New Approaches to Metal Free Asymmetric Catalysis

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Dedicated to my Mother, Father and
Especially to my Brother Roberto
For their constantly love and support.

* * *

Questo lavoro di Tesi di Ph.D. é dedicato a
Mia Madre, mio Padre ed
In particolar modo a mio Fratello Roberto
Per il loro continuo sostegno ed affetto

Abstract

This thesis embraces three main sections: the development of new molecular scaffolds for the organocatalytic Diels-Alder reaction, extension of the studies upon the α-effect and π-stacking interactions to acyl-ammonium catalysis and development of novel molecular structures for the aminocatalysed Baylis-Hillman reaction.

Chapter 1 describes some of the recent advances made in metal-free asymmetric catalysis and sets the work involved within this thesis into context.

Chapter 2 describes the investigation of the α-effect and the modulation of face-face π-π interactions as a platform for the development of a novel family of catalyst for the aminocatalysed Diels-Alder reaction. After initial investigation on the effect of different counter anions and alternative electron withdrawing groups within achiral catalysts, the α-effect and the face-face π-π interactions design concepts were combined within the structure of a series of arenes based on the 8-aryl menthamine scaffold. Experiments performed utilising (*E*)-cinnamaldehyde and cyclopentadiene provided clear indications that the π-stacking interaction incorporated within the architecture of the catalyst cloud drive the geometric control of the Diels-Alder adducts, showing a 54% *ee* (2*S*) utilising the naphthyl group as the aryl unit and a 30% *ee* (2*R*) with the 4-*N*,*N*-dimethyl aniline based catalyst.

Within *Chapter* 3 investigations into the α-effect was extended to an acyl-ammonium catalysis by preparation of a series of 4-aminopyridines containing a heteroatom in the α-position to the N'-1 nitrogen atom. Examination of this series of catalysts in the acylation of 1-cyclohexanol with acetic anhydride revealed that the α-effect has a detrimental effect in terms of reactivity. Moreover, alternative electronic interactions were examined to improve the nucleophilicity of 4-aminopyrimidines. Preparation of a novel set of catalysts for the enantioselective acylation of alcohols was also attempted.

Chapter 4 describes an investigation into the organocatalysed Baylis-Hillman reaction. Starting from previous work reported in literature, an initial analysis of solvent conditions showed that the presence of small amounts of water in organic solvents significantly improves the reactivity for the reaction catalysed by (*S*)-proline and imidazole to give up to a 80%. A series of (*S*)-proline and (*S*)-histidine derivatives were also investigated as an alternative to the catalytic system (*S*)-proline/imidazole for the asymmetric Baylis-Hillman reaction, providing an enantiomeric excess of 22% *ee* (*R*) with the 2-(2,3,4,5,6-pentafluorobenzamido)-(*S*)-histidine methyl ester derivative. Minor modification to this class of catalyst also showed that the presence of second amide unit significantly improved the reaction efficiency providing a pleasing 79% yield for the reaction performed in tetrahydrofuran. Finally, the catalytic system of (*S*)-proline/imidazole was combined into the structure of the dipeptide (*S*)-proline-(*S*)-histidine and was also examined as a potential catalyst for the asymmetric Baylis-Hillman reaction.

Acknowledgements

I would like to thank my supervisor Dr. Nick Tomkinson, the first “friendly face” met in Cardiff, for all his support and encouragement throughout my work at Cardiff University. It was his enthusiasm and excitement for chemistry has made my Ph.D. studies so enjoyable.

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

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Abbreviations

Ac	acetyl
AD	asymmetric desymmetrisation
APCI	atmospheric pressure chemical ionisation
Ar	aromatic
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
cat.	Catalyst
(cat)	catalytic amount
Cbz	benzyloxycarbonyl
CI	chemical ionisation
d	doublet
d	day(s)
DABCO	1,4-diaza-bicyclo[2.2.2]octane
DCC	1,3-dicyclohexylcarbodiimide
dba	(1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one
de	diastereomeric excess
dppp	1-(phenyl(3-(diphenylphosphino)propyl)phosphino)benzene
DFT	density functional theory
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNPH	2,4-dinitrophenylhydrazine
$E1_{cb}$	β-elimination
EDCI	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
EI	electron ionisation
EPSRC	Engineering and Physical Sciences Research Council
ES	electrosprayl
Et	ethy
ether	diethyl ether

EWG	electron withdrawing group
ee	enantiomeric excess
eq	equivalent(s)
FMO	frontier molecular orbital
FTIR	fourier transform infra-red
h	hour(s)
Hex	hexyl
HOBt	1-hydroxybenzotriazole hydrate
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	*iso*
β-ICD	4-(3-ethyl-4-oxa-1-azatricyclo-[4,4,0,03,8]dec-5-yl)-quinolin-6-ol
IR	infra red
k	kilo
KR	kinetic resolution
LA	Lewis acid
light petroleum	petroleum ether 40–60 °C
Lit.	literature
LRMS	low resolution mass spectrometry
LUMO	low unoccupied molecular orbital
m	*meta*
m	mass
m	multiplet
Me	methyl
min	minute(s)
mmol	millimole(s)
MO	molecular orbital
mol	mole(s)
mp	melting point
MTBE	methyl-*tert*-butylether
MVK	methyl vinyl ketone
Mw	microwave
n	*normal*

NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NMP	*N*-methyl pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
o	*orto*
p	*para*
p	pentet
PGA	prostaglandin A
PGE	Prostaglandin E
PGF	Prostaglandin
Ph	phenyl
PMP	*p*-methoxyphenyl
PPY	4-pyrrolidinopyridine
Pr	propyl
q	quartet
RDS	rate determining step
rot.	rotamer
r.t.	room temperature
s	singlet
s	selectivity
sept.	septet
S_nAr	nucleophilic aromatic substitution
t	tertiary
t	triplet
TBS	*tert*-butyldimethylsilyl
TCA	2,2,2-trichloroacetic acid
TCT	cyanuric chloride
tert	tertiary
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

TMS	trimethylsilyl
Ts	tosyl
v/v	volume/volume
vs.	versus
z	charge
Å	Angstroms
s	sigma
*	chiral
‡	transition state

Organocatalysis 1

Introduction

1.1 Aminocatalysis

In his autobiography "The Periodic Table", Primo Levi defines chemists as "the transformers of matter" underlining one of the major goals of chemistry, to produce in a controlled and economic fashion, valuable products from readily available starting materials.[1] Within this context, catalysis plays a fundamental role offering alternative energetic pathways, increasing the rate of the chemical transformations without affecting the final composition of the products or promoting undesired side-reactions. In order to satisfy these necessities, a large number of researchers from the different chemical disciplines are still active in the field of catalysis.

1.1.1 Chiral products

Since the spatial arrangement within molecules was recognised as an essential property of substances, asymmetric synthesis has devoted itself to the preparation of chiral products and the control of their absolute configuration.[2] This requirement is probably best appreciated in the context of biological systems where most drug-receptors are chiral. Hence, production of enantiomerically pure compounds has become a dominant theme in organic chemistry particularly under the pressure exercised on the pharmaceutical industry. This has driven the drug industry and academic research to continuously develop new methodologies for enhanced control of chiral compounds such as drugs candidates.[3] Undeniably, one of the most elegant and economic approaches to induce chirality into molecules is by using a small amount of a chiral controller. Organometallic catalysis has had a tremendous impact on organic chemistry offering a powerful way to achieve this goal. A plethora of metal-based catalysts that are able to perform a wide range of organic transformations enantioselectively have been developed by researchers in the last 30 years, so that the concept of asymmetric catalysis has become almost exclusively linked with the use of metals in a chiral environment.[4] This belief has been challenged in recent years by remarkable advances in the field of biocatalysis. In fact, the enhancement of enzyme performances by selective mutations or evolutionary methods, and the discovery of useful enzymes from novel organisms, has provided a fascinating alternative to traditional organometallic catalysis.[5] Over the past decade, between the extremes of transition metal catalysis and enzymatic transformations, a third protagonist in the quest for the catalytic production of enantiomerically pure organic molecules has emerged: *organocatalysis.*

1.1.2 Organocatalysis

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.[6,3a,4f] The historic roots of organocatalysis go back to 1928 when the German chemist Wolfgang Langenbeck used small organic compounds as catalyst to study and mimic the catalytic activity of enzymes. The same author coined the term "Organic Catalyst" in his publication that appeared in the same year.[7] Further sporadic examples of asymmetric organocatalysis were reported in the 1960's by Pracejus[8] and in the 1970's by Parrish et al.[9] However, it was not until 2000 that, the pioneering works of List[10] and MacMillan,[11] trigged many researchers to investigate organocatalysis.[12]

There are certainly considerable advantages to using metal complexes 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 metallic species offer, their use has several disadvantages, such as:

I. Frequently high economic costs;
II. The resulting toxicity and pollution associated with heavy metals;
III. The need for waste treatment and the possibility of product contamination by the metal.[13]
IV. The reactions usually need challenging operative conditions such as an inert atmosphere, absolute dry solvents and low temperature;

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 relatively inexpensive, and widely available as single stereoisomers;
III. The catalysts are often stable and robust compared to enzymes;
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;[14]

VI. Disposal of organic compounds is relatively straightforward.

Thus, organocatalysis represents a remarkable synthetic alternative to established organometallic transformations to both augment and complement existing methodology.

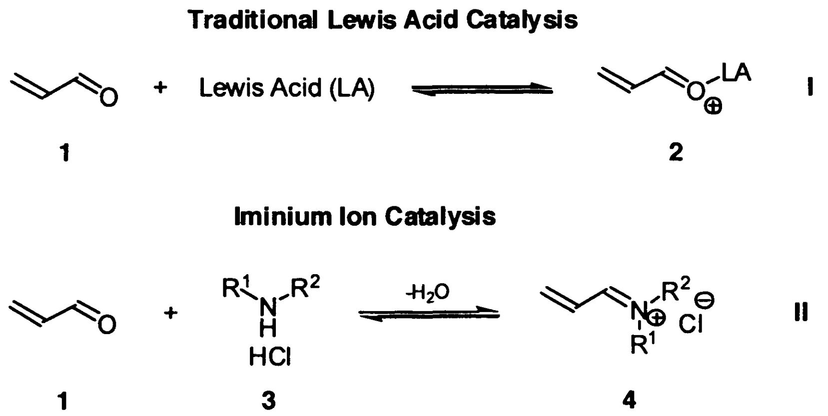
1.1.3 Aminocatalytic pathways

Within the wide panorama of organocatalysis, aminocatalysis has gained a prominent role as a powerful synthetic tool for a remarkable number of organic transformations. It is well known that structurally simple and stable chiral secondary amines and amino-acids facilitate iminium ion and enamine-based transformations with carbonyl compounds. Iminium ion catalysis utilises the activation of α,β-unsaturated carbonyl compounds by alteration of the orbital energy levels to facilitate a multitude of organic reactions Alternatively, enamine catalysis involves an enamine intermediate formed *via* the deprotonation of an iminium ion leading to a nucleophilic enamine which reacts in an analogues manner to that of enolates revealing the huge potential of this sort of catalysis. Furthermore, recent development of chiral aromatic and non-aromatic secondary amines has led to a novel class of more efficient acyl transfer catalysts for kinetic resolution of alcohols.

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

1.2 Iminium ion catalysis

Iminium ion catalysis was derived from analogous concepts previously utilised within Lewis acid catalysis. The first example of iminium ion catalysis came from the laboratories of MacMillan. They reasoned that the characteristic LUMO-lowering activation and kinetic lability of ligand substitution that enables Lewis acid catalyst turnover (**I**, Scheme 1) could also be applied to a carbogenic system that exists as a rapid equilibrium between an electron deficient and an electron rich state. With this in mind, they hypothesised that reversible formation of iminium ions, such as **4**, from α,β-unsaturated carbonyl compounds, **1**, and secondary amines, **3** (**II**, Scheme 1) would mimic the π-orbital dynamics of Lewis acid based catalysts. This provided the platform for a powerful and general catalyst technology.[11]



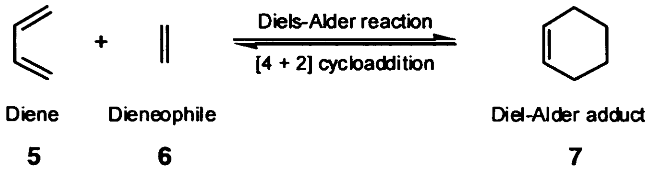
Scheme 1

The nature of iminium ion formation and properties of activated α,β-unsaturated carbonyl compounds presented this methodology as a valuable solution for two main categories of organic reaction, cycloadditions and conjugate additions. This section is dedicated to the analysis of structural motifs contained within these catalysts and the requirements for efficient transformations. This journey into iminium ion catalysis includes the Diels-Alder reaction, [3+2]-dipolar cycloadditions, cyclopropanations, conjugate additions, conjugate reduction and epoxidaction reactions. Literature findings are summarised with resulting conclusions combined as an overview of structural characteristics for iminium ion catalysis.

1.2.1 Cycloaddition

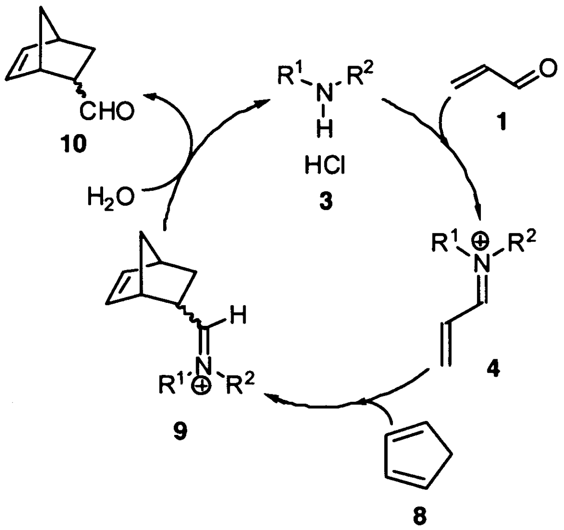
1.2.1.1 Diels-Alder reaction

The Diels-Alder reaction is a [4+2] cycloaddition reaction between a diene **5** and a dieneophile **6** (Scheme 2).



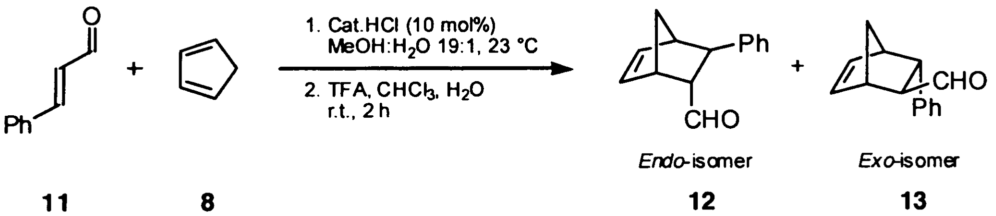
Scheme 2

The first highly enantioselective organocatalysed Diels-Alder reaction was reported by MacMillan in 2000.[11] This work showed that iminium ion catalysis could mimic the equilibrium dynamics and π-orbital electronics of Lewis acid based systems. It was envisaged that condensation of α,β-unsaturated aldehyde **1** with an enantiopure amine **3** would lead to the formation of an iminium ion **4** (Scheme 3). This intermediate should be sufficiently activated to engage a diene reaction partner **8** and form the iminium ion **9**. Subsequent hydrolysis should provide the enantioenriched cycloaddition product **10** and release the chiral amine catalyst.



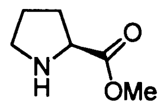
Scheme 3

Reactions were carried out between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8** with a series of secondary amine catalysts utilised as their hydrochloride salt (Scheme 4).



Scheme 4

Chiral amines tested included (*S*)-proline methyl ester **14** and (*N*-methyltryptophan) methyl ester **15**. These proved that catalytic quantities of secondary chiral amines could be successfully employed to catalyse the Diels-Alder cycloaddition between α,β-unsaturated carbonyl systems and dienes. Adducts **12** and **13** were obtained in excellent yields (higher than 80%) and moderate stereoselectivity (about 2.5:1 *exo*:*endo*, 48-59% *ee*) with reaction times ranging from eight to eighty four hours. Imidazolidinone **16** provide the highest levels of reactivity and enantioselectivity with 99% yield and 93% *ee* after only eight hours under the reported reaction conditions. This work subsequently showed that **16** was a general catalyst by reporting the reaction of a series of dienes with (*E*)-cinnamaldehyde **11** in good yield and enantioselectivity.



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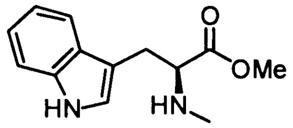

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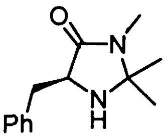


16

The high asymmetric induction observed in all the reactions involving catalyst **16** was consistent with iminium ion model **A** attained from theoretical calculations (Figure 1). Structure **A** revealed two stereocontrol elements:

I. The (*E*)-iminium ion is preferentially formed to avoid non-bonding interactions between the substrate olefin and the geminal methyl substituents;

II. The benzyl group attached to the imidazolidinone framework effectively shields the *Re*-face of the dienophile, leaving the *Si*-face exposed for the approach of the diene.

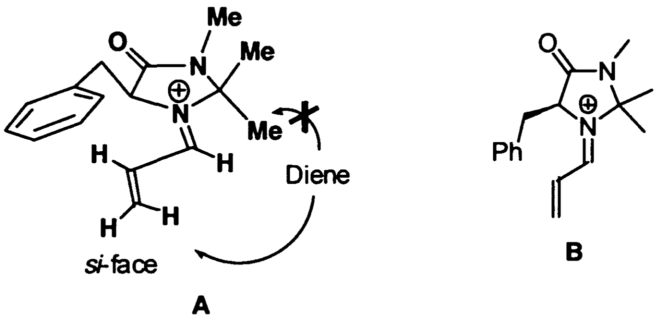
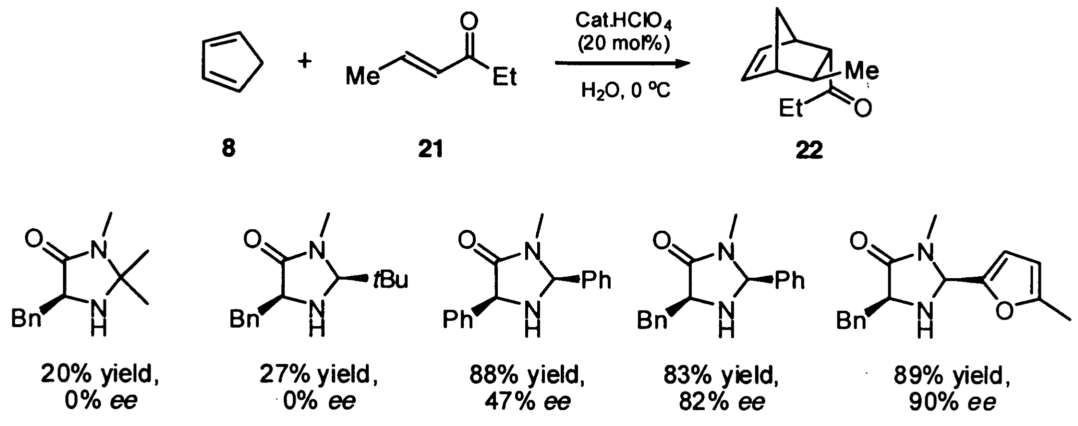


Figure 1

Subsequently, modifications of the structure of **16** led to the imidazolidinone-based family of catalysts **17**, **18**, **19** and **20**.[15] Surprisingly, the perchlorate salt of **16** and **17** showed low yields and no enantiomeric excess for the Diels-Alder reaction between cyclopentadiene **8** and 4-hexen-3-one **21** (Figure 2). Yields and enantiocontrol were improved throughout this set of imidazolidones to obtain the best result with catalyst **20** (89% yield, 90% *ee*).



8 **21** **22**

20% yield, 0% *ee* **16**

27% yield, 0% *ee* **17**

88% yield, 47% *ee* **18**

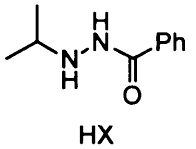
83% yield, 82% *ee* **19**

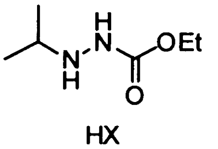
89% yield, 90% *ee* **20**

Figure 2

These imidazolidinone structures have been used in ionic liquids,[16] adapted to polymer supports[17,18] and natural product synthesis[19] with excellent results.

Tomkinson produced a series of acyclic catalysts based on derivatised hydrazines **23**-**26**.[20] Studies with these structures revealed the α-effect as an effective platform for iminium ion catalysis. It was observed that an arrangement of a tertiary centre on the reactive nitrogen together with a methyl substituent and an ethyl carbamate on the α-heteroatom led to a highly effective catalyst architecture **26**. **26**.HCl at a level of 10 mol% showed a pleasing 98% yield after four hours for the transformation described above (Scheme 4), performed in methanol at room temperature.


HX
23


HX
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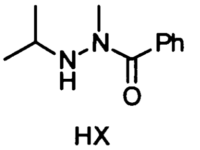
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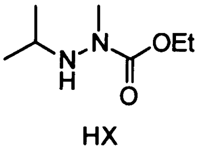
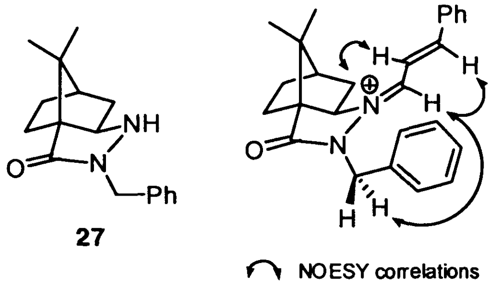

HX
26

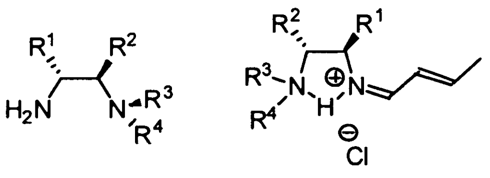
Based on this work, Ogilvie introduced the hydrazine unit in a tricyclic camphor-derived framework **27**.[21] These particular structures offered best results in water, with excellent yield and enantiocontrol across a broad selection of dienophiles. The iminium ion intermediate was examined utilising semiempirical calculations (PM3 in Spartan Pro) which indicated structure **28** (Figure 3) as the lowest energy conformer. Solution phase NOESY experiment of this species showed strong correlation between the hydrogens, consistent with the calculated structure. This examination suggested that the approach of dienes to the bottom-face of this conformer is facilitated by a reduced steric hindrance due to the catalyst scaffold.



27 **28**

Figure 3

A family of 1,2-diamino structures based on **29** were independently reported by Ha[22] and Ishihara[23] as an alternative acyclic catalysts for this reaction. These structures were thought to catalyse the Diels-Alder reaction with α,β-unsaturated aldehydes through the formation of iminium intermediate **30** (Figure 4). Activation of the imine to the cycloaddition was attributed to internal hydrogen bonding with the ammonium proton provided by a Brønsted acid co-catalyst (typically hydrochloric acid). Various **R** groups have been employed within these architectures with yields and enantioselectivities remaining high.

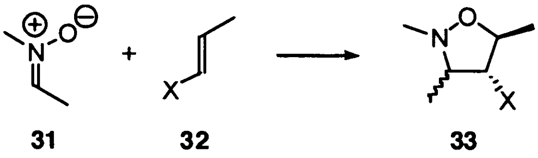


29 **30**

Figure 4

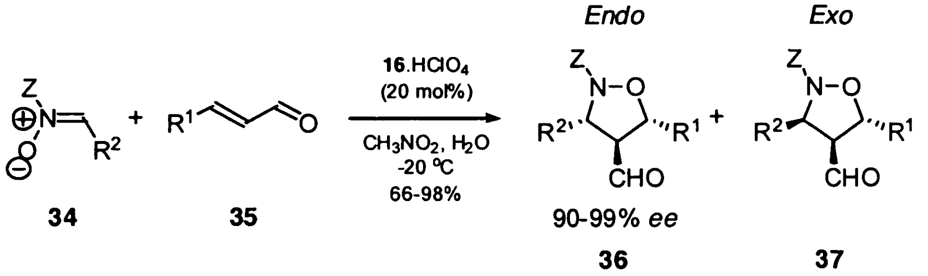
1.2.1.2 [3+2] Dipolar cycloaddition

The [3+2]-dipolar cycloaddition reaction between a nitrone **31** and an electron deficient olefin **32** to provide isoxazolidine **33** (Scheme 5) has recently received considerable attention in asymmetric synthesis.



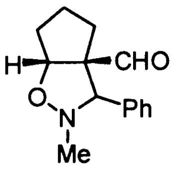
Scheme 5

MacMillan applied the LUMO-lowering activation of α,β-unsaturated aldehydes to this reaction with a good degree of success.[24] Catalyst **16** was evaluated in a series of cycloadditions with a variety of substrates (Scheme 6), showing good to excellent yields (66-98%) and high levels of stereoselectivity (90-99% *ee*). However, these results were obtained by prolonging the reaction time up to one hundred hours, testifying a low activity of **16** within this transformation. The high observed enantiocontrol using the imidazolidinone **16** was rationalised using the same model described for the Diels-Alder reaction in the previous *section 1.2.1.1.* Solid phase variants of this catalyst have been tested within this reaction, displaying slightly lower yields but retaining the enantioselectivities.[25]



Scheme 6

Karlsson reported poor yields and enantiomeric excesses (19% and *exo* 5% *ee*) during the synthesis of isoxazolidine **38** using the chiral imidazolidinone **16**.[26]



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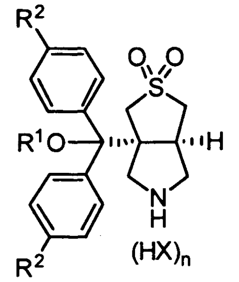
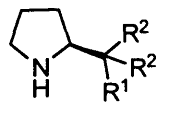
To increase both the reaction efficiency and the stereochemical control in the synthesis of **38**, the chiral pyrrolidine architectures **39** and **40** were investigated.



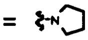
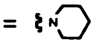
39

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



HX

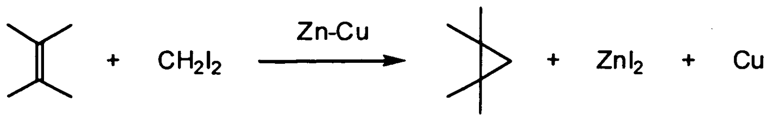
40

$R^1 = OH$ $R^2 = Me$
$R^1 = OH$ $R^2 = Ph$
$R^1 = OMe$ $R^2 = Me$
$R^1 =$  $R^2 = H$
$R^1 =$  $R^2 = H$ **41**

Initial tests were carried out with the bicyclic pyrrolidine **39** which gave **38** in reasonable yields (59-61%) and good enantiomeric excess (67-70% *ee*). The increase in rigidity and bulk of the catalyst framework was thought to account for the observed enhancements in reactivity and enantioselectivity. To further improve the yields and the stereocontrol a series of proline-based derivatives **40** were tested. Catalyst **41** provided the best enantioselectivity (91% *ee*) within this series, although with moderate yield (44%).

1.2.2 Cyclopropanation

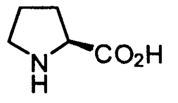
Cyclopropanation reactions are commonly carried out through the Simmons-Smith reaction involving the addition of an alkene **42** and a carbene, created *in situ* with a zinc-copper couple (Scheme 7).[27]



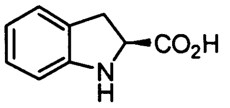
42 **43**

Scheme 7

MacMillan reported the cyclopropanation between a α,β-unsaturated aldehyde **35** and a stabilised ylide **48** catalysed by (*S*)-proline **44** and the dihydroindole **45**.[28] Surprisingly, imidazolidinones **16** and **17**, previously successfully applied to a range of organic transformation, failed to deliver the expected product **49**.

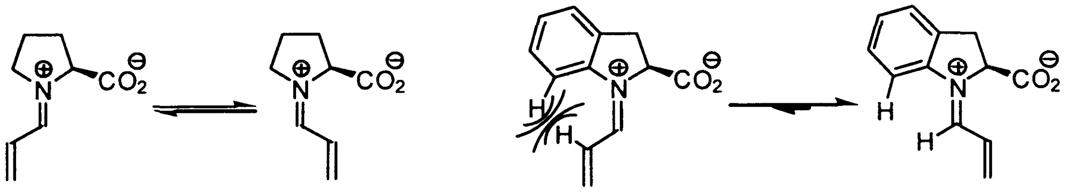


44



45

This atypical reaction pattern was attributed to necessary electrostatic interaction between the ylide carbanion and the zwitterionic iminium ion **46** and **47** able to facilitate the carbon-carbon bond formation (Figure 5). The different stereoselectivity showed by (*S*)-proline **44** and amino-acid **45** was rationalised assuming that the zwitterion **46** could readily populate both *E* and *Z* iminium isomers **46**, leading to a diminished enantiocontrol. In contrast, catalyst-derived zwitterion **47** would predominately populate the (*Z*)-iminium isomer to minimise Van der Waals interactions between the substrate olefin and the aryl hydrogen.



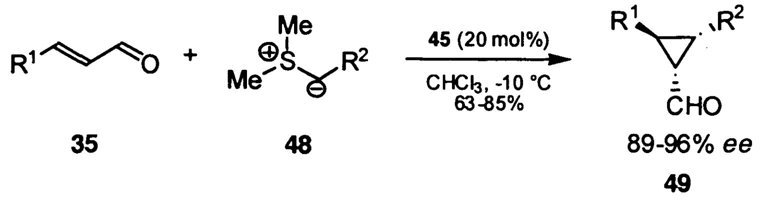
(*E*)-46 **(*Z*)-46** **(*E*)-47** **(*Z*)-47**

Poor iminium ion control

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

Figure 5

Catalyst **45** was subsequently tested in a series of experiments with a variety of α,β-unsaturated aldehydes and ylides with excellent levels of asymmetric induction (89-96% *ee*) and reaction efficiency (63-85% yield, Scheme 8).



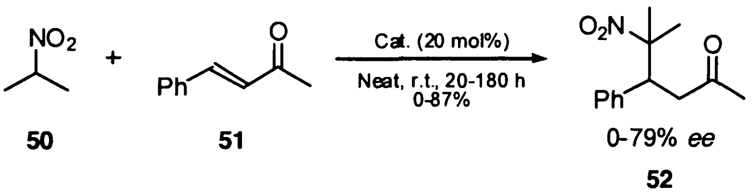
R^1 = n-Pr, Me, Ph, $(Me)_2CHCH_2$, $CH_2OAllyl$, $CH_2{=}CH(CH_2)_4$
R^2 = COPh, COPhp-OMe, t-Bu

Scheme 8

1.2.3 Addition reactions

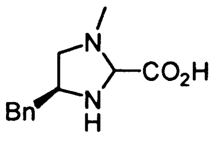
1.2.3.1 Conjugate addition reactions

Yamaguchi showed that a (*S*)-proline derived rubidium salt catalysed the addition of nitroalkanes to α,β-unsaturated carbonyl compounds.[29] It was postulated that the reaction could proceed *via* an iminium ion intermediate. Subsequently, Jørgensen screened different chiral amines as catalysts for the reaction of 2-nitropropane **50** with benzylideneacetone **51** (Scheme 9).[30] (*S*)-Proline **44** was found to be a poor catalyst for this transformation with low yield and enantioselectivity. Surprisingly, the MacMillan imidazolidinone **16** also failed to effectively catalyse this reaction.

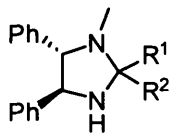


Scheme 9

Within this series of amines, imidazoline **53** and the 1,2-diphenyl-1,2-diamine derived catalyst **54**, prepared in the Jørgensen laboratories, provided good yields and selectivity, despite the fact that a mixture of diastereoisomers of **53** was used. Unfortunately, the addition showed long reaction times in order to achieve reasonable yields (20-180 h). Catalyst **53** was further examined with a variety of α,β-unsaturated ketones producing poor to excellent yields (5-99%) and enantiomeric excesses (34-86% *ee*).



53

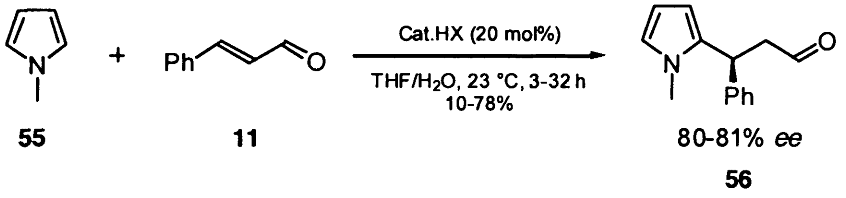


54

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

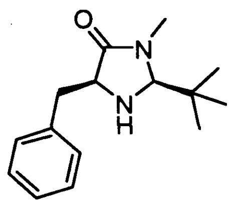
JØrgensen extended the investigation of imidazoline catalyst **53** to the conjugate addition of malonates to acyclic α,β-unsaturated enones.[31] It was found that sterically hindered malonates decreased the reaction rate leading to a low yield and levels of stereocontrol. However, medium-sized malonates (dibenzylmalonate) displayed excellent yields and enantioselectivities, although once again these reactions required extended reaction times (up to five days).

MacMillan developed an iminium ion catalysed strategy for the enantioselective Friedel-Craft alkylation of pyrroles.[32] Imidazolidinone **16** was initially evaluated using *N*-methyl pyrrole **55** with (*E*)-cinnamaldehyde **11** and a series of acid co-catalysts (Scheme 10). The outcomes revealed a strict relationship between the catalytic efficiency and acid strength. The best results were found with acids of a lower pK_a value such as trichloroacetic acid (64% yield and 81% *ee*) and trifluoroacetic acid (78% yield and 81% *ee*). A rationale similar to the Diels-Alder reaction was employed to explain the excellent stereoselectivities observed. Catalyst **16**.TFA was found to be general with respect to both the α,β-unsaturated aldehyde and the pyrrole component maintaining excellent levels of reaction efficiency and enantioselectivity.

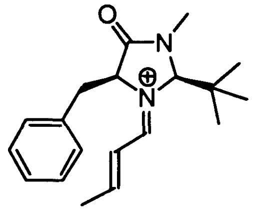


Scheme 10

MacMillan extended this synthetic strategy to the alkylation of indole-based substrates.[33] Despite structural similarities between pyrroles and the indole framework, catalyst **16**.TFA displayed a low reaction rate (83% yield and 56% *ee* in forty eight hours) for the addition of *N*-methylindole **58** to (*E*)-crotonaldehyde **59**. In order to overcome this limitation in indole reactivity a second imidazolidinone-based catalyst was developed. Preliminary kinetic studies indicated that the overall rates of iminium-catalysed reactions were influenced by the efficiency of both the initial iminium formation step and the carbon-carbon bond-forming event.

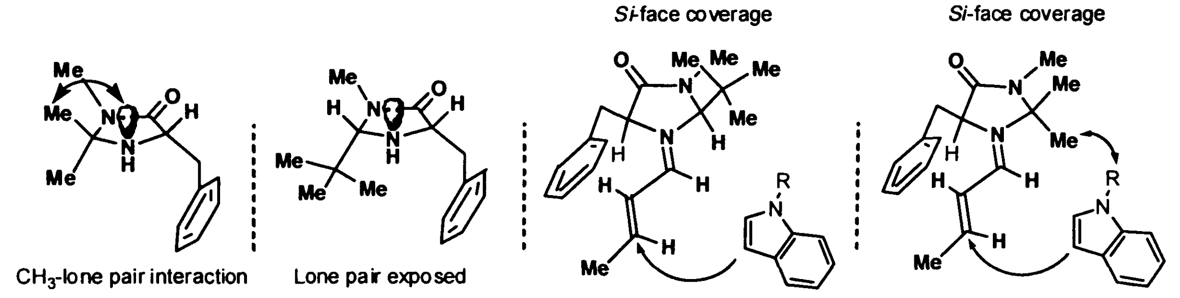


17



57

Theoretical studies[34] suggested that structure **17** could exhibit improvement of the reaction rate by accelerating the formation of the iminium ion through a more favourable orientation of the nitrogen lone pair away from structural impediment (**I** and **II**, Figure 6). Furthermore, substitution of the methyl group "*trans*" to the benzyl moiety with a hydrogen atom left the reactive enantioface of iminium ion **57** free from steric obstruction and hence facilitated the approach of the heteroaromatic substrate (**III** and **IV**). It was also envisaged that to reduce steric interaction between the substrate olefin and the *tert*-butyl group, the (*E*)-isomer of the iminium ion **57** was predomonantly formed.



Si-face coverage *Si*-face coverage

CH$_3$-lone pair interaction
I

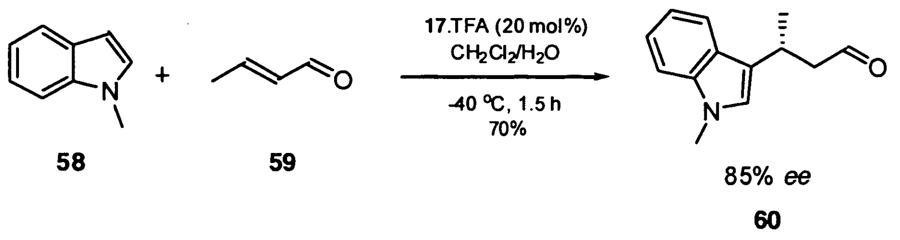
Lone pair exposed
II

Re-face addition unhindered
III

Re-face CH$_3$-substrate interaction
IV

Figure 6

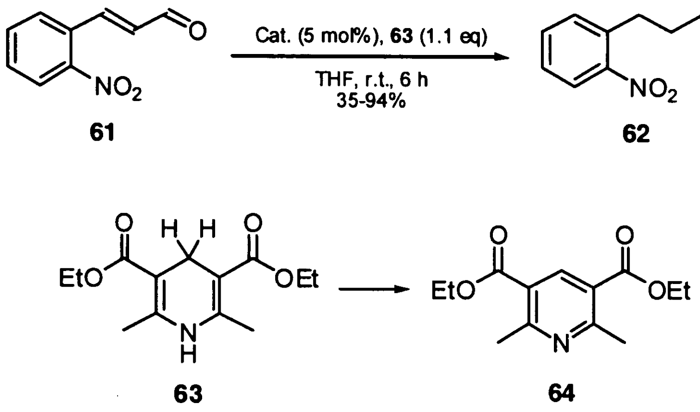
The enantioselective alkylation of *N*-methylindole **58** with (*E*)-crotonaldehyde **59** using catalyst **17**.TFA provided substituted indole **60** with high levels of reaction efficiency (70% yield) and enantioselectivity (85%, Scheme 11). This catalyst was shown to be general for the alkylation reaction of a variety of substituted indoles and α,β-unsaturated aldehydes. Subsequently, catalyst **17** has been utilised in Mukaiyama-Michael reactions,[35] as well as in the total synthesis of (-)-flustramine B[36] and in enantioselective organo-cascade reactions.[37]



Scheme 11

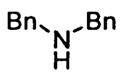
1.2.3.2 Conjugate reduction

Catalytic hydrogenation of α,β-unsaturated aldehydes has often shown low chemoselectivity, and functional groups sensitive to hydrogenation conditions such as benzyloxy, nitro and nitrile units are not tolerated. Until recently, these reactions required metal catalysts and/or stoichiometric amounts of metal hydrides. Alternative conjugate reductions have been realised with various substrate classes, however, a mild, general, highly chemoselective catalytic variant applicable to α,β-unsaturated aldehydes was not reported until recently. Iminium ion catalysis was extended to the conjugate reduction of α,β-unsaturated aldehydes. Formation of the iminium ion decreases the LUMO energy of the carbon-carbon double bond and facilitates the reaction with nucleophiles. The essential requirement for this reduction strategy was to identify a suitable hydride donor. List employed several ammonium salts at a level of 5 mol% to catalyse the conjugate reduction of *o*-nitrocinnamaldehyde (**61** to **62**), identifying the Hantzsch ester **63** as an excellent source of hydride (Scheme 12).[38]



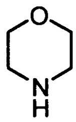
Scheme 12

Within this series of amines, dibenzylamine **65**, morpholine **66** and piperidine **67** provided the best yields (94%, 92% and 90% respectively) in five hours as their trifluoroacetate salts. Catalyst **65** was subsequently successfully used in the conjugate reduction of a series of α,β-unsaturated aldehydes with excellent yields.



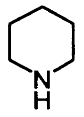
94%

65



92%

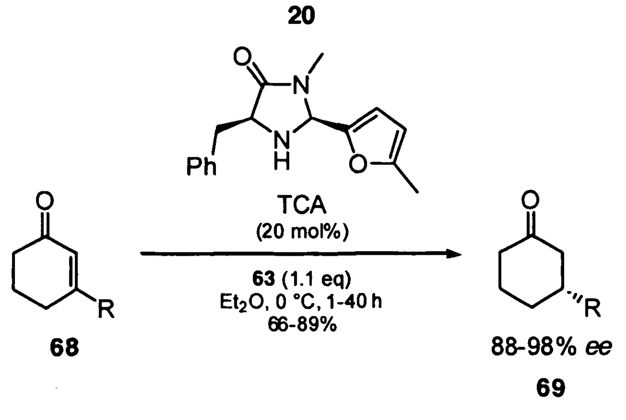
66



90%

67

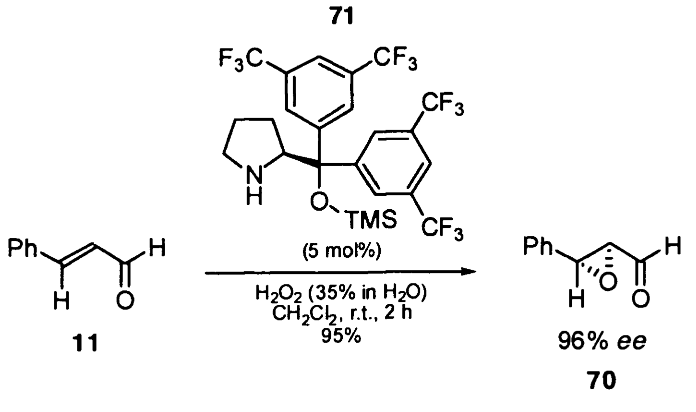
List also explored the asymmetric conjugate reduction with the imidazolidinone catalyst $17.Cl_3CO_2H$.[39] This investigation led to the discovery of an efficient asymmetric iminium ion catalysed conjugate reduction-intramolecular Michael reaction producing a series of five- and six-membered carbocycles in excellent yields (86-98%) with high enantioselectivity (86-96% *ee*).[40] MacMillan reported similar methodology for the reduction of cyclic[41] and acyclic[42] α,β-unsaturated carbonyl systems expanding the library of workable substrates (Scheme 13).



Scheme 13

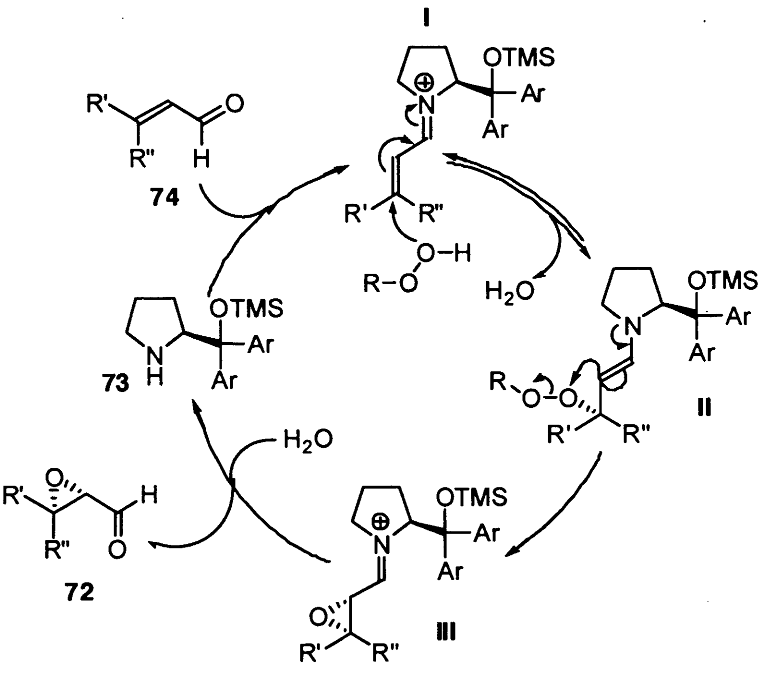
1.2.4 Epoxidation

The catalytic asymmetric epoxidation of α,β-unsaturated aldehydes holds a prominent place in asymmetric catalysis due to the synthetic value of the corresponding α,β-epoxy carbonyl compound. However, direct approaches to this particular class of epoxidations have not been reported until recently. Jørgensen described the epoxidation of (*E*)-cinnamaldehyde **11** catalysed with the proline derivative **71** (Scheme 14).[43] The reaction was carried out with 5 mol% of catalyst **71**, screening a variety of oxidants. Despite a wide range of observed conversions (3-95%), the stereoselectivity was generally good to excellent (53-96% *ee*) with the best result attained for the epoxidation performed with a solution of 35% hydrogen peroxide in water as oxidant (95% conversion, 96% *ee*).



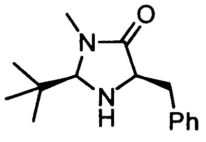
Scheme 14

The characteristic reaction mechanism proposed for the organocatalytic asymmetric epoxidation shows that the initial formation of the iminium intermediate **I** is followed by a nucleophilic attack of the peroxide to the β-carbon atom to form the enamine **II** (Scheme 15). The formation of the epoxide then takes place by a second attack of the nucleophilic enamine carbon atom **II** to the electrophilic peroxygen atom, followed by hydrolysis of the iminium intermediate **III**.



Scheme 15

MacMillan, has also, applied the LUMO-lowering activation of the carbon-carbon double bond to the epoxidation of α,β-unsaturated aldehydes catalysed by the imidazolidinone salt 75.TFA.[44] This investigation involved the use of the hypervalent iodine containing oxidant iodosobenzene (PhI=O) which provided moderate to excellent yield (45-100%) and enantiocontrol (73-93% *ee*,).

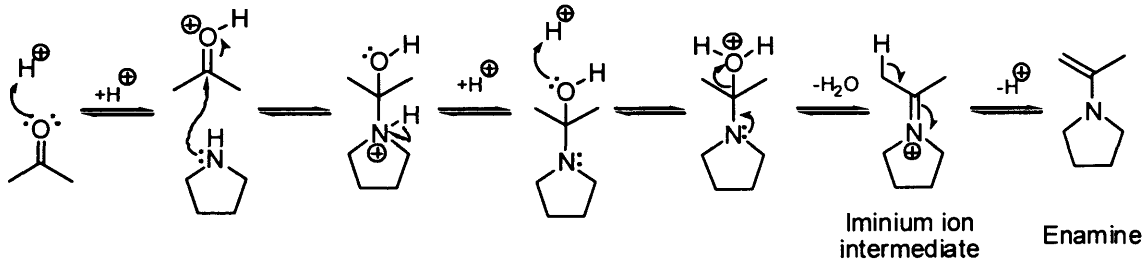


75

1.3 Enamine catalysis

1.3.1 Enamine reactions

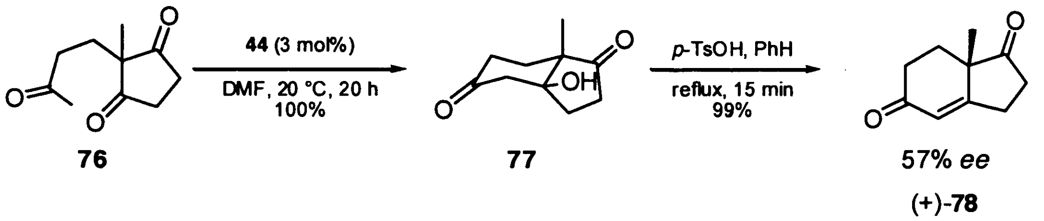
The ability of simple secondary amines to accelerate numerous chemical transformations through the reversible formation of enamine intermediates is well documented in the literature. As highlighted by the mechanism of formation of an enamine, this particular type of organocatalysis offers a powerful synthetic strategy for the rich variety of chemical reactions that occur through the α-position of carbonyl compounds (Scheme 16).[45] Most notable reactions from the current literature are the aldol, conjugate addition, the direct Mannich, α-substitutions and Baylis-Hillman reactions. This section of *Chapter One* will look in turn at each of these broad areas of chemistry and examine the necessary motifs employed within the catalyst structure for optimal reactivity.



Scheme 16

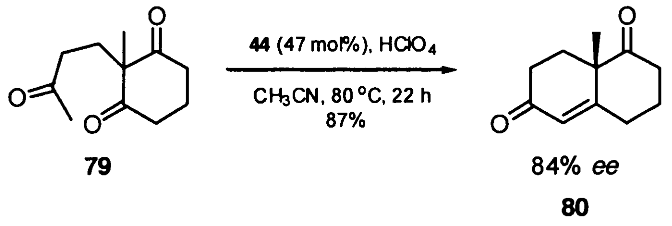
1.3.2 Early enamine catalysis

In the early 1970's, two groups independently reported the first intramolecular aldol reaction catalysed with a small amount of (*S*)-proline **44**. Hajos, Parrish and Oliveto aimed their initial investigation to find an alternative methodology to a previous synthesis of the optically active bicyclic ketone **78**.[46] During the course of these experiments, the importance of the hydrogen-bonding interaction in the transformation of **76** to **78** and the nature of the solvent emerged, leading to the use of the aprotic solvent *N*,*N*-dimethylformamide. (*S*)-proline **44** was tested under series of conditions to provide the ketone **78** in high yield and with 57% *ee* (Scheme 17).[47,9]



Scheme 17

Eder, Sauer and Wiechert showed a direct synthetic route through to **80** from the triketone **79** in the presence of (*S*)-proline **44** (10-200 mol%) and an acid co-catalyst (Scheme 18).[48] Product **80** was obtained in a pleasant 87% yield and 84% *ee*, showing that the optical purity of the enone was strongly dependent upon the substrate, amine catalyst, solvent and the acid co-catalyst.



Scheme 18

This asymmetric proline-catalysed intramolecular aldol process, labelled as the Hajos-Parrish-Eder-Sauer-Wiechert reaction,[49] has been applied to the synthesis of numerous steroids and terpenoids since its first publication in the 1970's.[50] Polymer-bound (*S*)-proline has also been employed to perform this reaction.[51]

1.3.3 Aldol reaction

1.3.3.1 Mechanism of the intramolecular aldol reaction

Within synthetic organic transformations, the aldol reaction has a prominent role as one the most important and widespread carbon-carbon bond forming reactions. This classic methodology is characterised by examples using preformed enolate equivalents or enolates formed *in situ* (Figure 7).[52] More recently, the asymmetric aldol reaction has found renewed interest using enamine catalysis as witnessed by the large number of publications released over the last ten years. The development carried out within this transformation has offered important basic stereochemical details useful not only for the aldol reaction itself but also for the other carbon-carbon bond forming reactions such as the Diels-Alder reaction and the Michael addition. Despite this, there still remains little evidence for the proposed enamine catalysed mechanism of this well known reaction.

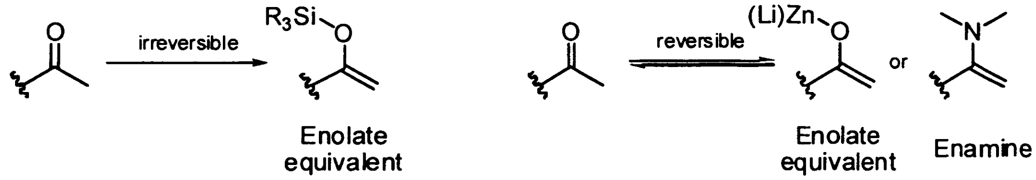
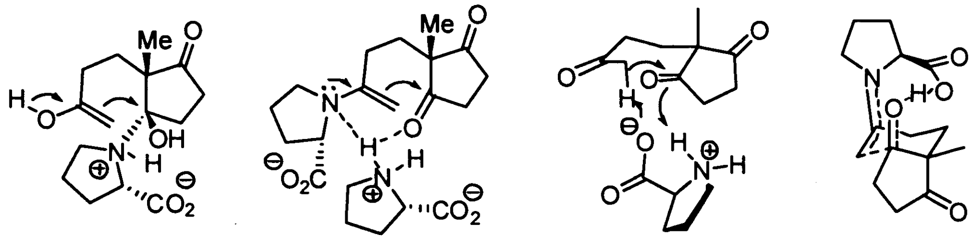


Figure 7

During the course of the last thirty years different enamine intermediate models for the Hajos-Parrish-Eder-Sauer-Wiechert have been proposed in an attempt to rationalise the observed stereoselectivity. Hajos proposed the "activation" of one of the enantiotopic acceptor carbonyl groups as a carbinol amine (**A**, Figure 8).[9] Agami and colleagues proposed a side chain mechanism which involved two molecules of (*S*)-proline **44** in the intermediate; one as an enamine with the other as a proton transfer mediator (**B**).[53] Swaminathan *et al.* proposed a heterogeneous aldolization mechanism on the surface of crystalline proline despite proline-catalysed aldol transformations usually being performed in a homogeneous environment (**C**).[54] More recently, List challenged this latter model with the proposal of a mono-proline enamine mechanism (**D**).[10a] A similar mechanism was proposed subsequently by Houk *et al.* on the basis of density functional theory (DFT) studies.[55] This last intermediate is currently thought to be the most accurate with new experimental evidence for its existence being reported.[56]

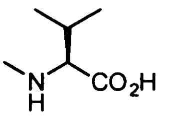


Hajos model **A** Agami model **B** Swaminathan model **C** Houk model **D**

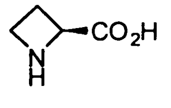
Figure 8

1.3.3.2 Aldol reaction

List[10a] and Barbas[57] scrutinised the aldol reaction between acetone **81** and *p*-nitrobenzaldehyde **82** catalysed by a series of amino-acids and secondary amines. These studies showed a heterogeneity of results in term of yield and stereoselectivity. The primary amino-acids histidine, valine, tyrosine, phenylalanine and the acyclic secondary amine **83** displayed poor yield (<10%) and no enantiomeric excess. This was also the case for four- and six-membered systems and analogues of proline substituted in the five-position



83



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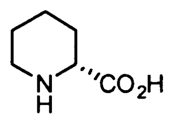

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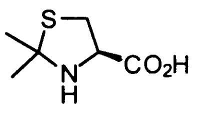

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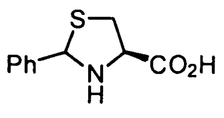
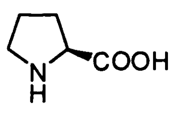


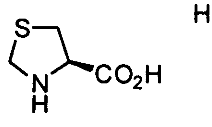
87

The proline analogues with a heteroatom in the four-position **86** and **87** or with a substituent in the three-position **90** offered great levels of conversions and asymmetric induction under the reaction conditions. A similar level of catalysis was also observed with the inclusion of a second heteroatom within the cyclic skeleton with a gem-dimethyl substitution in the three-position **90**.



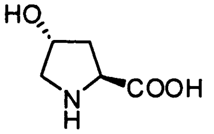
68%
76% *ee*

44



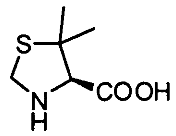
67%
73% *ee*

88



85%
78% *ee*

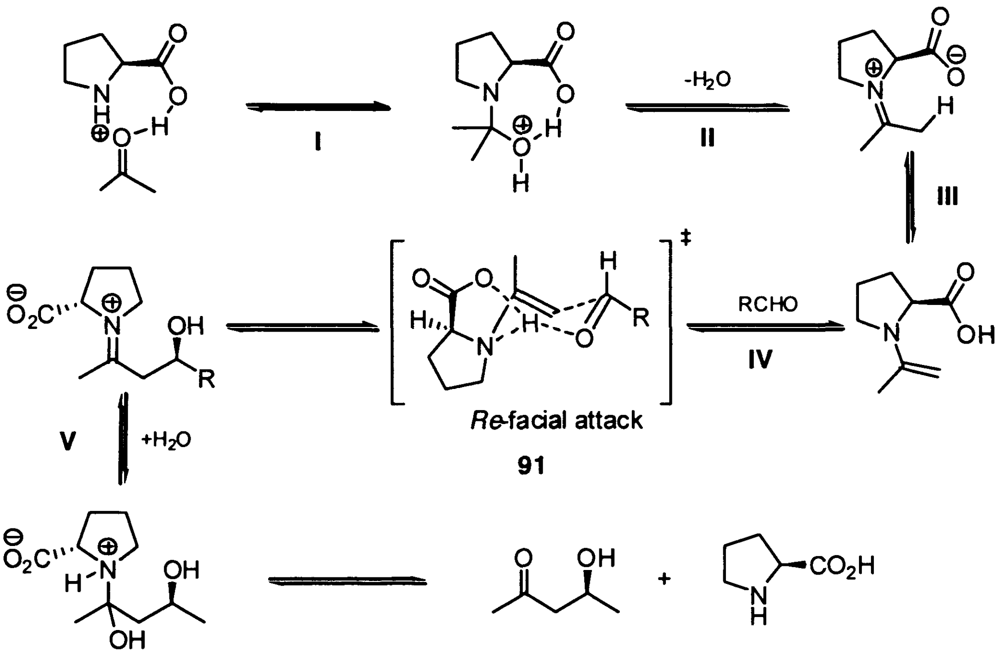
89



66%
86% *ee*

90

To interpret these results further knowledge of the mechanism of enamine formation and subsequent aldol reaction originally proposed by List is required (Scheme 19).[10a]



Scheme 19

List proposed that proline could operate as a "micro-aldolase" that provides both the nucleophilic amino group and an acid/base cocatalyst in the form of the carboxylate. This double nature of proline could facilitate each individual step of the mechanism, including the nucleophilic attack of the amino group **I**, the formation of the iminium intermediate **II** and enamine species **III**, the carbon-carbon bond forming step **IV**, and the hydrolysis of the second iminium-aldol intermediate **V** (Scheme 19). The enantioselectivity was explained assuming a metal-free version of a Zimmerman-Traxler type transition state **91** with a tricyclic hydrogen bonded framework which provides the observed enantiofacial selectivity. The proposed transition state **91** allows understanding of the enantioselectivity observed in the series of experiments performed by List and Barbas. The four- and six-membered systems, **84** and **85** would encompass alternative spatial arrangements between the carboxylic functionality and the transferable proton reducing the efficiency of the "proton-shuttle". Substitution at the four- and three-position would have limited effects on the catalyst reactivity being sufficiently away from the reactive centre, whereas substitution at the five-position could affect the reaction efficiency through steric interactions. This transition state model has found further support in later studies upon proline and its derivatives. List has reported that experimental evidence obtained for the ratios of the four stereoisomers of the aldol reaction between cyclohexanone and benzaldehyde catalysed by (*S*)-proline **44** corroborated quantum mechanical calculations based on the proposed transition states **91**.[55] Barbas[58] and Yamamoto[59] have theorised transition state structures for (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **A** and the pyrrolidine-based tetrazole, 5-(((*S*)-pyrrolidin-2-yl)methyl)-1*H*-tetrazole **B** respectively (Figure 10). These structures were derived from the previous model utilised with (*S*)-proline **44**.

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

A

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

B

Figure 9

MacMillan expanded the examples of the proline catalysed aldol reaction.[60] He has also employed the imidazolidinone **17**.HCl technology with good yields and stereoselectivities for an ample range of donor and acceptor groups.[61]

1.3.4 Conjugate addition

Although the conjugation addition is one of the most important carbon-carbon forming reactions within organic chemistry, it has received less attention than the aldol or Mannich reaction. Subsequent introduction of novel catalyst structures triggered off the expansion of this area of organocatalysis. Three different approaches have been proposed for the amine catalysed Michael reaction (Figure 10).[62] In the first mechanism the activation of the Michael acceptor is realised *via* iminium ion formation from an α,β-unsaturated carbonyl group and a chiral amine (**A**). Alternatively, the amine can play the role of a chiral base which forms an ion pair between the enolate and the chiral ammonium salt (**B**). Finally, the third mechanism involves the formation of a chiral enamine capable of reacting with the Michael acceptor (**C**).

