hydrolysis, hence, the addition of a small amount of water enhances the rate of catalytic turnover.

Upon consideration of these observations, it was evident that the optimum results, in terms of both yield and selectivity, were achieved when either acetonitrile containing 5% water, or anhydrous methanol, were used as the reaction medium. Performing the Diels-Alder cycloaddition between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**) in these solvent systems provided adduct **68** in good yield, with the *exo* isomer afforded in up to 33% ee.

Before adopting a standard solvent system with which to perform the remainder of our catalytic investigations, we first monitored the effect of concentration on the outcome of the aminocatalytic Diels-Alder cycloaddition. The results of this study are tabulated below (*Table* **16**).

Table **16**[a]: Results of the Study into Concentration Effects

Entry	Solvent	Concentration[b]	% Yield	*Exo* : *Endo*[c]	*Exo* % ee[d]
1	MeOH	0.033	60	65 : 35	27 (2*S*)
2	MeOH	0.1	82	65 : 35	23 (2*S*)
3	**CH_3CN[e]**	**0.033**	**58**	**66 : 34**	**33** (2*S*)
4	CH_3CN[e]	0.1	77	65 : 35	20 (2*S*)

(a) All reactions were carried out at 25°C for 48 hours with 10 mol% catalyst **320a** as its HCl salt. (b) Concentration of catalyst in $moldm^{-3}$. (c) All *exo*/*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture. (d) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative. (e) Water (5%) was added to the solvent system.

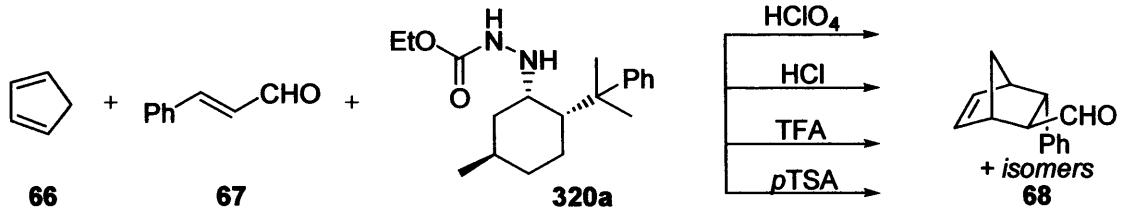
Considering the results above, it was immediately evident that an increase in concentration resulted in a higher yield of Diels-Alder adduct **68**, however, this was accompanied by a reduction in the enantioselection. Thus, it was decided that the original concentration (0.033 $moldm^{-3}$) was ideal for these systems. Comparable results, in terms of both yield and enantioselectivity, were provided by the use of both anhydrous methanol (*entry* **1**) and acetonitrile/water (19:1) (*entry* **3**) as the reaction medium. We elected to continue our catalytic studies using acetonitrile/water, since this solvent system allowed for the direct formation of Diels-Alder adduct **68**, eliminating the need to hydrolyse the dimethyl acetal **272** that results from the use of methanol as the solvent.

The results of our investigations (Tables **14**, **15** *&* **16**) *led us to adopt the use of 0.033 $moldm^{-3}$ catalyst in acetonitrile/water (19:1) for the remainder of our catalytic studies. Catalyst* **320a**,

when employed as an aminocatalyst in this reactive medium, promoted the Diels-Alder reaction between cyclopentadiene (**66**) *and E-cinnamaldehyde* (**67**) *to furnish a 58% yield of cycloaddition adduct* **68** *with 33% enantiomeric excess.*

4.7.4 Examination into the Protonic Acid Co-Catalyst

To probe the effect of the selected protonic acid co-catalyst on the yield and selectivity of the Diels-Alder reaction, a set of experiments were carried out using *E*-cinnamaldehyde (**67**) as the standard dienophile, with cyclopentadiene (**66**) consistently employed as the diene and hydrazide **320a** as the aminocatalyst. Each reaction was performed at a temperature of 25°C in an acetonitrile/water (19:1) solvent system (*Scheme* **180**). The results are shown below (*Table* **17**).



66 **67** **320a** **68**

Scheme **180**

Table **17**[a]: Results of the Study into Use of Various Protonic Acids

Entry	Protonic Acid	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	$HClO_4$	74	65 : 35	26 (2*S*)
2	**HCl**	**58**	**66 : 34**	**33** (2*S*)
3	***p*TSA**	**56**	**64 : 36**	**35** (2*S*)
4	TFA	28	68 : 32	32 (2*S*)

(a) All reactions were carried out in acetonitrile/water (19:1) for 48 hours at 25°C with 10 mol% catalyst **320a**. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative.

These results showed that the rate of reaction was enhanced as the pK_a of the protonic acid was increased. This indicated that iminium ion formation is the rate determining step of the catalytic cycle, which can be rationalised since a stronger acid should more readily protonate the carbonyl substrate, thus enabling a more rapid formation of the iminium ion species.

Similar *exo*/*endo* ratios were observed with all of the protonic acids employed. The Diels-Alder reaction proceeded to 74% completion in 48 hours when using perchloric acid (*entry* **1**), but a lower enantiomeric excess was observed compared to the use of hydrochloric acid (*entry*

2). *para*-Toluenesulfonic acid (*p*TSA) afforded a result comparable to that achieved with hydrochloric acid, while trifluoroacetic acid afforded a similar level of selectivity, although a lower yield of adduct **68** resulted with this protonic acid co-catalyst. Thus, the optimal result was provided by the use of either hydrochloric acid (*entry* **2**) or *para*-toluenesulfonic acid (*entry* **3**), and we opted to continue employing hydrochloric acid for our additional catalytic investigations.

From the above investigations (Sections **4.7.3** *and* **4.7.4**), *we had established that the ideal external variables for our catalytic runs involved the use of the aminocatalyst (0.033 moldm^{-3}) in a reaction medium of acetonitrile/water (19:1). In addition, hydrochloric acid was selected as the optimum protonic acid co-catalyst, and thus all further catalytic investigations were performed under these standard conditions.*

4.7.5 Study into the Effect of Temperature on Enantioselectivity

We went on to examine the effect of temperature on the stereochemical outcome of the Diels-Alder cycloaddition between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**) catalysed by the hydrochloride salt of hydrazide **320a**. Each reaction was performed under the standard conditions, and the results of this study are tabulated below (*Table* **18**).

Table **18**[a]: Results of the Study into the Effect of Temperature

Entry	Temperature °C	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	25	58	66 : 34	33 (2*S*)
2	0	28	69 : 31	38 (2*S*)
3	**-20**	**17**	**70 : 30**	**44 (2*S*)**

(a) All reactions were carried out in acetonitrile/water (19:1) for 48 hours using 10 mol% catalyst **320a** as its HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative.

This investigation revealed that the *exo*/*endo* ratio remained consistent as the reaction temperature was lowered. However, the reduced temperatures did compromise the rate of reaction and thus, lower yields resulted. Notably, an increase in enantioselectivity was observed at lower temperatures, which led to the formation of Diels-Alder adduct **68** with 44% enantiomeric excess when the reaction was performed at –20°C (*entry* **3**).

In summary, we had established that the enantioselectivity of the Diels-Alder cycloaddition, catalysed by hydrazine **320a**, *could be significantly increased by lowering of the reaction temperature. In fact, an 11% increase in the enantiomeric excess was observed on lowering the reaction temperature from 25°C to -20°C.*

4.7.6 Investigation into the Catalyst Loading

A prerequisite of any catalytic investigation is the discovery of the optimum catalytic loading. Expense is a valid consideration in the design of a catalyst and the lower the amount of catalyst employed, the more cost effective and appealing the process. We embarked upon an investigation into this matter, and performed Diels-Alder cycloadditions between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**), catalysed by hydrazide **320a** as its hydrochloric acid salt. Each reaction was performed in acetonitrile/water (19:1) for 48 hours at -20°C. The loading of catalyst **320a** was varied as tabulated below (*Table* **19**).

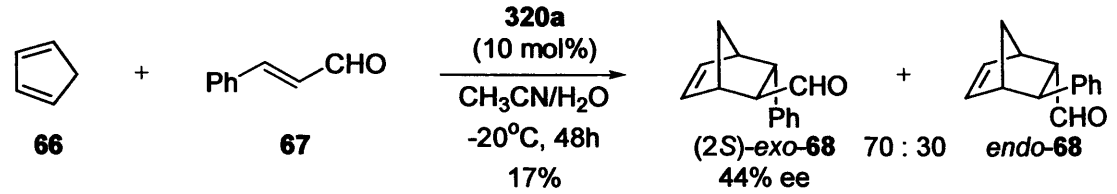
Table **19**[a]: Results of the Study into Catalyst Loading

Entry	Loading (mol%)	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	20	26	70 : 30	42 (2*S*)
2	10	17	70 : 30	44 (2*S*)
3	5	7	71 : 29	40 (2*S*)

(a) All reactions were carried out in acetonitrile/water (19:1) at -20°C for 48 hours with catalyst **320a** as its HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative.

The results of this study showed that lowering the catalyst loading of **320a** from 20 mol% to 5 mol% had no adverse effect on the observed selectivity (*entries* **1** and **3**). In terms of both the amount of catalyst needed and the observed enantioselectivity, the optimal result was achieved with a catalyst loading of 10 mol%, which afforded the *exo* isomer of adduct **68** with 44% ee in 48 hours at -20 °C (*entry* **2**).

From the above investigations (Tables **14** - **19**) *we were able to establish optimal reaction conditions for the Diels-Alder reactions catalysed by hydrazide* **320a**. *Use of 10 mol% of catalyst* **320a**, *as its hydrochloride salt, in the cycloaddition between cyclopentadiene* (**66**) *and E-cinnamaldehyde* (**67**), *led to the formation of the predominant exo isomer of adduct* **68** *with 44% enantiomeric excess, when performed in acetonitrile/water (19:1) at -20°C (Scheme* **181**).



Scheme **181**

The only variables in the next set of experiments would be the nature of the aminocatalyst.

4.8 Investigation into the Nature of the Carbonyl Substituent

With suitable catalytic reaction conditions discovered, we could now probe into the crux of our project, namely, the nature of our family of catalysts and their effects on the stereoselectivity of asymmetric carbon-carbon bond forming reactions. Catalyst **321**, derived from benzoic hydrazide (**288**), was synthesised as a direct comparison to catalyst **320** with respect to the nature of the carbonyl group attached to the α-heteroatom (*Figure* **94**).

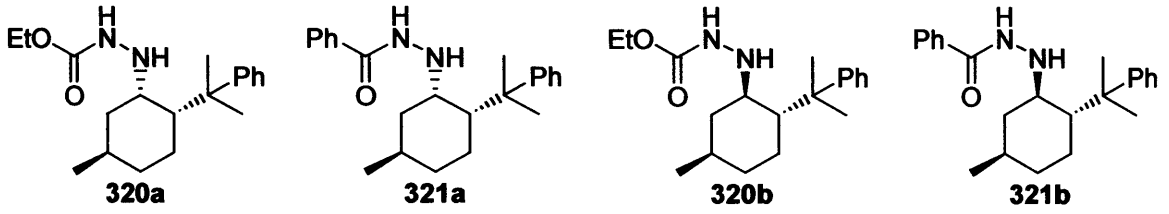


Figure **94**

The results of our study into the use of catalyst **321**, featuring similar electronic properties to hydrazide **320** but with modified steric properties, to promote the Diels-Alder reaction between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**) are shown below (*Table* **20**).

Table **20**[a]: Results of Experiments Using Catalysts with Modified Steric Properties

Entry	Catalyst	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	**320a**	17	70 : 30	44 (2*S*)
2	**321a**	3	60 : 40	-
3	**320b**	19	79 : 21	10 (2*R*)
4	**321b**	26	75 : 25	13 (2*R*)

(a) All reactions were carried out in acetonitrile/water (19:1) at -20°C for 48 hours with 10 mol% catalyst as an HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative.

We found that the use of hydrazide **321a**, incorporating a benzoic functionality, afforded a significantly decreased yield of Diels-Alder adduct **68**, when compared to the result achieved

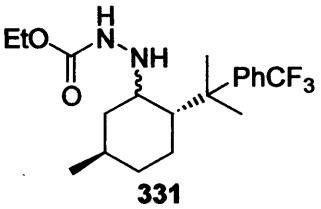
with catalyst **320a**. Consequently the stereochemical outcome of this reaction was not determined (*entry* **2**). The presence of this more bulky phenyl derivative may have sterically hindered the reactive site of **321a**, thus decreasing the rate of reaction.

Utilisation of hydrazide **320b**, diastereoisomer of **320a**, to catalyse the Diels-Alder cycloaddition afforded a similar yield and *exo*/*endo* ratio of adduct **68**, but a considerable reduction in the enantiomeric excess resulted, coupled with a reversal in the absolute stereochemistry of the major isomer (*entry* **3**). A comparable result was achieved by employment of catalyst **321b** (*entry* **4**), with a benzoate group in place of the ethoxy-carbonyl functionality, present in hydrazide **320b**.

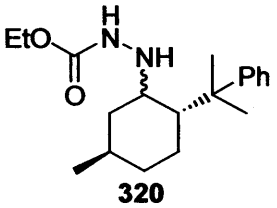
Thus, the use of benzoic hydrazide derived catalyst **321** *to promote the Diels-Alder cycloaddition afforded no improvement compared to the use of ethyl carbazate derived* **320**. *However, an important result was achieved with diastereomeric hydrazides* **320a** *and* **320b**, *which furnished opposite enantioselection to one another in the Diels-Alder reaction between cyclopentadiene* (**66**) *and E-cinnamaldehyde* (**67**).

4.9 Varying the Nature of the Aromatic Ring

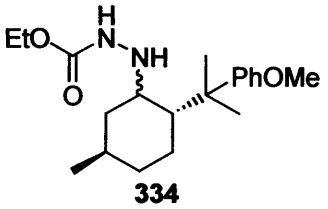
The main thrust of this project was to discover if, by modulating the electronic nature of the aromatic ring incorporated into catalysts **320**, **331**, **334** and **340** (*Figure* **95**), we could modulate the strength of the proposed face-face π–π interaction, which we postulated would occur between the catalyst and the α,β-unsaturated reagent upon formation of an iminium ion.



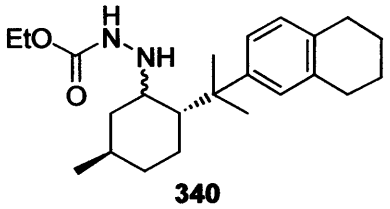
331



320



334

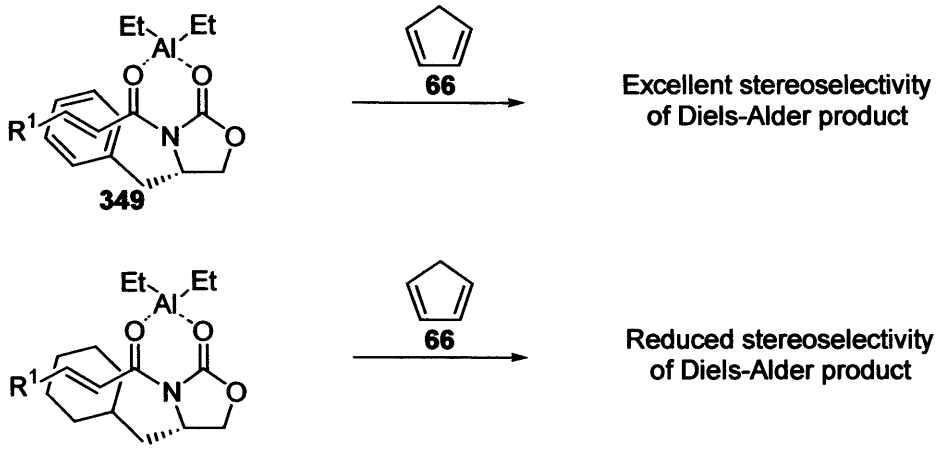


340

Figure **95**

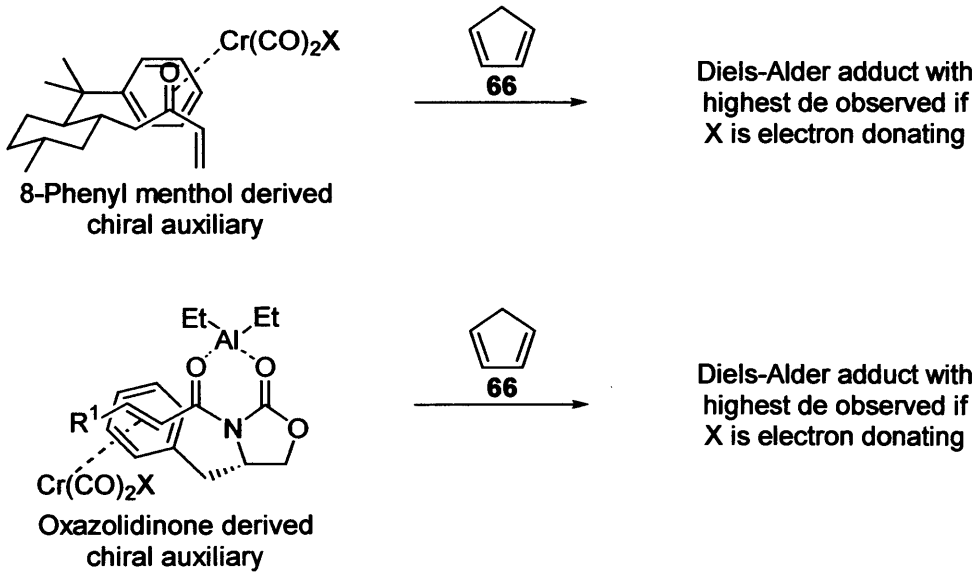
In the literature, attempts at the fine tuning of π-attractive interactions within catalysts have been very limited. In 1988, Evans and co-workers showed that direct replacement of the

arene portion of the oxazolidinone chiral controller **349** with a cyclohexyl group, led to the formation of Diels-Alder products with significantly reduced stereoselectivities. This observation was attributed to the loss of π–π interactions, which were postulated to fix the geometry of the substrate (*Scheme* **182**).[195]



Scheme **182**

In 1997, Jones and Chapman illustrated that ligand substitution of a complexed η^6-chromium carbonyl group, incorporated into the structure of classical chiral auxiliaries, affected the diastereomeric excess of the Diels-Alder product formed (*Scheme* **183**).[229]



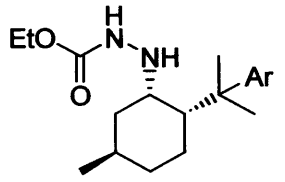
Scheme **183**

A trend in the adduct diastereomeric excess was observed that correlated with the electron donor capacity of the η^6-complexed arenes. These results, coupled with similar observations made by Whitesell[230] and Comins,[231] strongly suggested that an electronic effect was responsible for the increase in stereoselectivity, and that this effect could be modulated by tuning the π-donor ability of the arene.

The work carried out on these chiral auxiliaries was indeed informative, yet direct modulation of the electronics of the arene portion of a catalyst remained to be investigated. Indeed, a catalytic system is far more sensitive to changes in the electronic environment and fine-tuning is often very difficult. It was hoped that our comparisons in the next set of experiments would contribute to the pool of information regarding modulation of π-attractive interactions.

4.9.1 Comparison of the Aminocatalytic Family

We embarked upon an investigation into the effect of each catalyst (c.f. *Figure* **95**), containing slightly altered electronic properties, upon the enantioselectivities of the Diels-Alder product. The first set of experiments were carried out using the hydrazine catalysts with a *cis* relationship between the amino and aromatic cyclohexyl substituents (*Figure* **96**).



Ar = *p*-CF_3Ph **331a**
Ph **320a**
p-OMePh **334a**
H_4-Naph **340a**

Figure **96**

The results of these experiments are tabulated below (*Table* **21**).

Table **21**[a]: Results of Experiments Using Catalysts with Modified Electronics

Entry	Catalyst	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	**331a**	17	75 : 25	40 (2*S*)
2	**320a**	17	70 : 30	44 (2*S*)
3	**334a**	16	66 : 34	47 (2*S*)
4	**340a**	14	68 : 32	47 (2*S*)

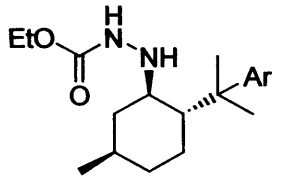
(a) All reactions were carried out in acetonitrile/water (19:1) at -20°C for 48 hours with 10 mol% catalyst as an HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative.

Surprisingly, analogous results were achieved with each of the aminocatalysts in terms of yield, *exo*/*endo* ratio and enantiomeric excess. In addition, the *exo*-(2*S*) isomer was formed preferentially with all four hydrazides. Therefore, modifications to the electronic nature of hydrazide **320a** had no effect on the stereochemical outcome of the Diels-Alder cycloaddition between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**). This suggested that the observed

enantioselectivity was a result of steric, rather than electronic, factors for this family of hydrazides with a *cis* relationship between the amino and aromatic cyclohexyl substituents.

In summary, this study suggested that the observed facial selectivity of the Diels-Alder cycloadditions, catalysed by our family of hydrazides with a cis relationship between the amino and aromatic cyclohexyl substituents, was a result of steric factors. Subtle modifications to the electronics of the aromatic ring incorporated into the structure of the catalysts had no effect on the stereochemical outcome of the cycloadditions, suggesting that the proposed π–π interactions are not in fact transpiring.

The next logical step was to repeat the set of catalytic Diels-Alder reactions using the family of hydrazides with a *trans* relationship between the amino and aromatic cyclohexyl substituents (*Figure* **97**).



Ar = *p*-CF_3Ph **331b**
Ph **320b**
p-OMePh **334b**
H_4-Naph **340b**

Figure **97**

The results of this catalytic study are shown below (*Table* **22**).

Table **22**[a]: Results of Experiments Using Catalysts with Modified Electronics

Entry	Catalyst	% Yield	*Exo* : *Endo*[b]	*Exo* % ee[c]
1	**331b**	21	74 : 36	7 (2*R*)
2	**320b**	19	79 : 21	10 (2*R*)
3	**334b**	25	65 : 35	21 (2*R*)
4	**340b**	24	63 : 37	39 (2*R*)

(a) All reactions were carried out in acetonitrile/water (19:1) at -20°C for 48 hours with 10 mol% catalyst as an HCl salt. (b) All *exo*/*endo* ratios were obtained from the ^{1}H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by chiral HPLC of the product as its 2,4-DNPH derivative.

The outcome of this experiment was pleasantly surprising. Each of the hydrazides employed afforded a similar yield and *exo*/*endo* ratio of Diels-Alder adduct **68**. Importantly, a significant increase in enantioselectivity was observed with the use of the "electron rich" hydrazide **334b** (21% ee, *entry* **3**), compared to "electron neutral" **320b** (10% ee, *entry* **2**) and "electron deficient" **331b** (7% ee, *entry* **1**). Thus, as the electron density of the aromatic ring incorporated into the catalyst structure was increased, the Diels-Alder adduct was formed with

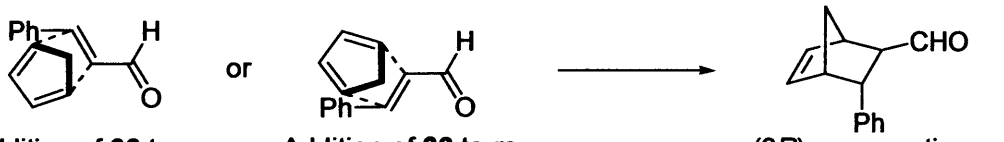
higher enantiomeric excess, suggesting that the observed enantioselection was due to electronic, rather than steric, factors for this family of hydrazides with a *trans* relationship between the amino and aromatic cyclohexyl derivatives. The *exo*-(2*R*) isomer was formed preferentially with each of these "*trans*"-hydrazides, in contrast to use of the "*cis*"-catalysts, which provided the *exo*-(2*S*) isomer in predominance (see *Table* **21**).

Furthermore, hydrazide **340b**, incorporating a tetrahydronaphthyl substituent, afforded a marked increase in the observed enantioselectivity of adduct **68** (*entry* **4**), compared to "electron rich" catalyst **334b**. Presumably, the presence of this larger substituent further aids in the shielding of one face of the dienophile, inducing an increased facial selectivity in the ensuing Diels-Alder cycloaddition with *E*-cinnamaldehyde (**67**).

In summary, upon consideration of our catalytic experiments (Table **22**), *there appeared to be a definite correlation between the electronic density of the aromatic ring incorporated into the catalyst, and the enantiomeric excess of the Diels-Alder adduct* **68** *formed. Although the observed enantioselectivities in these Diels-Alder experiments were not comparable with contemporary methods, we were encouraged by these results. It appeared that our postulations concerning the effect of face-face π–π interactions on the stereoselectivity of asymmetric reactions were accurate, since modulating the extent of this phenomenon led to various degrees of asymmetric induction in the catalysis of the Diels-Alder reaction.*

4.9.2 Proposed Iminium Ion Intermediate

During the cycloaddition between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**), catalysed by "electron rich" hydrazide **334b** as its hydrochloride salt, the *exo*-(2*R*) isomer was formed preferentially. Consideration of the absolute configuration of the major isomer formed enabled the postulation of a working model to explain the observed enantioselectivity. Thus, to form an excess of *exo*-(2*R*) adduct **68**, cyclopentadiene (**66**) must have preferentially reacted with the *re*-face of the α,β-unsaturated carbonyl component (*Figure* **98**).



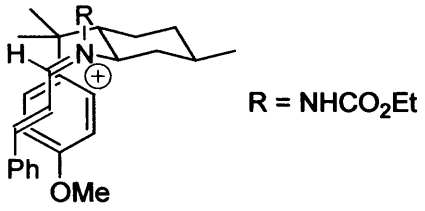
Addition of **66** to *re* face of **67** in *s-trans* conformation

Addition of **66** to *re* face of **67** in *s-cis* conformation

(2*R*)-*exo* enantiomer formed

Figure **98**

We propose that upon iminium ion formation of hydrazide **334b** with *E*-cinnamaldehyde (**67**), the preferred conformation of the complex (**350**) will be that shown below (*Figure* **99**), which is consistent with the asymmetric induction observed in our Diels-Alder experiments. In this conformation the π-system of the iminium species sits directly over the face of the aromatic ring, thus blocking one diastereoface from the approach of a reagent. Although there are other conformations that this complex can adopt, it is believed that our system will behave in a similar fashion to 8-phenyl menthol acrylates, with the two unsaturated systems lying parallel to each other as shown. Thus, the *si*-face of the α,β-unsaturated species should be shielded by the aromatic ring, leading to the facial selectivity observed in the reactions of these iminium ions.



350

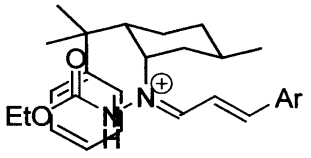
Figure **99**

This model is consistent with our original proposal that π-stacking could occur between the α,β-unsaturated component and the aromatic ring incorporated into the structure of the catalyst. This would also reinforce our catalytic results, in which a difference in the stereoselectivity of the Diels-Alder reaction was observed by modulation of the electronics of the catalysts' aromatic ring, achieved by utilisation of the "electron rich" aromatic **334b** and the "electron deficient" aromatic **331b**.

The fact that the enantiomeric excess of the Diels-Alder product was relatively low, however, suggests that other iminium ion intermediates also exist, and elimination of this problem needs careful consideration. It is also of great importance to appreciate that the thermodynamically favoured ground state geometry of a complex may not be the same as the reactive geometry (c.f. the Curtin-Hammett principal).[206]

With the "*cis*"-substituted catalysts (e.g. **320a**), the situation is a little more complex in that it is apparent that altering the nature of the aromatic functionality does not appear to have any direct influence on the enantioselectivities observed in the Diels-Alder cycloaddition. One possible explanation is that the proposed face-face π–π interaction is occurring between the electron-withdrawing group attached to the α-heteroatom and the aromatic ring. This

interaction would be consistent throughout the family of catalysts (**320a**, **331a**, **334a** and **340a**) as they all contain the same substituent and the differing aromatic ring as shown in *Figure* **100**. This possibility would require further investigation into the nature of the electron withdrawing group, which unfortunately was beyond the scope of this investigation.

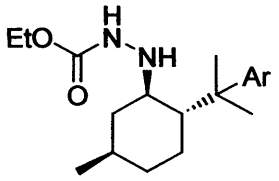


351

Figure **100**

4.10 Conclusions

During the course of this project we have established that the α-effect is a suitable platform for the acceleration of aminocatalytic transformations. An appropriate molecular scaffold was determined to enable efficient catalytic turnover, and the synthesis of a family of chiral aminocatalysts, based on 8-phenyl menthamine, was accomplished (*Figure* **101**).



Ar = *p*-CF_3Ph **331b**
Ph **320b**
p-OMePh **334b**
H_4-Naph **340b**

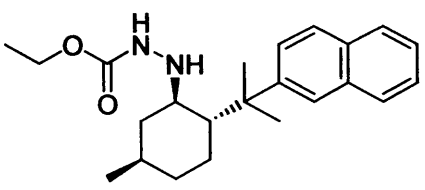
Figure **101**

Although competitive facial selectivities were not observed in the aminocatalytic Diels-Alder reactions promoted by our family of catalysts, our investigations into the modulation of face-face π–π interactions have been both informative and relevant. We showed that the electronic density of the π-donating moiety had a direct bearing on the strength of the π–π interactions with the π-accepting substrate, which hence affected the enantioselectivity of the asymmetric carbon-carbon bond forming reaction. As stated by Hunter, *"the magnitude of a non-covalent interaction is the sum of π-electron repulsions (interaction between the net charges on the atoms) and the interactions between the net charges and the π-electrons"*.[207] Thus, according to this postulation, an electron rich aromatic ring should be necessary to bring about the maximum interaction with an electron deficient α,β-unsaturated carbonyl compound. Our experimental observations reinforced this postulation.

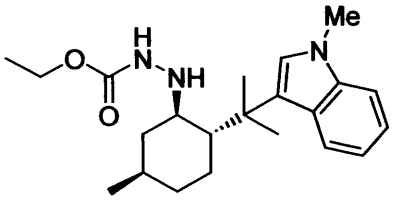
In conclusion, the results of our catalytic investigations were both encouraging and informative. Within this project we have probed into the nature of attractive face-face π–π interactions, and have displayed how subtle modifications to the electronic nature of the catalyst can affect the selectivity of catalytic asymmetric reactions.

4.11 Future Investigations

Our investigations into the use of our family of 8-phenyl menthamine aminocatalysts (see *Figure* **101**) indicated that the enantioselectivity observed in the Diels-Alder cycloadditions was a result of electronic, rather than steric, factors. Based on our experimental observations, one could expect the naphthyl or indolyl-based catalysts, **337b** or **341b**, to further enhance this enantioselectivity (*Figure* **102**).



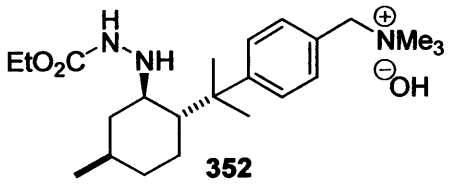
337b



341b

Figure **102**

Thus, further studies could provide an aminocatalyst capable of inducing high levels of enantioselectivity when employed to promote Diels-Alder cycloadditions. Moreover, this family of aminocatalysts could be used to promote other reactions involving α,β-unsaturated carbonyl compounds. For example, minor modifications to the catalyst structure could provide a novel asymmetric aminocatalyst for the Michael reaction (*Figure* **103**). It is well established that quaternary amines catalyse the conjugate addition reaction.[232] It has been shown that tetra-alkylammonium hydroxide compounds catalyse the addition of malonates to both cyclic and acyclic enones through ion pair control.[233] It is proposed that iminium ion formation, between the catalyst and the enone substrate, precedes deprotonation of the malonate by the quaternary tetra-alkylammonium hydroxide substituent and results in the nucleophile being delivered preferentially to one face of the substrate.



352

Figure **103**

Hydrazide **352** is a candidate for the catalysis of the asymmetric Michael reaction, the synthesis of which can easily be envisaged from the chemistry already developed, by simple modification of the aryl group in the initial conjugate addition reaction, and conversion to the quaternary ammonium salt using methods previously described.[233] This should quickly provide access to the desired structure **352**, containing the secondary amine, with an α-heteroatom, that should readily form the corresponding iminium ion with prochiral cyclic and acyclic α,β-unsaturated carbonyl compounds. This should allow for the deprotonation of a malonate substrate, whose delivery will be dictated by the catalyst structure, due to affinity of the malonate anion to the quaternary ammonium salt incorporated into the catalyst structure.