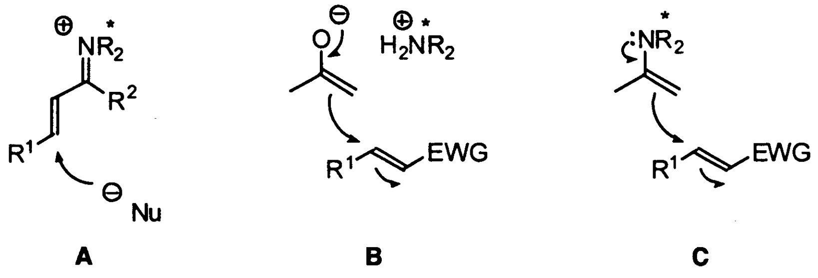
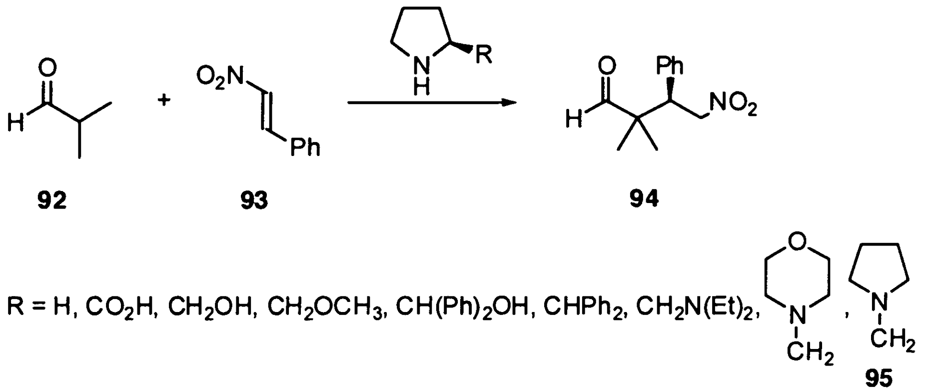


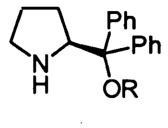
Figure 10

Barbas reported studies on a series of proline derivatives utilised to accelerate the direct asymmetric Michael reaction of α,α-disubstituted aldehydes **92** with β-nitrostyrenes **93** (Scheme 20).[63] The reactions were performed in the absence of an acid co-catalyst and with a catalytic amount of acid.



Scheme 20

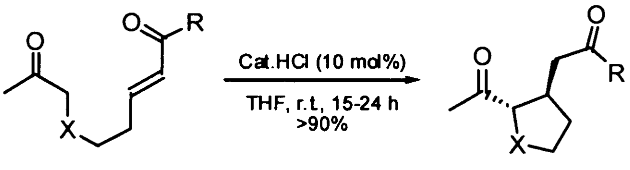
Generally, reactions were either slow or suffered from poor stereoselectivity. The most notable catalyst for this transformation was (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (**95**) which gave an excellent yield after thirty minutes (90%) with moderate enantioselectivity (50% *ee*). Addition of a small amount of acid slightly increased the stereocontrol and lowered the reaction times significantly. Further investigations on catalyst **95** showed consistent improvement in reactivity (96% yield) with good enantiocontrol (68% *ee*) after twenty four hours when the reaction was performed in DMSO:ether 3:7 mixture. Hayashi performed a similar Michael reaction between α-disubstituted aldehydes and nitrostyrene **93** catalysed with the proline derivatives **96-98**.[64]



R = TMS (trimethylsilyl) **96**
TES (triethylsilyl) **97**
TBS (*tert*-butyldimethylsilyl) **98**

Catalyst **96** completed the reaction in one hour at room temperature with a good 82% yield and excellent enantiomeric excess (99% *ee*). Subsequently, **96** proved to be a general catalyst for a series of nitrostyrenes and α-disubstituted aldehydes with satisfying yields and high levels of stereocontrol (>98% *ee*).

List used the hydrochloride salt of imidazolidinone **16** for the asymmetric intramolecular Michael reaction of a range of formyl enones **99**.[65] The reaction was performed at room temperature for fifteen to twenty four hours providing the diones **100** in yields and enantiomeric excesses greater than 90% (Scheme 21). List and colleagues assumed this intramolecular Michael reaction could proceed through an enamine mechanism. However, the high reactivity and enantioselectivity observed were also interpreted as possible evidence for a dual-activation mechanism involving both enamine and iminium ion catalysis.



99

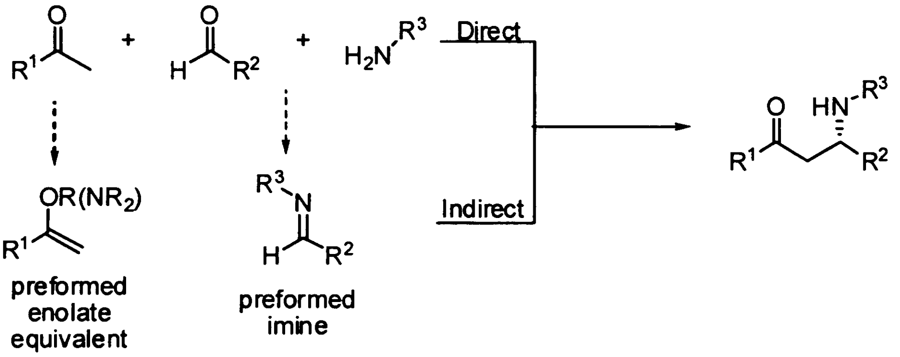
> 90% *ee*

100

Scheme 21

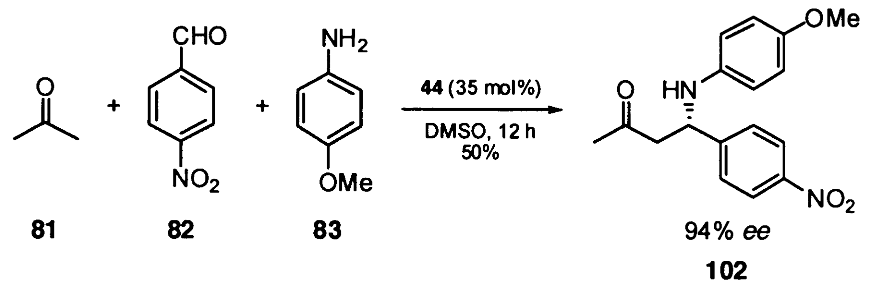
1.3.5 Direct Mannich reaction

The Mannich reaction is a powerful synthetic method for the preparation of nitrogen containing compounds. Due to the ubiquitous nature of nitrogen in drugs, natural products and agrochemical compounds this three component reaction has received increasing attention from organic chemists. Traditional synthetic strategies for this transformation includes two different approaches. As in the related aldol reaction, in the direct Mannich reaction the use of unmodified ketone donors has caused severe selectivity problems. Such limitations have been partially overcome by employing preformed enolate and/or imine equivalents (Scheme 22). Precedent for non-catalytic methods include the addition of preformed enamines to imines.[66,67,68]



Scheme 22

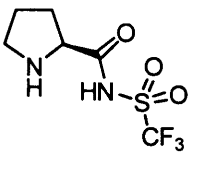
In recent years, researchers in the field of aminocatalysis have re-investigated the direct Mannich reaction offering alternative solutions for this three component transformation. List demonstrated that (*S*)-proline **44** catalyses the Mannich reaction between acetone **81**, *p*-nitrobenzaldehyde **82** and *p*-anisidine **83** in moderate yields (50%) and excellent stereoselectivity (94% *ee*, Scheme 23).[69] This experiment was based on the assumption that the nucleophilic addition of the proline enamine would be faster to an imine than to an aldehyde with imine formation with a primary amine being faster than concurrent aldolisation.



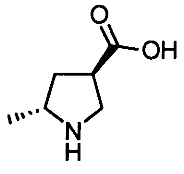
Scheme 23

Barbas showed that (S)-proline **44** is a general catalyst by synthesising a wide range of functionalised α-amino-acids, γ-lactones, oxime-functionalised amino-acids as well as pharmacological targets.[70] In addition, Hayashi expanded the library of Mannich adducts with a hydride reduction of the aldehyde forming a series of 1,3-amino-alcohols.[71]

This methodology was also extended to the investigation of alternative amine and amino-acid catalysts. List,[72] Barbas[73] and Córdova[74] independently examined a series of proline and pyrrolidine derivatives. Substitution on the 3- and 4-positions with a hydroxyl group on the proline scaffold reduced the reaction efficiency and the stereoselectivity. Exclusion of the carboxylic acid functionality resulted in no enantioselectivity, suggesting its involvement in asymmetric induction. Wang examined the pyrrolidine-sulfonamide catalyst **103** in a range of polar aprotic solvents observing good yields and excellent enantioselectivities.[75] Barbas, more recently, employed the β-amino acid **104** to catalyse the direct Mannich reaction with a range of aldehydes and a PMP (*N*-*p*-methoxyphenyl)-protected α-imino ester.[76] The reaction provided good results in a short reaction time of thirty minutes to three hours with good yield (54-92%) and remarkable enantioselectivity (>97% *ee*).

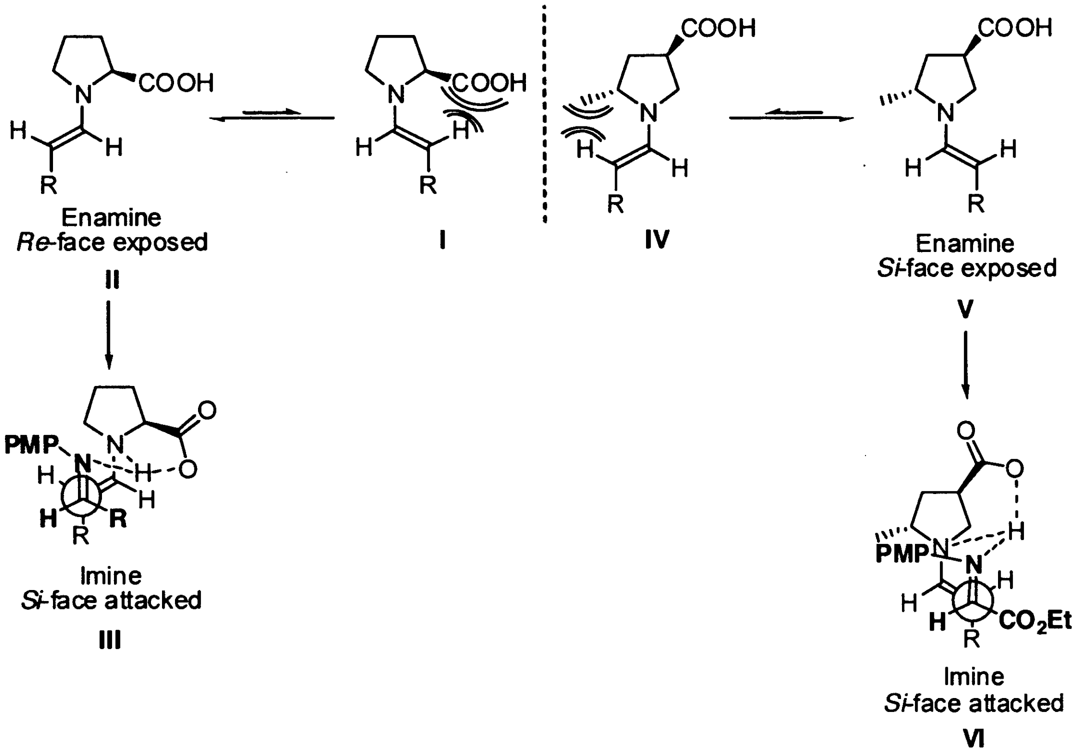


103



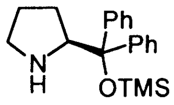
104

Within this work, Barbas proposed that the *Si*-face of the imine was selectively attacked by the *Si*-face of the enamine **V** formed with the catalyst **104**, whereas the carbon-carbon bond formation occurred at the *Re*-face of (*S*)-proline enamine intermediate **II** (Scheme 24). The conformation of the enamine **V** could be fixed through steric interactions between a substituent at the 5-position and the olefin moiety. The facial selectivity of the imine could also be controlled by a proton transfer that increases the electrophilicity of the imine.



Scheme 24

Córdova submitted the catalyst without the stereodirecting carboxylate unit **96** to a similar Mannich-type reaction between aldehydes and PMP-protected α-imino esters.[77] Despite the wide range of reactivity observed (45-68% yield), catalyst **96** showed high level of stereoselectivity with enantiomeric excesses higher than 97%.



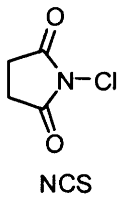
96

1.3.6 α-Substitution reactions

1.3.6.1 α-Halogenation

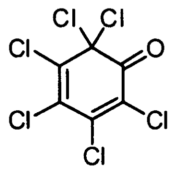
Stereoselective halogenation of organic molecules has become an important research field of the medicinal and agrochemical industries. The stereospecific replacement of carbon-hydrogen or carbon-methyl bonds with fluorine or chlorine substituents can often increase lipophilicity and metabolic stability without loss in substrate binding affinity.[78] Within this context, the α-halocarbonyl compound represents an important and versatile intermediate for the stereocontrolled construction of carbon-carbon, carbon-nitrogen, carbon-sulfur and carbon-oxygen bonds. Examples of metal-based process have been published within the last decade with Togni and Hintermann describing the first catalytic asymmetric α-fluorination of β-ketoesters by chiral titanium complexes.[79] Recently, organocatalysis has offered alternative tools for the direct α-heterofunctionalisation of aldehydes and ketones providing a novel set of small chiral molecules capable of catalysing the transformation efficiently.[80]

MacMillan has shown the use of (*S*)-proline **44** to catalyse the α-chlorination of aldehydes.[81] Although this amino-acid furnished an excellent yield at 4 °C (99%) with *N*-chlorosuccinimide (NCS) **105**, enantioselectivities were extremely poor (only 2% *ee*).



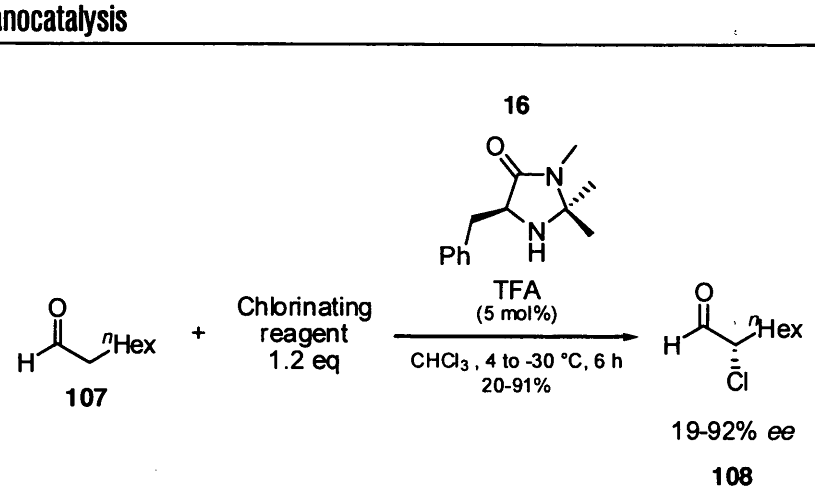
NCS

105



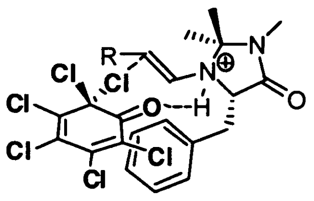
106

Use of imidazolidinone **16** provided poor results (20% yield and 19% *ee*) with NCS **105**, however, low temperatures combined with **106** displayed excellent yields (91%) and good enantioselectivities (92% *ee*, Scheme 25).



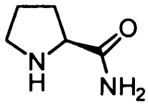
Scheme 25

MacMillan proposed the intermediate **109** to account for the increased enantioselectivity obtained with imidazolidinone **16**.TFA.



109

Jørgensen broadened the available catalyst structures for the α-chlorination of aldehydes reporting excellent reactivity (yields >90%) and enantiocontrol (70-97% ee) with the catalysts **110** and **111** and NCS **105** as the chlorine source.[82]



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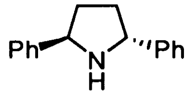
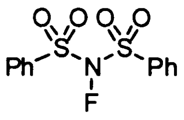
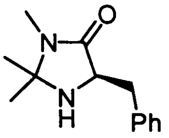


111

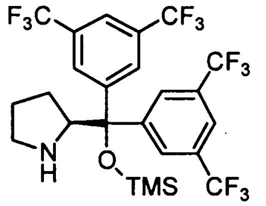
Preparation of α-fluoro, α-bromo, and α-iodo carbonyl compounds utilising enamine catalysis has been also achieved. MacMillan showed that imidazolidinone **113** was able to catalyse the α-fluorination of aldehydes in the presence of *N*-fluorodibenzenesulfonimide (NFSI) **112**, as the source of fluorine with good results (54-82% yield and 91-99% *ee*) accompanied with short reaction times.[83] Jørgensen achieved a further decrease of the reaction time and catalyst loading (1 mol%) catalysing the α-fluorination of 3-phenylpropanol with the proline derivative **71** in the presence of NFSI in methyl-*tert*-butylether (MTBE). This transformation was complete in two hours with yields >90% and up to 93% *ee*.



NFSI
112

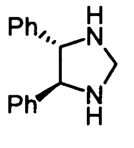


113



71

Jørgensen expanded this methodology to the α-bromoration and α-iodination of aldehydes and ketones with good to excellent yield and stereoselectivity observed with the catalysts **71** and **114** in the presence of the halogen sources **115** or **116**.[84]



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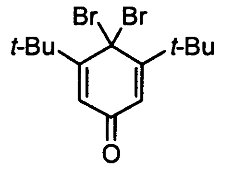

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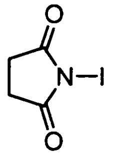
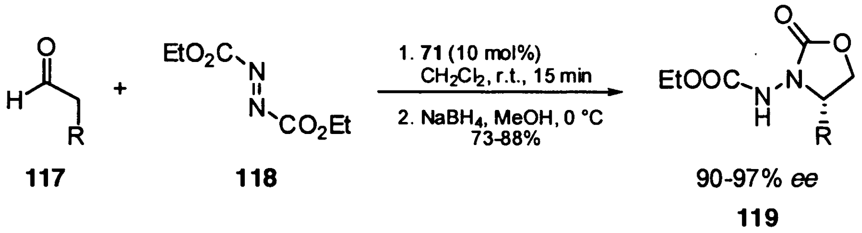


116

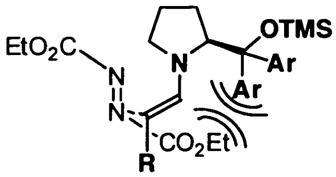
1.3.6.2 α-Amination

List[85] and Jørgensen[86] have independently carried out the (*S*)-proline **44** catalysed α-amination of a series of aldehydes, with the aza-electrophile **118**. Excellent yields and enantioselectivities (90-99% yield, >90% *ee*) were recorded throughout, highlighting the diverse nature of proline as an organocatalyst. More recently, Jørgensen has presented the pyrrolidine derivative **71** for the enantioselective α-amination of aldehydes **117** with diethyl azodicarboxylate **118** (Scheme 26).[87] The reaction was complete in 15 min at room temperature using **71** at a level of 10 mol% to give **119** in good yield (73-88%) and with excellent enantioselectivity (90-97% *ee*) after reduction and cyclization in the presence of sodium borohydride.



Scheme 26

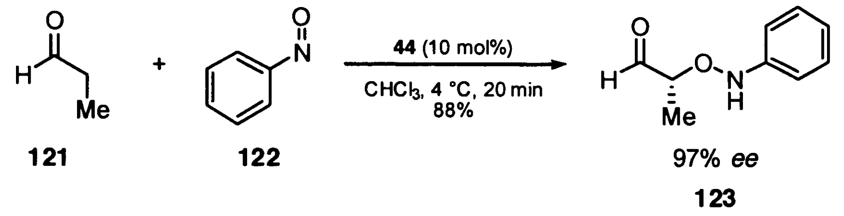
The author suggested that the observed asymmetric induction could be attributed to a steric-shielding mechanism as shown in transition state **120**.



120

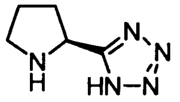
1.3.6.3 α-Aminooxylation

The α-oxycarbonyl group is a common feature of many natural and biologically active compounds and is also an important precursor in the synthesis of other building blocks. Zhong,[88] MacMillan[89] and Hyashi[90] independently reported within a very short space of time, the first example of the α-oxidation of aldehydes. (*S*)-Proline **44** was used successfully for the asymmetric α-oxyamination of propanal **121** with nitrosobenzene **122** (Scheme 27). This work was amenable to a variety of substrates with good yields and excellent levels of stereocontrol. The product **123** of the organocatalytic oxidation was found to be relatively unstable but it was conveniently reduced *in situ* with sodium borohydride. It was also demonstrated that the carbon-oxygen bond could be conveniently cleaved with copper sulfate ($CuSO_4$), Adam's catalyst or alternatively, by hydrogenolysis on Pd/C.[88,89,90]



Scheme 27

Due to the importance of the α-oxycarbonyl moiety, Yamamoto[91] and Wang[92] investigated the catalytic properties of other secondary amines **124**-**127**. The best results were achieved with the use of catalyst **124** at a level of 5 mol% for the α-aminooxylation of aldehydes and ketones. The reaction was performed in dimethylsulfoxide at room temperature providing good to high yields (65-95%) and excellent enantioselectivities (>98% *ee*) in a one hour period.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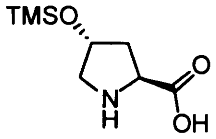
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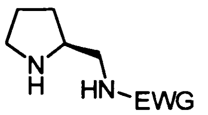
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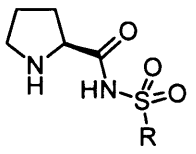
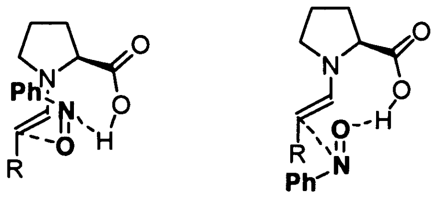

127

The common feature to all these catalysts is the acidic proton attached to the α-position of the pyrrolidine ring. It is believed that the role played by this functionality is not only to control the enantioselectivity as in other related proline catalysed reactions but also to control the regioselectivity of the reaction. Córdova[93] and Houk,[94] performed quantum mechanical computational studies on the two possible transition states **A** and **B** in attempts to explain the greater electrophilicity of the oxygen atom over the nitrogen atom of nitrosobenzene (Figure 11).



$E_{rel} = 0$ kcal mol^{-1} $E_{rel} = 2.5$ kcal mol^{-1}

A **B**

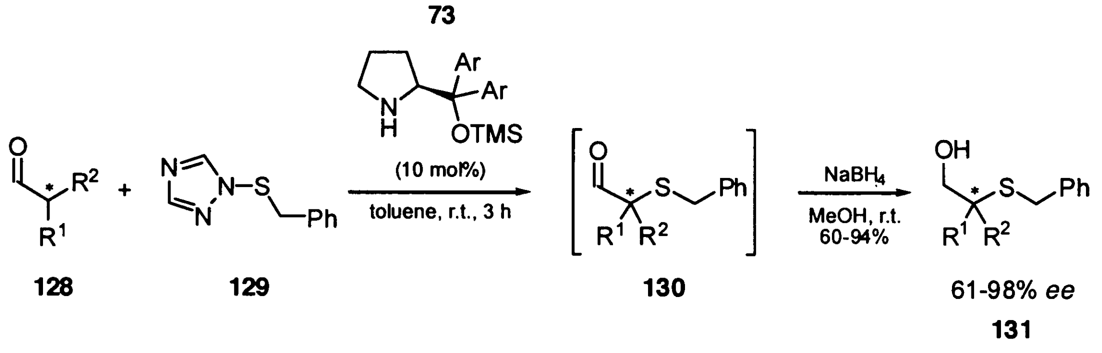
Figure 11

The higher energy calculated for the transition state **B** (E_{rel} = 2.5 kcal mol^{-1}) could account for the excellent chemoselectivity observed. The preferential protonation of the nitrogen atom could be a consequence of its higher basicity leading to the electrophilic attack of the enamine at the oxygen atom (transition state **A**, Figure 11).

Blackmond also studied the mechanism of this reaction observing a very interesting kinetic profile and a positive non-linear effect which accelerates the reaction rate.[95] These observations suggest the possibility for alternative and more complex catalytic cycles. On the other hand, Córdova did not observe a non-linear effect for the related reaction of ketones.[93]

1.3.6.4 α-Sulfenylation

As a last example of α-heterosubstitution, Jørgensen has reported the α-sulfenylation of a series of aldehydes.[96] Initially, (*S*)-proline **44** and its derivatives and a series of sulfenylation reagents were investigated within the α-sulfenylation of *iso*-valeraldehyde. The best results were obtained with the catalyst **73** and the sulfenylation reagent **129** with yield and enantioselectivity higher then 90%. It was observed that the introduction of a bulky group on the pyrrolidine scaffold prevented undesired interaction between the catalyst and the product **130** which lead to the formation of the α,α-disulfenylation by-product. Furthermore, protection of the free hydroxy unit with the trimethylsilyl group avoided the deactivation of the catalyst because of a secondary reaction with the sulfenylation reagent **129**. Subsequently, the scope of the reaction was tested using several aldehydes with an extension of the synthetic route to the alcohol **131** (Scheme 28). Product **131** was obtained in good to excellent yield (60-94%) and enantiomeric excess (61-98% *ee*) at room temperature in three hours.



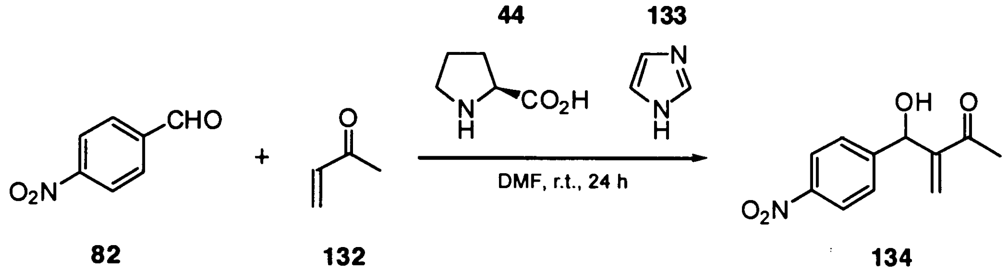
R^1 = *i*-Pr, Me, Et, Bn, Allyl, *t*-Bu, Ph
R^2 = H, Me
Ar = 3,5-CF_3-C_6H_3

Scheme 28

1.3.7 Baylis-Hillman reaction

The Baylis-Hillman reaction is a convenient process for the preparation of α-methylene-β-hydroxy carbonyl compounds from the corresponding α,β-unsaturated carbonyls with activated aldehydes. This transformation has seen an increasing popularity as a powerful synthetic method to prepare densely functionalised buildings blocks. Surprisingly, despite the fact that the Baylis-Hillman reaction involves the use of the α,β-unsaturated carbonyl system as a substrate, only few examples of enamine and iminium ion catalysed reactions are reported in the literature.[97,98]

Shi and co-workers reacted methyl vinyl ketone (MVK) **132**, with *p*-nitrobenzaldehyde **82** in the presence of catalytic amounts of (*S*)-proline **44** and a series of weak Lewis bases.[99] The reaction proceeded well with imidazole **133** to afford a good yield (60%) of the product **134** (Scheme 29). Increasing the amount of imidazole **133** and (*S*)-proline **44** up to 30 mol% gave **134** in an excellent yield (91%) under the same reaction conditions.

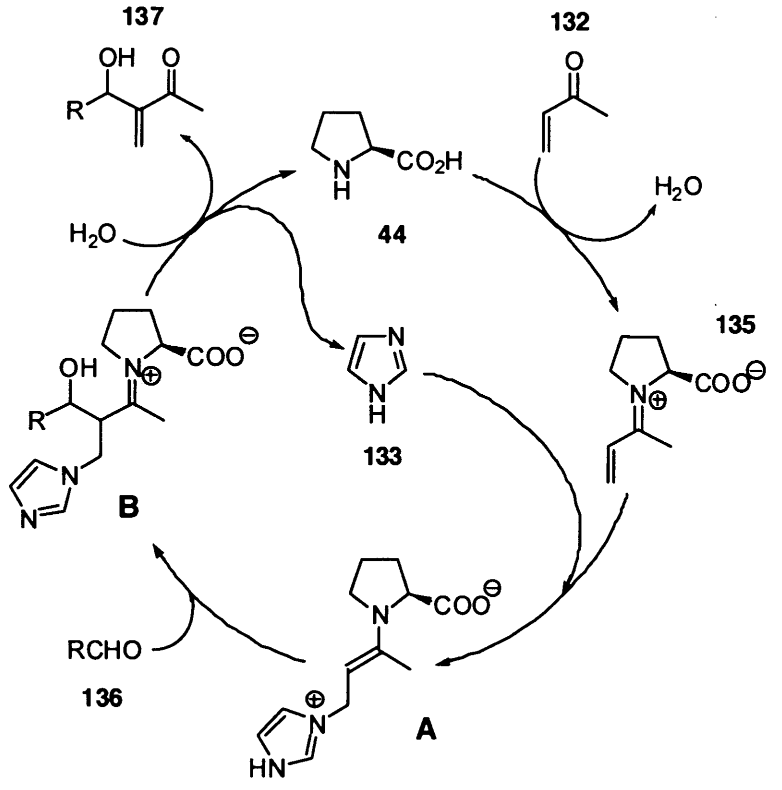


44 and **133** (10 mol%) = 60% yield
44 and **133** (30 mol%) = 91% yield

Scheme 29

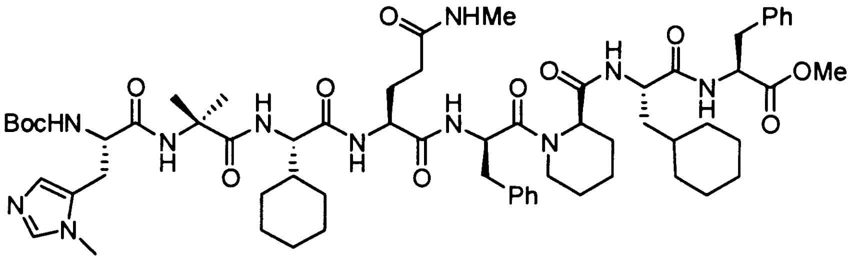
Several aryl-aldehydes were tested with methyl vinyl ketone **132**, (*S*)-proline **44** and imidazole **133** with the corresponding adducts **134** obtained in moderate to excellent yield (30-90%). In all cases the adduct was obtained with low enantioselectivity (5-10% *ee*).

The mechanism proposed by Shi for this transformation catalysed with (*S*)-proline **44** and imidazole **133** includes both enamine and iminium ion intermediates (scheme 30). (*S*)-Proline **44** reacts with methyl vinyl ketone **132** to form the zwiterionic iminium ion **135**, facilitating the conjugate addition of imidazole **133**. The resulting zwiterionic enamine **A** reacts with the aldehyde component in an aldol reaction to form the iminium ion **B**. The Baylis-Hillman product **137** is then formed *via* addition of water and hydrolysis of the iminium ion **B** to release the (*S*)-proline **44** and imidazole catalyst **133**.



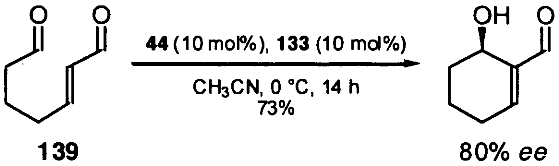
Scheme 30

Miller and co-workers, within their extensive work on peptide-based catalysts, found that the peptide **138** and (*S*)-proline **44** efficiently catalysed the reaction between methyl vinyl ketone (**132**) and a series of electron-deficient aromatic aldehydes with good to excellent yields (52-95%) and enantioselectivity (63-81% *ee*).[100] It was also noticed that the combination of **138** and (*R*)-proline led to the formation of the Baylis-Hillman adduct in 39% *ee* with a (*S*) absolute conformation whereas the use of the (*S*)-proline **44** provided **137** with the (*R*) configuration as the major enantiomer. These results suggested that the absolute sense of asymmetric induction was dictated by the stereochemistry of proline.



138

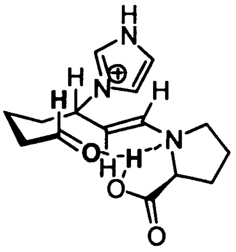
Hong[101] and Miller,[102] have reported independently the intramolecular Baylis-Hillman reaction catalysed with the combination of imidazole **133** and an α-amino-acid. Hong showed the use of imidazole **133** and (*S*)- or (*R*)-proline in the cyclization of the dialdehyde **139** to **140** with good yield (73%) and stereocontrol (80% *ee*) with (*S*)-proline **44** (Scheme 31).



139 **140**

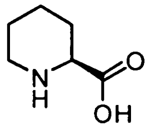
Scheme 31

The enantioselectivities observed were rationalised hypothesising that the reaction proceeds through the transition state **141**.

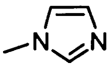


141

Miller reported that the catalytic system pipecolic acid **142** and *N*-methylimidazole **143** efficiently catalysed the intramolecular Baylis-Hillman reaction (82-94% yield and 51-84% *ee*). The reaction was best performed in protic solvents (THF:H_2O 3:1) to avoid dimerization of the starting materials.



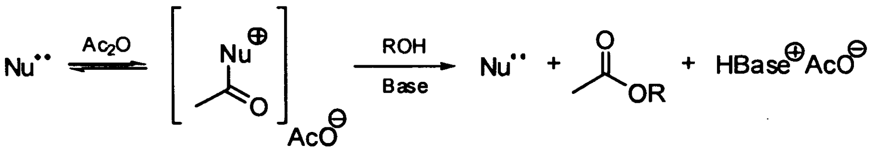
142



143

1.4 Acyl-ammonium catalysis

Nucleophiles have long been known to effectively catalyse the acylation of a wide range of alcohols (Scheme 32). Among nucleophilic catalysts, 4-(dimethylamino)pyridine (DMAP) is certainly one of the most famous and versatile. More recently, to meet the requirement for practical and efficient enantioselective acyl transfer agents a number of non-enzymatic chiral catalysts have been developed. Most of the notable structures have been designed to incorporate the 4-aminopyridine subunits into a chiral environment providing high levels of reactivity and selectivity.

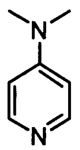


Scheme 32

This section of *Chapter One* is dedicated to the analysis of the structural motifs required for effective non-selective and selective acylation of alcohols. These will include 4-aminopyridines such as DMAP and related derivatives, and chiral acyl transfer agents such as the Fu, Fuji, Vedejs, Spivey, Miller and Birman catalysts.

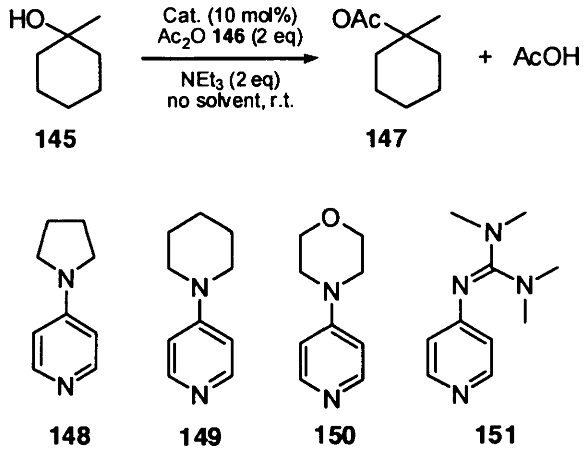
1.4.1 4-(Dialkylamino)pyridine

4-(Dialkylamino)pyridines are one of the most popular and well known catalysts for the esterification of alcohols and other important transformations involving acyl transfer.[103,104] The catalytic potential of this class of organic compound was reported in the late 1960's independently by Litvinenko[105] and Steglich.[106] They observed a 10^4-fold rate enhancement in the benzoylation of *m*-chloroaniline when 4-(dimethylamino)pyridine (DMAP) **144** was used instead of pyridine. Since this first indication, 4-(dialkylamino)pyridines were found to have general applicability for the catalysis of a wide variety of reactions,[107,108] including polymerisation variants.[14]



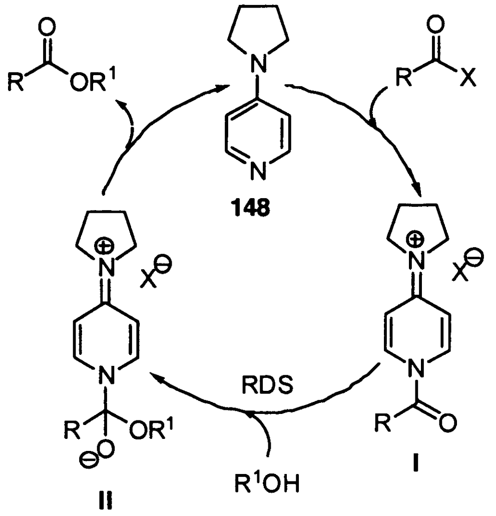
144

Hassner *et al.* compared the catalytic activity of a series of aminopyridine derivatives for the acylation of 1-methylcyclohexanol **145** with acetic anhydride **146** (Scheme 33).[109] Within this series were included DMAP **144**, 4-pyrrolidinopyridine (PPY) **148**, 4-piperidinopyridine **149**, 4-morpholinopyridine **150**, catalyst **151** and a variety of 2- and 3- substituted amino pyridines.



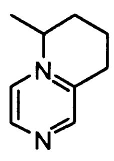
Scheme 33

The most effective acyl transfer agent was 4-pyrrolidinopyridine **148** with a relative rate of 2.4 compared to **144** as the reference. It was noted that the order of catalytic activity of 4-aminopyridine derivatives **148>144>149>150** mirrored the order of reactivity of cyclohexanone derived enamines towards electrophiles. Additionally, they observed a qualitative correlation between the degree of shielding of the pyridyl β-hydrogen atom in the ^1H NMR spectra of the catalytically active 4-aminopyridine derivative and their catalytic efficiency (see *section 3.3.3*). Hassner hypothesised that the extent of electronic conjugation between the lone pair of electrons of the exocyclic nitrogen atom and the carbonyl function through the pyridyl ring was a key factor in stabilising the acylpyridinium intermediate **I** (Scheme 34).

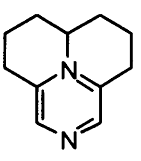


Scheme 34

Steglich and Mayr proposed the aminopyridines **152** and **153** in which the N'-1 nitrogen atom was incorporated in one or two six-membered ring as good candidates.[110] The design of these DMAP derivatives evolved from previous work of Hassner and studies upon the stabilization 4,4'-bis(dialkylamino)benzhydryl cations.[111] They reasoned that the conformational rigidity combined with inductive electron donating effects of an alkyl group in the *meta*-position could increase the electron density at the pyridine nitrogen atom, with consequent enhancement of the stabilization of the acylpyridinium salt.



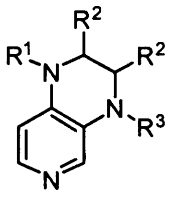
152



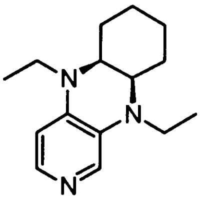
153

153 exhibited impressive catalytic activity in the acylation of 1-ethynylcyclohexanol with acetic anhydride **146** providing a kinetic rate six times higher than DMAP **144**. Catalyst **153** even outperformed **148** which was considered the best catalyst known for this transformation, by a factor of 2.5.

Zipse challenged, more recently, the latter catalyst examining a novel family of 3,4-diaminopyridines **154** in the acylation of 1-ethynylcyclohexanol with acetic anhydride **146** and *iso*-butyric anhydride.[112] The best result was obtained with compound **155**, whose catalytic performances were comparable to that of modified DMAP **153**. Zipse also reported the strong influence of the donor ability of the bridge (R^2) on the catalytic activity, while the presence of *N*-methyl or *N*-ethyl substituents (R^1 and R^3) appeared to be slightly less relevant.



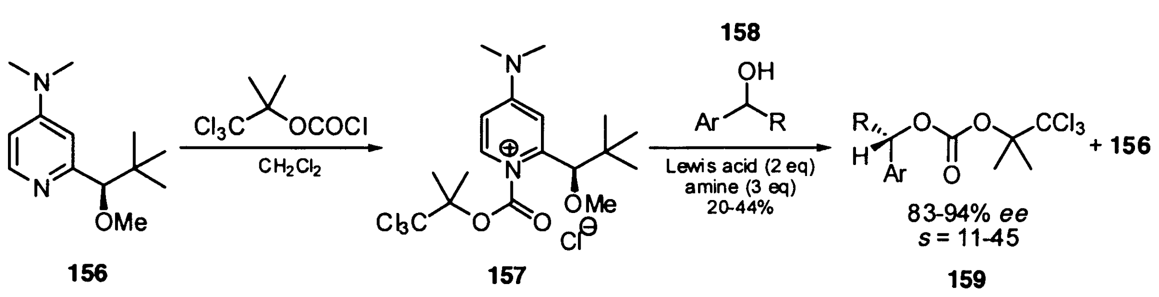
154



155

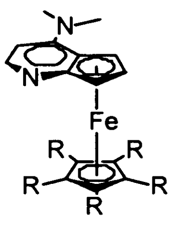
1.4.2 Enantioselective acylation

Over the last decade, the development of non-enzymatic catalysts for the kinetic resolution of alcohols has driven the interest of several research groups. The design of a number of these novel enantioselective acyl transfer agents has been based on the 4-alkylaminopyridines such as DMAP **144** and PPY **148**. Vedejs offered one of the first examples of a modified DMAP catalyst in the enantioselective acylation of a series of secondary alcohols (Scheme 35).[113] The pyridinium intermediate **157** was preformed and used in a stoichiometric amount in the presence of a Lewis acid and an amine as auxiliary base. This transformation showed good to excellent levels of enantiocontrol (83-94% *ee*) and selectivity (*s* = 11-45) with conversions ranging from 20% to 44% (with a theoretical yield limit of 50%).[114]

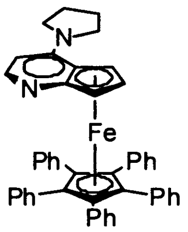


Scheme 35

Fu introduced the "planar chiral" DMAP derivatives **160**, **161** and **162** as enantioselective catalysts.[115] **160** was utilised at a level of 2 mol% for the kinetic resolution of a racemic mixture of 1-phenylethanol in the presence of acetic anhydride **146** showing poor enantiocontrol and low selectivity (*s* = 1.7). Thus, catalyst **160** was modified to structure **161** increasing the steric bulk of the lower cyclopentadienyl unit, by the incorporation of a Fe(C_5Ph_5) complex. **161** showed a significant advance in enantiocontrol (95% *ee*) and selectivity (*s* = 14) for the unreacted 1-phenylethanol with a conversion of 62%. This catalyst was subsequently demonstrated to be general at promoting the kinetic resolution of a series of secondary alcohols in high enantiomeric excess (92-99% *ee*) and selectivity (*s* = 2-10) at low (2-10%) and high conversions (51-69%). Further developments of the latter catalyst to the structure **162** with incorporation of a PPY unit in the catalyst architecture, led to an efficient acyl transfer agent for secondary alcohols and amines.[116]

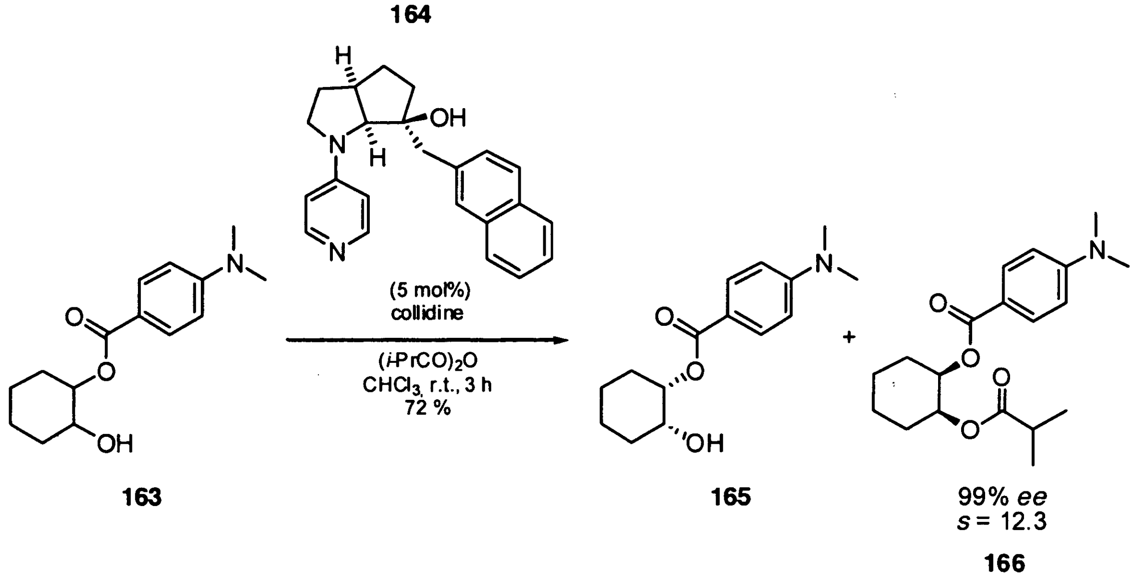


R = Me **160**
Ph **161**



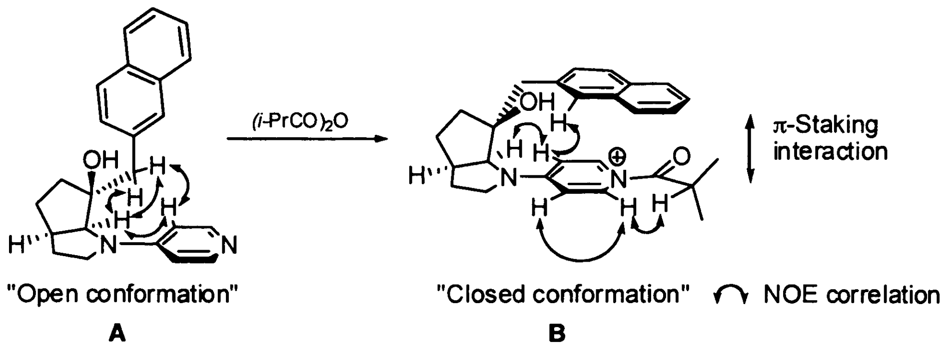
162

Fuji developed catalyst **164** for the enantioselective acyl transfer based on the well known PPY **148**.[117] **164** (5 mol %) was employed in the kinetic resolution of a racemic mixture of alcohol **163** in the presence of *iso*-butyric anhydride as the acylation agent (Scheme 36). The acylated product **166** was recovered in 99% *ee* and good selectivity (*s* = 12.3) at 72% conversion.



Scheme 36

Fuji's laboratory, through rigorous NOE ^{1}H NMR studies carried out on **164**, determined that in order to satisfy the steric hindrance requirements, the naphthalene group and the pyridine unit are positioned far away from each other in what was referred to as an "open conformation" (**A**, Figure 12). However, the formation of the acylpyridinium salt forces the catalyst to adopt the "closed conformation" **B** through a π-π interaction between the naphthalene group and the acylpyridinium moiety itself. This interaction is sufficient to block the *Si*-face of the carbonyl and leave the *Re*-face open to reaction with alcohols. Furthermore, it was proposed an additional π-stacking interaction between the aromatic unit of the substrate **163** and the electron poor acylpyridinium ion accounted for the high enantioselectivity observed.



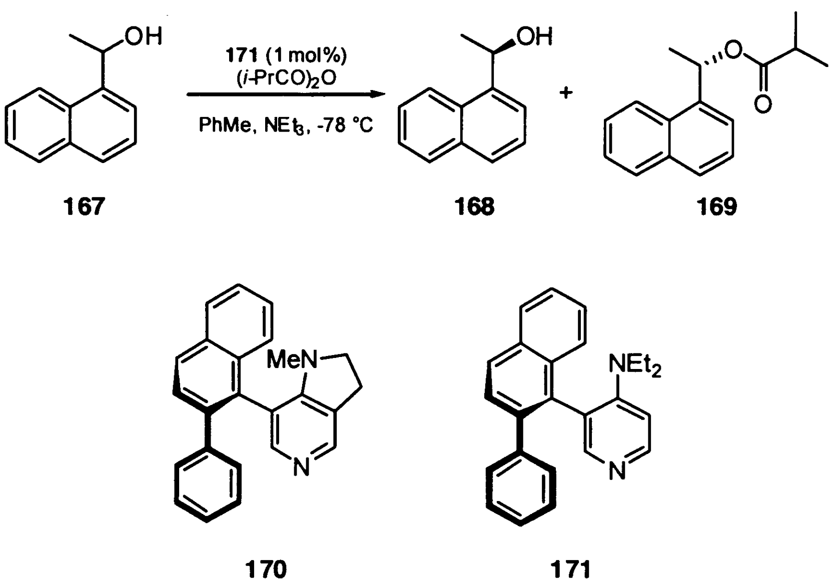
"Open conformation"
A

"Closed conformation"
B

NOE correlation

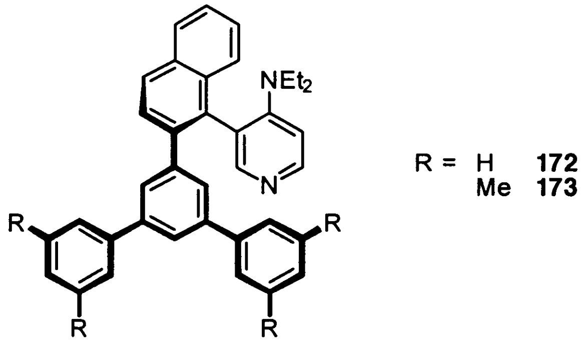
Figure 12

Spivey and co-workers examined the kinetic resolution of aryl alkyl secondary alcohols through the use of the axially chiral analogues of DMAP **170** and **171** (Scheme 37).[118] **171** showed good levels of enantiomeric excess for the acylated enantiomer **169** (84% *ee*) and selectivity (*s* = 24.5) at 42 % conversion. This catalyst revealed two drawbacks, requiring relative long reaction time (typically ten hours) and the use of low temperature (-78 °C) to obtain satisfactory levels in selectivity.

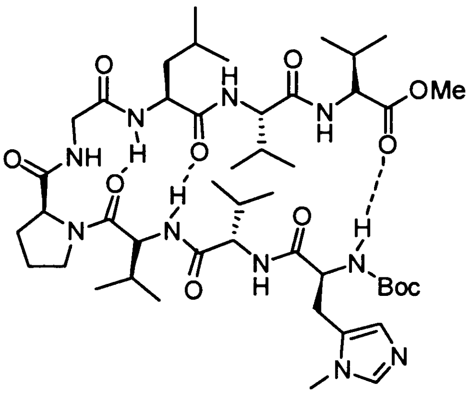


Scheme 37

More recently, Spivey's group has further investigated the enantioselective acylation of *sec*-alcohols introducing the terphenyl-containing catalysts **172** and **173** as an evolution of the previous modified DMAP **171**.[119] **172** and **173** showed modest increase in stereoselectivity and significant decrease in reactivity suffering from relatively long reaction times (**173** showed a 55% conversion in a twelve hour period).

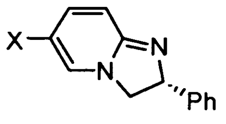


Miller *et al.* developed peptide catalysts containing an *N*-alkylimidazole subunit **174** for the enantioselective acylation of secondary alcohols with acetic anhydride **146** by the formation of an acyl imidazolium intermediate.[120] It was noted that an enhanced rigidity and an increased structural complexity led to highly enantioselective catalysts (selectivity observed up to *s* = 51).



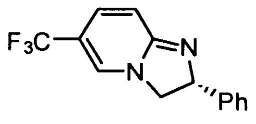
174

Recently, Birman has developed an alternative class of asymmetric acyl transfer catalyst based on 2,3-dihydroimidazo-[1,2-a]pyridine **175**.[121] Within this new family, catalyst **176** showed the best results in the acylation of secondary aryl carbinols with modest to excellent selectivity (*s* = 8-85) at conversions ranging from 21% to 55% in an average reaction time of eight hours (*s* = 85 was obtained after fifty two hours at 48% conversion, Scheme 37).

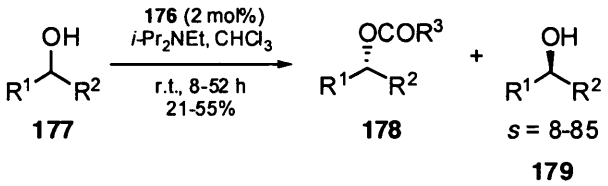


175

X = H, Br, NO, CF_3



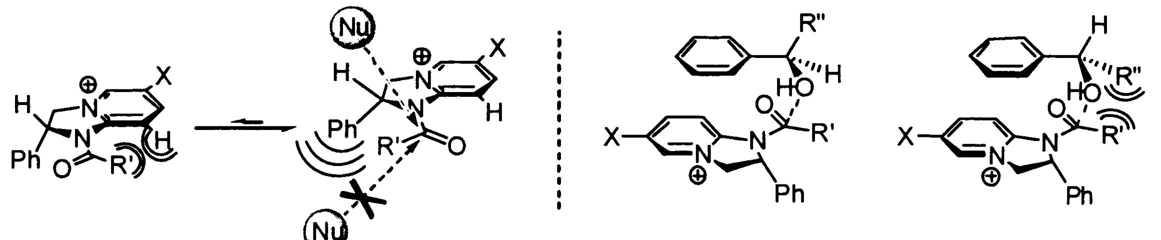
176



R^1 = Ph, 1-naphthyl, m-Me-C_6H_4, m-MeO-C_6H_4, m-Br-C_6H_4
o-Me-C_6H_6, 2,4,6-$Me_3C_6H_2$
R^2 = Me, Et, i-Pr, t-Bu
R^3 = Me, Et

Scheme 38

The high levels of enantioselectivity measured by Birman and co-workers were explained by hypothesising that the acylated catalyst assumes a preferential conformation **II** because of the greater steric interaction of the hydrogen at C-7 with the R' group (conformation **I**) than with the carbonyl oxygen (Figure 13). The phenyl unit would then prevent the approach of nucleophiles from the bottom face discriminating the two faces of the carbonyl. Furthermore, the experimental data suggested that the discrimination appeared to take place between the hydrogen and the alkyl group of the substrate, rather than between the phenyl and the alkyl group. Therefore, they proposed a model where the aryl group of the substrate is stacked on top of the pyridinium ring of the catalyst through π-π and cation-π interactions, while the alkyl group is repelled from the acyl portion for steric reasons (**III** and **IV**).

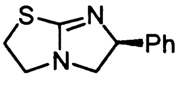


I II Favored III Disfavored IV

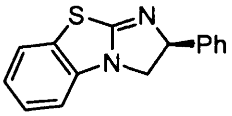
Figure 13

Very recently, Birman's laboratories have introduced and investigated a novel family of catalysts for the kinetic resolution of aryl *sec*-benzylic alcohols based on the commercially available tetramisole **180**.[122] Limited modifications of **180** to **181**, provided a remarkably enantioselective acyl transfer catalyst with unprecedented selectivity factors in the range 100-

350. Comparison of tetramisole **180** and **181** also suggested that an extended π-system in the structure of the catalyst significantly increased the chiral recognition of this class of substrates although it was not found to be essential.



180



181

1.5 Summary

Organocatalysis has had a significant impact on organic synthesis over the past ten years developing new catalytic asymmetric methodology for a significant number of organic reactions. Within this context, enamines, iminium ions and acyl-ammonium catalysis have claimed a prominent role providing novel synthetic solutions for a large number of organic transformations such as conjugate addition, nucleophilic substitution, Michael, Mannich, Diels-Alder and Baylis-Hillman reactions amongst others. Surprisingly, while the unique reactivity of enamines and iminium ions has long been used in organic synthesis, only recently, amines have been employed as catalysts despite the fact that they are readily available in enantiomerically pure form from several sources.

As discussed in this introduction, small chiral amines can be employed as catalysts for a wide variety of enantioselective transformations with high levels of reaction efficiency and enantiocontrol. For example, proline and its derivatives have successfully been used in carbon-carbon (aldol, Diels-Alder, Michael), carbon-oxygen (α-oxyamination), carbon-nitrogen (α-amination) and carbon-sulfur (α-sulfenylation) bond forming reactions. Furthermore, incorporation of simples aromatic and non-aromatic secondary amines such as DMAP **144** or tetramisole **180** within a chiral environment has led to the birth of a novel class of enantioselective acyl-ammonium transfer catalyst which have shown an impressive increase in catalytic efficiency and selectivity.

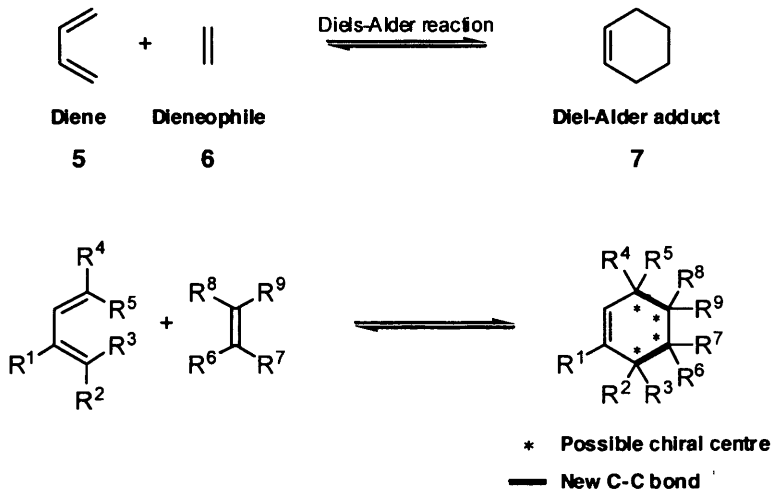
Although the rapid expansion of organocatalysis and aminocatalysis over the past few years have delivered a rich set of novel catalysts, additional investigations are required to further advance this methodology. For instance, even though the acylation of tertiary and secondary alcohols by the use of stereoselective acyl transfer catalysts has shown considerable improvement, the performances offered by enzymatic catalytic systems still remain significantly higher. Therefore, the need to improve reactivity and selectivity in an economic manner requires further investigations which promise to deliver more exciting discoveries.

Diels-Alder Reaction 2

Results and Discussion

2.1 Diels-Alder reaction

Since the Diels-Alder reaction was discovered in 1928[123] it has maintained a prominent role in the synthesis of complex targets. The reaction has had extensive use in medicinal chemistry and total synthesis as a powerful method to synthesise intricate compounds with several condensed rings such as hormones, terpenes, sesquiterpenes and alkaloids.[124] The [4+2] cycloaddition of a diene **5** and a dieneophile **6** (Scheme 39), generates not only a new cyclohexene ring **7** through the formation of two new s-bonds, but up to four contiguous stereocenters in one step.



Scheme 39

The importance that this reaction still plays in organic synthesis has driven the research of a large number of scientists towards new solutions and methodologies to deliver higher yielding and enantioselective transformations.[4a] Lewis acid catalysis has offered a plethora of synthetic strategies using the variegated reactivity of metals.[124b] Recently, organocatalysis has stood out as a new protagonist in the field of asymmetric synthesis (for more information see *section 1.2.1.1*).[11]

The vast number of publications related to aminocatalysis confirmed an increasing interest for amine-based catalysts. Several compounds have demonstrated remarkable catalytic activity;

however, the turnover rate and stereoselectivity shown by enzymes remains elusive leaving significant scope for further investigations of novel catalyst structures.

The work described in *Chapter Two* is aimed at exploring a new class of catalyst for the activation of α,β-unsaturated carbonyl compounds and also to probe the nature of face-face π-π interactions as a tool for the discrimination between the prochiral faces of α,β-unsaturated carbonyl compounds in aminocatalysed Diels-Alder reactions.

2.1.1 Nature of α,β-unsaturated carbonyl compounds and aminocatalysis

α,β-Unsaturated carbonyl compounds are recognised as useful pro-chiral starting materials for a range of aminocatalytic transformations, for example the Friedel-Crafts reaction,[32,33] Baylis-Hillman reaction,[125] intramolecular Michael reaction,[126] and cycloadditions ([3+2][127] or [4+2][128]), amongst others. The extensive utilization of α,β-unsaturated aldehydes, ketones and acrylates to achieve stereoselective transformations has drawn attention to the conformational aspects of α,β-unsaturated carbonyl systems. In work reported by Houk, the conformational preferences of this functional group were studied.[129] It was shown that the *s-cis* conformation is slightly favoured over the *s-trans* conformation for uncomplexed acrylates (acrylic acid **182** and methyl acrylate **183**), although the *s-trans* conformation is the most stable form for a simple α,β-unsaturated aldehyde such as acrolein **1** (Figure 14).

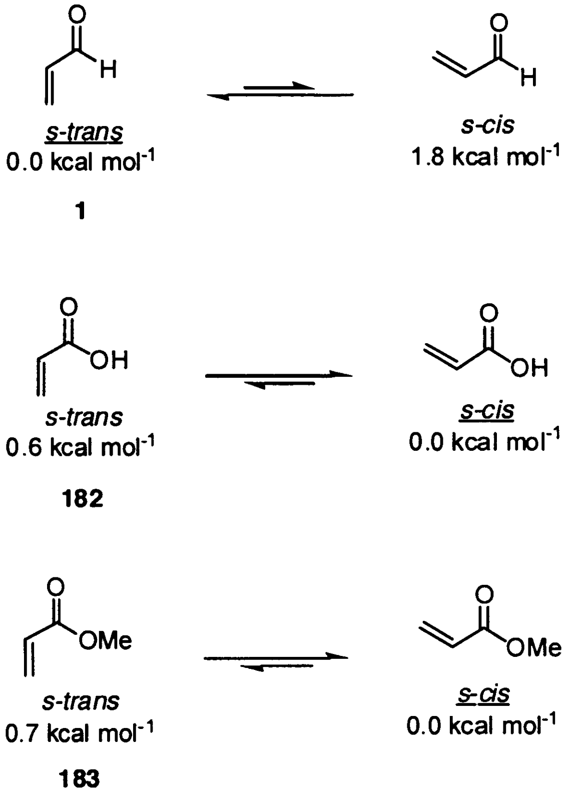


Figure 14

Complexation *via* a sigma (σ) orbital interaction between the lone pair located on the carbonyl oxygen and the metal of an achiral Lewis acid leads to four possible conformations shown in Figure 15. In this case, calculation and experiments performed by Houk indicates that Lewis acid complexation of these acrylates dramatically stabilised the *s-trans* conformation relative to the *s-cis*. This implies that Lewis acid catalysed activation of a α,β-unsaturated carbonyl compound proceeds preferentially through the *s-trans* conformation. Researchers should therefore acknowledge these findings as a valuable starting point in the design of new catalysts.

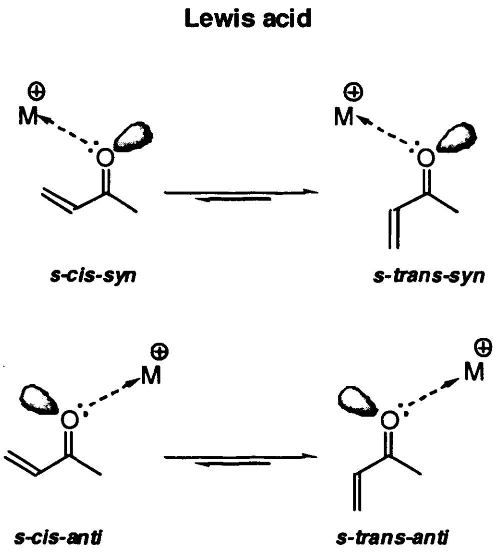


Figure 15

Recently, the Lowest Unoccupied Molecular Orbital (LUMO) lowering activation of α,β-unsaturated aldehydes and ketones has been achieved *via* iminium ion catalysis using a secondary amine as described by MacMillan.[15] The traditional complexation with a Lewis acid is replaced with π-bond formation resulting in only two possible arrangements for the activated species **184** (Figure 16). This new approach has constituted a valuable platform for the development of a wide range of chiral amines able to control the geometry of the iminium ion in carbon-carbon bond forming reactions (Figure 16).

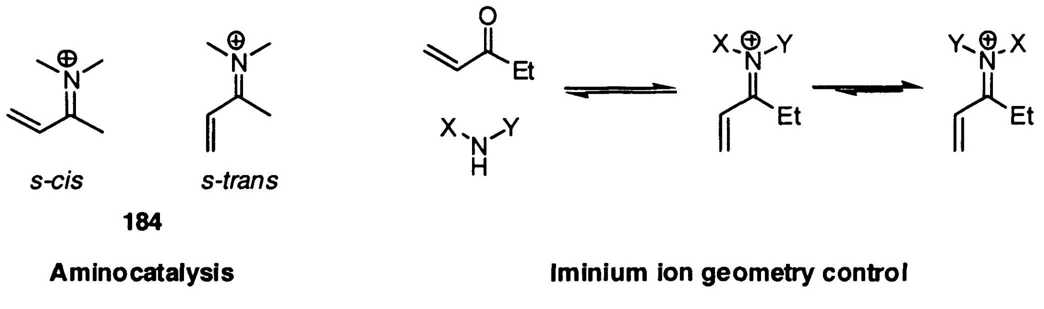
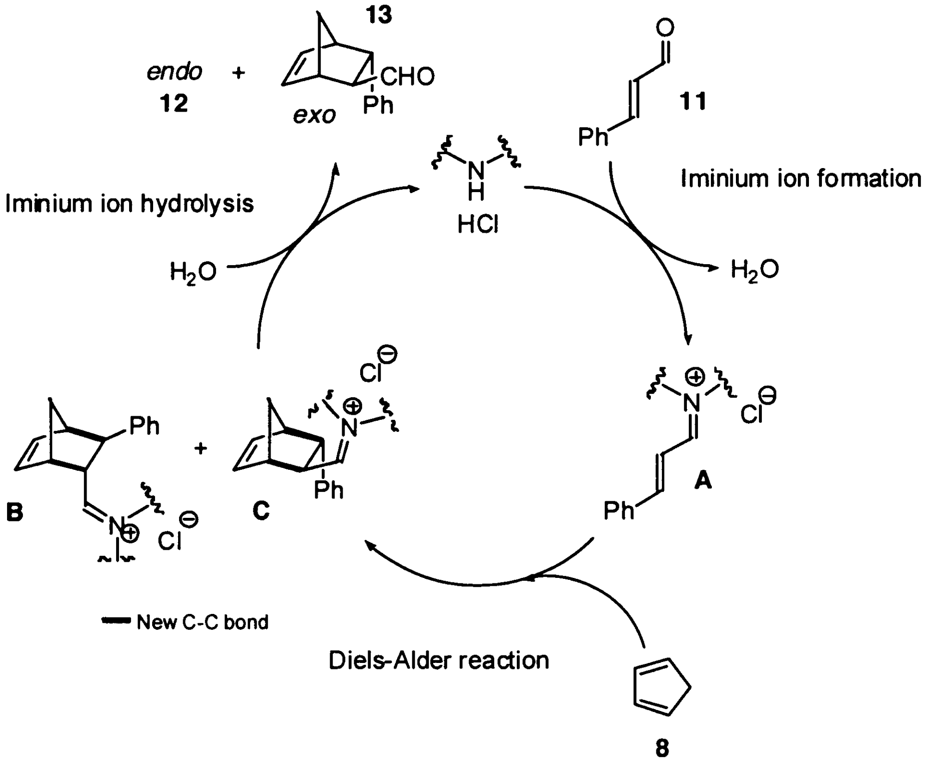


Figure 16

2.1.2 Diels-Alder catalytic cycle

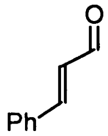
The proposed mechanism for the iminium ion catalysed Diels-Alder reaction is shown in Scheme 40.[11] Nucleophilic attack of the secondary amine lone pair on the carbonyl of the α,β-unsaturated aldehyde **11** initiates the catalytic process. This condensation leads to the formation of a new activated species, the iminium ion **A**, and has been proposed to be the Rate Determining Step (RDS) for this catalytic cycle.[33] The formation of the iminium ion lowers the energy levels of the LUMO of the α,β-unsaturated system and decreases the energy gap between the Highest Occupied Molecular Orbital (HOMO) of the diene **8** and the LUMO of the dieneophile providing a high level of overlap between these two sets of orbitals. These alternative energy pathways accelerates the reaction rate of the [4+2] cycloaddition in the second step, providing the Diels-Alder adducts as their iminium ions **B** and **C**. In the last step, the water present in the system facilitates the hydrolysis of iminium ion releasing the Diels-Alder adducts **12** and **13**, regenerating the catalyst.



Scheme 40

2.1.3 Diels-Alder substrates

A diversity of secondary amines have been used as catalysts adopting this strategy. Literature precedent has shown the potential of this class of compounds to catalyse the Diels-Alder reaction between α,β-unsaturated aldehydes and various dienes.[11] Within our group, the reaction between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8** was employed to evaluate our catalysts. As a standard protocol, the two substrates were tested for twenty four hours with 10 mol% catalyst loading, to provide reasonable reaction rates.[130]



(*E*)-cinnamaldehyde

11

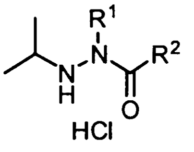
cyclopentadiene

8

2.2 Proposed catalyst design

2.2.1 Previous work within the group

The investigation of secondary hydrazines as a novel class of catalyst in organocatalysis is one of the main interest within Tomkinson's research group. As reported by Cavill and Jones, the acyclic secondary amines with structure **185** have shown excellent catalytic activity in the Diels-Alder reaction *via* iminium ion catalysis.[131] It has been suggested than in order to increase the catalytic turnover and generate the activated iminium ion a high level of nucleophilicity in the amine is required.[11] It is also well known that the nucleophilicity of a heteroatom can be greatly increased by the introduction of an adjacent heteroatom bearing a lone pair of electrons. This is known as the a-effect.



185

R^1 = H, Me, *t*-Bu
R^2 = Ph, OEt

2.2.2 The a-effect

The first definition for the α-effect was enunciated by the Glossary of Terms used in Physical Organic Chemistry as *"the enhancement of nucleophilicity that is found when the atom adjacent to a nucleophilic site bears a lone pair of electrons"*.[132] This definition turns out to be somewhat ambiguous since no reference nucleophile is specified. Thus, subsequently, the α-effect was redefined as *"the positive deviation of an α-nucleophile (an α-nucleophile being an unshared pair of electrons on an atom adjacent to the nucleophilic site) from the Brønsted-type plot of log K_{nuc} versus pK_a constructed for a series of normal related nucleophiles"*.[133] This particular phenomenon was first reported in 1947 but did not receive its name until 1962 when Edwards and Pearson coined the term "*α-effect*".[134]

The numerous theoretical and experimental studies reported in the literature testify that the mystery about the origins of these observations is still open. Several plausible explanations have been offered including:

I. Repulsion of adjacent pairs of electrons promotes the destabilisation of the ground state of the nucleophile.[135]

II. The transition state is stabilised by the inclusion of an extra pair of electrons.[136]

III. The solvation of the reactive site is reduced due the presence of the nearby extra pair of electrons.[137]

IV. Electron pair-pair repulsion raising the nucleophile's highest occupied molecular orbital (HOMO).[138]

The a-effect is generally believed to emerge from several contributions. Ground state destabilisation due to the pair-pair repulsion is often cited as the principal source of this phenomenon. Theoretical explanation suggests that a linear combination of the atomic orbitals results in a new set of two molecular orbitals (Figure 17). The out-of-phase combination is raised by an additional amount of energy (ΔE_i) relative to the in-phase combination, thus leading to an overall destabilisation of the system. The enhanced nucleophilicity can then arise from two different causes:

I. The overall increase in energy of the molecule's ground state (ΔE_i) and/or;

II. The increase in energy ($\Delta E+\Delta E_i$) of the HOMO itself.

In accordance with Frontier Molecular Orbital (FMO) Theory, the rate enhancements measured are due to reduction of the energy gap between the HOMO of the nucleophile and the LUMO of the substrate which promotes a greater overlap of orbitals.

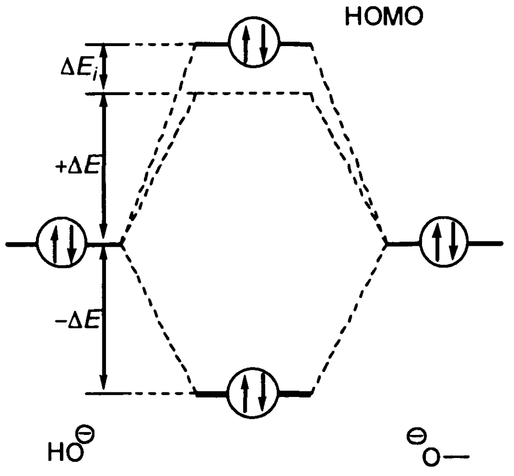
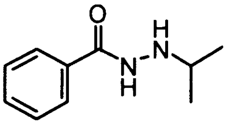


Figure 17

While a number of models have been proposed, the origins of the a-effect remains elusive and not completely understood. To date, the vast amount of experimental data collected does not allow the construction of a unique theory capable of accounting for this phenomenon. On the other hand, the incontrovertible reactivity shown by the a-nucleophiles can be a valuable basis for the design of a new class of catalyst.

2.2.3 Proposed aminocatalyst design

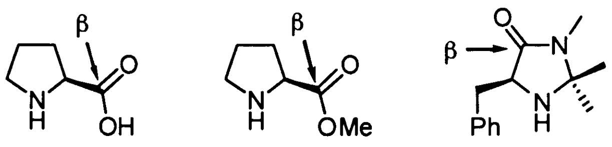
One of the most interesting result in the iminium ion catalysed Diels-Alder reaction within the group was shown by the catalyst **23**.



23

The design of this molecule was based on two findings:

I. The nucleophilicity of a secondary amine can be significantly increased by the a-effect;
II. Molecules such as (*S*)-proline **44**, (*S*)-proline methyl ester **14**, as well as imidazolidinone catalyst **16**, have shown a noteworthy catalytic activity in a number of reactions in organocatalysis. The analysis of these compounds shows they contain an electron withdrawing carbonyl functionality in a β-position from the nucleophilic amine group (Figure 18).



44 **14** **16**

Figure 18

The structure of the catalyst **23** has incorporated both these characteristics into a disubstituted hydrazide with an electron withdrawing carbonyl functionality in the β-position to the nucleophilic amine (i.e. attached to the α-heteroatom). Moreover, initial investigations involving the catalyst **23**, showed remarkable levels of catalytic activity when it was utilised as a HX salt. In this context, previous work revealed that as the pK_a of the acid co-catalyst increased, the length of time necessary for the reaction to proceed increased (Table 1).[20] The first series of catalytic runs also highlighted how the characteristic *endo:exo* ratio 1:2 of the mixture of Diels-Alder adducts was not affected as different counter ions were employed. Therefore, we sought to prepare a new set of salts for the catalyst **23** introducing, Br^-, I^-, and PF_6^- as counter-ions (the HCl salt of **23** was used as a standard in the catalytic cycle) in the attempt to affect the usual *endo:exo* ratio.

Table 1. Results of the study into the use of various protonic acids of catalyst **23**.[a]

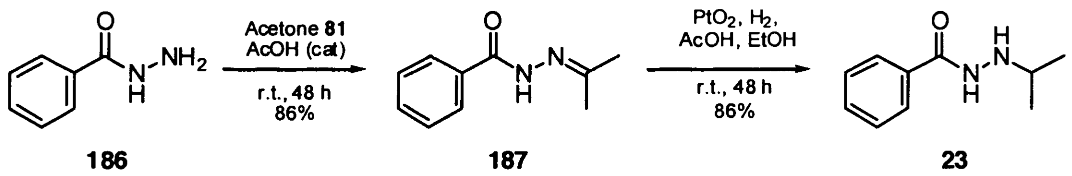
Entry	Protonic Acid	pK_a	Time (h)	Yield (%)	*Exo*:*Endo*[b]
1	HCl	-8	6	82	67:33
2	TFA	0.2	24	81	67 33
3	$MeSO_3H$	-2	48	74	64:36
4	PhCOOH	4.2	48	10	53:47

(a) All reactions were carried out in methanol:H_2O 19:1 at room temperature with 10 mol% catalyst **23**. (b) All *exo:endo* ratios were obtained from the ^1H NMR of the crude reaction mixture.

2.3 Catalysis: initial investigations

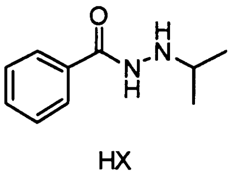
2.3.1 Synthesis of benzoic acid *N-iso*-propylhydrazide and its salts.

Our synthetic investigations were initiated by preparation of the hydrazate **23**.[131] Benzoichydrazide **186** was stirred in an excess of acetone for two days at room temperature in the presence of a catalytic amount of acetic acid (Scheme 41). After aqueous work-up, hydrazone **187** was recovered in an 86% yield, without any further purification required. Hydrazone **187** was then reduced by stirring with Adam's catalyst (PtO_2) in a solution of ethanol and acetic acid, under an atmosphere of hydrogen for two days at room temperature. The mixture was filtered through a plug of Celite® and neutralised with saturated aqueous sodium bicarbonate. Evaporation of the organic phase afforded the desired benzoic acid *N'*-*iso*-propylhydrazide **23** in an 86% yield (74% overall yield from commercially available benzoichydrazide **186**), without further purification.



Scheme 41

The HCl salt **188** of this amine was prepared by treating the compound **23** with gaseous hydrochloric acid bubbled through ether for two hours. The excess of acid and solvent was then evaporated under reduced pressure. A similar procedure was followed to prepare the HBr and HI salts **189** and **190** respectively (see *section 5.2*, general procedure **D**). The hexafluorophosphoric acid (HPF_6) salt **191** was made by dissolving the amine **23** in a mixture of hexafluorophosphoric acid (60% in water) and dichloromethane. The solution was stirred for two hours and the excess of acid and solvent was removed *in vacuo*.

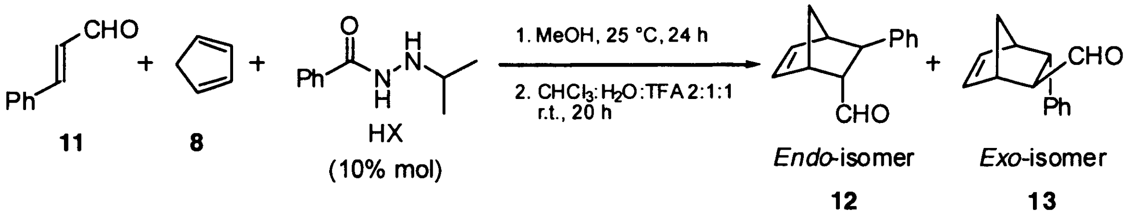


HX = HCl **188**
HBr **189**
HI **190**
HPF_6 **191**

Having prepared these four salts we were then in a position to investigate if altering the size of the counter-anion had any effect on the *endo*:*exo* ratio observed in the Diels-Alder reaction.

2.3.2 Standard catalytic test

To verify the efficiency of our catalysts in the Diels-Alder cycloaddition we decided to use the reaction employed within previous work in the group between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8**.[131] The aldehyde (1 eq) and the catalyst (10 mol%) were stirred for five minutes in methanol, to commence the formation of iminium ion (Scheme 42). Freshly cracked cyclopentadiene (3 eq) was added into the mixture and the reaction was allowed to stir for twenty four hours at 25 °C. The reaction was stopped *via* removal of cyclopentadiene **8** under reduced pressure, then the mixture was stirred for an additional twenty hours in a biphasic system prepared with chloroform, water and trifluoroacetic acid. This further work up was necessary to hydrolyse the dimethyl acetals formed during the catalytic reaction and generate the Diels-Alder adducts as a combination of aldehydes **12** and **13**. This procedure concludes with a basic work up to remove the acid and a purification by flash column chromatography to isolate the desired target compound 3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde as its *exo*-**13** and *endo*-**12** isomers.



HX = HCl **188**
HBr **189**
HI **190**
HPF_6 **191**

Scheme 42

2.3.3 Analysis of the Diels-Alder results

The rapid monitoring of the relative reactivity of a series of secondary amines was conveniently achieved by ^{1}H NMR analysis of the crude reaction mixture of the Diels-Alder reaction.[131] The different chemical environments of the three aldehydes appeared as three distinct signals in the ^{1}H NMR spectra (Figure 19). The aldehyde signal of (*E*)-cinnamaldehyde **11** is located at δ9.64 between the signals of the *exo*-**13** isomer at δ9.85 and *endo*-**12** isomer at δ9.53. The integration of these signals was employed to determine the conversion from the crude reaction mixture and the *endo:exo* ratio of the Diels-Alder products. The relative integrations of the product peaks could also be used to determine which variety of catalysis had occurred. In general, the iminium ion catalysed Diels-Alder reaction showed a prevalence of the *exo*-adduct with an *endo:exo* ratio close to 1:2.

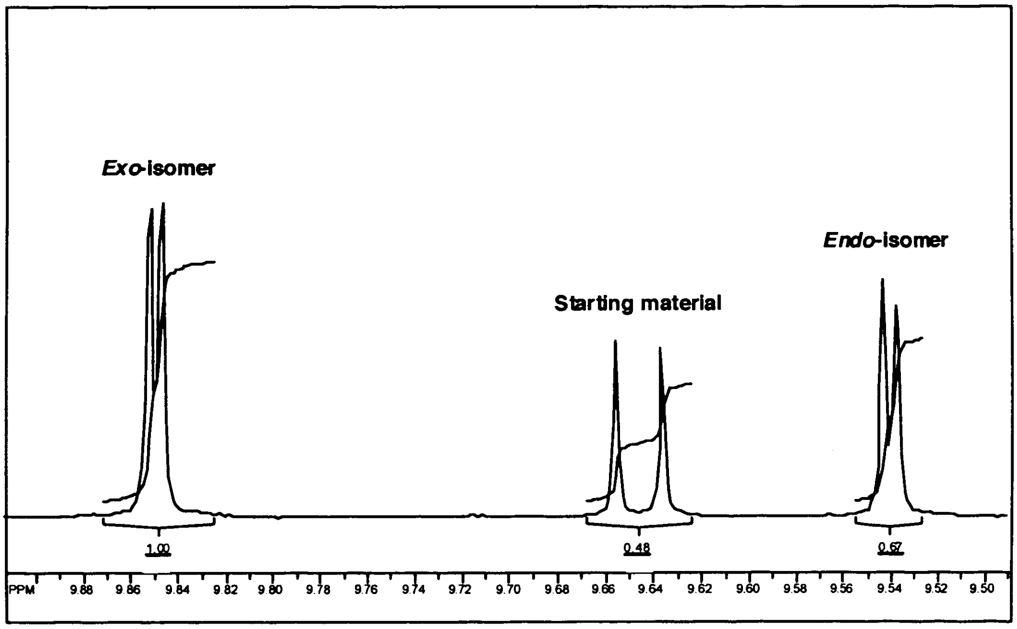


Figure 19

2.3.4 Counter-anion effect verification

This new set of salts **188-191** was tested in the Diels-Alder reaction under the catalytic conditions described above (see *section 2.3.1*). In line with previous tests carried out within the group the HCl salt of **23** showed a notable catalytic activity in the reaction between cyclopentadiene **8** and (*E*)-cinnamaldehyde **11**, providing a 97% conversion to the adducts after twenty four hours (Table 2, entry 1). Increasing the size and the nature of the counter-anions revealed similar levels of activity 97% (Table 2, entries 2-4).

Table 2. Results of the study into the use of various counter-anions in the Diels-Alder reaction.[a]

Entry	HX salt of **23**	*Endo:Exo*[b]	Conversion (%)[c]
1	**188**	33:67	97
2	**189**	35:65	97
3	**190**	32:68	98
4	**191**	30:70	98

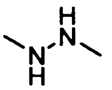
(a) Reactions were carried out at 25 °C for 24 h with 10 mol% catalyst in methanol. (b) *Endo:exo* ratios determined by ^{1}H NMR of crude reaction mixture. (c) All conversions obtained as described in *section 2.3.3.*

Despite the presence of different counter-anions with increasing size, the diastereomeric ratio of the reaction products was not affected. All the salts showed an *endo:exo* ratio of approximately 1:2 that confirmed the occurrence of an iminium ion catalysed reaction (Table 2). It was reasoned that due to the polar nature of the solvent the counter-anion was remote from the iminium ion during the bond formation and had little influence. However, this is not consistent with the lack of the effect using the non-coordinating anion PF_6^- (Table 2, entry 4).[139]

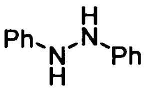
2.4 An alternative electron withdrawing group

2.4.1 Methanesulfonate group

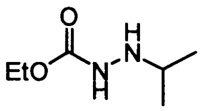
Previous experiences accumulated within the group showed that the reaction rate was increased by the presence of an electron withdrawing carbonyl functionality in the β-position of the nucleophilic nitrogen (Table 3).[131] Curiosity into what lay behind the need for an electron withdrawing group (EWG) on the α-heteroatom, led us to synthesise a further compound varying the nature of this group. Hence, we modified the catalyst **23** replacing the carbonyl unit with a methanesulfonate group.



192



193



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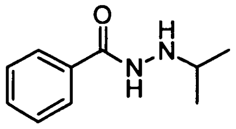


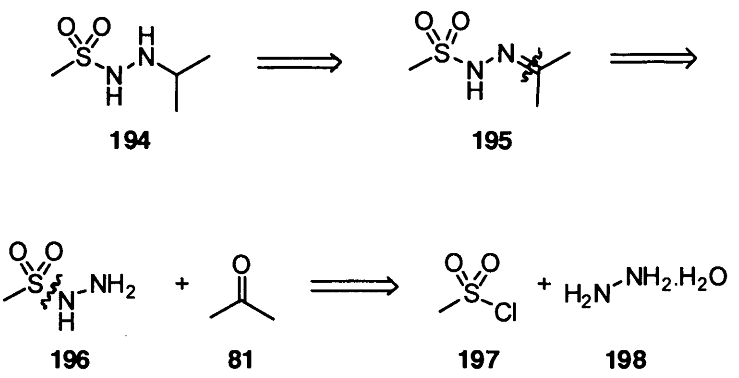
23

Table 3. Results of the study into catalyst structure.[a]

Entry	Catalyst	Time (h)	Yield (%)[e]
1[d]	**192**	48	37
2[c]	**193**	48	17
3[c]	**24**	6	74
4[c]	**11**	24	97

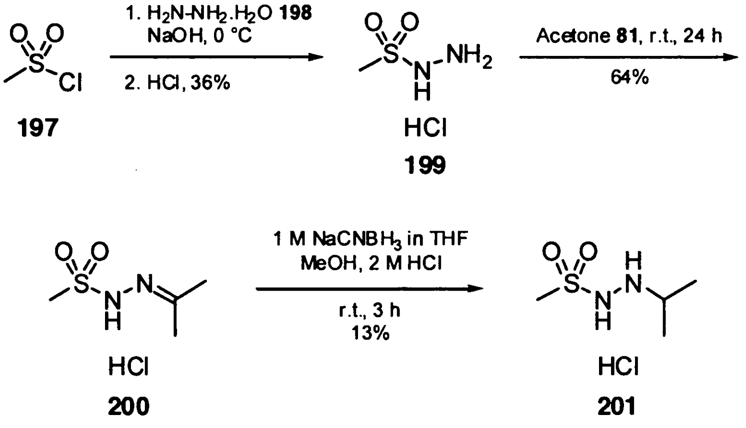
(a) All reactions were carried out in methanol:H_2O 19:1 at room temperature with 10 mol% catalyst. (c) Catalyst used as its hydrochloride salt. (d) Catalyst used as a bis-hydrochloride salt. (e) Isolated yield.

Analysis of hydrazide **194** revealed that synthesis could be achieved from the corresponding methanesulfonyl chloride **197**. After reaction of hydrazine hydrate **198** with methane sulfonyl chloride **197**, the catalyst **194** could be obtained *via* a reductive amination protocol a similar method to that utilised in the preparation of **23** (Scheme 43).



Scheme 43

To a stirred solution of hydrazine hydrate **198** in water methanesulfonyl chloride **197** was added slowly at 0 °C (Scheme 44).[140] After the addition of 2 M aqueous sodium hydroxide such that temperature did not exceed 8 °C, the mixture was treated with hydrochloric acid. A small amount of di-methanesulfonyl hydrazide precipitated from the reaction mixture was filtered off before the volatiles were removed under reduced pressure. The crude product was recrystallised twice from boiling ethanol to give the sulfonamide **199** as its HCl salt in 36% yield. Compound **199** was subsequently stirred at room temperature for twenty four hours in an excess of acetone **81**. The hydrochloride salt **200** which precipitated out of solution on formation was filtered and purified by recrystallisation from ethanol/ether to provide a colourless solid in 64% yield. The Adam catalyst (PtO_2), employed previously in the synthesis of **23**, was utilised in the first attempt to reduce the carbon-nitrogen double bond. Compound **30** was allowed to react for forty eight hours at room temperature under an atmosphere of hydrogen. We adopted the same work up described in the synthesis of catalyst **23** (see *section 2.2.4*) but only the non-reacted free-base starting material **195** was recovered. Because of the lack of reactivity of the catalyst for our substrate, we decided to employ a more specific reducing agent for the carbon-nitrogen double bond using sodium cyanoborohydride ($NaCNBH_3$). To a stirred solution of the hydrochloride salt **200** and sodium cyanoborohydride (1 M solution in tetrahydrofuran) in methanol was added 2 M hydrochloric acid at a rate sufficient to maintain pH of three to four. After three hours the pH was adjusted to 1 and the methanol was removed under reduced pressure before a basic work up which afforded the desired catalyst **194** as a colourless oil. This oil was treated with 2 M hydrochloric acid in ether to prepare the more stable HCl salt **201** in a yield of 13% (overall yield 3%). Due the high solubility of the oil **194** in water, the last step of this synthesis showed poor yields despite numerous extractions of the aqueous phase. However, the small amount of this catalyst isolated was sufficient to perform the catalytic runs using our standard protocol.



Scheme 44

2.4.2 Diels-Alder cycloaddition catalysed by sulfonyl hydrazide

The standard Diels-Alder cycloaddition of (*E*)-cinnamaldehyde **11** and cyclopentadiene **8** was employed to verify the catalytic efficiency of the hydrochloric salt **201** (See *Section 2.3.1*). The result of this investigation is tabulated below (Table 4).

Table 4. Result of the study into EWG effect.[a]

Catalyst	Time (h)	*Endo:Exo*[b]	Conversion (%)[c]
201	24	42:58	69

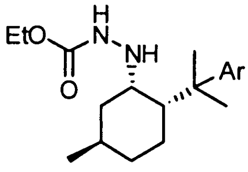
(a) Reactions were carried out in methanol at 25 °C for 24 hours with 10 mol% catalyst. (b) *Endo:exo* ratios determined by ^1H NMR of crude reaction mixture. (c) The conversion was obtained as described in *section 2.3.3.*

Catalyst **201** showed a slight preference for the *exo* isomer which could be attributed to a cycloaddition catalysed *via* an iminium ion process. Surprisingly, this reaction offered a disappointing conversion of 69% after twenty four hours, a result rather distant from the outcomes observed with catalyst **23**. However sulfonyl hydrazide **201**, performed well when compared to the catalysts without an electron withdrawing group **192** and **193**, confirming that an electron withdrawing group in the ß-position relative to the nucleophilic nitrogen has an effect on the reaction rate. Unfortunately, the increase of the electron withdrawing strength did not correspond to the acceleration of the reaction rate we hoped for. The decrease in the conversion could be due to the presence of two oxygen atoms on the sulfur group increasing the steric hindrance. Additionally, the electron withdrawing effect may be counteracting the contribution of the a-effect.

2.5 Proposed catalyst design for the asymmetric Diels-Alder reaction

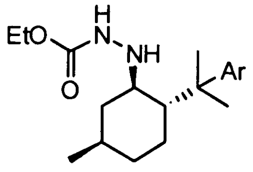
2.5.1 Previous work within the group

Preliminary studies of acyclic secondary amines as organocatalysts for the Diels-Alder reaction, suggested that a hydrazide with structure **185** could be used as an interesting template for the design of a new family of asymmetric catalysts. A second suggestion came from the impressive asymmetric induction demonstrated by the 8-aryl menthol chiral auxiliary in a plethora of organic transformations involving α,β-unsaturated carbonyl systems.[141] It has been proposed that the high level of asymmetric induction observed for these reactions is due to a face-face π-π interaction between the unsaturated carbonyl moiety and the aromatic ring incorporated in the structure of the auxiliary, which are ideally situated for such an interaction to exist. Therefore, following these two suggestions, Cavill and Tomkinson developed a new family of catalysts based on the structures **202** and **203** for an iminium ion catalysed Diels-Alder reaction (Figure 20).[131]



Cis-catalyst

202



Trans-catalyst

203

	Cis catalysts	*Trans* catalysts
Ar = *p*-CF$_3$Ph	**204**	**208**
Ph	**205**	**209**
p-OMePh	**206**	**210**
H$_4$-Naphtyl	**207**	**211**

Figure 20

In an attempt to alter the electronic density on the aromatic ring, this first set of hydrazides was prepared introducing three different aryl units, as well as the simple phenyl group used as reference (Figure 20). All the catalysts were submitted to a series of catalytic tests with (*E*)-cinnamaldehyde **11** and cyclopentadiene **8** (Table 5).

Table 5. Results of experiments using catalysts with modified electronics.[a]

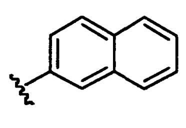
Entry	Catalyst	*Endo*:*Exo*[b]	*Exo* (%) *ee*[c]	Entry	Catalyst	*Endo*:*Exo*[b]	*Exo* (%) *ee*[c]
1	**204**	25:75	40 (2*S*)	5	**208**	36:74	7 (2*R*)
2	**205**	30:70	44 (2*S*)	6	**209**	21:79	10 (2*R*)
3	**206**	34:66	47 (2*S*)	7	**210**	35:65	21 (2*R*)
4	**207**	32:68	47 (2*S*)	8	**211**	37:63	39 (2*R*)

(a) All reactions were carried out in $CH_3CN:H_2O$ 19:1 at -20 °C for 48 h with 10 mol% catalyst as an HCl salt. (b) All *exo*:*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture. (c) Enantiomeric excesses were determined by HPLC of the product as 2,4-DNPH derivative using a reverse phase Chiaralcel OD-R column eluting with $CH_3CN:H_2O$ 8:2 at a rate of 0.5 mL/min (detector wavelength 365 nm).

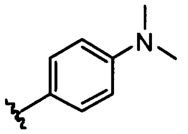
Catalysts **204-207**, with a "*cis*" relationship between the amino unit and the aromatic group, showed analogous results in terms of *endo*:*exo* ratio and enantiomeric excess (Table 5, entries 1-4). In addition, the *exo*-(2*S*) isomer was formed preferentially with all four hydrazides. These outcomes suggested that modifications to the electronic nature of the aromatic group had no effect on the stereochemical control of the Diels-Alder adducts **12** and **13**. The observed enantioselectivity was attributed to steric interactions rather than electronic factors for this family of hydrazides.

Hydrazides **208-211** with a "*trans*" relationship between the amino unit and the aromatic group, showed a similar *endo*:*exo* ratio of the Diels-Alder adducts **12** and **13**. Also, an increase in enantioselectivity when an electron donating substituent was introduced on the aromatic ring was observed. Starting from the electron deficient hydrazide **208** (7% *ee* (2*R*), Table 5, entry 5) the geometric control of adducts **12** and **13** was increased up to 21% *ee* (2*R*) (Table 5, entry 7) with the electron rich hydrazide **210**. A further improvement in enantioselectivity was achieved with hydrazide **211**, incorporating a tetrahydronaphthyl substituent on the catalyst structure, which provided a pleasing 39% *ee* (2*R*) (Table 5, entry 8). This outcome was attributed to a presumably additional shielding effect between the large substituent and one face of the dienophile, inducing an increased facial selectivity in the ensuing Diels-Alder cycloaddition with (*E*)-cinnamaldehyde **11**. Additionally, 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.

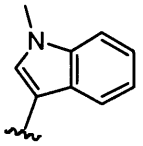
Indications collected from these preliminary results were used to design a second group of hydrazides based on the scaffolds **202** and **203**. We therefore sought to increase the π-stacking interaction introducing large aromatic architectures and electron rich aryl groups on our arenes such as naphthalene **212**, *N,N*-dimethylaniline **213** and *N*-methylindole **58**.



212



213

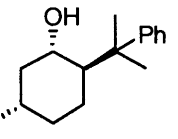


58

An extensive investigation regarding the best reaction conditions was also carried out by Cavill with a variety of solvents and temperatures. A mixture of acetonitrile and water 19:1, was reported as the best optimal solvent using this catalytic class for this cycloaddition which we decided to adopt in our investigation.

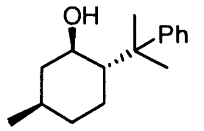
2.5.2 8-phenyl menthol and π-stacking interactions

Since its introduction in 1975 by Corey and Ensley, [142] 8-phenyl menthol **214** and **215** has been widely studied and utilised as a chiral auxiliary in organic chemistry. Auxiliaries **214** and **215** have provided dramatically superior levels of diastereomeric discrimination when compared to other commonly used chiral auxiliaries, such as menthol **216**.



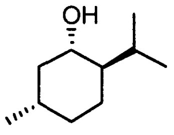
(+)-8-phenyl menthol

214



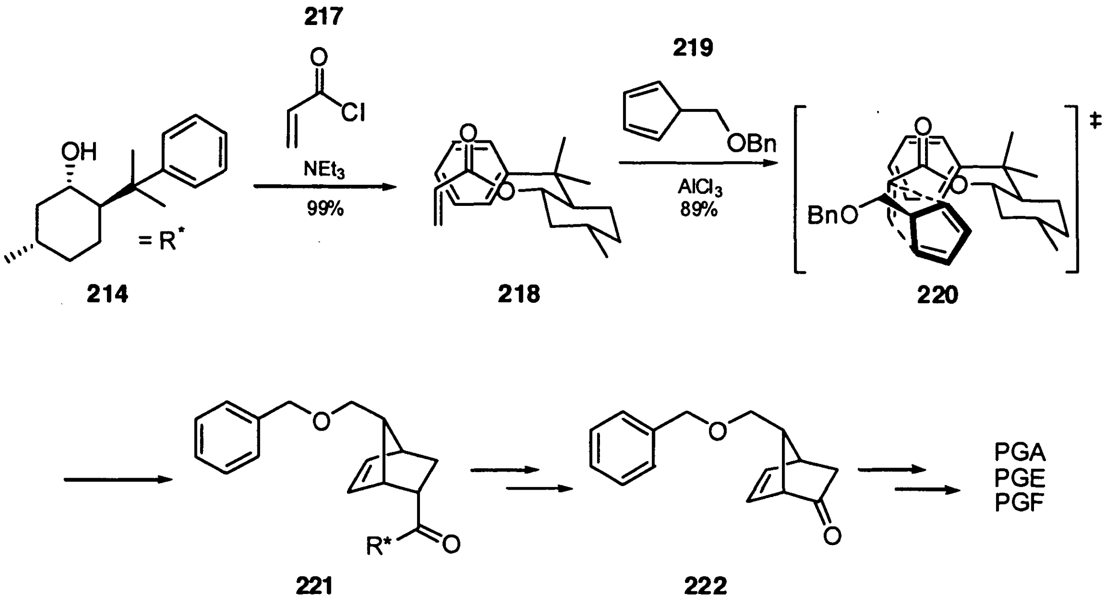
(-)-8-phenyl menthol

215



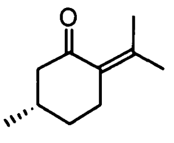
216

Corey designed 8-phenyl menthol **214** and **215** as a chiral auxiliary for use in the synthesis of a key prostaglandin intermediate, in order to circumvent the need for classical chemical resolution. The key step in this synthesis was the formation of the intermediate **221** *via* a Diels-Alder reaction between acrylate **218** and 5-benzyloxymethyl-cyclopentadiene **219**. The high diastereomeric selectivity required for this transformation was achieved by incorporating the auxiliary **214** on route to intermediate **218**. The Diels-Alder cycloaddition furnished adduct **221** in 89% yield and 97% diastereomeric excess (Scheme 45).[142] Synthesis of chiral auxiliary **214** was carried out from (-)-pulegone **223**, under the protocol described by Ort.[143]

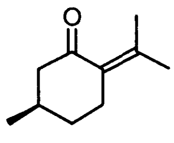


Scheme 45

Unfortunately, the use of (+)-8-phenyl menthol **214** as a general chiral auxiliary has been restricted by the prohibitive cost of (-)-pulegone **223**. However, its enantiomer (-)-8 phenyl menthol **215**, which can be formed from (+)-pulegone **224**, has been extensively used as a chiral auxiliary for several chemical transformations including the ene reaction,[144] conjugate additions,[145] as well as [3+2][146] and [4+2][142] cycloadditions.



(-)-pulegone
223



(+)-pulegone
224

It has been postulated that the impressive levels of stereocontrol observed for the use of 8-phenyl menthol **214** and **215** as a chiral auxiliary result from an interaction between the aromatic ring and the acrylate group. This π-shielding of the rear face of the unsaturated unit forces the reaction selective to the top face, leading to the observed stereoselectivity (**A**, Figure 21). The nature of this interaction may either be of steric origin, merely serving as physical barrier against the approach to the shielded face, or of electronic origin, wherein a stabilising interaction is generated between the two components. When the intramolecular distance between a pendant aryl group and a unsaturated moiety is within the 3-4 Å range (**A**), both categories of interactions are frequently labelled as p-stacking, regardless of whether a stabilising interaction exists. In recent reports, the p-stacking interaction has been defined as a positive attractive interaction, either face-to-face (**B**) or face-to-edge (**C**), between the p-cloud of an unsaturated system and the aryl moiety (Figure 21).[141]

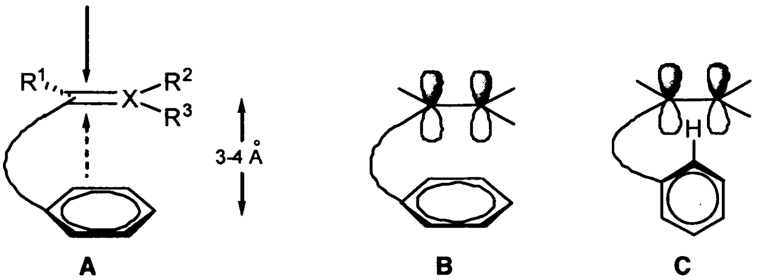
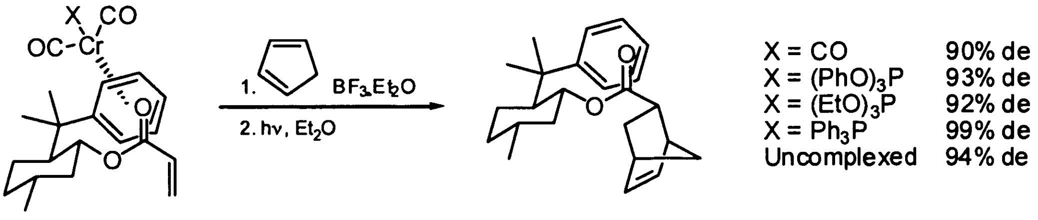


Figure 21

A Diels-Alder cycloaddition between cyclopentadiene **8** and a series of arenes **225** was used by Jones and Chapman to investigate the tuning of the π-π interaction.[147] The geometry of the stacking face of the aryl group was left unchanged, but its electronic density was influenced by ligand substitution of a complexed η6-chromium carbonyl group (Scheme 46).

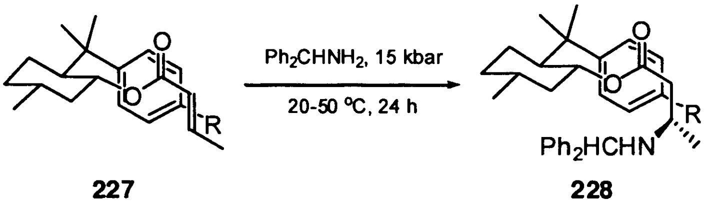


225 **226**

Scheme 46

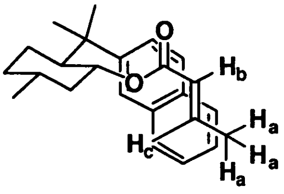
The results summarised in Scheme 46 revealed a direct correlation between the electron donor capacity of the ?6 complex and the diastereomeric excess observed in the Diels –Alder cycloaddition. Although variations of steric hindrance do not considerably effect the diastereoselectivity, the diastereomeric excesses observed are clearly dominated by the nature of the ligand used, confirming the presence of additional electronic effects. These results, coupled with similar observations reported by others authors,[148] suggested that the π-π interaction can be modulated by tuning the p-donor ability of the arene.

In order to study the π-π interaction, a different approach was developed by D'Angelo.[149] The conjugate addition of amines to 8-aryl menthol crotonates was investigated through structural modifications of the aryl group, which provided valuable insight into the requirements for effective stereocontrol and therefore π-stacking interactions (Scheme 47).



Scheme 47

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. 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 **229**, whereas the crotonate methyl protons H_a were only shifted upfield significantly in the 2-naphthyl menthol crotonate (Figure 22). 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.



229

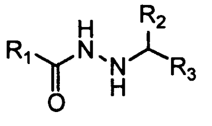
Figure 22

2.5.3 Proposed catalyst design

Our principal aim within this part of the project was to discover if a combination of the α-effect and p-shielding interaction within a chiral scaffold would lead to a new family of catalysts suitable to promote reactivity and stereocontrol in an iminium ion catalysed Diels-Alder reaction involving α,β-unsaturated carbonyl compounds. We decided to base the design of our catalysts on the following observations:

I. The high levels of diastereomeric control demonstrated in a range of chemical transformations highlight that 8-aryl menthol derivatives are attractive chiral scaffolds from which to begin in the synthesis of a new catalyst;

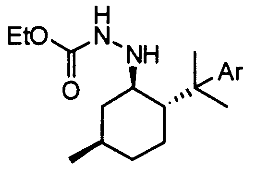
II. Generic structure **230** has been identified as a suitable molecular scaffold with which to promote a variety of aminocatalytic transformations involving α,β-unsaturated carbonyl compounds (see *section 2.2.1*);



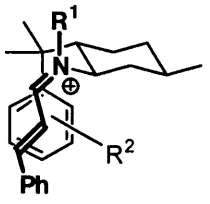
230

III. The proposed π-π interaction could be modulated by the simple introduction of a series of aromatic units with different characteristics into the structure **203**.

We sought to integrate some of the features of the 8-phenyl menthol chiral auxiliary **214** and **215**, into the design of our catalyst architecture **203**. Thus, we planned to synthesise a new set of 8-aryl menthamines **203**, containing a hydrazine subunit with an electron withdrawing group attached to the α-heteroatom. Moreover, in order to avoid a unwanted secondary π-π interaction with the iminium ion, it was decided to adopt an electron withdrawing carbonyl group without aromatic units such as the carbo-ethoxy group (EtOCO).



203



231

R^1 = NHCO$_2$Et

Reaction of 8-aryl menthamine **203** with an α,β-unsaturated carbonyl compound should provide iminium ion **231**, with the possibility of an attractive π-π interaction between the aromatic group and the α,β-unsaturated moiety. Thus, the π-stacking interaction should block the iminium ion into a parallel conformation with the aromatic element **A**, leading to an efficient shielding of the internal face of the iminium moiety **B** from the approach of a reagent (Figure 23).

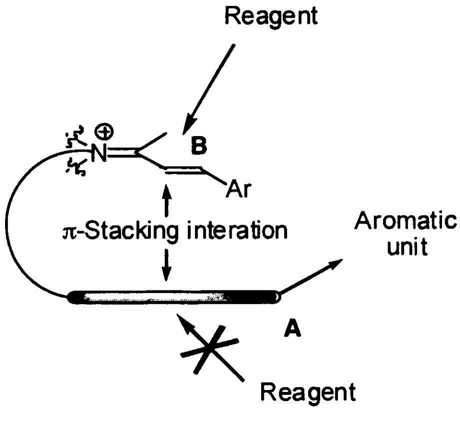
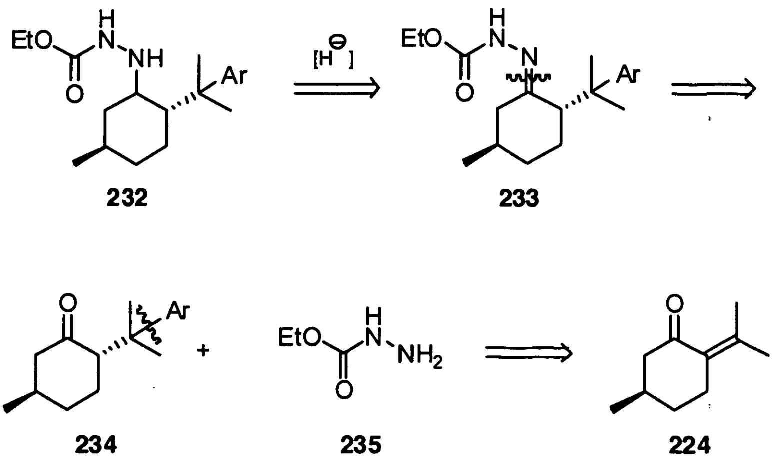


Figure 23

Subtle modifications to the electronics of the aromatic ring of **203** should enable an investigation into the effect on the strength of the proposed π-stacking interactions and hence on the selectivity observed in catalytic asymmetric transformations.

2.5.4 Retrosynthetic analysis

Synthesis of the amine **232** was based on the retrosynthetic analysis shown in Scheme 48.

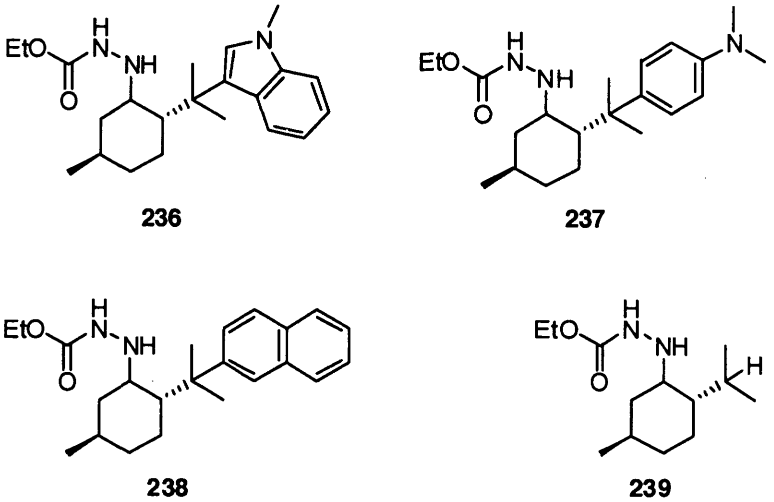


Scheme 48

Conjugate addition, with subsequent equilibration, following the procedure of Ort, should provide 8-aryl-menthone **234** from commercially available (*R*)-(+)-pulegone **224**.[143] Modifications to the aromatic group should be achieved by using a variety of nucleophiles in the conjugate addition step. The condensation of 8-aryl-menthone **234** with ethyl carbazate **235** should provide hydrazone **233**, which could be converted to hydrazide **232** *via* a subsequent reduction step.

Following this simple retrosynthetic analysis, we could gain access to a valuable synthetic tool to alter the nature of the aromatic functionality introducing a variety of aromatic groups with different characteristics (Figure 24). We therefore planned to synthesise four catalysts with the following substituents in the 8-position:

I. Arene **236** with a large aromatic surface and electron rich p-system, using the *N*-methyl indole group;
II. Catalyst **237** with an electron rich aromatic ring incorporating *N*,*N*-dimethyl aniline;
III. Arene **238** with a large aromatic structure using the 2-naphthyl group;
IV. Catalyst **239** which could be used as reference where the aromatic group was replaced by a simple proton.



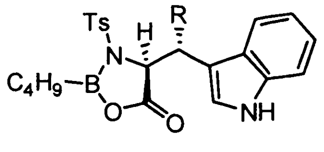
236 **237**

238 **239**

Figure 24

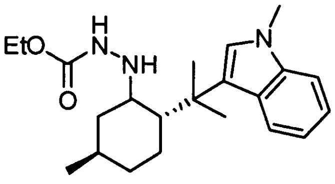
2.5.5 A large and electron rich aromatic unit: *N*-methyl indole

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 be involved with π-π interactions, and this indole subunit was incorporated by Corey into the structure of his oxazaborolidine catalyst **240**, which provided unprecedented levels of enantioselectivity when employed as a catalyst for Diels-Alder cycloadditions between bromoacrolein and cyclopentadiene **8**.[150]



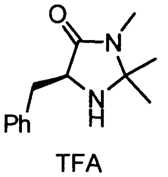
240

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.

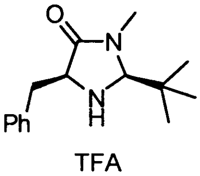


236

The Friedel-Crafts reaction, promoted by a Lewis acid such as $AlCl_3$, or 1,4 conjugate addition promoted by a Grignard reagent in the presence of a copper(I) salt, are the traditional methods used to perform the alkylation of aromatic or heteroaromatic compounds. Recently, the asymmetric alkylation of pyrroles, indoles and electron rich benzenes has been reported by MacMillan using imidazolidinone catalysts **16** and **17**.[32,151] These aminocatalysts led to the formation of conjugate addition products in high yields and exceptional levels of enantiomeric excess.

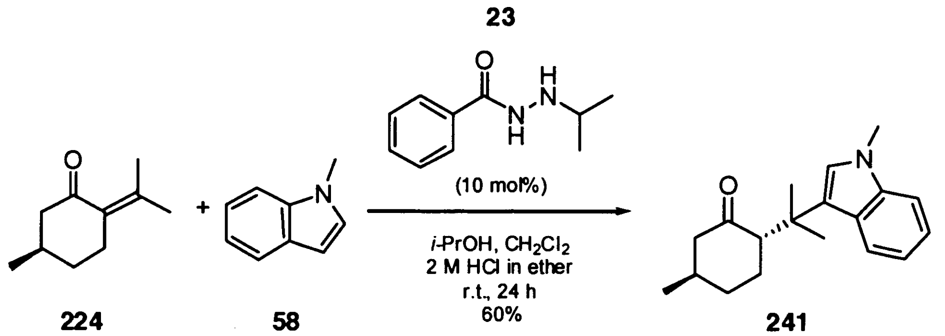


TFA
16



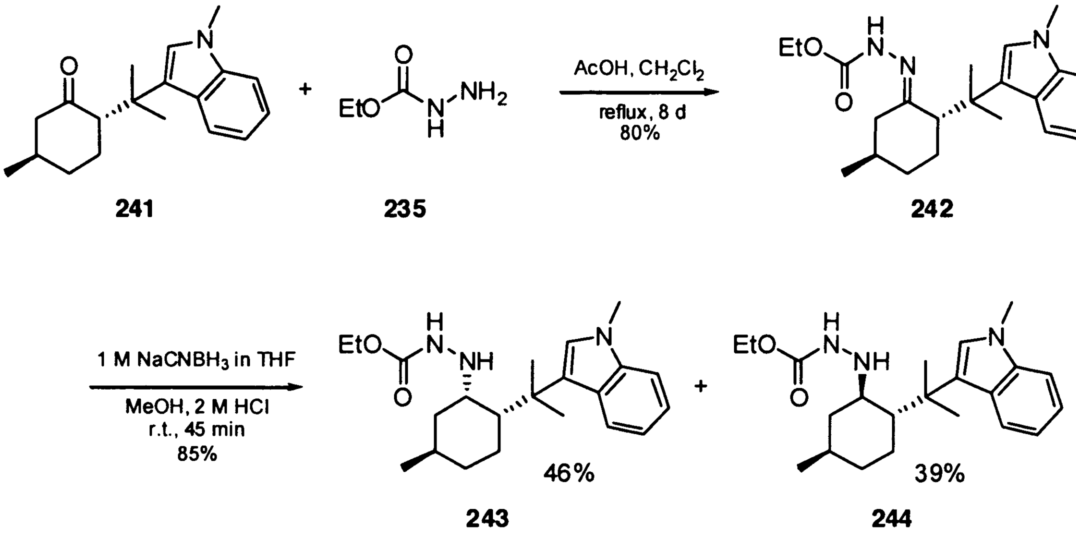
TFA
17

In order to commence the synthesis of our catalyst **236**, we decided to examine the catalytic capacity of the hydrazide **23** to promote the conjugate addition between *N*-methylindole **58** and (*R*)-(+)-pulegone **224**. The starting materials were stirred in a mixture of *iso*-propanol and dichloromethane at room temperature in the presence of 10 mol% catalyst **23** as its trifluoroacetic acid salt. The reaction was monitored for two weeks by TLC but only a small amount of product **241** was detected. Previously, Cavill and Jones demonstrated that the strength of the acid co-catalyst within iminium ion catalysed transformation was crucial.[131] It was shown that the catalytic ability of hydrazides possessing a scaffold similar to **23** increased significantly when a strong acid co-catalyst such as hydrochloric acid or perchloric acid ($HClO_4$) was used. Therefore, we decided to replace trifluoroacetic acid with a solution of 2 M HCl in ether and repeat the Michael addition under the same conditions described above (Scheme 49). After twenty-four hours, the solvent was removed and the crude reaction mixture was purified by column chromatography to give the ketone **241** as a colourless solid in 60% yield as a single diastereoisomer.



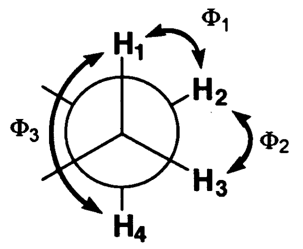
Scheme 49

The ketone **241** was allowed to react with ethyl carbazate **235** in the presence of acetic acid for 8 days at reflux to provide the hydrazone **242** in 80% yield once again as a single isomer (Scheme 50). Reduction to the corresponding hydrazine was then attempted under the reaction conditions applied previously for the synthesis of hydrazine **23**, but we found that use of Adam's catalyst returned a complex mixture which was not possible to purify with the possible degradation of the indole aromatic moiety. Once again, the reduction of the carbon-nitrogen bond was achieved employing sodium cyanoborohydride. Separation of the two diastereoisomers was accomplished by column chromatography, which afforded hydrazide *N'*-(5-methyl-2-(2-(1-methyl-1*H*-indol-3-yl)propan-2-yl)cyclohexyl)hydrazinecarboxylic acid ethyl ester as the (1*S*,2*R*,5*R*)-diastereoisomer **243** and the (1*R*,2*R*,5*R*)-diastereoisomer **244** respectively in 46% and 39% isolated yield (total yield 85%, overall yield 41%).

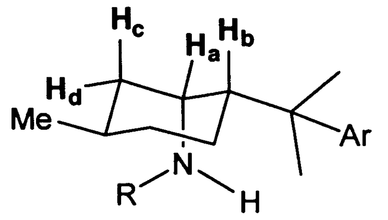


Scheme 50

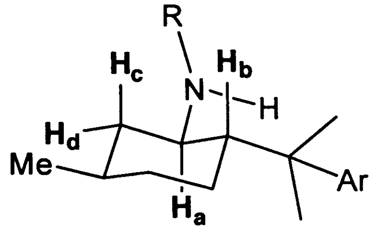
The relative geometry of each of the diastereoisomers **243** and **244** was determined using ^{1}H NMR coupling constants. For hydrazide **243** the proton **H$_a$**, a to the amino group, is in an equatorial position and couples with the two axial protons **H$_b$**, and **H$_c$** and the equatorial proton **H$_d$** (Figure 25).



$\Phi_1 = 60°$, $^3J_{ae} \cong 3$ Hz
$\Phi_2 = 60°$, $^3J_{ee} \cong 3$ Hz
$\Phi_3 = 180°$, $^3J_{aa} \cong 10$ Hz



243



244

Figure 25

Therefore, two equatorial-axial (with a angle $\Phi \sim 60°$, $^3J \sim 3$ Hz) and one equatorial-equatorial (with a angle $\Phi \sim 60°$, $^3J \sim 3$ Hz) coupling constants should be observed. For this reason, the ^{1}H NMR peak corresponding to the proton **H$_a$** in **243** were a double-double-doublet, with three small coupling constants which was observed as a broad singlet shape in the ^{1}H NMR spectra (Figure 26).

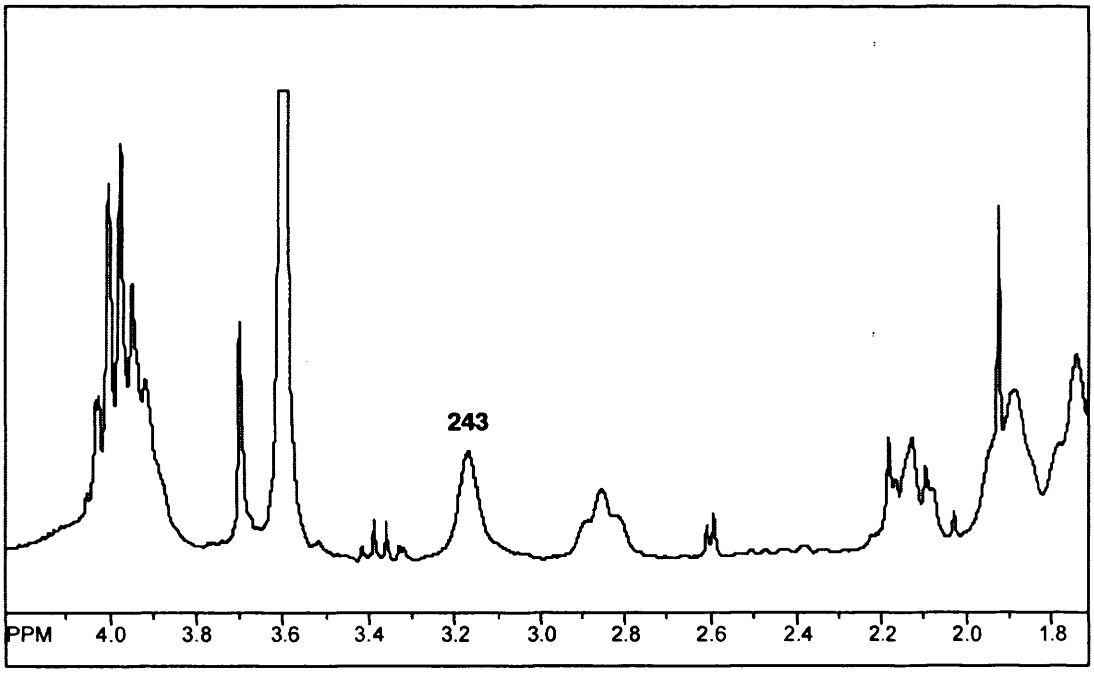
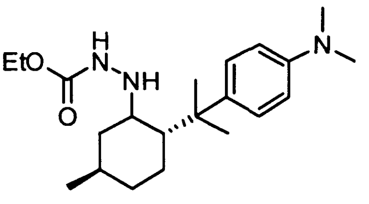


Figure 26

The diastereoisomer **244** shows the proton **H$_a$** in the axial position. In that position, two large axial-axial (protons **H$_b$** and **H$_c$**; angle $\Phi \sim 180°$, $^3J \sim 10$ Hz) and one small equatorial-axial (proton **H$_d$**; angle $\Phi \sim 60°$, $^3J \sim 3$ Hz) coupling constants were observed. The resulting peak for the proton **H$_a$** in **244** was observed as a double-double-doublet, which had the apparent aspect of a broad triplet (Figure 26). The ^{1}H NMR spectra of each of the diastereoisomers confirmed our analysis and allowed us to confidently assign the relative stereochemistry of **243** and **244**.