Hydrazide **352** *could therefore represent the first acyclic catalyst for the iminium ion accelerated asymmetric Michael reaction, and thus reinforce the concepts incorporated into our catalytic design.*

Chapter 5: Experimental

5.1 Experimental Techniques

Reagents were obtained from Aldrich, Lancaster and Fluka chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[234] Dichloromethane was dried by refluxing over, and distilling from calcium hydride. Methanol was dried by refluxing over magnesium, followed by distillation. Tetrahydrofuran was obtained dry by distillation from sodium benzophenone ketyl under nitrogen. Acetonitrile was dried by refluxing over, and distilling from calcium hydride. Benzene and toluene were dried over sodium wire for 24 hours prior to use. Triethylamine was distilled from calcium hydride and dried over potassium hydroxide. Anhydrous ethyl acetate was obtained by pre-drying with anhydrous magnesium sulfate and anhydrous diethyl ether was obtained by distillation from sodium benzophenone ketyl. The *iso*propanol, hexanes and acetonitrile used for HPLC analysis were of analytical grade and >99% purity. The water used for HPLC analysis was deionised and distilled prior to use. Light petroleum refers to petroleum ether 40-60°C; ether refers to diethyl ether; THF is tetrahydrofuran.

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,[222] which consists of twelve test tubes with suba-seals and nitrogen inlets, a stirrer plate and a bath for cooling. The cryostat used for low temperature reactions was a HAAKE EK90 immersion cooler. 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.

Flash chromatography refers to column chromatography using head pressure by means of compressed air according to the procedure of Still,[235] 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. The abbreviation dec. is used for compounds that decomposed above the temperature specified.

The optical rotation, $[\alpha]_D$, of chiral non-racemic compounds, was analysed using an Optical Activity AA-1000 polarimeter at room temperature, using the sodium D line.

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 or as a nujol mull between sodium chloride plates. All absorptions are quoted in cm^{-1}.

^1H NMR spectra (δ_H) were recorded in deuteriochloroform (unless otherwise stated) using a Bruker DPX 400 instrument (400 MHz), with ^{13}C NMR spectra (δ_C) recorded at 100 MHz. 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 ^1H NMR and 77.30 ($CHCl_3$), centre line, for ^{13}C NMR. The abbreviations s, d, t, q m and br, denote singlet, doublet, triplet, quartet, muliplet 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 electrospray ionisation (APcI) unless otherwise stated. APcI refers to atmospheric pressure chemical ionisation; CI is chemical ionisation (ammonia); EI refers to electron ionisation.

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 = 0.00055Da).

High pressure liquid chromatography (HPLC) was performed using a Hewlett Packard 1100 series chromatographic pump and injector. Detection was *via* a selective wavelength UV detector.

5.2 General Procedures

(a) Lewis Acid Catalysed Diels-Alder Cycloaddition[172a,202]

The ligand (10 mol%) was dissolved in dichloromethane (20 mL/mmol ligand) under an inert atmosphere. The Lewis acid (10 mol%) was added and the solution cooled to 0°C (immersion cooler), and stirring was continued at this temperature for 1 hour. The α,β-unsaturated aldehyde (1 equiv.) was added and the solution cooled to –78°C. After stirring at this temperature for 30 minutes the diene (5 equiv.) was added. The reaction mixture was stirred for 24/48 hours before addition of ethanol (1 mL). The reaction mixture was allowed to warm slowly to room temperature, water was added and the mixture was extracted with diethyl ether. The aqueous layer was further extracted with diethyl ether (x2), and the ethereal extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude product.

(b) Iminium Ion Catalysed Diels-Alder Cycloaddition[7]

The catalyst (10 mol%) was dissolved in the relevant solvent system (~30 mL/mmol catalyst). The acid co-catalyst (10 mol%) was added and stirring was continued for 10 minutes before addition of the α,β-unsaturated aldehyde (1 equiv.). After stirring for 15 minutes the solution was taken to the relevant reaction temperature and cyclopentadiene (3 equiv.) was added. The reaction mixture was stirred for 24/48 hours before addition of water and extraction with diethyl ether. The aqueous layer was further extracted with diethyl ether (x2), and the ethereal extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated to afford the crude product.

The salt of the catalyst was pre-formed if hydrochloric acid was used as the acid co-catalyst; the catalyst was dissolved in diethyl ether, 2.0M ethereal hydrogen chloride (3 equiv.) was added and the solution was evaporated *in vacuo* to afford the catalyst as its hydrochloride salt.

(c) Hydrolysis of the Dimethyl-Acetal Diels-Alder Adduct[7]

The dimethyl-acetal Diels-Alder adduct was dissolved in chloroform (2 mL/mmol). Water (1 mL/mmol) and trifluoroacetic acid (1 mL/mmol) were added and the solution was stirred at room temperature for 4 hours. The reaction mixture was neutralised with saturated sodium bicarbonate solution and extracted with diethyl ether. The aqueous layer was further

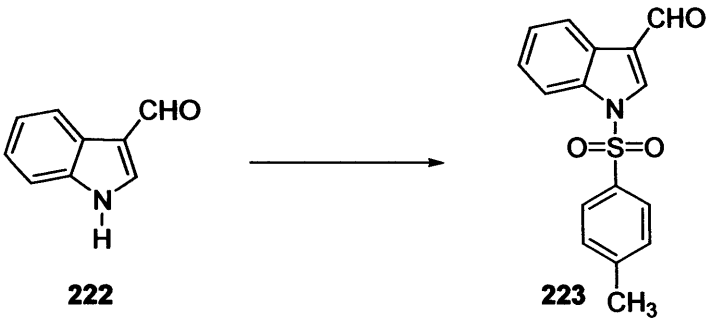
extracted with diethyl ether (x2), and the ethereal extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude product.

(d) 2,4-Dinitrophenylhydrazine Derivatisation Of The Diels-Alder Adduct[201]

The Diels-Alder adduct was dissolved in ethanol (2 mL/mmol), and 2,4-dinitrophenylhydrazine (1.2 equiv.) was added. The reaction mixture was stirred for 2 hours at room temperature. Water was added and the mixture was extracted with diethyl ether. The aqueous layer was further extracted with diethyl ether (x2), and the ethereal extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude product.

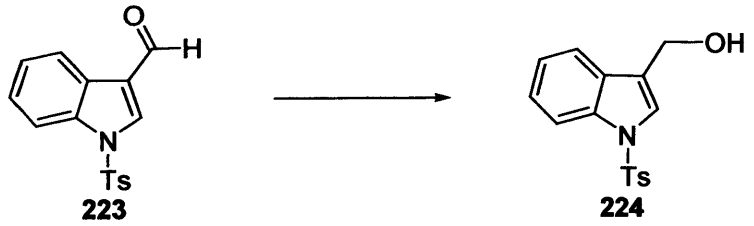
5.3 Experimental Procedures

1-(Toluene-4-sulfonyl)-1*H*-indole-3-carboxaldehyde 223[184]



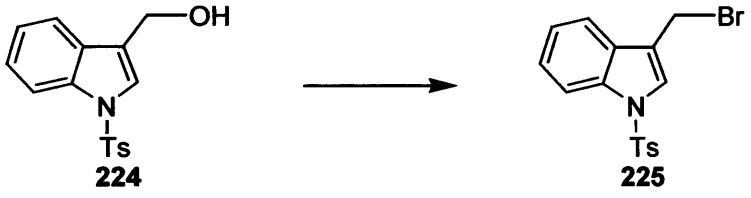
A mixture of indole-3-carboxaldehyde (**222**) (10.04g, 68.9 mmol) and toluene-4-sulfonyl chloride (19.72g, 103.3 mmol) in freshly distilled triethylamine (150 mL) was heated to 90-95°C for two hours. After cooling to ambient temperature, the reaction mixture was poured into ice-cold water, stored at +4°C for one hour, and filtered. The insoluble product was washed with water and air-dried. The crude product was dissolved in dichloromethane, filtered through a plug of silica and the filtrate was concentrated to afford the *title compound* **223** (16.54g, 80%) as a pale yellow powder; mp 147-149°C [lit.[184] mp 148-150°C]; Found 300.0697 MH^+ $C_{16}H_{13}NO_3S$ requires 300.0689); ν_{max} (nujol)/cm^{-1} 1664 (CHO), 1538, 1188, 1174, 970, 760, 660; δ_H (400 MHz, $CDCl_3$) 9.99 (1H, s, C*H*O), 8.16 (1H, d, *J* 7.7 Hz, Ar*H*), 8.15 (1H, s, H-2), 7.86 (1H, d, *J* 7.7 Hz, Ar*H*), 7.76 (2H, d, *J* 8.4 Hz, H-3'), 7.28 (2H, m, H-5, H-6), 7.18 (2H, d, *J* 8.4 Hz, H-2'), 2.25 (3H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 187.6 (CHO), 148.3 (C), 138.5 (CH), 138.5 (C), 137.3 (C), 136.4 (C), 132.5 (CH), 129.4 (CH), 128.4 (CH), 127.2 (CH), 124.7 (CH), 124.4 (C), 115.4 (CH), 23.8 (CH_3); *m/z* (APcI) 300.3 (MH^+, 100%), 78.9 (12); data consistent with the literature precedent.

[1-(Toluene-4-sulfonyl)-1*H*-indol-3-yl]methanol 224



1-(Toluene-4-sulfonyl)-1*H*-indole-3-carboxaldehyde (**223**) (2.50g, 8.4 mmol) was stirred in methanol (85 mL) and cooled to 0°C. Sodium borohydride (1.35g, 8.4 mmol) was added under an inert atmosphere. Stirring was continued at 0°C until starting material was no longer detected by TLC. After this time (1 hour) HCl (2M, 38 mL) was added cautiously, and the solution was extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **224** (2.51g, quant.) as a colourless powder; mp 109-110°C [lit.[236] mp 105-107°C]; Found 301.0762 (M^+ $C_{16}H_{15}NO_3S$ requires 301.0767); ν_{max} (nujol)/cm^{-1} 3378 (OH), 1595, 1495, 1363, 1134, 1019, 817, 750; δ_H (400 MHz, $CDCl_3$) 7.92 (1H, d, *J* 7.7 Hz, Ar*H*), 7.71 (2H, d, *J* 8.3 Hz, H-3''), 7.54 (1H, d, *J* 7.7 Hz, Ar*H*), 7.48 (1H, s, H-2'), 7.27 (1H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 7.19 (1H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 7.15 (2H, d, *J* 8.3 Hz, H-2''), 4.75 (2H, s, CH_2OH), 2.27 (3H, s, $ArCH_3$); δ_C (100 MHz, $CDCl_3$) 145.5 (C), 135.8 (C), 135.5 (C), 130.3 (CH), 129.9 (C), 127.2 (CH), 125.4 (CH), 124.2 (CH), 123.7 (CH), 122.8 (C), 120.3 (CH), 114.1 (CH), 57.5 (CH_2), 22.0 (CH_3); *m/z* (EI) 301.1 (M^+, 30%), 129.1 (20), 118.1 (35), 91.1 (100), 65.1 (45); data consistent with the literature precedent.

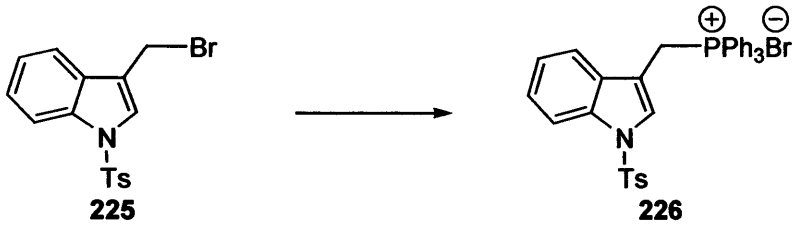
3-Bromomethyl-1-(toluene-4-sulfonyl)-1*H*-indole 225



[1-(Toluene-4-sulfonyl)-1*H*-indol-3-yl]methanol (**224**) (2.51g, 8.3 mmol) was stirred in dichloromethane (80 mL) and phosphorous tribromide (0.95 mL, 10.0 mmol) was added dropwise. Stirring was continued for 1 hour at ambient temperature, water (100 mL) was added and the mixture was extracted with diethyl ether (2 x 50 mL). The extracts were washed with brine, dried ($MgSO_4$) and concentrated to give the *title compound* **225** (2.84g, 94%) as a colourless powder; mp 142-143°C [lit.[237] mp 143-145°C] δ_H (400 MHz, $CDCl_3$) 7.96(1H, d, *J* 7.7 Hz, Ar*H*), 7.77 (2H, d, *J* 8.3 Hz, H-3'), 7.64 (1H, s, H-2), 7.64 (1H, d, *J* 7.7 Hz, Ar*H*), 7.32 (2H, m, H-5, H-6), 7.28 (2H, d, *J* 8.3 Hz, H-2'), 4.52 (2H, s, $ArCH_2Br$), 2.25 (3H, s, $ArCH_3$); δ_C (100 MHz, $CDCl_3$) 145.7 (C), 135.7 (C), 135.4 (C), 130.5 (CH), 129.5 (C), 127.3 (CH), 125.7 (CH), 125.4 (CH), 123.9 (CH), 120.3 (CH), 119.3 (C), 114.1 (CH), 24.2

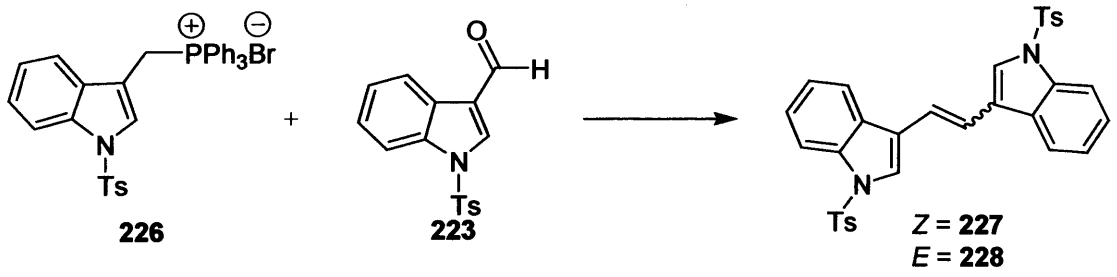
(CH_2), 22.0 (CH_3); *m/z* (APcI) 284.3 ($M^{\bullet+}$-$Br^{\bullet}$, 100%), 117.2 (44), 107.1 (45); data consistent with the literature precedent.

Triphenyl[1-(toluene-4-sulfonyl)-1*H*-indol-3-ylmethyl]phosphonium bromide 226



3-Bromomethyl-1-(toluene-4-sulfonyl)-1*H*-indole (**225**) (2.70g, 7.4 mmol), was stirred in benzene (125 mL) and triphenylphosphine (1.95g, 7.4 mmol) was added. The reaction mixture was stirred at reflux temperature under an inert atmosphere for 24 hours and filtered to afford the *title compound* **226** (2.90g, 72%) as a colourless powder; mp 210°C (dec.); Found 546.1656 ($M^{\bullet+}$-$Br^{\bullet}$ $C_{34}H_{29}BrNO_2PS$ requires 546.1651); ν_{max} (nujol)/cm^{-1} 1587, 1487, 1437 (P-Ar), 1376, 1175, 819, 758, 745, 670; δ_H (400 MHz, $CDCl_3$) 7.83 (1H, d, *J* 7.6 Hz, Ar*H*), 7.72 (8H, m, Ar*H*), 7.55 (7H, m, Ar*H*), 7.38 (3H, m, Ar*H*), 7.13 (3H, m, Ar*H*), 6.95 (1H, d, *J* 7.6 Hz, Ar*H*), 6.85 (1H, dd, *J* 7.6, 7.6 Hz, Ar*H*), 5.54 (2H, s, ArCH_2), 2.27 (3H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 144.5 (C), 134.3 (CH), 133.6 (C), 133.5 (CH), 133.4 (C), 129.5 (CH), 129.4 (CH), 129.2 (C), 127.6 (CH), 126.1 (CH), 124.4 (CH), 122.8 (CH), 118.8 (CH), 117.4 (C), 116.5 (C), 112.6 (CH), 22.6 (CH_2), 20.8 (CH_3); *m/z* (APcI) 546.6 ($M^{\bullet+}$-$Br^{\bullet}$, 100%), 59.0 (8).

(*Z*)- and (*E*)-1,2-Bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethene 227 and 228



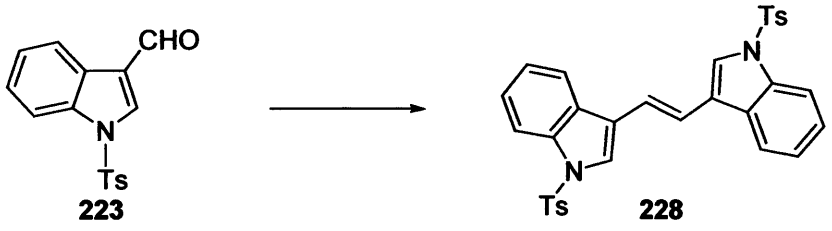
Triphenyl[1-(toluene-4-sulfonyl)-1*H*-indol-3-ylmethyl]phosphonium bromide (**226**) (2.38g, 4.3 mmol) was dissolved in tetrahydrofuran (50 mL) and the solution was cooled to 0°C. *n*-Butyllithium (2.5M, 1.72 mL, 4.3 mmol) was added dropwise, and this solution was added *via* a canula to a solution of 1-(toluene-4-sulfonyl)-1*H*-indole-3-carboxaldehyde (**223**) (1.29g, 4.3

mmol) in tetrahydrofuran (50 mL) at 0°C with stirring. The solution was warmed to ambient temperature and stirring was continued for 24 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give a yellow oil. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (30:70), afforded the *cis*-alkene **227** (0.48g, 20%) as a colourless powder and the *trans*-alkene **228** (0.34g, 14%) as a yellow powder.

(*Z*)-Alkene 227; mp 139-143°C; Found 567.1408 (MH^+ $C_{32}H_{26}N_2O_4S_2$ requires 567.1407); ν_{max} (nujol)/cm^{-1} 1594 (C=C), 1556, 1492, 1387, 1170, 814, 732; δ_H (400 MHz, $CDCl_3$) 7.91 (2H, d, *J* 7.8 Hz, Ar*H*), 7.57 (4H, d, *J* 8.3 Hz, H-3"), 7.41 (2H, s, H-2'), 7.30 (2H, d, *J* 7.8 Hz, Ar*H*), 7.25 (2H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 7.15 (4H, d, *J* 8.3 Hz, H-2"), 7.05 (2H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 6.64 (2H, s, C=C*H*), 2.27 (6H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 145.5 (C), 135.3 (C), 135.0 (C), 130.5 (CH), 130.0 (C), 127.2 (CH), 125.3 (CH), 124.6 (CH), 123.7 (CH), 121.3 (CH), 120.4 (CH), 119.3 (C), 114.1 (CH), 22.0 (CH_3); *m/z* (APcI) 567.4 (MH^+, 100%), 566.6 (43), 117.2 (22), 65.1 (45), 59.0 (78).

(*E*)-Alkene 228; mp 220°C (dec.); Found 567.1407 (MH^+ $C_{32}H_{26}N_2O_4S_2$ requires 567.1407); ν_{max} (nujol)/cm^{-1} 1596 (C=C), 1555, 1493, 1365, 1171, 976, 810, 746; δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* 7.6 Hz, Ar*H*), 7.75 (2H, d, *J* 7.6 Hz, Ar*H*), 7.71 (4H, d, *J* 8.3 Hz, H-3"), 7.65 (2H, s, H-2'), 7.26 (4H, m, H-5', H-6'), 7.14 (2H, s, C=C*H*), 7.13 (4H, d, *J* 8.3 Hz, H-2"), 2.25 (6H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 145.5 (C), 136.0 (C), 135.4 (C), 130.5 (CH), 130.4 (CH), 129.4 (C), 127.3 (CH), 127.2 (CH), 125.5 (CH), 124.1 (CH), 121.3 (C), 120.7 (CH), 114.3 (CH), 22.0 (CH_3); *m/z* (APcI) 567.4 (MH^+, 100%), 300.3 (76), 284.3 (23), 107.0 (24), 59.1 (58).

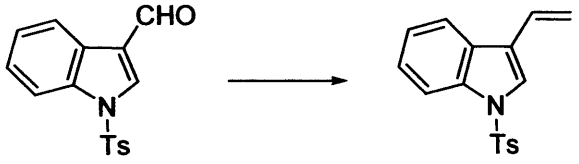
(*E*)-1,2-Bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethene 228



223 **228**

Titanium tetrachloride (5.13 mL, 46.5 mmol) was added slowly at –10°C to a stirred suspension of zinc powder (7.19g, 109.8 mmol) in dry tetrahydrofuran (100 mL) under an inert atmosphere. A solution of 1-(toluene-4-sulfonyl)-1*H*-indole-3-carboxaldehyde (**223**) (5.00g, 16.7 mmol) in dry tetrahydrofuran (200 mL) was added dropwise at reflux temperature and stirring was continued for five hours. The reaction mixture was cooled to ambient temperature with stirring, and quenched by cautious addition of saturated sodium bicarbonate solution (300 mL). The solution was filtered through celite® and the filtrate was added to a separating funnel with diethyl ether (50 mL). The organic layer was collected and the aqueous layer was further extracted with diethyl ether (2 x 50 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with dichloromethane/light petroleum (60:40), afforded the *title compound* **228** (1.74g, 38%) as a pale yellow powder; characterisation as before.

1-(Toluene-4-sulfonyl)-3-vinyl-1*H*-indole 229

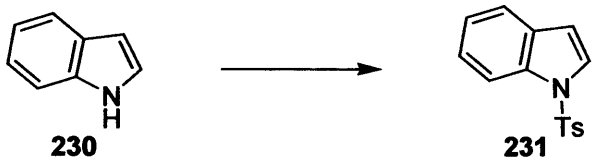


223 **229**

Methyltriphenylphosphonium bromide (6.68g, 18.7 mmol) was stirred in tetrahydrofuran (100 mL) under an inert atmosphere. The solution was cooled to 0°C and *n*-butyllithium (2.5M, 9 mL, 22.5 mmol) was added dropwise. This solution was added *via* a canula to a solution of 1-(toluene-4-sulfonyl)-1*H*-indole-3-carboxaldehyde (**223**) (4.00g, 13.4 mmol) in tetrahydrofuran (75 mL) at 0°C with stirring. The reaction mixture was warmed to ambient temperature and stirring was continued for 24 hours. Water (75 mL) was added and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (20:80), afforded the *title compound* **229** (2.37g, 60%) as a colourless powder; mp 97–99°C [lit.[238] mp 84-86°C]; Found 298.0900 (MH^+ $C_{17}H_{15}NO_2S$ requires 298.0896); ν_{max} (nujol)/cm^{-1} 3119, 1636 (C=C), 1598, 1493, 1373, 1178, 993, 917, 816, 750; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* 7.8 Hz, Ar*H*), 7.60 (2H, d, *J* 8.2 Hz, H-3'), 7.57 (1H, d, *J* 7.8 Hz, Ar*H*), 7.49 (1H, s, H-2), 7.18 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 7.09 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 6.94 (2H, d, *J* 8.2 Hz, H-2'), 6.60 (1H,

dd, *J* 17.8, 11.4 Hz, H_2C=C*H*), 5.63 (1H, d, *J* 17.8 Hz, C=C*H*H), 5.18 (1H, d, *J* 11.4 Hz, C=CH*H*), 2.04 (3H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 145.5 (C), 135.9 (C), 135.5 (C), 130.3 (CH), 129.4 (C), 128.0 (CH), 127.3 (CH), 125.3 (CH), 124.5 (CH), 123.9 (CH), 121.3 (C), 120.8 (CH), 115.8 (CH_2), 114.1 (CH), 22.0 (CH_3); *m/z* (APcI) 298.3 (MH^+, 100%), 155.1 (15), 59.1 (36); data consistent with the literature precedent.

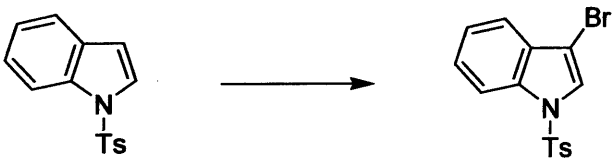
1-(Toluene-4-sulfonyl)-1*H*-indole 231



230 **231**

Indole (**230**) (3.00g, 25.6 mmol) was stirred in tetrahydrofuran (50 mL) under an inert atmosphere. The solution was cooled to 0°C and *n*-butyllithium (2.5M, 14.3 mL, 35.9 mmol) was added dropwise. A solution of toluene-4-sulfonyl chloride (6.83g, 35.9 mmol) in tetrahydrofuran (60 mL) was added *via* a canula. The solution was warmed to room temperature and stirring was continued for three hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (50 mL) and the organic layer was collected. The aqueous layer was further extracted with ethyl acetate (3 x 30 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$) and reduced. Trituration with diethyl ether afforded the *title compound* **231** (4.48g, 65%) as a colourless powder; mp 80-82°C [lit.[185] mp 86°C]; Found 272.0747 (MH^+ $C_{15}H_{13}NO_2S$ requires 272.0740); ν_{max} (nujol)/cm^{-1} 1596, 1494, 1369, 1168, 811, 756; δ_H (400 MHz, $CDCl_3$) 7.91 (1H, d, *J* 7.8 Hz, Ar*H*), 7.68 (2H, d, *J* 8.1 Hz, H-3'), 7.48 (1H, d, *J* 3.3 Hz, H-2), 7.44 (1H, d, *J* 7.8 Hz, Ar*H*), 7.22 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 7.15 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 7.12 (2H, d, *J* 8.1 Hz, H-2'), 6.57 (1H, d, *J* 3.3 Hz, H-3), 2.21 (3H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 145.4 (C), 135.7 (C), 135.2 (C), 131.2 (C), 130.3 (CH), 127.2 (CH), 126.7 (CH), 125.0 (CH), 123.7 (CH), 121.8 (CH), 113.9 (CH), 109.5 (CH), 22.0 (CH_3); *m/z* (APcI) 272.1 (MH^+, 100%), 155.1 (35), 107.0 (22); data consistent with the literature precedent.

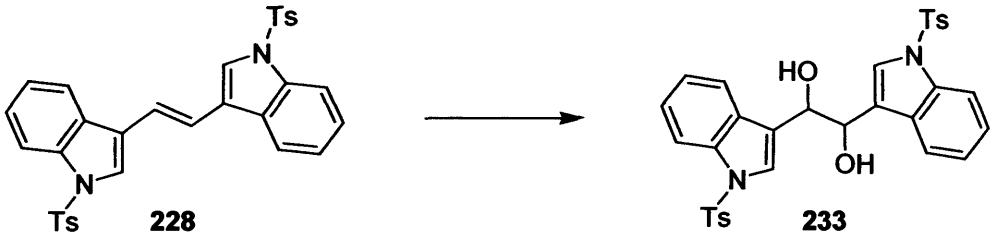
3-Bromo-1-(toluene-4-sulfonyl)-1*H*-indole 232[185]



231 **232**

1-(Toluene-4-sulfonyl)-1*H*-indole (**231**) (1.65g, 6.1 mmol) was added to carbon tetrachloride (28 mL) under an inert atmosphere. A solution of bromine (0.39 mL, 7.6 mmol) in carbon tetrachloride (28 mL) was added dropwise over 30 minutes and stirring was continued for two hours. The dark solution was poured onto saturated sodium bicarbonate solution (60 mL). The organic layer was collected, washed with aqueous sodium thiosulfite solution (60 mL), brine, dried ($MgSO_4$) and reduced. Crystallisation from absolute ethanol gave the *title compound* **232** (1.87g, 88%) as a colourless solid; mp 115–117°C [lit.[185] mp 120-123°C]; Found 350.9767 (M^+ $C_{15}H_{12}{}^{81}BrNO_2S$ requires 350.9752), 348.9778 (M^+ $C_{15}H_{12}{}^{79}BrNO_2S$ requires 348.9772); ν_{max} (nujol)/cm^{-1} 1597, 1492, 1365, 1172, 814, 745; δ_H (400 MHz, $CDCl_3$) 7.90 (1H, d, *J* 7.7 Hz, Ar*H*), 7.66 (2H, d, *J* 8.3 Hz, H-3'), 7.53 (1H, s, H-2), 7.38 (1H, d, *J* 7.7 Hz, Ar*H*), 7.27 (1H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 7.19 (1H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 7.09 (2H, d, *J* 8.3 Hz, H-2'), 2.19 (3H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 145.8 (C), 135.2 (C), 134.6 (C), 130.4 (CH), 130.2 (C), 127.3 (CH), 126.2 (CH), 125.2 (CH), 124.3 (CH), 120.5 (CH), 114.0 (CH), 100.0 (C), 22.0 (CH_3); *m/z* (EI) 351 (M^+, 72%), 349 (M^+, 73%), 194 (57), 155 (64), 91 (100), 64 (64); data consistent with the literature precedent.

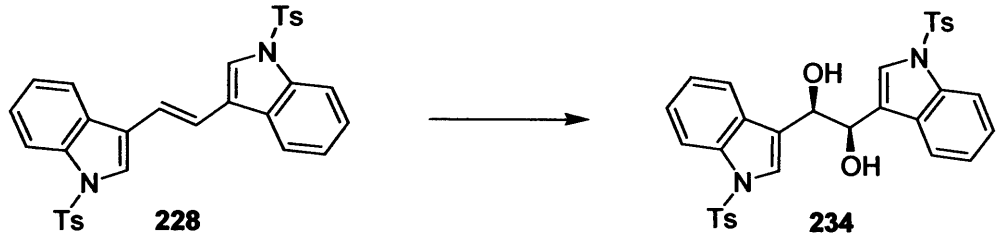
(±)-1,2-Bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethane-1,2-diol 233



Potassium ferricyanide (0.87g, 2.7 mmol), potassium carbonate (0.37g, 2.7 mmol), potassium osmate dihydrate (5mg, 12 μmol), quinuclidine (27mg, 0.25 mmol) and methanesulfonamide (84mg, 0.88 mmol) were stirred together at ambient temperature for 30 minutes before addition of tetrahydrofuran (5 mL) and water (5 mL). 1,2-Bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethene (**228**) (0.50g, 0.88 mmol) was added and stirring was continued at room temperature for 3 days. Sodium sulfite (1.3g, 10.3 mmol) was added and the mixture was stirred for one hour before addition of dichloromethane (50 mL). The organic layer was collected and the aqueous layer was further extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with aqueous potassium hydroxide solution (2M, 50 mL), brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with dichloromethane/methanol (96:4), afforded the *title compound* **233** (0.46g,

87%) as a colourless powder; mp 102-104°C; Chiral HPLC analysis using a Chiralpak AD column, wavelength 290 nm, eluting with gradient solvent system, hexanes/*iso*propanol (75:25), increasing to hexanes/*iso*propanol (70:30) after 20 minutes, flow rate of 1.0 mL/min separated the racemic sample, t_1 = 35.9 minutes (50%); t_2 = 51.2 minutes (50%).

(+)-1,2-Bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethane-1,2-diol 234



Potassium ferricyanide (1.74g, 5.3 mmol), potassium carbonate (0.73g, 5.3 mmol), potassium osmate dihydrate (9mg, 24 μmol), $(DHQD)_2PHAL$ (0.39g, 0.5 mmol) and methanesulfonamide (0.17g, 1.8 mmol) were stirred together at ambient temperature for 30 minutes before addition of tetrahydrofuran (10 mL) and water (10 mL). The solution was cooled to 0°C and 1,2-bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethene (**228**) (1.00g, 1.8 mmol) was added. Stirring was continued at 0°C for 4 days. Sodium sulfite (2.64g, 21.0 mmol) was added and the reaction mixture was stirred for one hour before addition of dichloromethane (60 mL). The organic layer was collected and the aqueous layer was further extracted with dichloromethane (3 x 60 mL). The combined organic extracts were washed with aqueous potassium hydroxide solution (2M, 60 mL), brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with dichloromethane/methanol (96:4) gave the *title compound* **234** (0.89g, 84%) as a colourless crystalline solid; λ_{max} 290 nm (EtOH); mp 102-104°C; Chiral HPLC analysis using a Chiralpak AD column, wavelength 290 nm, eluting with gradient solvent system, hexanes/*iso*propanol (75:25), increasing to hexanes/*iso*propanol (70:30) after 20 minutes, flow rate of 1.0 mL/min separated the chiral sample, t_1 = 36.2 minutes (98.7%); t_2 = 51.4 minutes (1.3%): 97.4% ee (see *Appendix* **A1**, page 265); $[\alpha]_D^{20}$ +30.2° (*c* 1.01, $CHCl_3$); Found 618.1727 (MNH_4^+ $C_{32}H_{28}N_2O_6S_2$ requires 618.1727); ν_{max} (nujol)/cm^{-1} 1565, 1493, 1375, 1173, 1019, 812, 746; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 7.7 Hz, Ar*H*), 7.44 (4H,d, *J* 8.3 Hz, H-3''), 7.33 (2H, s, H-2'), 7.25 (2H, d, *J* 7.7 Hz, Ar*H*), 7.13 (2H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 7.01 (4H, d, *J* 8.3 Hz, H-2''), 6.92 (2H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 5.09 (2H, s, C*H*OH), 3.27 (2H, s, O*H*), 2.19 (6H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 145.5 (C), 135.4 (C), 135.2 (C),

130.4 (CH), 129.2 (C), 127.0 (CH), 125.3 (CH), 124.8 (CH), 123.7 (CH), 121.7 (C), 120.5 (CH), 114.0 (CH), 71.6 (CH), 22.0 (CH_3); *m/z* (CI) 618.3 (MNH_4^+, 0.4%), 146.1 (22), 132.1 (100), 118.1 (86), 108.1 (31).