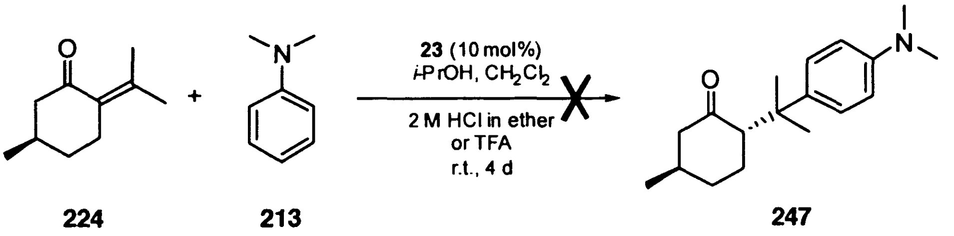
2.5.6 An electron rich aromatic moiety: *N,N*-dimethyl aniline

Despite a reduced aromatic surface compared to 8-naphthyl **212** or *N*-methyl indole unit **58**, the *N,N*-dimethyl aniline moiety **213** offered the opportunity to investigate an alternative electron rich aromatic structure. The strong electron donation provided by the nitrogen lone pair of the 4-dimethyl amino group, is able to significantly increase the electronic density of the p-system in the aromatic component. We therefore sought to integrate an *N,N*-dimethyl aniline moiety into our catalyst structure **237** in the hope that this would lead to higher levels of asymmetric induction in aminocatalytic transformations by means of an enhancement of a p-p interaction between the aromatic unit and the α,β-unsaturated aldehyde.



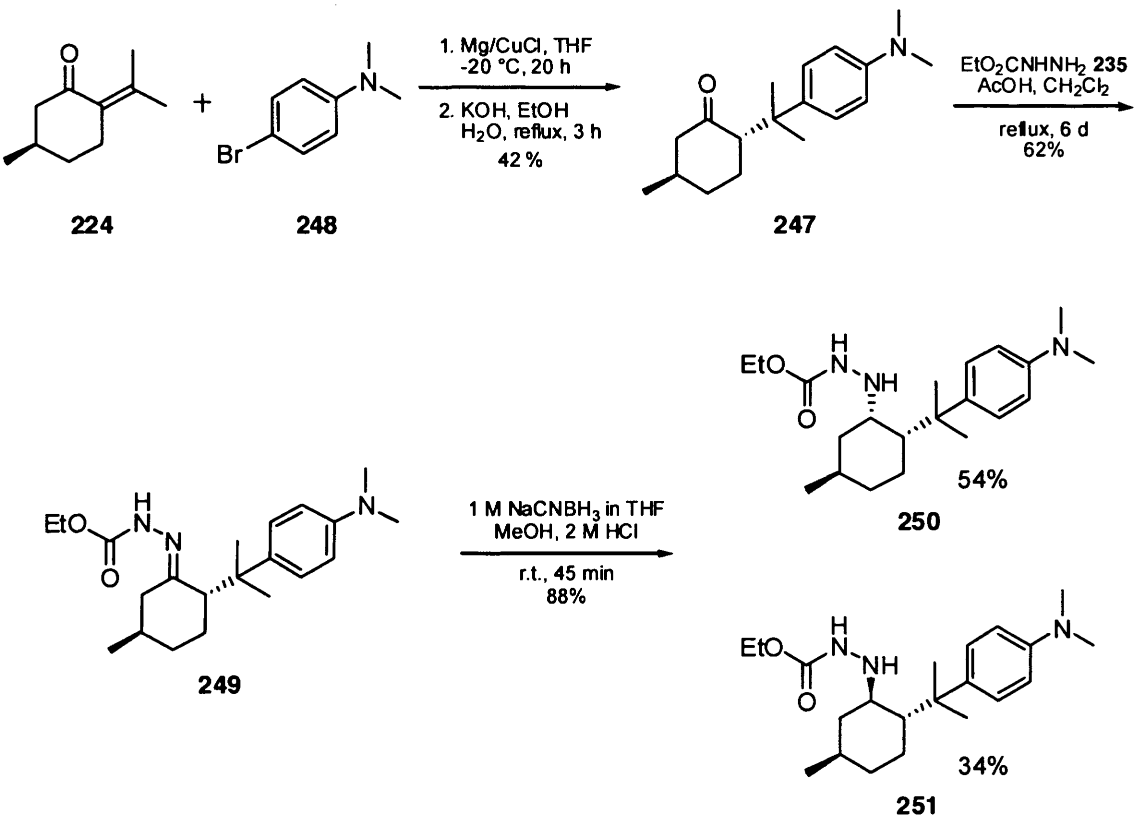
237

Initially, synthesis of ketone **247** was envisaged from (*R*)-(+)-pulegone **224** and *N,N*-dimethyl aniline **213** *via* a conjugate addition under aminocatalytic reaction conditions (Scheme 51). The ketone **224** was reacted with the aniline **213** in the presence of 10 mol% of the hydrazide **23** as catalyst together with 10 mol% of trifluoroacetic acid or 2 M hydrochloric acid as co-catalyst in *iso*-propanol and dichloromethane at room temperature. The reaction was monitored by TLC for four days without providing any indication that the desired compound had formed. The aminocatalytic strategy employed to prepare the ketone **241** in attractive yields proved ineffective within this transformation. The difference in nucleophility between *N*-methyl indole **58** and the *N,N*-dimethyl aniline **213** could explain the divergent behavior observed in this transformation.



Scheme 51

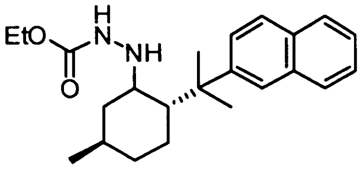
Therefore, we decided to gain access to the ketone **247** through a more traditional approach. The alkylation was accomplished in 42% yield by conjugate addition of the Grignard reagent of 4-bromo-*N,N*-dimethyl aniline **248** to (*R*)-(+)-pulegone **224**, catalysed by copper(I) chloride (CuCl) under the protocol described in the procedure of Ort (Scheme 52).[143] Subsequently, condensation with ethyl carbazate **235** provided the hydrazone **249** in 62% yield after purification by column chromatography. Reduction to the corresponding hydrazides **250** and **251** was then performed under analogous conditions to those employed for the preparation of hydrazides **243** and **244**. This produced a mixture of two diastereoisomers which were separated by flash column chromatography providing hydrazide *N'*-(2-(2-(4-(dimethylamino) phenyl)propan-2-yl)-5-methylcyclohexyl) hydrazine-carboxylic acid ethyl ester as its (1*S*,2*R*,5*R*)-diastereoisomer **250** and the (1*R*,2*R*,5*R*)-diastereoisomer **251** in 54% and 34% yields respectively (total yield 88%, overall yield 23%).



Scheme 52

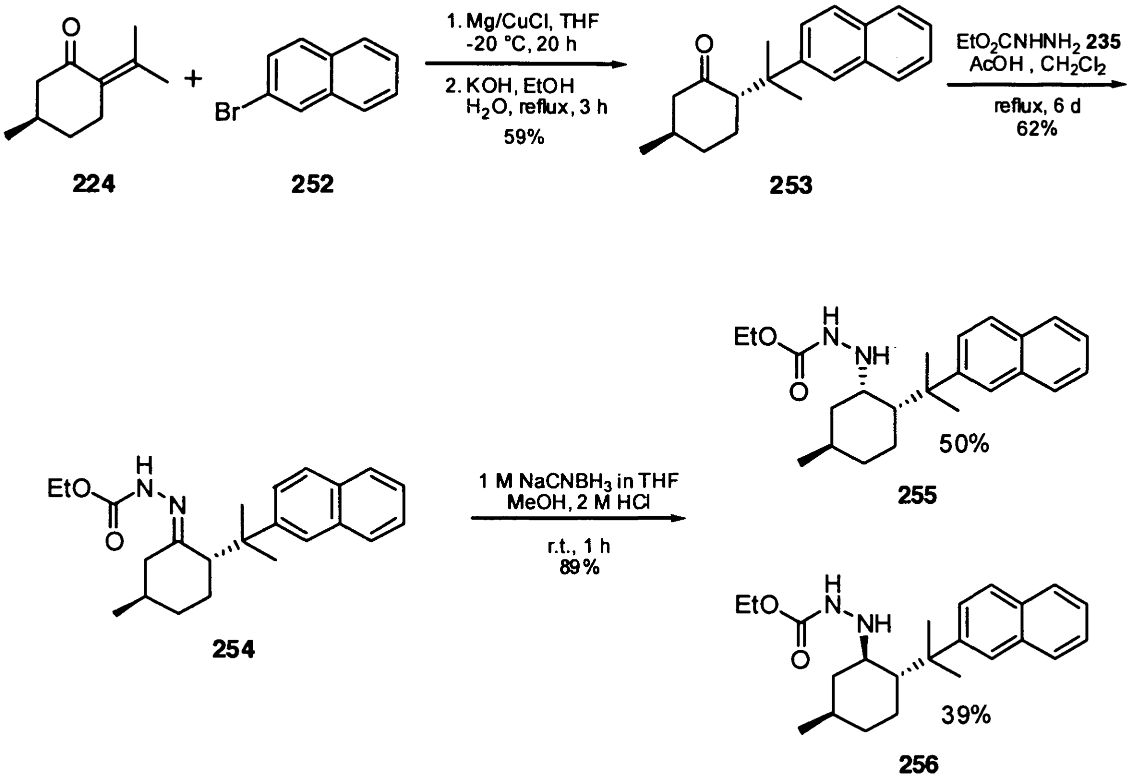
2.5.7 A large aromatic architecture: 8-naphthyl substitution

Chiral auxiliaries based on the 8-aryl menthol architecture were employed to substantially alter diastereofacial discrimination in a number of conjugate addition reactions, as reported by D'Angelo.[149] Within this investigation he demonstrated that higher levels of selectivity were obtained when utilising 8-naphthyl-based auxiliaries compared to the use of 8-phenyl menthol **214** and **215**. It was suggested that the presence of the larger aromatic group led to an improved overlap of the double bond of the substrate with the aromatic rings of the naphthyl unit providing an enhanced level of stereocontrol. As a result of these findings, we decided to introduce a large aromatic moiety such as the naphthyl group into the structure of our 8-aryl menthamine catalysts.



238

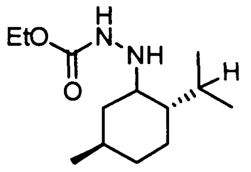
Synthesis of the compounds **255** and **256** began with a conjugate addition of the Grignard reagent derived from 2-bromonaphthalene **252** to (*R*)-(+)-pulegone **224**, in the presence of copper(I) chloride (CuCl), assuming that the synthetic route would be very similar to that adopted in the preparation of catalysts **250** and **251** (Scheme 53). After equilibration of the ketone **253** with potassium hydroxide (59% yield), the purified compound was reacted with ethyl carbazate **235** under acidic conditions for six days at reflux to provide the hydrazone **254** in 62% yield. Reduction of hydrazone **254** was carried out with a solution of 1 M sodium cyanoborohydride ($NaCNBH_3$) in tetrahydrofuran which after purification and separation by column chromatography gave *N'*-(5-methyl-2-(2-(naphthalen-2-yl)propan-2-yl)hydrazinecarboxylic acid ethyl ester as its (1*S*,2*R*,5*R*)-diastereoisomer **255** and the (1*R*,2*R*,5*R*)-isomer **256** in 50% and 39% isolated yield respectively, providing a total yield of 89% (overall yield 33%).



Scheme 53

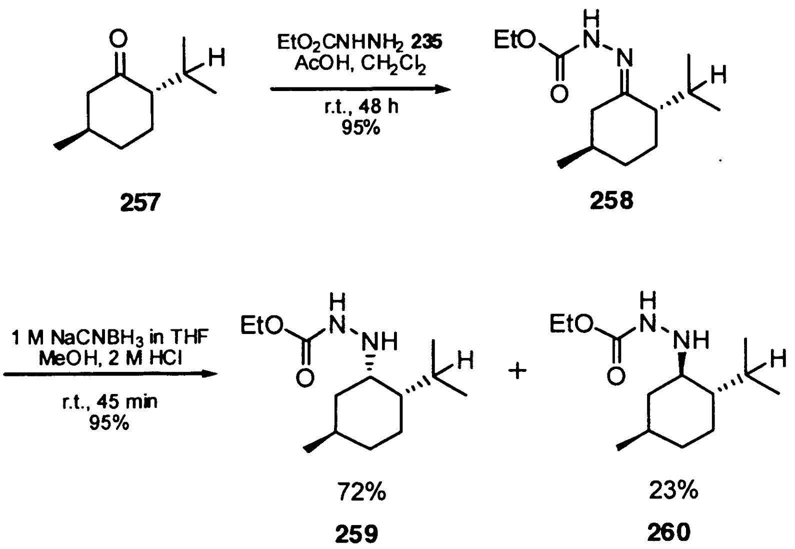
2.5.8 Without aromatic group

We envisaged that gaining access to catalyst **239** would create an opportunity for comparisons between a secondary amine designed on our scaffold without the aromatic system and the catalysts described above (**255**, **256**, **243**, **244**, **250** and **251**). We hoped that this would provide an indication of the actual degree of the proposed face-face p-p interaction in the discrimination of α,β-unsaturated carbonyl compounds.



239

Compounds **259** and **260** were prepared following a simple and consolidated synthetic pathway employed in the previous syntheses (Scheme 54). (*L*)-Menthone **257** was reacted with ethyl carbazate **235** for two days at room temperature under acidic conditions to provide the hydrazone **258** in 95% yield after purification by column chromatography. Reduction with a 1 M solution of sodium cyanoborohydride ($NaCNBH_3$) in tetrahydrofuran led to a mixture of two diastereomeric amines which were separated by flash column chromatography to give *N'*-(2-*iso*-propyl-5-methylcyclohexyl)hydrazinecarboxylic acid ethyl ester as its (1*S*,2*S*,5*R*)-diastereoisomer **259** in 72% yield and the (1*R*,2*S*,5*R*)-diastereoisomer **260** in 23% yield (total yield 95%, overall yield 90%)

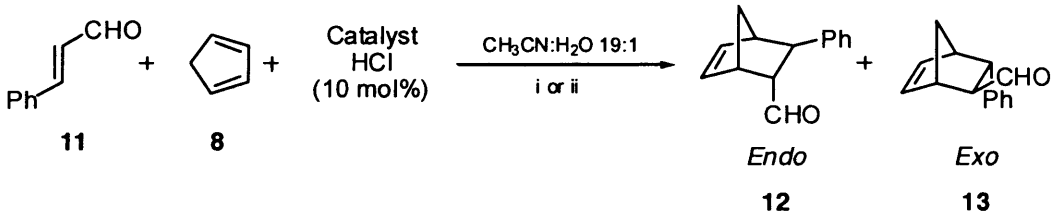


Scheme 54

2.6 Investigation of catalysts in the asymmetric Diels-Alder reaction

2.6.1 Standard catalytic test

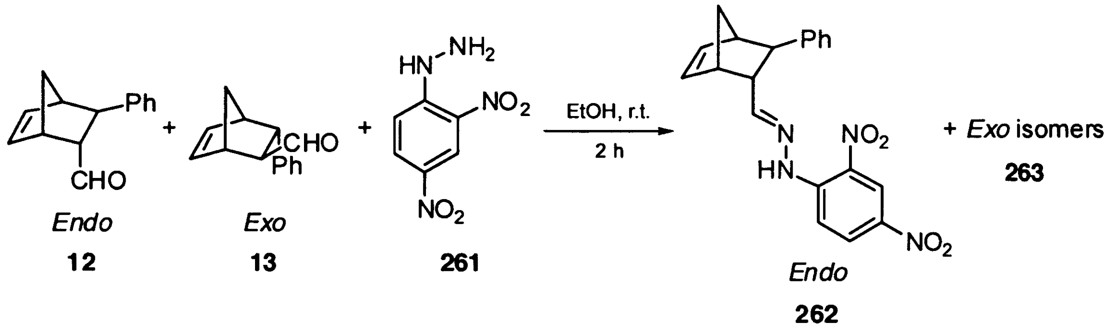
In order to investigate our catalysts as candidates in the asymmetric Diels-Alder reaction, a procedure developed within the group was followed.[131] Each of the catalysts prepared (loading 10 mol%) was allowed to react with (*E*)-cinnamaldehyde **11** (1 eq) and cyclopentadiene **8** (3 eq) in $CH_3CN:H_2O$ 19:1 at 25 °C for twenty four hours (reaction conditions (i), Scheme 55) or at -20 °C for seventy two hours (reaction conditions (ii), Scheme 55). After aqueous work up, the *endo:exo* ratio of the Diels-Alder adducts **12** and **13** was determined from the ^1H NMR of the crude reaction mixture.



(i) 24 h, 25 °C; (ii) 72 h, -20 °C

Scheme 55

The resolution and the determination of enantiomeric excess were obtained by chiral-phase HPLC analysis. In order to improve the resolution of the HPLC and allow a better separation of the peaks, the 2,4-dinitrophenylhydrazone derivatives of the Diels-Alder adducts **262** and **263** were prepared, following previous experience acquired by members of our laboratory.[152] The purified aldehydes **12** and **13** were treated with a slight excess of 2,4-dinitrophenylhydrazine **261** at room temperature for 2 hours to provide the 2,4-dinitrophenylhydrazone derivatives **262** and **263** (Scheme 56). The mixture was purified by flash column chromatography before determining the enantiomeric excess.



Scheme 56

2.6.2 Analysis of asymmetric Diels-Alder results

The *endo*:*exo* ratio of the aldehydes **12** and **13** was determined by analysis of the ^1H NMR of the crude reaction mixture, utilising the same method illustrated previously in this *Chapter* (*section 2.2.4*). The analysis of the 2,4-dinitrophenylhydrazone derivatives **262** and **263** was performed using a reverse phase Chiaralcel OD-R column eluting with $CH_3CN:H_2O$ 8:2 at a rate of 0.5 mL/min (detector wavelength 365 nm).[152] The four isomers produced by the aminocatalysed Diels-Alder cycloaddition between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8**, generated four different signals with the following retention times (Figure 27):

I. *Endo*-diastereoisomers at $t_1 = 30.7$ min (2*S*), and $t_2 = 36.5$ min (2*R*);
II. *Exo*-diastereoisomers at $t_3 = 41.8$ min (2*S*), and $t_4 = 51.4$ min (2*R*).

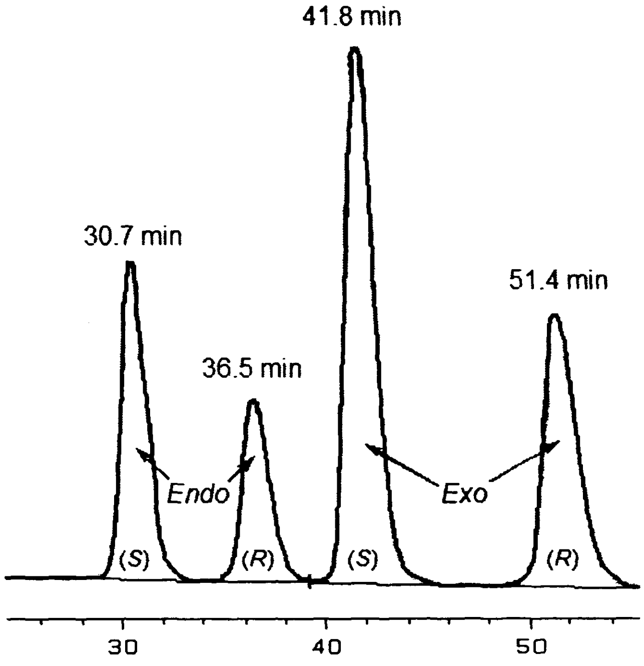


Figure 27

This protocol provided us with a convenient and cheap tool to evaluate the capacity of our catalysts to induce chirality in the iminium ion catalysed Diels-Alder reaction.

2.6.3 Investigation of our aminocatalytic family

The preparation of our aminocatalytic family was successfully achieved following a simple and scalable methodology (Figure 28). Gaining access to catalysts **255**, **256**, **243**, **244**, **250** and **251** we had a further opportunity to explore the nature of π-stacking interactions and the α-effect in our catalytic system. Synthesis of compounds **259** and **260** also allowed us to obtain insight into the origin of any enantiomeric excess observed. The absence of an aromatic unit on our catalyst **259** and **260** provided a useful tool to probe if the π-π interaction between the internal face of aromatic moiety and the iminium ion was an active element in geometric control.

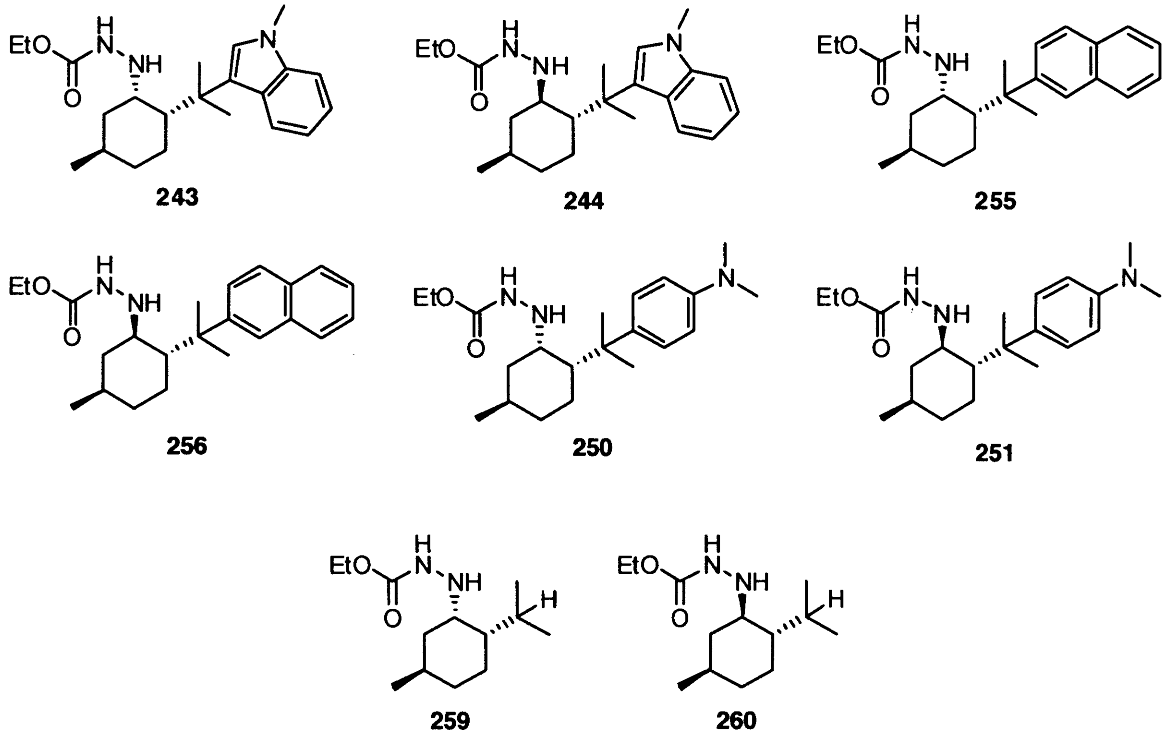
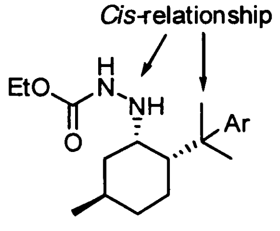


Figure 28

With this new set of molecules in hand, we continued our investigation submitting our catalysts to the Diels-Alder reaction between *trans*-cinnamaldehyde **11** and cyclopentadiene **8**, employing each catalyst as a hydrochloride salt at loadings of 10 mol%.

2.6.4 Comparison of the aminocatalytic family

The initial set of experiments were carried out using the hydrazide catalysts with a *cis* relationship between the amine and aromatic cyclohexyl substituents (Figure 29). The results of these experiments are tabulated below (Table 6).



202

Figure 29

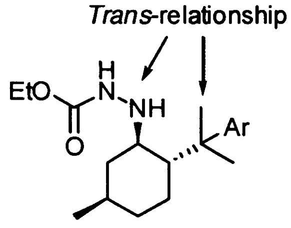
Table 6. Results of experiments using *cis*-catalysts with modified electronics.[a]

Entry	Catalyst	Yield (%)	*Endo:Exo*[b]	*Endo* (%) *ee*[c]	*Exo* (%) *ee*[c]
1	**259**	58	37:63	58 (2*S*)	22 (2*S*)
2	**243**	16	34:66	10 (2*S*)	22 (2*S*)
3	**250**	7	36:64	32 (2*S*)	38 (2*S*)
4	**255**	24	37:63	45 (2*S*)	41 (2*S*)

(a) All reactions were carried out in $CH_3CN:H_2O$ 19:1 at 25 °C for 24 h with 10 mol% catalyst as HCl salt. (b) All *exo:endo* ratios were obtained from the ^1H NMR of the crude reaction mixture. (c) Enantiomeric excess was determined by HPLC of the product as its 2,4-DNPH derivative using a reverse phase Chiaralcel OD-R column; see *section 2.6.2.*

Analysis of Table 6 revealed that the aromatic units have had a detrimental effect on the yields. The usual *endo:exo* ratio of 1:2 suggested the occurrence of an iminium-ion catalysed Diels-Alder reaction. In addition, the *endo*-(2*S*) and *exo*-(2*S*) isomers were formed preferentially with each of the four hydrazides examined. Modifications to the electronic nature of arenes **243**, **250** and **255** had no significant effect on the stereochemical outcome of the Diels-Alder cycloaddition. The *endo*-isomers from the reaction between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8** gave an encouraging 58% *ee* (2*S*) for hydrazide **259** (Table 6, entry 1) suggesting that the observed enantioselectivity was due to the steric effects of the menthamine scaffold rather than electronic subtleties. The results collected for the *exo*-isomers were more interesting. The increment of enantioselectivity observed for the arenes **250** and **255** (38% *ee* (2*S*) and 41% *ee* (2*S*) respectively, Table 6, entries 3-4) compared to the non-aromatic hydrazide **259** (22% *ee* (2*S*), Table 6, entry 1) indicates that the diastereomeric control could be due to electronic factors, rather than the steric constraints of menthamine. In this case, the introduction of a large aromatic structure **212** and an electron rich aromatic group **213** increased the enantiomeric excess observed suggesting that the proposed π-stacking interactions are possibly occurring.

The next logical step was to repeat this set of catalytic Diels-Alder reactions using the family of hydrazides with a *trans*-relationship between the nucleophilic amine and aromatic substituents (Figure 30). The results of this catalytic study are shown below (Table 7).



203

Figure 30

Table 7. Results of experiments using *trans-catalysts* with modified electronics.[a]

Entry	Catalyst	Yield (%)	*Endo:Exo*[b]	*Endo* (%) *ee*[c]	*Exo* (%) *ee*[c]
1	**260**	99	37:63	32 (2*S*)	4 (2*S*)
2	**244**	41	40:60	55 (2*S*)	7 (2*S*)
3	**251**	19	37:63	12 (2*R*)	25 (2*R*)
4	**256**	73	40:60	7 (2*S*)	2 (2*R*)

(a) All reactions were carried out in $CH_3CN:H_2O$ 19:1 at 25 °C for 24 h with 10 mol% catalyst as HCl salt. (b) All *exo:endo* ratios were obtained from the ^1H NMR of the crude reaction mixture. (c) Enantiomeric excess was determined by HPLC of the product as its 2,4-DNPH derivative using a reverse phase Chiaralcel OD-R column; see *section 2.6.2.*

The outcomes of these experiments showed a more complex pattern when compared to the *cis*-catalysts. The quantitative yield obtained for the non-aromatic catalyst **260** confirmed that the presence of aromatic group attached in the 8-position negatively affects the catalytic activity of our catalysts (Table 7, entry 1). However, the result achieved for catalyst **256** seems to be more intriguing. Although this arene possesses a cumbersome aromatic group like catalysts **244** and **251**, a pleasant 73% yield was observed (Table 7, entry 4). The yields observed for the Diels-Alder reaction with others catalysts **244** and **251** were substantially lower for these nitrogen containing systems when compared to the purely hydrocarbon naphthalene system. It appears therefore that for catalyst **244** and **251** a secondary effect occurs reducing the catalytic activity. Each of the catalysts employed provided the usual 1:2 *endo:exo* ratio in the Diels-Alder cycloaddition. An increase in the enantioselectivity was found for the *endo*-isomer with the use of the 8-*N*-methyl indole hydrazide **244** (55% *ee* (2*S*),

Table 7, entry 2), and the electron rich compound **251** (12% *ee* (2*R*), Table 7, entry 3) compared to the catalyst **260** (32% *ee* (2*S*), Table 7, entry 1). *Exo*-isomers of hydrazide **251** showed a more consistent gap providing a 25% *ee* (2*R*) (Table 7, entry 3) compared to 4% *ee* (2*S*) found with **260** (Table 7, entry 1). The outcomes examined for catalyst **251** (Table 7, entry 3) and to a lesser extent for the catalyst **244** suggest that the observed enantioselection is due to electronic factors, rather than the merely steric hindrance generated by the structure of menthanamine, for this family of hydrazides.

In order to acquire further data for a better evaluation of the first series of experiments, each hydrazide was re-submitted to a second group of catalytic tests performed at -20 °C for seventy two hours under our protocol (see *section 2.6.1*). All the results collected are tabulated below (Table 8 and Table 9).

Table 8. Results of experiments using *cis*-catalysts with modified electronics.[a]

Entry	Catalyst	Yield (%)	*Endo*:*Exo*[b]	*Endo* (%) *ee*[c]	*Exo* (%) *ee*[c]
1	**259**	6	31:69	41 (2*S*)	29 (2*S*)
2	**243**	2	40:60	19 (2*S*)	39 (2*S*)
3	**250**	0	0:0	0	0
4	**255**	3	34:66	52 (2*S*)	54 (2*S*)

(a) All reactions were carried out in CH_3CN:H_2O 19:1 at -20 °C for 24 h with 10 mol% catalyst as HCl salt. (b) All *exo*:*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture. (c) Enantiomeric excess was determined by HPLC of the product as its 2,4-DNPH derivative using a reverse phase Chiaralcel OD-R column; see *section 2.6.2.*

Except for a drastic decrease in yields, each of the hydrazides showed similar results in terms *endo*:*exo* ratio and enantiomeric excess. Reduction of the temperature caused a detrimental effect on the reaction turnover and did not substantially alter the enantioselectivity observed. The data collected showed that a large aromatic group (**255**, Table 8, entry 4) enhances enantioselectivity compared to the non-aromatic catalyst **259** (Table 8, entry 1). Unfortunately, no product was recovered from the experiment using hydrazide **250**, so that an evaluation of the stereochemical outcome with this catalyst at low temperature was not possible.

Table 9. Results of experiments using *trans*-catalysts with modified electronics.[a]

Entry	Catalyst	Yield (%)	*Endo*:*Exo*[b]	*Endo* (%) *ee*[c]	*Exo* (%) *ee*[c]
1	**260**	28	36:64	24 (2*S*)	8 (2*S*)
2	**244**	3	33:67	23 (2*S*)	9 (2*S*)
3	**251**	3	33:67	22 (2*R*)	30 (2*R*)
4	**256**	8	40:60	8 (2*S*)	1 (2*S*)

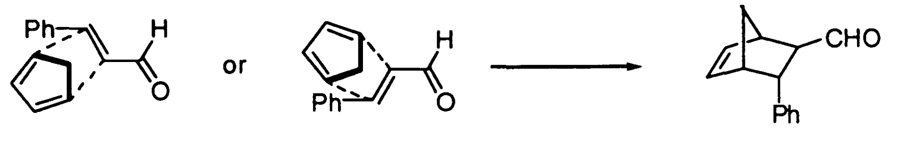
(a) All reactions were carried out in CH_3CN:H_2O 19:1 at -20 °C for 24 h with 10 mol% catalyst as HCl salt. (b) All *exo*:*endo* ratios were obtained from the ^1H NMR of the crude reaction mixture. (c) Enantiomeric excess was determined by HPLC of the product as its 2,4-DNPH derivative using a reverse phase Chiaralcel OD-R column; see *section 2.6.2*.

In a similar manner, the outcomes obtained with the *trans*-hydrazides for this Diels-Alder cycloaddition performed at low temperature (Table 9) were consistent with the experiments carried out at 25 °C (Table 7). Once again, catalyst **251** showed a clear preference of the (2*R*)-isomer, increasing the enantiomeric excess for both the *endo*- and *exo*-isomers (Table 9, entry 3) compared to the non-aromatic catalyst **260** (Table 9, entry 1). This result corroborated the hypothesis that enantioselection was enhanced by subtle electronic factors.

Introduction of aromatic units in the 8-position of the menthamine scaffold caused a negative effect in terms of catalytic activity particularly for the *cis*-catalysts **243**, **250** and **255** which have provided substantially lower yields when compared to the results observed with *trans*-hydrazides **244**, **251** and **256**. It is possible that the aromatic unit possesses a favourable orientation in the *trans*-catalysts, enhancing the nucleophilic attack of the secondary amine on the α,β-unsaturated aldehyde. The yields obtained were also affected by the intrinsic nature of the aromatic group incorporated into our catalysts. The steric requirements of the dimethylamino and *N*-methyl indole catalysts (**250**, **251**, **243** and **244**) are similar to those of the naphthalene catalysts (**255** and **256**). However, the yields observed for the Diels-Alder reaction were substantially lower for these nitrogen containing systems compared to the purely hydrocarbon naphthalene system. It appears therefore that increasing the electron density on the aromatic is detrimental to catalytic activity and rather than increasing the proposed p-p interaction a secondary effect is present. The *endo*:*exo* ratio was not affected by the different aromatic groups employed, giving the typical ratio of 1:2. The results obtained for the non-aromatic hydrazides **259** and **260** allowed us to define the extent of enantioselective control due to the steric encumbrance of the scaffold of menthanamine. Utilising these outcomes as reference, we have observed improvements in enantioselectivity for both *cis*- and *trans*-catalysts, attributable to additional electronic effects. It appeared that reaction was reasonable, since modulating the extent of this phenomenon led to some increase in asymmetric induction. As a last note, it is an interesting point that the hydrazides with *cis*-conformation and *trans*-conformation resulted in the opposite sense of asymmetric induction in the Diels-Alder adducts despite the fact that both were prepared from the same natural isomer of pulegone. One of the major problems with the use of this auxiliary in synthesis is the prohibitive cost of the unnatural isomer and this observation certainly warrants further study.

2.6.5 Proposed iminium ion intermediate

During the cycloaddition between cyclopentadiene **8** and *E*-cinnamaldehyde **11**, catalysed by our hydrazides as hydrochloride salts, we have observed a series of interesting results in terms of stereoselective control. For instance, *trans*-catalyst **251** showed a preference for the (*R*) absolute configuration relative to the general preference of (*S*) absolute configuration provided from the *trans*-catalyst **260** where no aromatic ring was present. Therefore, utilising the outcomes obtained for the catalysts **250** and **251** as example, consideration of the absolute configuration of the major isomer formed enabled the postulation of a working model to explain the observed enantioselectivity. To form an excess of the *exo*-(2*R*) adduct **13**, cyclopentadiene **8** must preferentially react with the *Re*-face of the α,β-unsaturated carbonyl component (Figure 31).



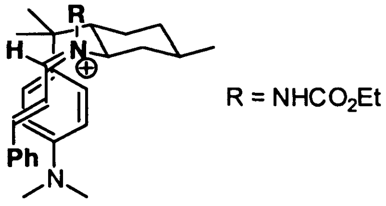
Addition of **8** to *Re* face of **11** in *s-trans* conformation

Addition of **8** to *Re* face of **11** in *s-cis* conformation

(2*R*)-*exo* enantiomer formed

Figure 31

We propose that upon iminium ion formation of hydrazide **251** with (*E*)-cinnamaldehyde **11**, the preferred conformation of the complex **264** could be that shown in Figure 32, which is consistent with the asymmetric induction observed in our Diels-Alder experiments. In this conformation the π-system of the iminium ion sits directly over the face of the aromatic ring, thus blocking one diastereoface from the approach of cyclopentadiene **8**. 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.

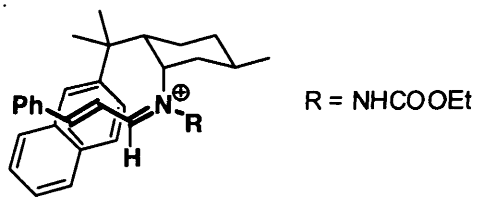


264

Figure 32

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 electronic density of the aromatic ring incorporated into the catalyst.

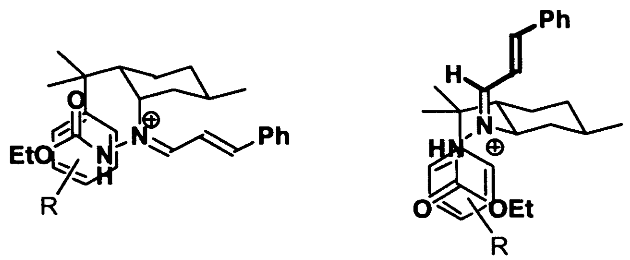
Similar considerations can be deduced for the *cis*-substituted catalysts. For example, 8-naphthyl-arene **255** demonstrated improvement in control compared to the non-aromatic containing hydrazide **259**. Thus, it is possible to apply an analogous model to **255** as illustrated in Figure 33.



265

Figure 33

However, the low levels of enantiomeric excess observed for our catalysts could be due to different factors. 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 for both *cis*- and *trans*-hydrazides. Under this hypothesis, because of the removal of the p-shielding effect, both the faces of the iminium ion would become available to the approach of cyclopentadiene **8**, leading to a decrease in the geometric control of the Diels-Alder products (Figure 34). .



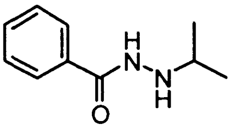
Cis-hydrazide **266**

Trans-hydrazide **267**

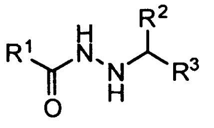
Figure 34

2.7 Conclusions

Within our group, we had established that the α-effect was a suitable platform for the acceleration of aminocatalytic transformations.[130,131] Hydrazide **23** provided a similar level of reactivity to pyrrolidine-based proline methyl ester **14**, when employed in the catalysis of Diels-Alder cycloaddition reactions. The preliminary aim of this project was to reassess the capacity of the HCl **188**, HBr **189**, HI **190** and HPF_6 **191** salts of catalyst **23** to affect the *endo:exo* ratio in the Diels-Alder adducts (see *section 2.3.3*). The counter-anions introduced into the catalytic system provided the usual 1:2 *endo:exo* ratio even though counter-anions with increasing size and non-coordinating interaction were examined. Thus, we can conclude that the counter anion has no effect in the diastereoselectivity of iminium ion catalysed Diels-Alder reaction.

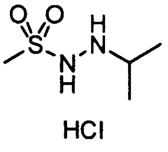


23



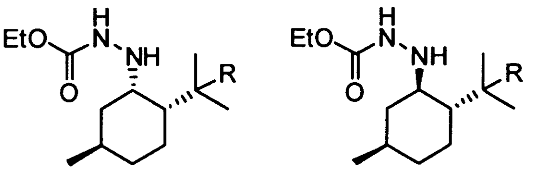
230

In order to improve the yields we also examined the effect of increasing the strength of the electron withdrawing group incorporated into the structure of our hydrazides **230**. With the purpose of satisfying these requirements, the benzoate group in catalyst **23** was replaced with a methansulfonate unit into the hydrazide **201** (*section 2.4.2*). Use of this compound as its hydrochloride salt in Diels-Alder catalysis between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8** provided a consistent lowering in observed yields (69% isolated yield in twenty four hours) compared to the results obtained with catalyst **23** (97% isolated yield in twenty four hours). A plausible explanation is that along with an augmented steric encumbrance caused by the two oxygen atoms on the sulfur group, the methansulfonate group provides an increased electron withdrawing effect, reducing the a-effect and the nucleophilicity of catalyst **201**. It is noteworthy that sulfonylhydrazide **201**, performed well when compared to the catalysts without an electron withdrawing group confirming that an electron withdrawing group in the ß-position from the nucleophilic nitrogen has a positive effect on the reaction rate.



201

The work of Cavill also showed the opportunity to integrate the a-effect and the structural feature of hydrazides **230** into chiral aminocatalysts for the Diels-Alder cycloaddition.[131a] This investigation provided evidence that the catalysts based on the scaffold of 8-aryl menthamine could promote asymmetric induction on the products of the Diels-Alder cycloaddition between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8**. Enantiomeric excesses observed were partially attributed to the face-face p-p interaction between the aromatic group incorporated into the structure of the catalyst. These results showed that improvements in enantiomeric excess were in line with increase in the electronic density on the aromatic ring. Hence, the tuning of electronic density on the aromatic ring appeared a decisive element in the enantiocontrol. Within our project, this study on the nature of the face-face p-p interaction was extended preparing a second set of aminocatalysts based on the 8-aryl menthamine scaffold (Figure 35).



Cis-catalyst *Trans*-catalyst

R =	*Cis* catalyst	*Trans* catalyst
3-*N*-methyl indol	**243**	**244**
p-(Me)$_2$NPh	**250**	**251**
Naphthyl	**255**	**249**
H	**259**	**253**

Figure 35

This group of hydrazides were tested in two series of Diels-Alder cycloadditions between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8**, utilising the hydrochloric acid salt of each catalyst at 10 mol% loading. The reaction was carried out under two different sets of reaction conditions, (i) at 25 °C for twenty four hours and (ii) -20 °C for seventy two hours. The behavior of the catalysts was consistent in yield, *endo:exo* ratio and enantioselectivity observed at both 25 °C and -20 °C. Data from these experiments proved complex and difficult to interpret due to the lack of any clear trend. The best yields were reported for the non-aromatic containing hydrazides **259** and **260** under both sets of the reaction conditions employed (see *section 2.6.4*). Moreover, it was evident that the catalysts with a *trans*-

relationship showed yields higher than those observed with the hydrazides with a *cis*-relationship. Thus, the presence of an aromatic unit manifests a detrimental effect in terms of yield particularly for the *cis*-hydrazides **243**, **250**, **255** and **259**. In this conformation the aromatic unit may posses an unfavourable orientation which reduces the accessibility of the nucleophilic nitrogen to efficiently form the active iminium ion intermediate. It was also noticed that there was anomalous behaviour with the arenes with aromatic groups containing nitrogen atoms (*cis* **243** and **250**, *trans* **244** and **251**) when compared to the catalyst possessing a hydrocarbon aromatic structure (*cis* **255**, *trans* **256**). Although the steric requirement for these arenes was almost identical, the catalysts with the naphthyl component **255** and **256** constantly had yields twice as high relative to the *N*-methyl indole-arene **243** and **244** and the dimethyl aniline-arene **250** and **251**. Therefore, it appears that the electron rich aromatic unit containing nitrogens atoms caused a consistent decrease in the yield rather than improving the enantiomeric excess. This may be due to the presence of an additional basic nitrogen complicating the form of the free catalyst. The use of a large and electron rich aromatic architecture did not affect the *endo:exo* ratio. Each of the catalysts tested delivered an *endo:exo* ratio of about 1:2, suggesting the occurrence of iminium ion-catalysed Diels-Alder cycloaddition.

Enantiocontrol of *endo*-isomer **12** showed by *cis*-catalysts **243**, **250**, **255** and **259** is due to the scaffold of the menthamine. In fact, for the Diels-Alder reaction carried out at 25 °C, an unexpected 58% *ee* (2*S*) was attained for the non-aromatic hydrazide **259**, while the best performance measured with the arenes proposed was 45% *ee* (2*S*) with the naphthyl-arene **255**. A similar trend in terms of enantiomeric excess was found for catalytic runs performed at -20 °C. The outcomes accomplished with the *cis*-hydrazides in enantioselectivity for the *exo*-isomer were more satisfying. The *exo*-(2*S*) isomer was formed preferentially with all four hydrazides. The 8-naphthyl-hydrzine **255** furnished an enantiomeric excess of 41% (2*S*) at 25 °C and 54% (2*S*) at -20 °C compared to the reference values of 22% *ee* (2*S*) at 25 °C and 29% *ee* (2*S*) at -20 °C found with catalyst **259**. The improvement in enantioselectivity is not simply attributable to steric interactions generated by the scaffold of our secondary amines but also to electronic interactions between the catalyst and substrates.

Experiments performed with the *trans*-hydrazides reinforced this hypothesis (Table 9). Considering the experiments performed at -20 °C, arene **251** showed a preference for the (*R*) absolute configuration, providing a 22% *ee* (2*R*) for *endo*-isomer and 30% *ee* (2*R*) for *exo*-

isomer. The Diels-Alder reaction carried out at the same temperature with the non-aromatic hydrazide **260** catalysed this transformation with the opposite sense in terms of absolute configuration compared to **251**, highlighting a preference for the (*S*) configuration (24% *ee* (2*S*) for the *endo*-isomer and 8% *ee* (2*S*) for the *exo*-isomer). Similar conclusions can be deduced for the Diels-Alder reaction performed at 25 °C. The divergent behaviours observed for the catalysts **251** and **260** suggest that the enantioselection is due to electronic factors, rather than just steric hindrance of the architecture of our scaffold.

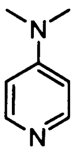
Although the observed enantioselectivities in these Diels-Alder experiments were not comparable with contemporary methods, our investigations into the modulation of face-face π-π interactions have provided a clear indication that the initial assumption was correct. We showed that the electronic density of the π-donating moiety had a direct bearing on the strength of the π-π interactions with the π-accepting substrate, which affected the enantioselectivity of the asymmetric carbon-carbon bond forming reaction.

Acyl-Ammonium Catalysis 3

Results and Discussion

3.1 4-(Dimethylamino)pyridine

The reaction of anhydrides and pyridine with alcohols is a mild, dependable and general method for the preparation of the corresponding acetates.[153] In 1967, Litvinenko and Kirichenko, found in the course of kinetic studies that replacing pyridine by 4-(dimethylamino)pyridine (DMAP) **144** resulted in a rate increase of *ca* 10^4 for the benzoylation of *m*-chloroaniline.[105] Subsequentialy, DMAP **144** has become a standard reagent for acylation,[153] esterification,[154] macrolactonization[155] and silylation reactions,[156] to mention a few applications. The detailed reaction mechanism for transformations catalysed by 4-(dialkylamino)pyridines has recently come under renewed scrutiny. [157] In particular, recent reports have shown that when the 4-amino moiety is conformationally fixed in a ring fused to the pyridine the catalytic activity of 4-aminopyridine is increased further. 4-Pyrrolidinopyridine (PPY) **148**[158] and the tricyclic compound **153**[110] are more effective acylation catalysts than DMAP **144**.



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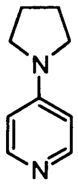

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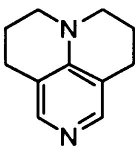
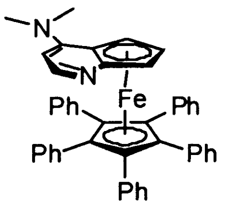


153

The kinetic resolution of alcohols by non-enzymatic acylation catalysts has also been the focus of intense interest. Over the last decade publications have reported chirally modified derivatives of 4-aminopyridine as novel catalysts for enantioselective acyl transfer.[159] A number of such derivatives, notably Fu's planar-chiral DMAP **161**,[160] Fuji's chiral PPY **164**,[117] and the Spivey axially chiral DMAP derivative **268**[118] offer practically useful levels of enantioselectivity in acylative kinetic resolutions (KRs)[161] or asymmetric desymmetrisations (ADs)[162] of alcohols.



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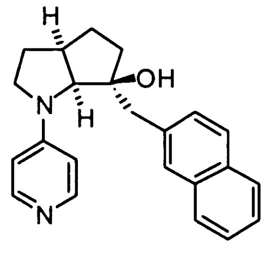

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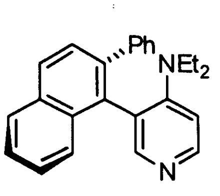
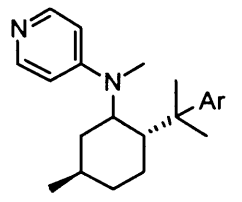


268

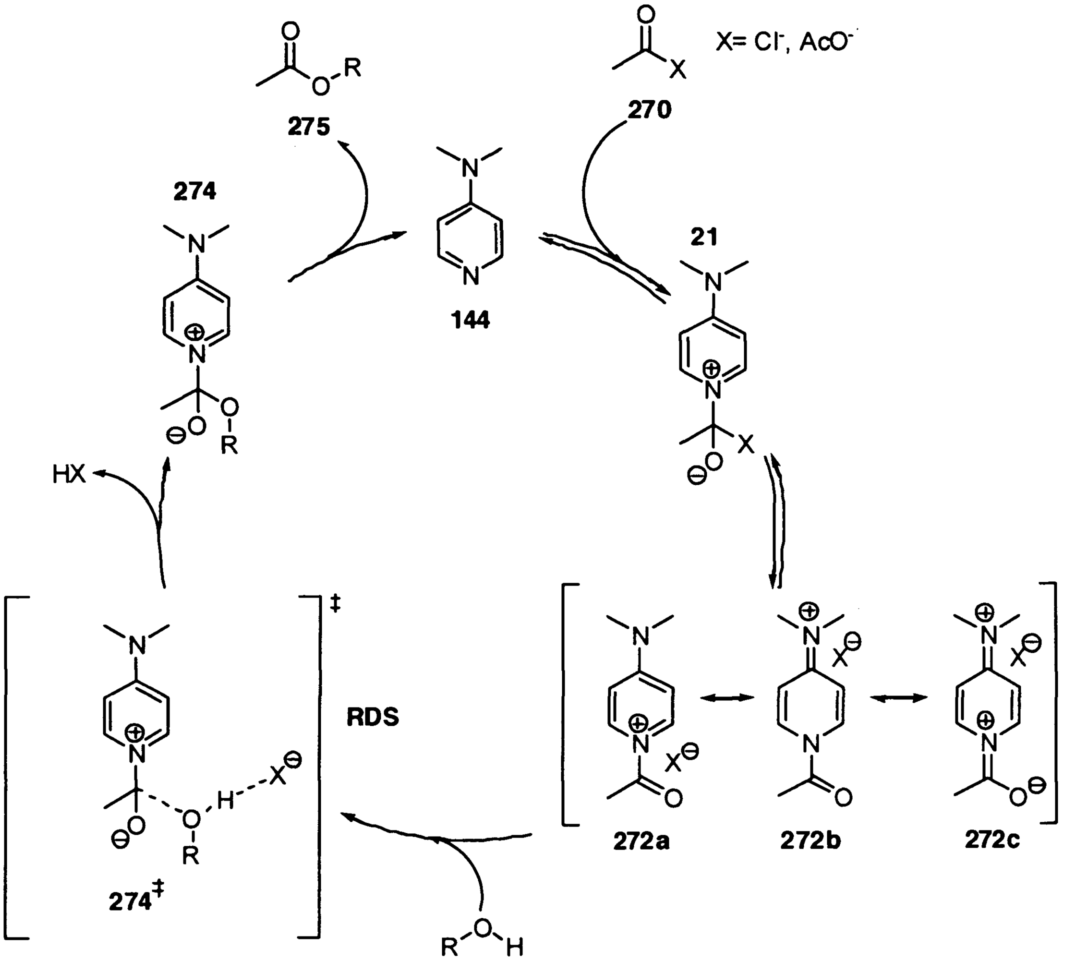
On account of these results, the work described in *Chapter Three* is focused on the development of a new family of catalysts to enhance the acylation activity of 4-aminopyridine by utilisation of the α-effect. It was also considered the opportunity to study a novel class of DMAP derivatives suitable for selective acylation of chiral alcohols based on the scaffold **269**.



269

3.1.1 Mechanism of the DMAP catalysed acylation

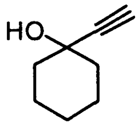
4-(Dimethylamino)pyridine **144** is a well known catalyst for the esterification of alcohols with an anhydride and also various other synthetically useful transformations involving acyl transfer.[163,104] The proposed mechanism for the acylation of alcohols catalysed by DMAP **144** begins with a reversible nucleophilic attack on the acyl donor **270** to form the *N*-acylpyridinium salt **272** *via* the tetrahedral intermediate **271** (Scheme 57). The formation and stability of the salt **272** depends on various factors such as the influence of steric hindrance, the nucleophilicity of the pyridine, stabilization of the acyl group by conjugation (**272a**↔**272b**↔**272c**), nature of the anion X^- (e.g. Cl^- or AcO^-) and solvent polarity. Irreversible nucleophilic addition of the alcohol **273** to salt **272** with concomitant proton transfer assisted by the anion X^- (through transition state **274**‡) leads to the second tetrahedral intermediate **274**. The efficiency of the counter anion X^- to deprotonate the alcohol-nucleophile in the transition state **274**‡ is believed a crucial aspect in the catalytic cycle, so that the formation of the species **274** has been indicated as the Rate Determining Step (RDS) for this transformation.[157a] Formation of ester **275** and release of DMAP **144** conclude this catalytic cycle.



Scheme 57

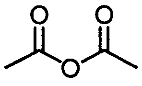
3.1.2 Acylation substrates

Since their introduction to synthetic chemistry, 4 dialkylamino pyridines have been revealed as powerful and versatile nucleophilic group transfer agents for a plethora of chemical transformations.[163] Within our work, we adopted the acylation of 1-ethynylcyclohexanol **276** with the acyl donor being acetic anhydride **146** as our standard protocol to compare the activities of the catalysts prepared. As reported previously in the literature, kinetic evaluations involving this substrate required 4 to 5 hours with 10 mol% catalyst loading.[157a] Moreover, as a result of distinct proton NMR signals for the starting materials and products, the reaction could be monitored by NMR spectroscopy, allowing an accurate and practical comparison of individual catalysts.



1-Ethynylcyclohexanol

276



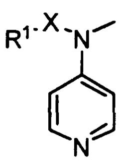
Acetic anhydride

146

3.2 DMAP derivatives: proposed catalyst design

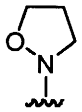
3.2.1 Design concepts

Previous experience within the group had demonstrated that the use of the a-effect for catalysing the Diels-Alder cycloaddition through iminium ion formation could be an appealing synthetic strategy (for more information see *Chapter Two*). Within this phase of the project, we attempted to extend the use of this phenomenon to nucleophilic catalysis. Therefore, we embarked upon an investigation into the synthesis of modified DMAP derivatives based on the structure **277**.



277

X = O, N
R^1 = Me, PhCO

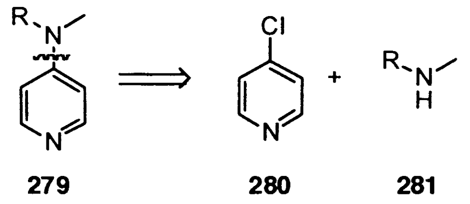


278

We sought to integrate the a-effect into the architecture of our modified DMAP family **277**, replacing one of the methyl groups with a substituent possessing either a α-nitrogen or an α-oxygen atom. It was thought that electronic repulsion between generated the lone pairs present on the two heteroatoms could enhance the formation of the conjugated intermediate **272**.[135] The negative charge generated by this could increase the nucleophilicity of the modified DMAPs and accelerate the formation of the intermediate **271** and the *N*-acylpyridinuim salt **272**. Thus, an increase of negative charge by increased conjugation promoted through the α-effect could lead to an increase in the reaction rate. We planned, therefore, to synthesise pyridines with architecture **277** through a simple synthetic pathway founded on a direct nucleophilic aromatic substitution between an activated aromatic compound and a secondary amine, which were either commercially available or previously prepared within the group. The influence of the group R^1 was also scrutinised by the introduction of a variety of characteristics, which could reasonably be expected to affect catalytic ability of the compounds. The activity of the R^1 group was evaluated utilising a weak electron donating substituent such as a methyl group, an electron withdrawing unit such as a benzoyl group (PhCO) and incorporating the 4-amino nitrogen and an α-oxygen into the heterocycle **278**.

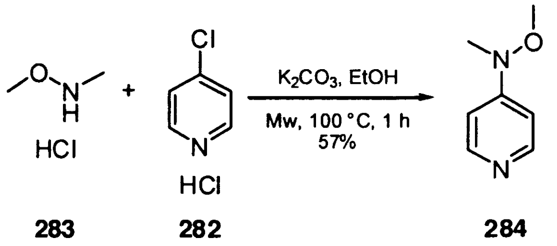
3.2.2 DMAP derivatives synthesis

Retrosynthetic analysis of the modified 4-aminopyridines **279** suggested that the synthesis of this compound could be achieved through the direct nucleophilic aromatic substitution (S_NAr) of secondary amine **281** on the commercially available 4-chloropyridine **280** (Scheme 58).[164]



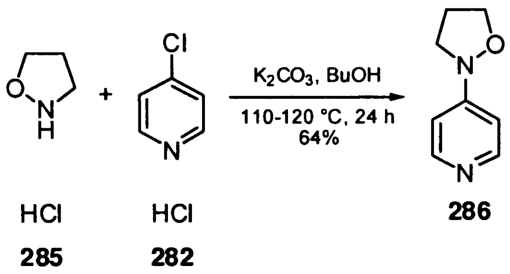
Scheme 58

A mixture of 4-chloropyridine hydrochloride **282** and *N*-methoxymethylamine hydrochloride **283** in ethanol was irradiated with microwaves at a temperature of 100 °C for 60 minutes (Scheme 59). This transformation was carried out in the presence of an excess of potassium carbonate to neutralise the hydrochloride salts **282** and **283**. The crude reaction mixture was treated with water and extracted with ethyl acetate, and the organic phase was concentrated under reduced pressure to provide, after purification by repeated trituration in petroleum ether *N*-methoxy-*N*-methylpyridin-4-amine **284** as a colourless solid in 57% isolated yield.



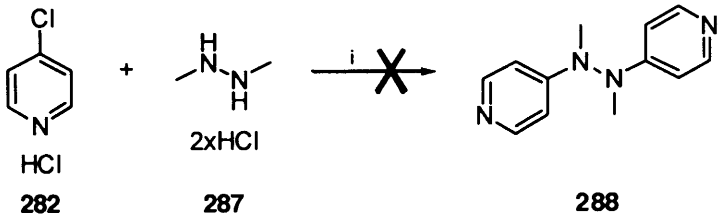
Scheme 59

A mixture of 4-chloropyridine hydrochloride **282** and the isoxazolidine hydrochloride **285** was stirred in butanol in the presence of an excess of potassium carbonate at 110-120 °C for twenty four hours (Scheme 60). The resulting crude reaction mixture showed a complex mixture of product and side-products which required initial purification by flash column chromatography followed by a subsequent recrystallization from dichloromethane and diethyl ether to give 4-(isoxazolidin-2-yl)pyridine **286** as a colourless solid in 64% isolated yield.



Scheme 60

Synthesis of 1,2-dimethyl-1,2-di(pyridin-4-yl)hydrazine **288** was attempted using dimethylhydrazine **287** as the nucleophile (Scheme 61). 1,2-Dimethylhydrazine dihydrochloride **287** was allowed to react with 4-chloropyridine hydrochloride **282** under a series of conditions reported below (Table 10).



(i) All reaction conditions are reported in Table 10

Scheme 61

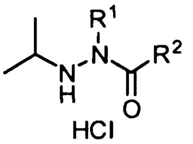
Table 10. Reaction conditions attempted for the synthesis of **287**.

Entry	Base	Solvent	Temperature	Time (h)
1	K_2CO_3	EtOH	r.t.	5 days
2	K_2CO_3	EtOH	reflux	24
3	NEt_3	NMP	reflux	24
4	NEt_3	NMP	150 °C, Mw	1
5	K_2CO_3	NMP	150 °C, Mw	1
6	K_2CO_3	BuOH	150 °C, Mw	1
7	K_2CO_3	BuOH	refulx	24
8	K_2CO_3	No solvent	melted salts	3

Despite the high nucleophilicity of compound **287** only a complex mixture of side-products was recovered after each reaction attempted. Increase of temperature, and variation in solvents and bases employed failed to provide the desired compound **288**.

3.2.3 Introduction of electron withdrawing group

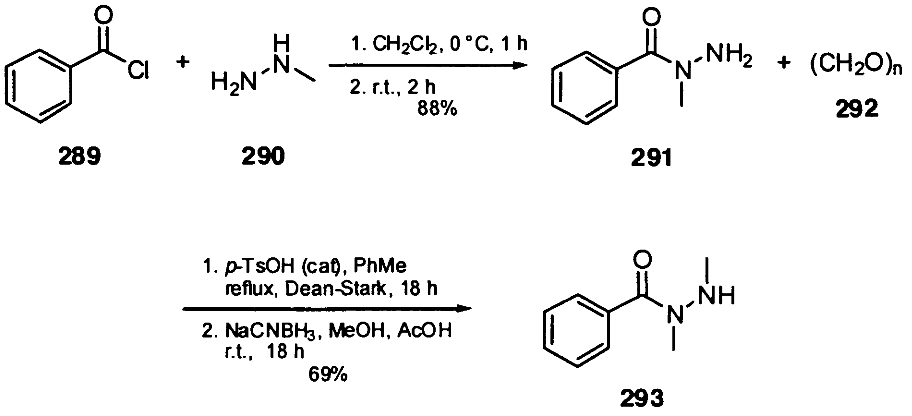
Previous experiences accumulated within the group underlined how the presence of an electron withdrawing carbonyl functionality in the β-position from the nucleophilic nitrogen considerably increased the reactivity of the hydrazides with structure **185** in the iminium ion catalysed Diels-Alder reaction (see *Chapter Two, section 2.2.2* and *2.4.1*).[130,131] Hence, we sought to introduce this concept in the design of the 4-aminopyridine derivatives, incorporating a benzoyl unit on the modified DMAP scaffold.



185

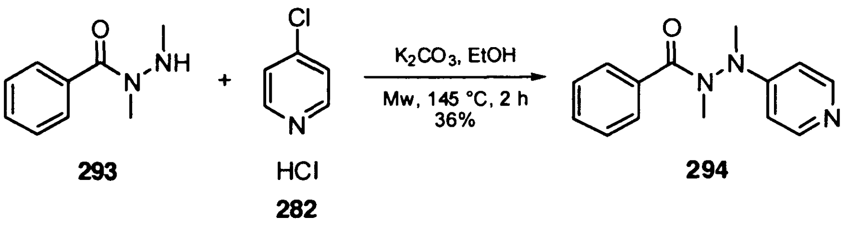
R^1 = H, Me, *t*-Bu
R^2 = Ph, OEt

According to the procedure reported by Hulme and McNab,[165] a solution of *N*-methyl hydrazine **290** (1.5 M) in dichloromethane was added a diluted solution of aroyl chloride **289** (0.15 M) in dichloromethane slowly at 0 °C under nitrogen and the resulting solution was stirred for one hour (Scheme 62). This high dilution of compound **289** was required to prevent the formation of undesired by products including 1- and 2- substituted hydrazides and diacyl hydrazines. The reaction was allowed to stir for an additional two hours at room temperature before basic work up with saturated sodium carbonate and extraction with dichloromethane. Evaporation of the volatiles provided *N*-methylbenzohydrazide **291** as a colourless solid in 88% isolated yield. Hydrazide **291** was reacted with para-formaldehyde **292** in toluene in the presence of a catalytic amount of *p*-toluensulfonic acid at reflux under Dean-Stark conditions for eighteen hours. The toluene was replaced with methanol and the mixture was treated with sodium cyanoborohydride at room temperature for eighteen hours. After work up, the reaction gave *N*,*N'*-dimethylbenzohydrazide **293** as a colourless oil in 69% isolate yield.



Scheme 62

Synthesis of 4-aminopyridine **294** was completed by microwave irradiation of compound **293** and 4-chloropyridine hydrochloride **282** in ethanol at 145 °C for two hours (Scheme 63). To neutralise the hydrochloric acid formed during the reaction and release the secondary amine **293** as a free base, the reaction was carried out with an excess of potassium carbonate. After the work up, the mixture was purified by column chromatography to give *N*,*N'*-dimethyl-*N'*-(pyridin-4-yl)benzohydrazide **294** as a pale yellow solid in 36% isolated yield (overall yield 22%).

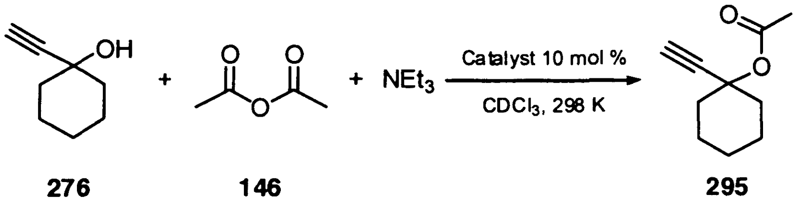


Scheme 63

3.3 Kinetic tests

3.3.1 Kinetic procedure

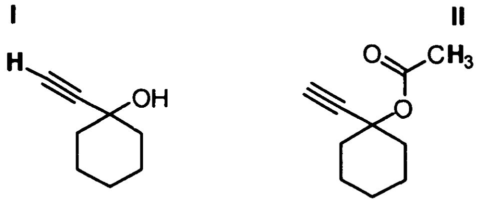
Acylation of 1-ethynylcyclohexanol **276** with acetic anhydride **146** catalysed by 4-aminopyridine has been reported as a useful and practical method to evaluate the reactivity of the acyl-transfer agents.[153] Therefore, we decided to adopt the same protocol for a rapid measure of the catalytic activity of our modified DMAPs. The reaction was performed utilising a clean and dry NMR tube which was charged with alcohol **276** (1 eq), catalyst (10 mol% loading), triethylamine as auxiliary base (3 eq) and deuterated chloroform (1 mL, Scheme 64). The last component added to the mixture was acetic anhydride **146** (2 eq). The addition of the anhydride **146** was considered as the starting point of the reaction (t = 0 min). The sample was immediately introduced into the NMR machine (500 MHz) and monitored for five hours at a temperature of 298 K, acquiring a spectrum every 12 minutes for a total of 25 scans.



Scheme 64

3.3.2 Analysis of kinetic results

Within our work, we were concerned with monitoring the relative reactivity of a series of 4-aminopiridines. This was conveniently done through ^1H NMR analysis of the spectra collected from the acylation tests. Due to the different chemical environments of the acetylenic proton **I** of the starting material **276** and the proton of methyl group **II** in the acetylated alcohol **295** had a unique and discrete signal in the ^1H NMR spectrum (Figure 36).



276 **295**

Figure 36

It has been shown that the signals corresponding to the proton **I** and proton **II** appeared at roughly δ2.36 and δ1.96 respectively (Figure 37).[153,157] Integration of these signals were utilised to calculate the conversions for each scan acquired, and thus to monitor reaction progress. Integration of peak **II** needed a further simple calculation. In fact, integration obtained for the compound **276** considers only one proton, whereas the value attained for the peak **II** takes the integration of three protons into account. Thus, the value calculated for this peak was reduced to one/third before estimation of the conversions.

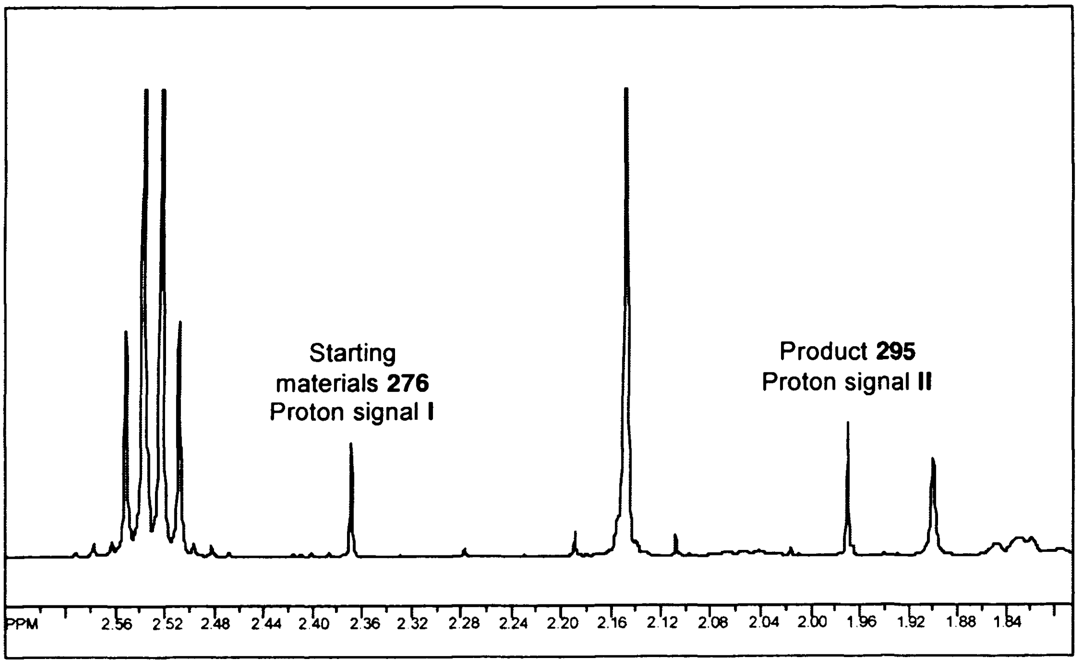
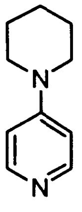


Figure 37

3.3.3 Pyridyl β-hydrogen and conjugation effect

Hassener *et al.* scrutinised the catalytic reactivity of a series of DMAP analogues (reported below) in the acylation of 1,1-diphenylethanol **297** with acetic anhydride **146** (Table 11).[109] They inferred that the extent of the conjugation between the lone pair of the 4-amino group and the carbonyl function through the pyridine ring was a crucial factor in stabilising the acylpyridinium intermediate **272**. It was also noted that the degree of shielding of the pyridyl ß-hydrogen H_β atoms in the ^1H NMR spectra of 4-aminopyridine derivatives and their catalytic efficiency were qualitatively correlated. Thus, the intensity of the electron donation by the exocyclic nitrogen atom towards the aromatic ring is reflected by the chemical shift for the β-hydrogen H_β of the initial DMAP derivative (Figure 38).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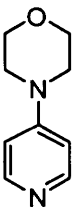
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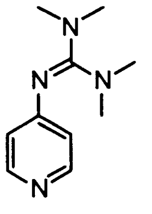

151

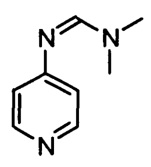
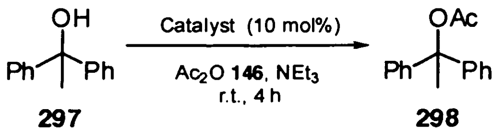
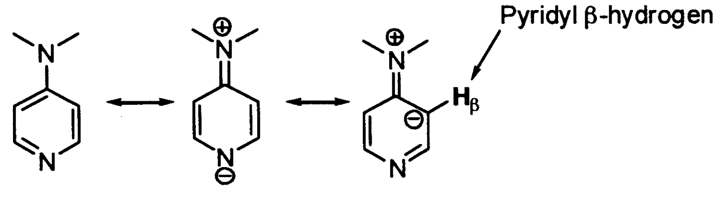

296

Table 11. Correlation between the shielding of the pyridyl β-hydrogen atoms H_β in the ^1H NMR spectra and the catalytic efficiency of the 4-aminopyridine derivatives.



Entry	Catalyst	Rel. rate	$\delta(H_\beta)$ (ppm)
1	**148**	1	6.38
2	**151**	0.90	6.55
3	**144**	0.63	6.48
4	**149**	0.40	6.55
5	**296**	0.30	6.92
6	**150**	0.12	6.67

This observation reported by Hassner's laboratory provided a practical method to evaluate the electronic conjugation between the aromatic part and amino unit of the DMAP derivatives. In addition, analysis of the pyridyl β-hydrogen H_β chemical shift represents a further element to scrutinise the reactivity of our 4-aminopyridines.



144 **A** **B**

Figure 38

3.4 Substituted 4-aminopyridines

With suitable catalysts prepared we tested our initial hypothesis within the acylation transformation of 1-ethynylcyclohexanol **276** with acetic anhydride **146**. Preliminary experiments were performed to define background reaction as well as, with pyridine, DMAP **144** and PPY **147**, references to allow an accurate evaluation of our catalysts.

3.4.1 Preliminary tests: background reaction

Kinetic tests performed in the absence of catalyst was aimed to evaluate background reaction due to the tertiary amine employed as auxiliary base. In a similar fashion, the experiment was carried out with a 10 mol% loading of pyridine to give a clear indication about the catalytic activity strictly attributable to pyridine nucleophilicity itself. The results collected are plotted in Figure 39.

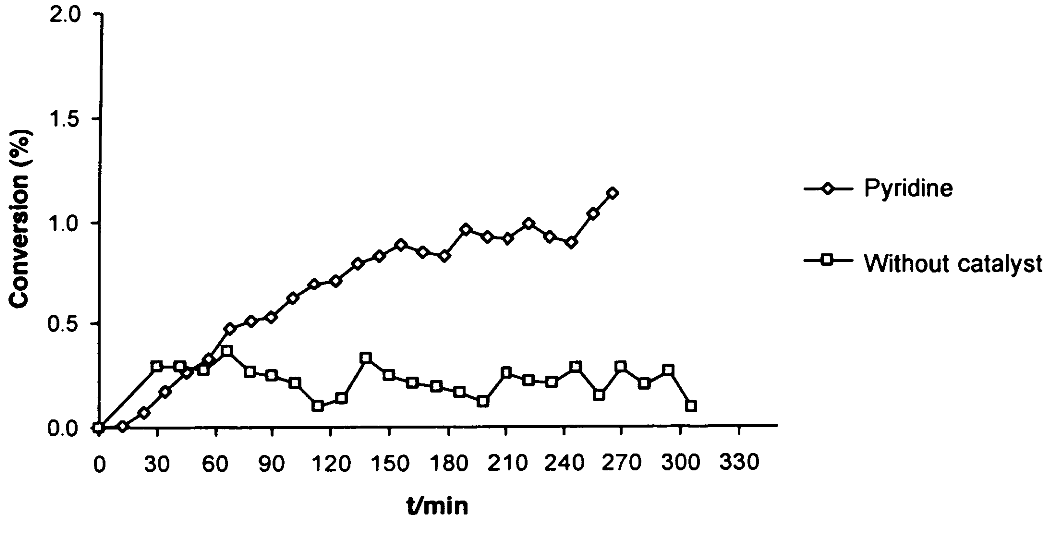


Figure 39

The transformation accomplished using triethylamine as auxiliary base provided a conversion lower than 0.5% after five hours (Figure 39). Thus, the sole function of the tertiary amine was to maintain the basic conditions required for this transformation. The curve attained without catalyst could be considered as the baseline of the subsequent kinetic runs.

The reaction performed with pyridine at a level of 10 mol% showed a low reaction rate delivering a poor 1% conversion after five hours. This experiment illustrated catalytic activity attributed to the nucleophilicity of pyridine. The lack of electron donating substituents such as the 4-dialkylamino unit attached to the aromatic ring does not permit an efficient stabilization of intermediate **271** and acylpyridinium **272**. Hence, this result allows definition of the "bottom limit" of the electron donation, allowing us a reasonable comparative analysis of the catalytic improvement due to the α-effect.

3.4.2 Preliminary tests: DMAP and PPY

The kinetic protocol was also performed with a second group of experiments utilising DMAP **144** and the more reactive PPY **148** as catalyst at a loading of 10 mol%. The data measured for these experiments are plotted in Figure 40.

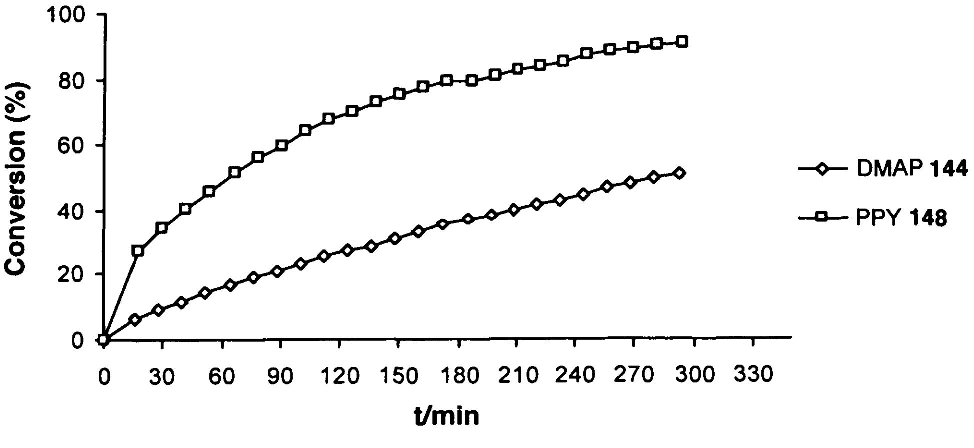


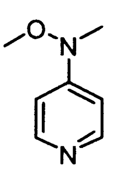
Figure 40

In line with the literature, the ability to catalyse the acylation of the tertiary alcohol **276** with DMAP **144** and PPY **148** is impressive.[157] 4-(Dimethylamino)pyridine **144** provided a 50% conversion in five hours showing a regular slope (Figure 40). A remarkable 91% was delivered by PPY **148** in an analogous time. The slope of the curve reveals that the level of

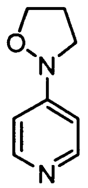
51% of conversion was reached after just one hour, highlighting the high catalytic activity of **148**. The remarkable performances indicate that conjugation of the lone pair of the 4-amino group with the aromatic ring, significantly increases the stabilization of the *N*-acylpyridinium (**271** and **272a**↔**272b**↔**272c**) followed by the rate determining reaction with the alcohol (**274**‡ and **274**). Thus, the experiments carried out with DMAP **144** and PPY **148** offered us two additional elements for evaluation of the extent of the α-effect in the catalytic capacity of our catalysts.

3.4.3 Investigation into the α-effect

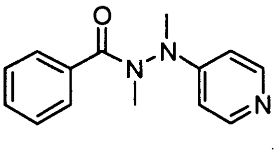
With catalysts **284**, **286** and **294** prepared, we embarked upon an investigation into the effect of the presence of a α-heteroatom attached to the N'-1 nitrogen.



284



286



294

The results obtained for this set of experiments are reported below (Figure 41)

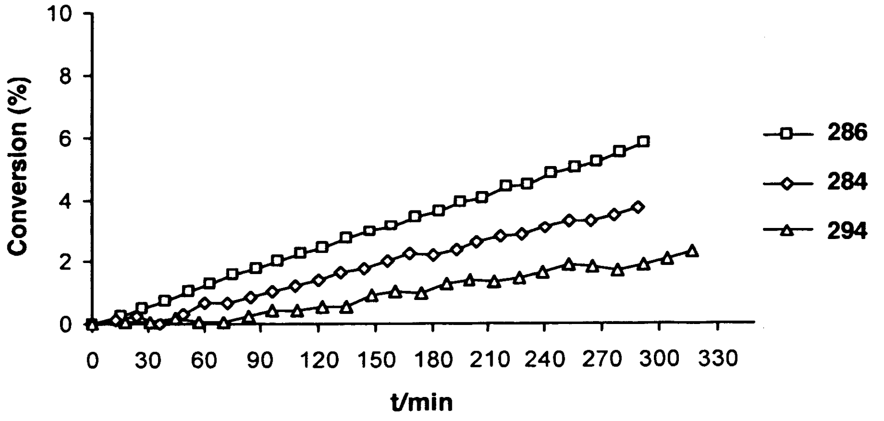


Figure 41

The results of the kinetic runs for the catalysts **286**, **284** and **294** showed a disappointingly poor catalytic activity. Conversions of 3%, 4% and 6% for **294**, **284** and **286** respectively were achieved after the standard reaction time of five hours. The low level in conversions observed for these tests indicated that each of catalysts has suffered from an insufficient conjugation between the lone pair of the 4-amino moiety and the pyridine ring. This hypothesis was corroborated by the high chemical shifts measured for the pyridyl β-hydrogens in catalysts **286**, **284** and **294** (δ6.60, δ6.75 and δ6.77 respectively) relative to those of DMAP **144** (δ6.48) and PPY **147** (δ6.38). The lack of this interaction decreased the capacity of our catalysts to stabilise the acylpyridinium complex **271** and **272**, and increases the turn over time. An explanation could be that due to the steric encumbrance and strong electronic repulsions between the 4-amino moiety and the π-system of the pyridine ring of the catalyst could bring about rotation around the C-N bond **a** (Figure 42). Thus, the orbital with the lone pair of the N'-1 nitrogen atom (**b**) and the aromatic π-system (**c**) would assume an orientation almost perpendicular. Such a distortion of this bond would prevent an optimal overlap of orbital **b** and **c**, reducing the extent of conjugation between the N'-1 nitrogen atom lone pair and the pyridine π-system.

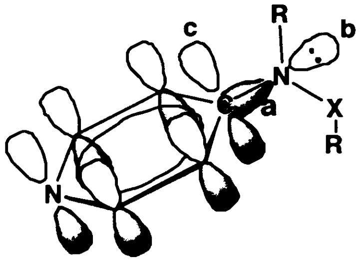


Figure 42

The poor conversion observed for the kinetic runs performed with 1-ethynylcyclohexanol **276** and acetic anhydride **146** revealed that the influence of the different substituents attached to the α-heteroatom was substantially irrelevant.

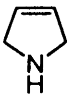
The α-effect failed to deliver significant enhancement in reactivity for this group of catalysts. It appeared that electron density on the pyridine ring, hence, the nucleophilicity and the ability to stabilise the intermediate **271** and the *N*-acylpyridinium salt **272** is decreased rather than increased by use of the α-effect Such a lack of conjugation between these the π-system orbitals of the heterocycle and the lone pair of the N'-1 nitrogen atom is mirrored by their catalytic activity, therefore our catalysts have reactivity similar to that of pyridine (1% in five hours, Figure 39, see *section 3.4.1*).

3.5 An alternative 4-alkylamino group

The earlier series of kinetic tests revealed the symmetry of the catalyst is a determining factor in the reactivity of the 4-aminopyridines. It was also observed that the α-effect failed to deliver improvement in catalytic reactivity as expected. Hence, the design of our catalysts was subjected to re-examination.

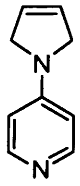
3.5.1 Proposed catalytic design

Catalyst **284**, **286** and **294** had shown a low level of turnover compared to the performances offered by DMAP **144** in the acylation of 1-ethynylcyclohexanol **276**, after the first cycle of kinetic runs. However, the hypothesis that the electronic repulsion between the lone pair of the 4-amino nitrogen and a secondary source of negative charge incorporated into the 4-amino substituent could help the formation of the reactive intermediate was not observed. The lack of symmetry due to electronic repulsion and steric factors occurred between the α-heteroatom and the pyridine ring were most likely the principle cause for diminishment in reactivity of our catalysts. Therefore, we decided to incorporate an electronic repulsive effect into the design of the 4-amino group attached to pyridine. Furthermore, a high level of symmetry for this catalyst was preserved. 2,5-Dihydro-1*H*-pyrrole **299** satisfied both the requirements.



2,5-dihydro-1*H*-pyrrole

299



300

Secondary amine **299** shows a structure quite similar to PPY **147** with a double bond in the five membered ring. The electronic cloud of the double bond should generate an additional repulsion effect with the lone pair of nitrogen so that the electronic donation of the amino group should be increased. Moreover, this π-bond promotes two additional secondary effects:

1. The double bond forces the cyclic amine to assume a planar conformation and;

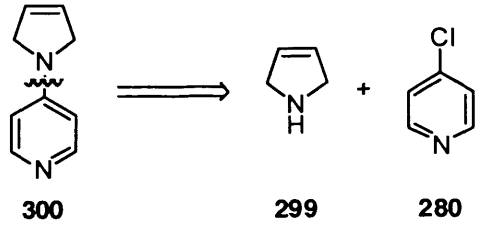
II. The increased strain of the five membered ring causes a reduction of the carbon-nitrogen-carbon angles, reducing the steric repulsion with the β-hydrogens of the pyridine ring.

Both of these factors should facilitate an optimal orientation between the lone pair of nitrogen and the electronic cloud of pyridine ring enhancing further the conjugation effects.

The characteristics of 2,5-dihydro-1*H*-pyrrole **299**, electronic repulsion and a planar conformation, offered us the opportunity to investigate a novel modified DMAP **144** for acylation of tertiary alcohol **276**.

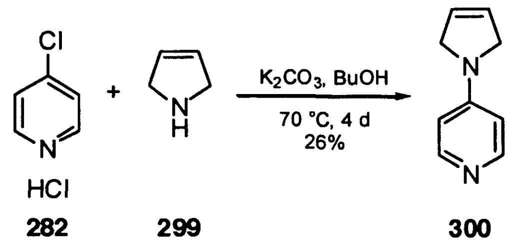
3.5.2 4-(2*H*-Pyrrol-1(5*H*)-yl)pyridine synthesis

Following a similar retrosynthetic analysis illustrated in *section 3.2.2*, synthesis of **300** should be achieved *via* a nucleophilic aromatic substitution of the secondary amine **299** on 4-chloropyridine **280** (Scheme 65).



Scheme 65

4-Chloropyridine hydrochloride **282** and 2,5-dihydro-1*H*-pyrrole **299** were reacted in butanol at 70 °C for four days in the presence of a large excess of potassium carbonate (Scheme 66). The mixture was quenched with water and, after work up, the crude reaction mixture was purified by chromatography to give 4-(2*H*-pyrrol-1(5*H*)-yl)pyridine **300** as a white solid in 26% isolated yield.



Scheme 66

300 was found covered by a brown patina after twenty-four hours and its solubility in organic solvent was drastically diminished, revealing it to be an air-sensitive compound. Thus, catalyst **300** was subsequent utilised immediately after synthesis, however, it could be stored at low temperature (-20 °C) under an inert atmosphere.

300 showed intensely shielded pyridyl ß-hydrogen atoms with a chemical shift equal to 6.30 ppm. Comparison of this value with the chemical shift of PPY-pyridyl ß-hydrogen (equal to 6.38 ppm) suggested that the electronic communication between the lone pair of the N'-1 nitrogen atom and the aromatic ring should be even higher in our modified DMAP. Thus, the ^{1}H NMR analysis of **300** hinted a catalytic behaviour comparable, if not better, to that of PPY **148** itself.

3.5.3 Kinetic test catalysed by 4-(2*H*-pyrrol-1(5*H*)-yl)pyridine

The results of the kinetic tests carried out with molecule **300** are plotted in Figure 43

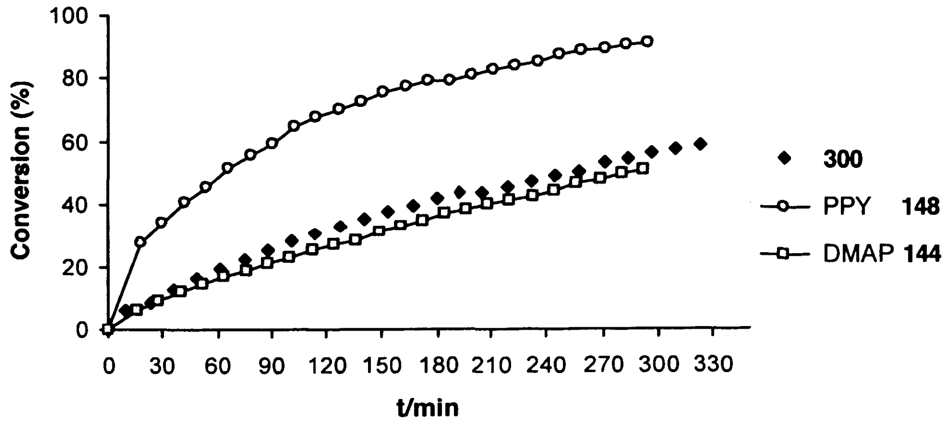


Figure 43

Surprisingly, **300** showed a reaction pathway quite similar to the catalytic activity typical of DMAP **144** (Figure 43). Such a result was completely unexpected and disappointing, although the catalyst **300** displayed interesting spectroscopic characteristics and a structural affinity to PPY **148** (see previous *section 3.5.2*). In order to avoid possible contamination and degradation of the catalyst, this acylation experiment was repeated with a second batch of compound **300**. The catalyst **300** was employed immediately after purification. In spite of all precautions utilised this catalytic test delivered an identical outcome.

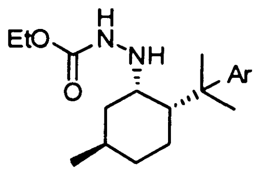
To the best of our knowledge, this is the first example of the chemical shift of the β-hydrogen and the catalytic activity of the pyridine derivative **300** not being directly related. Although frustrating this is an interesting and potentially useful observation.

3.6 Asymmetric kinetic resolution

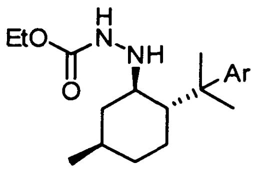
Until recently, the kinetic resolution of alcohols has remained the exclusive domain of enzymatic acylation catalysts. Throughout the last decade a number of researchers have been involved in the design of novel organic molecules suitable to catalyse enantioselective acyl transfer.[161,162] Modified 4-aminopyridines have found wide use in this field of organic chemistry, offering excellent levels of reactivity and enantioselectivity.[159] However, many of the catalysts developed have showed drawbacks such as lengthy synthesis and complicated purification procedures,[166,115] leaving room for further improvement. On account of these results, we decided to dedicate the second part of this phase of the project to prepare a novel family of modified DMAP derivatives for the kinetic resolution of alcohols.

3.6.1 Proposed catalyst design

A large number of publications have established that face-face π-π interactions are a suitable platform with which to promote enantioselective transformations (for more information see *Chapter Two, section 2.5.2*). Within the work described in *Chapter Two* we introduced this concept into the design of our 8-aryl methyl hydrazides **202** and **203**. Examination of the structure of our catalysts showed that we could rapidly gain access to alternative structures with only minor modifications to the synthetic route. Therefore, we decided to further the investigation of face-face π-π interactions within the context of alcohol kinetic resolution.

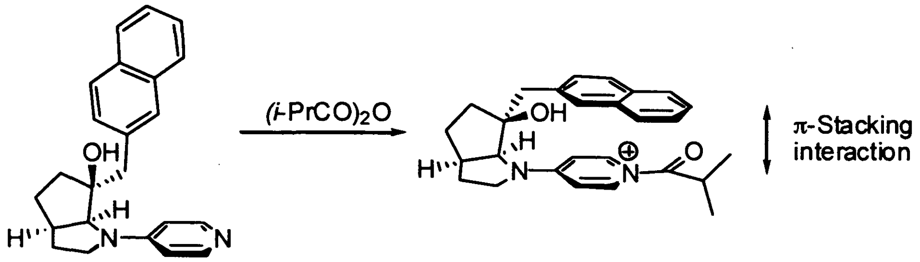


202



203

Within the work of Fuji, catalyst **164** was reported as a molecule which could induce high levels of stereocontrol through the formation of the intermediate **B** (Figure 44).[117] It was reasoned that the formation of the acylpyridinium salt of **164** triggered the reorganisation of the catalyst into the "closed conformation" **B**. NOE-NMR studies suggested that this reorganization was facilitated by the participation of an additional face-face π-π interaction between the naphthalene unit and the *N*-acyliminium moiety. The π-stacking effect regulates the direction of substrate approach.

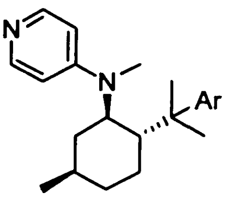


"Open conformation"
A

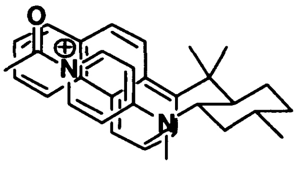
"Closed conformation"
B

Figure 44

In a similar fashion to the Fuji catalyst, an 8-aryl menthamine scaffold offered the interesting opportunity to create a DMAP derivate that could have the capability of fixing the orientation of the pyridyl ring through a face-face π–π interaction, rendering the pyridyl ring in a chiral environment **301**. This interaction should provide the required shielding of the bottom face of the *N*-acyliminium moiety driving the approach of the substrate towards the top-side of the *N*-acylpyridinium group **301**.



269

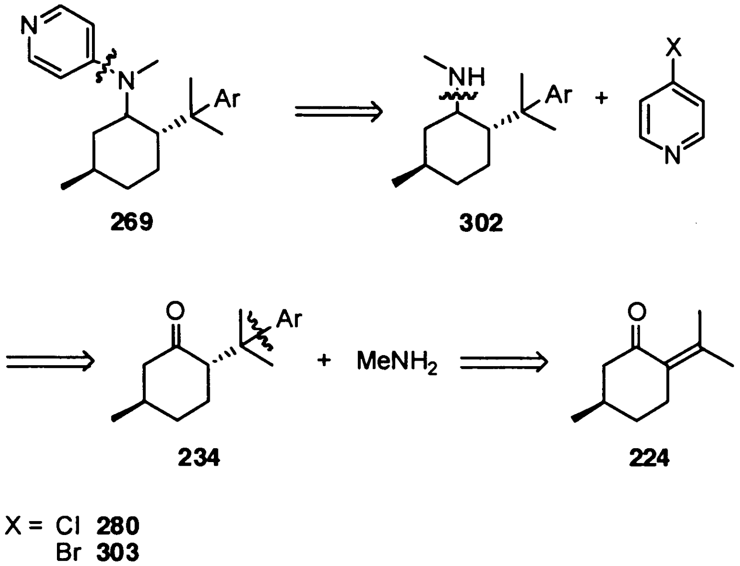


301

Therefore, we embarked on the synthesis of a novel family of modified DMAPs based on the scaffold **269** to extend the exploration into the face-face π-π interaction. Subtle modifications to the extension of the aromatic surface of **269** should enable an investigation into the tuning of the strength of this phenomenon. Minor modification to the previous synthetic pathway, employed for the preparation of our 8-aryl hydrazides **202** and **203**, was necessary to realise this novel set of target molecules.

3.6.2 Retrosynthetic analysis

Retrosynthetic analysis of our proposed DMAP derivatives **269**, shows a prospective synthesis from commercially available (*R*)-(+)-pulegone **224** (Scheme 67).



Scheme 67

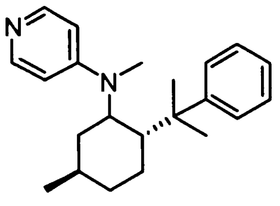
Conjugate addition, with subsequent equilibration,[143] should provide 8-aryl menthone **234** from commercially available (*R*)-(+)-pulegone **224**. Modifications to the aromatic group should be achievable by using a variety of nucleophiles in the conjugate addition step. Following a reductive amination protocol, reaction of 8-aryl menthone **234** with methyl amine and subsequent reduction should provide the amine **302**. Nucleophilic aromatic substitution ($\mathrm{S_NAr}$) of secondary amine **302** on 4-chloropyridine **280** should provide the compound **269**. Alternatively, the introduction of the pyridine unit should be possible *via* arylation using Buchwald type technology.[167]

The retrosynthetic analysis described above (Scheme 67) is quite similar to that utilised for the synthesis of our hydrazides **202** and **203** (*Chapter Two, section 2.5.4*) except in the last step, we proposed to utilise a nucleophilic aromatic substitution ($\mathrm{S_NAr}$). Prior to optimisation of the aryl unit, we decided to examine methods for the introduction of the pyridyl group.

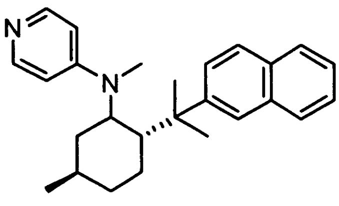
Once the optimal procedure for introduction of the pyridine unit had been determined, modifications to the nature of the aromatic functionality would ensue. We planned to synthesise four novel modified DMAP arenes with the following characteristics:

I. Aromatic groups with increasing size such as benzene **304**, naphthalene **305**, phenanthralene **306** and;

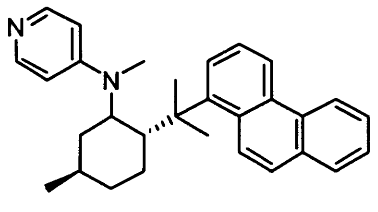
II. A catalyst without aromatic unit **307** to establish the extent of any π-stacking interaction.



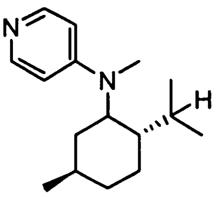
304



305



306

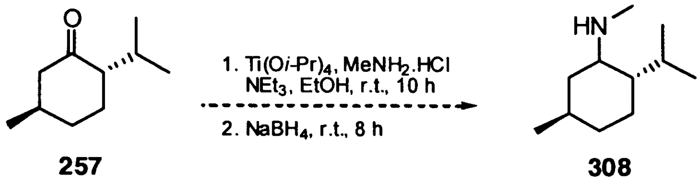


307

This new set of catalysts should enable an investigation into the effect on the strength of the proposed face-face π-π interaction.

3.6.3 Menthamine derivatives synthesis

Synthesis of our family of 4-alkyl pyridines **269** began with the preparation of the catalyst **307**, which could allow us to optimise this synthetic route in the latter stages of our strategy. Therefore, we adopted an analogous reductive amination protocol described by Bhattacharyya[168] to prepare the menthamine precursor **308** (Scheme 68). (*L*)-Menthone **257**, titanium(IV) *iso*-propoxide and methylamine hydrochloride was stirred in dry ethanol in the presence of triethylamine, at room temperature for ten hours under an inert atmosphere. Subsequently, sodium borohydride was added as reducing agent and the mixture was stirred for an additional eight hours, to provide after an acidic/basic work up, a crude of reaction in 25% crude yield.

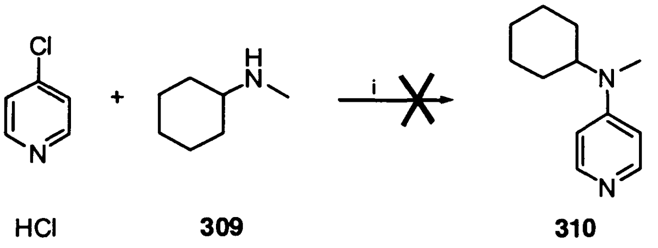


Scheme 68

Unfortunately, any attempt at further purification and separation of this mixture of diastereoisomers by chromatographic techniques failed. Moreover, the spectroscopic data colleted for this mixture provided contradictory and no conclusive indication of formation of the desired menthamine precursor **308**. Several attempts were made to alter this protocol to prepare **308** without success. Thus, at this stage of our investigation, we chose to turn our attention towards the crucial step of introduction of the pyridine ring into the catalyst scaffold before investigating an alternative strategy for the synthesis of menthamine derivatives.

3.6.4 Direct S$_N$Ar approach

Although considerably less stericaly hindered compared to the amine **302**, *N*-methylcyclohexylamine **309** is structurally similar to the parent amine **302**. We considered this compound could represent a useful model for our target system. As a first approach to the synthesis of **310** a direct nucleophilic aromatic substitution (S$_N$Ar) with 4-chloropyridine hydrochloride **282** and *N*-methylcyclohexylamine **309** under a variety of reaction conditions was examined (Scheme 69).


HCl 282 309 310

(i) All reaction conditions examined are reported in Table 12

Scheme 69

The results obtained from these series of experiments are reported in Table 12.

Table 12. Reaction conditions attempted in the synthesis of **310**.

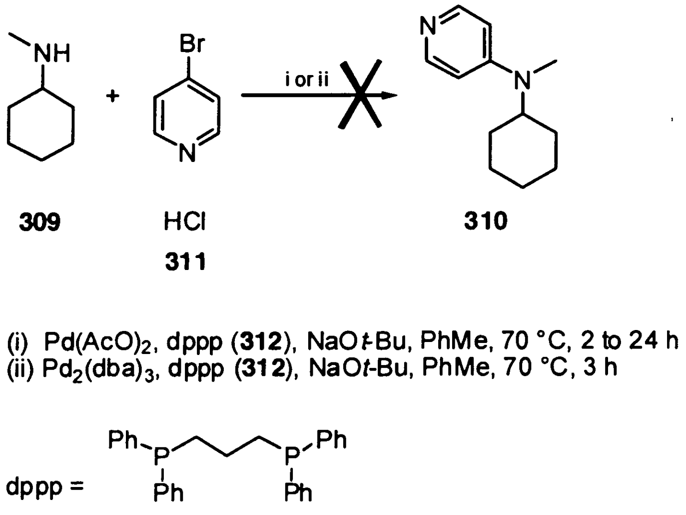
Entry	Solvente	Base	Conditions	Time
1	Pyridine	Pyridine	Mw, 120 °C	1 h
2	BuOH	K_2CO_3	Mw, 140 °C	1 h
3	Dioxane	K_2CO_3	Mw, 120 °C	1 h
4	Toluene	K_2CO_3	Mw, 110 °C	1 h
5	NEt_3	NEt_3	Mw, 150 °C	1 h
6	Pyridine	Pyridine	90 °C	15 h
7	BuOH	K_2CO_3	reflux	2 d
8	NMP	K_2CO_3	reflux	24 h
9	No solvent	K_2CO_3	200 °C	3 h

The reaction was performed in the presence of a variety of inorganic and organic bases such as potassium carbonate, pyridine and triethylamine. Reaction temperature was also increased choosing a range of solvents with increasing boiling point such as triethylamine (88 °C), pyridine (115 °C), toluene (110 °C), butanol (118 °C) and *N*-methyl pyrrolidine (202 °C), or melting the starting materials at 200 °C without solvent. Different reaction conditions were investigated using microwave irradiation or by use of traditional conductive heating to heat the mixture for reaction times ranging from one hour to two days. None of these reaction conditions provided any indication of the target pyridine **310** by examination of the ^1H NMR of the crude reaction mixture.

3.6.5 Buchwald protocol

Direct nucleophilic aromatic substitution (S_NAr) failed to deliver the desired formation of the carbon-nitrogen bond between the 4-chloropyridine **280** and the secondary amine **309**. Thus, in an attempt to introduce the pyridine ring, palladium catalysis was examined according to the Buchwald procedure for synthesis of aryl amines. [167]

An oven dried Schlenk tube was charged with the amine **309**, 4-bromo pyridine hydrochloride **294**, the catalyst palladium(II) acetate ($Pd(AcO)_2$), the ligand dppp **312** and finally sodium *tert*-butoxide under an inert atmosphere (reaction conditions (i), Scheme 70). All the starting materials, catalyst and ligand had been stored under dry conditions (in a desiccator or in the oven). The reaction was stirred in dry, freshly distilled toluene at 70 °C for two hours under an atmosphere of nitrogen. ^1H NMR analysis revealed that no reaction had occurred. The transformation was repeated increasing the reaction time to twenty four hours but only the starting materials were recovered.



309 **311** **310**

(i) $Pd(AcO)_2$, dppp (**312**), NaO*t*-Bu, PhMe, 70 °C, 2 to 24 h
(ii) $Pd_2(dba)_3$, dppp (**312**), NaO*t*-Bu, PhMe, 70 °C, 3 h

312

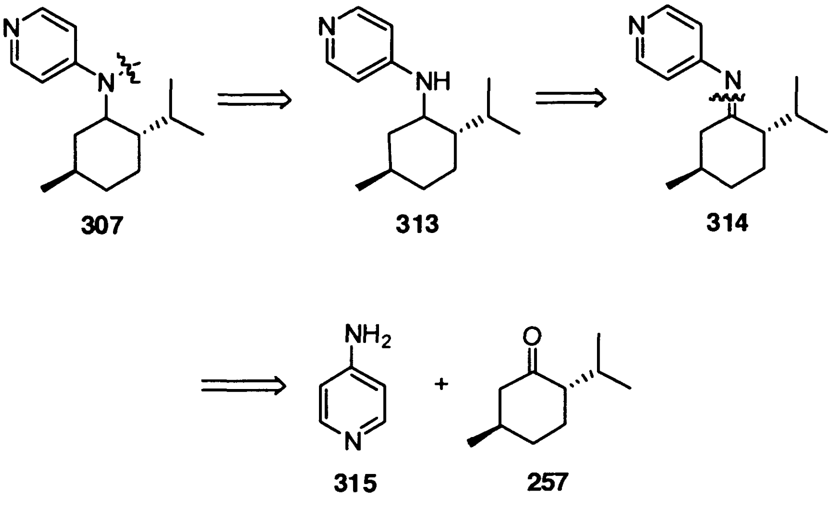
Scheme 70

We decided to replicate this protocol replacing the palladium(II) source with palladium(0). The catalyst selected was $Pd_2(dba)_3$. The reaction was set up as described above and stirred at 70 °C for three hours (reaction conditions (ii), Scheme 70). Once again only the unreacted starting materials were recovered. Subsequently to these results, careful examination of the vast literature related to the Buchwald-Hartwig coupling showed no indication that such a hindered amine would participate in this reaction. We therefore decided to modify our synthetic strategy.

3.6.6 Dean-Stark protocol

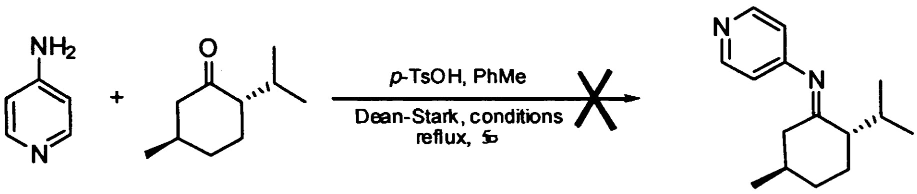
The synthetic route based on the retrosynthesis illustrated in *section 3.6.2* proved inappropriate to prepare our modified DMAPs. Thus, we decide to attempt a second approach to gain the access to our catalysts. Within the work of Bagley, the condensation of cyclic ketones and a heteroanilines catalysed by *p*-toluensulfonic acid under Dean-Stark conditions was reported. [169] With these findings, we envisaged to redefine the initial retrosynthetic analysis. (*L*)-menthone **257** was used to optimise this procedure.

Retrosynthetic analysis for compound **307** suggested that this could be achieved from commercially available 4-aminopyridine **315** and (*L*)-menthone **257** (Scheme 71). Condensation of 4-aminopyridine **315** and (*L*)-menthone **257** under Dean-Stark conditions should provide the imine **314**. A subsequent reduction with sodium cyanoborohydride or sodium borohydride should yield the secondary amine **313**. After protection of the secondary amine **313** with a Boc-group a second reduction with lithium aluminium hydride should provide the tertiary amine **307**.



Scheme 71

Synthesis of compound **314** was attempted setting up the experiment following the literature precedent[169] stirring a mixture of (*L*)-menthone **257** and 4-aminopyridine **315** in toluene at reflux in the presence of a catalytic amount of *p*-toluensulfonic acid under Dean-Stark conditions (Scheme 72). Unfortunately, the reaction was monitored by TLC for 5 days without any indication of the compound **314**.



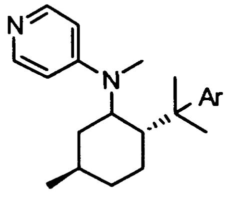
315 **257** **314**

Scheme 72

Frustrated by a series of poor results in this area, we decided to abandon this part of our research endeavours.

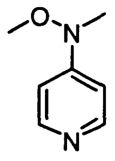
3.7 Conclusions

The work described in this chapter was intended to broaden our investigations of the α-effect and π-staking interactions as suitable platforms for the design of novel acyl-transfer catalysts. We hoped to improve the nucleophilicity of our modified DMAPs by utilising the α-effect. Further exploration of face-face π-π interactions was also envisaged through the preparation of a novel family of arenes **269** based on the 8-aryl menthamine scaffold.



269

The difficulties encountered during the synthesis and purification of the modified DMAPs limited the number of catalysts prepared. However, the small set of compounds prepared demonstrated that the α-effect failed to deliver any improvement in reactivity as we expected. **294**, **284** and **286** showed low levels of catalytic activity (3%, 4% and 6% respectively) after five hours, which was attributed to a decrease of electron conjugation between the 4-amino moiety and the pyridine ring. This electronic deficiency on the aromatic unit was also highlighted by the high chemical shifts measured for the pyridyl β-hydrogens for **286**, **284** and **294** (δ6.60, δ6.75 and δ6.77 respectively) relative to those of DMAP **144** (δ6.48) or PPY **117** (δ6.38). Such a lack of conjugation was probably due to electronic and steric repulsive interactions which diminished an optimal overlap between the π-system of the aromatic heterocycle and the N'-1 nitrogen lone pair, reducing the reactivity of our catalysts to that of pyridine (1% in five hour). Hence, the observations demonstrated that the enhancement of reactivity and nucleophilicity of our catalysts by the α-effect through the aromatic ring did not occur.



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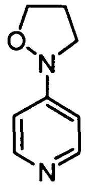

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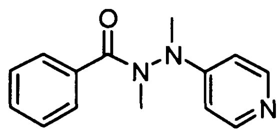
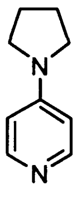


294

Catalyst **300** was based on different design concepts. In this catalyst, we decided to abandon the α-effect and adopt a repulsive electronic effect. In spite of noteworthy NMR characteristics (chemical shift of pyridyl β-hydrogen atoms δ6.30 ppm) when compared to the bench-mark catalyst PPY **147** (chemical shift of pyridyl β-hydrogen atoms δ6.38 ppm), **300** showed a catalytic activity quite similar to that DMAP **144**. A rationalisation of this observation is not possible with the data obtained.



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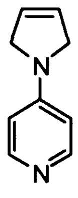


300

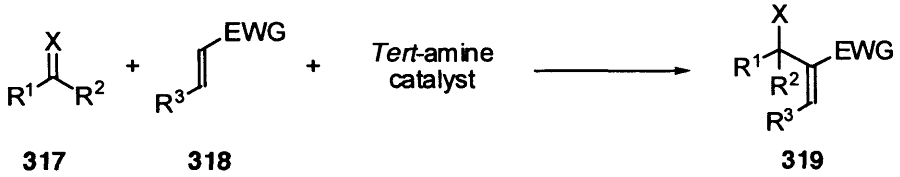
Preparation of a novel chiral DMAP family of 4-aminopyridines **269** for the stereoselective acylation of alcohols was frustrated by problems encountered in the preparation of these compounds. Although a variety of methodologies were attempted, the formation of the carbon-nitrogen bond between the secondary amine and the pyridine ring was not accomplished. Hence, we could not proceed the proposed investigation of face-face π-π interactions as a suitable platform for the kinetic resolution of alcohols. Development of new and more general methods for direct formation of the carbon-heteroatom bonds could offer the opportunity to synthesise our 4-aminopyridines **269**.

Baylis-Hillman Reaction 4

Results and Discussion

4.1 The Baylis-Hillman reaction

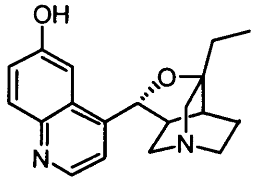
The Baylis-Hillman reaction has had a mixed fortune within organic chemistry in the last three decades. Though this reaction is a promising and fascinating way to create a carbon-carbon bond and results in a new chiral centre in a densely functionalised product, it eluded the attention of scientists for almost a decade (Scheme 73). The first report of this reaction dates back to 1972 in a German patent filed by A. B. Baylis and M. E. D. Hillman,[170] ten years later, in the early 80's, organic chemists started looking at this reaction and exploring various aspects of this important transformation, leading to the publication of three major reviews and a large number of research papers. [97,125,171]



R^1 = aryl, alkyl
R^2 = H, COOR, alkyl
R^3 = H, Me
X = O, NCOOR, NTs, NSO_2Ph
EWG = COR, CHO, CN, COOR, $CONH_2$, $PO(OEt)_2$, SO_3Ph, SO_2Ph, SOPh

Scheme 73

The synthetic potential of this reaction has driven the attention of organic chemists towards alternative solutions to overcome the disadvantage associated with the Baylis-Hillman reaction namely, a slow reaction time and the difficulty in attaining good levels of stereocontrol. Complementary to metal-based catalysts,[97] innovative synthetic methodologies have been developed involving novel families of metal-free catalysts. The β-ICD catalyst **320** reported by Hatakeyama,[172] the modified DABCO **321** developed by Hiroma[173] and the pyrrolizidine **322** described by Barrett[174] represent three relevant examples, amongst the successes achieved by of organic chemists in the development of a catalytic asymmetric version of the Baylis-Hillman reaction.



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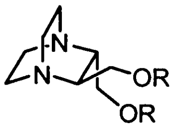

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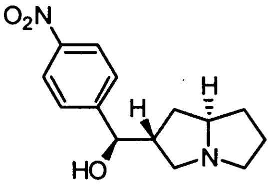
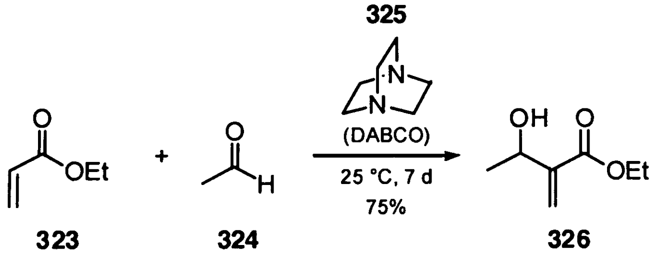


322

The aim of the work described in *Chapter Four* was to design and develop a new class of amine suitable for the catalysis of the asymmetric Baylis-Hillman reaction through an aminocatalysed process.

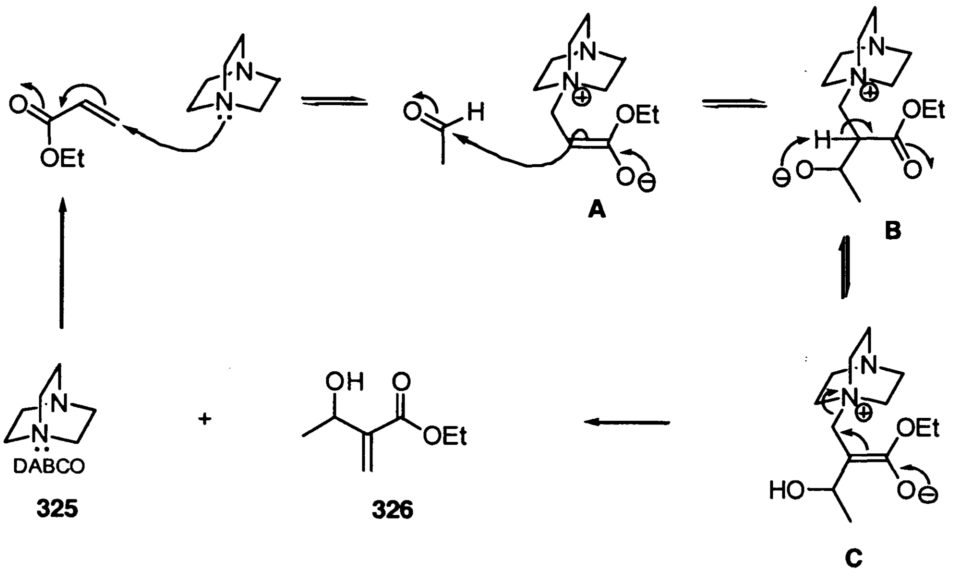
4.1.1 Baylis-Hillman reaction mechanism

As reported by Baylis and Hillman the reaction between ethyl acrylate **323** and acetaldehyde **324** catalysed by 1,4-diaza-bicyclo[2.2.2]octane **325** (DABCO) takes seven days to produce the adduct **326** in a reasonable yield of 75% (Scheme 74).



Scheme 74

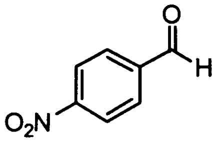
The reaction involves the coupling of the a-position of activated alkenes with carbon electrophiles under the catalytic influence of a tertiary amine, providing a simple method for the synthesis of densely functionalised molecules.[171e] The accepted mechanism of this reaction proceeds through an initial Michael addition between the activated olefin **323** and a tertiary amine DABCO **325** to provide the zwitterionic enolate **A** (Scheme 75). The enolate **A** reacts with the aldehyde in an aldol manner to generate the zwitterionic alkoxide **B**. Subsequent proton migration starts the $E1_{cb}$ elimination step (**C**), releasing the catalytic tertiary amine **325** and providing the Baylis-Hillman adduct **326**.

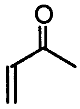


Scheme 75

4.1.2 Baylis-Hillman substrates

Over the last decade there have been a large number of reports examining all the three essential components of the reaction: the activated alkene; the electrophile; and the catalyst. Alkenes activated by a wide variety of Electron Withdrawing Groups (EWG), coupled with a number of carbon electrophiles have been exploited to provide a wide range of multifunctional molecules (see Scheme 73, *section 4.1*).[171e] An ample choice of aliphatic, aromatic, and hetero-aromatic aldehydes have also been utilised as the primary source of electrophiles in obtaining an interesting class of Baylis-Hillman adduct under different reaction conditions. However, the slow reaction rate usually observed for this transformation and the fascinating complexity of its reaction mechanism provided a strong motivation from which to start our investigation. Therefore, from the rich choice of substrates, we decided to adopt the reaction between 4-nitro-benzaldehyde **82** and methyl vinyl ketone **132**, to compare the activities of the catalysts prepared.


4-Nitrobenzaldehyde
82


Methyl vinyl ketone
132

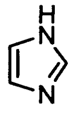
Literature precedent utilising these substrates typically required twenty four to eighty hours at room temperature with 30 mol% catalyst in order to achieve reasonable yields for the trasformation.[99]

4.2 Definition of a general protocol

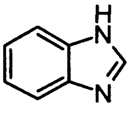
4.2.1 Literature precedent: The Shi protocol

As reported in the patent filed by Baylis and Hillman in 1972, the reaction between methyl acrylate and acetaldehyde catalysed by DABCO **325** takes seven days to obtain yields of 75%. The main drawback of this reaction is the extremely slow reaction rate. Therefore, primary efforts have been directed to increase the reaction rate.

Shi and co-workers investigated the Baylis-Hillman reaction between aldehydes and methyl vinyl ketone **132** catalysed by (*S*)-proline **44** in the presence of weak Lewis bases such as triethyl amine, benzimidazole **327**, pyridine and imidazole **133**.[99]

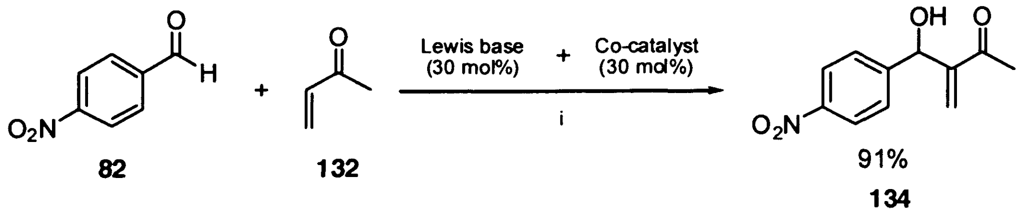


133



327

The reaction was performed with 30 mol% loading of a Lewis base and co-catalyst in a number of different solvents, at room temperature, to provide the adduct **134** in excellent yields (Scheme 76).



82 **132** 91% **134**

(i) All reaction condictions examined are reported in Table 13

Scheme 76

The experiments set up by Shi's group demonstrated that the Baylis-Hillman reaction between *p*-nitrobenzaldehyde **82** and methyl vinyl ketone **132** occurred only when (*S*)-proline and the

Lewis base were both present in the reaction mixture, providing yields up to 91% (Table 13). All the solvents tested offered comparable yields when imidazole **133** was used as the Lewis base (Table 13, entries 1-4). The successive experiments proved that the reaction is extremely sensitive to the nature of the Lewis base utilised. Utilising benzimidazole **327** or triethyl amine as a Lewis base reduced the yields of the Baylis-Hillman product **134** under the same reaction conditions (Table 13, entries 5 and 6). The same reaction was repeated replacing imidazole **133** with pyridine but no product was recovered (Table 13, entry 7).