Use of ^{1}H NMR to Determine the Enantiopurity of Compound 234

The enantiomeric excess of diol **234** was determined by ^{1}H NMR experiments using the europium *tris*[3-heptafluoropropylhydroxymethylene)-(+)-camphorate derivative, $Eu(hfc)_3$, as a chiral shift reagent. The racemic diol **233** was first used to establish which, if any, of the proton signals would split on addition of $Eu(hfc)_3$.

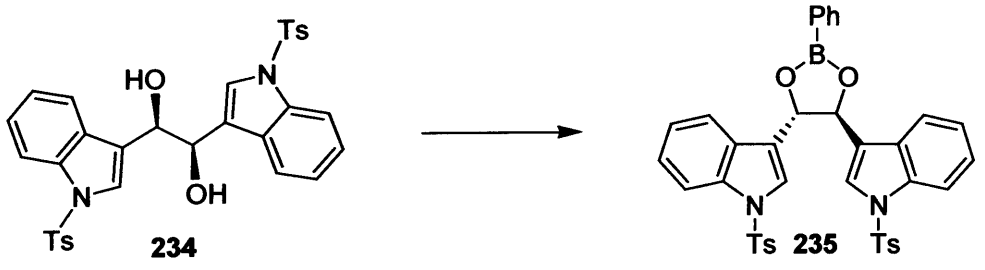
	Mass	Vol. $CDCl_3$
Racemic diol 233	7.5 mg	0.5 mL
$Eu(hfc)_3$	15 mg	0.5 mL

An equimolar solution of $Eu(hfc)_3$ and diol **233** were prepared using the quantities shown above. Successive addition of dropwise aliquots of $Eu(hfc)_3$ produced a chemical shift for the signal at 6.92 ppm, corresponding to the aromatic proton in the 5-position of the indole ring, which was split into two double doublets of equal intensity, confirming the presence of two enantiomers for the racemic modification (see *Appendix* **A2**, page 266).

	Mass	Vol. $CDCl_3$
Chiral diol 234	7.5 mg	0.5 mL
$Eu(hfc)_3$	15 mg	0.5 mL

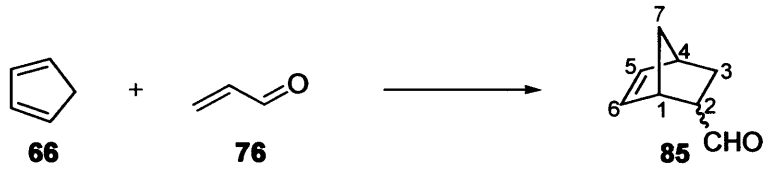
Using the quantities shown above, successive dropwise additions of $Eu(hfc)_3$ produced a chemical shift of 6.92 ppm to 7.63 ppm for the proton H-5 on the indole ring of **234**. The signal at 7.63 ppm failed to split, indicating an enantiomeric excess of at least 97% for diol **234** (see *Appendix* **A2**, pages 267-268).

2-Phenyl-4,5-bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-[1,3,2]-dioxaborolane 235



Phenyl boronic acid (6.3mg, 50.8 μmol) was added to (+)-1,2-bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethane-1,2-diol (**234**) (31mg, 50.8 μmol) in toluene (3 x 10 mL), with azeotropic removal of water to afford the *title compound* **235** (35mg, quant.) as a colourless powder; mp 127-129°C; Found 686.1714 (M^+ $C_{38}H_{31}BN_2O_6S_2$ requires 686.1711); ν_{max} (nujol/cm^{-1}) 1600, 1306, 1174, 810, 748, 703; δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* 8.1 Hz, Ar*H*), 7.88 (2H, d, *J* 6.8 Hz, Ar*H*), 7.70 (4H, d, *J* 8.4 Hz, H-3"), 7.51 (2H, s, H-2'), 7.36 (4H, m, Ar*H*), 7.27 (2H, dd, *J* 8.1, 7.6 Hz, Ar*H*), 7.17 (4H, d, *J* 8.4 Hz, H-2"), 7.09 (3H, m, Ar*H*), 5.66 (2H, s, C*H*OB), 2.27 (6H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 145.4 (C), 135.7 (C), 135.3 (CH), 134.9 (C), 132.2 (CH), 130.1 (CH), 128.1 (CH), 127.9 (C), 127.0 (CH), 125.3 (CH), 124.3 (CH), 123.6 (CH), 120.8 (C), 120.2 (CH), 114.0 (CH), 79.0 (CH), 21.6 (CH_3); other quaternary carbon not observed; *m/z* (EI) 686.2 (M^+, 2%), 531.4 (1), 427.2 (1), 385.2 (5), 128.0 (36), 91.1 (100), 44.2 (100).

Bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde 85[239]



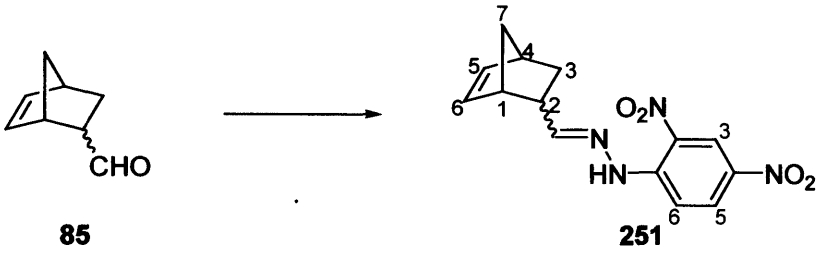
66 **76** **85**

The *title compound* **85** was prepared according to the general procedure for the Lewis-acid catalysed Diels-Alder cycloaddition reactions given in *Section* **5.2.a**. The reaction was carried out between cyclopentadiene (**66**) and acrolein (**76**) to afford the Diels-Alder adduct **85**. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (10:90), afforded the *title compound* **85** as a colourless liquid. Data consistent with the literature precedent.

***Endo*-Diastereoisomer 85**; ν_{max} (film/cm^{-1}) 1715 (CHO), 1598 (C=C); δ_H (400 MHz, $CDCl_3$) 9.44 (1H, d, *J* 2.9 Hz, C*H*O), 6.23 (1H, dd, *J* 5.7, 3.1 Hz, C=C*H*), 6.01 (1H, dd, *J* 5.7, 2.8 Hz, C=C*H*), 3.27 (1H, br, H-1), 3.00 (1H, br, H-4), 2.93 (1H, dddd, *J* 9.8, 2.9, 2.9, 2.9 Hz, H-2), 1.93 (1H, br, H-3), 1.51–1.43 (2H, m, H-3, CH*H*), 1.33 (1H, br, C*H*H); δ_C (100 MHz, $CDCl_3$) 205.2 (CHO), 138.1 (CH), 131.8 (CH), 52.2 (CH), 49.6 (CH_2), 45.0 (CH), 42.7 (CH), 27.6 (CH_2); *m/z* (EI) 122 (M^+, 7%), 91 (11), 77 (12), 66 (100), 65 (19).

***Exo*-Diastereoisomer 85**; ν_{max} (film/cm^{-1}) 1715 (CHO), 1598 (C=C); δ_H (400 MHz, $CDCl_3$) 9.81 (1H, d, *J* 2.1 Hz, C*H*O), 6.21 (1H, dd, *J* 5.6, 3.0 Hz, C=C*H*), 6.15 (1H, dd, *J* 5.6, 3.1 Hz, C=C*H*), 3.14 (1H, br, H-1), 3.00 (1H, br, H-4), 2.30 (1H, dddd, *J* 8.7, 4.1, 2.1, 2.1 Hz, H-2), 1.98 (1H, ddd, *J* 12.0, 4.1, 4.1 Hz, H-3), 1.51–1.38 (2H, m, H-3, CH*H*), 1.30 (1H, br, C*H*H); δ_C (100 MHz, $CDCl_3$) 204.2 (CHO), 138.6 (CH), 135.3 (CH), 51.8 (CH), 45.9 (CH_2), 44.3 (CH), 41.8 (CH), 27.1 (CH_2) ; *m/z* (EI) 122 (M^+, 7%), 91 (11), 77 (12), 66 (100), 65 (19).

N-Bicyclo[2.2.1]hept-5-en-2-ylmethylene-N'-(2,4-dinitrophenyl)hydrazine 251[201]



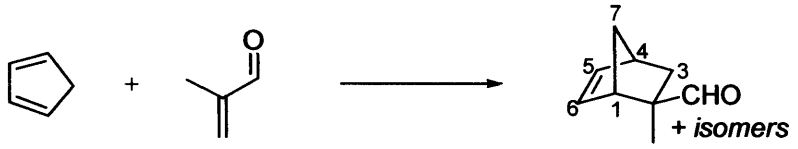
85 **251**

The *title compound* **251** was prepared according to the general procedure in *Section* **5.2.d** for the DNPH derivatisation of Diels-Alder adducts. Bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**85**) was reacted with 2,4-dinitrophenylhydrazine to provide compound **251**. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (10:90), afforded the *title compound* **251** as a yellow powder; Chiral HPLC analysis using a Chiralcel OD column, wavelength 359 nm, eluting with hexanes/*iso*propanol (99:1), flow rate of 1.0 mL/min, separated the chiral sample, retention times of 63.6 and 75.7 minutes (*endo*-diastereoisomers), 92.8 and 99.9 minutes (*exo*-diastereoisomers) (see *Appendix* **A3**, page 269). Data consistent with the literature precedent.

***Endo*-Diastereoisomer 251**; λ_{max} 359 nm (EtOH); mp 123-125°C [lit.[201] mp 125-127°C]; Found 302.1006 (M^+ $C_{14}H_{14}N_4O_4$ requires 302.1010); ν_{max} (nujol/cm^{-1}) 3286 (NH), 1707 (C=C), 1618 (C=N), 1522, 1336, 832; δ_H (400 MHz, $CDCl_3$) 10.90 (1H, s, N*H*), 9.04 (1H, d, *J* 2.5 Hz, H-3'), 8.22 (1H, dd, *J* 9.6, 2.5 Hz, H-5'), 7.83 (1H, d, *J* 9.6 Hz, H-6'), 7.09 (1H, d, *J* 6.6 Hz, N=C*H*), 6.22 (1H, dd, *J* 5.6, 3.1 Hz, C=C*H*), 5.96 (1H, dd, *J* 5.6, 2.3 Hz, C=C*H*), 3.04 (2H, br, H-2, H-1), 2.92 (1H, br, H-4), 2.03 (1H, br, H-3), 1.47 (1H, br, CH*H*), 1.32 (1H, br, C*H*H), 1.12 (1H, br, H-3); δ_C (100 MHz, $CDCl_3$) 157.0 (CH), 145.1 (C), 138.5 (CH), 132.1 (CH), 130.0 (CH), 128.7 (C), 123.6 (CH), 116.5 (CH), 49.7 (CH_2), 47.0 (CH), 42.7 (CH), 42.1 (CH), 30.9 (CH_2); other quaternary carbons not observed; *m/z* (APcI) 302.8 (MH^+, 100%), 236.8 (95).

***Exo*-Diastereoisomer 251**; λ_{max} 359 nm (EtOH); mp 123-125°C [lit.[201] mp 125-127°C]; Found 302.1006 (M^+ $C_{14}H_{14}N_4O_4$ requires 302.1010); ν_{max} (nujol/cm^{-1}) 3286 (NH), 1707 (C=C), 1618 (C=N), 1522, 1336, 832; δ_H (400 MHz, $CDCl_3$) 11.25 (1H, s, N*H*), 9.05 (1H, d, *J* 2.6 Hz, H-3'), 8.25 (1H, dd, *J* 9.9, 2.6 Hz, H-5'), 7.85 (1H, d, *J* 9.9 Hz, H-6'), 7.52 (1H, d, *J* 6.2 Hz, N=C*H*), 6.13 (1H, dd, *J* 5.5, 3.2 Hz, C=C*H*), 6.08 (1H, dd, *J* 5.5, 2.8 Hz, C=C*H*), 3.04 (1H, br, H-1), 2.92 (1H, br, H-4), 2.35 (1H, br, H-2), 1.76 (1H, ddd, *J* 11.9, 3.9, 3.9 Hz, H-3), 1.47 (1H, br, CH*H*), 1.39 (1H, br, H-3), 1.32 (1H, br, C*H*H); δ_C (100 MHz, $CDCl_3$) 156.2 (CH), 138.2 (CH), 137.6 (CH), 135.6 (CH), 123.5 (CH), 116.5 (CH), 46.8 (CH), 45.8 (CH_2), 42.7 (CH), 41.8 (CH), 30.5 (CH_2); other quaternary carbons not observed; *m/z* (APcI) 302.8 (MH^+, 100%), 236.8 (95).

2-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde 248[239]

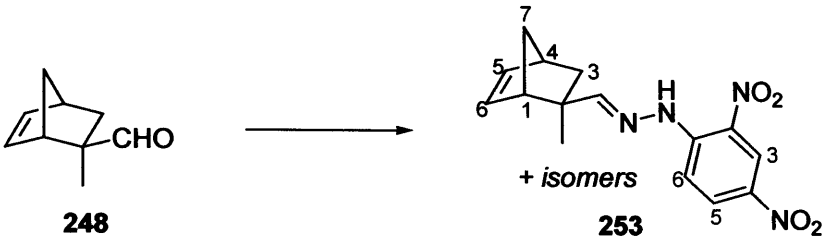


66 **252** **248**

The *title compound* **248** was prepared according to the general procedure for the Lewis-acid catalysed Diels-Alder cycloaddition reactions given in *Section* **5.2.a**. The reaction was carried out between cyclopentadiene (**66**) and methacrolein (**252**) to afford the Diels-Alder adduct **248**. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (10:90), afforded the *title compound* **248** as a colourless liquid; ^1H NMR δ_H (400 MHz, $CDCl_3$) 9.69 (1H, s, C*H*O (*exo*)), 9.40 (1H, s, C*H*O (*endo*)); data consistent with the literature precedent.

***Exo*-Diastereoisomer 248**; ν_{max} (film/cm^{-1}) 1718 (CHO), 1597 (C=C); δ_H (400 MHz, $CDCl_3$) 9.69 (1H, s, C*H*O), 6.30 (1H, dd, *J* 5.6, 3.0 Hz, C=C*H*), 6.11 (1H, dd, *J* 5.6, 3.1 Hz, C=C*H*), 2.89 (1H, br, H-1), 2.82 (1H, br, H-4), 2.25 (1H, dd, *J* 11.9, 3.8 Hz, H-3), 1.39 (2H, m, H-7), 1.02 (3H, s, CH_3), 0.76 (1H, br, H-3); *m/z* (EI) 136 (M^+, 3%), 91 (9), 79 (12), 66 (100), 65 (23).

N-(2,4-Dinitrophenyl)-N'-(2-methylbicyclo[2.2.1]hept-5-en-2-ylmethylene)hydrazine 253

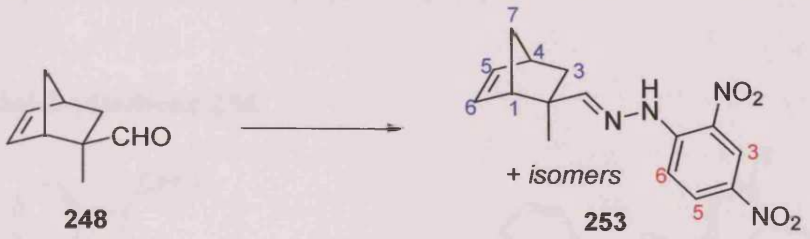


The *title compound* **253** was prepared according to the general procedure given in *Section* **5.2.d** for the DNPH derivatisation of Diels-Alder adducts. 2-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**248**) was reacted with 2,4-dinitrophenylhydrazine to provide compound **253**. Purification by flash chromatography on silica, eluting with ethyl acetate/light petroleum (10:90), afforded the *title compound* **253** as a yellow powder; Chiral HPLC analysis using a Chiralcel OJ column, wavelength 359 nm, eluting with hexanes/*iso*propanol (99.2:0.8), flow rate of 0.7 mL/min, separated the chiral sample, retention times of 78.1 and 84.1 minutes (*endo*-diastereoisomers), 104.5 and 113.2 minutes (*exo*-diastereoisomers) (see *Appendix* **A3**, page 270).

***Exo*-Diastereoisomer 253**; λ_{max} 359 nm (EtOH); mp 157-158°C; Found 316.1167 (M^+ $C_{15}H_{16}N_4O_4$ requires 316.1166); ν_{max} (nujol/cm^{-1}) 1654 (C=C), 1618 (C=N), 1509, 1331, 801; δ_H (400 MHz, $CDCl_3$) 10.96 (1H, s, N*H*), 9.07 (1H, d, *J* 2.6 Hz, H-3'), 8.24 (1H, dd, *J* 9.6, 2.6 Hz, H-5'), 7.87 (1H, d, *J* 9.6 Hz, H-6'), 7.58 (1H, s, N=C*H*), 6.23 (1H, dd, *J* 5.6, 3.0 Hz, C=C*H*), 6.08 (1H, dd, *J* 5.6, 3.1 Hz, C=C*H*), 2.87 (1H, br, H-4"), 2.69 (1H, br, H-1"), 2.26 (1H, dd, *J* 11.9, 3.9 Hz, H-3"), 1.50-1.40 (2H, m, H-7"), 1.06 (3H, s, CH_3), 0.90 (1H, dd, *J* 11.9, 2.7 Hz, H-3"); δ_C (100 MHz, $CDCl_3$) 160.2 (CH), 145.3 (C), 138.8 (CH), 133.6 (CH), 130.0 (CH), 123.6 (CH), 116.6 (CH),51.1 (CH), 48.0 (CH_2), 46.1 (C), 43.4 (CH), 37.4 (CH_2), 24.1 (CH_3); other quaternary carbons not observed; *m/z* (APcI) 317.2 (MH^+, 5%), 250.8 (15), 117.9 (27), 78.9 (100).

***Endo*-Diastereoisomer 253**; λ_{max} 359 nm (EtOH); mp 157-158°C; Found 316.1167 (M^+ $C_{15}H_{16}N_4O_4$ requires 316.1166); ν_{max} (nujol/cm^{-1}) 1654 (C=C), 1618 (C=N), 1509, 1331, 801; δ_H (400 MHz, $CDCl_3$) 10.85 (1H, s, N*H*), 9.05 (1H, d, *J* 2.6 Hz, H-3'), 8.22 (1H, dd, *J* 9.5, 2.6 Hz, H-5'), 7.82 (1H, d, *J* 9.5 Hz, H-6'), 7.29 (1H, s, N=C*H*), 6.16 (1H, dd, *J* 5.7, 3.2 Hz, C=C*H*), 6.03 (1H, dd, *J* 5.7, 2.8 Hz, C=C*H*), 2.87 (1H, br, H-4"), 2.62 (1H, br, H-1"), 2.26

_N_-(2,4-Dinitrophenyl)-_N'_-(2-methylbicyclo[2.2.1]hept-5-en-2-ylmethylene)hydrazine 253



248 **253**

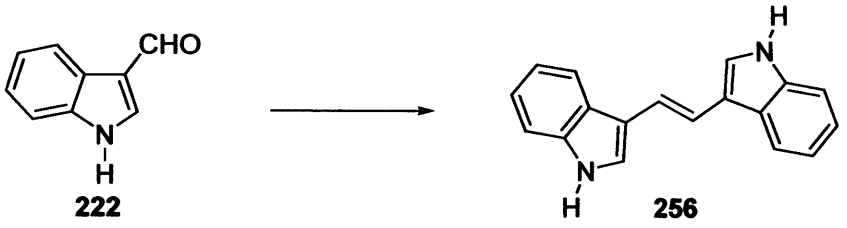
The *title compound* **253** was prepared according to the general procedure given in *Section* **5.2.d** for the DNPH derivatisation of Diels-Alder adducts. 2-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**248**) was reacted with 2,4-dinitrophenylhydrazine to provide compound **253**. Purification by flash chromatography on silica, eluting with ethyl acetate/light petroleum (10:90), afforded the *title compound* **253** as a yellow powder; Chiral HPLC analysis using a Chiralcel OJ column, wavelength 359 nm, eluting with hexanes/*iso*propanol (99.2:0.8), flow rate of 0.7 mL/min, separated the chiral sample, retention times of 78.1 and 84.1 minutes (*endo*-diastereoisomers), 104.5 and 113.2 minutes (*exo*-diastereoisomers) (see *Appendix* **A3**, page 270).

***Exo*-Diastereoisomer 253**; λ_{max} 359 nm (EtOH); mp 157-158°C; Found 316.1167 (M^+ $C_{15}H_{16}N_4O_4$ requires 316.1166); ν_{max} (nujol/cm^{-1}) 1654 (C=C), 1618 (C=N), 1509, 1331, 801; δ_H (400 MHz, $CDCl_3$) 10.96 (1H, s, N*H*), 9.07 (1H, d, *J* 2.6 Hz, H-3'), 8.24 (1H, dd, *J* 9.6, 2.6 Hz, H-5'), 7.87 (1H, d, *J* 9.6 Hz, H-6'), 7.58 (1H, s, N=C*H*), 6.23 (1H, dd, *J* 5.6, 3.0 Hz, C=C*H*), 6.08 (1H, dd, *J* 5.6, 3.1 Hz, C=C*H*), 2.87 (1H, br, H-4"), 2.69 (1H, br, H-1"), 2.26 (1H, dd, *J* 11.9, 3.9 Hz, H-3"), 1.50-1.40 (2H, m, H-7"), 1.06 (3H, s, CH_3), 0.90 (1H, dd, *J* 11.9, 2.7 Hz, H-3"); δ_C (100 MHz, $CDCl_3$) 160.2 (CH), 145.3 (C), 138.8 (CH), 133.6 (CH), 130.0 (CH), 123.6 (CH), 116.6 (CH),51.1 (CH), 48.0 (CH_2), 46.1 (C), 43.4 (CH), 37.4 (CH_2), 24.1 (CH_3); other quaternary carbons not observed; *m/z* (APcI) 317.2 (MH^+, 5%), 250.8 (15), 117.9 (27), 78.9 (100).

***Endo*-Diastereoisomer 253**; λ_{max} 359 nm (EtOH); mp 157-158°C; Found 316.1167 (M^+ $C_{15}H_{16}N_4O_4$ requires 316.1166); ν_{max} (nujol/cm^{-1}) 1654 (C=C), 1618 (C=N), 1509, 1331, 801; δ_H (400 MHz, $CDCl_3$) 10.85 (1H, s, N*H*), 9.05 (1H, d, *J* 2.6 Hz, H-3'), 8.22 (1H, dd, *J* 9.5, 2.6 Hz, H-5'), 7.82 (1H, d, *J* 9.5 Hz, H-6'), 7.29 (1H, s, N=C*H*), 6.16 (1H, dd, *J* 5.7, 3.2 Hz, C=C*H*), 6.03 (1H, dd, *J* 5.7, 2.8 Hz, C=C*H*), 2.87 (1H, br, H-4"), 2.62 (1H, br, H-1"), 2.26

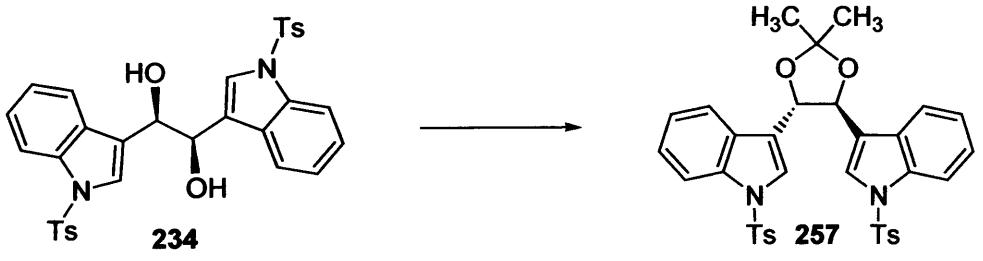
(1H, br, H-3"), 1.50-1.40 (2H, m, H-7"), 1.18 (3H, s, C*H*$_3$), 0.85 (1H, br, H-3"); *m/z* (APcI) 317.2 (MH^+, 5%), 250.8 (15), 117.9 (27), 78.9 (100).

1,2-Bis(1*H*-indol-3-yl)ethene 256



Titanium tetrachloride (4.3 mL, 39.0 mmol) was added slowly at –10°C to a stirred suspension of zinc powder (6.00g, 92.0 mmol) in dry tetrahydrofuran (50 mL). A solution of indole-3-carboxaldehyde (**222**) (2.04g, 14.0 mmol) in dry tetrahydrofuran (250 mL) was added dropwise at reflux temperature and stirring was continued for 5 hours under an inert atmosphere. The reaction mixture was cooled with stirring, and quenched by cautious addition of saturated sodium bicarbonate solution (200 mL). The solution was filtered through celite® and the filtrate was added to a separating funnel with diethyl ether (50 mL). The organic layer was collected and the aqueous layer was further extracted with diethyl ether (2 x 50 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with ethyl acetate/light petroleum (50:50), afforded the *title compound* **256** as a brown solid; δ_H (400 MHz, C_3D_6O) 9.77 (2H, s, N*H*), 7.37 (2H, d, *J* 7.8 Hz, Ar*H*), 7.22 (2H, d, *J* 7.8 Hz, Ar*H*), 6.95 (2H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 6.95 (4H, s, Ar*H*, C=C*H*), 6.87 (2H, dd, *J* 7.8, 7.8 Hz, Ar*H*); *m/z* 259.4 (MH^+, 100%), 178.2 (9), 144.1 (13), 130.1 (21).

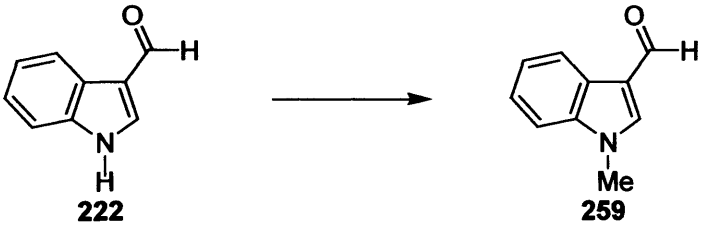
2,2-Dimethyl-4,5-di[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-[1,3]-dioxolane 257



Pyridinium *para*-toluenesulfonate (11mg, 0.04 mmol) was added to a stirred solution of (+)-1,2-bis[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethane-1,2-diol (**234**) (0.25g, 0.42 mmol)

and 2,2-dimethoxypropane (0.5 mL, 4.2 mmol) in dichloromethane (2 mL) at ambient temperature. Stirring was continued for 24 hours before addition of saturated sodium bicarbonate solution (5 mL). The organic layer was collected and the aqueous fraction was further extracted with diethyl ether (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and reduced to give the *title compound* **257** (0.21g, 80%) as a colourless powder; mp 168-170°C; $[\alpha]_D^{20}$ +0.5° (*c* 0.44, $CHCl_3$); Found 658.2038 (MNH_4^+ $C_{35}H_{32}N_2O_6S_2$ requires 658.2040); ν_{max} (nujol/cm^{-1}) 1596 (C=C), 1493 (C=C), 1373, 1175, 1125, 813, 748; δ_H (400 MHz, $CDCl_3$) 7.88 (2H, d, *J* 7.9 Hz, Ar*H*), 7.60 (4H, d, *J* 8.2 Hz, H-3"), 7.40 (2H, s, H-2'), 7.19 (4H, m, Ar*H*), 7.10 (4H, d, *J* 8.2 Hz, H-2"), 6.95 (2H, dd, *J* 7.9, 7.9 Hz, Ar*H*), 5.16 (2H, s, C*H*OC), 2.23 (6H, s, ArCH_3), 1.63 (6H, s, C(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 145.6 (C), 135.8 (C), 135.2 (C), 130.4 (CH), 128.9 (C), 127.2 (CH), 125.4 (CH), 125.0 (CH), 123.7 (CH), 120.7 (CH), 118.5 (C), 114.2 (CH), 110.1 (C), 77.9 (CH), 27.6 (CH_3), 22.0 (CH_3); *m/z* (EI) 658 (MNH_4^+, 22%), 583 (7), 312 (100), 100 (20).

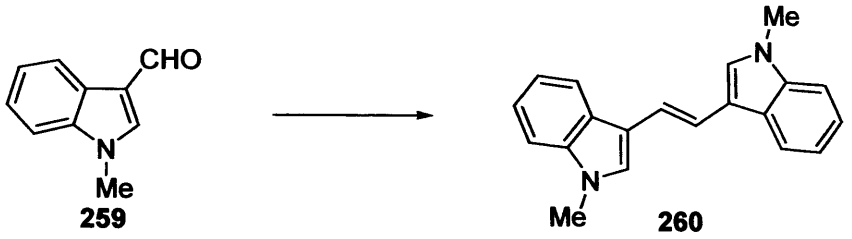
1-Methyl-1*H*-indole-3-carboxaldehyde 259[208]



222 **259**

Sodium hydroxide solution (30%, 105 mL), tetrabutylammonium bromide (1.11g, 3.4 mmol), and methyl iodide (2.25 mL, 36.2 mmol) were added to a vigorously stirred solution of indole-3-carboxaldehyde (**222**) (5.00g, 34.4 mmol) in benzene (105 mL). Stirring was continued at room temperature for 48 hours, the organic layer was collected, and the aqueous layer was further extracted with benzene (2 x 40 mL). The combined organic extracts were washed with potassium hydroxide solution (10%, 40 mL), brine, dried ($MgSO_4$) and concentrated to give the *title compound* **259** (4.53g, 83%) as a colourless solid; mp 64-65°C [lit.[208] mp 68-70°C]; Found 160.0763 (MH^+ $C_{10}H_9NO$ requires 160.0757); ν_{max} (nujol)/cm^{-1} 2748, 1640 (CHO), 1619, 1467, 748; δ_H (400 MHz, $CDCl_3$) 9.34 (1H, s, C*H*O), 8.20 (1H, d, *J* 7.9 Hz, Ar*H*), 7.52 (1H, s, H-2), 7.21 (3H, m, Ar*H*), 3.71 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 184.9 (CH), 140.0 (CH), 138.3 (C), 125.5 (CH), 124.4 (CH), 123.3 (CH), 122.3 (CH), 118.3 (CH), 110.4 (CH), 34.1 (CH_3); *m/z* (APcI) 160.0 (MH^+, 100%), 131.9 (2), 104.8 (1); data consistent with the literature precedent.