Table 13. Results of the study into the Baylis-Hillman reaction.[a]

Entry	Lewis base	Solvent	Time (h)	Yield (%)
1	Imidazole **133**	DMF	24	91
2	Imidazole **133**	DMSO	24	90
3	Imidazole **133**	THF	24	87
4	Imidazole **133**	Chloroform	24	88
5	Benzimidazole **327**	DMF	24	45
6	Et_3N	DMF	36	66
7	Pyridine	DMF	40	0

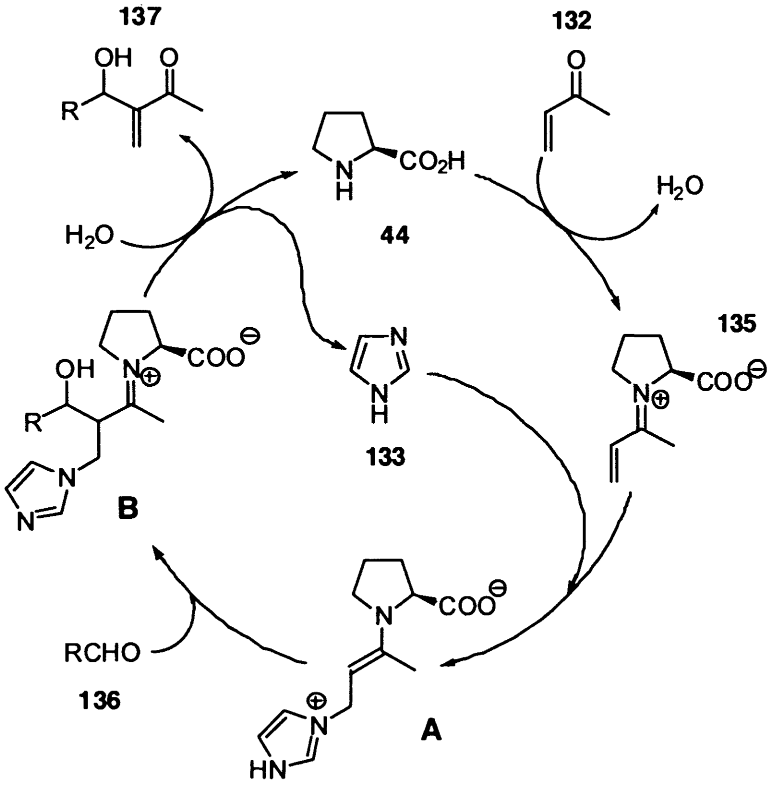
(a) Baylis-Hillman reaction of 4-nitrobenz aldehyde **82** (1 eq) and methyl vinyl ketone **132** (3 eq) at room temperature in the presence of Lewis base (30 mol%) and (*S*)-proline **44** (30 mol%).

In all cases reported, the adduct **134** was obtained with very low enantiomeric excess (<5%), despite the fact (*S*)-proline **44** was used as a co-catalyst.

Taking inspiration from Shi's work, we decided to begin our exploration of the Baylis-Hillman reaction from the transformation between 4-nitrobenzaldehyde **82** and methyl vinyl ketone **132** in the presence of imidazole **133** as catalyst and of (*S*)-proline **44** as co-catalyst. The initial investigation was aimed to optimise the reaction conditions reducing catalyst loading from 30 mol% to 10 mol%.

4.2.2 Proposed Baylis-Hillman catalytic cycle

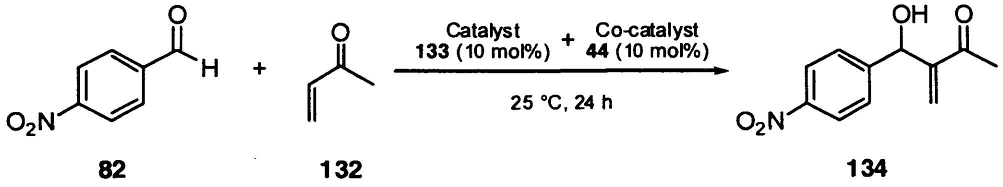
The catalytic cycle proposed by Shi's group for this reaction is quite similar to the mechanism of the traditional Baylis Hillman reaction (see *section 4.1.1*, Scheme 75).[99] The formation of the iminium ion **135** between (*S*)-proline **44** and methyl vinyl ketone **132** in the first step generates a new activated olefin, which reacts quickly with imidazole **133** in a conjugate addition to form the zwitterionic enamine **A** (Scheme 77). The enamine **A** undergoes an aldol type nucleophilic attack on the aldehyde **136** to form the zwitterionic iminium **B**. A proton migration starts the $E1_{cB}$ elimination which releases the catalyst (imidazole **133**) and the co-catalyst ((*S*)-proline **44**) in the presence of water, providing the desired Baylis-Hillman adduct **137**.



Scheme 77

4.2.3 Initial catalytic test procedure

The initial experimental procedure followed to determine the catalytic activity of our aminocatalysts in the Baylis-Hillman reaction involved 4-nitrobenzaldehyde **82** and methyl vinyl ketone **132**. Aldehyde **82** (1 eq) and α,β-unsaturated ketone **132** (3 eq) were stirred in the presence of imidazole **133** (10 mol%) and (*S*)-proline **44** (10 mol%), in a suitable solvent for twenty four hours at 25 °C (Scheme 78). The reaction was quenched with a solution of saturated sodium bicarbonate and extracted with dichloromethane. The organic phase was washed with water and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica to provide the adduct 3-(hydroxy(4-nitrophenyl)methyl)but-3-en-2-one **134**.



Scheme 78

4.2.4 Analysis of the Baylis-Hillman results

We envisaged that the rapid evaluation of conversions by ^{1}H NMR analysis could be advantageous. Due to the different chemical environments of the starting material **82** and the product **134** two distinct signals in the ^{1}H NMR spectra were observed (Figure 45). The signal of the aldehyde proton in 4-nitro-benzoaldehyde **82** is located at δ10.05 and the signal of the benzylic proton in the Baylis-Hillman adduct **134** was observed as a singlet at δ5.66. The integration of these signals was employed as an effective tool to determine conversions from the crude reaction mixture.

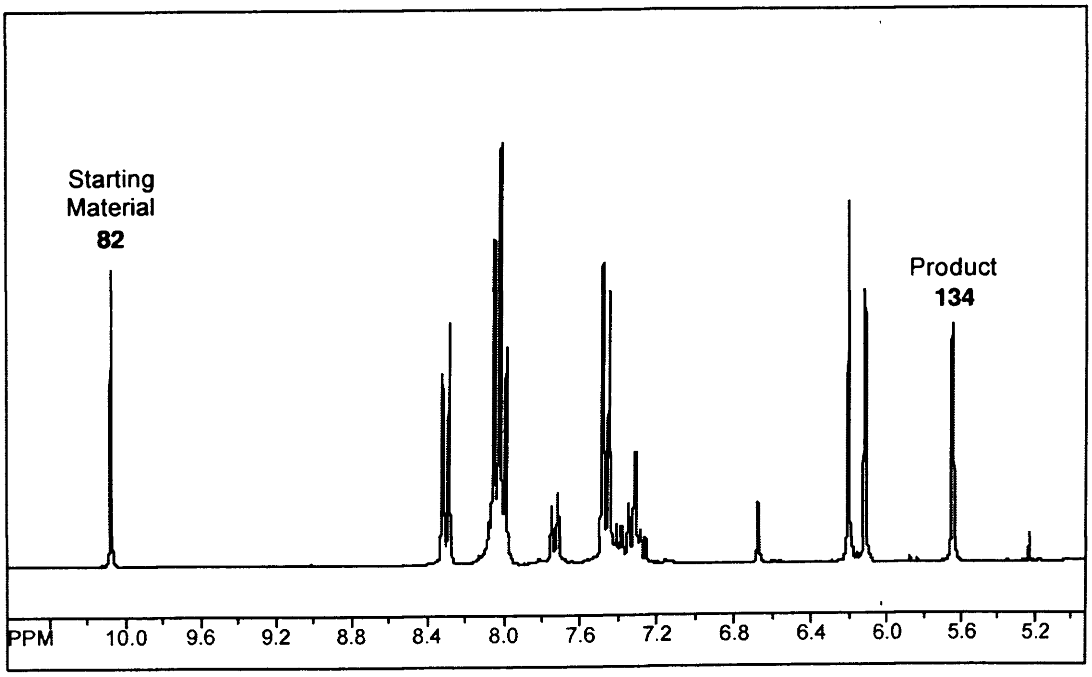


Figure 45

Determination of enantiomeric excess of adduct **134** was carried out by HPLC using a Chiarakel OJ column, eluting with hexane:*iso*-propanol 9:1 at a rate of 1.0 mL/min (detector wavelength at 273 nm). The two enantiomers produced by the reaction between 4-nitrobenzoladehyde **82** and methyl vinyl ketone **90** had the following retention times (Figure 46):

I. (*S*) enantiomer at t_1 = 32.5 min;
II. (*R*) enantiomer at t_2 = 35.3 min (see *section 5.2*, general procedure **F**, for determination of absolute stereochemistry of Baylis-Hillman adduct **134**).

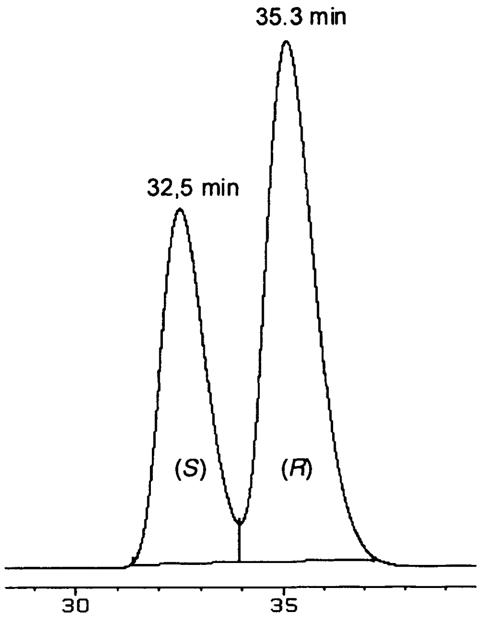


Figure 46

4.2.5 Solvent investigation

As a starting point, we investigated the reaction between methyl vinyl ketone **132** and 4-nitrobenzaldehyde **82** following the conditions described in the work of Shi.[99] In line with the literature, the best solvent found for this transformation was *N*,*N*-dimethylformamide, indicating that a polar solvent was the best option for the catalytic cycle. Initially, the reaction was performed at room temperature in the presence of 10 mol% of imidazole **133** and (*S*)-proline **44** at 1 M concentration with respect to the aldehyde. After twenty four hours this gave the expected product **134**, but in a reduced 61% isolated yield, lower than that reported (Table 14, entry 1). The reduced loading utilised in this first catalytic run was believed to be a plausible reason the lower yield obtained. Therefore, a second test was carried out by increasing the loading of the catalyst **133** and co-catalyst **44** to 30 mol% under the same reaction conditions. Surprisingly, an unexpected and disappointing 54% isolated yield was observed.

In an attempt to rationalise this result, it was reasoned that the *N,N*-dimethylformamide used may have been contaminated by trace amounts of water in the reaction carried out by Shi. Numerous authors have noted in other iminium ion catalysed transformations that the addition of small amounts of water was crucial in increasing reaction rate.[11, 175] In the light of these findings, we decided to investigate the effects associated with the use of wet *N,N*-dimethylformamide. The Shi protocol was repeated using 10 mol% of catalyst and co-catalyst progressively increasing the amount of water present in the reaction mixture. The experimental results obtained are tabulated in Table 14 and plotted in Figure 47.

Table 14. Solvent study into the Shi protocol.[a]

Entry	Solvent		Yield (%)	*ee* (%)[c]
1	DMF[b]		54	0
2	DMF		61	0
3	DMF:H_2O	19:1	62	0
4	DMF:H_2O	9:1	80	0
5	DMF:H_2O	7.5:2.5	40	0
6	DMF:H_2O	1:1	30	0
7	H_2O		13	0

(a) All reactions performed at 1 M concentration in dry solvents at 25 °C for 24 h with 10 mol% (*S*)-proline **44** and imidazole **133**. (b) Reaction performed with 30 mol% (*S*)-proline **44** and imidazole **133**. (c) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4*.

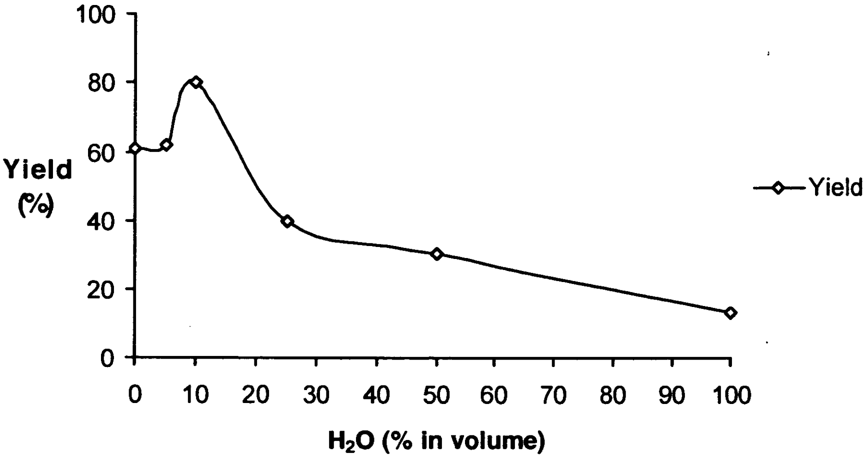


Figure 47

The data collected from these experiments testify a complex behaviour depending on the amount of water in the organic solvent. Starting from a 61% isolated yield for the reaction performed in absolute *N,N*-dimethylformamide, the plot raises up to a maximum of 80% isolated yield with an optimal solvent ratio of 9:1 DMF:H_2O (Table 14, entry 3). Increasing the amount of water beyond this led to a gradual decrease in the observed yields (Table 14, entries 4-6). Evidence of the formation of side-products was noticed following the catalytic runs by TLC or analysing the ^1H NMR of crude reaction mixture as reported in the literature.[176] It also appeared that the formation of side-products was increased when the amount of water added to *N,N*-dimethylformamide was higher than 10% v/v. Unfortunately, any attempt to separate and characterised these by-products failed because of difficulties purifying the crude reaction mixture.

Miller and co-workers have reported tetrahydrofuran to be an effective solvent for the proline catalysed Baylis-Hillman reaction in the presence of a complex chiral base, the products being isolated in high yield and good enantiomeric excess.[177,100] Therefore, given the practical convenience and the lower polarity of tetrahydrofuran when compared to DMF, we also examined this solvent in four different combinations of organic solvent:H_2O (tetrahydrofuran and THF:H_2O 19:1, 9:1, 1:1). All results tabulated in Table 15 were performed in the presence of 10 mol% of imidazole **133** and (*S*)-proline **44**, under the standard reaction conditions.

Table 15. Solvent study into the Shi protocol.[a]

Entry	Solvent		Yield (%)	*ee* (%)[b]
1	THF		27	0
2	THF:H_2O	19:1	62	0
3	THF:H_2O	9:1	30	0
4	THF:H_2O	1:1	32	0

(a) All reactions performed at 1 M concentration in dry solvents at 25 °C for 24 h with 10 mol% (*S*)-proline **44** and imidazole **133**. (b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4*.

Once again, the addition of water displayed a similar manner to that previously observed with *N*,*N*-dimethylformamide. The initial yield of 27% obtained utilising dry tetrahydrofuran (Table 15, entry 1), was improved up to 62% in a 19:1 mixture of THF:H_2O (Table 15, entry 2). Increasing the amount of water beyond this level led to a lowering of the amount of isolated product (Table 15, entry 3-4).

4.2.6 Concentration investigation

The second factor investigated was the concentration of the reactants employed in our tests. It was hypothesised that an increased concentration of the aldehyde **82** could improve the yields obtained. Thus, all experiments were repeated at 2 M concentration with respect to the aldehyde **82**, under the protocol employed in *section 4.2.5*. The results of these experiments are tabulated below (Table 16 and Table 17).

Experiments carried out in absolute *N*,*N*-dimethylformamide and wet *N*,*N*-dimethylformamide showed a similar pattern to that observed in the reaction performed at 1 M concentration (Table 14).

Table 16. Concentration study into the Shi protocol.[a]

Entry	Solvent		Yield (%)	*ee* (%)[b]
1	DMF		60	0
2	DMF:H_2O	19:1	75	0
3	DMF:H_2O	9:1	80	0
4	DMF:H_2O	1:1	34	0

(a) All reactions performed at 2 M concentration in dry solvents at 25 °C for 24 h with 10 mol% (*S*)-proline **44** and imidazole **133**. (b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4.*

A 9:1 DMF:H_2O mixture provided the best result offering a 80% isolated yield, although the 19:1 DMF:H_2O combination improved yields from 62% up to 75% (Table 16, entry 2 and 3). Once again, further additions of water to the organic solvent, drastically decreased the yields to a level 34% (table 16, entry 4). Despite the reactions being performed in a more concentrated environment, the yield did not showed any improvement.

The second group of catalytic runs carried out in absolute tetrahydrofuran and wet tetrahydrofuran showed that a 2 M concentration had detrimental effect on the reaction efficiency (Table 17).

Table 17. Concentration study into the Shi protocol.[a]

Entry	Solvent		Yield (%)	*ee* (%)[b]
1	THF		43	0
2	THF:H_2O	19:1	30	0
3	THF:H_2O	9:1	40	0
4	THF:H_2O	1:1	36	0

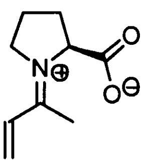
(a) All reactions performed at 2 M concentration in dry solvents at 25 °C for 24 h with 10 mol% (*S*)-proline **44** and imidazole **133**. (b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4.*

In spite of a slight improvement in the yields in the reaction performed in tetrahydrofuran, THF:H_2O 9:1 and THF:H_2O 1:1 (Table 17, entry 1, 3 and 4) the mixture THF:H_2O 19:1 gave a disappointing and unexpected 30% isolated yield (Table 17, entry 2) in contrast to the 62% obtained under similar conditions at 1 M concentration (Table 15, entry 2).

reaction at 1 M concentration and the absence of any strong benefit using a more concentrated solution, a 1 M concentration was adopted to run all subsequent catalytic tests.

4.2.7 Wet solvent

The exact role of water in the mechanism proposed by Shi (see *section 4.2.2*) is unclear at present, however, it has been noted in other iminium ion catalysed transformations that water is a crucial additive to bring about effective reaction rates. For example, in the Diels-Alder reaction of α,β-unsaturated aldehydes, MacMillan and co-workers stated that *"in the absence of water, lower reaction rates were observed, with optimal reaction conditions involving a 19:1 MeOH:H$_2$O mixture"*.[11] Similar conclusions were also reported by Ogilvie and Lemay when monitoring the iminium ion catalysed Diels-Alder reaction between (*E*)-cinnamaldehyde **11** and cyclopentadiene **8**.[175] In this report, it was shown that iminium ion formation was considerably more facile in a 19:1 mixture of nitromethane and water, when compared to nitromethane as the sole reaction solvent. Within the report of Ogilvie describing the beneficial effects of small amounts of water, it was proposed that the effect of water on iminium ion formation was due to an increase in the supply of available H^+, accelerating proton transfers involved in iminium ion formation. This may also be the case in the current work, whereby the activated iminium ion **135** (see *section 4.2.2*, Scheme 77) is formed more rapidly in the presence of water, suggesting a general acid catalysed mechanism.



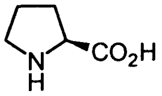
135

4.3 Asymmetric Baylis-Hillman reaction: proline derivatives

At this stage of the project, we turned our attention towards the search for a suitable combination of catalyst and co-catalyst to perform the Baylis-Hillman reaction in an asymmetric manner. These two elements were initially examined by preparing a series of proline and imidazole derivatives to test in the Baylis-Hillman reaction of 4-nitrobenzaldehyde **82** and methyl vinyl ketone **132**, under a defined protocol. Thus, our first aim was to identify proline and imidazole analogous which were likely to improve reactivity and lead to asymmetric induction.

4.3.1 Proline

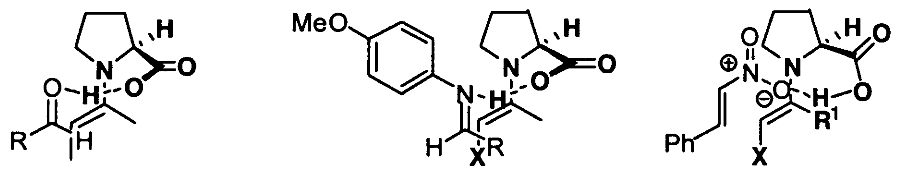
Although an intramolecular proline-catalysed aldol reaction was discovered in the early 1970s, it was only recently that the noteworthy catalytic activity of (*S*)-proline **44** has been intensively explored.[9,48b] In 2000, List reported the first proline-catalysed intermolecular aldolisations with good yields and high levels of asymmetric induction.[10] Subsequently, this methodology has been extended to other substrate combinations such as aldehyde to aldehyde, aldehyde to ketone and ketone to ketone.[48b] In the same year, MacMillan's group utilised a cyclic five-membered secondary amine to catalyse a Diels-Alder cycloaddition between an α,β-unsaturated aldehyde and a diene.[11] Since these pioneering works were published, the area of organocatalysis has witnessed the birth of new structures based on (*S*)-proline **44** that provide exceptional levels of asymmetric induction for a variety of different reaction processes.



44

There are several reasons for the importance of (*S*)-proline **44** 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 act as acid or base, and can facilitate chemical transformations in concert, similar to enzymatic catalysis. Whilst these criteria apply to all amino-acids, (*S*)-proline **44** is a secondary, cyclic, pyrrolidine-based amino-acid. (*S*)-Prolines 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 other cyclic ones such as piperidine.[178] The carboxylate moiety further contributes to this by acting as a general Brønsted acid co-catalyst.

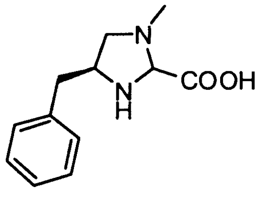
(*S*)-Proline **44** has been employed not only in the asymmetric catalysis of intra- and intermolecular aldol reactions, but also in Mannich[69] and Michael[179] reactions. Its effectiveness is due to the formation of an enamine intermediate upon reaction with a carbonyl substrate. The adjacent carboxylic 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.[10b] Proposed transition states for the intramolecular aldol, Mannich and Michael reactions are shown in Figure 48.



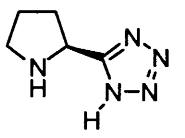
Aldol Condensation   Mannich Reaction   Michael Reaction

Figure 48

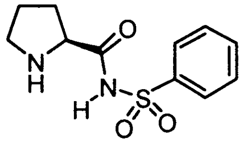
Within our preliminary investigation, we observed an interesting behaviour in the yields for the Baylis-Hillman reaction catalysed by a combination of (*S*)-proline **44** and imidazole **133** in the presence of dry and wet solvent (see *section 4.2*). Unfortunately, in spite of (*S*)-proline **44** being a chiral compound, the Baylis-Hillman adducts **134** were recovered as a racemic mixture. Therefore, we decided to explore another four proline analogues reported to be effective in the field of aminocatalysis. The Jørgensen catalyst **53**, catalyst **124**, the Ley catalyst **328** and commercial available (*S*)-prolinol **329** offered us the possibility to consider different structural features incorporated on a proline type scaffold.



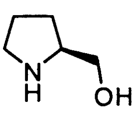
53



124



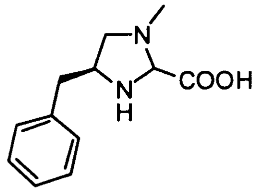
328



329

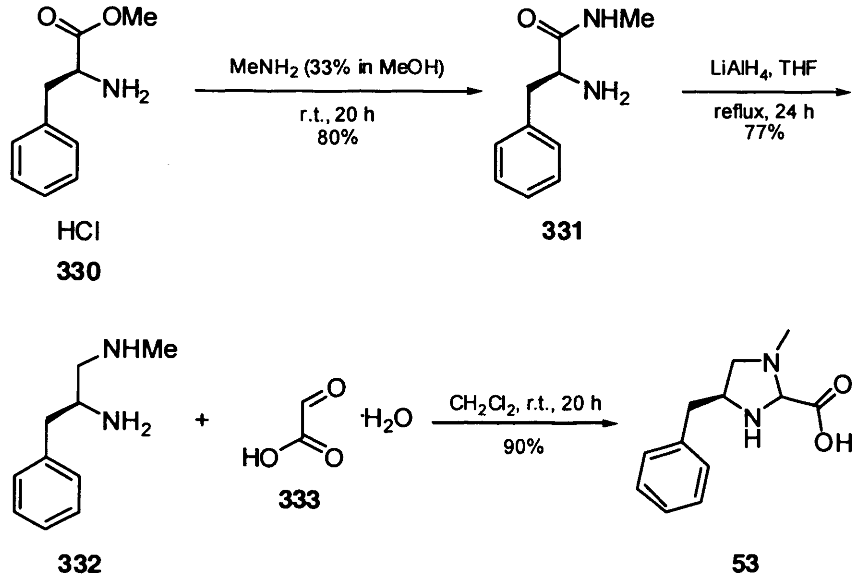
4.3.2 Jørgensen catalyst

Imidazolidine **53**, was developed by the laboratory of Jørgensen as a catalyst to accelerate the Michael addition of nitroalkanes to α,β-unsaturated enones in high yields and enantiomeric excess.[30] It was reasoned that the high level of stereocontrol could be attributed to the benzyl group which would shield the *Re*-face of α,β-unsaturated enones in the iminium ion intermediate. We thought that this structural characteristic could be used to promote improvement in the stereoselectivity of the Baylis-Hillman transformation between 4-nitrobenzaldehyde **82** and methyl vinyl ketone **132**.



53

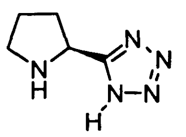
The synthesis of compound **53** was achieved following the method reported in literature.[30] (*S*)-Phenylalanine methyl ester hydrochloride **330** and a methanolic solution of methyl amine were allowed to react overnight at room temperature to give (*S*)-phenylalanine-*N*-methylamide **331** in 80% isolated yield (Scheme 79).[11] The amide **331** was treated with lithium aluminium hydride ($LiAlH_4$) in refluxing tetrahydrofuran for twenty four hours to provide the diamine **332** as a colourless oil in 77% isolated yield after purification by flash column chromatography. Condensation with an equimolar amount of glyoxylic acid monohydrate **333** was performed in dichloromethane at room temperature for twenty hours which gave (4*S*)-4-benzyl-1-methylimidazolidine-2-carboxylic acid **53** in 90% isolated yield (overall yield 55%). The catalyst **53** was obtained as a hygroscopic colourless solid in a configurationally stable 2:1 mixture of diastereoisomers. All attempts to separate the diastereoisomers by chromatographic techniques failed.



Scheme 79

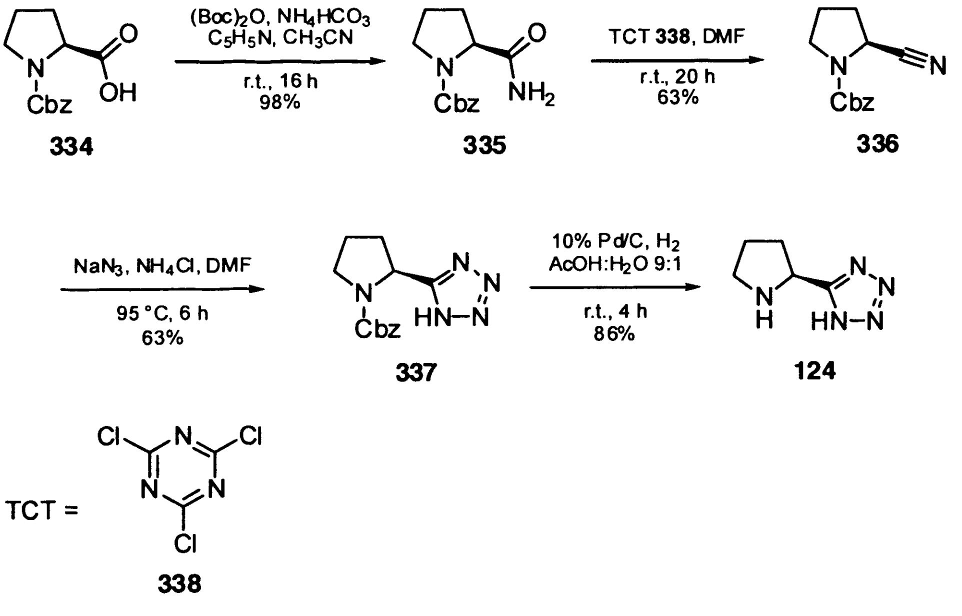
4.3.3 (*S*)-Tetrazole proline derivative

Tetrazole derivatives have been broadly utilised in medicinal chemistry as bioisosteres for carboxylic acids due to the similarity in pK_a. Additionally, introduction of this functionality often leads to an increased solubility in organic solvents. Recently, compound **124** has found a place in the field of organocatalysis as a proline analogue for aldol[180] and *O*-nitroso aldol reactions[181] as well as Michael additions to nitro-olefins.[182] Within our exploration of suitable proline derivatives, we thought tetrazole **124** would provide a valuable alternative to (*S*)-proline **44**. Hence, we decided to include this compound into our set of co-catalysts.



124

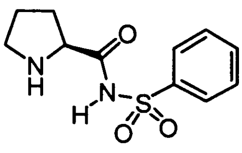
Catalyst **124** was prepared starting with the conversion of carbobenzyloxy-(*S*)-proline **44** into the corresponding amide.[91] The compound **334**, *tert*-butoxycarbonyl anhydride and ammonium bicarbonate were stirred for sixteen hours in acetonitrile in the presence of pyridine to give the amide **335** in 98% isolated yield (Scheme 80). Nitrile **336** was obtained by treating the amide **335** with cyanuric chloride **338** in *N*,*N*-dimethylformamide for twenty hours at ambient temperature.[183] The compound **336** was purified by passing through a short plug of silica to provide a colourless powder in 63% yield. The formation of the tetrazole was realised by reacting the nitrile **336** with sodium azide and ammonium chloride in dry *N*,*N*-dimethylformamide at 90-95 °C for six hours to give the carbobenzyloxy protected catalyst **337** in 63% isolated yield. Deprotection of catalyst **337** was carried out utilising 10% palladium on charcoal in a mixture 9:1 of acetic acid:H_2O under a hydrogen atmosphere. After purification, the deprotection provided 5-((*S*)-pyrrolidin-2-yl)-1*H*-tetrazole **124** in 86% isolated yield (overall yield 33%).



Scheme 80

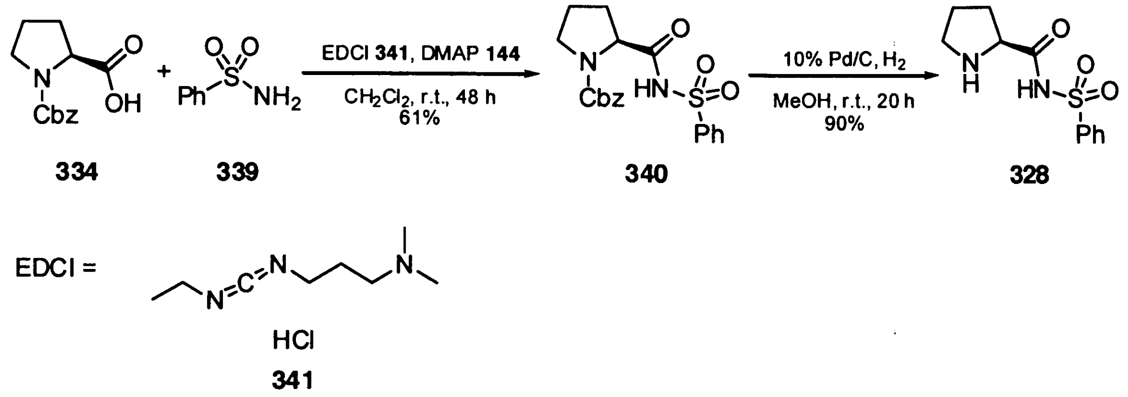
4.3.4 Ley catalyst

As reported by Ley *et al.*, proline derivative **328** was involved in a study on the organocatalysed asymmetric Mannich, nitro-Michael and aldol reactions.[184] Acyl sulfonamide **328** was proposed as an alternative to (*S*)-proline **44** in organocatalytic transformations, owing to the acidity of the sulfonamidic proton. This derivatised proline catalyst has shown good to excellent yields and enantioselectivities under a range of diverse reaction conditions. Furthermore, compound **328** proved to have high solubility in a wide range of solvents. Hence, we decided to examine the Ley catalyst **328** within our standard Baylis-Hillman reaction as an alternative to (*S*)-proline **44**.



328

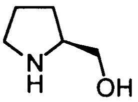
Synthesis of co-catalyst **328** was accomplished following the methodology described in the literature.[184] A stirred solution of (*S*)-carbobenzyloxy proline **334** in dichloromethane was allowed to react with benzenesulfonamide **339**, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) **341** using 4-(dimethylamino)pyridine **144** as catalyst, for two days at room temperature (Scheme 81). The mixture was quenched with ethyl acetate and treated with 1 M aqueous hydrochloric acid before purification by flash column chromatography to provide the (*S*)-carbobenzyloxy protected proline derivative **340** in 61% isolated yield. Deprotection of **340** was performed employing 10% palladium on charcoal in methanol under an atmosphere of hydrogen. The mixture was stirred for twenty hours before removal of the catalyst by filtration through Celite®. The filtrate was concentrated under reduced pressure and purified by flash column chromatography to give the catalyst (2*S*)-*N*-(2-pyrrolidine-2-carbonyl)-benzenesulfonamide **328** in 90% isolated yield (overall yield 55%).



Scheme 81

4.3.5 Prolinol

(*S*)-Prolinol **329** has been successfully employed in organocatalysed asymmetric Michael addition of aldehydes and ketones to β-nitroalkanes[185] and aldol reactions.[186] We believed this amino-alcohol could offer the opportunity to investigate the role played by the carboxylic acid functionality in the reactivity and selectivity of the co-catalyst. Co-catalyst (*S*)-prolinol was acquired from Aldrich and directly utilised in the catalytic tests.



329

4.3.6 Typical experimental procedure

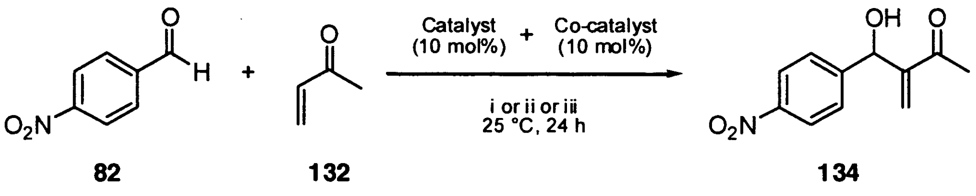
The catalytic procedure adopted to test our molecules in the Baylis-Hillman reaction followed the procedure described in *section 4.2.3.* A mixture of 4-nitrobenzaldehyde **82** (1 eq) and methyl vinyl ketone **132** (3 eq) was reacted at 25 °C for twenty four hours in the presence of 10 mol% catalyst and co-catalyst (Scheme 82). We decided to employ three different solvents within this investigation:

1. Dry *N*,*N*-dimethylformamide as a polar aprotic solvent;

II. Dry tetrahydrofuran as an apolar aprotic solvent to promote possible hydrogen bond interactions;

III. A mixture of 9:1 DMF:H_2O which provided the best yields in our initial experiments within this area (see *section 4.2.5* and *4.2.6*)

All the catalytic tests were carried out utilising 1 M concentration with respect to the aldehyde **82** with a typical reaction volume of 1 mL. The Baylis-Hillman adduct **134** was obtained as a pale orange solid after the work up and purification.

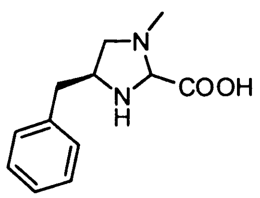


(i) Dry DMF; (ii) Dry THF; (iii) DMF:H_2O 9:1

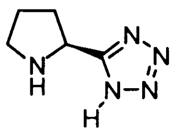
Scheme 82

4.3.7 Proline analogues investigation

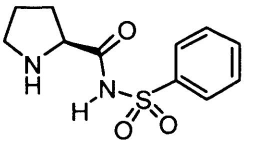
With the new set of proline analogues prepared (catalysts **53**, **124**, **328** and **329**) we submitted our molecules in conjunction with imidazole **133** to the Baylis-Hillman reaction under the conditions previously described.



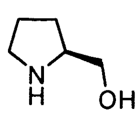
53



124



328



329

The results of these series of tests are reported in Table 18.

Table 18. Results of experiments using proline analogues.[a]

Entry	Co-catalyst	Solvent	Yield (%)	*ee* (%)[b]	Entry	Co-catalyst	Solvent	Yield (%)	*ee* (%)[b]
1	**53**	THF	23	0	9	**328**	DMF:H_2O 9:1	40	0
2	**53**	DMF	14	0	10	**329**[c]	THF	2	0
3	**53**	DMF:H_2O 9:1	7	0	11	**329**[c]	DMF	8	0
4	**124**	THF	8	0	12	**329**[c]	DMF:H_2O 9:1	15	0
5	**124**	DMF	28	0	13	**44**	THF	27	0
6	**124**	DMF:H_2O 9:1	28	0	14	**44**	DMF	61	0
7	**328**	THF	26	0	15	**44**	DMF:H_2O 9:1	80	0
8	**328**	DMF	19	0					

(a) Reactions were carried out in dry solvent for 24 h with 10 mol% imidazole **133** and co-catalyst. (b) Enantiomeric excess determined by HPLCusing a Chiaralcel OJ column; see *section 4.2.4*. (c) Reaction were performed in the presence of 10 mol% of methansulfonic acid

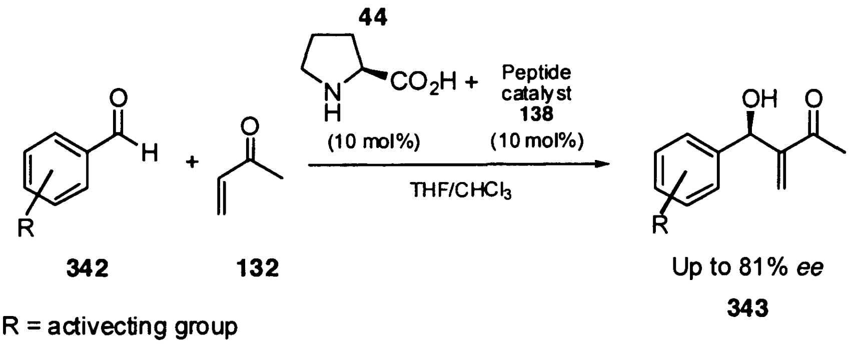
All the catalysts tested (**53**, **124**, **328** and **329**) showed a reduced catalytic activity compared to the outcomes previously observed for the Baylis-Hillman reaction catalysed by (*S*)-proline **44** and imidazole **133** (Table 18, entry 13-15). However, once again, for each catalyst tested the best yields were obtained in wet solvents (Table 18, entries 6, 9 and 12) except for the reactions ran with catalyst **53** which resulted in a 23% yield in a non-protic environment (Table 18, entry 1). Unfortunately, our set of proline analogous failed to deliver any stereochemical control of the Baylis-Hillman adduct **134**. Despite the introduction of different structural motifs, the enantiomeric excess observed was the same as those reported for the Baylis-Hillman reaction carried out under the Shi protocol. The benzyl group attached to the chiral centre in the δ-position, close to the nucleophilic nitrogen, on the Jørgensen catalyst **53** proved ineffective to induce asymmetry in Baylis-Hillman products **134** (Table 18, entries 1-3). In a similar fashion, the substitution of the carboxylic function on the proline scaffold with a tetrazole unit (catalyst **124**) decreased the catalytic activity without delivering any enantiomeric excesses (Table 18, entries 4-6). The importance of a carboxylic acid unit adjacent to the nucleophilic nitrogen was confirmed by the experiments performed with catalyst **329**. Although (*S*)-prolinol **329** was employed in combination with methansulfonic acid at 10 mol% (0.1 eq) with the purpose of mimicking the acidic conditions provided by (*S*)-proline **44**, we observed the lowest yields for this series of catalytic runs (Table 18, entries 10-12). Thus, the function of the carboxylic unit is not only to provide a source of H^+ during the reaction (see *section 4.2.7*) but also affects the catalytic activity of the secondary amine.

4.4 Asymmetric Baylis-Hillman reaction: imidazole derivatives

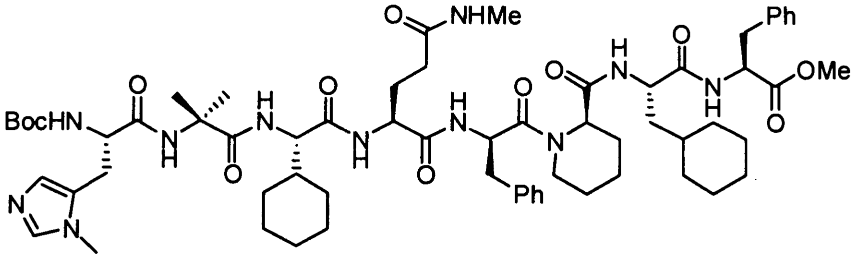
Although (*S*)-proline **44** and its analogous **53**, **124**, **328** and **329** have been successfully utilised to catalyse a number of organic reactions providing excellent stereocontrol, they had failed to provide us with the improved asymmetric induction we had expected. Therefore, before the design of a second set of secondary amines, we decided to examine the second catalytic element employed in the Shi protocol, imidazole **133**.

4.4.1 Proposed histidine-based catalyst design

Within the context of histidine-dependent catalysts, the studies carried out by Miller *et al.* represent one of the most intriguing examples of the use of peptides in organocatalysis. As reported by the author, histidine-based peptides have demonstrated appealing potential in several nucleophile and general base catalysed process.[177a] The Baylis-Hillman reaction was also studied within this work. In an analogous manner to the work of Shi,[99] it was found that the use of proline as co-catalyst in combination with histidine-based peptide **138** dramatically accelerated the reaction rate, providing enantiomeric excess of up to 81% for the adducts **343** (Scheme 83). During these studies, it was also noticed that shorter peptide chain lengths led to lower selectivity; in contrast, a selectivity plateau was observed in the range from 7 to 10 residues.

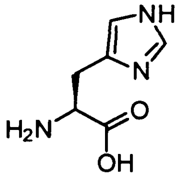


Scheme 83



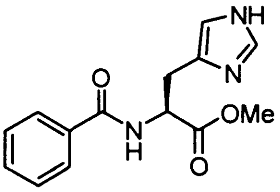
138

At this stage of the project, we aimed to prepare a simple chiral derivative of imidazole **133** based on (*S*)-histidine **344**. It was decided to introduce only minor modifications to the amino-acid to improve our understanding of the catalyst behaviour in the Baylis-Hillman reaction, avoiding the complexity of the Miller polypeptide **138**.



344

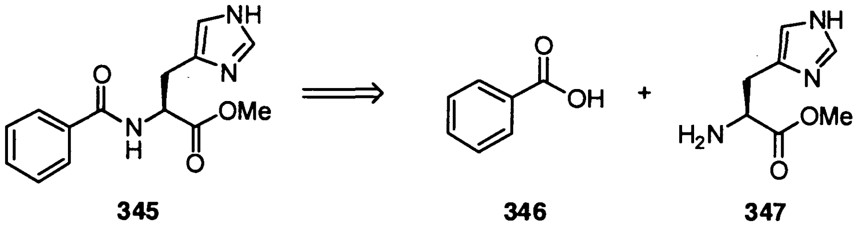
We decided to prepare the histidine derivative **345** where both the acid and amine functional groups were protected as ester and amide derivatives respectively, preventing undesired secondary interactions. The preparation of compound **345** should provide a modified imidazole with a new chiral centre with additional steric requirements due to the benzoyl moiety. Additionally, we envisaged it would also posses a better solubility profile compared to simple (*S*)-histidine **344** in non-aqueous solvents.



345

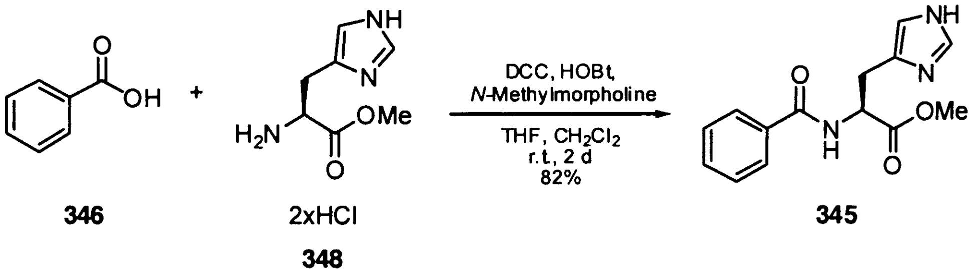
4.4.2 Synthesis of benzoamidic histidine methyl ester derivative

Retrosynthetic analysis suggested that compound **345** could be prepared through a classic amide coupling procedure between benzoic acid **346** and (*S*)-histidine methyl ester **347** both of which were commercially available (Scheme 84)



Scheme 84

In accordance with the methodology described by Kukla,[187] to a stirred mixture of benzoic acid **346**, 1-hydroxybenzotriazole hydrate (HOBt), (*S*)-histidine methyl ester dihydrochloride **348** and *N*-methylmorpholine in tetrahydrofuran was added a solution of 1,3-dicyclohexylcarbodiimide (DCC) in dichloromethane at 0 °C under an atmosphere of nitrogen (Scheme 85). With the addition completed, the mixture was warmed to room temperature and stirred for an additional two days. After removal of side-products by filtration and basic work up, the compound **345** was purified by flash column chromatography to give (*S*)-methyl 2-(benzamido)-3-(1*H*-imidazol-4-yl)propanoate **345** as pale yellow solid in 82% isolated yield.



Scheme 85

4.4.3 Investigation into benzoamidic histidine methyl ester derivative

With the synthesis complete, we submitted **345** and (*S*)-proline **44** to the Baylis-Hillman reaction between 4-nitrobenzaldehyde **82** and methyl vinyl ketone **132** under the conditions described previously (see *section 4.3.6*). The results are reported in Table 19.

Table 19. Results of the study into catalytic system benzoamidic histidine derivative **345** and (*S*)-proline **44**.[a]

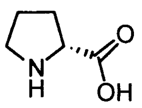
Entry	Solvent[a]	Temperature	Yield (%)	*ee* (%)[b]
1	DMF	25 °C	23	0
2	DMF:H_2O 9:1	25 °C	72	0
3	THF	25 °C	38	14 (*R*)
5	THF	50 °C	32	0
6	THF	0 °C	7	12 (*R*)

(a) Reactions were carried out in dry solvent for 24 h with 10 mol% catalyst **345** and (*S*)-proline **44**. (b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4*.

The use of wet *N*,*N*-dimethylformamide as solvent showed the best yield, providing the product in 72% in DMF:H_2O 9:1 (Table 19, entry 2). Once again, the capacity of water to improve reactivity was confirmed. The reaction carried out in tetrahydrofuran offered a 38% yield after twenty four hours and an encouraging 14% *ee* (*R*), the first enantiomeric excess observed during this part of the project (Table 19, entry 3). This result was attributed to weak hydrogen bonding interactions facilitated by the use of an apolar solvent like tetrahydrofuran, rather than a specific steric factor. Hence, we decided to run two additional experiments at 0 and 50 °C to better define the outcome observed. The reaction performed at 50 °C showed no enantiomeric excess indicating that a small increase in energy of the reaction system was sufficient to destroy any possible interaction (Table 19, entry 5). The experiment carried out at 0 °C was not useful, due to the formation of a heterogeneous mixture during the catalytic test which decreased the observed yield (7%) rather than improve the enantiomeric excess (12% *ee* (*R*), Table 19, entry 5). This outcome was probably due to the poor solubility of **345** in tetrahydrofuran at low temperature.

4.4.4 Investigation into the relationship between chiral centre of proline and 2-benzoamidic (*S*)-histidine derivative

Subsequently, catalyst **345** was re-submitted to the Baylis-Hillman reaction with racemic (±)-proline, (*R*)-proline **349** and (*S*)-proline **44** all in the presence of 10 mol% of the histidine derivative **345**, under the promising reaction conditions described in Table 19. All the results are tabulated below (Table 20).



349

Table 20. Investigation into the proline chiral centre.[a]

Entry	Co-catalyst	Yield (%)	*ee* (%)[b]
1	(±)-proline	32	6 (*R*)
2	(*R*)-proline **349**	27	14 (*S*)
3	(*S*)-proline **44**	38	14 (*R*)

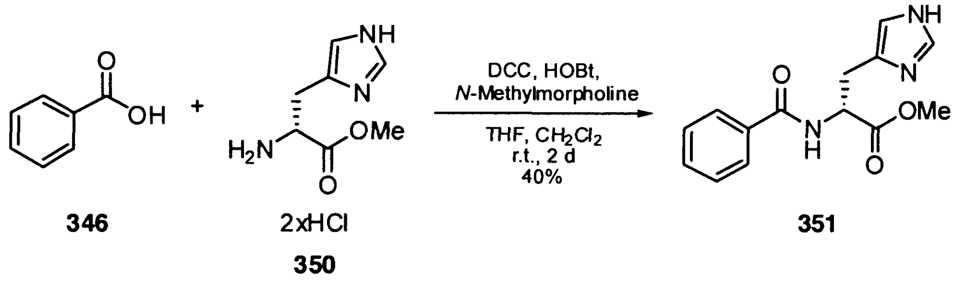
(a) Reactions were carried out in dry THF at 25 °C for 24 h with 10 mol% catalyst **345** and co-catalyst. (b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4*.

Histidine derivative **345** in combination with racemic (±)-proline resulted in a decrease to 6% *ee* (*R*), showing that the chiral centre of proline plays a role in geometric control of the Baylis-Hillman adduct (Table 20, entry 1). That hypothesis was corroborated by the experiment performed with the (*R*)-proline **349** which provided 14% *ee* (*S*), the Baylis-Hillman adduct **134** having the opposite absolute configuration with respect to that obtained with co-catalyst **44** (Table 20, entry 2 and 3). Hence, it seems that the configuration of the chiral centre of the proline is a determining factor in the control of the stereoselectivity of the Baylis-Hillman product **134**. A similar observation was also reported by Miller *et al.*[177b]

4.4.5 Analysis of histidine chiral centre

4.4.5.1 Preparation of 2-benzoamidic (*R*)-histidine derivative

The influence of the histidine chiral centre was also investigated by preparing an analogue of compound **345** from (*R*)-histidine methyl ester dihydrochloride **350**. Synthesis of compound **351** was accomplished following the same procedure utilised to prepare catalyst **345** (Scheme 86). Coupling of (*R*)-histidine methyl ester dihydrochloride **350** with benzoic acid **346** gave, after purification by flash column chromatography, (*R*)-methyl 2-(benzamido)-3-(1*H*-imidazol-4-yl)propanoate **351** as a pale yellow solid in 40% isolated yield.



Scheme 86

4.4.5.2 Investigation into the 2-benzoamidic (*R*)-histidine derivative chiral centre

Catalyst **351** was analysed under standard Baylis-Hillman reaction conditions in dry tetrahydrofuran for twenty four hours (Table 21).

Table 21. Investigation into the histidine chiral centre.[a]

Entry	Catalyst	Yield (%)	*ee* (%)[b]
1	**351**	26	0
2	**345**	38	14 (*R*)

(a) Reactions were carried out in dry THF at 25 °C for 24h with 10 mol% catalyst and (*S*)-proline **44**.
(b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4*.

Unexpectedly, **351** showed a reduction in the yields obtained and no enantiomeric excess when used in conjunction with (*S*)-proline **44** (Table 21, entry 1). Thus, the use of histidine analogues with (*R*) absolute configuration caused a detrimental effect on the reaction rate and stereochemical outcome. The observations collected in this last catalytic run and during the previous experiments (see *section 4.4.3 and 4.4.4*) highlighted the importance of the "cooperation" between the chiral centres of catalyst and co-catalyst. In fact, combinations of the different absolute configuration of proline and histidine derivatives have led to different outcomes in terms of yields and enantiomeric excesses, showing that the reaction mechanism is significantly more complex then the simple catalytic cycle proposed in *section 4.4.6.*

4.4.6 Investigation into the catalyst loading

A prerequisite of any catalytic investigation is the discovery of the optimal catalytic loading. We embarked upon the investigation of the relationship between the catalyst **345** and co-catalyst **44** loading. The Baylis-Hillman transformation between 4-nitrobenzaldehyde **82** and methyl vinyl ketone **132** was carried out in dry tetrahydrofuran for twenty four hours under the protocol previously reported. The loadings of catalyst **345** and co-catalyst **44** were varied as tabulated below (Table 22).

Table 22. Results of the study into catalyst **345** and co-catalyst **44** loading.[a]

Entry	**345** (mol%)	**44** (mol%)	Yield (%)	*ee* (%)[b]
1	10	10	38	14 (*R*)
2	10	20	37	0
3	20	10	39	13 (*R*)
4	20	20	57	17 (*R*)

(a) All reactions were carried out in dry THF at 25 °C for 24 h. (b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4.*

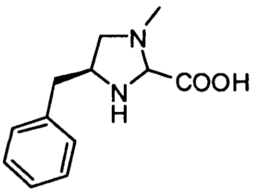
These results showed that increasing the catalyst and co-catalyst loadings from 10 mol% to 20 mol% improved the yield up to 57% without significantly affecting the stereochemical outcome (Table 22, entry 1-4). Surprisingly, the reaction performed with an excess of (*S*)-proline **44** displayed no enantiomeric excess (Table 22, entry 2). Comparing this outcome with the enantiomeric excess obtained for the reaction carried out with an excess of **345** (13%

ee (*R*), Table 22, entry 3) showed that a large excess of (*S*)-proline was detrimental to the control of absolute stereoselectivity with the reaction

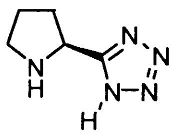
The observations above showed modest increment in yield and no substantial improvements in stereoselectivity as the catalyst and co-catalyst loading were increased to 20 mol%. Hence, because the data did not justify the use of large amount of catalyst, we decided to adopt 10 mol% as standard loading to perform the next set of experiments.

4.4.7 Co-catalyst investigation

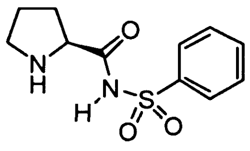
With catalyst loading defined, we decide to evaluate the catalytic ability of **345** in combination with three different proline analogues as well as the amino-acid **142**. All reactions were performed at a level of 10 mol% of catalyst and co-catalyst in dry tetrahydrofuran following our standard protocol (Table 23).



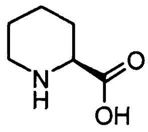
53



124



328



142

Table 23. Results of experiments using different co-catalysts.[a]

Entry	Co-catalyst	Yield (%)	*ee* (%)[b]
1	**53**	10	0
2	**124**	8	0
3	**328**	8	0
4	**142**	16	10 (*R*)
5	**44**	38	14 (*R*)

(a) All reactions were carried out in dry THF at 25 °C for 24 h with 10 mol% catalyst **345** and co-catalyst. (b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4.*

This set of proline analogues and amino-acid **142** showed a decrease in yield and did not promote enantioselectivity. Co-catalyst **142** offered the best performance with a poor 16%

features incorporated into the proline scaffold (**53**, **124** and **328**) or the use of (*S*)-proline **44** homologue **142**, negatively affected the reaction rate and the enantiocontrol when they were employed with histidine derivative **345** as catalyst.

4.5 2-Carboxamido histidine methyl ester derivatives

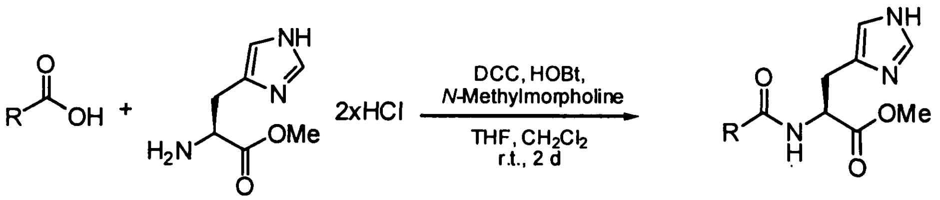
4.5.1 Preparation of histidine derivatives

Investigation into the amidic-histidine derivatives was continued throughout the analysis of the 2-amide unit. In order to rationalise the effects of this group on the reactivity and enantioselectivity obtained with **353**, a series of catalysts were prepared utilising a variety of carboxylic acids. Hence, modifications of the 2-carboxamido group were made utilising:

I. Substituted benzamides with electron withdrawing groups such as 3,5-bis(trifluoromethyl)benzamido **354**, 3,5-dinitrobenzamido **355** and 2,3,4,5,6-pentafluorobenzamido **356**;
II. aromatic and non-aromatic bulky groups such as *tert*-butyl **359**, trichloromethyl **360**, trityl **361** groups and 1-naphthyl **357** and 2-naphthyl **358**;
III. Substituted benzamide with an electron donating group such as 3-methoxybenzamido **362**.

1-naphthyl **358** and 2-naphthyl **359** were also employed to explore π-stacking interactions between the catalyst and 4-nitrobenzaldehyde **82**.

Synthesis of these amidic-histidine derivatives was accomplished following the methodology employed to prepare catalyst **345** (see *section 4.4.2*). A mixture of the carboxylic acid **352**, 1-hydroxybenzotriazole hydrate (HOBt), (*S*)-histidine methyl ester dihydrochloride **348** and *N*-methylmorpholine in tetrahydrofuran was added to a solution of 1,3-dicyclohexylcarbodiimide (DCC) in dichloromethane at 0 °C under a atmosphere of nitrogen (Scheme 87). The mixture was warmed to room temperature and allowed to react for two days. The basic work up and purification by flash column chromatography completed the procedure to give amidic-histidine derivatives **353**.

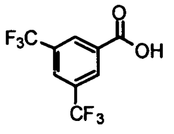
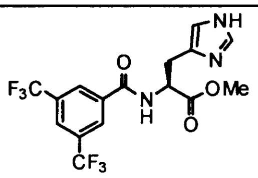
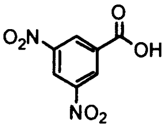
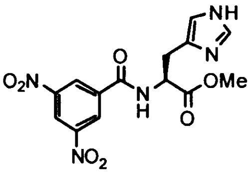
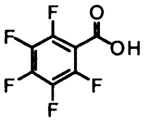
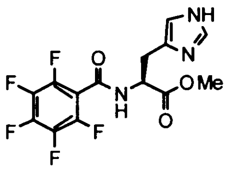
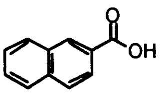
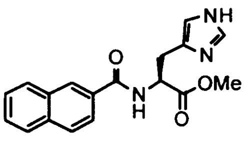
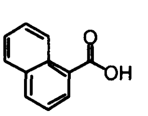
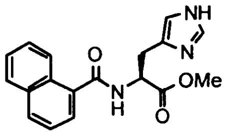
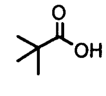
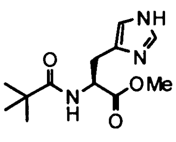


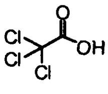
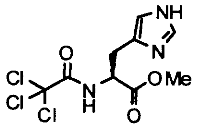
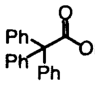
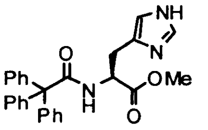
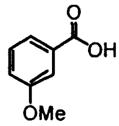
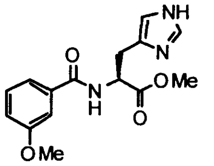
352 **348** **353**

Scheme 87

All the catalysts prepared are reported in Table 24 with name, structure and yield of each compound.

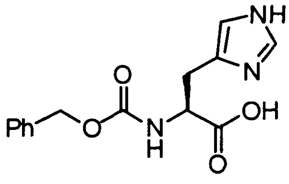
Table 24 2-carboxamido histidine methyl ester derivatives synthesis.

Entry	Carboxylic acid	Compound	Structure	Name	Yield (%)
1		**354**		(*S*)-methyl 2-(3,5-bis(trifluoromethyl)benzamido)-3-(1*H*-imidazol-4-yl)propanoate	46
2		**355**		(*S*)-methyl 2-(3,5-dinitrobenzamido)-3-(1*H*-imidazol-4-yl)propanoate	23
3		**356**		(*S*)-methyl 2-(2,3,4,5,6-pentafluorobenzamido)-3-(1*H*-imidazol-4-yl)propanoate	22
4		**357**		(*S*)-methyl 2-(2-naphthamido)-3-(1*H*-imidazol-4-yl)propanoate	73
5		**358**		(*S*)-methyl 2-(1-naphthamido)-3-(1*H*-imidazol-4-yl)propanoate	63
6		**359**		(*S*)-methyl 3-(1*H*-imidazol-4-yl)-2-(pivalamido)propanoate	41

7		**360**		(*S*)-methyl 2-(2,2,2-trichloroacetamido)-3-(1*H*-imidazol-4-yl)propanoate	23
8		**361**		(*S*)-methyl 2-(2,2,2-triphenylacetamido)-3-(1*H*-imidazol-4-yl)propanoate	47
9		**362**		(*S*)-methyl 2-(3-methoxybenzamido)-3-(1*H*-imidazol-4-yl)propanoate	71

4.5.2 Investigation with histidine derivatives

Histidine derivatives **354-362** were submitted to a series of catalytic tests with 4-nitrobenzaldehyde **82** and methyl vinyl ketone **132** in dry tetrahydrofuran under our standard protocol. Compound **363** was added to this series of experiments.



363

The results of this study are outlined below (Table 25).

Table 25. Investigation into the 2-carboxamido histidine methyl ester derivatives.[a]

Entry	Catalyst	Yield (%)	*ee* (%)[b]	Entry	Catalyst	Yield (%)	*ee* (%)[b]
1	**354**	41	21 (*R*)	7	**360**	18	8 (*R*)
2	**355**	41	21 (*R*)	8	**361**	14	8 (*R*)
3	**356**	27	22 (*R*)	9	**362**	37	14 (*R*)
4	**357**	27	16 (*R*)	10	**363**[c]	23	9 (*R*)
5	**358**	22	15 (*R*)	11	**345**	38	14 (*R*)
6	**359**	20	15 (*R*)				

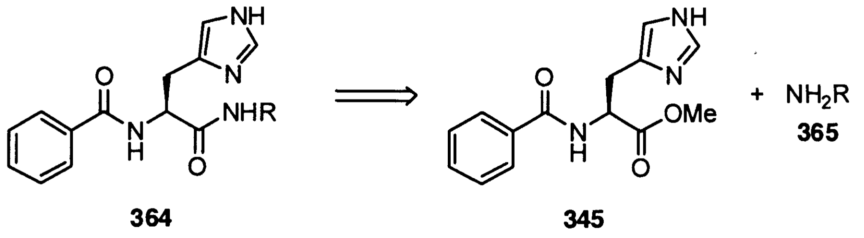
(a) All reactions were carried out in dry THF at 25 °C for 24 h with 10 mol% catalyst and (*S*)-proline **44**. (b) Enantiomeric excess determined by chiral HPLC using a Chiaralcel OJ column; see *section 4.2.4*. (c) Compound **363** is commercially available.

Histidine derivatives with electron poor aromatic groups **354-363** showed an interesting enhancement in enantiocontrol of the Baylis-Hillman adduct **134** which was obtained with an enantiomeric excesses up to 22% *ee* (*R*) (Table 25, entries 1-3). These observations suggested that electronic deficiency of these aromatic units could withdraw electron density throughout the architecture of the amide to affect the proton attached to the N-2 nitrogen atom. Thus, the increase of the partial positive charge present on this hydrogen atom could reinforce hydrogen bonding interactions between the catalyst and the substrates, improving reactivity and enantioselectivity. Catalyst **357-361** displayed a consistent loss in yield and enantiomeric excess, indicating that the use of bulky amidic moieties have caused a detrimental effect on the reaction (Table 25, enties 4-8). Furthermore, naphthyl-containing catalysts **357** and **358** provided enantiomeric excesses (16% *ee* (*R*), 15% *ee* (*R*) respectively, Table 25, enties 4 and 5) quite similar to **345** (Table 25, entry 11). An enantiomeric excess of 15% *ee* (*R*) was also observed with the *tert*-butyl-containing catalyst **359** (Table 25, entry 6). Hence, the enantioselectivity showed by **345** and the other aromatic-containing histidine derivatives does not seem to be connected to π-stacking interactions between the catalyst and the aromatic aldehyde **82**. In the same fashion, the electron rich catalyst **362** failed to delivery any improvement in enantiocontrol (14% *ee* (*R*), Table 25, entry 9). As a last note, **363** gave a clear indication that the deprotected carboxylic functionality of (*S*)-histidine negatively affected the reactivity and the enantioselectivity of this transformation.

4.5.3 Benzoamidic histidine diamide synthesis

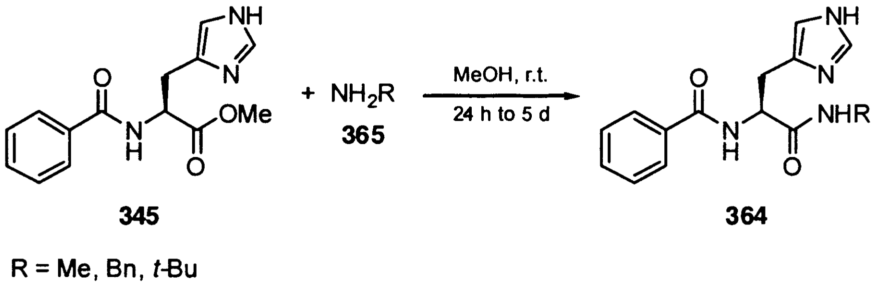
Examination into the architecture of amidic-histidine derivative **345** proceeded by altering the ester moiety. Catalysts **354**, **355** and **356** demonstrated that the amidic functionality could play an active role in the enhancement of the catalytic qualities of **345**. Therefore, we sought to incorporate a second amidic group on the scaffold of our catalyst.

Retrosynthetic analysis of **364** suggested that synthesis of a novel set of diamides could be achieved from catalyst **345** and a primary amine **365** through a simple amidation procedure (Scheme 88).



Scheme 88

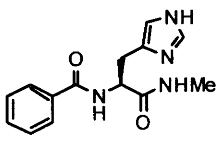
Catalyst **345** was treated with a methanolic solution of the amine **365** at room temperature for twenty four hours to five days (Scheme 89). The volatiles were removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography to provide the diamide **364**. Unfortunately, the reaction performed in the presence of a methanolic solution of the *tert*-butyl amine failed to give the desired diamide **368**. The reaction was monitored by TLC for five days.

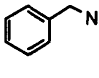
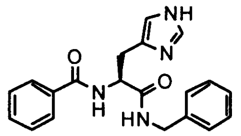
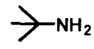
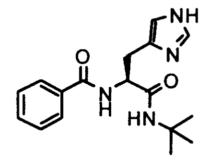


Scheme 89

All the catalysts prepared are reported in Table 26 with name, structure and yield for each compound.

Table 26. Synthesis of diamide-catalysts.

Entry	Amine	Compound	Structure	Name	Yield (%)
1	$MeNH_2$	**366**[a]		*N*-((*S*)-1-(methylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethyl)benzamide	90

2		**367**^{b}		*N*-((*S*)-1-(benzylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethyl)benzamide	65
3		**368**^{c}		*N*-((*S*)-1-(*tert*-butylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethyl)benzamide	0

(a) **335** was stirred for 24 h in a methanolic solution of methyl amine (33% v/v). (b) **335** was stirred for 48 h in a methanolic solution of benzyl amine (30% v/v). (c) **335** was stirred for 5 days in a methanolic solution of *tert*-butyl amine (30% v/v).

4.5.4 Diamides histidine derivatives analysis

Catalyst **366** and **367** were submitted to the standard Baylis-Hillman reaction reaction conditions in dry tetrahydrofuran for twenty hours. The outcomes are tabulated below (Table 27).

Table 27. Investigation into the diamides-catalysts **355** and **356**^{a}.

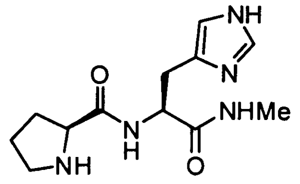
Entry	Catalyst	Solvent	Yield (%)	*ee* (%)^b
1	**366**	THF	79	18 (*R*)
2	**367**	THF	27	0
3	**345**	THF	38	14 (*R*)
4	**133**	DMF:H_2O 9:1	80	0

(a) All reactions were carried out in dry THF at 25 °C for 24 h with 10 mol% catalyst and (*S*)-proline **44**. (b) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4*.

Diamide **366** showed an excellent yield of 79% and 18% *ee* (*R*) (Table 27, entry 1). The result attained with this catalyst is comparable to the result observed in the reaction performed with (*S*)-proline **44** and imidazole **133** in the optimal solvent conditions DMF:H_2O 9:1 (Table 27, entry 4). Modification of **345** into the diamide **366** demonstrated that the amidic functionalities could play a crucial role in improvement of the reaction rate. Unfortunately, catalyst **367** displayed a complete opposite trend providing a poor yield and no enantiomeric excess (Table 27, entry 2). This outcome could be attributed to steric hindrance generated by the benzyl group.

4.6 (*S*)-Proline-(*S*)-histidine dipeptide catalyst

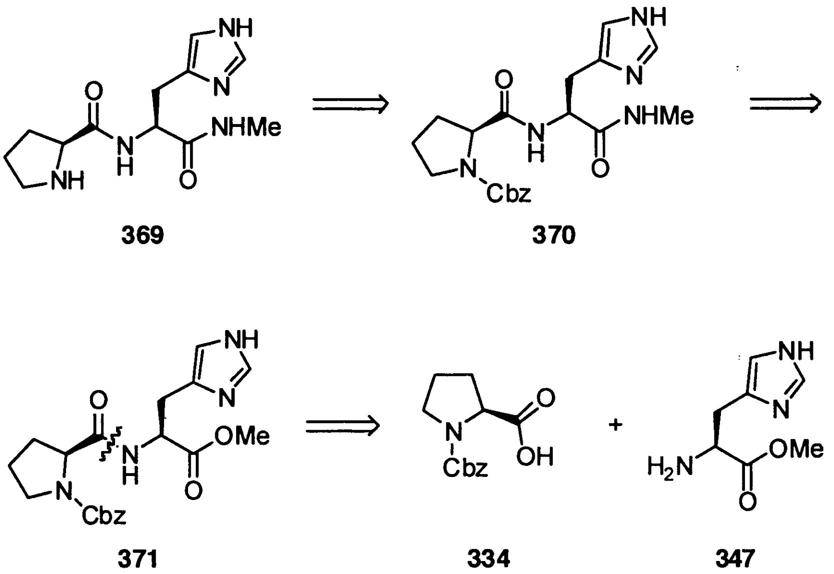
As a natural evolution of the (*S*)-proline **44** and (*S*)-histidine **344** catalytic system, we decided to fuse the co-catalyst and catalyst into a single molecule. Therefore, we decided to combine both the amino-acids into the simple dipeptide (*S*)-proline-(*S*)-histidine **369**. Moreover, previous experiments proved that additional amidic units could significantly improve the reaction rate. Hence, as a further design detail, we sought to replace the ester group of (*S*)-histidine methyl ester **347** residue with a *N*-methyl amide unit.



369

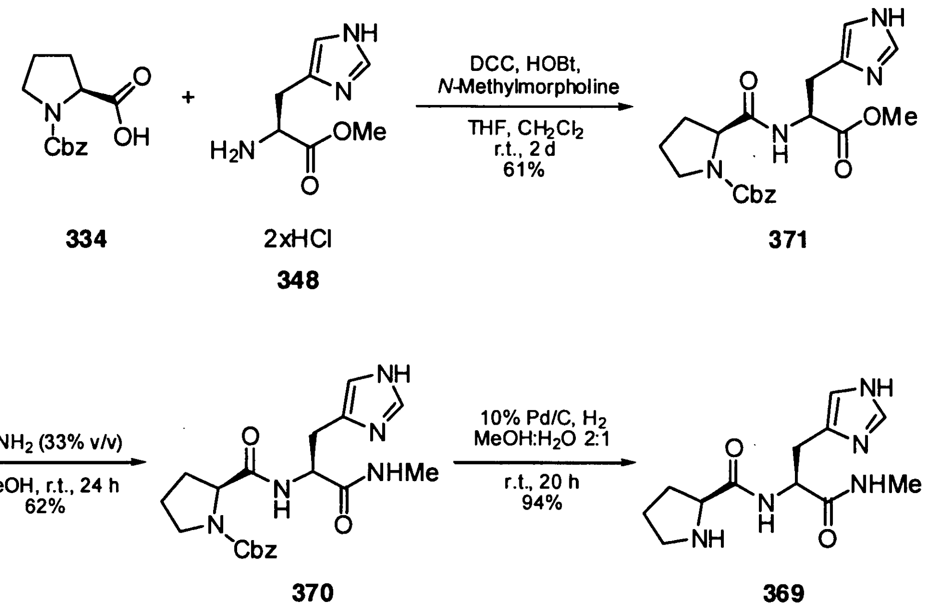
4.6.1 (*S*)-Proline-(*S*)-histidine *N*-methyl amide synthesis

Retrosynthetic analysis of dipeptide **369** showed a synthetic route from the commercially available (*S*)-Cbz proline **334** and (*S*)-histidine methyl ester dihydrochloride **348** (Scheme 90). Amide coupling, following the procedure of Kukla,[187] should provide dipetide **371**. Subsequent amidation with methyl amine and deprotection of the proline should give (*S*)-proline-(*S*)-histidine *N*-methyl amide **369**.



Scheme 90

To a stirred mixture of (*S*)-Cbz proline **334**, 1-hydroxybenzotriazole hydrate (HOBt), (*S*)-histidine methyl ester dihydrochloride **348** and *N*-methylmorpholine in tetrahydrofuran was added a solution of 1,3-dicyclohexylcarbodiimide (DCC) in dichloromethane at 0 °C under a atmosphere of nitrogen (Scheme 91). With the addition completed, the mixture was warmed to room temperature and stirred for two days to give the dipeptide **371** in 61% isolated yield. Subsequent treatment with a solution of methyl amine (33% v/v) in methanol provided the carbobenzyloxy protected (*S*)-proline-(*S*)-histidine *N*-methyl amide **370** in 62% isolated yield. Deprotection of **370** was achieved utilising palladium (10%) on carbon under a atmosphere of hydrogen which after filtration through a plug of Celite®, gave (2*S*)-*N*-((*S*)-1-(methylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethyl)pyrrolidine-2-carbox-amide **369** as a pale yellow solid in 94% isolated yield (overall yield 36%).



Scheme 91

4.6.2 Analysis of (*S*)-Proline-(*S*)-histidine *N*-methyl amide results

The reactivity of dipeptide **369** was examined under our standard Baylis-Hillman reaction protocol, performing the reaction in dry DMF:H_2O 9:1, dry *N*,*N*-dimethylformamide and dry tetrahydrofuran. In order to mimic the acidic conditions associated to the use of (*S*)-proline **44**, methansulfonic acid (10 mol%) was also added in a second series of catalytic runs. The data collected for these experiments are reported below (Table 28).

Table 28. Result of the study into the catalyst **369**.[a]

Entry	Solvent	Additive	Yield (%)	*ee* (%)[c]
1	DMF:H_2O 9:1	$MeSO_3H$[b]	5	5 (*R*)
2	DMF:H_2O 9:1	None	54	0
3	DMF	$MeSO_3H$[b]	6	9 (*R*)
4	DMF	None	16	0
5	THF	$MeSO_3H$[b]	0	0
6	THF	None	32	0

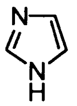
(a) All reactions were carried out in solvent at 25 °C for 24 h with 10 mol% catalyst **369**. (b) Reaction was performed in the presence 10 mol% of metansulfonic acid. (c) Enantiomeric excess determined by HPLC using a Chiaralcel OJ column; see *section 4.2.4*.

The use of catalyst **369** as a free-base delivered 54% as the highest yield with DMF:H_2O 9:1 as the solvent, demonstrating once again the significant role of water in the improvement of reactivity (Table 28, entry 1). All the conditions explored failed to provide enantiomeric excesses when **369** was utilised as the free-base (Table 28, entries 2, 4 and 6). A combination of this catalyst and methansulfonic acid displayed poor yields. Modest enantiomeric excesses up to 9% (*R*) for the reactions carried out in a polar solvent were also observed (Table 28, entries 1, and 3).

Catalyst **369** failed to replicate the reactivity observed with (*S*)-proline **44** and imidazole **133** under similar conditions (80% yield, Table 15, entry 4). This novel structure also showed a lower level of enantiocontrol in the Baylis-Hillman adduct **134** relative to the transformation catalysed with (*S*)-proline **44** and the (*S*)-histidine derivatives **354-356**. Thus, it appeared that further studies and modifications of the architecture of **369** would be the best method to further optimise this system.

4.7 Conclusions

This phase of the project involved an exploration of the diverse features of the organocatalysed Baylis-Hillman reaction. Following examination of the work of Shi,[99] we investigated the reaction environment as well as modification of (*S*)-proline **44** and imidazole **133** catalyst system, in an attempt to find a suitable combination of catalyst and co-catalyst for the asymmetric Baylis-Hillman transformation.



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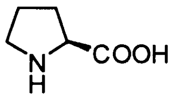
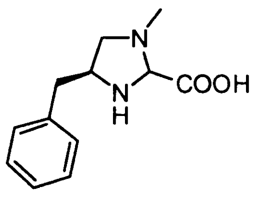


44

Preliminary studies into the optimisation of the reaction conditions revealed that the Baylis-Hillman reaction between 4-nitrobenzaldehyde **82** and methyl vinyl ketone **132** catalysed by **133** (10 mol%) and co-catalyst **44** (10 mol%) was highly sensitive to the amount of water contained in the reaction medium. Addition of a small quantity of water up to a level of 10% v/v for *N*,*N*-dimethylformamide and 5% v/v for tetrahydrofuran improved the yields to a maximum of 80% and 62% respectively. Further increment of the percentage of water present into the organic solvent led to a dramatic decrease in yields observed. Unfortunately, despite the chiral nature of (*S*)-proline **44**, the Baylis-Hillman adduct **134** was recovered as a racemic mixture. Therefore, with the general catalytic procedure defined, we turned our attention to modification of the catalyst architecture. Firstly, we investigated the co-catalyst within our standard Baylis-Hillman reaction through the use of proline analogues **53**, **124**, **328**, and **329**.



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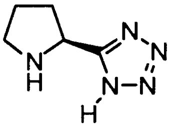

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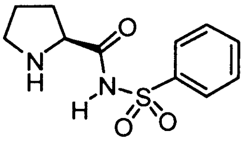
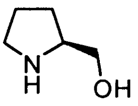
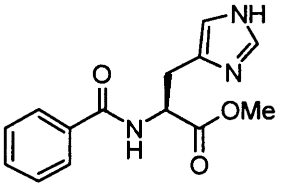


328



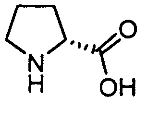
329

This set of catalysts (**53**, **124**, **328**, and **329**) showed a diminished catalytic activity compared to the outcomes observed for the same transformation catalysed by (*S*)-proline **44** and imidazole. The best yield of 40% was obtained for **328** using DMF:H_2O 9:1 as the solvent system. Moreover, in spite of this group of proline analogues having different structural motifs, each of catalysts examined failed to deliver any enantioselectivity. These observations suggested that to avoid a drastic decline in reactivity and geometric control of the catalyst system, modification of the structure of proline should be avoided.



345

Another component of the catalytic system was also examined through the preparation of 2-benzoamidic histidine derivative **345**. Catalyst **345** gave a pleasing 72% yield in DMF:H_2O 9:1 with 0% *ee* and a interesting 38% yield in dry tetrahydrofuran with 14% *ee* (*R*). This enantiomeric excess was attributed to weak hydrogen bonding interactions rather than steric effects. Furthermore, subsequent experiments carried out in dry tetrahydrofuran showed that the absolute configuration of the Baylis-Hillman product **134** was governed principally by the absolute configuration of the proline chiral centre. The transformation performed in the presence of (*R*)-proline **349** as co-catalyst provided the adduct **134** with an enantiomeric excess of 14% with the (*S*)-enantiomer as the major product. In addition, the enantiomeric excess decreased to a 6% (*R*) when (±)-proline was used as co-catalyst. In contrast, the reaction performed with the 2-benzoamidic derivative **351** and (*S*)-proline **44** displayed a poor 26% isolated yield and no enantiomeric excess. All the observations collected highlighted that the enantioselective control originated from a "cooperative"-behaviour of the catalyst and co-catalyst chiral centres.



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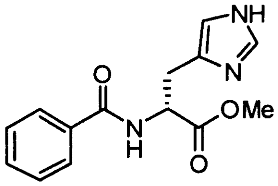
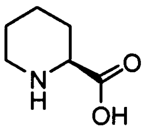


351

Study into the catalyst loading showed that increasing the amount of the histidine derivative **345** and (*S*)-proline **44** from 10 mol% to 20 mol% improved yields up to a modest 57% without affecting the enantioselectivity (17% *ee* (*R*)). Surprisingly, the reaction performed in dry tetrahydrofuran with an excess of (*S*)-proline **44** displayed no enantiomeric excess.

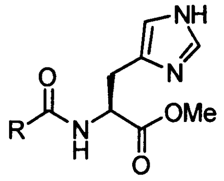
In an attempt to enhance the enantiocontrol of adduct **134**, catalyst **345** was submitted to a series of catalytic runs in dry tetrahydrofuran with the co-catalyst **53**, **124**, **328** and the amino-acid **142**.



142

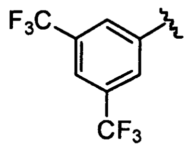
This set of co-catalysts and histidine derivative **345** showed a decrease in yield and enantioselectivity. Co-catalyst **142** offered the best performance with a 16% isolated yield and 10% *ee* (*R*). As previously observed, the outcome obtained from our standard Baylis-Hillman reaction seem to be particularly affected by modification of the proline scaffold.

The histidine derivative **345** was subsequently elaborated, to further investigate the structural requirements of this architecture for enhanced catalysis of the Baylis-Hillman reaction. This included the preparation of a series of amide derivatives **354**-**362** and the synthesis of the diamides **366** and **367**.

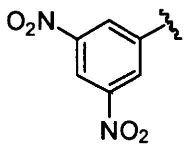


353

R =



354



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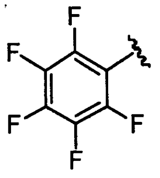

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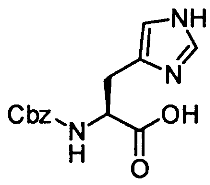

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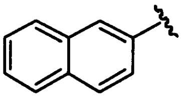

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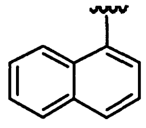

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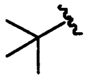

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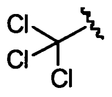

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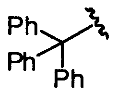

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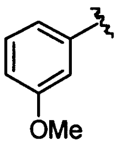
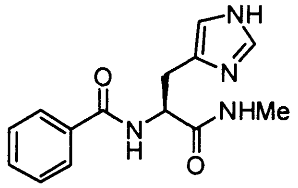


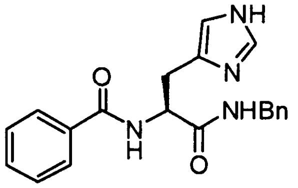
362

Catalysts **354**-**362** and commercially available **363** were submitted to our standard Baylis-Hillman reaction for evaluation with (*S*)-proline **44** as co-catalyst and dry tetrahydrofuran as solvent. **354**, **355** and **356** provided 41%, 41% and 27% yield respectively and an increment in enantiomeric excess up to 22% (*R*). The introduction of strong electron withdrawing groups on the aromatic ring of the amide group promoted the enhancement of the enantioselectivity, maintaining the same level of reactivity (**354** and **355**). The remaining catalysts in this set **357**-**361** showed that bulky aromatic and non-aromatic groups or electron rich arenes **362** was detrimental to both yield and enantioselectivity.

In a similar fashion, diamides **366** and **367** were evaluated under our standard protocol.



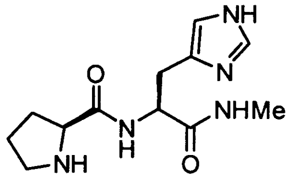
366



367

Diamide **366** led to a doubling of the yields observed with a 79% isolated yield in 18% *ee* (*R*). The result attained with **366** highlighted that the amide functionality plays an important role in the catalyst reactivity. In contrast, catalyst **367** displayed a poor 27% yield and no enantiomeric excess. Outcomes from this series of experiments highlighted that an increase of the steric encumbrance on the architecture of **345** inevitably led to a drastic decrease in yields and enantioselectivity.

Finally, as a natural evolution of the (*S*)-proline **44**/(*S*)-histidine **344** catalytic system and the result observed with **366**, we prepared the dipeptide **369**. Reaction rate and levels of enantiocontrol with **369** were examined within our standard Baylis-Hillman reaction in a variety of solvents. The catalyst was utilised as a free-base and in conjunction with 10 mol% of methanesulfonic acid to simulate the protic environment generated by (*S*)-proline **44**.



369

The use of catalyst **369** as a free-base gave a 54% yield in DMF:H_2O 9:1 and no enantiomeric excess. All the conditions explored failed to provide enantiomeric excesses when **369** was utilised as a free-base catalyst. On the other hand, the combination of **369** and methanesulfonic acid displayed poor yields and modest enantiomeric excesses up to 9% (*R*) for the reactions carried out in the polar solvent were observed.

The complexity of the Baylis-Hillman reaction renders this transformation intriguing. Our observations have clearly shown that both yields and asymmetric induction are highly sensitive to the architecture of the catalyst and co-catalyst employed, as well as the polarity of the reaction medium. Such a complexity, mirrored in the variability of the results observed, has also provided a clear indication that the reaction mechanism proposed in literature[99] is insufficient to account for the outcomes observed. Certainly, further investigations are required to theorise a plausible transition state which involves the co-operation of two different amines within the catalytic process. These further studies of the organocatalysed Baylis-Hillman reaction could allow for the elucidation of the optimal secondary amine, nucleophilic amine and solvent to bring this reaction in line with those reported in the contemporary literature.

Experimental

5

5.1 Experimental techniques

Reagents were obtained from Aldrich, Avocado, Lancaster and Fluka chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[188] 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. *N,N*-Dimethylformamide was dried by stirring over phosphorus pentoxide for 48 h followed by distillation from calcium hydride. Triethylamine was distilled from calcium hydride and dried over potassium hydroxide. Anhydrous ethyl acetate was obtained by pre-drying with anhydrous magnesium sulphate. 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, 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,[189] using Merck Kieselgel 60 H silica or Matrix silica 60.

Microwave irradiation experiments were performed using a self-tunable CEM Discover^{TM} focused monomodal microwave synthesiser at the given temperature by varying the irradiation power. All irradiation experiments were carried out in a pressure-rated glass tube (10 mL) with temperature control using the instrument's in-built IR sensor.

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, $[\alpha]_D^{20}$, of chiral non-racemic compounds, was analysed using an Optical Activity AA-1000 polarimeter at 20 °C, 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 an Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 500 (500 MHz), with ^{13}C NMR spectra (δ_C) recorded at 100 MHz or 125 MHz respectively. Chemical shifts (δ_H and δ_C) were recorded in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 ($CHCl_3$) for ^1H NMR and 77.30 ($CHCl_3$), centre line, for ^{13}C NMR. The abbreviations s, d, t, q, sept., m, br and rot. denote singlet, doublet, triplet, quartet, septet, multiplet, broadened resonances and rotamer respectively; all coupling constants were recorded in hertz (Hz).

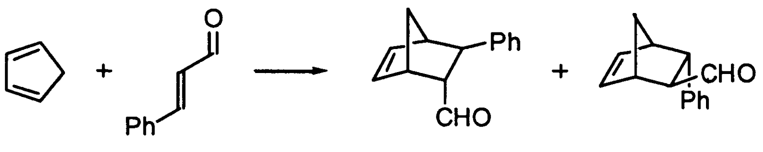
Low resolution mass spectrometric data was determined using a Fisons VG Platform II Quadrapole instrument using electrospray ionisation (ES) unless otherwise stated. APCI refers to atmospheric pressure chemical ionisation; CI is chemical ionisation (ammonia); EI refers to electron ionisation; ES refers to electrospray.

High resolution mass-spectrometric data was obtained courtesy of the EPSRC Mass Spectrometry Service at the University of Wales, Swansea, UK, using the ionisation methods specified. Calculated accurate masses are of the parent ion (exclusive of an electron, mass = 0.00055Da).

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

Iminium ion catalysed Diels-Alder cycloaddition: general procedure A[11]



8 **11** **12** **13**

(*E*)-Cinnamaldehyde **9** (252 mg, 1.9 mmol, 0.24 mL, 1.0 eq) was added to a solution of catalyst (10 mol%, 0.19 mmol) in methanol (2 mL) at 25 °C and the resulting mixture was stirred for 5 minutes to initiate iminium ion formation. Freshly cracked cyclopentadiene **8** (376 mg, 5.7 mmol, 0.46 mL, 3 eq) was added in a single aliquot and stirring was continued for 24 hours. The volatiles were removed under reduced pressure and the resulting organics were hydrolysed in chloroform (2 mL), water (1 mL) trifluoroacetic acid (1 mL) mixture over night. Saturated sodium hydrogen carbonate solution (20 mL) was added to neutralise the solution and the aqueous phase was extracted with dichloromethane (2x20 mL). The combined organics were washed with water (10 mL) and dried (Na_2SO_4) prior to the removal of the volatiles under reduced pressure to afford the crude product. ^{1}H NMR of the crude reaction mixture was used to establish the conversion to the products and *exo*:*endo* ratios through the integration of aldehyde peaks at: (400 MHz, $CDCl_3$) δ_H 9.85 (*exo*), 9.64 ((*E*)-cinnamaldehyde **11**), 9.53 (*endo*). The products were then purified by flash column chromatography eluting with ethyl acetate:light petrol 1:9 resulting in a mixture of the *exo*- and *endo*-isomers of 3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **12** and **13** as a pale yellow oil. ^{1}H NMR, ^{13}C NMR and IR data were consistent with previously reported literature values;[190]

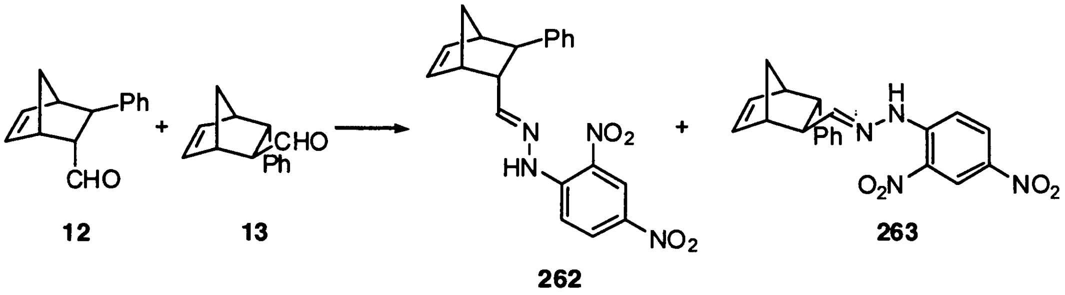
***Endo*-diastereoisomer 12**; IR (thin film) 1718, 1601, 1497 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.53 (d, *J* = 2.1, 1H, CHO), 7.40-7.00 (m, 5H, ArH), 6.36 (dd, *J* = 5.6, 3.6 Hz, 1H, CH=CH) 6.10 (dd, *J* = 5.6, 3.6 Hz, 1H, CH=CH), 3.30-3.21 (m, 1H, CHPh), 3.12-2.96 (m, 2H, CHCH$_2$), 2.95-2.88 (m, 1H, CHCHO), 1.46-1.49 (m, 2H, CH$_2$); ^{13}C NMR(100 MHz, $CDCl_3$) δ_C 203.7 (s), 139.3 (d), 133.8 (d), 128.6 (d), 128.1 (d), 127.8 (s), 126.2 (d), 60.8 (d), 48.4 (d), 47.2 (t), 45.6 (d), 45.2 (d); LRMS (EI, $[M]^+$) m/z 198 (10%), 132 (89), 131 (100), 103 (52), 77 (21), 66 (54).

***Exo*-diastereoisomer 13**; IR (thin film) 1718, 1601, 1497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.85 (d, J = 2.0 Hz, 1H, CHO), 7.40-7.00 (m, 5H, ArH), 6.27 (dd, J = 5.6, 3.6 Hz, 1H, CH=CH), 6.01 (dd, J = 5.6, 3.6 Hz, 1H, CH=CH), 3.66 (dd, J = 5.0, 3.4 Hz, 1H, CHPh), 3.25-3.05 (m, 2H, $CHCH_2$), 2.55-2.45 (m, 1H, CHCHO), 1.65-1.45 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.9 (s), 136.6 (d), 136.3 (d), 128.6 (d), 128.2 (d), 127.9 (s), 126.4 (d), 59.5 (d), 48.5 (d), 47.6 (t), 45.5 (d), 45.4 (d); LRMS (EI, $[M]^+$) m/z 198 (0.1%), 132 (89), 131 (100), 103 (52), 77 (21), 66 (54).

Asymmetric iminium ion catalysed Diels-Alder cycloaddition: general procedure B[152c]

(*E*)-Cinnamaldehyde **11** (252 mg, 1.9 mmol, 240 µL, 1 eq) was added to a solution of catalyst (10 mol%, 0.19 mmol) in $CH_3CN:H_2O$ 19:1 (2 mL) at 25 °C and the resulting mixture was stirred for 5 minutes to initiate iminium ion formation. Freshly cracked cyclopentadiene **8** (376 mg, 5.7 mmol, 46 µL, 3 eq) was added in a single aliquot and stirring was continued at 25 °C for 24 hours or at -20 °C for 72 hours. Saturated sodium hydrogen carbonate solution (18 mL) was added to neutralise the solution and the aqueous phase was extracted with dichloromethane (2x20 mL). The combined organics were washed with water (10 mL) and dried (Na_2SO_4) prior to the removal of the volatiles under reduced pressure to afford the crude product. ^1H NMR of the crude reaction mixture was used to establish the conversion to the products and *exo*:*endo* ratios through the integration of aldehyde peaks at: (400 MHz, $CDCl_3$) δ_H 9.80 (*exo*), 9.65 ((*E*)-cinnamaldehyde **11**), 9.53 (*endo*). The products were then purified by flash column chromatography eluting with ethyl acetate:light petrol 1:9 resulting in a mixture of the *exo*- and *endo*-isomers of 3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **12** and **13** as a pale yellow oil. ^1H NMR, ^{13}C NMR and IR data were consistent with previously reported literature values (see general procedure **A**).[190]

2,4-Dinitrophenylhydrazine derivatisation of the Diels-Alder adduct: general procedure C[152b]



3-Phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **12** and **13** was dissolved in ethanol (2.0 mL/mmol), and 2,4-dinitrophenylhydrazine **261** (1.2 eq) was added. The reaction mixture was stirred for 2 hours at room temperature. Water (10 mL) was added and the mixture was extracted with diethyl ether (3x20 mL). The aqueous layer was further extracted with diethyl ether (2x20 mL), and the ethereal extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to afford the crude product. Purification by flash column chromatography, eluting with ethyl acetate:light petroleum 1:9, afforded a mixture of the *endo*- and *exo*-isomers *N*-(2,4-dinitrophenyl)-*N'*-(3-phenylbicyclo[2.2.1]hept-5-en-2-ylmethylene)hydrazine **262** and **263** as a yellow powder. Chiral HPLC analysis using a Chiralcel OD-R column, wavelength 365 nm, eluting with $CH_3CN:H_2O$ 8:2, flow rate of 0.5 mL/min, separated the chiral sample, retention times of 30.7 (2*S*) and 36.5 (2*R*) minutes (*endo*-diastereoisomers respectively), 41.8 (2*S*) and 51.4 (2*R*) minutes (*exo*-diastereoisomers respectively). ^1H NMR, ^{13}C NMR and IR data were consistent with previously reported literature values;[152c]

***Endo*-Diastereoisomer 262**; mp (ethyl acetate/light petroleum) 160-162 °C; IR (nujol mull) 3289, 1618, 1586, 1518, 1502, 1334 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 11.04 (s, 1H, NNH), 9.05 (d, J = 2.3 Hz, 1H, ArH), 8.22 (dd, J = 9.6, 2.3 Hz, 1H, ArH), 7.83 (d, J = 9.6 Hz, 1H, ArH), 7.27-7.13(m, 6H, N=CH, ArH), 6.44 (dd, J = 5.5, 3.1 Hz, 1H, CH=CH), 6.14 (dd, J = 5.5, 2.6 Hz, 1H, CH=CH), 3.14-3.01 (m, 3H, $CHCH_2CH$, CHCH=N), 2.83-2.71 (m, 1H, CHPh), 1.87-1.74 (m, 1H, CHH), 1.69-1.55 (m, 1H, CHH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.5 (d), 145.0 (s), 143.6 (s), 139.6 (d), 134.1 (d), 130.0 (d), 128.7 (d), 127.3 (d), 126.3 (d), 123.5 (d), 116.6 (d), 51.1 (d), 49.0 (d), 48.4 (d), 47.4 (d), 47.3 (t); other quaternary carbons not observed; LRMS (APCI, $[M+H]^+$) m/z 378.9 (51%), 338.4 (40), 144.9 (35), 106.9 (100);

***Exo*-Diastereoisomer 263**; mp (ethyl acetate/light petroleum) 160-162 °C; IR (nujol mull) 3289, 1618, 1586, 1518, 1502, 1334 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.05 (d, *J* 2.5 Hz, 1H, ArH), 8.22 (dd, *J* = 9.7, 2.5 Hz, 1H, ArH), 7.85 (d, *J* = 9.7 Hz, 1H, ArH), 7.66 (d, *J* = 6.1 Hz, 1H, N=CH), 7.26-7.14 (m, 5H, ArH), 6.33 (dd, *J* = 5.6, 3.1 Hz, 1H, CH=CH), 6.03 (dd, *J* = 5.6, 2.8 Hz, 1H, CH=CH), 3.52 (dd, *J* = 4.8, 3.7 1H, Hz, CHCHN), 3.28-3.17 (m, 1H, $CHCH_2CH$), 3.09-2-90 (m, 1H, $CHCH_2CH$), 2.63 (ddd, *J* = 6.1, 4.8, 1.4 Hz, 1H, CHPh), 1.77-1.63 (m, 1H, CHH), 1.60 (ddd, *J* = 9.4, 9.4, 1.6 Hz, 1H, CHH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 154.9 (d), 145.0 (s), 142.7 (s), 137.8 (s), 136.7 (d), 135.9 (d), 128.8 (s), 128.7 (d), 128.2 (d), 127.8 (d), 126.4 (d), 123.5 (d), 116.6 (d), 49.9 (d), 48.9 (d), 48.7 (d), 48.1 (d), 47.5 (t); LRMS (APCI, $[M+H]^+$) m/z 378.9 (51%), 338.4 (40), 144.9 (35), 106.9 (100).

HX gas generation: general procedure D

Preparation of the HCl **188**, HBr **189** and HI **190** salts of the catalyst **23** was achieved through the use of the apparatus displayed in Figure 49. A three necked round bottom flask **A** (1 L) was charged with a adequate amount of MX salt (NaCl or KBr or KI) and fitted with a pressure equalising dropping funnel **B** (100 mL) containing concentrated sulphuric acid (>98%). **A** was connected *via* a Drechsel bottle **C** (500 mL) to a second two necked round bottom flask **D** (500 mL) containing a stirred ethereal solution of catalyst **23**. The HX gas was allowed to bubble through the solution utilising a metal needle **E**. To vent and neutralise the excess of HX gas the second neck of the flask **D** was connected by a second Drechsel bottle **F** (500 mL) to a conical flask **G** containing a solution of sodium hydroxide (2 M). Joints and glass stopper were carefully sealed utilising Lab-grade silicon grease and Teflon film. Polyethynele tubes were employed to transfer the gasses between flasks.

Concentrated sulphuric acid (50 mL) was slowly and carefully dropped over the MX salt (typically 100 g of NaCl or KBr or IH). The resulting HX gas was allowed to bubble through the ethereal solution (50 mL) of **23** for two hours. The needle was removed and the mixture was stirred for additional 3 hours. The volatiles were removed under reduced pressure to provide the **23**.HX salt.

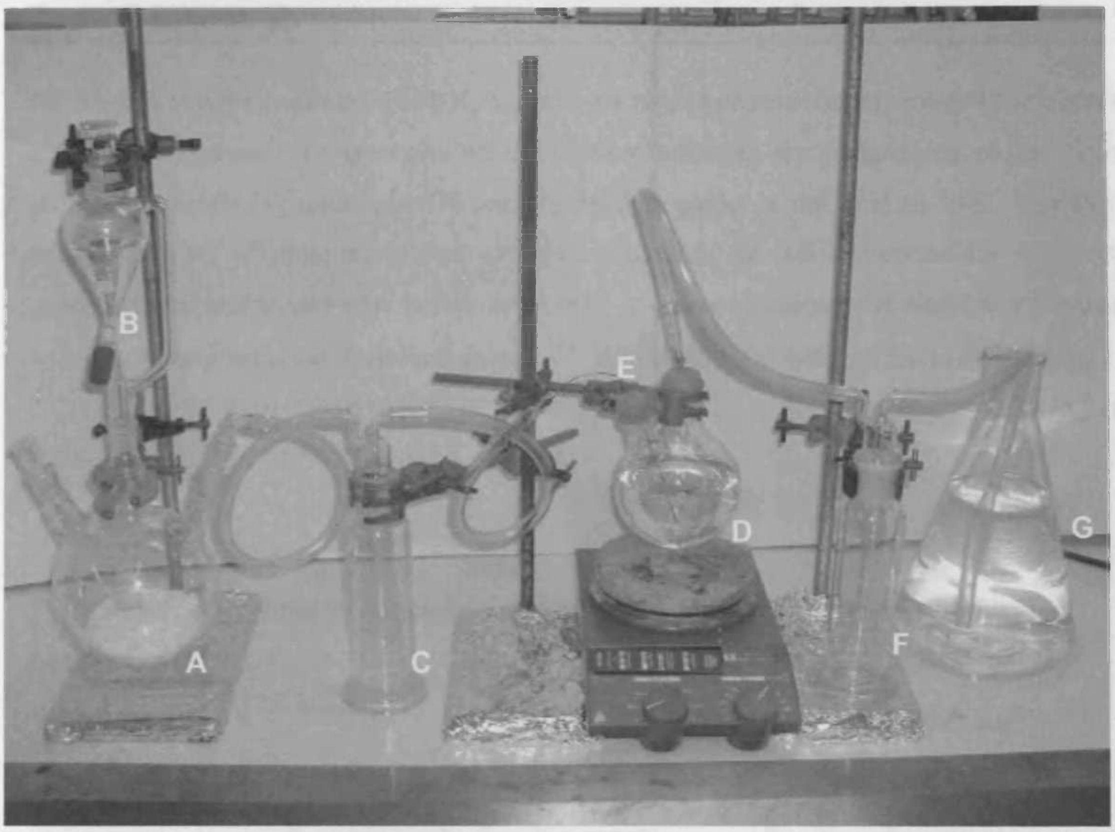
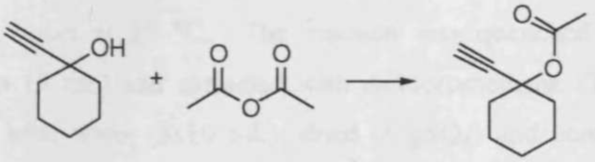


Figure 49

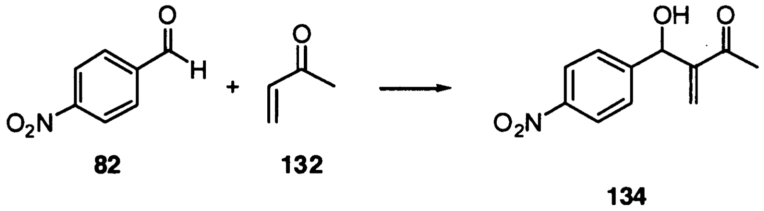
Kinetic test procedure for the acylation of 1-ethynylcyclohexanol: general procedure E[153]



276 **146** **295**

1-Ethynylcyclohexanol **276** (25 mg, 0.2 mmol, 2 eq) was dissolved in deuterated chloroform (1 mL) within a clean and oven-dried NMR tube. Subsequently, the catalyst (20 μmol, 10 mol% loading) and triethylamine (61 mg, 0.6 mmol, 84 μL, 6 eq) were added and the mixture was gently shaken. Finally, acetic anhydride **146** (41 mg, 0.4 mmol, 39 μL, 4 eq) was added. The addition of the anhydride **146** was considered as the start time of the reaction (t = 0 min). The sample was immediately introduced into the NMR (500 MHz) machine and monitored for 5 hours at a temperature of 298 K, acquiring a new spectrum roughly every 12 minutes for a total of 25 scans. Conversions were evaluated utilising the integrations of the alkynyl proton of the starting materials **276** and the methyl group of the product **295**. Due to the varying number of protons involved in this calculation, the value obtained for the methyl group was reduced to one/third before estimation of the conversions. ^{1}H NMR was consistent with previously reported literature values;[191] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.62 (s, 1H, CCH), 2.08-2.18 (m, 2H, CHHCCHH), 2.05 (s, 3H, CH_3), 1.92-1.80 (m, 2H, CHHCCHH), 1.70-1.30 (m, 6H, $CH_2CH_2CH_2$).

Typical experimental procedure for the Baylis-Hillman reaction: general procedure F[99]



To a solution of the catalyst (10 mol%, 0.1 mmol), the co-catalyst (10 mol%, 0.1 mmol) and 4-nitrobenzaldehyde **82** (151 mg, 1.0 mmol, 1 eq) in the relevant solvent system (1 mL) was added methyl vinyl ketone **132** (210 mg, 3.0 mmol, 0.25 mL, 3 eq) and the resulting solution was stirred for 24 hours at 25 °C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3x10 mL). The organic phase was washed with water (3x10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:light petroleum 3:7, to give 3-(Hydroxy(4 nitrophenyl)methyl)but-3-en-2-one **134** as a orange solid. ^{1}H NMR, ^{13}C NMR and IR data were consistent with previously reported literature values;[99] mp (ethyl acetate/light petroleum) = 79-81 °C; IR (nujol mull) 3419, 2922, 1732, 1660, 1652 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.17 (d, *J* = 8.9 Hz, 2H, ArH), 7.54 (d, *J* = 8.9 Hz, 2H, ArH), 6.30-6.22 (m, 1H, CHH), 6..05-6.02 (m, 1H, CHH), 5.66 (br d, J = 5.0 Hz, 1H, CHOH), 3.37 (br d, *J* = 5.6 Hz, 1H, CHOH), 2.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_H 200.0 (s), 149.0 (s), 148.9 (s), 147.3 (s), 127.7 (t), 127.2 (d), 123.5 (d), 72.2

(d), 26.3 (q); LRMS (CI, $[M+NH_4]+$) m/z 239.1 (100%); HRMS (CI, $[M+NH_4]+$) exact mass calcd for ($C_{11}H_{15}N_2O_4$) requires m/z 239.1026, found m/z 239.1028.

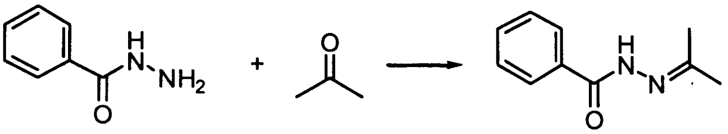
The absolute stereochemistry of the major adduct **134** was determined by comparing the sign of the specific rotation with reported literature data.[173] Measurement of the optical rotation and comparison to literature showed the sample to be of the (*R*)-configuration: $[\alpha]_D^{20} = -1.38$ ($c = 4.35$, $CHCl_3$) was calculated utilising the adduct **134** obtained from the Baylis-Hillman reaction performed under the conditions described above catalysed with (*S*)-histidine derivate **356** (see *section 4.5.2*, Table 25, entry 3, 22% *ee* (*R*)); literature for 3-((*R*)-hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (*R*)-**134**: $[\alpha]_D^{20} = -12.1$ ($c = 0.53$, $CHCl_3$)

2-Carboxamido histidine methyl ester derivatives synthesis: general procedure G

1,3-Dicyclohexylcarbodiimide (850 mg, 4.13 mmol) in dry dichloromethane (13 mL) was added to a stirred, heterogeneous mixture of carboxylic acid **352** (4.13 mmol), 1-hydroxybenzotriazole hydrate (560 mg, 4.35 mmol), (*S*)-histidine methyl ester dihydrochloride **348** (1.00 g, 4.13 mmol), and *N*-methylmorpholine (832 mg, 8.24 mmol, 0.9 mL) in dry tetrahydrofuran (50 mL) at 0 °C under a nitrogen atmosphere. After 2 hours, the ice bath was removed and the reaction was stirred at room temperature for 2 days. The reaction mixture was then cooled to 0 °C and stirred for an additional 1 hour. The solid urea was filtered off and the filtrate concentrated under reduced pressure. The crude residue was dissolved in chloroform (30 mL) and washed with brine, saturated sodium hydrogen carbonate solution, and brine once again. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to provide the crude product.

5.3 Experimental Procedures

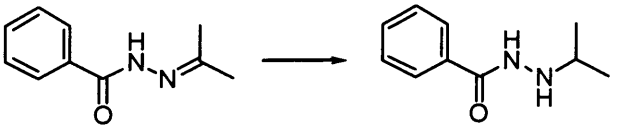
N'-(Propan-2-ylidene)benzohydrazide 187[131a]



186 **81** **187**

Benzoic hydrazide **186** (5.00 g, 36.7 mmol) was stirred in an excess of acetone **81** (17 mg, 0.3 mmol, 22.0 mL), containing acetic acid (42 mg, 0.7 mmol, 40 μL), for 48 hours at room temperature. Water (30 mL) was added and the reaction mixture was extracted with dichloromethane (3x30 mL). The combined organic extracts were dried (Na_2SO_4) and reduced *in vacuo* to afford the *title compound* **187** (5.57 g, 86%) as a colourless solid; mp (dichloromethane) 141-143 °C [lit.[131a] mp 142-143 °C]; IR (nujol mull) 3221, 1655, 1578, 1578, 1531, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.70 (s, 1H, NH), 7.79 (d, *J* = 7.1 Hz, 2H, ArH), 7.52 (t, *J* = 7.1 Hz, 1H, ArH), 7.44 (t, *J* = 7.1 Hz, 2H, ArH), 2.15 (s, 3H, CH_3), 1.97 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 164.6 (s), 156.9 (s), 134.1 (s), 132.1 (d), 129.0 (d), 127.6 (d), 26.0 (q), 17.3 (q); LRMS (EI, $[M]^+$) *m/z* 176 (8%), 161 (50), 105 (100); HRMS (EI, $[M]^+$) exact mass calcd for ($C_{10}H_{12}N_2O$) requires *m/z* 176.0950, found *m/z* 176.0950.

Benzoic acid *N'*-*iso*-propylbenzohydrazide 23[131a]

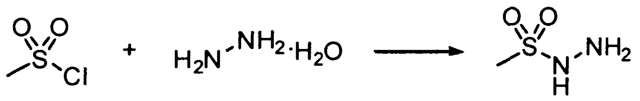


187 **23**

Platinum(IV) oxide (68 mg, 0.3 mmol) was placed in a nitrogen flushed flask with ethanol (12 mL) and acetic acid (6 mL). *N'*-(Propan-2-ylidene)benzoic hydrazide **187** (2.50 g, 14.2 mmol) was added, the flask was charged with hydrogen and stirred for 48 hours at room temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (180 mL). The volatiles were removed under reduced pressure and the aqueous phase was extracted with diethyl ether (5x50 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure to give the *title compound* **23** (2.18 g, 86%) as a colourless powder; mp (diethyl ether) 110-112 °C [lit.[192] mp 115-117 °C], IR (nujol mull) 3289, 1640, 1537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (s, 1H, NHNHCH), 7.69 (d, J = 7.7 Hz, 2H, ArH), 7.46 (t, J = 7.7 Hz, 1H, ArH), 7.38 (t, J = 7.7 Hz, 2H, ArH), 4.81 (s, 1H, NHNHCH), 3.18 (sept., J = 6.2 Hz, 1H, $CH(CH_3)_2$), 1.05 (d, J = 6.2 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.5 (s), 132.9 (s), 131.9 (d), 128.7 (d), 126.9 (d), 51.4 (d), 20.9 (q); LRMS (EI, $[M]^+$) *m/z* 178 (3%), 163 (9), 122 (13), 105 (100); HRMS (EI, $[M]^+$) exact mass calcd for ($C_{10}H_{14}N_2O$) requires *m/z* 178.1106, found *m/z* 178.1105.

The HCl, HBr and HI salt of **23** were prepared according to the general procedure **D**. Treatment of **23** with gaseous HCl gave the corresponding salt **188** as a colourless solid; mp (diethyl ether) = 216-218 °C. Treatment of **23** with gaseous HBr provided the corresponding salt **189** as a colourless solid; mp (diethyl ether) = 79-82 °C. Treatment of **23** with gaseous HI gave the corresponding salt **190** as a pale yellow solid; mp (diethyl ether) = 164-166 °C.

Methanesulfonylhydrazide hydrochloride 199[140]

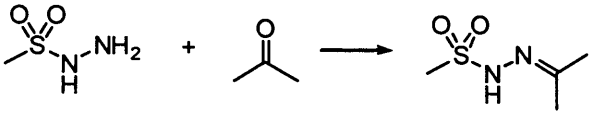


197 **198** HCl **199**

Methanesulfonyl chloride **197** (5.75 g, 50.0 mmol) was added slowly to a stirred ice-cold solution of hydrazine hydrate **198** (2.50 g, 50.0 mmol) in water (7.5 mL), followed by sodium hydroxide (2 M, 25 mL), such that the temperature did not exceed 8 °C. On completion, concentrated hydrochloric acid (12.7 M, 25 mL) was added, which led to the precipitation of a small amount of di-methanesulfonyl hydrazide, which was filtered off. The filtrate was concentred *in vacuo* and the resulting residue recrystallised twice from boiling ethanol to give the *title compound* **199** (2.62 g, 36%) as a colourless crystalline solid; mp (ethanol) = 152-153

°C; IR (nujol mull) 3440, 2652, 1953, 1461, 1376 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ_H 3.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, D_2O) δ_C 38.4 (q).

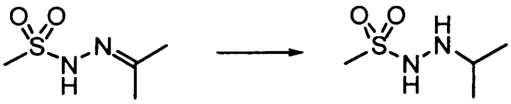
N-Iso-propylidene-*N'*-methanesulfonylhydrazone hydrochloride 200



HCl **199** + **81** → HCl **200**

Methanesulfonylhydrazide hydrochloride **199** (1.00 g, 8.8 mmol) was stirred in an excess of acetone **81** (17 mg, 0.3 mmol, 20.0 mL) at room temperature for 24 hours. The solvent was removed *in vacuo* and the solid residue was recrystallised twice from ethanol/diethyl ether to give the *title compound* **200** (1.05 g, 64%) as a colourless solid; mp (ethanol/diethyl ether) = 120 °C dec; IR (nujol mull) 3410, 1977, 1672, 1462, 1351, 1165, 784 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 (s, 1H, SO_2NH), 3.02 (s, 3H, CH_3SO_2), 2.01 (s, 3H, CH_3), 1.82 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.7 (s), 38.6 (q), 25.7 (q), 17.6 (q).

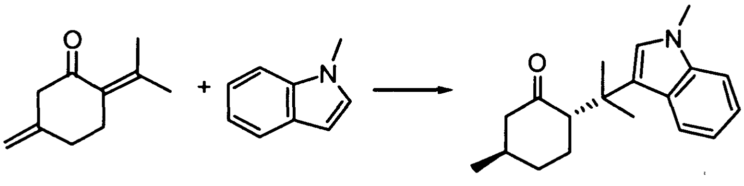
Methanesulfonic acid *N'-iso*-propyl hydrazide hydrochloride 201



HCl **200** → HCl **201**

To a stirred solution of *N-iso*-propylidene-*N'*-methanesulfonylhydrazone hydrochloride **200** (400 mg, 2.14 mmol) in methanol (3 mL) was added a solution sodium cyanoborohydride in tetrahydrofuran (1 M, 133 mg, 2.14 mL, 2.14 mmol) at room temperature, followed by 2 M hydrochloric acid at a rate sufficient to maintain a pH of 2-3. After 10-15 minutes the pH changed less rapidly and the mixture was allowed to stir for an additional 3 hours. The pH was lowered to 1 and the volatiles were removed under reduced pressure. The resulting residue was taken up in water (10 mL) and the pH adjusted to 8 with 20% potassium carbonate and extracted with diethyl ether (6x20 mL). The ethereal extracts were dried ($MgSO_4$) and concentrated to afford an oil, which was dissolved in diethyl ether (10 mL) and the solution was treated with hydrochloric acid in diethyl ether (2 M, 0.5 mL) to give a solid, which was recrystallised from ethanol/diethyl ether to afford the *title compound* **201** (54 mg, 13%,) as a colourless solid; mp (ethanol/diethyl ether) = 100-103 °C; IR (nujol mull) 1942, 1562, 1462, 1348 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ_H 3.42 (sept, J = 6.5 Hz, 1H, $CH(CH_3)_2$), 3.10 (s, 3H, CH_3), 1.14 (d, J = 6.5 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, D_2O) δ_H 54.5 (d) 39.8 (q) 16.9 (q).

(2*S*,5*R*)-5-Methyl-2-(2-(1-methyl-1*H*-indol-3-yl) propan-2-yl)cyclohexanone 241

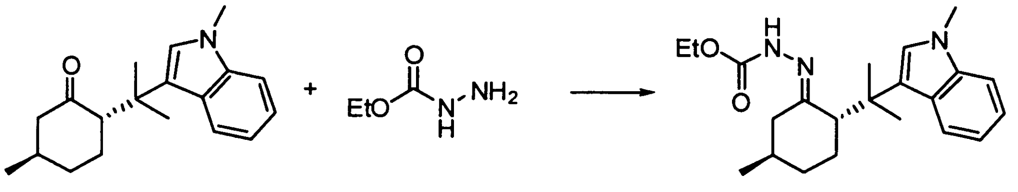


224 **58** **241**

Benzoic acid *N'*-*iso*-propyl hydrazide **23** (125 mg, 0.7 mmol, 10 mol%) was added to a solution of dichloromethane (5 mL) containing *iso*-propanol (0.9 mL) at ambient temperature. Hydrochloric acid in diethyl ether (2 M, 29 mg, 0.8 mmol, 440 μL) was added and stirring was continued for 10 minutes before addition of (*R*)-(+)-pulegone **224** (1.00 g, 6.6 mmol). After stirring for an additional 15 minutes, *N*-methylindole **58** (570 mg, 4.4 mmol) was added in one portion. The reaction was stirred at room temperature for 24 h, and then the solvent was removed by rotary evaporation to give an oil. The crude oil was purified by flash column chromatography in dichloromethane to provide the *title compound* **241** (747 mg, 60%) diastereomerically pure as a colourless solid; mp (dichloromethane) = 99-101 °C; IR (nujol mull) 3049, 2952, 2873, 1707, 1612, 1543, 1484, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.64 (d, J = 8 Hz, 1H, ArH), 7.20 (d, J = 8.13 Hz, 1H, ArH), 7.10 (dd, J = 8.0, 7.0 Hz, 1H, ArH), 6.97 (dd, J = 8.0, 7.0 Hz, 1H, ArH), 6.73 (s, 1H, ArH), 3.67 (s, 3H, NCH_3), 2.98 (ddd, J = 12.6, 4.7, 1.0 Hz, 1H, CH_2CCH), 2.19 (ddd, J = 12.4, 4.1, 1.9 Hz, 1H, CHHCCH), 1.98 (ddd, J = 12.5, 12.5, 1.5 Hz, 1H, CHHCCH), 1.82-1.59 (m, 3H,

CH_3CH, CHHCHH), 1.55 (s, 3H, CH_3CCH_3), 1.42 (s, 3H, CH_3CCH_3), 1.35 (dddd, *J* = 12.5, 12.5, 12.5, 3 Hz, 1H, CH_2CHH), 1.08 (dddd, *J* = 12.5, 12.5, 12.5, 3 Hz, 1H, $CHHCH_2$), 0.86 (d, *J* = 6.3 Hz, 3H, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 215.0 (s), 138,1 (s), 126.5 (d), 126.1 (s), 124.6 (s), 121.4 (d), 121.3 (d), 118.6 (d), 109.8 (d), 57.5 (d), 52.9 (t), 36.9 (s), 32.8 (q), 33.0 (d), 30.1 (t), 29.8 (q), 27.4 (t), 23.6 (q), 22.7 (q); LRMS (APCI, $[M+H]^+$) *m/z* 284 (100%), 173 (10), 172 (70); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{19}H_{26}NO$) requires *m/z* 284.2009, found *m/z* 284.2008; $[\alpha]_D^{20}$ = +56.5 (*c* = 0.57, $CHCl_3$).