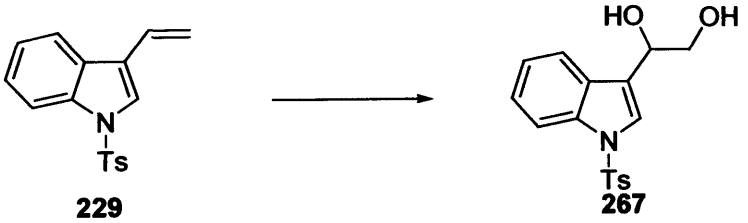
1,2-Bis(1-methyl-1*H*-indol-3-yl)ethene 260



259 **260**

Titanium tetrachloride (9.65 mL, 87.5 mmol) was added slowly at –10°C to a stirred suspension of zinc powder (13.49g, 206.4 mmol) in dry tetrahydrofuran (100 mL). A solution of 1-methyl-1*H*-indole-3-carboxaldehyde (**259**) (5.04g, 31.4 mmol) in dry tetrahydrofuran (400 mL) was added dropwise at reflux temperature and stirring was continued for 5 hours under an inert atmosphere. The reaction mixture was cooled with stirring, and quenched by cautious addition of saturated sodium bicarbonate solution (250 mL). The solution was filtered through celite® and the filtrate was added to a separating funnel with diethyl ether (50 mL). The organic layer was collected and the aqueous layer was further extracted with diethyl ether (2 x 50 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with dichloromethane/light petroleum (40:60), afforded the *title compound* **260** (1.46g, 33%) as a yellow powder; mp 205–207°C [lit.[240] mp 203-204°C]; Found 287.1548 (MH^+ $C_{20}H_{18}N_2$ requires 287.1543); ν_{max} (nujol)/cm^{-1} 1611, 1545, 953, 740; δ_H (400 MHz, $CDCl_3$) 7.93 (2H, d, *J* 7.6 Hz, Ar*H*), 7.25 (2H, d, *J* 7.6 Hz, Ar*H*), 7.20 (2H, dd, *J* 7.6, 7.6 Hz, Ar*H*), 7.20 (2H, s, H-2'), 7.13 (2H, dd, *J* 7.6, 7.6 Hz, Ar*H*), 7.13 (2H, s, C=C*H*), 3.72 (6H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 138.0 (C), 127.2 (CH), 126.6 (C), 122.4 (CH), 120.6 (CH), 120.0 (CH), 118.5 (CH), 115.4 (C), 109.8 (CH), 33.3 (CH_3); *m/z* (APcI) 287.4 (MH^+, 100%), 144.0 (31), 58.9 (65); data consistent with the literature precedent.

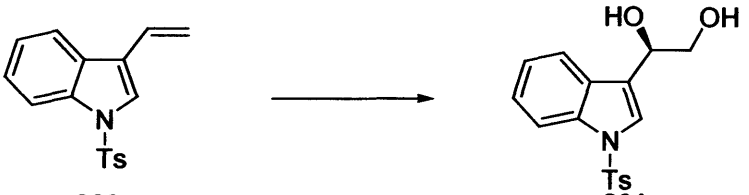
(±)-1-[1-(Toluene-4-sulfonyl)-1*H*-indol-3-yl]ethane-1,2-diol 267



229 **267**

Potassium ferricyanide (0.83g, 2.5 mmol), potassium carbonate (0.35g, 2.5 mmol), potassium osmate dihydrate (5mg, 11 μmol), quinuclidine (26mg, 0.25 mmol) and methanesulfonamide (81mg, 0.84 mmol) were stirred together at ambient temperature for 30 minutes before addition of tetrahydrofuran (5 mL) and water (5 mL). 1-(Toluene-4-sulfonyl)-3-vinyl-1*H*-indole (**229**) (0.25g, 0.8 mmol) was added and stirring was continued at room temperature for 48 hours. Sodium sulfite (1.3g, 10.3 mmol) was added and the mixture was stirred for one hour before addition of dichloromethane (20 mL). The organic layer was collected and the aqueous layer was further extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with aqueous potassium hydroxide solution (2M, 20 mL), brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether, afforded the *title compound* **267** (0.20g, 71%) as a colourless solid; mp 144-145°C; Chiral HPLC analysis using a Chiralcel OD column, wavelength 251 nm, eluting with hexanes/*iso*propanol (85:15), flow rate of 0.6 mL/min, separated the racemic sample, t_1 = 36.6 minutes (50%); t_2 = 42.0 minutes (50%).

(–)-1-[1-(Toluene-4-sulfonyl)-1*H*-indol-3-yl]ethane-1,2-diol 261

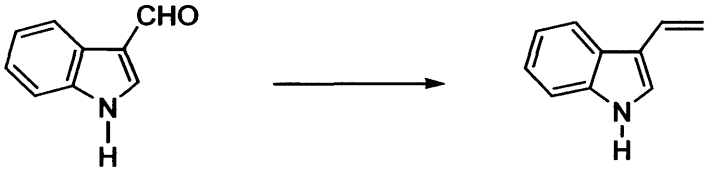


229 **261**

Potassium ferricyanide (3.32g, 10.1 mmol), potassium carbonate (1.39g, 10.1 mmol), potassium osmate dihydrate (17mg, 45 μmol), $(DHQD)_2PHAL$ (0.73g, 0.94 mmol) and methanesulfonamide (0.32g, 3.4 mmol) were stirred together at ambient temperature for 30 minutes before addition of tetrahydrofuran (20 mL) and water (20 mL). The solution was cooled to 0°C and 1-(toluene-4-sulfonyl)-3-vinyl-1*H*-indole (**229**) (1.00g, 3.4 mmol) was added. Stirring was continued at 0°C for 4 days. Sodium sulfite (5.1g, 40.6 mmol) was added and the reaction mixture was stirred for one hour before addition of dichloromethane (50 mL). The organic layer was collected and the aqueous layer was further extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with aqueous potassium hydroxide solution (2M, 50 mL), brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (10:90), followed by crystallisation from ethanol/water (80:20), gave the *title compound* **261**

(0.94g, 85%) as a colourless crystalline solid; λ_{max} 251 nm (EtOH); mp 144-145°C; Chiral HPLC analysis using a Chiralcel OD column, wavelength 251 nm, eluting with hexanes/*iso*propanol (85:15), flow rate of 0.6 mL/min, separated the chiral sample, t_1 = 36.0 minutes (90.6%); t_2 = 42.9 minutes (9.4%): 81.2% ee (see *Appendix* **A4**, page 271); $[\alpha]_D^{20}$ –41.5° (*c* 1.05, $CHCl_3$); Found 331.0874 (MH^+ $C_{17}H_{17}NO_4S$ requires 331.0873); ν_{max} (nujol)/cm^{-1} 3333 (OH), 1595, 1492, 1376, 1172, 1074, 817, 753; δ_H (400 MHz, $CDCl_3$) 7.92 (1H, d, *J* 8.1 Hz, Ar*H*), 7.71 (2H, d, *J* 8.4 Hz, H-3"), 7.53 (2H, m, Ar*H*), 7.26 (1H, dd, *J* 8.1, 8.1 Hz, Ar*H*), 7.16 (3H, m, Ar*H*), 5.00 (1H, ddd, *J* 7.5, 3.8, 3.8 Hz, C*H*CH_2), 3.84 (1H, ddd, *J* 11.3, 7.1, 3.8 Hz, CH*H*OH), 3.76 (1H, ddd, *J* 11.3, 7.5, 4.8 Hz, C*H*HOH), 2.49 (1H, d, *J* 3.8 Hz, CHO*H*), 2.27 (3H, s, ArCH_3) 1.99 (1H, dd, *J* 7.1, 4.8 Hz, CH_2O*H*); δ_C (100 MHz, $CDCl_3$) 145.5 (C), 135.7 (C), 135.5 (C), 130.4 (CH), 129.1 (C), 127.3 (CH), 125.4 (CH), 123.9 (CH), 123.7 (CH), 122.3 (C), 120.4 (CH), 114.2 (CH), 69.0 (CH), 66.9 (CH_2), 22.0 (CH_3); *m/z* (EI) 331 (M^+, 3%), 284 (37), 155 (35), 130 (52), 91 (100).

3-Vinyl-1*H*-indole 268

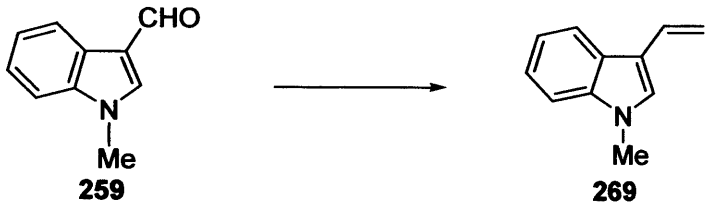


222 **268**

Methyltriphenylphosphonium bromide (17.25g, 48.2 mmol) was stirred in tetrahydrofuran (250 mL) under an inert atmosphere and the solution was cooled to 0°C. *n*-Butyllithium (2.5M, 23.2 mL, 57.9 mmol) was added dropwise and stirring was continued for 20 minutes before the addition of this solution *via* a canula to a solution of indole-3-carboxaldeyde (**222**) (5.00g, 34.4 mmol) in tetrahydrofuran (150 mL) at 0°C. The reaction mixture was warmed to ambient temperature and stirring was continued for 48 hours before the addition of water (100 mL). The organic layer was collected and the aqueous fraction was further extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with ethyl acetate/light petroleum (20:80), afforded the *title compound* **268** (1.58g, 32%) as a yellow solid; mp 130–132°C; Found 144.0807 (MH^+ $C_{10}H_9N$ requires 144.0808); ν_{max} (nujol)/cm^{-1} 3402 (NH), 1614, 1544, 1011, 926, 739; δ_H (400 MHz, $CDCl_3$) 7.80 (2H, m, Ar*H*, N*H*), 7.19 (1H, d, *J* 8.0 Hz, Ar*H*), 7.11 (2H, m, H-5, H-6), 7.04 (1H, s, H-2), 6.80 (1H,

dd, *J* 17.8, 11.3 Hz, C*H*=CH_2), 5.62 (1H, dd, *J* 17.8, 1.3 Hz, CH=CH*H*), 5.09 (1H, dd, *J* 11.3, 1.3 Hz, CH=C*H*H); δ_C (100 MHz, $CDCl_3$) 165.1 (C), 137.2 (C), 129.9 (CH), 126.0 (C), 124.0 (CH), 122.9 (CH), 120.8 (CH), 120.5 (CH), 111.8 (CH), 111.1 (CH_2); *m/z* (APcI) 143.8 (MH^+, 51%), 107.1 (100).

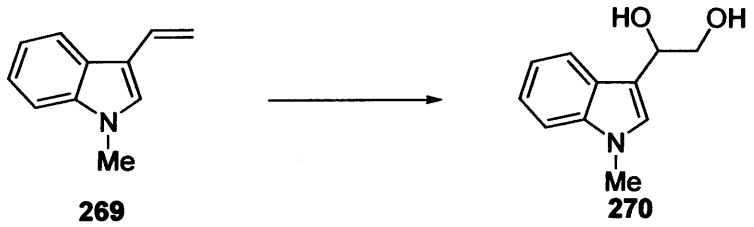
1-Methyl-3-vinyl-1*H*-indole 269



259 **269**

Methyltriphenylphosphonium bromide (12.56g, 35.2 mmol) was stirred in dry tetrahydrofuran (170 mL) under an inert atmosphere. The solution was cooled to 0°C and *n*-butyllithium (2.5M, 16.9 mL, 42.2 mmol) was added dropwise. Stirring was continued for 20 minutes at 0°C before the addition of this solution *via* a canula to a solution of *N*-methylindole-3-carboxaldehyde (**259**) (4.00g, 25.1 mmol) in tetrahydrofuran (130 mL) at 0°C. After warming to room temperature stirring was continued for 24 hours and water (100 mL) was added. The organic fraction was collected and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (20:80), afforded the *title compound* **269** (2.81g, 71%) as a yellow liquid; Found 158.0961 (MH^+ $C_{11}H_{11}N$ requires 158.0964); ν_{max} (nujol)/cm^{-1} 1659 (C=C), 1610, 1539, 1012, 906, 733; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, d, *J* 7.9 Hz, Ar*H*), 7.16–7.01 (3H, m, Ar*H*), 6.92 (1H, s, H-2), 6.76 (1H, dd, *J* 17.8, 11.2 Hz, C*H*=CH_2), 5.57 (1H, dd, *J* 17.8, 1.1 Hz, CH=C*H*H), 5.03 (1H, dd, *J* 11.2, 1.1 Hz, CH=CH*H*), 3.54 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 138.5 (C), 130.7 (CH), 129.5 (CH), 127.1 (C), 123.0 (CH), 121.1 (CH), 121.0 (CH), 114.9 (C), 110.6 (CH), 110.5 (CH_2), 33.1 (CH_3); *m/z* (APcI) 158 (MH^+, 100%), 144 (27), 132 (22).

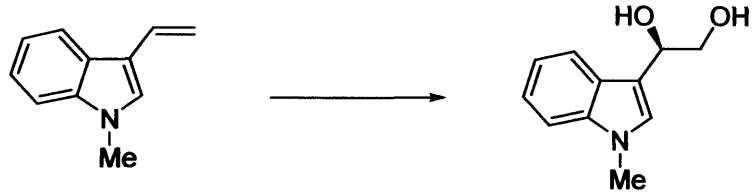
(±)-1-(1-Methyl-1*H*-indol-3-yl)ethane-1,2-diol 270



269 **270**

Potassium ferricyanide (3.15g, 1.0 mmol), potassium carbonate (1.32g, 1.0 mmol), potassium osmate dihydrate (16mg, 43 μmol), quinuclidine (92mg, 0.9 mmol) and methanesulfonamide (0.31g, 3.2 mmol) were stirred together at ambient temperature for 30 minutes before addition of tetrahydrofuran (10 mL) and water (10 mL). 1-Methyl-3-vinyl-1*H*-indole (**269**) (0.50g, 3.2 mmol) was added and stirring was continued at room temperature for 5 days. Sodium sulfite (4.95g, 39.2 mmol) was added and the mixture was stirred for one hour before addition of dichloromethane (40 mL). The organic layer was collected and the aqueous layer was further extracted with dichloromethane (2 x 40 mL). The combined organic extracts were washed with aqueous potassium hydroxide solution (2M, 40 mL), brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with dichloromethane/ methanol (94:6), afforded the *title compound* **270** (0.68g, quant.) as a pale yellow solid; mp 87-89°C; Chiral HPLC analysis using a Chiralcel OD column, wavelength 285 nm, eluting with hexanes/*iso*propanol (80:20), flow rate of 0.6 mL/min, separated the racemic sample, t_1 = 38.0 minutes (49%); t_2 = 42.9 minutes (51%).

(–)-1-(1-Methyl-1*H*-indol-3-yl)ethane-1,2-diol 263



269 **263**

Potassium ferricyanide (9.42g, 28.6 mmol), potassium carbonate (3.96g, 28.6 mmol), potassium osmate dihydrate (48mg, 0.13 mmol), $(DHQD)_2PHAL$ (2.07g, 2.7 mmol) and methanesulfonamide (0.90g, 9.5 mmol) were stirred together at ambient temperature for 30 minutes before addition of tetrahydrofuran (30 mL) and water (30 mL). The solution was cooled to 0°C and 1-methyl-3-vinyl-1*H*-indole (**269**) (1.50g, 9.5 mmol) was added. Stirring was continued at 0°C for 4 days. Sodium sulfite (14.66g, 116.4 mmol) was added and the reaction mixture was stirred for one hour before addition of dichloromethane (60 mL). The organic layer was collected and the aqueous layer was further extracted with dichloromethane (2 x 60 mL). The combined organic extracts were washed with aqueous potassium hydroxide solution (2M, 60 mL), brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with ethyl acetate/light petroleum (30:70), afforded the *title compound* **263** (1.12g, 62%) as a colourless solid; λ_{max} 285 nm (EtOH); mp 87-89°C; Chiral

HPLC analysis using a Chiralcel OD column, wavelength 285 nm, eluting with hexanes/*iso*propanol (80:20), flow rate of 0.6 mL/min, separated the chiral sample, t_1 = 60.8 minutes (77.8%); t_2 = 70.7 minutes (22.3%): 55.4% ee (see *Appendix* **A5**, page 272); $[\alpha]_D^{20}$ – 3.0° (*c* 1.00, $CHCl_3$); ν_{max} (nujol)/cm^{-1} 3382 (OH), 1607, 1548, 1078, 739; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 7.8 Hz, Ar*H*), 7.23 (1H, d, *J* 7.8 Hz, Ar*H*), 7.17 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 7.05 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 6.98 (1H, s, H-2'), 5.04 (1H, dd, *J* 7.0, 4.5 Hz, C*H*OH), 3.80 (2H, m, CH_2OH), 3.65 (3H, s, NCH_3), 2.71 (1H, br, CHO*H*), 2.60 (1H, br, CHO*H*); δ_C (100 MHz, $CDCl_3$) 139.4 (C), 129.1 (CH), 128.5 (C), 124.3 (CH), 121.8 (CH), 121.7 (CH), 116.4 (C), 111.9 (CH), 71.2 (CH), 69.4 (CH_2), 35.1 (CH_3); *m/z* (EI) 173 (M^+-H_2O, 24%), 144 (100).

3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde 68

66 **67** **68**

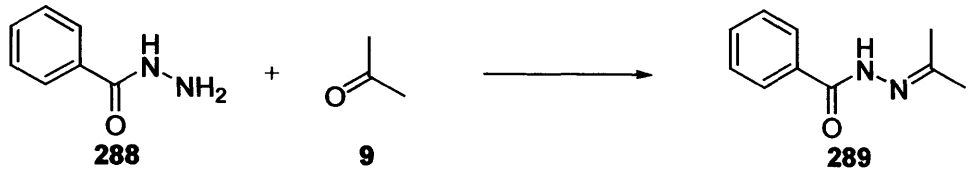
The *title compound* **68** was prepared according to the general procedure for the Lewis-acid catalysed Diels-Alder cycloaddition reactions given in *Section* **5.2.a**. The reaction was carried out between cyclopentadiene (**66**) and *E*-cinnamaldehyde (**67**) to afford the Diels-Alder adduct **68**. Purification by flash chromatography on silica, eluting with ethyl acetate/hexanes (10:90), afforded the *title compound* as a pale yellow liquid. Data consistent with the literature precedent.

***Exo*-Diastereoisomer 68**; ν_{max} (film/cm^{-1}) 2717 (CHO), 1718, 1601, 1497, 748, 700; δ_H (400 MHz, $CDCl_3$) 9.92 (1H, d, *J* 1.9 Hz, C*H*O), 7.24 (5H, m, Ar*H*), 6.34 (1H, dd, *J* 5.4, 3.4 Hz, C=C*H*), 6.07 (1H, dd, 5.4, 2.8 Hz, C=C*H*), 3.72 (1H, dd, *J* 3.8, 3.8 Hz, H-3), 3.22 (2H, m, H-1, H-4), 2.60 (1H, ddd, *J* 3.8, 1.9, 1.9 Hz, H-2), 1.63 (2H, m, CH*H*, C*H*H); δ_C (100 MHz, $CDCl_3$) 202.9 (CHO), 136.6 (CH), 136.3 (CH), 128.6 (CH), 128.2 (CH), 127.9 (C), 126.4 (CH), 59.5 (CH), 48.5 (CH), 47.6 (CH_2), 45.5 (CH), 45.4 (CH); *m/z* (EI) 198 (M^+, 0.1%), 132 (89), 131 (100), 103 (52), 77 (21), 66 (54).

***Endo*-Diastereoisomer 68**; ν_{max} (film/cm^{-1}) 2717 (CHO), 1718, 1601, 1497, 748, 700; δ_H (400 MHz, $CDCl_3$) 9.64 (1H, d, *J* 1.9 Hz, C*H*O), 7.36–7.19 (5H, m, Ar*H*), 6.46 (1H, dd, *J* 5.6,

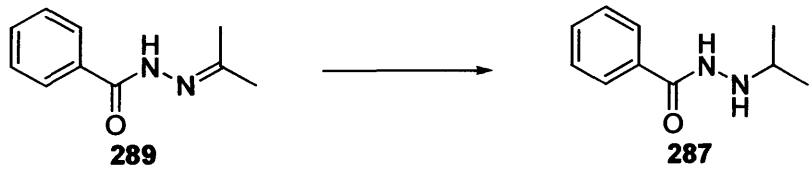
3.2 Hz, C=C*H*), 6.22 (1H, dd, 5.6, 2.8 Hz, C=C*H*), 3.38 (1H, br, H-3), 3.15 (2H, m, H-1, H-4), 3.02 (1H, ddd, *J* 3.9, 1.9, 1.9 Hz, H-2), 1.85–1.66 (2H, m, CH*H*, C*H*H); δ_C (100 MHz, $CDCl_3$) 203.7 (CHO), 139.3 (CH), 133.8 (CH), 128.6 (CH), 128.1 (CH), 127.8 (C), 126.2 (CH), 60.8 (CH), 48.4 (CH), 47.2 (CH_2), 45.6 (CH), 45.2 (CH); *m/z* (EI) 198 (M^+, 0.1%), 132 (89), 131 (100), 103 (52), 77 (21), 66 (54).

Benzoic acid *iso*propylidene hydrazide 289



Benzoic hydrazide (**288**) (5.00g, 36.7 mmol) was stirred in an excess of acetone (**9**) (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 dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to afford the *title compound* **289** (5.57g, 86%) as a colourless solid; mp 141–143°C [lit.[241] mp 142-143°C]; Found 176.0950 (M^+ $C_{10}H_{12}N_2O$ requires 176.0944); ν_{max} (nujol)/cm^{-1} 3221 (NH), 1655 (C=O), 1578 (C=N), 1578, 1531, 1490, 718, 668; δ_H (400 MHz, $CDCl_3$) 8.70 (1H, s, N*H*), 7.79 (2H, d, *J* 7.1 Hz, Ar*H*), 7.52 (1H, t, *J* 7.1 Hz, Ar*H*), 7.44 (2H, dd, *J* 7.1, 7.1 Hz, Ar*H*), 2.15 (3H, s, CH_3), 1.97 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 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) 176 (M^+, 8%), 161 (50), 105 (100), 77 (31); data consistent with the literature precedent.

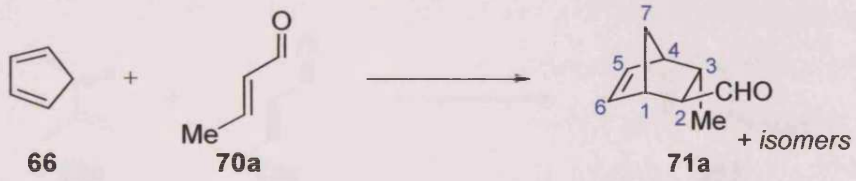
Benzoic acid *N'-iso*propylhydrazide 287



Platinum oxide (68mg, 0.3 mmol) was placed in a nitrogen flushed flask and ethanol (12 mL) and acetic acid (6 mL) were added. Benzoic acid *iso*propylidene hydrazide (**289**) (2.50g, 14.2 mmol) was added, the flask was charged with hydrogen and stirring was continued for 48 hours at ambient temperature. The reaction mixture was filtered over celite® and the filtrate was neutralised with saturated sodium bicarbonate solution. The organic layer was collected

and the aqueous fraction was further extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **287** (2.18g, 86%) as a colourless powder; mp 110–112°C [lit.[242] mp 115-117°C]; Found 178.1105 (M^+ $C_{10}H_{14}N_2O$ requires 178.1101); ν_{max} (nujol)/cm^{-1} 3289 (NH), 1640 (C=O), 1537, 725, 693; δ_H (400 MHz, $CDCl_3$) 7.70 (1H, s, N*H*), 7.69 (2H, d, *J* 7.7 Hz, Ar*H*), 7.46 (1H, t, *J* 7.7 Hz, Ar*H*), 7.38 (2H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 4.81 (1H, s, N*H*), 3.18 (1H, sept., *J* 6.2 Hz, C*H*(Me)$_3$), 1.05 (6H, d, *J* 6.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 167.5 (C=O), 132.9 (C), 131.9 (CH), 128.7 (CH), 126.9 (CH), 51.4 (CH), 20.9 (CH_3); *m/z* (EI) 178 (M^+, 3%), 163 (9), 122 (13), 105 (100), 77 (34), 58 (20); data consistent with the literature precedent.

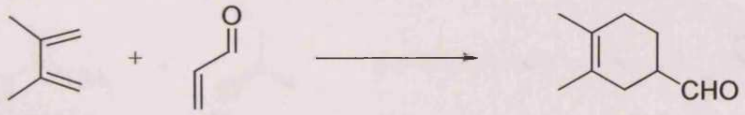
3-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde 71a[239]



66 **70a** **71a**

The *title compound* **71a** was prepared according to the general procedure for the Lewis-acid catalysed Diels-Alder cycloaddition reactions given in *Section* **5.2.a**. The reaction was carried out between cyclopentadiene (**66**) and *E*-crotonaldehyde (**70a**) to afford the Diels-Alder adduct **71a**. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 9.78 (1H, d, *J* 2.7 Hz, C*H*O (*exo*)), 9.37 (1H, d, *J* 3.3 Hz, C*H*O (*endo*)); ^{1}H NMR consistent with the literature precedent.

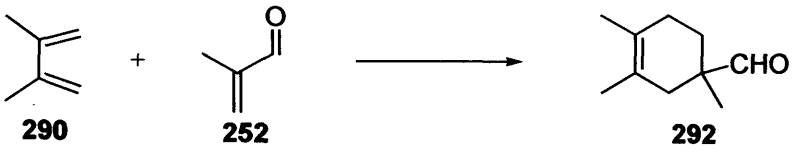
3,4-Dimethylcyclohex-3-enecarboxaldehyde 291[239]



290 **76** **291**

The *title compound* **291** was prepared according to the general procedure for the Lewis-acid catalysed Diels-Alder cycloaddition reactions given in *Section* **5.2.a**. The reaction was carried out between 2,3-dimethylbuta-1,3-diene (**290**) and acrolein (**76**) to afford the Diels-Alder adduct **291**. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 9.70 (1H, d, *J* 1.5 Hz, C*H*O); ^{1}H NMR consistent with the literature precedent.

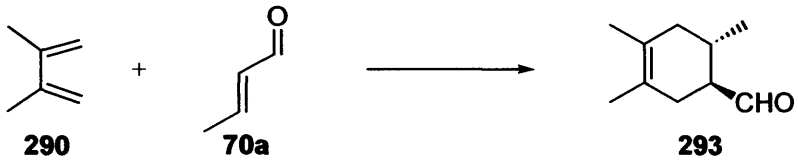
1,3,4-Trimethylcyclohex-3-enecarboxaldehyde 292[239]



290 **252** **292**

The *title compound* **292** was prepared according to the general procedure for the Lewis-acid catalysed Diels-Alder cycloaddition reactions given in *Section* **5.2.a**. The reaction was carried out between 2,3-dimethylbuta-1,3-diene (**290**) and methacrolein (**252**) to afford the Diels-Alder adduct **292**. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 9.38 (1H, s, C*H*O); ^{1}H NMR consistent with the literature precedent.

3,4,6-Trimethylcyclohex-3-enecarboxaldehyde 293[239]



290 **70a** **293**

The *title compound* **293** was prepared according to the general procedure for the Lewis-acid catalysed Diels-Alder cycloaddition reactions given in *Section* **5.2.a**. The reaction was carried out between 2,3-dimethylbuta-1,3-diene (**290**) and *E*-crotonaldehyde (**70a**) to afford the Diels-Alder adduct **293**. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 9.69 (1H, d, *J* 1.8 Hz, C*H*O); ^{1}H NMR consistent with the literature precedent.

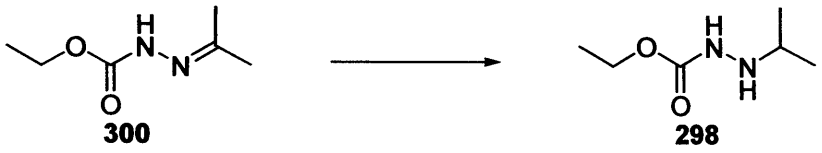
***N'-Iso*propylidene-hydrazinecarboxylic acid ethyl ester 300**

284 **9** **300**

Ethyl carbazate (**284**) (2.20g, 21.1 mmol) was stirred in an excess of acetone (**9**) (10 mL), containing acetic acid (30 μL, 0.5 mmol), for 24 hours at ambient temperature. Water (20 mL) was added and the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to afford the *title compound* **300** (2.75g, 90%) as a colourless solid; mp 72-73°C [lit.[243] mp

75-76°C]; Found 144.0898 (M^+ $C_6H_{12}N_2O_2$ requires 144.0893); ν_{max} (nujol)/cm^{-1} 3236 (NH), 1730 (C=O), 1649 (C=N), 1530, 1239; δ_H (400 MHz, $CDCl_3$) 7.94 (1H, s, N*H*), 4.06 (2H, q, *J* 6.4 Hz, OCH_2), 1.83 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.11 (3H, t, *J* 6.4 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 154.4 (C), 151.0 (C), 61.6 (CH_2), 25.4 (CH_3), 16.3 (CH_3), 14.5 (CH_3); *m/z* (EI) 144 (M^+, 19%), 98 (93), 44 (100), 41 (69); data consistent with the literature precedent.

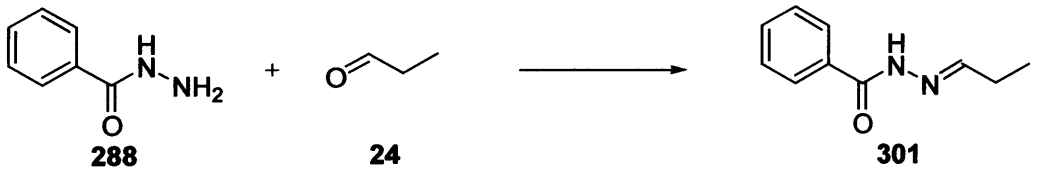
N'-*Iso*propyl-hydrazinecarboxylic acid ethyl ester 298



300 **298**

Platinum oxide (17mg, 73 μmol) was placed in nitrogen flushed flask and ethanol (3.4 mL) and acetic acid (1.7 mL) were added. *N'-Iso*propylidene-hydrazinecarboxylic acid ethyl ester (**300**) (0.50g, 3.5 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. The organic layer was collected and the aqueous fraction was further extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **298** (0.43g, 85%) as a colourless viscous liquid; Found 146.1053 (M^+ $C_6H_{14}N_2O_2$ requires 146.1050); ν_{max} (film)/cm^{-1} 3314 (NH), 1701 (C=O), 1529, 1266; δ_H (400 MHz, $CDCl_3$) 6.59 (1H, s, N*H*), 4.13 (2H, q, *J* 6.9 Hz, OCH_2), 3.15 (1H, sept, *J* 6.6 Hz, C*H*$(Me)_2$), 1.24 (3H, t, *J* 6.9 Hz, OCH_2CH_3), 1.01 (6H, d, *J* 6.6 Hz, $CH(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 158.0 (C=O), 61.7 (CH_2), 51.2 (CH), 20.9 (CH_3), 15.0 (CH_3); *m/z* (EI) 146 (M^+, 21%), 131 (100), 103 (64), 85 (91), 43 (74).

Benzoic acid propylidene-hydrazide 301

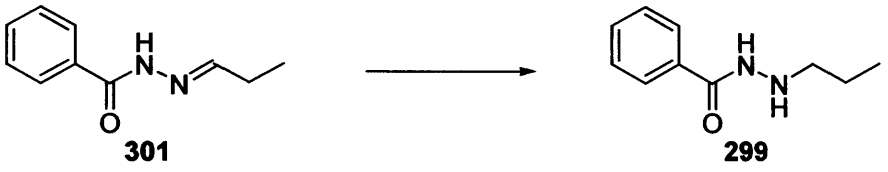


288 **24** **301**

Benzoic hydrazide (**288**) (6.00g, 44.1 mmol) was stirred in an excess of propionaldehyde (**24**) (25 mL, 0.4 mmol), containing acetic acid (48 μL, 0.8 mmol), for 24 hours at ambient temperature. Water (30 mL) was added and the reaction mixture was extracted with

dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to afford the *title compound* **301** (6.15g, 79%) as colourless needles; mp 95–97°C; Found 176.0947 (M^+ $C_{10}H_{12}N_2O$ requires 176.0944); ν_{max} (nujol)/cm^{-1} 3246 (NH), 1650 (C=O), 1628 (C=N), 1579, 1542, 1492, 726, 674; δ_H (400 MHz, $CDCl_3$) 11.00 (1H, s, N*H*), 7.84 (2H, d, *J* 7.4 Hz, Ar*H*), 7.81 (1H, t, *J* 5.4 Hz, N=C*H*), 7.42 (1H, t, *J* 7.4 Hz, Ar*H*), 7.30 (2H, dd, *J* 7.4, 7.4 Hz, Ar*H*), 2.24 (2H, m, CH_2), 1.00 (3H, t, *J* 7.5 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 165.1 (C), 154.7 (CH), 133.5 (C), 132.2 (CH), 128.8 (CH), 128.0 (CH), 26.3 (CH_2), 11.2 (CH_3); *m/z* (EI) 176 (M^+, 1%), 147 (9), 121 (14), 103 (100), 105 (97), 77 (49).

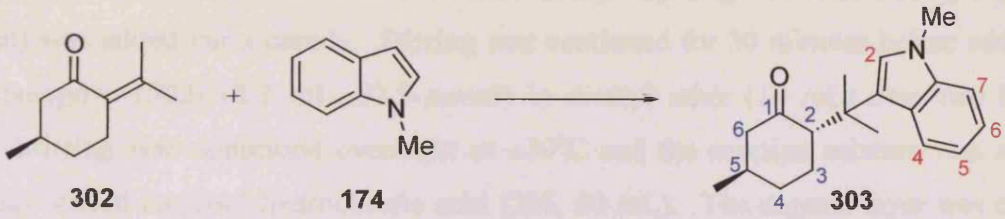
Benzoic acid *N'*-propylhydrazide 299



301 **299**

Platinum oxide (16mg, 60 μmol) was placed in nitrogen flushed flask and ethanol (2.8 mL) and acetic acid (1.4 mL) were added. Benzoic acid propylidene-hydrazide (**301**) (0.50g, 2.8 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. The organic layer was collected and the aqueous fraction was further extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether, afforded the *title compound* **299** (0.14g, 28%) as a colourless solid; mp 58–60°C [lit.[242] mp 67-70°C]; Found 179.1176 (MH^+ $C_{10}H_{14}N_2O$ requires 179.1179); ν_{max} (nujol)/cm^{-1} 3279 (NH), 1632 (C=O), 1579, 1535, 1466, 726, 678; δ_H (400 MHz, $CDCl_3$) 8.10 (1H, s, N*H*), 7.69 (2H, d, *J* 7.0 Hz, Ar*H*), 7.44 (1H, t, *J* 7.0 Hz, Ar*H*), 7.36 (2H, dd, *J* 7.0, 7.0 Hz, Ar*H*), 4.52 (1H, s, N*H*), 2.83 (2H, t, *J* 7.2 Hz, NCH_2), 1.49 (2H, tq, *J* 7.2, 7.2 Hz, NCH_2CH_2), 0.88 (3H, t, *J* 7.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 167.8 (C), 133.5 (C), 132.4 (CH), 129.2 (CH), 127.4 (CH), 54.7 (CH_2), 21.8 (CH_2), 12.1 (CH_3); *m/z* (APcI) 178.9 (MH^+, 100%), 176.8 (19); data consistent with the literature precedent.

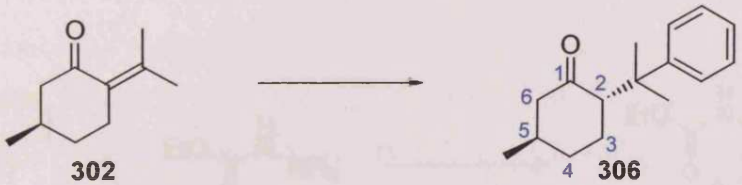
8-(*N*-Methyl-1*H*-indol-3-yl) menthone 303



302 **174** **303**

Benzoic acid *N'-iso*propylhydrazide (**287**) (0.34g, 1.9 mmol) was added to a solution of dichloromethane (25 mL) containing *iso*propanol (4 mL) at ambient temperature. Trifluoroacetic acid (0.15 mL, 1.9 mmol) was added and stirring was continued for 10 minutes before addition or (*R*)-(+)-pulegone (**302**) (4.6 mL, 28.6 mmol). After stirring for an additional 10 minutes, *N*-methylindole (**174**) (2.44 mL, 19.1 mmol) was added in one portion and stirring was continued for 48 hours at ambient temperature. The reaction mixture was filtered through a plug of silica and the filtrate was concentrated *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (20:80), afforded the *title compound* **303** (5.00g, 93%) as a pale yellow liquid; $[\alpha]_D^{20}$ +56.5° (*c* 0.57, $CHCl_3$); Found 284.2009 (MH^+ $C_{19}H_{25}NO$ requires 284.2009); ν_{max} (film)/cm^{-1} 1706 (C=O), 1614, 1484, 1381, 738; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 7.8 Hz, Ar*H*), 7.20 (1H, d, *J* 7.8 Hz, Ar*H*), 7.11 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 6.98 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 6.72 (1H, s, H-2'), 3.63 (3H, s, NCH_3), 2.98 (1H, dd, *J* 9.4, 6.0 Hz, H-2), 2.44 (1H, dd, *J* 13.0, 6.0 Hz, H-6_{ax}), 2.16 (1H, m, H-5), 1.96 (1H, ddd, *J* 13.0, 5.1, 1.3 Hz, H-6_{eq}), 1.63–1.33 (4H, m, H-3_{ax}, H-3_{eq}, H-4_{ax}, H-4_{eq}), 1.53 (3H, s, gem CH_3), 1.43 (3H, s, gem CH_3), 0.83 (3H, d, *J* 7.1 Hz, 5-CH_3); δ_C (100 MHz, $CDCl_3$) 213.3 (C=O), 137.8 (C), 126.2 (CH), 125.8 (C), 123.4 (C), 121.1 (CH), 121.1 (CH), 118.4 (CH), 109.5 (CH), 57.3 (CH), 50.6 (CH_2), 37.1 (C), 32.7 (CH_3), 32.5 (CH), 31.5 (CH_2), 27.7 (CH_3), 25.4 (CH_2), 23.8 (CH_3), 19.5 (CH_3); *m/z* (APcI) 284.6 (MH^+, 31%), 172.5 (100).

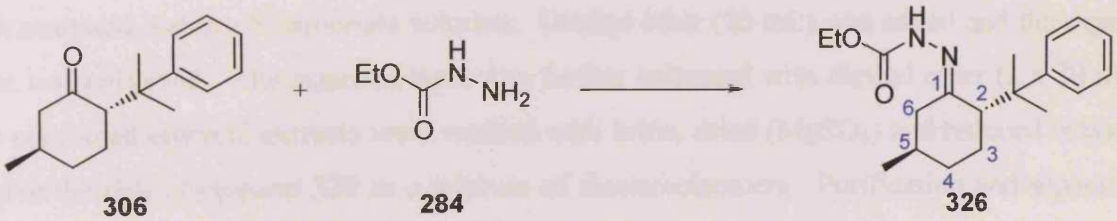
8-Phenyl menthone 306[223]



302 **306**

Copper bromide (0.88g, 6.1 mmol) and diethyl ether (14 mL) were added to a nitrogen flushed flask. The solution was cooled to –20°C and phenylmagnesium bromide (3M, 30 mL, 90 mmol) was added *via* a canula. Stirring was continued for 30 minutes before addition of (*R*)-(+)-pulegone (**302**) (8.7 mL, 52.5 mmol) in diethyl ether (10 mL) over two hours at –20°C. Stirring was continued overnight at –20°C and the reaction mixture was added to vigorously stirred ice-cold hydrochloric acid (2M, 60 mL). The organic layer was collected and the aqueous layer was saturated with ammonium chloride and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (40 mL) and reduced *in vacuo*. The crude product was dissolved in ethanol (120 mL) containing water (16 mL) and potassium hydroxide (14.0g, 250 mmol) was added. The solution was heated to reflux temperature and stirring was continued for 3 hours. After cooling to ambient temperature the solution was reduced *in vacuo* to a volume of about 40 mL. Water (100 mL) was added and the aqueous solution was saturated with sodium chloride and extracted with diethyl ether (4 x 20 mL). The combined ethereal extracts were dried (Na_2SO_4) and reduced *in vacuo*. Purification by column chromatography on silica, eluting with diethyl ether/light petroleum (5:95), afforded the *title compound* **306** (8.59g, 71%) as a pale yellow liquid; $[\alpha]_D^{20}$ –45.0° (*c* 1.00, $CHCl_3$); Found 230.1667 (M^+ $C_{16}H_{22}O$ requires 230.1665); ν_{max} (film)/cm^{-1} 1710 (C=O), 1600, 1497, 1365, 771, 700; δ_H (400 MHz, $CDCl_3$) 7.24 (2H, d, *J* 8.1 Hz, Ar*H*), 7.18 (2H, dd, *J* 8.1, 7.3 Hz, ArH), 7.05 (1H, t, *J* 7.3 Hz, Ar*H*), 2.58 (1H, dd, *J* 12.7, 4.5 Hz, H-2), 2.14 (1H, ddd, *J* 12.5, 4.0, 2.0 Hz, H-6_{eq}), 1.91 (1H, dd, *J* 12.5, 12.5 Hz, H-6_{ax}), 1.68 (3H, m, H-3_{ax}, H-3_{eq}, H-5), 1.75–1.62 (1H, m, H-4_{eq}), 1.37 (3H, s, gem CH_3), 1.31 (3H, s, gem CH_3), 1.51 (1H, ddd, *J* 12.7, 12.7, 3.2 Hz, H-4_{ax}), 0.86 (3H, d, *J* 6.4 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 211.2 (C=O), 150.0 (C), 128.1 (CH), 125.8 (CH), 125.6 (CH), 59.5 (CH), 52.4 (CH_2), 39.1 (C), 36.3 (CH), 34.7 (CH_2), 29.1 (CH_2), 26.6 (CH_3), 23.9 (CH_3), 22.4 (CH_3); *m/z* (EI) 230 (M^+, 13%), 119 (100), 112 (57), 91 (50), 41 (12); data consistent with the literature precedent.

N'-[5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexylidene]hydrazinecarboxylic acid ethyl ester 326



306 **284** **326**

Acetic acid (1.2 mL, 19.6 mmol) was added to a solution of 8-phenyl menthone (**306**) (6.00g, 26.1 mmol) in ethanol (40 mL). Ethyl carbazate (**284**) (3.80g, 36.5 mmol) was added and stirring was continued at ambient temperature for 48 hours. Water (50 mL) was added and the aqueous solution was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (40:60), afforded the *title compound* **326** (6.06g, 73%) as a colourless solid; mp 99-101°C; $[\alpha]_D^{20}$ –46.0° (*c* 1.03, $CHCl_3$); Found 317.2220 (MH^+ $C_{19}H_{28}N_2O_2$ requires 317.2224); ν_{max} (nujol)/cm^{-1} 3246 (NH), 1703 (C=O), 1600, 1497, 1336, 1244, 760, 699; δ_H (400 MHz, $CDCl_3$) 7.65 (1H, s, N*H*), 7.32 (2H, d, *J* 7.6 Hz, Ar*H*), 7.20 (2H, dd, *J* 7.6, 7.6 Hz, Ar*H*), 7.08 (1H, t, *J* 7.6 Hz, Ar*H*), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH$_3$), 2.43 (1H, dd, *J* 11.4, 4.3 Hz, H-2'), 2.30 (1H, dd, *J* 13.5, 3.8 Hz, H-6'$_{eq}$), 1.62 (1H, br, H-6'$_{ax}$), 1.50-0.80 (5H, m), 1.47 (3H, s, gem CH_3), 1.40 (3H, s, gem CH_3), 1.26 (3H, t, *J* 7.1 Hz, CH$_2$CH_3), 0.85 (3H, d, *J* 6.3 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 155.5 (C), 150.3 (C), 127.6 (CH), 126.4 (CH), 125.8 (C), 125.2 (CH), 61.5 (CH_2), 54.4 (CH), 40.4 (C), 35.1 (CH_2), 34.4 (CH_2), 33.4 (CH), 28.7 (CH_2), 26.7 (CH_3), 25.0 (CH_3), 22.3 (CH_3), 14.7 (CH_3); *m/z* (APcI) 317.0 (MH^+, 100%), 228.0 (23), 198.9 (12).

N'-[5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl]hydrazinecarboxylic acid ethyl ester 320

326 **320**

Platinum oxide (54mg, 0.24 mmol) was placed in a nitrogen flushed flask and ethanol (8.5 mL) and acetic acid (4.3 mL) were added. *N'*-[5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexylidene]hydrazinecarboxylic acid ethyl ester (**326**) (3.00g, 9.5 mmol) was added, the flask was charged with hydrogen, and stirring was continued for 48 hours at ambient temperature. The reaction mixture was filtered through celite® and the filtrate was neutralised with saturated sodium bicarbonate solution. Diethyl ether (20 mL) was added and the organic layer was collected. The aqueous layer was further extracted with diethyl ether (2 x 20 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **320** as a mixture of diastereoisomers. Purification and separation

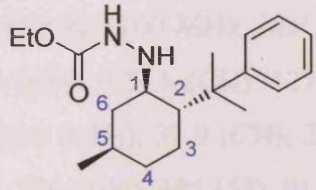
by column chromatography on silica, eluting with diethyl ether/light petroleum (20:80), afforded diastereoisomer **320a** (2.16g, 72%) as a colourless liquid and diastereoisomer **320b** (0.50g, 17%) as a pale yellow liquid.

(1*S*, 2*S*, 5*R*)-Diastereoisomer 320a

320a

$[\alpha]_D^{20}$ +13.3° (*c* 1.04, $CHCl_3$); Found 319.2377 (MH^+ $C_{19}H_{30}N_2O_2$ requires 319.2380); ν_{max} (film)/cm^{-1} 3333 (NH), 1708 (C=O), 1601, 1512, 1501, 1370, 1254, 770, 701; δ_H (400 MHz, MeOD) 7.47 (2H, d, *J* 7.6 Hz, Ar*H*), 7.29 (2H, dd, *J* 7.6, 7.6 Hz, Ar*H*), 7.16 (1H, t, *J* 7.6 Hz, Ar*H*), 4.09 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.27 (1H, br, H-1'), 1.92-1.73 (3H, m, H-3'$_{ax}$, H-3'$_{eq}$, H-6'), 1.62-1.51 (3H, m, H-4', H-5', H-6'), 1.51 (3H, s, gem CH_3), 1.44 (3H, s, gem CH_3), 1.24 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 0.88-0.79 (2H, m, H-2', H-4'), 0.83 (3H, d, *J* 6.4 Hz, $CHCH_3$); δ_C (100 MHz, MeOD) 158.2 (C), 149.2 (C), 127.6 (CH), 126.5 (CH), 125.3 (CH), 60.5 (CH_2), 56.6 (CH), 52.2 (CH), 39.8 (C), 38.2 (CH_2), 36.0 (CH_2), 27.7 (CH_3), 26.1 (CH_3), 25.4 (CH), 22.1 (CH_2), 21.5 (CH_3), 13.7 (CH_3); *m/z* (APcI) 319.0 (MH^+, 100%).

(1*R*, 2*S*, 5*R*)-Diastereoisomer 320b

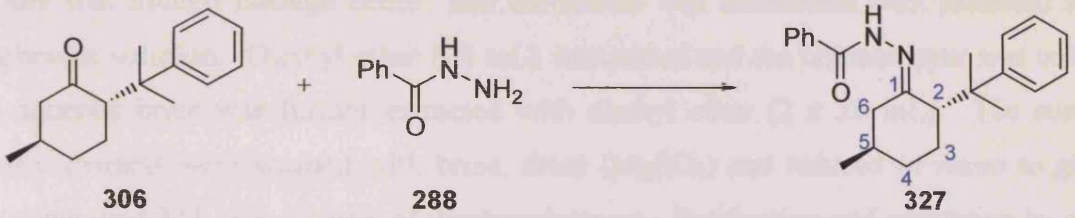


320b

$[\alpha]_D^{20}$ –26.7° (*c* 0.53, $CHCl_3$); Found 319.2377 (MH^+ $C_{19}H_{30}N_2O_2$ requires 319.2380); ν_{max} (film)/cm^{-1} 3346 (NH), 1714 (C=O), 1599, 1495, 1380, 1260, 766, 702; δ_H (400 MHz, MeOD) 7.36 (2H, d, *J* 7.6 Hz, Ar*H*), 7.18 (2H, dd, *J* 7.6, 7.6 Hz, Ar*H*), 7.03 (1H, t, *J* 7.6 Hz, Ar*H*), 3.90 (2H, q, *J* 6.9 Hz, OCH_2CH_3), 2.68 (1H, ddd, *J* 11.0, 11.0, 3.1 Hz, H-1'), 1.82 (2H, m, H-3, H-6'$_{eq}$), 1.73 (1H, ddd, *J* 11.0, 11.0, 3.0 Hz, H-6'$_{ax}$), 1.61 (1H, br, H-5'), 1.42 (3H, s, gem CH_3), 1.20 (1H, br, H-3'), 1.08 (3H, s, gem CH_3), 1.08 (4H, m, OCH_2CH_3, H-4'), 0.83 (1H, br, H-4'), 0.77 (3H, d, *J* 6.5 Hz, $CHCH_3$), 0.61 (1H, ddd, *J* 11.0, 11.0, 11.0 Hz, H-2'); δ_C (100 MHz, MeOD) 157.6 (C), 151.8 (C), 128.3 (CH), 125.6 (CH), 125.6 (CH), 61.5 (CH),

60.6 (CH_2), 49.2 (CH), 40.0 (CH_2), 39.4 (C), 35.1 (CH_2), 30.8 (CH), 26.8 (CH_2), 21.6 (CH_3), 20.5 (CH_3), 19.7 (CH_3), 13.8 (CH_3); *m/z* (APcI) 319.0 (MH^+, 100%).

Benzoic acid [5-methyl-2-(1-methyl-1-phenylethyl)cyclohexylidene]hydrazide 327



306 **288** **327**

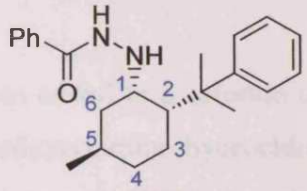
Acetic acid (0.4 mL, 6.5 mmol) was added to a solution of 8-phenyl menthone (**306**) (2.00g, 8.7 mmol) in ethanol (12 mL). Benzoic hydrazide (**288**) (1.41g, 10.4 mmol) was added and stirring was continued at ambient temperature for 24 hours. Water (40 mL) was added and the aqueous solution was extracted with ethyl acetate (2 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/hexanes (50:50), afforded the *title compound* **327** (2.06g, 68%) as a colourless solid; mp 129-131°C; $[\alpha]_D^{20}$ –36.5° (*c* 1.02, $CHCl_3$); Found 348.2205 (M^+ $C_{23}H_{28}N_2O$ requires 348.2202); ν_{max} (nujol)/cm^{-1} 3219 (NH), 1650 (C=O), 1639 (C=N), 1536, 1362, 752, 689; δ_H (400 MHz, MeOD) 7.86 (2H, d, *J* 7.5 Hz, Ar*H*), 7.53 (6H, m, Ar*H*), 7.29 (2H, dd, *J* 7.5, 7.5 Hz, Ar*H*), 7.14 (2H, dd, *J* 7.1, 7.1 Hz, Ar*H*), 2.73 (2H, m, H-2', H-6'), 1.88-0.98 (4H, m), 1.59 (3H, s, gem CH_3), 1.54 (3H, s, gem CH_3), 0.94 (3H, d, *J* 6.3 Hz, CHCH_3); δ_C (100 MHz, MeOD) 221.2 (C=O), 169.1 (C), 149.8 (C), 133.7 (C), 131.4 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 126.0 (CH), 125.1 (CH), 54.2 (CH), 40.3 (C), 36.2 (CH_2), 33.0 (CH_2), 32.9 (CH), 27.7 (CH_2), 27.1 (CH_3), 23.6 (CH_3) 21.1 (CH_3); *m/z* (EI) 348 (M^+, 3%), 230 (100), 105 (58), 91 (21), 77 (17).

Benzoic acid *N*'-[5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl]hydrazide 321

327 **321**

Platinum oxide (69mg, 30 μmol) was placed in a nitrogen flushed flask and ethanol (1.5 mL) and acetic acid (0.8 mL) were added. Benzoic acid [5-methyl-2-(1-methyl-1-phenylethyl) cyclohexylidene]hydrazide (**327**) (0.50g, 1.4 mmol) was added, the flask was charged with hydrogen, and stirring was continued for 48 hours at ambient temperature. The reaction mixture was filtered through celite® and the filtrate was neutralised with saturated sodium bicarbonate solution. Diethyl ether (20 mL) was added and the organic layer was collected. The aqueous layer was further extracted with diethyl ether (2 x 20 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **321** as a mixture of diastereoisomers. Purification and separation by column chromatography on silica, eluting with diethyl ether/light petroleum (40:60), afforded diastereoisomer **321a** (0.14g, 28%) as a colourless solid and diastereoisomer **321b** (0.10g, 19%) as a colourless oil.

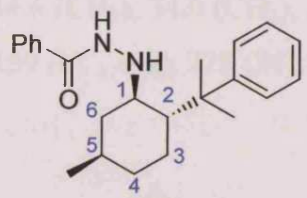
(1*S*, 2*S*, 5*R*)-Diastereoisomer 321a



321a

mp 140-142°C; $[\alpha]_D^{20}$ –13.3° (*c* 0.06, $CHCl_3$); ν_{max} (nujol)/cm^{-1} 3251 (NH), 1624 (C=O), 1576, 1542, 1363, 770, 700; δ_H (400 MHz, $CDCl_3$) 7.59 (2H, d, *J* 7.5 Hz, Ar*H*), 7.39 (4H, m, Ar*H*), 7.23 (2H, dd, *J* 7.5, 7.5 Hz, Ar*H*), 7.14 (2H, dd, *J* 7.5, 7.5 Hz, Ar*H*), 6.95 (1H, br, N*H*), 4.85 (1H, br, N*H*), 3.01 (1H, br, H-1'), 1.79-1.17 (7H, m), 1.43 (3H, s, gem CH_3), 1.39 (3H, s, gem CH_3), 0.76 (4H, m, H-2', CHCH_3); δ_C (100 MHz, $CDCl_3$) 174.9 (C), 166.7 (C), 149.8 (C), 131.6 (CH), 128.7 (CH), 127.9 (CH), 126.7 (CH), 126.6 (CH), 125.6 (CH), 57.9 (CH), 52.0 (CH), 40.4 (C), 38.7 (CH_2), 36.0 (CH_2), 27.9 (CH_3), 26.9 (CH_3), 26.2 (CH), 25.7 (CH_2), 19.5 (CH_3); *m/z* (APcI) 351.0 (MH^+, 89%); 79.0 (100).

(1*R*, 2*S*, 5*R*)-Diastereoisomer 321b



321a

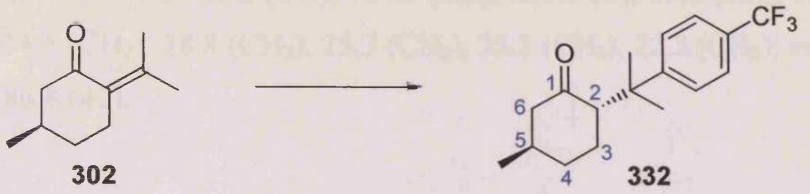
ν_{max} (nujol)/cm^{-1} 3246 (NH), 1654 (C=O), 1579, 1527, 1370, 740, 702; δ_H (400 MHz, $CDCl_3$) 7.48 (2H, d, *J* 7.3 Hz, Ar*H*), 7.43 (2H, dd, *J* 7.3, 7.3 Hz, Ar*H*), 7.30 (4H, m, Ar*H*), 7.10 (2H, dd, *J* 7.1 Hz, Ar*H*), 6.25 (1H, br, N*H*), 4.51 (1H, br, N*H*), 2.82 (1H, ddd, *J* 10.7, 10.7, 3.3 Hz, H-1'), 1.92-0.78 (8H, m), 1.19 (3H, s, gem CH_3), 1.15 (3H, s, gem CH_3), 0.80 (3H, d, *J* 6.5 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 175.0 (C), 166.7 (C), 152.9 (C), 131.5 (CH), 128.4 (CH), 128.3 (CH), 126.8 (CH), 126.0 (CH), 125.5 (CH), 61.7 (CH), 49.7 (CH), 40.6 (CH_2), 39.8 (C), 35.2 (CH_2), 31.8 (CH), 31.6 (CH_3), 25.7 (CH_2), 22.3 (CH_3), 20.8 (CH_3); *m/z* (APcI) 351.0 (MH^+, 89%); 79.0 (100).

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone *O*-methyl oxime 329

306 **329**

Acetic acid (0.3 mL, 4.9 mmol) was added to a solution of 8-phenyl menthone (**306**) (1.50g, 6.5 mmol) in ethanol (9 mL). Methoxylamine hydrochloride (0.76g, 9.1 mmol) was added and stirring was continued at ambient temperature for 48 hours. Water (25 mL) was added and the aqueous solution was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with ethyl acetate/hexanes (5:95), afforded the *title compound* **329** (1.08g, 64%) as a colourless liquid; $[\alpha]_D^{20}$ –19.4° (*c* 1.03, $CHCl_3$); Found 259.1939 (M^+ $C_{17}H_{25}NO$ requires 259.1936); ν_{max} (film)/cm^{-1} 1639 (C=N), 1600, 1497, 1365, 1050, 759, 700; δ_H (400 MHz, $CDCl_3$) 7.36 (2H, d, *J* 7.5 Hz, Ar H), 7.27 (2H, dd, *J* 7.5, 7.5 Hz, Ar*H*), 7.14 (1H, t, *J* 7.5 Hz, Ar*H*), 3.74 (3H, s, OCH_3), 3.00 (1H, ddd, *J* 13.2, 4.4, 1.6 Hz, H-6$_{eq}$), 2.42 (1H, dd, *J* 11.6, 4.4 Hz, H-2), 1.69-1.58 (3H, m, H-4, H-3, H-5), 1.52 (3H, s, gem CH_3), 1.44 (3H, s, gem CH_3), 1.37-1.00 (3H, m, H-6$_{ax}$, H-3, H-4), 0.93 (3H, d, *J* 6.5 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 159.4 (C), 150.6 (C), 127.7 (CH), 126.1 (CH), 125.3 (CH), 61.1 (CH_3), 52.9 (CH), 40.2 (C), 34.6 (CH_2), 34.0 (CH_2), 33.3 (CH), 28.7 (CH_2), 26.9 (CH_3), 24.9 (CH_3), 22.3 (CH_3); *m/z* (EI) 259 (M^+, 1%), 228 (34), 212 (68), 141 (100), 131 (42), 119 (81), 91 (66).

8-(4-Trifluoromethylphenyl) menthone 332

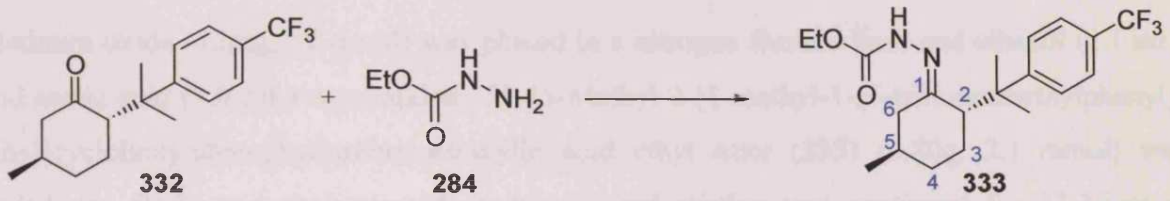


302 **332**

Magnesium turnings (2.20g, 90.5 mmol) were added to diethyl ether (10 mL) in a nitrogen-flushed flask fitted with a reflux condenser, carrying a calcium chloride drying tube, and a dropping funnel. 1-Bromo-4-trifluoromethylbenzene (1.5 mL, 10 mmol) was added in one portion, one crystal of iodine was added, and the solution was gently heated until self-refluxing began. 1-Bromo-4-trifluoromethylbenzene (13.8 mL, 90 mmol) was added at such a rate that gentle reflux was maintained. Heating was continued at reflux temperature for one hour after the addition was complete before cooling to ambient temperature. Diethyl ether (20 mL) was added and this solution was added *via* a canula to a vigorously stirred suspension of copper bromide (0.88g, 6.1 mmol) in diethyl ether (14 mL) at –20°C. Stirring was continued for 30 minutes before addition of (*R*)-(+)-pulegone (**302**) (8.7 mL, 52.5 mmol) in diethyl ether (10 mL) over two hours at –20°C. Stirring was continued overnight at –20°C and the reaction mixture was added to vigorously stirred ice-cold hydrochloric acid (2M, 60 mL). The organic layer was collected and the aqueous layer was saturated with ammonium chloride and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (40 mL) and reduced *in vacuo*. The crude product was dissolved in ethanol (120 mL) containing water (16 mL) and potassium hydroxide (14.0g, 250 mmol) was added. The solution was heated to reflux temperature and stirring was continued for 3 hours. After cooling to ambient temperature the solution was reduced *in vacuo* to a volume of about 40 mL. Water (100 mL) was added and the aqueous solution was saturated with sodium chloride and extracted with diethyl ether (4 x 20 mL). The combined ethereal extracts were dried (Na_2SO_4) and reduced *in vacuo*. Purification by column chromatography on silica, eluting with diethyl ether/light petroleum (10:90), afforded the *title compound* **332** (10.19g, 65%) as a colourless solid; mp 38-40°C; $[\alpha]_D^{20}$ –58.7° (*c* 1.02, $CHCl_3$); Found 299.1617 (MH^+ $C_{17}H_{21}F_3O$ requires 299.1617); ν_{max} (nujol)/cm^{-1} 1715 (C=O), 1617, 1362, 1328, 1166, 838; δ_H (400 MHz, $CDCl_3$) 7.43 (2H, d, *J* 8.4 Hz, H-3', H-5'), 7.36 (2H, d, *J* 8.4 Hz, H-2', H-6'), 2.63 (1H, dd, *J* 13.0, 4.6 Hz, H-2), 2.12 (1H, dd, *J* 12.4, 2.2 Hz, H-6_{eq}), 1.89 (1H, dd, *J* 12.4, 12.4 Hz, H-6_{ax}), 1.73 (2H, m, H-3, H-5), 1.43–1.18 (3H, m), 1.37 (3H, s, gem

CH_3), 1.27 (3H, s, gem CH_3), 0.86 (3H, d, *J* 6.1 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 210.5 (C=O), 154.2 (C), 127.8 (C), 126.2 (CH), 124.8 (CH), 123.1 (C), 59.2 (CH), 52.1 (CH_2), 39.2 (C), 36.2 (CH), 34.5 (CH_2), 28.8 (CH_2), 25.3 (CH_3), 25.2 (CH_3), 22.2 (CH_3); *m/z* (APcI) 298.9 (MH^+, 100%), 186.8 (42).

N'-{5-Methyl-2-[1-methyl-1-(4-trifluoromethylphenyl)ethyl]cyclohexylidene}hydrazine-carboxylic acid ethyl ester 333



Acetic acid (0.2 mL, 3.0 mmol) was added to a stirred solution of 8-(4-trifluoromethylphenyl) menthone (**332**) (1.20g, 4.0 mmol) in ethanol (5.5 mL). Ethyl carbazate (**284**) (0.50g, 4.8 mmol) was added and stirring was continued at ambient temperature for 72 hours. Water (20 mL) was added and the aqueous solution was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (40:60), afforded the *title compound* **333** (1.12g, 72%) as a colourless solid; mp 147-149°C; $[\alpha]_D^{20}$ –19.6° (*c* 1.02, $CHCl_3$); Found 385.2103 (MH^+ $C_{20}H_{27}F_3N_2O_2$ requires 385.2097); ν_{max} (nujol)/cm^{-1} 3252 (NH), 1691 (C=O), 1617 (C=N), 1328, 1156, 840; δ_H (400 MHz, $CDCl_3$) 7.58 (1H, s, N*H*), 7.44 (4H, m, Ar*H*), 4.15 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 2.41 (1H, dd, *J* 11.9, 4.0 Hz, H-2'), 2.36 (1H, d, *J* 12.4, 12.4 Hz, H-6'$_{ax}$), 1.72 (1H, dd, *J* 12.4, 2.4 Hz, H-6'$_{eq}$), 1.70-0.90 (5H, m), 1.50 (3H, s, gem CH_3), 1.37 (3H, s, gem CH_3), 1.25 (3H, t, *J* 7.0 Hz, CH_2CH_3), 0.88 (3H, d, *J* 6.5 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 154.5 (C), 127.4 (C), 127.1 (C), 126.8 (CH), 125.8 (C), 124.4 (CH), 123.1 (C), 61.5 (CH_2), 54.3 (CH), 40.4 (C), 35.0 (CH_2), 34.5 (CH_2), 33.6 (CH), 28.8 (CH_2), 26.7 (CH_3), 25.4 (CH_3), 22.3 (CH_3), 14.6 (CH_3); *m/z* (APcI) 385.0 (MH^+, 100%), 198.9 (11).

N'-{5-Methyl-2-[1-methyl-1-(4-trifluoromethylphenyl)ethyl]cyclohexyl}hydrazine-carboxylic acid ethyl ester 331

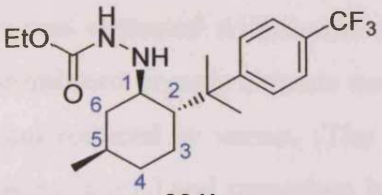
Platinum oxide (12mg, 52 μmol) was placed in a nitrogen flushed flask and ethanol (2.1 mL) and acetic acid (1.0 mL) were added. *N'*-{5-Methyl-2-[1-methyl-1-(4-trifluoromethylphenyl)-ethyl]cyclohexylidene}hydrazinecarboxylic acid ethyl ester (**333**) (0.80g, 2.1 mmol) was added, the flask was charged with hydrogen, and stirring was continued for 72 hours at ambient temperature. The reaction mixture was filtered through celite® and the filtrate was neutralised with saturated sodium bicarbonate solution. Diethyl ether (25mL) was added and the organic layer was collected. The aqueous layer was further extracted with diethyl ether (2 x 25 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **331** as a mixture of diastereoisomers. Purification by column chromatography on silica, eluting with diethyl ether/light petroleum (40:60), followed by preparative chiral HPLC using a preparative Chiralcel OD column, cooled to –10°C, wavelength 216 nm, eluting with hexanes/*iso*propanol (99:1), flow rate of 6.0 mL/min, separated the sample, t_1 = 58 minutes; t_2 = 82 minutes, to afford diastereoisomer **331a** (0.41g, 51%) as a colourless liquid and **331b** (0.27g, 34%) as a colourless liquid.

(1*S*, 2*S*, 5*R*)-Diastereoisomer 331a

$[\alpha]_D^{19}$ +9.7° (*c* 1.26, $CHCl_3$); Found 387.2256 (MH^+ $C_{20}H_{29}F_3N_2O_2$ requires 387.2254); ν_{max} (film)/cm^{-1} 3361 (NH), 1713 (C=O), 1619, 1328, 1168, 841; δ_H (400 MHz, MeOD) 7.55 (2H, d, *J* 8.4 Hz, Ar*H*), 7.47 (2H, d, *J* 8.4 Hz, Ar*H*), 3.97 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.01 (1H, br, H-1'), 1.81-0.69 (8H, m), 1.40 (3H, s, gem CH_3), 1.38 (3H, s, gem CH_3), 1.12 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 0.72 (3H, d, *J* 6.4 Hz, $CHCH_3$); δ_C (100 MHz, MeOD) 158.3 (C), 127.5 (C),

127.1 (CH), 125.9 (C), 124.3 (CH), 123.2 (C), 60.5 (CH_2), 56.8 (CH), 51.9 (CH), 40.3 (C), 38.0 (CH_2), 35.8 (CH_2), 26.5 (CH_3), 26.0 (CH_3), 25.5 (CH), 22.0 (CH_2), 21.3 (CH_3), 13.6 (CH_3); *m/z* (APcI) 387.0 (MH^+, 100%).

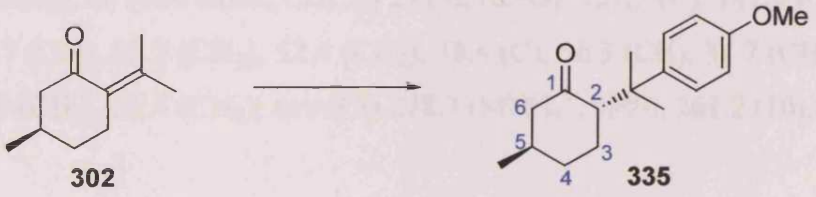
(1*R*, 2*S*, 5*R*)-Diastereoisomer 331b



331b

$[\alpha]_D^{20}$ −1.8° (*c* 0.67, $CHCl_3$); Found 387.2256 (MH^+ $C_{20}H_{29}F_3N_2O_2$ requires 387.2254); ν_{max} (film)/cm^{-1} 3361 (NH), 1711 (C=O), 1614, 1328, 1168, 758; δ_H (400 MHz, MeOD) 7.56 (2H, d, *J* 8.4 Hz, Ar*H*), 7.50 (2H, d, *J* 8.4 Hz, Ar*H*), 3.95 (2H, q, *J* 6.8 Hz, OCH_2CH_3), 2.65 (1H, ddd, *J* 11.0, 11.0, 3.6 Hz, H-1'), 1.83-0.80 (7H, m), 1.47 (3H, s, gem CH_3), 1.13 (3H, s, gem CH_3), 1.11 (3H, t, *J* 6.8 Hz, OCH_2CH_3), 0.80 (3H, d, *J* 6.5 Hz, $CHCH_3$), 0.62 (1H, ddd, *J* 11.5, 11.5, 11.0 Hz, H-6'$_{ax}$); δ_C (100 MHz, MeOD) 156.6 (C), 127.7 (C), 126.3 (CH), 125.8 (C), 124.9 (CH), 123.1 (C), 61.8 (CH), 60.7 (CH_2), 49.3 (CH), 40.0 (CH_2), 39.8 (C), 34.9 (CH_2), 30.9 (CH), 29.9 (CH_3), 29.5 (CH_3), 26.7 (CH_2), 20.7 (CH_3), 13.8 (CH_3); *m/z* (APcI) 387.0 (MH^+, 100%).

8-(4-Methoxyphenyl) menthone 335[244]

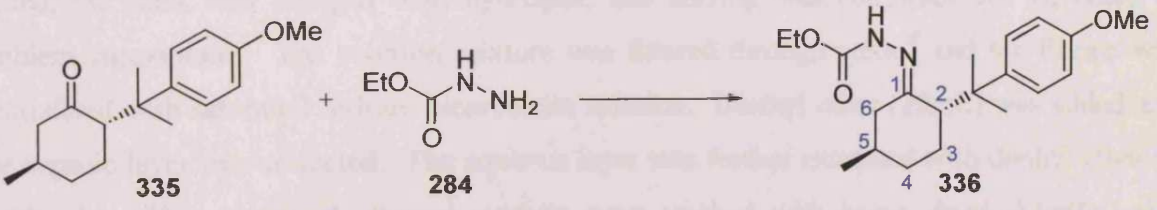


302 **335**

Magnesium turnings (2.43g, 100 mmol) were added to diethyl ether (10 mL) in a nitrogen-flushed flask fitted with a reflux condenser, carrying a calcium chloride drying tube, and a dropping funnel. 4-Methylanisole (1.3 mL, 11 mmol) was added in one portion, one crystal of iodine was added, and the solution was gently heated until self-refluxing began. 4-Methylanisole (11.9 mL, 99 mmol) was added at such a rate that gentle reflux was maintained. Heating was continued at reflux temperature for one hour after the addition was complete before cooling to ambient temperature. Diethyl ether (25 mL) was added and this

solution was added *via* a canula to a vigorously stirred suspension of copper bromide (0.97g, 6.7 mmol) in diethyl ether (15 mL) at –20°C. Stirring was continued for 30 minutes before addition of (*R*)-(+)-pulegone (**302**) (9.6 mL, 58 mmol) in diethyl ether (10 mL) over two hours at –20°C. Stirring was continued overnight at –20°C and the reaction mixture was added to vigorously stirred ice-cold hydrochloric acid (2M, 65 mL). The organic layer was collected and the aqueous layer was saturated with ammonium chloride and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (45 mL) and reduced *in vacuo*. The crude product was dissolved in ethanol (135 mL) containing water (18 mL) and potassium hydroxide (15.5g, 275 mmol) was added. The solution was heated to reflux temperature and stirring was continued for 3 hours. After cooling to ambient temperature the solution was reduced *in vacuo* to a volume of about 40 mL. Water (100 mL) was added and the aqueous solution was saturated with sodium chloride and extracted with diethyl ether (4 x 25 mL). The combined ethereal extracts were dried (Na_2SO_4) and reduced *in vacuo*. Purification by column chromatography on silica, eluting with ethyl acetate/light petroleum (5:95), afforded the *title compound* **335** (10.47g, 69%) as a colourless solid; mp 56-58°C; $[\alpha]_D^{20}$ –42.0° (*c* 1.02, $CHCl_3$); Found 278.2112 (MNH_4^+ $C_{17}H_{24}O_2$ requires 278.2115); ν_{max} (nujol)/cm^{-1} 1713 (C=O), 1610, 1362, 1250, 1184, 1122, 841; δ_H (400 MHz, $CDCl_3$) 7.18 (2H, d, *J* 7.9 Hz, H-2', H-6'), 6.75 (2H, d, *J* 7.9 Hz, H-3', H-5'), 3.71 (3H, s, OCH_3), 2.54 (1H, dd, *J* 12.9, 4.2 Hz, H-2), 2.16 (1H, ddd, *J* 12.5, 1.8, 1.8 Hz, H-6_{eq}), 1.94 (1H, dd, *J* 12.5, 12.5 Hz, H-6_{ax}), 1.71 (2H, m, H-3, H-5), 1.40–1.31 (2H, m, H-3, H-4_{eq}), 1.36 (3H, s, gem CH_3), 1.31 (3H, s, gem CH_3), 1.18 (1H, br, H-4_{ax}), 0.89 (3H, d, *J* 6.3 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 211.6, (C=O), 157.3 (C), 142.0 (C), 126.8 (CH), 113.2 (CH), 59.7 (CH), 55.2 (CH_3), 52.4 (CH_2), 38.4 (C), 36.3 (CH), 34.7 (CH_2), 29.1 (CH_2), 26.7 (CH_3), 24.0 (CH_3), 22.4 (CH_3); *m/z* (CI) 278.3 (MNH_4^+, 39%), 261.2 (10), 149.1 (100).

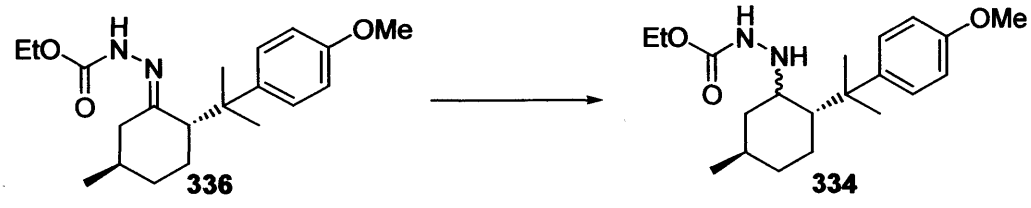
N'-{2-[1-(4-Methoxyphenyl)-1-methylethyl]-5-methylcyclohexylidene}hydrazine-carboxylic acid ethyl ester 336



335 **284** **336**

Acetic acid (0.13 mL, 2.3 mmol) was added to a solution of 8-(4-methoxyphenyl) menthone (**335**) (0.75g, 2.9 mmol) in ethanol (4.6 mL). Ethyl carbazate (**284**) (0.45g, 4.3 mmol) was added and stirring was continued at ambient temperature for 72 hours. Water (20 mL) was added and the aqueous solution was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (50:50), afforded the *title compound* **336** (0.70g, 70%) as a colourless solid; mp 129-130°C; $[\alpha]_D^{20}$ –41.9° (*c* 1.04, $CHCl_3$); Found 347.2326 (MH^+ $C_{20}H_{30}N_2O_3$ requires 347.2329); ν_{max} (nujol)/cm^{-1} 3236 (NH), 1687 (C=O), 1608 (C=N), 1510, 1294, 1184, 1122, 834; δ_H (400 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.7 Hz, H-2''', H-6'''), 6.72 (2H, d, *J* 8.7 Hz, H-3''', H-5'''), 4.15 (2H, q, *J* 7.4 Hz, OCH_2CH_3), 3.68 (3H, s, OCH_3), 2.33 (2H, m, H-2', H-6'), 1.59 (2H, m, H-6', H-3'), 1.54-1.09 (3H, m), 1.43 (3H, s, gem CH_3), 1.37 (3H, s, gem CH_3), 1.23 (3H, t, *J* 7.4 Hz, CH_2CH_3), 0.92 (1H, br, H-4'), 0.83 (3H, d, *J* 6.3 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 157.1 (C), 155.8 (C), 142.3 (C), 127.8 (C), 127.5 (CH), 112.9 (CH), 61.4 (CH_2), 55.1 (CH_3), 54.5 (CH), 39.8 (C), 35.0 (CH_2), 34.2 (CH_2), 33.3 (CH), 28.5 (CH_2), 27.1 (CH_3), 25.1 (CH_3), 22.3 (CH_3), 14.6 (CH_3); *m/z* (APcI) 347.2 (MH^+, 54%), 149.1 (100).

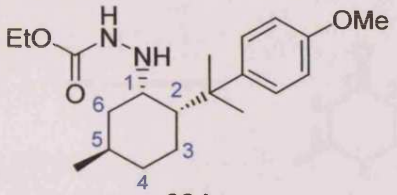
N'-{2-[1-(4-Methoxyphenyl)-1-methylethyl]-5-methylcyclohexyl}hydrazinecarboxylic acid ethyl ester 334



Platinum oxide (12mg, 51 μmol) was placed in a nitrogen flushed flask and ethanol (2.0 mL) and acetic acid (1.0 mL) were added. *N'*-{2-[1-(4-Methoxyphenyl)-1-methylethyl]-5-methylcyclohexylidene}hydrazinecarboxylic acid ethyl ester (**336**) (0.70g, 2.0 mmol) was added, the flask was charged with hydrogen, and stirring was continued for 72 hours at ambient temperature. The reaction mixture was filtered through celite® and the filtrate was neutralised with saturated sodium bicarbonate solution. Diethyl ether (25mL) was added and the organic layer was collected. The aqueous layer was further extracted with diethyl ether (2 x 25 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **334** as a mixture of diastereoisomers. Separation

and purification by column chromatography on silica, eluting with diethyl ether/light petroleum (30:70), afforded diastereoisomer **334a** (0.22g, 31%) as a colourless viscous liquid and **334b** (0.19g, 28%) as a colourless viscous liquid.

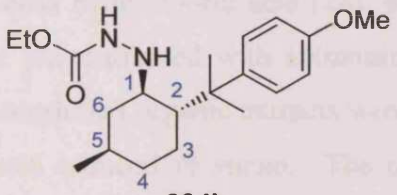
(1*S*, 2*S*, 5*R*)-Diastereoisomer 334a



334a

$[\alpha]_D^{19}$ +4.0° (*c* 0.99, $CHCl_3$); Found 349.2486 (MH^+ $C_{20}H_{32}N_2O_3$ requires 349.2486); ν_{max} (nujol)/cm^{-1} 1716 (C=O), 1610, 1513, 1378, 1265, 1187, 833; δ_H (400 MHz, MeOD) 7.35 (2H, d, *J* 8.5 Hz, H-2''', H-6'''), 6.82 (2H, d, *J* 8.5 Hz, H-3''', H-5'''), 4.06 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.73 (3H, s, OCH_3), 3.26 (1H, br, H-1'), 1.81-1.54 (7H, m), 1.46 (3H, s, gem CH_3), 1.38 (3H, s, gem CH_3), 1.21 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 0.79 (1H, br, H-2'), 0.80 (3H, d, *J* 6.4 Hz, $CHCH_3$); δ_C (100 MHz, MeOD) 156.6 (C), 156.0 (C), 139.3 (C), 126.0 (CH), 111.3 (CH), 59.0 (CH_2), 55.0 (CH), 52.7 (CH_3), 50.8 (CH), 37.6 (C), 36.7 (CH_2), 34.5 (CH_2), 26.6 (CH_3), 24.8 (CH_3), 23.8 (CH), 20.6 (CH_2), 20.0 (CH_3), 12.2 (CH_3); *m/z* (APcI) 349.2 (MH^+, 100%), 286.8 (6).

(1*R*, 2*S*, 5*R*)-Diastereoisomer 334b

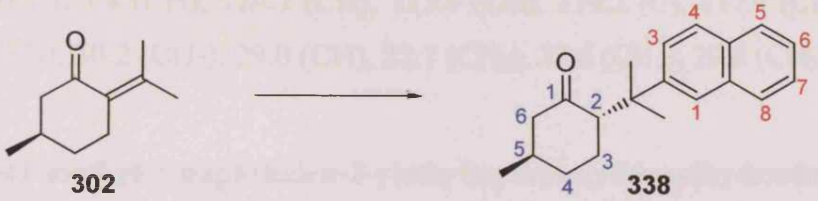


334b

$[\alpha]_D^{20}$ −11.7° (*c* 0.53, $CHCl_3$); Found 349.2486 (MH^+ $C_{20}H_{32}N_2O_3$ requires 349.2486); ν_{max} (nujol)/cm^{-1} 3331 (NH), 1716 (C=O), 1609, 1512, 1369, 1251, 1183, 1149, 832; δ_H (400 MHz, MeOD) 7.33 (2H, d, *J* 8.1 Hz, H-2''', H-6'''), 6.82 (2H, d, *J* 8.1 Hz, H-3''', H-5'''), 3.99 (2H, q, *J* 6.7 Hz, OCH_2CH_3), 3.72 (3H, s, OCH_3), 2.72 (1H, ddd, *J* 11.2, 11.2, 3.3 Hz, H-1'), 1.94-1.25 (5H, m), 1.45 (3H, s, gem CH_3), 1.16 (4H, m, H-5', CH_2CH_3), 1.12 (3H, s, gem CH_3), 0.90 (1H, dddd, *J* 12.7, 12.7, 12.7, 2.7 Hz, H-4'$_{ax}$), 0.85 (3H, d, *J* 6.5 Hz, $CHCH_3$), 0.67 (1H, ddd, *J* 11.2, 11.2, 11.2 Hz, H-6'$_{ax}$); δ_C (100 MHz, MeOD) 156.2 (C), 156.0 (C), 142.0 (C), 124.9 (CH), 111.9 (CH), 60.0 (CH), 59.0 (CH_2), 52.6 (CH_3), 47.6 (CH), 38.4 (CH_2), 37.0

(C), 33.4 (CH_2), 29.5 (CH_3), 29.3 (CH), 25.1 (CH_2), 19.7 (CH_3), 18.4 (CH_3), 12.0 (CH_3); *m/z* (APcI) 349.3 (MH^+, 43%), 71.2 (100).

8-(2-Naphthyl) menthone 338[244]

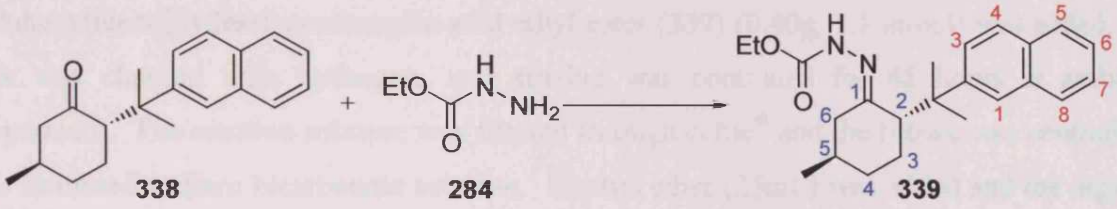


302 **338**

Magnesium turnings (2.20g, 90.5 mmol) were added to diethyl ether (10 mL) in a nitrogen-flushed flask fitted with a reflux condenser, carrying a calcium chloride drying tube, and a dropping funnel. 2-Bromonaphthalene (2.07g, 10 mmol) was added in one portion, one crystal of iodine was added, and the solution was gently heated until self-refluxing began. 2-Bromonaphthalene (18.63g, 90 mmol) was added at such a rate that gentle reflux was maintained. Heating was continued at reflux temperature for one hour after the addition was complete before cooling to ambient temperature. Diethyl ether (20 mL) was added and this solution was added *via* a canula to a vigorously stirred suspension of copper bromide (0.88g, 6.1 mmol) in diethyl ether (14 mL) at –20°C. Stirring was continued for 30 minutes before addition of (*R*)-(+)-pulegone (**302**) (8.7 mL, 52.5 mmol) in diethyl ether (10 mL) over two hours at –20°C. Stirring was continued overnight at –20°C and the reaction mixture was added to vigorously stirred ice-cold hydrochloric acid (2M, 60 mL). The organic layer was collected and the aqueous layer was saturated with ammonium chloride and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (40 mL) and reduced *in vacuo*. The crude product was dissolved in ethanol (120 mL) containing water (16 mL) and potassium hydroxide (14.0g, 250 mmol) was added. The solution was heated to reflux temperature and stirring was continued for 3 hours. After cooling to ambient temperature the solution was reduced *in vacuo* to a volume of about 40 mL. Water (100 mL) was added and the aqueous solution was saturated with sodium chloride and extracted with diethyl ether (4 x 20 mL). The combined ethereal extracts were dried (Na_2SO_4) and reduced *in vacuo*. Purification by column chromatography on silica, eluting with diethyl ether/light petroleum (20:80), afforded the *title compound* **338** (8.98g, 61%) as a colourless viscous liquid; ν_{max} (film)/cm^{-1} 3052, 1619, 1586, 1356, 815, 744; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, *J* 7.8 Hz, H-5'), 7.84 (1H, d, *J* 7.8 Hz, H-8'), 7.72 (1H, d, *J*

8.3 Hz, H-4'), 7.43 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 7.37 (1H, d, *J* 8.3 Hz, H-3'), 7.31 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 7.19 (1H, s, H-1'), 2.58 (1H, dd, *J* 16.5, 3.7 Hz, H-2), 2.28 (2H, m, H-6_{eq}, H-6_{ax}), 2.05-1.38 (5H, m), 1.36 (3H, s, gem CH_3), 1.36 (3H, s, gem CH_3), 1.06 (3H, d, *J* 6.5 Hz, CHCH_3); δ_C (100 MHz, MeOD) 151.3 (C=O), 146.8 (C), 132.3 (C), 129.1 (CH), 127.2 (CH), 126.7 (CH), 125.4 (CH), 124.3 (CH), 123.0 (CH), 119.2 (C), 117.4 (CH), 49.7 (CH), 40.2 (C), 31.3 (CH_2), 30.2 (CH_2), 29.0 (CH), 22.7 (CH_3), 22.6 (CH_3), 20.8 (CH_3), 20.7 (CH_2).

N'-[5-Methyl-2-(1-methyl-1-naphthalen-2-ylethyl)cyclohexylidene]hydrazinecarboxylic acid ethyl ester 339



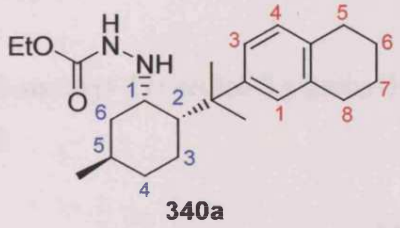
338 **284** **339**

Acetic acid (0.15 mL, 2.7 mmol) was added to a stirred solution of 8-(2-naphthyl) menthone (**338**) (1.00g, 3.6 mmol) in ethanol (5.3 mL). Ethyl carbazate (**284**) (0.52g, 5.0 mmol) was added and stirring was continued at ambient temperature for 72 hours. Water (20 mL) was added and the aqueous solution was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (40:60), afforded the *title compound* **339** (0.69g, 52%) as a pale yellow solid; mp 116-117°C; $[\alpha]_D^{20}$ –43.6° (*c* 1.00, $CHCl_3$); Found 367.2384 (MH^+ $C_{23}H_{30}N_2O_2$ requires 367.2380); ν_{max} (nujol)/cm^{-1} 3205 (NH), 1691 (C=O), 1613 (C=N), 1339, 822, 752; δ_H (400 MHz, $CDCl_3$) 7.70 (4H, m, Ar*H*), 7.51 (1H, d, *J* 8.7 Hz, Ar*H*), 7.34 (2H, m, Ar*H*), 4.17 (2H, q, *J* 7.1 Hz, OCH_2CH$_3$), 2.54 (1H, dd, *J* 11.5, 4.2 Hz, H-2'), 2.34 (1H, d, *J* 12.3 2.4 Hz, H-6'$_{ax}$), 1.60-1.28 (5H, m), 1.57 (3H, s, gem CH_3), 1.51 (3H, s, gem CH_3), 1.24 (3H, t, *J* 7.1 Hz, CH_2CH_3), 0.90 (1H, dddd, *J* 12.5, 12.5, 12.5, 2.6 Hz, H-4'$_{ax}$), 0.84 (3H, d, *J* 6.3 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 155.6 (C), 147.8 (C), 133.2 (C), 131.6 (C), 128.0 (CH), 127.3 (CH), 127.1 (CH), 125.6 (CH), 125.4 (CH), 125.2 (CH), 124.7 (CH), 61.6 (CH_2), 54.0 (CH), 40.7 (C), 34.8 (CH_2), 34.1 (CH_2), 33.3 (CH), 28.5 (CH_2), 26.9 (CH_3), 24.8 (CH_3), 22.4 (CH_3), 14.6 (CH_3); other quaternary carbon not observed; *m/z* (APcI) 367.2 (MH^+, 100%), 199.2 (25), 169.1 (39).

N'-{5-Methyl-2-[1-methyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]cyclohexyl} hydrazinecarboxylic acid ethyl ester 340

Platinum oxide (6.6mg, 27 μmol) was placed in a nitrogen flushed flask and ethanol (1.1 mL) and acetic acid (0.6 mL) were added. *N'*-[5-Methyl-2-(1-methyl-1-naphthalen-2-ylethyl)-cyclohexylidene]hydrazinecarboxylic acid ethyl ester (**339**) (0.40g, 1.1 mmol) was added, the flask was charged with hydrogen, and stirring was continued for 48 hours at ambient temperature. The reaction mixture was filtered through celite® and the filtrate was neutralised with saturated sodium bicarbonate solution. Diethyl ether (25mL) was added and the organic layer was collected. The aqueous layer was further extracted with diethyl ether (2 x 25 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **340** as a mixture of diastereoisomers. Separation and purification by column chromatography on silica, eluting with diethyl ether/light petroleum (20:80), afforded diastereoisomer **340a** (0.21g, 51%) as a colourless solid and **340b** (0.12g, 28%) as a colourless solid.

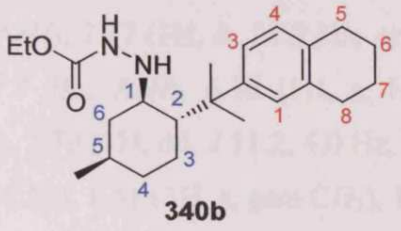
(1*S*, 2*S*, 5*R*)-Diastereoisomer 340a



mp 68-70°C; $[\alpha]_D^{19}$ +1.0° (*c* 1.03, $CHCl_3$); Found 373.2852 (MH^+ $C_{23}H_{36}N_2O_2$ requires 373.2850); ν_{max} (nujol)/cm^{-1} 3331 (NH), 1731 (C=O), 1504, 1246, 827; δ_H (400 MHz, MeOD) 7.10 (2H, m, Ar*H*), 6.90 (1H, d, *J* 8.4 Hz, Ar*H*), 4.04 (2H, q, *J* 6.9 Hz, OCH_2CH_3), 3.25 (1H, br, H-1'), 2.68 (4H, d, *J* 16.5 Hz, $ArCH_2$), 1.84 (1H, br, H-2'), 1.82-1.69 (2H, m, H-4_{ax}, H-4_{eq}), 1.73 (4H, m, $ArCH_2CH_2$), 1.52 (3H, m, H-5', H-$6'_{eq}$, H-$6'_{ax}$), 1.44 (3H, s, gem CH_3), 1.34 (3H, s, gem CH_3), 1.20 (3H, t, *J* 6.9 Hz, OCH_2CH_3), 0.84-0.73 (2H, m, H-$3'_{ax}$, H-$3'_{eq}$), 0.78 (3H, d, *J* 6.4 Hz, $CHCH_3$); δ_C (100 MHz, MeOD) 156.6 (C), 144.1 (C), 134.3 (C), 132.3 (C), 126.7

(CH), 125.7 (CH), 122.3 (CH), 58.9 (CH_2), 55.0 (CH), 50.7 (CH), 37.7 (C), 36.7 (CH_2), 34.5 (CH_2), 27.8 (CH_2), 27.0 (CH_2), 26.5 (CH_3), 24.6 (CH_3), 23.8 (CH), 21.7 (CH_2), 21.6 (CH_2), 20.6 (CH_2), 19.9 (CH_3), 12.1 (CH_3); *m/z* (APcI) 373.0 (MH^+, 100%).

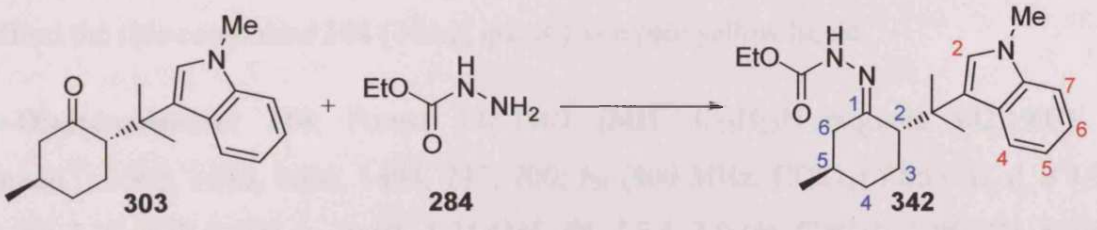
(1*R*, 2*S*, 5*R*)-Diastereoisomer 340b



340b

mp 42-44°C; $[\alpha]_D^{20}$ –31.3° (*c* 0.53, $CHCl_3$); Found 373.2852 (MH^+ $C_{23}H_{36}N_2O_2$ requires 373.2850); ν_{max} (nujol)/cm^{-1} 3331 (NH), 1718 (C=O), 1501, 1265, 827; δ_H (400 MHz, MeOD) 7.13 (1H, d, *J* 7.8 Hz, H-3'''), 7.11 (1H, s, H-1'''), 6.95 (1H, d, *J* 7.8 Hz, H-4'''), 4.00 (2H, q, *J* 6.4 Hz, OCH_2CH_3), 2.70 (5H, m, H-1', $ArCH_2$), 1.96-1.69 (4H, m), 1.75 (4H, m, $ArCH_2CH_2$), 1.43 (3H, s, gem CH_3), 1.37-1.12 (2H, m), 1.16 (3H, t, *J* 6.4 Hz, OCH_2CH_3), 1.12 (3H, s, gem CH_3), 0.92 (1H, dddd, *J* 12.9, 12.9 12.9, 2.9 Hz, H-4'$_{ax}$), 0.86 (3H, d, *J* 6.4 Hz, $CHCH_3$), 0.68 (1H, ddd, *J* 11.9, 11.9, 11.9 Hz, H-6'$_{ax}$); δ_C (100 MHz, MeOD) 147.2 (C), 135.1 (C), 132.7 (C), 127.3 (CH), 124.7 (CH), 120.9 (CH), 60.0 (CH), 59.0 (CH_2), 47.5 (CH), 38.4 (CH_2), 37.1 (C), 33.4 (CH_2), 29.4 (CH), 29.3 (CH_3), 27.6 (CH_2), 26.9 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 21.5 (CH_2), 19.7 (CH_3), 18.2 (CH_3), 11.9 (CH_3); other quaternary carbon not observed; *m/z* (APcI) 373.0 (MH^+, 100%);

***N*'-{5-Methyl-2-[1-methyl-1-(1-methyl-1*H*-indol-3-yl)ethyl]cyclohexylidene}hydrazine-carboxylic acid ethyl ester 342**

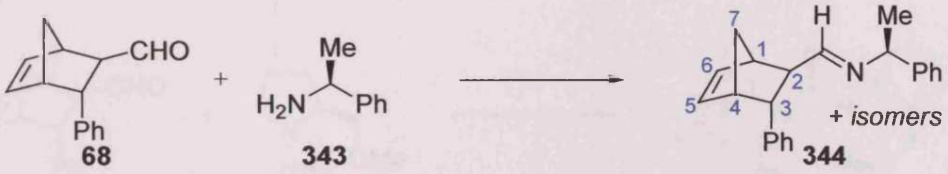


303 **284** **342**

Acetic acid (0.6 mL, 10.4 mmol) was added to a solution of 8-(*N*-methyl-1*H*-indol-3-yl) menthone (**303**) (4.00g, 14.1 mmol) in ethanol (20 mL). Ethyl carbazate (**284**) (2.06g, 19.8 mmol) was added and stirring was continued at ambient temperature for 48 hours. Water (30 mL) was added and the aqueous solution was extracted with ethyl acetate (2 x 30 mL). The

combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography on silica, eluting with diethyl ether/light petroleum (40:60), afforded the *title compound* **342** (3.92g, 81%) as a pale solid; mp 100-102°C; $[\alpha]_D^{20}$ –18.8° (*c* 1.01, $CHCl_3$); Found 370.2490 (MH^+ $C_{22}H_{31}N_3O_2$ requires 370.2489); ν_{max} (nujol)/cm^{-1} 3246 (NH), 1687 (C=O), 1609 (C=N), 1537, 1341, 1220, 731; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 7.7 Hz, Ar*H*), 7.17 (1H, d, *J* 7.7 Hz, Ar*H*), 7.08 (1H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 6.95 (1H, dd, *J* 7.7, 7.7 Hz, Ar*H*), 6.76 (1H, s, H-2'''), 4.18 (2H, q, *J* 6.8 Hz, OCH_2CH_3), 3.61 (3H, s, NCH_3), 2.79 (1H, dd, *J* 11.2, 4.0 Hz, H-2'), 2.36 (1H, br, H-6'), 1.67-1.40 (4H, m), 1.61 (3H, s, gem CH_3), 1.51 (3H, s, gem CH_3), 1.34-0.81 (2H, m), 1.24 (3H, t, *J* 6.8 Hz, CH_2CH_3), 0.81 (3H, d, *J* 5.7 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 212.3 (C=O), 156.7 (C=N), 137.7 (C), 126.7 (C), 126.1 (CH), 124.1 (C), 121.5 (CH), 120.8 (CH), 118.2 (CH), 109.4 (CH), 61.5 (CH_2), 52.1 (CH), 38.1 (C), 34.9 (CH_2), 34.2 (CH_2), 33.4 (CH), 32.6 (CH_3), 28.9 (CH_2), 27.6 (CH_3), 24.2 (CH_3), 22.4 (CH_3), 14.7 (CH_3); *m/z* (APcI) 370 (MH^+, 100%), 173 (6), 172 (42).

(3-Phenylbicyclo[2.2.1]hept-5-en-2-ylmethylene)-(1-phenylethyl)amine 344



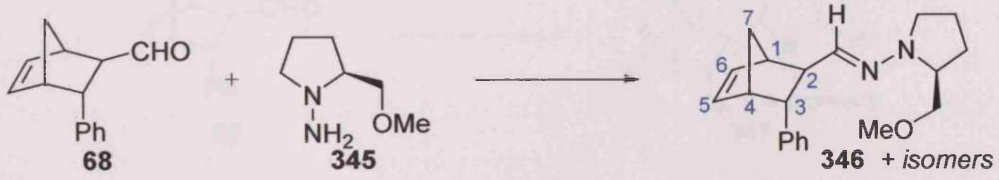
5-(-)-α-Methylbenzylamine (**343**) (10mg, 89 μmol) was added to a stirred solution of 3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**68**) (16mg, 81 μmol) in dichloromethane (0.5 mL) containing 4Å molecular sieves. Stirring was continued for 4 hours at room temperature, the solution was filtered through glass wool and the filtrate was reduced *in vacuo* to afford the *title compound* **344** (24mg, quant.) as a pale yellow liquid.

***Exo*-Diastereoisomer 344**; Found 302.1901 (MH^+ $C_{22}H_{23}N$ requires 302.1903); ν_{max} (film/cm^{-1}) 3062, 1660, 1600, 1494, 731, 700; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, d, *J* 4.9 Hz, *H*C=N), 7.30-7.07 (10H, m, Ar*H*), 6.24 (1H, dd, *J* 5.4, 3.0 Hz, C=C*H*), 5.95 (1H, dd, *J* 5.4, 2.6 Hz, C=C*H*), 4.27 (1H, q, *J* 6.7 Hz, $CHCH_3$), 3.49 (1H, dd, *J* 4.9, 4.9 Hz, H-3'), 3.13 (1H, br, C=CHC*H*), 2.89 (1H, br, C=CHC*H*), 2.47 (1H, ddd, *J* 4.9, 4.9, 1.2 Hz, H-2'), 1.64 (1H, br, CH*H*), 1.47 (1H, br, C*H*H), 1.40 (3H, d, *J* 6.7 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 166.0 (CH), 145.3 (C), 143.7 (C), 137.2 (CH), 137.1 (0.72CH), 135.7 (0.28CH), 128.5 (CH), 128.4

(CH), 128.0 (CH), 126.7 (CH), 126.5 (CH), 126.0 (CH), 69.6 (CH), 53.6 (CH), 52.2 (CH), 48.3 (CH), 47.9 (CH), 47.2 (CH_2), 24.9 (CH_3); *m/z* (APcI) 302 (M^+, 24%), 236 (100), 162 (81).

***Endo*-Diastereoisomer 344**; Found 302.1901 (MH^+ $C_{22}H_{23}N$ requires 302.1903); ν_{max} (film/cm^{-1}) 3062, 1660, 1600, 1494, 731, 700; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 4.5 Hz, *H*C=N), 7.30-7.07 (10H, m, Ar*H*), 6.31 (1H, dd, *J* 5.6, 3.2 Hz, C=C*H*), 6.08 (0.29H, dd, *J* 5.6, 2.7 Hz, C=C*H*), 6.03 (0.71H, dd, *J* 5.6, 2.7 Hz, HC=C*H*), 4.19 (1H, q, *J* 6.5 Hz, C*H*CH_3), 3.03 (2H, m, H-3', C=CHC*H*), 2.89 (1H, br, C=CHC*H*), 2.74 (0.7H, br, H-2'), 2.67 (0.3H, br, H-2'), 1.70-1.37 (2H, m, CH*H*, C*H*H), 1.43 (3H, d, *J* 6.5 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 166.7 (CH), 144.4 (C), 138.8 (0.31CH), 138.6 (0.69CH), 134.4 (0.68CH), 134.3 (0.32CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 126.7 (CH), 126.6 (CH), 125.9 (CH), 69.4 (CH), 53.9 (CH), 52.2 (CH), 48.2 (CH), 47.9 (CH), 47.3 (CH_2), 25.0 (CH_3); other quaternary carbon not observed; *m/z* (APcI) 302 (M^+, 24%), 236 (100), 162 (81).

(2-Methoxymethylpyrrolidin-1-yl)-(3-phenylbicyclo[2.2.1]hept-5-en-2-ylmethylene)-amine 346



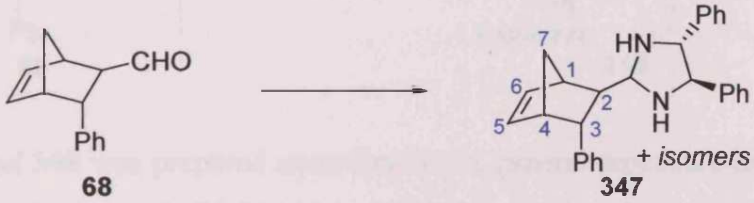
(*S*)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (**345**) (12mg, 89 μmol) was added to a stirred solution of 3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**68**) (16mg, 81 μmol) in dichloromethane (0.5 mL) containing 4Å molecular sieves. Stirring was continued for 2 hours at room temperature, the solution was filtered through glass wool and the filtrate was reduced *in vacuo* to afford the *title compound* **346** (25mg, quant.) as a yellow liquid.

***Exo*-Diastereoisomer 346**; Found 311.2116 (MH^+ $C_{20}H_{26}N_2O$ requires 311.2118); ν_{max} (film/cm^{-1}) 3051, 1600, 1494, 1117, 738, 702; δ_H (400 MHz, $CDCl_3$) 7.15 (5H, m, Ar*H*), 6.73 (1H, d, *J* 5.8 Hz, *H*C=N), 6.24 (1H, dd, *J* 5.5, 3.1 Hz, C=C*H*), 5.92 (1H, dd, *J* 5.5, 2.7 Hz, C=C*H*), 3.40 (2H, d, *J* 6.9 Hz, CH_2OCH_3), 3.36-3.18 (3H, m, H-3", NCH_2), 3.28 (3H, s, OCH_3), 3.08 (1H, br, C=CHC*H*), 2.76 (1H, br, C=CHC*H*), 2.67 (1H, tt, *J* 6.9, 6.9 Hz, NC*H*CH_2), 2.43 (1H, ddd, *J* 5.8, 5.8, 1.6 Hz, H-2"), 1.84-1.47 (6H, m); δ_C (100 MHz, $CDCl_3$)

144.2 (C), 141.6 (0.72CH), 141.4 (0.28CH), 137.4 (0.75CH), 137.3 (0.25CH), 135.2 (CH), 128.0 (CH), 127.8 (CH), 125.7 (CH), 74.6 (CH_2), 59.3 (CH_3), 51.5 (CH), 50.3 (CH_2), 50.0 (CH), 49.2 (CH), 49.1 (CH), 48.2 (CH), 47.2 (CH_2), 26.5 (CH_2), 22.1 (CH_2); *m/z* (APcI) 311.2 (MH^+, 100%), 245.2 (26).

***Endo*-Diastereoisomer 346**; Found 311.2116 (MH^+ $C_{20}H_{26}N_2O$ requires 311.2118); ν_{max} (film/cm^{-1}) 3051, 1600, 1494, 1117, 738, 702; δ_H (400 MHz, $CDCl_3$) 7.15 (5H, m, Ar*H*), 6.32 (2H, m, *H*C=N, C=C*H*), 6.11 (0.7H, dd, *J* 5.6, 2.8 Hz, C=C*H*), 6.08 (0.3H, dd, *J* 5.6, 2.8 Hz, C=C*H*), 3.40-3.23 (7H, m, OCH_3, CH_2OCH_3, NCH_2), 3.13 (1H, br, H-3"), 2.95 (1H, br, C=CHC*H*), 2.85 (2H, m, C=CHC*H*, H-2"), 1.84-1.47 (7H, m); δ_C (100 MHz, $CDCl_3$) 144.9 (C), 142.3 (0.73CH), 142.2 (0.27CH), 138.6 (0.72CH), 138.5 (0.28CH), 134.8 (0.30CH), 134.7 (0.70CH), 128.3 (CH), 127.4 (CH), 125.7 (CH), 74.7 (CH_2), 59.3 (CH_3), 51.2 (CH), 50.4 (CH_2), 49.9 (CH), 49.6 (CH), 49.5 (CH), 48.4 (CH), 47.1 (CH_2), 29.7 (CH_2), 22.2 (CH_2); *m/z* (APcI) 311.2 (MH^+, 100%), 245.2 (26).

(*R*,*R*)-4,5-Diphenyl-2-(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)imidazolidine 347



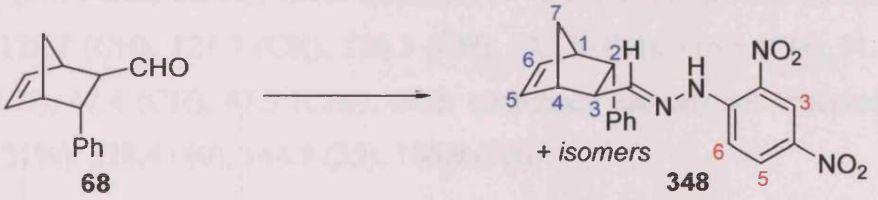
(*R*,*R*)-1,2-Diphenylethylene diamine (19mg, 89 μmol) was added to a stirred solution of 3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**68**) (16mg, 81 μmol) in dichloromethane (0.5 mL) containing 4Å molecular sieves. Stirring was continued for 2 hours at room temperature, the solution was filtered through glass wool and the filtrate was reduced *in vacuo* to afford the *title compound* **347** (32mg, quant.) as a yellow liquid.

***Exo*-Diastereoisomer 347**; Found 393.2322 (MH^+ $C_{28}H_{28}N_2$ requires 393.2325); ν_{max} (film/cm^{-1}) 1654, 1601, 1494, 737, 699; δ_H (400 MHz, $CDCl_3$) 7.42-6.87 (15H, m, Ar*H*), 6.35 (1H, dd, *J* 5.2, 3.0 Hz, C=C*H*), 5.87 (1H, dd, *J* 5.2, 2.7 Hz, C=C*H*), 4.32 (1H, d, *J* 8.3 Hz, H-2), 4.10-3.91 (2H, m, H-4, H-5), 3.26 (1H, br, H-3'), 2.95 (2H, m, C=CHC*H*), 1.82 (2H, m, H-2', C*H*H), 1.47 (1H, br, CH*H*); δ_C (100 MHz, $CDCl_3$) 144.2 (C), 143.2 (C), 141.2 (C), 137.6 (CH), 134.8 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.7 (CH), 126.2 (CH), 80.3 (CH), 71.4 (CH), 69.0 (CH), 53.5 (CH), 49.8 (CH),

48.9 (CH), 47.8 (CH_2), 46.3 (CH); *m/z* (APcI) 393.2 (MH^+, 88%), 327.1 (100), 196.0 (64), 106.2 (36).

***Endo*-Diastereoisomer 347**; Found 393.2322 (MH^+ $C_{28}H_{28}N_2$ requires 393.2325); ν_{max} (film/cm^{-1}) 1654, 1601, 1494, 737, 699; δ_H (400 MHz, $CDCl_3$) 7.42-6.87 (15H, m, Ar*H*), 6.21 (1H, dd, *J* 5.4, 2.6 Hz, C=C*H*), 6.15 (1H, dd, *J* 5.4, 2.7 Hz, C=C*H*), 4.40 (1H, d, *J* 8.3 Hz, H-2), 4.10-3.78 (2H, m, H-4, H-5), 3.26 (1H, br, H-3'), 3.06 (1H, br, C=CHC*H*), 2.79 (1H, br, C=CHC*H*), 1.82 (2H, m, H-2', C*H*H), 1.47 (1H, br, CH*H*); δ_C (100 MHz, $CDCl_3$) 145.4 (C), 143.3 (C), 141.5 (C), 139.0 (CH), 134.5 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.1 (CH), 127.4 (CH), 126.9 (CH), 126.8 (CH), 126.6 (CH), 126.0 (CH), 80.6 (CH), 71.3 (CH), 69.6 (CH), 53.6 (CH), 50.4 (CH), 48.9 (CH), 47.7 (CH_2), 46.6 (CH); *m/z* (APcI) 393.2 (MH^+, 88%), 327.1 (100), 196.0 (64), 106.2 (36).

N-(2,4-Dinitrophenyl)-N'-(3-phenylbicyclo[2.2.1]hept-5-en-2-ylmethylene)hydrazine 348



The *title compound* **348** was prepared according to the general procedure in *Section* **5.2.d** for the DNPH derivatisation of Diels-Alder adducts. 3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**68**) was reacted with 2,4-dinitrophenylhydrazine to provide compound **348**. Purification by flash chromatography on silica, eluting with ethyl acetate/light petroleum (10:90), afforded the *title compound* **348** as a yellow powder; Chiral HPLC analysis using a Chiralcel OD-R column, wavelength 215 nm, eluting with acetonitrile/water (80:20), flow rate of 0.5 mL/min, separated the chiral sample, retention times of 30.7 and 36.5 minutes (*endo*-diastereoisomers), 41.8 and 51.4 minutes (*exo*-diastereoisomers) (see *Appendix* **A7**, page 274).

***Exo*-Diastereoisomer 348**; λ_{max} 215 nm (EtOH); mp 160-162°C; Found 379.1402 (MH^+ $C_{20}H_{18}N_4O_4$ requires 379.1401); ν_{max} (nujol/cm^{-1}) 3289 (NH), 1618 (C=N), 1586, 1518, 1502, 1334, 833, 743, 701; δ_H (400 MHz, $CDCl_3$) 9.05 (1H, d, *J* 2.5 Hz, H-3'), 8.22 (1H, dd, *J* 9.7, 2.5 Hz, H-5'), 7.85 (1H, d, *J* 9.7 Hz, H-6'), 7.66 (1H, d, *J* 6.1 Hz, N=C*H*), 7.21 (5H, m, Ar*H*), 6.33 (1H, dd, *J* 5.6, 3.1 Hz, C=C*H*), 6.03 (1H, dd, *J* 5.6, 2.8 Hz, C=C*H*), 3.52 (1H, dd, *J* 4.8,

3.7 Hz, H-3"), 3.21 (1H, br, C=CHC*H*), 2.99 (1H, br, C=CHC*H*), 2.63 (1H, ddd, *J* 6.1, 4.8, 1.4 Hz, H-2"), 1.71 (1H, br, CH*H*), 1.60 (1H, ddd, *J* 9.4, 9.4, 1.6 Hz, C*H*H); δ_C (100 MHz, $CDCl_3$) 154.9 (CH), 145.0 (C), 142.7 (C), 137.8 (C), 136.7 (CH), 135.9 (CH), 128.8 (C), 128.7 (CH), 128.2 (CH), 127.8 (CH), 126.4 (CH), 123.5 (CH), 116.6 (CH), 49.9 (CH), 48.9 (CH), 48.7 (CH), 48.1 (CH), 47.5 (CH_2); *m/z* (APcI) 378.9 (MH^+, 51%), 338.4 (40), 144.9 (35), 106.9 (100).

***Endo*-Diastereoisomer 348**; λ_{max} 215 nm (EtOH); mp 160-162°C; Found 379.1402 (MH^+ $C_{20}H_{18}N_4O_4$ requires 379.1401); ν_{max} (nujol/cm^{-1}) 3289 (NH), 1618 (C=N), 1586, 1518, 1502, 1334, 833, 743, 701; δ_H (400 MHz, $CDCl_3$) 11.04 (1H, s, N*H*), 9.05 (1H, d, *J* 2.3 Hz, H-3'), 8.22 (1H, dd, *J* 9.6, 2.3 Hz, H-5'), 7.83 (1H, d, *J* 9.6 Hz, H-6'), 7.18 (6H, m, N=C*H*, Ar*H*), 6.44 (1H, dd, *J* 5.5, 3.1 Hz, C=C*H*), 6.14 (1H, dd, *J* 5.5, 2.6 Hz, C=C*H*), 3.09 (1H, br, C=CHC*H*), 3.07 (2H, br, C=CHC*H*, H-3"), 2.78 (1H, br, H-2"), 1.81 (1H, br, CH*H*), 1.61 (1H, br, C*H*H); δ_C (100 MHz, $CDCl_3$) 155.5 (CH), 145.0 (C), 143.6 (C), 139.6 (CH), 134.1 (CH), 130.0 (CH), 128.7 (CH), 127.3 (CH), 126.3 (CH), 123.5 (CH), 116.6 (CH), 51.1 (CH), 49.0 (CH), 48.4 (CH), 47.4 (CH), 47.3 (CH_2); other quaternary carbons not observed; *m/z* (APcI) 378.9 (MH^+, 51%), 338.4 (40), 144.9 (35), 106.9 (100).

Chapter 6: References

6.1 References

[1] Lord Todd, lecture "Chemie in Vergangenheit und Gegenwart" delivered on the occasion of the presentation of the Goldenes Doktordiplom, Universität Frankfurt, October 16, 1981.

[2] Movassaghi, M.; Jacobsen, E. N. *Nature* **2002**, *298*, 1904.

[3] For more information see; www.nobel.se/chemistry/laureates/2001/

[4] Williams, J. M. J. *Catalysis in Asymmetric Synthesis*; Sheffield Academic Press, **1999**.

[5] For recent reviews on the use of organic compounds as asymmetric organocatalysts see: (a) Jarvo, E. R.; Miller, S. J. *Tetrahedron*, **2002**, *58*, 2481; (b) Dalko, P.I.; Moisan, L. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3726; (c) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 529.

[6] Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**.

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

[8] It has been estimated that the pK_a of acetone decreases from p$K_a \approx 20$ to p$K_a \approx 8$ after conversion to an iminium ion. Depending on the strength of the base, the rate of proton removal from the α-carbon increases by a factor of 10^5-10^8, see (a) Bender, M. L.; Williams, A. *J. Am. Chem. Soc.* **1966**, *88*, 2502; (b) Roberts, R.D.; Ferran, H. E.; Gula, M. J.; Spencer, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 7054.

[9] List, B. *Synlett* **2001**, *11*, 1675.

[10] Knoevenagel reaction, review: Tietze, L. F. In *Comprehensive Organic Synthesis*, Vol 2: Trost, B. M., Ed.; Pergamon Press: New York. **1991**, 341-394.

[11] Fubini, B.; Aréan, L. O. *Chem. Soc. Rev.* **1999**, *28*, 373.

[12] Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401.

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

[14] (a) Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds. German Patent DE 2102623, July 29, **1971**; (b) Hajos, Z.G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

[15] (a) Eder, U.; Sauer, G.; Wiechert, R. Optically active 1,5-Indanone and 1,6-Napthalenedione. German Patent DE 2014757, Oct 7, 1971; (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

[16] Several variations of this name are used in the literature.

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

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

[19] Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108.

[20] (a) Agami, C.; Meynier, F.; Puchot, C.; Guilhem, J.; Pascard, C *Tetrahedron* **1984**, *40*, 1031; (b) Agami, C.; Puchot, C.; Sevestre, H. *Tetrahedron Lett.* **1986**, *27*, 1501.

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

[22] (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911; (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

[23] Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.

[24] (a) Baldwin, J. E.; Lusch, M. J. *Tetrahedron*, **1982**, *38*, 2939; (b) Baldwin, J. E. *J. Chem. Soc. Commun.* **1976**, 734.

[25] Cycloaldolisation reactions are formally *Enolexo-* or *enolendo-exo-trig* processes. As all intramolecular aldolisations are by definition *exo-trig* processes, they are referred to simply as *Enolexo* or *enolendo* aldolisations.

[26] Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 2785.

[27] Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595.

[28] For a review on the catalytic asymmetric aldol reaction, see: (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1352; (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357; (c) Gröger, H.; Vogl, E.M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137; (d) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417.

[29] For an exception see: Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Org. Chem.* **1998**, *63*, 918.

[30] (a) Turner, J. M.; Bui, T.; Lerner, R. A.; Barbas III, C. F.; List, B. *Chem. Eur. J.* **2000**, *6*, 2772; (b) List, B.; Shabat, D.; Barbas III, C.F.; Lerner, R. A. *Chem. Eur. J.* **1998**, 881; (c) Barbas III, C. F.; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Bjornestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I. A.; Lerner, R. A. *Science* **1997**, *278*, 2085.

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

[32] List, B. *Tetrahedron* **2002**, *58*, 5573.

[33] List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573.

[34] Szöllősi, G.; London, G.; Balāspiri, L.; Somlai, C.; Bartōk, M. *Chirality* **2003**, *15*, S90.

[35] Notz, W.; List, B. *J. Am Chem. Soc.* **2000**, *122*, 7386.

[36] (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1995**, *34*, 1059; (b) Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

[37] Liu, H.; Peng, L.; Zhang, T.; Li, Y. *New J. Chem.* **2003**, *27*, 1159.

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

[39] Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620.

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

[41] For a review of enamine chemistry see: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.

[42] Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, *8*, 1245.

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

[44] Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220.

[45] Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262.

[46] Córdova, A.; Notz, W.; Barbas III, C. F. *Chem. Commun.* **2002**, 3024.

[47] Peng, Y.-Y.; Din, Q.-P.; Li, Z.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3871.

[48] Loh, T.-P.; Feng, L.-C.; Yang, H.-Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741.

[49] Kotrusz, P.; Kmentová, I.; Gotov, B.; Toma, Š.; Solčániová, E. *Chem. Commun.* **2002**, 2510.

[50] Benaglia, M.; Celentano, G.; Cozzi, F. *Adv. Synth. Catal.* **2001**, *343*, 171.

[51] Chowdari, N. S.; Ramachary, D. B.; Córdova, A.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 9591.

[52] Peng, L.; Liu, H.; Zhang, T.; Zhang, F.; Mei, T.; Li., Y.; Li, Y. *Tetrahedron Lett.* **2003**, *44*, 5107.

[53] Rankin, K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem. A.* **2002**, *106*, 5155.

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

[55] Bøgevig, A.; Gothelf, K. V.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 5652.

[56] (a) Baylis, A. B.; Hillman, M. E. D. German Patent DE2155113, **1972**; (b) Baylis, A. B.; Hillman, M. E. D. *Chem. Abstr.* **1972**, *77*, 34174.

[57] (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (b) Langer, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3049.

[58] Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2002**, *43*, 127.

[59] (a) Kloetzel, M. C., *Organic Reactions*, Vol. IV: Wiley. **1948**, Chapter 1; (b) Bonnesen, P. V.; Puckett, C. L.; Honeychuck, R. V.; Hersch, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 607.

[60] Diels, O.; Alder, K, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

[61] Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

[62] Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

[63] For a review on asymmetric Diels-Alder reactions see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1668; (b) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289.

[64] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

[65] Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas III, C. F.; *Tetrahedron Lett.* **2002**, *43*, 3817.

[66] Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 6743.

[67] Weinreb, S. M. *Comprehensive Organic Synthesis*, Vol. V: Pergamon Press: Oxford. **1991**, 401.

[68] Alder, K. *Neuere Methoden der Praparativen Organischen Chemie*, Verlag Chemie, Berlin, **1943**, 251.

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

[70] Recent examples include: (a) Xiong, H.; Hsung, R. P.; Shen, L.; Haln, J. M. *Tetrahedron Lett.* **2002**, *43*, 4449; (b) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174; (c) Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001**, *3*, 425.

[71] Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058.

[72] Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449.

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

[74] Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923.

[75] Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782.

[76] Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, *33*, 1587.

[77] Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2596.

[78] List, B.; Castello, C. *Synlett* **2001**, *11*, 1687.

[79] Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4233.

[80] For reviews on the Mannich reaction see: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1044; (b) Kleinnmann, E. F. In *Comprehensive Organic Synthesis*, Vol. II: Trost, B. M., Ed.; Pergamon Press: New York. **1991**, Chapter 4.1.

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

[82] Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208

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

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

[85] Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas III, C. F. *Tetrahedron Lett.* **2001**, *42*, 199.

[86] Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842.

[87] Córdova, A.; Watanabe, S.-I.; Tanaka, F.; Notz, W.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866.

[88] Córdova, A. *Synlett* **2003**, 1651.

[89] Córdova, A.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 7749.

[90] Watanabe, S.-I.; Córdova, A.; Tanaka, F.; Barbas III, C. F. *Org. Lett.* **2002**, *4*, 4519.

[91] Córdova, A.; Barbas III, C. F. *Tetrahedron Lett.* **2003**, *44*, 1923.

[92] Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

[93] McMurry, J. In *Organic Chemistry*, 4th Ed; Brooks/Cole Publishing. **1996**, 914-917.

[94] Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford. **1992**.

[95] For reviews on the Michael reaction see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis*, **2001**, 171; (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033; (c) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*, Vol. III: Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin. **1999**, 1105-1120; (d)Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*, Vol. III: Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin. **1999**, 1121-1139.

[96] Stork, G.; Brizzolara, A.; Landesman, H.; Smuszkovicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

[97] (a) Martens, J.; Luebben, S. *Tetrahedron* **1991**, *47*, 1205; (b) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta.* **1982**, *65*, 1637; (c) Yamada, S.; Hiroi, K.; Aiwa, K. *Tetrahedron Lett.* **1969**, *48*, 4233.

[98] Seebach, D.; Golinski, J. *Helv. Chim. Acta.* **1981**, *64*, 1413.

[99] For a review see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

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

[101] Enders, D.; Seki, A. *Synlett* **2002**, 26.

[102] Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.

[103] Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559.

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

[105] Betancort, J. M.; Barbas III, C. F. *Org. Lett.* **2001**, *3*, 3737.

[106] Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151.

[107] Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.

[108] Yamaguchi, M.; Yokota, N.; Minami, T. *J. Am. Chem. Soc.* **1991**, 1088.

[109] (a) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223; (b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520; (c) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233; (d) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176.

[110] Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331.

[111] Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 661.

[112] Friedel, C.; Crafts, J. M. *Bull. Soc. Chim. Fr.* **1877**, *27*, 530.

[113] (a) Olah, G. A.; Krishnamurti, R.; Prakesh, G. K. S. In *Comprehensive Organic Synthesis*, Vol. III: Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, Chapter 1.8; (b) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry*; Marcel Dekker: New York, **1984**; (c) *Friedel Crafts Chemistry*; Olah, G. A., Ed.; Wiley: New York, **1973**; (d) *Friedel-Crafts and Related Reactions*, Vol. I-IV; Olah, G. A., Ed.; Wiley-Interscience: New York, **1963-65**.

[114] (a) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517; (b) Saaby, S.; Fang, X. M.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4114; (c) Jensen, K. M.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 160.

[115] (a) Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry*, Vol. III; Springer-Verlag: Heidelberg, **1999**; (b) Strell, A.; Kalojanoff, R. *Chem. Ber.* **1954**, *87*, 1954.

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

[117] (a) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th Ed.; Thieme: Stuttgart; New York, **2001**; (b) (*S*)-Ketorolac: Guzman, A.; Yuste, F.; Toscano, R. A.; Young, J. M.; Vanhorn, A. R.; Muchowski, J. M. *J. Med. Chem.* **1986**, *29*, 589; (c) Viminol: Della Bella, D. *Boll. Chim. Farm.* **1972**, *111*, 5.

[118] Cipiciani, A.; Clementi, S.; Linda, P.; Marino, G.; Savelli, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1284.

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

[120] (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413; (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

[121] Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

[122] *Comprehensive Asymmetric Catalysis*, Vol. III: Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg. **1999**, Chapter 5, 121.

[123] (a) Hayashi, T. *Synlett* **2001**, 879; (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479; (c) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

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

[125] (a) Zoloft: McRae, A. L.; Brady, K. T. *Expert Opin. Pharmacotherapy* **2001**, *2*, 883; (b) Detrol: Hills, C. J.; Winter, S. A.; Balfour, J. A. *Drugs* **1998**, *55*, 813.

[126] Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2411.

[127] Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387.

[128] Heydorn, W. E. *Expert Opin. Invest. Drugs* **1999**, *8*, 417.

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

[130] (a) Birkinshaw, J. H.; Raistrick, H. *Biochem. J.* **1934**, *228*, 828; (b) Asano, M.; Kameda, Y. *J. Pharm. Soc. Jpn.* **1941**, *61*, 80.

[131] Pekdemir, T.; Tokunaga, S.; Ishigami, Y.; Hong, H.-J. *J. Surfactants Detergents* **2000**, *3*, 43.

[132] Yamazaki, S.; Suzuki, H.; Ishigami, Y. *Kagaku Gijutsu Hokoku* **1988**, *83*, 125.

[133] Laue, T.; Plagens, A. In *Named Organic Reactions*; Wiley: Chichester. **2000**, 232-236.

[134] Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas III, C. F. *J. Am. Chem. Soc.* **1997**, *119*, 8131.

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

[136] (a) Yet, L. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 875; (b) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561; (c) Arend, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2873; (d) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207; (e) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (f) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889; (g) Williams, R. M. In *Synthesis of Optically Active a-Amino Acids*; Pergamon: Oxford, **1989**.

[137] Reviews: (a) Genet, J.-P.; Greck, C.; Lavergne, D. In *Modern Amination Methods*: Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, **2000**, Chapter 3; (b) Greck, C.; Genet, J.-P. *Synlett* **1997**, 741; (c) Boche, G. In *Stereoselective Synthesis*, Vol. 9: Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, Germany, **1996**, 5133-5157; (d) Krohn, K. In *Organic Synthesis Highlights*; VCH: Weinheim, Germany, **1991**, 45-53.

[138] (a) Gennari, C.; Columbo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394; (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 6395; (c) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397; (d) Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923.

[139] (a) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595; (b) Yamishita, Y.; Ishitani, H.; Kobayashi, S. *J. Can. Chem.* **2000**, *78*, 666.

[140] Juhl. K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420.

[141] Duthaler, R. O. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 975.

[142] Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1790.

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

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

[145] Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 9922.

[146] (a) Enders, D.; Reinhold, U. *Liebigs Ann.* **1996**, 11; (b) Enders, D.; Reinhold, U. *Synlett* **1994**, 792.

[147] Gonzalez, I.; Jou, G.; Caba, J. M.; Albericio, F.; Lloyd-Williams, P.; Giralt, E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1427.

[148] (a) Suami, T.; Tadano, K.; Iimura, Y.; Yokoo, H. *J. Carbohydrate Chem.* **1986**, *5*, 1; (b) Merrer, Y. Le.; Dureault, A.; Gravier, C.; Languin, D.; Depezay, J. C. *Tetrahedron Lett.* **1985**, *26*, 319; (c) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984.

[149] (a) Hayashi, Y.; Kanayama, J.; Yamaguchi, J.; Shoji, M. *J. Org. Chem.* **2002**, *67*, 9443; (b) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767.

[150] (a) Colombo, L; Giacomo, M. D. *Tetrahedron Lett.* **1999**, *40*, 1977; (b) Review: Eliel, E. L. In *Asymmetric Synthesis 2A*; Morrison, J. D., Ed.; Academic Press: New York, **1983**, 125.

[151] Reviews: (a) Kanai, M.; Hamashima, Y.; Takamura, M.; Shibasaki, M. *J. Syn. Org. Chem.* **2001**, *59*, 766; (b) Mori, A.; Inoue, S. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, **1999**; 983.

[152] (a) Effenberger, F.; Null, V.; Ziegler, T. *Tetrahedron Lett.* **1992**, *33*, 5157; (b) Pederson, R. L.; Liu, K. K.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897.

[153] (a) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253; (b) Enders, D.; Bhushan, V. *Tetrahedron Lett.* **1988**, *29*, 2437; (c) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173-178, 183-194; (d) Enders, D. In *Asymmetric Synthesis*, Vol. III; Morrison, J. D., Ed; Academic Press: Orlando, **1984**, 275.

[154] For an enzymatic synthesis, see: Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11743.

[155] Zhong, G. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4247.

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

[157] Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293.

[158] (a) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1999**, *10*, 1843; (b) Cho, B. T.; Chun, Y. S. *J. Org. Chem.* **1998**, *63*, 5280; (c) Hanessian, H. In *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon: Oxford, **1983**.

[159] (a) Wills, M.; Tye, H. *J. Chem. Soc., Perkin Trans 1* **2001**, 1729; (b) In *Asymmetric Catalysis*: Sainsbury, M., Ed.; Elsevier. **2001**; (c) In *Catalytic Asymmetric Synthesis*, Second Edition; Ojima, I., Ed; VCH: New York. **2000**.

[160] Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, First Edition; VCH: New York. **1993**.

[161] Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*, First Edition; VCH: New York. **1993**.

[162] Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

[163] Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *96*, 876.

[164] Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.

[165] Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2603.

[166] Confalone, P. N.; Huie, E. M. *Org. Synth.* **1988**, *36*, 1.

[167] Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.

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

[169] (a) Otera, J. In *Modern Carbonyl Chemistry*; Wiley-VCH: Weinheim. **2000**; (b) Shambayati, S.; Schreiber, S.L. In *Comprehensive Organic Synthesis*; Trost, B.M. Ed.; Pergamon: Oxford. **1991**.

[170] Gao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979.

[171] (a) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M.D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290; (b) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.

[172] (a) Hawkins, J. M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657; (b) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794.

[173] Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917.

[174] (a) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412; (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.

[175] Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951.

[176] (a) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483; (b) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041; (c) Furata, K.; Maruyama, T.; Yamamoto, H. *Synlett* **1991**, 439.

[177] Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561.

[178] Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907.

[179] For recent reviews, see: (a) Jones, G. B. *Tetrahedron* **2001**, *57*, 7999; (b) Jones, G. B.; Chapman, B. J. *Synthesis* **1994**, 475.

[180] (a) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953; (b) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616.

[181] Jones, G.B.; Guzel, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2023.

[182] (a) Heck, R. F. In *Palladium Reagents in Organic Syntheses*; Academic Press: New York. **1985**; (b) Ryabov, A. D. *Synthesis* **1985**, 233; (c) Heck, R. F. *Org. React.* **1982**, *27*, 345; (d) Heck, R. F.; Dieck, H. A. *J. Am. Chem. Soc.* **1974**, *96*, 1133.

[183] (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513; (b) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708.

[184] Vangveravong, S.; Kanthasamy, A.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1998**, *41*, 4995.

[185] Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899.

[186] (a) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177; (b) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009.

[187] Dyker, G.; Körning, J.; Stirner, W. *Eur. J. Org. Chem.* **1998**, 149.

[188] Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095.

[189] Carruthers, W. In *Cycloaddition Reactions in Organic Chemistry*; Pergamon: Oxford. **1990**.

[190] Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1650.

[191] (a) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987; (b) Furata, K.; Kanematzu, A; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 7231; (c) Furata, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.

[192] Kishi, Y.; Aratani, M.; Fukuyama, F.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217.

[193] Danishefsky, S. J.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

[194] Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380.

[195] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

[196] Pikul, S.; Corey, E. J. *Org. Synth.* **1991**, *71*, 22.

[197] Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814.

[198] Rebiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 119.

[199] Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431.

[200] (a) Claire L. Jones, *Ph.D. Thesis, Cardiff University*, **2003**; (b) Lisa D. Harris, *Ph.D. Thesis, Cardiff University*, **2003**.

[201] Hall, A.; Harris, L. D.; Jones, C. L.; Jenkins, R, L.; Tomkinson, N. C. O. *Tetrahedron Lett.* **2003**, *44*, 111.

[202] Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992.

[203] Amendola, M. C.; Stockman, K. E.; Hoic, D. A.; Davis, W. M.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 7267.

[204] Ruiz-Lopez, M. F.; Assfield, X.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1993**, *115*, 8780.

[205] Corey, E. J.; Loh, T.–P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945.

[206] Gladysz, J. A.; Boone, B. J., *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 550.

[207] Hunter, C. A. *Chem. Soc. Rev.* **1994**, *23*, 101.

[208] Kutschy, P.; Dzurilla, M.; Takasugi, M.; Török, M.; Achbergerová, I.; Homzová, R.; Rácová, M. *Tetrahedron* **1998**, *54*, 3549.

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

[210] (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.

[211] Fleming, I. In *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: Chichester. **1976**.

[212] (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.

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

[214] Wolfe, S.; Mitchell, D. J.; Schlegal, H. B.; Minot, C.; Eisenstein, O. *Tetrahedron Lett.* **1982**, *23*, 615.

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

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

[217] For other explanations, see (a) Herschlag, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1990**, *112*, 1951; (b) Hudson, R. F. Hansell, D. P.; Wolfe, S.; Mitchell, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1406.

[218] Hoz, S.; Buncel, E. *Isr. J. Chem.* **1985**, *26*, 313, and references there-in.

[219] Cavill, J. L.; Peters, J.-U.; Tomkinson, N. C. O. *J. Chem. Soc., Chem. Commun.* **2003**, 728.

[220] Corey, E. J.; Gross, A. W. *J. Org. Chem.* **1985**, *50*, 5391.

[221] Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (See also references 171a, 172, 174a and 202).

[222] For information on Radley's products visit; www.Radleys.com

[223] Ort, O. *Org. Synth.* **1987**, *65*, 203.

[224] Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989.

[225] Oppolzer, W.; Loher, H. J. *Helv. Chim. Acta* **1981**, *64*, 2808.

[226] Binger, P.; Brinkmann, A.; Richter, W. J. *Tetrahedron Lett.* **1983**, *24*, 3599.

[227] (a) Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181; (b) Oppolzer, W.; Robbiani, C.; Battig, K. *Helv. Chim. Acta* **1980**, *63*, 2015.

[228] d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112.

[229] Jones, G. B.; Chapman, B. J. *Synlett* **1997**, 439.

[230] Whitesell, J. K.; Lawrence, R. M.; Chen, H. H. *J. Org. Chem.* **1986**, *51*, 4779.

[231] Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

[232] (a) Yanovskaya, L. A.; Kryshtal, G. V.; Kulganek, V. V. *Russ. Chem. Rev.* **1984**, *53*, 744; (b) Bergmann, E. D.; Ginsburg. D.; Pappo, R. *Org. React.* **1959**, *10*, 179.

[233] Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805.

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

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

[236] (a) Aggarwal, R.; Benedetti, F.; Berti, F.; Buchini, S.; Colombatti, A.; Dinon, F.; Galasso, V.; Norbedo, S. *Chem. Eur. J.* **2003**, *9*, 3132; (b) Benedetti, F.; Berti, F.; Colombatti, A.; Ebert, C.; Linda, P.; Tonizzo, F. *J. Chem. Soc., Chem. Commun.* **1996**, *12*, 1417.

[237] Marchand, P.; Le Borgne, M.; Duflos, M.; Robert-Piessard, S.; Le Baut, G.; Ahmadi, M.; Hartmann, R. W.; Palzer, M. *Pharm. Pharmacol. Commun.* **1998**, *4*, 211.

[238] Yang, C.-G.; Wang, J.; Tang, X.-X.; Jiang, B.; *Tetrahedron: Asymmetry* **2002**, *13*, 383.

[239] (a) Fé de la Torre, M.; Cruz Caballero, M.; Whiting, A. *Tetrahedron* **1999**, *55*, 8547 and references there-in; (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049 and references there-in.

[240] (a) Huenig, S. *Justus Liebigs Ann. Chem.* **1976**, 1039; (b) Huenig, S. *Tetrahedron Lett.* **1972**, 643.

[241] (a) El-Gazzar, A.-R. B. A.; Scholten, K.; Guo, Y.; Weissenbach, K.; Hitzler, M. G.; Roth, G.; Fischer, H.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, *14*, 1999; (b) Pei L.-W.; Peng, S.-Y.; Magrath, J. *Synthesis* **1995**, *4*, 435; (c) Majchrzak, M. W.; Bekhazi, M.; Tse-Sheepy, I.; Warkentin, J. *J. Org. Chem.* **1989**, *54*, 1842; (d) Palla, G.; Predieri, G.; Domicino, P.; Vignali, C.; Turner, W. *Tetrahedron* **1986**, *42*, 3649.

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

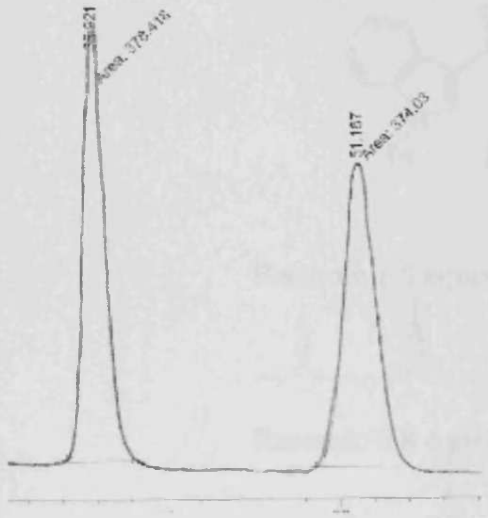
[243] Rosenblum, M.; Nayak, V.; DasGupta, S. K.; Longroy, A. *J. Am. Chem. Soc.* **1963**, *85*, 3874.

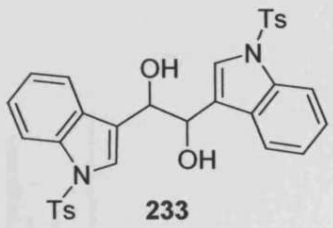
[244] Yang, D.; Xu, M.; Bian, M.-Y. *Org. Lett.* **2001**, *3*, 111.

Appendix A: Determination of Enantiomeric Excess

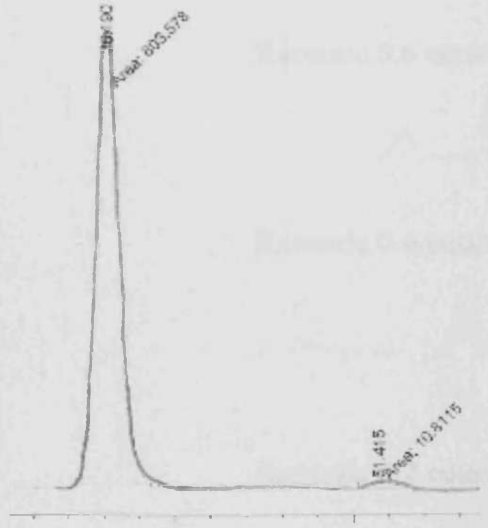
Appendix **A1**

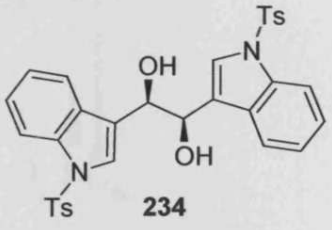
HPLC Traces of Compounds 233 and 234 to Determine ee





233



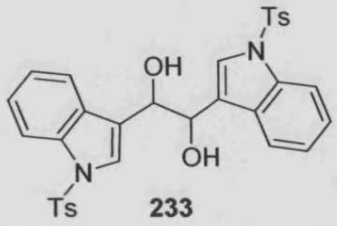


234

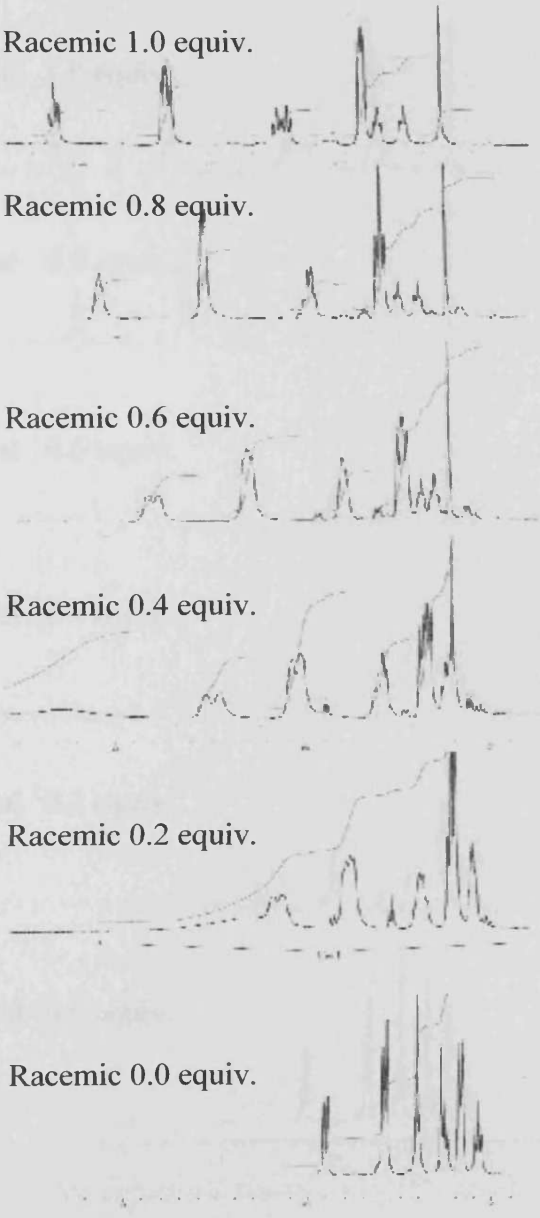
Chiral HPLC analysis using a Chiralpak AD column, detecting at wavelength 290 nm, eluting with hexanes/isopropanol (75:25); increased to hexanes/isopropanol (70:30) after 20 minutes, at 1.0 mL/min. Separated the chiral sample, t_1 = 36.2 min (98.7%); t_2 = 51.4 min (1.3%): ***97.4% ee****.*

Appendix **A2**

^{1}H NMR of Diol 233 on Addition of Eu(hfc)$_3$

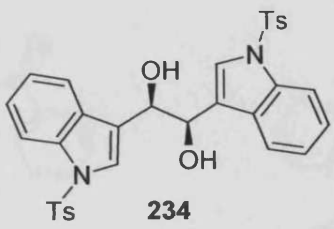


233

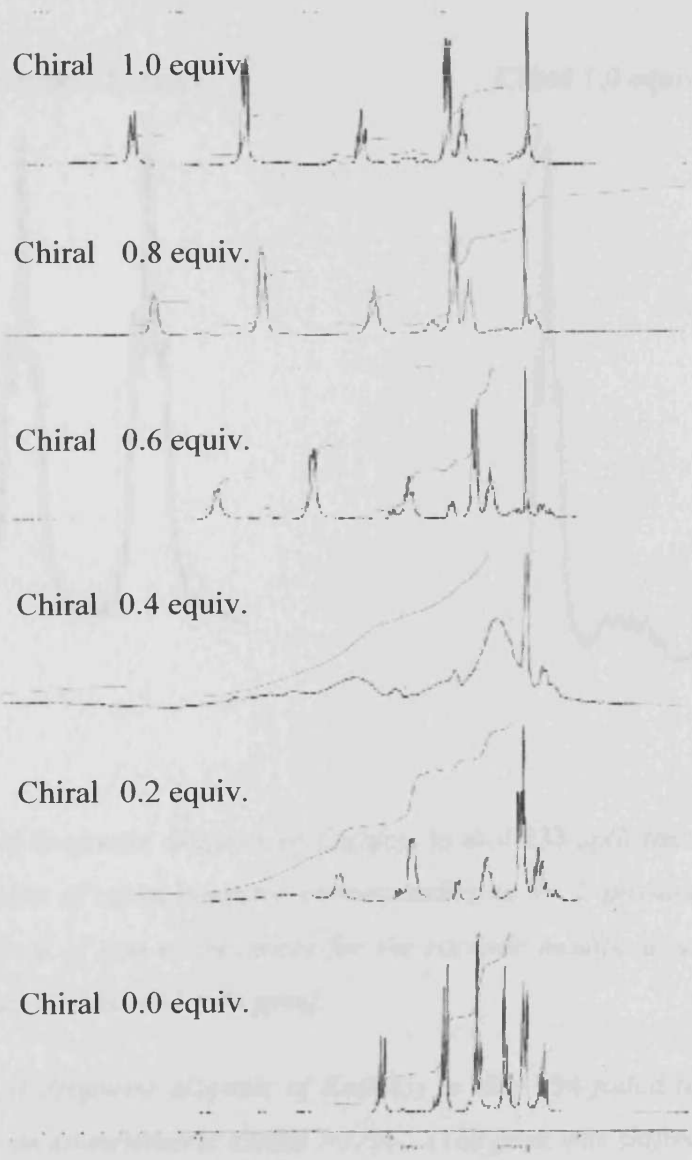


Appendix **A2**

^{1}H NMR of Diol 234 on Addition of Eu(hfc)$_3$

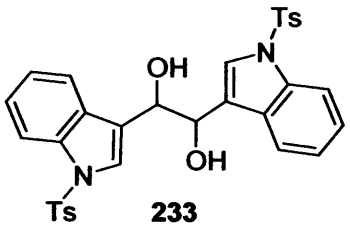


234

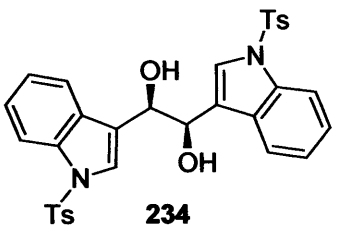


Appendix **A2**

^{1}H NMR of Diols 233 and 234 in Titration Experiment



233



234

Racemic 1.0 equiv.

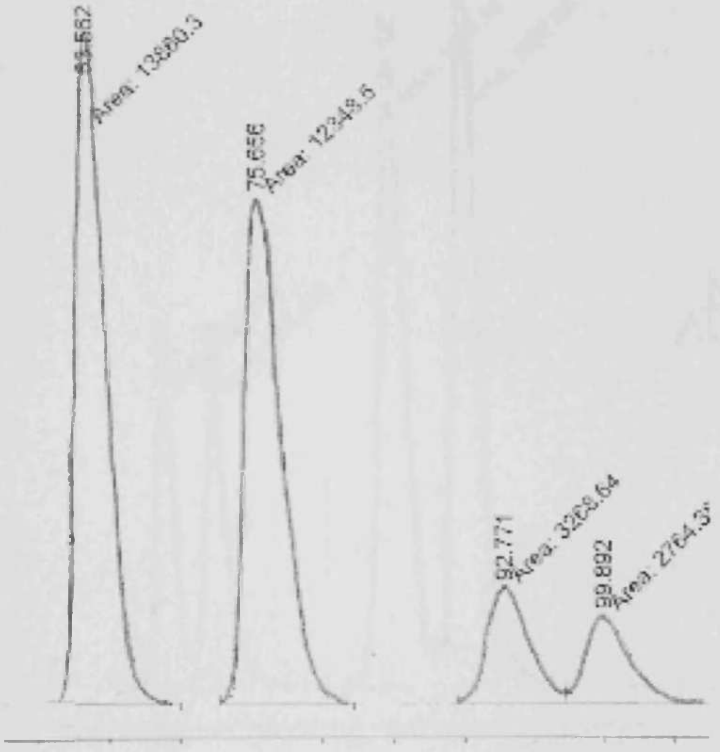
Chiral 1.0 equiv.

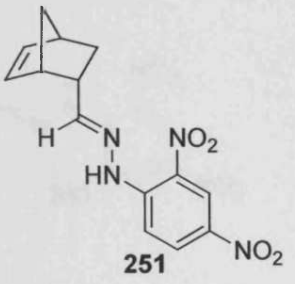
Successive addition of dropwise aliquots of Eu(hfc)$_3$ to diol **233** *split the signal at 6.92 ppm, into two double doublets of equal intensity, corresponding to the 5–position of the indole ring, confirming the presence of two enantiomers for the racemic modification of diol* **233**. *(The two peaks were shifted to 7.60 and 7.46 ppm).*

Successive addition of dropwise aliquots of Eu(hfc)$_3$ to diol **234** *failed to split the signal at 6.92 ppm, indicating an enantiomeric excess >97%. (The peak was shifted to 7.63 ppm).*

Appendix **A3**

HPLC Trace of Compound 251 to Determine ee



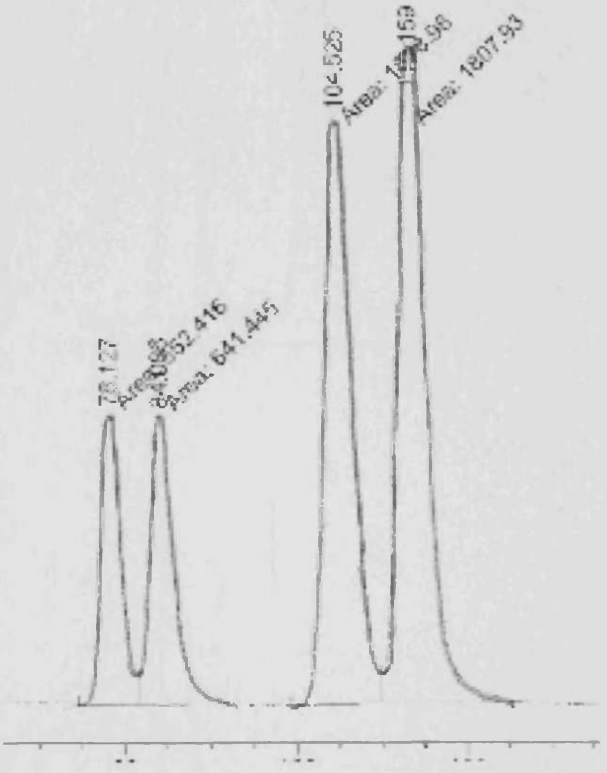


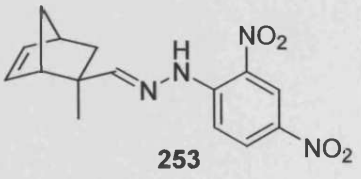
251

Chiral HPLC analysis using a Chiralcel OD column, detecting at wavelength 359 nm, eluting with hexanes/isopropanol (99:1), at 1.0 mL/min. Separated the chiral sample; t_1 = 63.6 min, t_2 = 75.7 min (endo-diastereoisomers); t_3 = 92.8 min, t_4 = 99.9 min (exo-diastereoisomers).

Appendix **A3**

HPLC Trace of Compound 253 to Determine ee



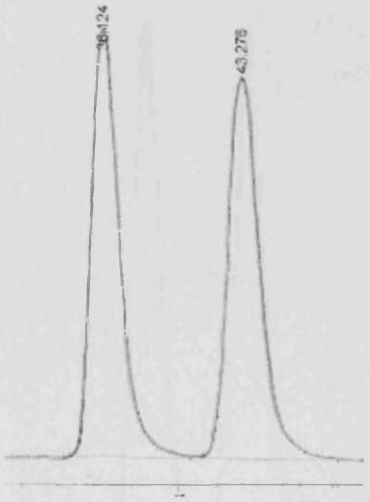


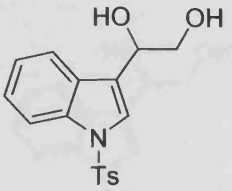
253

Chiral HPLC analysis using a Chiralcel OJ column, detecting at wavelength 359 nm, eluting with hexanes/isopropanol (99.2:0.8), at 0.7 mL/min. Separated the chiral sample; t_1 = 78.1 min, t_2 = 84.1 min (endo-diastereoisomers); t_3 = 104.5 min, t_4 = 113.2 min (exo-diastereoisomers).

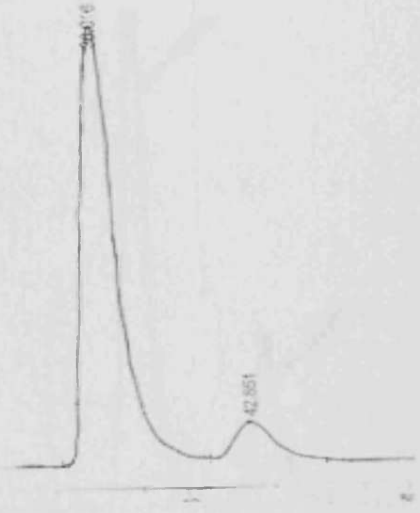
Appendix **A4**

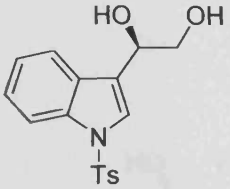
HPLC Traces of Compounds 261 and 267 to Determine ee





267



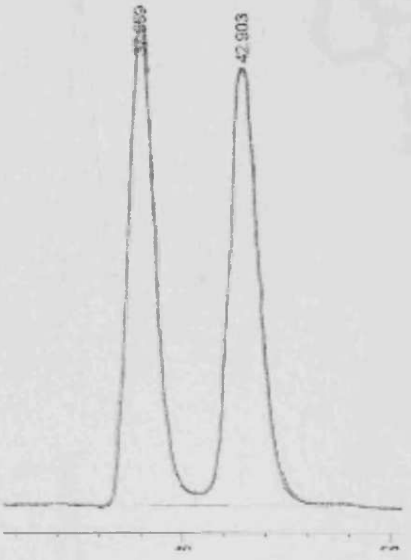


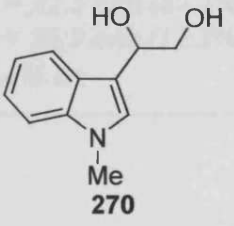
261

Chiral HPLC analysis using a Chiralcel OD column, detecting at wavelength 251 nm, eluting with hexanes/isopropanol (85:15) at 0.6 mL/min. Separated the chiral sample (t_1 = 36.0 min (90.7%); t_2 = 42.9 min (9.4%): ***81.3% ee****.*

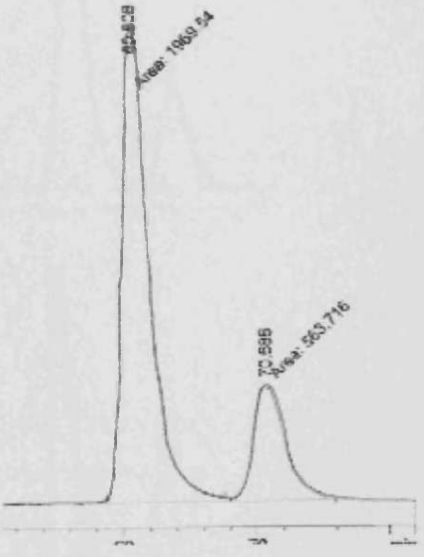
Appendix **A5**

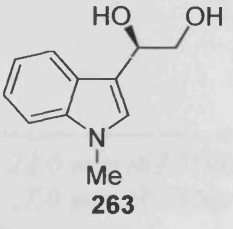
HPLC Traces of Compounds 263 and 270 to Determine ee





270



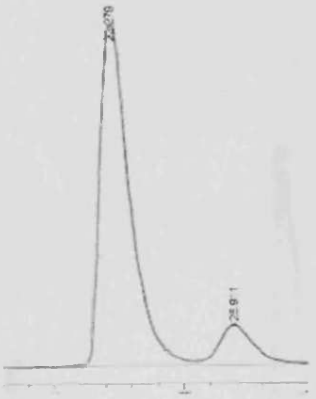


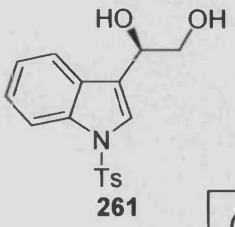
263

Chiral HPLC analysis using a Chiralcel OD column, detecting at wavelength 285 nm, eluting with hexanes/isopropanol (80:20) at 0.6 mL/min. Separated the chiral sample (t_1 = 60.8 min (77.8%); t_2 = 70.7 min (22.3%): ***55.4% ee****.*

Appendix **A6**

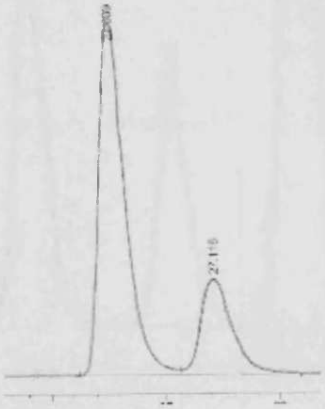
HPLC Traces of Compounds 261 to Determine ee of Spiked Samples



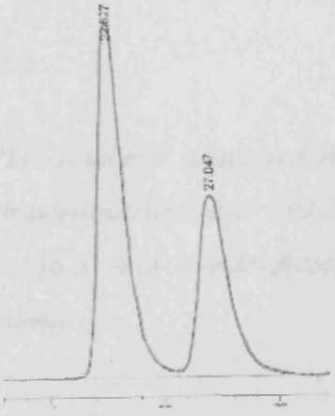


261

(t_1 = 22.3 min (87.7%); t_2 = 26.9 min (12.3%): ***75.4% ee.***



(t_1 = 22.6 min (75.7%); t_2 = 27.1 min (24.3%): ***51.4% ee.***

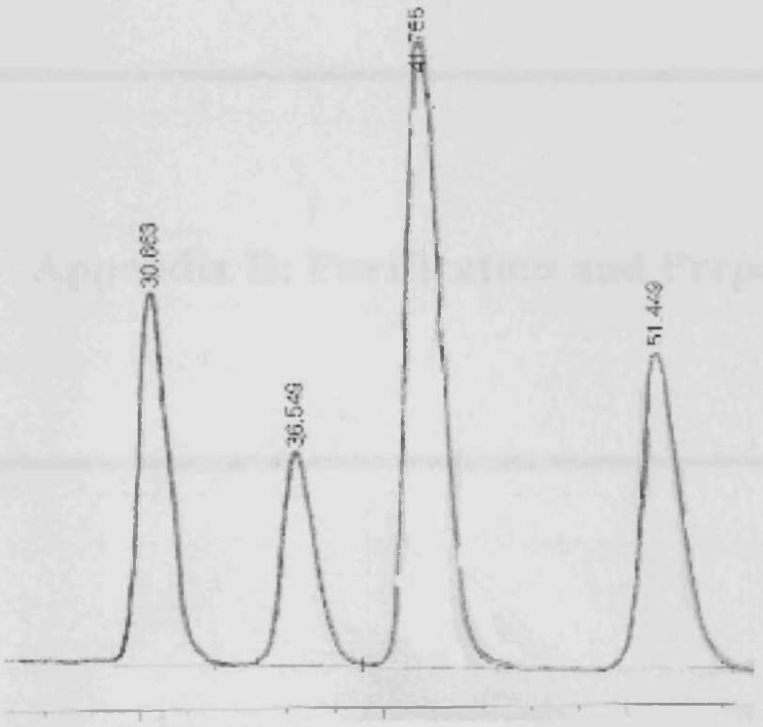


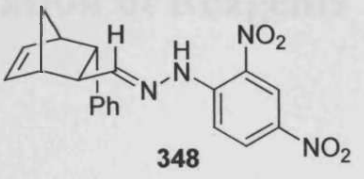
(t_1 = 22.6 min (62.5%); t_2 = 27.0 min (37.5%): ***25.0% ee.***

Chiral HPLC analysis using a Chiralcel OD column, detecting at wavelength 251 nm, eluting with hexanes/isopropanol (85:15) at 1.0 mL/min.

Appendix **A7**

HPLC Trace of Compound 348 to Determine ee





348

Chiral HPLC analysis using a Chiralcel OD-R column, detecting at wavelength 215 nm, eluting with acetonitrile/water (80:20), at 0.5 mL/min. Separated the chiral sample; t_1 *= 30.7 min,* t_2 *= 36.5 min (endo-diastereoisomers);* t_3 *= 41.8 min,* t_4 *= 51.4 min (exo-diastereoisomers).*

Appendix B: Purification and Preparation of Reagents

Reagents were obtained from Aldrich, Lancaster and Fluka chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[234]

Acetonitrile

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

Benzene

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

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.

Lewis acids

The 1M Lewis acids were transferred by canula to a nitrogen filled Schlenk tube and stored in the fridge.

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.