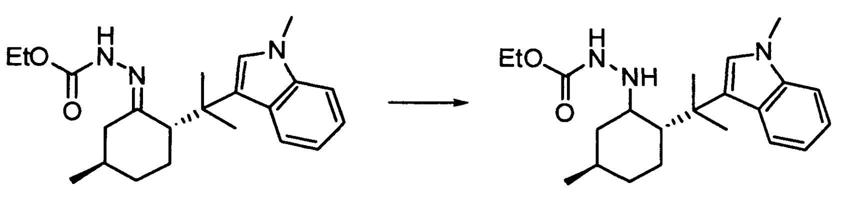
N'-(*E*)-((2*S*,5*R*)-5-Methyl-2-(2-(1-methyl-1*H*-indol-3-yl) propan-2-yl)cyclohexylidene) hydrazinecarboxylic acid ethyl ester 242



241 **235** **242**

Acetic acid (72 mg, 1.2 mmol, 70 μL) was added to a stirred solution of (2*S*,5*R*)-5-methyl-2-(2-(1-methyl-1*H*-indol-3-yl) propan-2-yl)cyclohexanone **241** (460 mg, 1.6 mmol) in dichloromethane (5 mL). Ethyl carbazate **235** (340 mg, 3.3 mmol) was added and stirring was continued at reflux for 8 days. Saturated sodium hydrogen carbonate solution (10 mL) was added and the aqueous solution was extracted with ethyl acetate (3x30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography, eluting with diethyl ether/light petroleum 3:7, afforded the *title compound* **242** (466 mg, 80%) as a colourless solid; mp (light petroleum/diethyl ether) = 70-72 °C; IR (nujol mull) 3243, 3448, 2952, 2870, 1696, 1612, 1483, 1379, 1333 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (d, *J* = 7.5 Hz, 1H, ArH), 7.69 (s, 1H, CONHN), 7.28 (d, *J* = 7.5 Hz, 1H, ArH), 7.18 (dd, *J* = 8.0, 7.5 Hz, 1H, ArH), 7.04 (dd, *J* = 8.0, 7.5 Hz, 1H, ArH), 6.86 (s, 1H, ArH), 4.27 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.73 (s, 3H, NCH_3), 2.29-2.85 (m, 1H, CH_2CCH), 2.42-2.35 (m, 1H, CHHCCH), 1.69 (s, 3H, CH_3CCH_3), 1.59 (s, 3H, CH_3CCH_3), 1.71-1.49 (m, 4H, CHHCCH, CH_3CH, CHHCHH), 1.34 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.45-1.30 (m, 1H, $CHHCH_2$), 0.91 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.01-0.81 (m, 1H, CH_2CHH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.6 (s), 155.6 (s), 137.0 (s), 126.7 (s), 126.0 (d), 123.9 (s), 121.3 (d), 120.7 (d), 118.0 (d), 109.2 (d), 57.8 (t), 51.9 (d), 40.1 (s), 37.9 (t), 34.6 (t), 32.5 (d), 29.0 (q), 27.6 (t), 27.4 (q), 22.5 (q), 22.3 (q), 14.5 (q); LRMS (APCI, $[M+H]^+$) *m/z* 172 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{22}H_{32}N_3O_2$) requires *m/z* 370.2489, found *m/z* 370.2485; $[\alpha]_D^{20}$ = +13.8 (*c* = 1, diethyl ether).

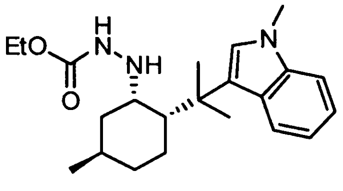
N'-(5-Methyl-2-(2-1-methyl-1*H*-indol-3-yl)propan-2-yl)cyclohexyl)hydrazinecarboxylic acid ethyl ester 236



242 **236**

To a stirred solution of *N'*-(*E*)-((2*S*,5*R*)-5-methyl-2-(2-(1-methyl-1*H*-indol-3-yl) propan-2-yl)cyclohexyli-dene) hydrazinecarboxylic acid ethyl ester **242** (250 mg, 0.67 mmol) in methanol (1 mL) was added a solution sodium cyanoborohydride in tetrahydrofuran (1 M, 42 mg, 0.67 mmol, 670 μL) at room temperature, followed by 2 M hydrochloric acid at a rate sufficient to maintain a pH of 2-3. After 10-15 minutes the pH changed less rapidly and the mixture was allowed to stir for an additional 45 minutes. The pH was lowered to 1 and the volatiles were removed under reduced pressure. The resulting residue was taken up in water (10 mL) and the pH adjusted to 8 with 20% potassium carbonate and extracted with diethyl ether (3x30 mL). The ethereal extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the *title compound* **243** and **244** as a mixture of diastereoisomers. Separation by flash column chromatography, eluting with diethyl ether:light petroleum 1:1, afforded diastereoisomer **243** (116 mg, 46%) and **244** (96 mg, 39%) as colourless solids;

(1*S*,2*R*,5*R*)-Diastereoisomer 243

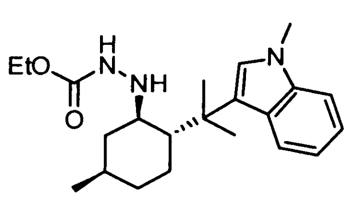


243

mp (diethyl ether/light petroleum) = 55-57 °C, IR (nujol mull) 3317, 3049, 2925, 1708, 1613, 1464, 1368 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (d, *J* = 8.0 Hz, 1H, ArH), 7.29 (d, *J* = 8.0 Hz, 1H, ArH), 7.20 (dd, *J* = 8.0, 7.0 Hz, 1H, ArH), 7.07 (dd, *J* = 8.0, 7.0 Hz, 1H, ArH), 6.97 (s, 1H, ArH), 5.86 (s, 1H, CONHNH), 4.11 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.74 (s, 3H, NCH_3), 3.37-3.23 (m, 1H, NHNHCH), 2.06-1.93 (m, 1H, CH_2CHCH), 1.90-1.70 (m, 3H, CHHCHCH, CH_3CH, CH_2CHH), 1.58 (s, 3H, CH_3CCH_3), 1.55 (s, 3H, CH_3CCH_3), 1.68-1.50 (m, 2H, CHHCHH), 1.23 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 0.83 (d, *J* = 6.0 Hz, 3H, CH_3CH), 0.93-0.81 (m, 2H, CHHCHH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.3 (s), 137.6 (s), 127.2 (s), 126.4 (d), 123.3 (d), 121.6 (d), 120.8 (s), 118.2 (d), 109.3 (d), 61.0 (t), 57.2 (d), 49.9 (d), 38.4 (s), 37.4 (t), 32.5 (q), 28.3 (q), 27.3 (q), 25.9 (d), 22.6 (t), 22.3 (t), 14.5 (q); LRMS (APCI, $[M+H]^+$) *m/z* 372 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{22}H_{34}N_3O_2$) requires *m/z* 372.2646, found *m/z* 372.2644; $[\alpha]_D^{20}$ = +2.0 (*c* = 1, diethyl ether).

Treatment with dry ethereal HCl (1 M, 5.0 mmol, 5.0 mL) gave the corresponding salt **243**.HCl as a colourless solid; mp (diethyl ether) = 88-90 °C.

(1*R*,2*R*,5*R*)-Diastereoisomer 244



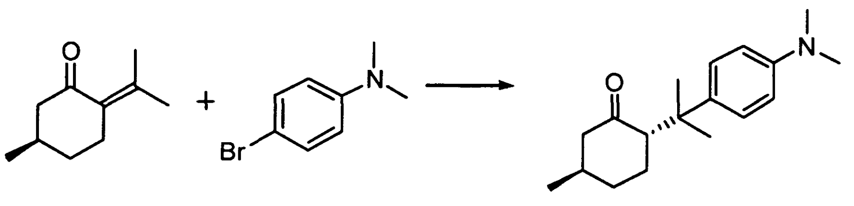
244

mp (diethyl ether/light petroleum) = 59-61 °C; IR (nujol mull) 3319, 3051, 2953, 2920, 1717, 1465, 1371, 1329 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (d, *J* = 8.0 Hz, 1H, ArH), 7.29

(d, J = 8.0 Hz, 1H, ArH), 7.21 (dd, J = 8.0, 7.5 Hz, 1H, ArH), 7.11 (dd, J = 8.0, 7.5 Hz, 1H, ArH), 6.94 (s, 1H, ArH), 5.56 (s, 1H, CONHNH), 4.1-3.99 (m, 2H, OCH_2CH_3), 3.73 (s, 3H, NCH_3), 3.01-2.91 (m, 1H,CH_2CHCH), 2.29-2.18 (m, 1H, CH_2CHCH), 2.07-1.97 (m, 1H, CH_2CHH), 1.92-1.83 (m, 1H, CHHCHCH), 1.79-1.70 (m, 1H, $CHHCH_2$), 1.59 (s, 3H, CH_3CHCH_3), 1.39 (s, 3H, CH_3CCH_3), 1.41-1.33 (m, 1H, CH_3CH), 1.30-1.11 (m, 4H, OCH_2CH_3, CH_2CHH), 0.89 (d, J = 6.5 Hz, 3H, $CHCH_3$), 1.04-0.92 (m, 1H, CHHCHCH), 0.85-0.71 (m, 1H, $CHHCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.0 (s), 137.9 (s), 126.4 (s), 125.5 (s), 124.3 (d), 121.5 (d), 121.1 (d), 118.5 (d), 109.5 (d), 61.0 (t), 60.7 (d), 46.2 (d), 39.8 (t), 36.4 (s), 35.1 (t), 32.6 (q), 30.9 (d), 30.0 (q), 26.5 (t), 22.3 (q), 22.1 (q), 14.4 (q); LRMS (APCI, $[M+H]^+$) m/z 372 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{22}H_{34}N_3O_2$) requires m/z 372.2646, found m/z 372.2643; $[\alpha]_D^{20}$ = +3.6 (c = 1, diethyl ether).

Treatment with dry ethereal HCl (1 M, 5.0 mmol, 5.0 mL) gave the corresponding salt **244**.HCl as a colourless solid; mp (diethyl ether) = 100-102 °C.

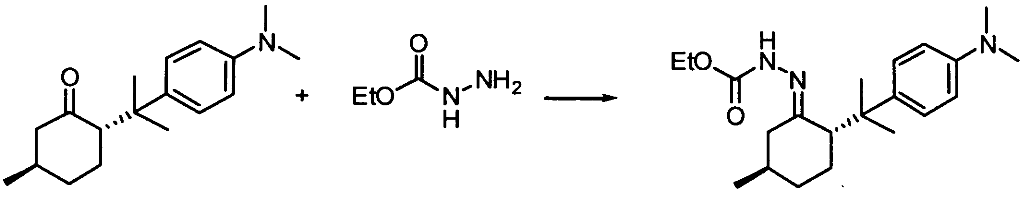
(2*S*,5*R*)-2-(2-(4-(Dimethylamino)phenyl)propan-2-yl)-5-methylcyclohexanone 247



224 **248** **247**

Magnesium turnings (2.20 g, 90.5 mmol) were added to tetrahydrofuran (10 mL) in a nitrogen-flushed flask fitted with a reflux condenser, equipped with a calcium chloride drying tube, and a dropping funnel. 4-Bromo-*N*,*N*-dimethylbenzenamine **248** (2.00 g, 10.0 mmol) was added in one portion, one crystal of iodine was added, and the solution was gently heated until self-refluxing began. 4-Bromo-*N*,*N*-dimethylbenzenamine **248** (18.00 g, 90.0 mmol) was added at such a rate that gentle reflux was maintained. Reflux was continued for 1 hour after the addition was complete, followed by cooling to ambient temperature. To the cooled solution was added tetrahydrofuran (30 mL), and this solution was then transferred *via* canula to a vigorously stirred suspension of copper (I) bromide (880 mg, 6.1 mmol) in tetrahydrofuran (14 mL) at -20 °C. Stirring was continued for 30 minutes before addition of (*R*)-(+)-pulegone **224** (7.98 g, 52.5 mmol, 8.7 mL) in diethyl ether (10 mL) over 2 hours at -20 °C. Stirring was continued for 20 hours at -20 °C and the reaction mixture was added to vigorously stirred ice-cold hydrochloric acid (2 M, 60 mL). The organic layer was collected and the aqueous layer was saturated with ammonium chloride and extracted with diethyl ether (3x20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (40 mL) and concentrated under reduced pressure. The crude product was dissolved in ethanol (120 mL) containing water (16 mL) and potassium hydroxide (14.00 g, 250.0 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 (4x20 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography, eluting with diethyl ether:light petroleum 1:9, afforded the *title compound* **247** (5.96 g, 42%) as a colourless solid; mp (diethyl ether /light petroleum) = 78-80 °C; IR (nujol mull) 2955, 2804, 1704, 1614, 1523, 1443 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.13 (d, *J* = 8.9 Hz, 2H, ArH-2, ArH-6), 6.62 (d, *J* = 8.9 Hz, 2H, ArH-3, ArH-5), 2.84 (s, 6H, CH_3NCH_3), 2.51 (ddd, *J* = 12.6, 4.2, 1.1 Hz, 1H, CH_2CCH), 2.17 (ddd, *J* = 12.2, 4.2, 2.2 Hz, 1H, CHHCCH), 1.95 (ddd, *J* = 12.2, 12.2, 1.1 Hz, 1H, CHHCCH); 1.87-1.60 (m, 3H, CH_2CHCH_2, CHHCHH), 1.36 (s, 3H, CH_3CCH_3), 1.31 (s, 3H, CH_3CCH_3), 1.45-1.05 (m, 2H, CHHCHH), 0.89 (d, *J* = 6.2 Hz, 3H, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 210.8 (s), 147.3 (s), 136.9 (s), 125.4 (d), 111.2 (d), 58.7 (d), 51.4 (t), 39.7 (q), 37.1 (s), 35.3 (d), 33.7 (t), 28.1 (t), 26.1 (q), 22.3 (q), 21.3 (q); LRMS (APCI, $[M+H]^+$) *m/z* 274 (100%), 162 (20); HRMS (ES, $[M+H]^+$), exact mass calcd for ($C_{18}H_{28}NO$) requires *m/z* 274.2165, found *m/z* 274.2168; $[\alpha]_D^{20}$ = -38.5 (*c* = 1, diethyl ether).

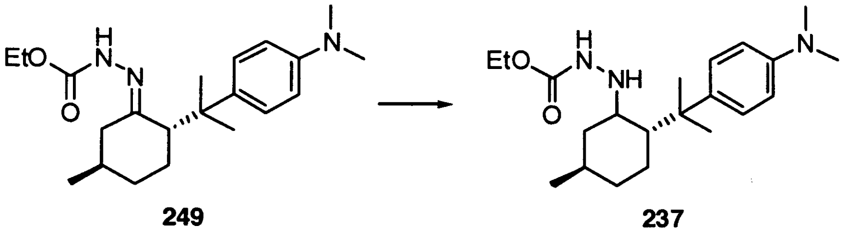
N'-(*E*)-((2*S*,5*R*)-2-(2-(4-(Dimethylamino)phenyl)propan-2-yl)-5-methylcyclohexylidene)hydrazinecarboxylic acid ethyl ester 249



247 **235** **249**

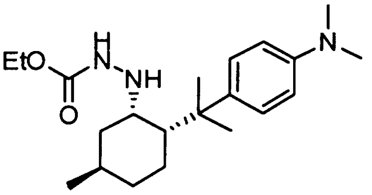
Acetic acid (300 μL, 5.3 mmol) was added to a stirred solution of (2*S*,5*R*)-2-(2-(4-(dimethylamino)phenyl)propan-2-yl)-5-methylcyclohexanone **247** (1.93 g, 7.1 mmol) in dichloromethane (20 mL). Ethyl carbazate **235** (1.48 g, 14.2 mmol) was added and stirring was continued at reflux for 6 days. Saturated sodium hydrogen carbonate solution (10 mL) was added and the aqueous solution was extracted with ethyl acetate (3x30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography, eluting with ethyl acetate:light petroleum 1:9, gave the *title compound* **249** (1.58 g, 62%) as a colourless solid; mp (ethyl acetate/light petroleum) = 130-132 °C; IR (nujol mull) 3244, 2950, 1697, 1613, 1520, 1444, 1335 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.62 (s, 1H, CONHN), 7.25 (d, J = 8.7 Hz, 1H, ArH-2, ArH-6), 6.69 (d, J = 8.7 Hz, 1H, ArH-3, ArH-5), 4.25 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.91 (s, 6H, CH_3NCH_3), 2.44 (dd, J = 11.1, 4.7 Hz, 1H, CH_2CCH), 2.38-2.27 (m, 1H, CHHCCH), 1.48 (s, 3 H, CH_3CCH_3), 1.44 (s, 3H, CH_3CCH_3), 1.74-1.18 (m, 5H, CHHCCH, CH_3CH, CHHCHH), 1.33 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.90 (d, J = 6.3 Hz, 3H, CH_3CH), 1.05-0.82 (m, 1H, $CHHCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.2 (s), 154.2 (s), 148.2 (s), 138.0 (s), 127.1 (d), 112.1 (d), 51.5 (t), 54.3 (d), 40.8 (s), 39.7 (q), 34.5 (t), 33.7 (t), 32.8 (d), 28.1 (t), 27.7 (q), 24.5 (q) , 22.3 (q), 14.6 (q); LRMS (APCI, $[M+H]^+$) m/z 360 (65%), 163 (10), 162 (100); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{21}H_{34}N_3O_2$) requires m/z 360.2646, found m/z 360.2647; $[\alpha]_D^{20}$ = +6.6 (c = 1, diethyl ether).

N'-(2-(2-(4-(Dimethylamino) phenyl)propan-2-yl)-5-methylcyclohexyl)hydrazinecarboxylic acid ethyl ester 237



To a stirred solution of *N'*-(*E*)-((2*S*,5*R*)-2-(2-(4-(dimethylamino)phenyl)propan-2-yl)-5-methylcyclohexylidene) hydrazinecarboxylic acid ethyl ester **249** (1.72 g, 4.8 mmol) in methanol (7 mL) was added a solution sodium cyanoborohydride in tetrahydrofuran (1 M, 297 mg, 4.8 mmol, 4.8 mL) at room temperature, followed by 2 M hydrochloric acid at a rate sufficient to maintain a pH of 2-3. After 10-15 minutes the pH changed less rapidly and the mixture was allowed to stir for an additional 45 minutes. The pH was lowered to 1 and the volatiles were removed under reduced pressure. The resulting residue was taken up in water (20 mL) and the pH adjusted to 8 with 20% potassium carbonate and extracted with diethyl ether (3x30 mL). The ethereal extracts were washed with brine, dried ($MgSO_4$) and the volatiles were removed under reduced pressure to give the *title compound* **250** and **251** as a mixture of diastereoisomers. Separation by flash column chromatography, eluting with diethyl ether:light petroleum 1:1, afforded diastereoisomer **250** (935 mg, 54%) and **251** (528 mg, 34%) as colourless solids;

(1*S*,2*R*,5*R*)-Diastereoisomer 250

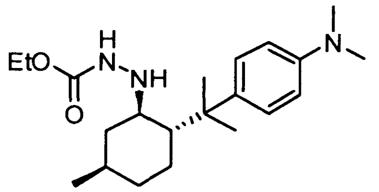


mp (diethyl ether/light petroleum) = 34-37 °C; IR (nujol mull) 3335, 2954, 1711, 1613, 1516, 1454, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.31 (d, *J* = 8.0 Hz, 2H, ArH-2, ArH-6), 6.71 (d, *J* = 8.0 Hz, 2H, ArH-3, ArH-5), 5.77 (s, 1H, CONHNH), 4.12 (q, *J* = 7.5 Hz, 2H,

OCH_2CH_3), 3.33-3.23 (m, 1H, NHNHCH), 2.93 (s, 6H, CH_3NCH_3), 1.88-1.79 (m, 1H, CHHCHCH), 1.79-1.68 (m, 2H, CH_2CHCH, CH_2CHH), 1.47 (s, 3H, CH_3CCH_3), 1.38 (s, 3H, CH_3CCH_3), 1.41-1.35 (m, 6H, OCH_2CH_3, CH_3CH, CHHCHH), 0.81 (d, *J* = 6.5 Hz, 3H, CH_3CH), 0.93-0.72 (m, 2H, CHHCHCH, $CHHCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 157.4 (s), 148.8 (s), 142.3 (s), 127.4 (d), 112.2 (d), 61.0 (t), 56.6 (d), 52.2 (d), 40.6 (q), 39.1 (s), 38.4 (t), 36.2 (t), 28.7 (q), 27.3 (q), 25.8 (d), 22.5 (t), 22.3 (q), 14.6 (q); LRMS (APCI, $[M+H]^+$) *m/z* 362 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{21}H_{36}N_3O_2$) requires *m/z* 362.2802, found *m/z* 362.2802; $[\alpha]_D^{20}$ = -18.6 (*c* = 1, diethyl ether).

Treatment with a solution of HCl, prepared dissolving acetyl chloride (202 mg, 2.59 mmol, 183 μL, 1 eq) in dry methanol (5 mL), gave the corresponding salt **250**.HCl as a colourless solid; mp (diethyl ether) = 128-130 °C.

(1*R*,2*R*,5*R*)-Diastereoisomer 251

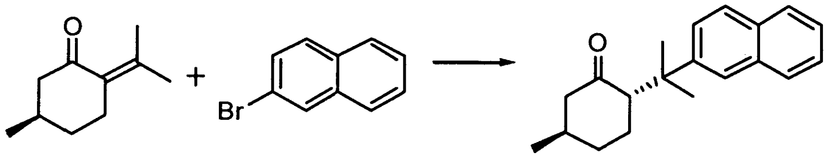


251

mp (diethyl ether/light petroleum) = 34-36 °C; IR (nujol mull) 3327, 3045, 2935, 1709, 1614, 1518, 1453, 1342, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.32 (d, *J* = 8.5 Hz, 2H, ArH-2, ArH-6), 6.74 (d, *J* = 8.5 Hz, 2H, ArH-3, ArH-5), 5.44 (m, 1H, CONHNH), 4.05 (q, *J* = 6.5 Hz, 2H, OCH_2CH_3), 2.92 (s, 6H, CH_3NCH_3), 2.89-2.77 (m, 1H, NHNHCH), 1.98 (dddd, *J* = 13.0, 3.0, 3.0, 3.0 Hz, 1H, CH_2CHH), 1.88 (dddd, *J* = 12.5, 2.5, 2.5, 2.5 Hz, 1H, $CHHCH_2$), 1.81-1.68 (m, 2H, CHHCHCH), 1.46 (s, 3H, CH_3CCH_3), 1.15 (s, 3H, CH_3CCH_3), 1.50-1.10 (m, 5H, OCH_2CH_3, CH_3CH, CH_2CHH), 0.87 (d, 3H, *J* = 6.5 Hz, CH_3CH), 0.97-0.84 (m, 2H, $CHHCH_2$, CHHCHCH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 157.1 (s), 140.1 (s), 147.7 (s), 129.0 (d), 113.1 (d), 60.9 (t), 49.3 (d), 49.0 (d), 40.7 (q), 40.0 (q), 38.5 (s), 35.2 (t), 32.0 (t), 31.1 (q), 30.3 (d), 26.8 (t), 22.3 (q), 20.4 (q), 14.5 (q); LRMS (APCI, $[M+H]^+$) *m/z* 362 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{21}H_{36}N_3O_2$) requires *m/z* 362.2802, found *m/z* 362.2806; $[\alpha]_D^{20}$ = +42.4 (*c* = 1, diethyl ether).

Treatment with a solution of HCl, prepared dissolving acetyl chloride (114 mg, 1.48 mmol, 103 µL, 1 eq) in dry methanol (5 mL), gave the corresponding salt **251**.HCl as a colourless solid; mp (diethyl ether) = 112-114 °C.

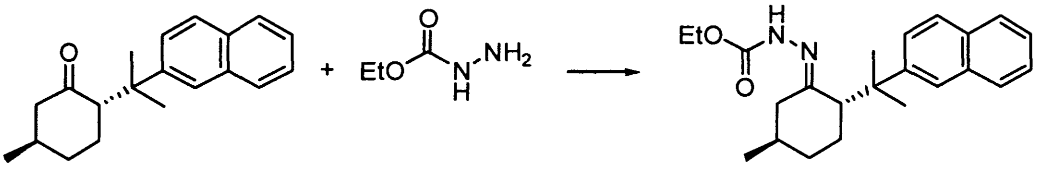
(2*S*,5*R*)-5-methyl-2-(2-(naphthalen-2-yl) propan-2-yl)cyclohexanone 253[193]



224 **252** **253**

Magnesium turnings (2.20 g, 90.5 mmol) were added to tetrahydrofuran (10 mL) in a nitrogen-flushed flask fitted with a reflux condenser, carrying a calcium chloride drying tube, and a dropping funnel. 2-Bromonapthalene **252** (2.10 g, 10.0 mmol) was added in one portion, one crystal of iodine was added, and the solution was gently heated until self-refluxing began. 2-Bromonapthalene **252** (18.60 g, 90.0 mmol) was added at such a rate that gentle reflux was maintained. Reflux was continued for 1 hour after the addition was complete, followed by cooling to ambient temperature. To the cooled solution was added tetrahydrofuran (30 mL), and this solution was then transferred *via* canula to a vigorously stirred suspension of copper (I) bromide (880 mg, 6.1 mmol) in tetrahydrofuran (14 mL) at -20 °C. Stirring was continued for 30 minutes before addition of (*R*)-(+)-pulegone **224** (7.98 g, 52.5 mmol, 8.7 mL) in diethyl ether (10 mL) over 2 hours at -20 °C. Stirring was continued for 20 hours at -20 °C and the reaction mixture was added to a vigorously stirred ice-cold hydrochloric acid (2 M, 60 mL). The organic layer was collected and the aqueous layer was saturated with ammonium chloride and extracted with diethyl ether (3x20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (40 mL) and concentrated under reduced pressure. The crude product was dissolved in ethanol (120 mL) containing water (16 mL) and potassium hydroxide (14.00 g, 250.0 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 (4x20 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography, using light petroleum then diethyl ether:light petroleum 1:9 as the eluents, gave the *title compound* **253** (8.67 g, 59%) as a colourless oil; IR (thin film) 3055, 2952, 2868, 1710, 1631, 1598, 1504, 1454, 1371, 1319 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.84-7.77 (m, 3H, ArH), 7.75 (s, 1H, ArH), 7.52 (d, J = 8.5 Hz, 1H, ArH), 7.49-7.41 (m, 2H, ArH), 2.80 (dd, J = 13.0, 4.5 Hz, 1H, CH_2CCH), 2.28 (dd, J = 12.5, 4.0 Hz, 1H, CHHCCH), 2.6 (dd, J = 12.5, 12.5 Hz, 1H, CHHCCH), 1.93-1.70 (m, 3H, CHCHHCHH), 1.57 (s, 3H, CH_3CCH_3), 1.54 (s, 3H, CH_3CCH_3), 1.55-1.43 (m, 1H, CH_2CHH), 1.31-1.21 (m, 1H, $CHHCH_2$), 0.98 (d, J = 6.0 Hz, 3H, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 211.3 (s), 147.2 (s), 133.1 (s), 131.5 (s), 127.9 (d), 127.5 (d), 127.2 (d), 125.7 (d), 125.2 (d), 124.4 (d), 124.2 (d), 59.1 (d), 52.3 (t), 39.2 (s), 36.2 (d), 34.6 (t), 29.0 (q), 26.7 (q), 23.4 (t), 22.2 (q); LRMS (APCI, $[M+H]^+$) m/z 170 (15%), 169 (100); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{20}H_{25}O$) requires m/z 281.1900, found m/z 281.1901; $[\alpha]_D^{20}$ = -23.9 (c = 1, diethyl ether);

N'-(E)-((2S,5R)-5-methyl-2-(2-(naphthalen-2-yl)propan-2-yl)cyclohexylidene)hydrazinecarboxylic acid ethyl ester 254

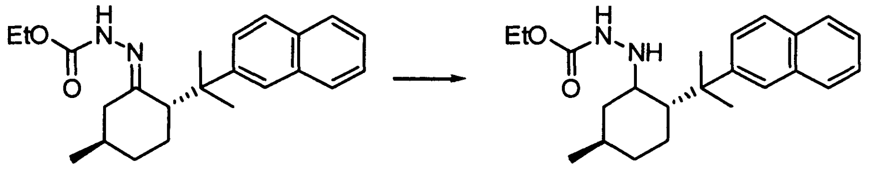


253 **235** **254**

Acetic acid (210 mg, 3.5 mmol, 200 μL) was added to a stirred solution of (2*S*,5*R*)-5-methyl-2-(2-(naphthalen-2-yl) propan-2-yl)cyclohexanone **253** (1.30 g, 4.7 mmol) in dichloromethane (14 mL). Ethyl carbazate **235** (970 mg, 9.3 mmol) was added and stirring was continued at reflux for 6 days. Saturated sodium hydrogen carbonate solution (10 mL) was added and the aqueous solution was extracted with ethyl acetate (3x30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography, eluting with ethyl acetate:light petroleum 1:1, gave the *title compound* **254** (1.07 g, 62%) as a pale yellow solid; mp (diethyl ether/light petroleum) = 124-126 °C; IR (nujol mull) 3242, 3055, 2952, 1694, 1598, 1504, 1454, 1380, 1335 cm^{-1}; ^1H NMR (400

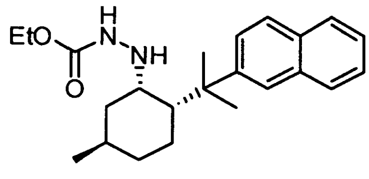
MHz, $CDCl_3$) δ_H 7.92 (s, 1H, CONHN), 7.84-7.76 (m, 4H, ArH), 7.59 (d, J = 8.5 Hz, 1H, ArH), 7.48-7.38 (m, 2H, ArH), 4.26 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 2.66 (dd, 1H, J = 11.0, 3.0 Hz, CH_2CCH), 2.51-2.38 (m, 1H, CHHCCH), 1.65 (s, 3H, CH_3CCH_3), 1.51 (s, 3H, CH_3CCH_3), 1.72-1.38 (m, 4H, CHHCCH, CH_3CH, CHHCHH), 1.34 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.46-1.29 (m, 1H, $CHHCH_2$), 0.93 (s, 3 H, CH_3CH), 1.05-0.92 (m, 1H, CH_2CHH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.1 (s), 154.5 (s), 147.6 (s), 133.0 (s), 131.4 (s), 127.9 (d), 127.2 (d), 127.0 (d), 125.5 (d), 125.3 (d), 125.1 (d), 124.6 (d), 61.6 (t), 53.9 (d), 40.6 (s), 34.8 (t), 34.0 (t), 33.2 (d), 28.4 (t), 26.7 (q), 24.7 (q), 22.2 (q), 14.5 (q); LRMS (APCI, $[M+H]^+$) m/z 367 (100%), 162 (30); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{23}H_{31}N_2O_2$) requires m/z 367.2380, found m/z 367.2378; $[\alpha]_D^{20}$ = -21.0 (c = 1, diethyl ether).

N'-(5-methyl-2-(2-(naphthalen-2-yl)propan-2-yl)hydrazinecarboxylic acid ethyl ester 238


254 **238**

To a stirred solution of *N'*-(*E*)-((2*S*,5*R*)-5-methyl-2-(2-(naphthalen-2-yl)propan-2-yl)cyclohexylidene)hydrazinecarboxylic acid ethyl ester **254** (1.08 g, 2.9 mmol) in of methanol (5 mL) was added a solution of sodium cyanoborohydride in tetrahydrofuran (1 M, 180 mg, 2.9 mmol, 2.9 mL) and hydrochloric acid 2 M at a rate sufficient to maintain a pH 4/3 at room temperature. After 10-15 minutes the pH changed less rapidly and the mixture was allowed to stir an additional 1 hour. The pH was lowered to 1 and the volatiles removed under reduced pressure. The residue was taken up in water (20 mL) and the pH adjusted to 8 with 20% potassium carbonate and extracted with diethyl ether (3x30 mL). The ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* **255** and **256** as a mixture of diastereoisomers. Separation by flash column chromatography, using diethyl ether:light petroleum 1:1 as the eluent, provided diastereoisomer **255** (533 mg, 50%) and diastereoisomer **256** (417 mg, 39%) as colourless solids;

(1*S*,2*R*,5*R*)-Diastereoisomer 255

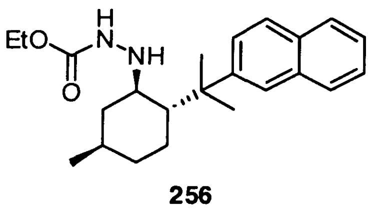


255

mp (diethyl ether/light petroleum) = 38-40 °C; IR (nujol mull) 3331, 3056, 2924. 1713, 1631, 1598, 1454, 1373, 1331 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.88 (s, 1H, ArH), 7.86-7.77 (m, 3H, ArH), 7.61-7.56 (m, 1H, ArH), 7.49-7.41 (m, 2H, ArH), 5.81 (s, 1H, CONHNH), 4.16-4.06 (m, 3H, OCH_2CH_3), 3.29-3.20 (m, 1H, NHNHCH), 1.90-1.83 (m, 1H, CHHCHCH), 1.81-1.66 (m, 3H, CH_2CHH, CH3CH, CH_2CHCH), 1.59 (s, 3H, CH_3CCH_3), 1.55 (s, 3H, CH_3CCH_3), 1.63-1.51 (m, 1H, $CHHCH_2$), 1.24-1.17 (m, 4H, OCH_2CH_3, CH_2CHH), 0.83 (d, *J* = 6.4 Hz, 3H, CH_3CH), 0.92-0.80 (m, 2H, CHHCHCH, $CHHCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.4 (s), 146.8 (s), 133.1 (s), 131.6 (s), 128.0 (d), 127.2 (d), 127.2 (d), 125.7 (d), 125.4 (d), 125.3 (d), 124.9 (d), 61.1 (t), 57.0 (d), 51.7 (d), 40.3 (s), 38.4 (t), 36.0 (t), 29.6 (q), 27.7 (q), 27.2 (d), 25.8 (t), 22.3 (q), 14.4 (q); LRMS (APCI, $[M+H]^+$) *m/z* 369 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{23}H_{33}N_2O_2$) requires *m/z* 369.2537, found *m/z* 369.2536; $[\alpha]_D^{20}$ = -6.2 (*c* = 1, diethyl ether).

Treatment with dry ethereal HCl (1 M, 5.0 mmol, 5.0 mL) gave the corresponding salt **255**.HCl as a colourless solid; mp (diethyl ether) = 84-86 °C.

(1*R*,2*R*,5*R*)-Diastereoisomer 256

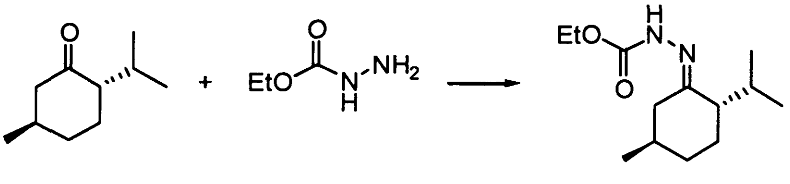


256

mp (diethyl ether/light petroleum) = 48-51 °C; IR (nujol mull) 3333, 3054, 2954, 1714, 1630, 1598, 1505, 1455, 1371 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.9 (s, 1H, ArH), 7.87-7.81 (m, 2H, ArH), 7.79 (d, *J* = 7.7 Hz, 1H, ArH), 7.61 (d, *J* = 8.8 Hz, 1H, ArH), 7.48-7.41 (m, 2H, ArH), 5.61 (s, 1H, CONHNH), 4.09-3.97 (m, 2H, OCH_2CH_3), 3.00-2.90 (m, 1H, NHNHCH), 2.03-1.95 (m, 2H, CHHCHCH), 1.94-1.88 (m, 1H, CH_2CHH), 1.79-1.73 (m, 1H, $CHHCH_2$), 1.66 (s, 3H, CH_3CCH_3), 1.41-1.33 (m, 1H, CH_3CH), 1.26 (s, 3H, CH_3CCH_3), 1.30-1.20 (m, 1H, CHHCHCH), 1.18-1.12 (m, 3H, OCH_2CH_3), 0.89 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 1.03-0.80 (m, 2H, CHHCHH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 156.9 (s), 149.5 (s), 133.5 (s), 131.7 (s), 128.2 (d), 128.1 (d), 127.4 (d), 125.9 (d), 125.5 (d), 124.7 (d), 123.1 (d), 61.3 (d), 61.1 (t), 48.9 (d), 39.8 (s), 39.7 (t), 35.1 (t), 31.4 (d), 31.0 (q), 26.8 (t), 22.2 (q), 21.0 (q), 14.4 (q); LRMS (APCI, $[M+H]^+$) *m/z* 369 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{23}H_{33}N_2O_2$) requires *m/z* 369.2537, found *m/z* 369.2532; $[\alpha]_D^{20}$ = +21.6 (*c* = 1, diethyl ether).

Treatment with dry ethereal HCl (1 M, 5.0 mmol, 5.0 mL) gave the corresponding salt **256**.HCl as a colourless solid; mp (diethyl ether) = 104-106 °C.

N'-((2*S*,5*R*)-2-*iso*-propyl-5-methylcyclohexylidene) hydrazinecarboxylic acid ethyl ester 258

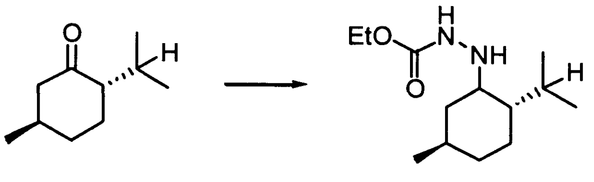


257 **235** **258**

To a stirred solution of (*L*)-menthone **257** (1.85 g, 12.0 mmol, 12.2 mL) in dichloromethane (10 mL) was added acetic acid (540 mg, 9.0 mmol, 0.5 mL). Ethyl-carbazate **235** (1.25 g, 12.0 mmol) was added and the mixture was allowed to react for 48 hours at room temperature. Saturated sodium hydrogen carbonate solution (10 mL) was added and the aqueous solution was extracted with ethyl acetate (3x30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography, eluting with ethyl acetate/light petroleum 3:7, afforded the *title compound* **258** (2.73 g, 95%) as a colourless oil; IR (thin film) 3252, 2953, 2888, 1697, 1524, 1454, 1381, 1335 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.77 (s, 1H, CONHN), 4.15 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 2.40-2.31 (m, 1H, CHHCNCH), 2.06-2.18 (m, 1H, CH_2CHCH_2), 1.96-1.63 (m, 4H, CHHCHCHH, CHHCNCH, CH_3CHCH_3), 1.43-1.38 (m, 1H, CH_2CHH), 1.23 (t, *J* =

7.0 Hz, 3H, OCH_2CH_3), 1.19-1.07 (m, 1H, $CHHCH_2$), 0.90 (d, J = 6.4 Hz, 3H, CH_3CHCH_3), 0.85 (d, J = 6.6 Hz, 3H, CH_3CHCH_3), 0.83 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 158.0 (s), 154.4 (s), 61.4 (t), 50.5 (d), 32.8 (t), 31.4 (t), 27.0 (d), 26.9 (d), 26.3 (t), 22.5 (q), 21.4 (q), 19.2 (q), 14.6 (q); LRMS (APCI, $[M+H]^+$) *m/z* 241 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{13}H_{25}N_2O_2$) requires *m/z* 241.1911, found *m/z* 241.1909; $[\alpha]_D^{20}$ = -18.0 (c = 1, diethyl ether).

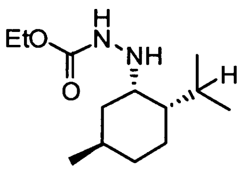
N'-(2-*iso*-propyl-5-methylcyclohexyl)hydrazinecarboxylic acid ethyl ester 239



258 **239**

To a stirred solution of *N'*-((2*S*,5*R*)-2-*iso*-propyl-5-methylcyclohexylidene) hydrazinecarboxylic acid ethyl ester **258** (197 mg, 0.8 mmol) in of methanol (1.5 mL) was added a solution of sodium cyanoborohydride in tetrahydrofuran (1 M, 50 mg, 0.8 mmol, 0.8 mL) and hydrochloric acid 2 M at a rate sufficient to maintain a pH 4-3 at room temperature. After 10-15 minutes the pH changed less rapidly and the mixture was allowed to stir an additional 45 minutes. The pH was lowered to 1 and the volatiles removed under reduced pressure. The residue was taken up in water (10 mL) and the pH adjusted to 8 with 20% potassium carbonate and extracted with diethyl ether (3x30 mL). The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **259** and **260** as a mixture of diastereoisomers. Separation by flash column chromatography, eluting with diethyl ether:light petroleum 1:1, gave diastereoisomer **259** (143 mg, 72%) and diastereoisomer **260** (45 mg, 23%) as colourless oils;

(1*S*,2*S*,5*R*)-Diastereoisomer 259

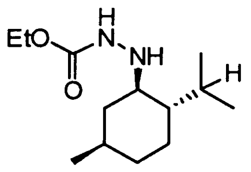


259

IR (thin film) 3333, 2915, 2868, 1712, 1456, 1370 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 6.27 (s, 1H, CONHNH), 4.07 (q, *J* = 7.0 Hz, 2H, OCH$_2$CH$_3$), 3.31-3.25 (m, 1H, NHNHCH), 1.89-1.80 (m, 1H, CHHCHCH), 1.76-1.60 (m, 2H, CH$_3$CH, CH$_2$CHH), 1.59-1.51 (m, 1H, CHHCH$_2$), 1.43-1.34 (m, 1H, CH$_2$CHCH$_3$), 1.18 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH$_3$), 1.30-1.15 (m, 1H, CH$_2$CH), 1.05-0.97 (m, 3H, CH CH$_3$), 0.85 (d, *J* = 6.5 Hz, 3H, CH$_3$CCH$_3$), 0.77 (d, *J* = 6.5 Hz, 3H, CH$_3$CCH$_3$), 0.94-0.72 (m, 3H, CHHCHCHH, CHCHCH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 157.6 (s), 61.2 (t), 55.0 (d), 47.3 (d), 40.0 (s), 37.5 (t), 35.5 (t), 28.9 (d), 25.5 (d), 24.7 (t), 22.5 (q), 21.8 (q), 20.5 (q), 14.6 (q); LRMS (APCI, [M+H]$^+$) *m/z* 243 (100%); HRMS (ES, [M+H]$^+$) exact mass calcd for (C$_{13}$H$_{27}$N$_2$O$_2$) requires *m/z* 243.2067, found *m/z* 243.2069; $[\alpha]_D^{20}$ = +45 (*c* = 1, methanol).

Treatment with dry ethereal HCl (1 M, 5.0 mmol, 5.0 mL) gave the corresponding salt **259**.HCl as a colourless solid; mp (diethyl ether) = 127-129 °C.

(1*R*,2*S*,5*R*)-Diastereoisomer 260

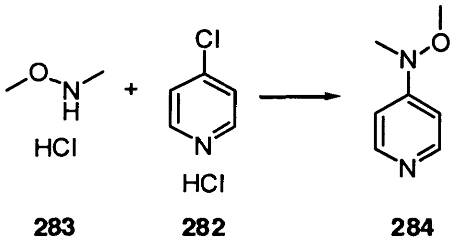


260

IR (thin film) 3112, 2958, 1738, 1537, 1462 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 9.04 (s, 1H, CONHNH), 4.29 (q, *J* = 7.0 Hz, 2H, OCH$_2$CH$_3$), 3.33 (ddd, *J* = 11.5, 11.0, 3.5 Hz, 1H, NHNHCH), 2.37-2.21 (m, 2H, CH$_3$CHCH$_3$, CHHCHCH), 1.84-1.64 (m, 3H, CHHCHH, CH$_2$CHCH), 1.32 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH$_3$), 1.26-1.22 (m, 2H, CH$_3$CH, CHHCHCH), 0.99 (d, J = 6.5 Hz, 3H, CH_3CHCH_3), 0.96 (d, J = 6.0 Hz, 3H, CH_3CHCH_3), 0.91 (d, J = 7.0 Hz, 3H, CH_3CH), 1.12-0.86 (m, 2H, CHHCHH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.6 (s), 61.2 (t), 55.0 (d), 47.3 (d), 40.2 (t), 35.5 (t), 28.9 (d), 25.5 (d), 24.7 (t), 22.5 (q), 21.9 (q), 20.5 (q), 14.6 (q); LRMS (APCI, $[M+H]^+$) *m/z* 243 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{13}H_{27}N_2O_2$) requires *m/z* 243.2067, found *m/z* 243.2062; $[\alpha]_D^{20}$ = -58.5 (c = 1, methanol).

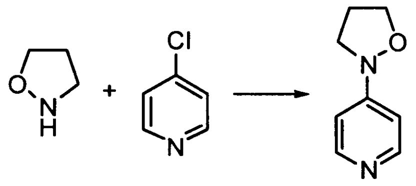
Treatment with dry ethereal HCl (1 M, 5.0 mmol, 5.0 mL) gave the corresponding salt **260**.HCl as a colourless solid; mp (diethyl ether) = 140-142 °C.

N-Methoxy-*N*-methylpyridin-4-amine 284



In a 5 mL reaction vial, 4-chloropyridine hydrochloride **282** (400 mg, 2.6 mmol), *N*-methoxymethyl-amine hydrochloride **283** (300 mg, 3.1 mmol) and potassium carbonate (1.28 g, 9.3 mmol) and ethanol (2 mL) were mixed and capped. The mixture was irradiated at 100 °C (100 watt, 150 psi) for 1 hour. Water (5 mL) was added and the aqueous layer was extracted with diethyl ether (3x30 mL), dried (Na_2CO_3) and concentrated *in vacuo*. Purification by trituration with light petroleum gave the *title compound* **284** (206 mg, 57%) as a colourless solid; mp (light petroleum) = 56-58 °C; IR (nujol mull) 3032, 2909, 2821, 1643, 1600, 1547, 1423 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.34 (d, J = 5.0 Hz, 2H, PyH-2, PyH-6), 6.76 (d, J = 5.0 Hz, 2H, PyH-3, PyH-5), 3.72 (s, 3H, OCH_3), 3.12 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.0 (s), 150.0 (d), 108.3 (d), 60.7 (q), 40.1 (q); LRMS (APCI; $[M+H]^+$) *m/z* 139 (100%), 123 (8); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_7H_{11}N_2O$) requires *m/z* 139.0866, found *m/z* 139.0867;

4-(Isoxazolidin-2-yl)pyridine 286

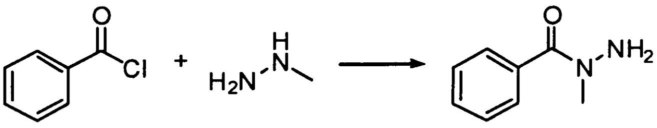


HCl HCl

285 **282** **286**

4-Chloropyridine hydrochloride **282** (154 mg, 1.0 mmol) was added to a stirred solution of isoxazolidine hydrochloride **285** (109 mg, 1.0 mmol) in butanol (3 mL). Potassium carbonate (552 mg, 4.0 mmol) was added and the mixture was heated at 110-120 °C for 24 hours. Water (5 mL) was added and the aqueous solution was extracted with dichloromethane (3x20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude reaction was purified by flash column chromatography, eluting with dichloromethane:methanol:triethyl amine 10:1:0.1 and a crystallization from dichloromethane/ether to afford the *title compound* **286** (95 mg, 64%) as a colourless solid; mp (dichloromethane/diethyl ether) = 174-175 °C; IR (nujol mull) 3407, 3070, 2890, 1649, 1567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.26 (d, J = 5.6 Hz, 2H, PyH-2, PyH-6), 6.76 (d, J = 5.6 Hz, 2H, PyH-3, PyH-5), 3.88 (t, J = 7.2 Hz, 2H, OCH_2), 3.46 (t, J = 7.3 Hz, 2H, NCH_2), 2.21 (tt, J = 7.2, 7.3 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9 (s), 149.8 (d), 108.7 (d), 66.4 (t), 51.1 (t), 28.3 (t); LRMS (APCI, $[M+H]^+$) m/z 151 (100%), 121 (10); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_8H_{11}N_2O$) requires m/z 151.0866, found m/z 151.0866.

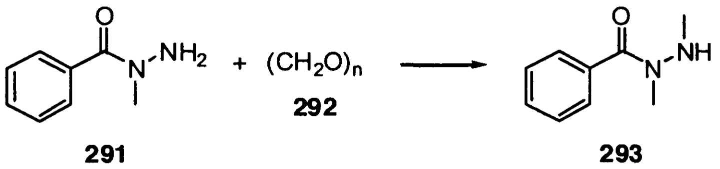
N-Methylbenzohydrazide 291[165]



289 **290** **291**

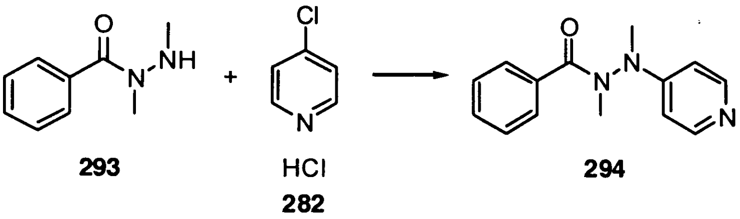
To a solution of methylhydrazine **290** (3.46 g, 75.3 mmol, 4 mL) in dichloromethane (50 mL) at 0 °C was added to a solution of benzoyl chloride **289** (1.05 g, 7.5 mmol, 0.9 mL) in dichloromethane (50 mL) slowly via syringe pump under an atmosphere of nitrogen. After stirring at 0 °C for 1 hour the reaction was warmed to room temperature and stirred for a further 2 hours. The reaction mixture was then poured onto saturated sodium carbonate solution (30 mL) and extracted with dichloromethane (3x30 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **291** (994 mg, 88%) as a colourless oil with no further purification required. ^1H NMR was consistent with previously reported literature values;[194] ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.55-7.45 (m, 5H, ArH), 4.65 (br s, 2H, NH_2), 3.18 (s, 3H, CH_3).

N,N'-dimethylbenzohydrazide 293[165]



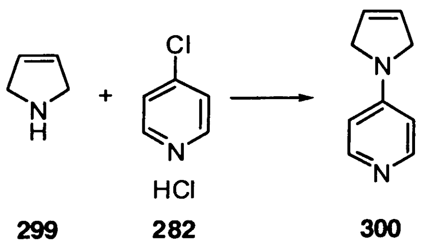
To a stirred solution of *N*-Methylbenzohydrazide **291** (625 mg, 4.2 mmol) in toluene (17 mL) was added paraformaldehyde **292** (125 mg, 4.2 mmol). The reaction was heated at reflux under Dean-Stark conditions for 18 hours. The toluene was removed under reduced pressure and replaced with methanol (17 mL). Sodium cyanoborohydride (285 mg, 4.6 mmol) and acetic acid (276 mg, 4.6 mmol, 263 μL) were added and the reaction mixture was stirred at room temperature for an additional 18 hours. Saturated sodium carbonate solution (10 mL) was added and the aqueous solution was extracted with dichloromethane (3x20 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* **293** (472 mg, 69%) as a colourless oil with no further purification required. Spectroscopic data was consistent with the literature;[195] ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.68-7.26 (m, 5H, ArH), 5.82 (br s, 2H, NH), 3.13 (s, 3H, NCH_3NH), 2.67 (s, 3H, $NHCH_3$); LRMS (ES, $[M+H]^+$) *m/z* 165 (100%), 147 (10), 118 (15); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_9H_{13}N_2O$) requires *m/z* 165,1022, found *m/z* 165,1020.

N,N'-Dimethyl-*N'*-(pyridin-4-yl)benzohydrazide 294



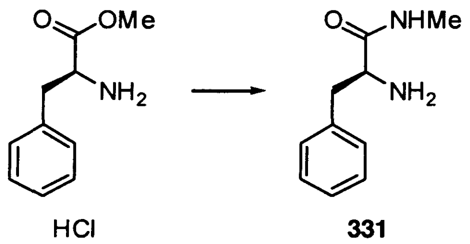
In a 10 mL reaction vial, 4-chloropyridine hydrochloride **282** (300 mg, 20 mmol), *N,N'*-dimethylbenzohydrazide **293** (328 mg, 1.0 mmol), potassium carbonate (690 mg, 5.0 mmol) and ethanol (2 mL) were mixed and capped. The mixture was irradiated at 145 °C (300 watt, 200 psi) for 2 hours. Water (5 mL) was added and the aqueous layer was extracted with dichloromethane (3x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, gave the *title compound* **294** (87 mg, 36%) as a pale yellow solid; mp (ethyl acetate/methanol) = 137-139 °C; IR (nujol mull) 1644, 1590, 1499, 1419 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.38 (d, J = 4.9 Hz, 2H, PyH-2, PyH-6), 7.29-7.15 (m, 5H, ArH), 6.59 (d, J = 4.9 Hz, 2H, PyH-3, PyH-5), 3.98 (s, 3H, $CONCH_3$), 3.19 (s, 3H, $PyNCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 173.2 (s), 152.6 (s) 150.6 (d), 134.4 (s), 130.6 (d), 128.0 (d), 126.7 (d), 107.4 (d), 37.6 (q), 30.6 (q); LRMS (ES, $[M+H]^+$) *m/z* 242 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{14}H_{16}N_3O$) requires *m/z* 242.1288, found *m/z* 242.1288.

4-(2*H*-Pyrrol-1(5*H*)-yl)pyridine 300



4-Chloropyridine hydrochloride **282** (1.09 g, 7.25 mmol) was added to a stirred solution of 2,5-dihydro-1*H*-pyrrole **299** (500 mg, 7.25 mmol) in butanol (10 mL). Potassium carbonate (2.00 g, 15.5 mmol) was added and the mixture was heated at 60-70 °C for 4 days. Water (10 mL) was added and the aqueous solution was extracted with dichloromethane (3x20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude reaction was purified by flash column chromatography, eluting with diethyl ether:methanol 9:1 to afford the *title compound* **300** (285 mg, 26%) as a colourless solid; mp (diethyl ether/methanol) = 98-100 °C; IR (nujol mull) 1669, 1594, 1548, 1488, 1319 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.17 (d, J = 5.1 Hz, 2H, PyH-2, PyH-6), 6.30 (d, J = 5.1 Hz, 2H, PyH-3, PyH-5), 5.92-5.88 (m, 2H, CH=CH), 4.10-4.04 (m, 4H, CH_2NCH_2); ^{13}C NMR (100 MHz, MeOD) δ_C 154.8 (s), 145.1 (d), 126.7 (d), 108.4 (d), 55.4 (t); LRMS (ES, $[M+H]^+$) *m/z* 147 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_9H_{11}N_2$) requires *m/z* 147.0917, found *m/z* 147.0916.

(*S*)-2-Amino-*N*-methyl-3-phenylpropanamide 331[11]

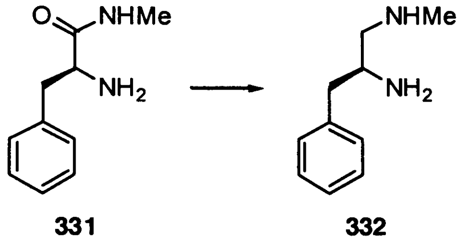


330

331

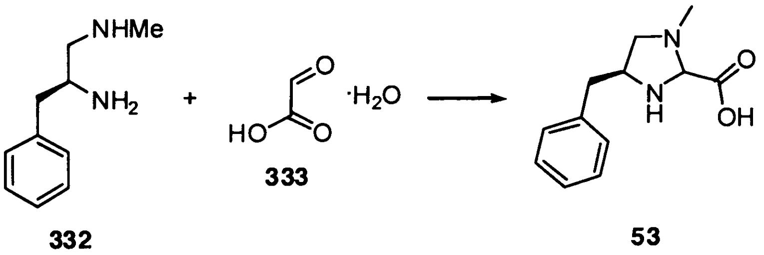
To a solution of *N*-methylamine in methanol (8 M, 3.78 g, 121.9 mmol, 5.0 mL) was added (*S*)-phenylalanine methyl ester hydrochloride **330** (2.00 g, 9.3 mmol). The resulting solution was stirred at room temperature for 20 hours until the amino ester was consumed by TLC. The resulting solution was concentrated to provide the *title compound* **331** (1.32 g, 80% yield) as a white solid requiring no further purification. Spectroscopic data was consistent with the literature;[11] ^{1}H NMR (400 MHz, d$_6$-DMSO) δ_H 7.35-7.05 (m, 5H, ArH), 3.54 (dd, J = 9.5, 4.0 Hz, 1H, CHHAr), 3.22 (dd, J = 13.7, 4.0 Hz, 1H, CHHAr), 2.75 (d, J = 5.0, 3H, NCH_3), 2.60 (dd, J = 9.5, 13.7 Hz, 1H, $CHCH_2$), 1.20 (br s, 2H, $CHNH_2$).

(*S*)-*N*¹-Methyl-3-phenylpropane-1,2-diamine 332[30]



Lithium aluminium hydride (270 mg, 7.1 mmol) was added to a solution of (*S*)-2-amino-*N*-methyl-3-phenylpropanamide **331** (800 mg, 4.7 mmol) in tetrahydrofuran (30 mL). The resulting mixture was refluxed for 24 hours until the starting material consumed by TLC. A minimal amount of water (0.5 mL) was added and the aqueous solution was filtered and extracted with dichloromethane (3x20 mL). The volatiles were dried ($MgSO_4$) and removed under reduced pressure. Purification by flash column chromatography, eluting with methanol, provided the *title compound* **332** (594 mg, 77%) as a colourless oil. ^{1}H NMR, and ^{13}C NMR data were consistent with previously reported literature values;[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.30 (t, *J* = 7.3 Hz, 2H, ArH), 7.25-7.18 (m, 5H, ArH), 3.15-3.08 (m, 1H, $CHNH_2$), 2.79 (dd, *J* = 13.4, 4.8 Hz, 1H, ArCHH), 2.67 (dd, *J* = 11.7, 3.9 Hz, 1H, $CHHNCH_3$), 2.54-2.45 (m, 2H, ArCHH, $CHHNCH_3$), 2.44 (s, 3H, $NHCH_3$), 1.56-1.40 (m, 3H, $CHNH_2$, $NHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 139.1 (s), 129.2 (d), 128.5 (d), 126.3 (d), 58.2 (t), 52.2 (d), 42.8 (t), 36.5 (q).

(4*S*)-4-Benzyl-1-methylimidazolidine-2-carboxylic acid 53[30]



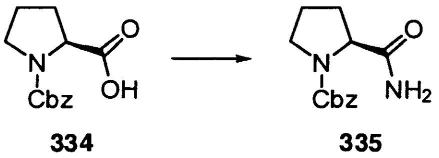
(*S*)-*N*¹-methyl-3-phenylpropane-1,2-diamine **332** (410 mg, 2.5 mmol) was dissolved in dichloromethane (10 mL) containing glyoxylic acid monohydrate **333** (231 mg, 2.5 mmol).

The resulting solution was stirred at room temperature for 20 hours. The volatiles were removed under reduced pressure to afford the *title compound* **53** (495 mg, 90%) as a slightly hydroscopic colourless solid in a 2:1 mixture of diastereomers with no further purification required. Spectroscopic data was in accordance to literature precedent;[30]

Major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33-7.20 (m, 5H, ArH), 4.21 (s, 1H, CHCO), 3.77-3.60 (m, 1H, $CHCH_2$), 3.48-3.41 (m, 1H, ArCHH), 3.18 (dd, J = 5.7, 13.0 Hz, 1H, ArCHH), 2.91-2.50 (m, 2H, CH_2NCH_3), 2.90 (s, 3H, CH_3);

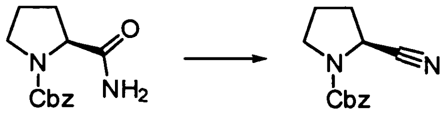
Minor diastereomer; ^{1}H-NMR (400 MHz, CDCl3) δ_H 7.33-7.20 (m, 5H, ArH), 4.13 (s, 1H, CHCO), 4.07-3.95 (m, 1H, $CHCH_2$), 3.71-3.64 (m, 1H, ArCHH), 3.05 (dd, J = 6.4, 13.3 Hz, 1H, ArCHH), 2.90-2.53 (m, 2H, CH_2NCH_3), 2.85 (s, 3H, CH_3).

(*S*)-Benzyl 2-carbamoylpyrrolidine-1-carboxylate 335[183]



(*S*)-Carbobenzyloxy proline **334** (1.00 g, 4.0 mmol), *tert*-butoxycarbonyl anhydride (1.15 g, 5.25 mmol) and ammonium bicarbonate (390 mg, 4.95 mmol) were placed in nitrogen flushed flask and acetonitrile (15 mL) was added. The reaction flask was sealed and pyridine (194 mg, 2.45 mmol, 197 μL) was added slowly. The reaction was stirred at room temperature for 16 hours. Water (15 mL) was added and the resulting aqueous solution was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* **335** (977 mg, 98%) as a colourless solid with no further purification required. Spectroscopic data was in accordance to literature precedent;[181] ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.40-7.28 (m, 5H, ArH), 6.71 (br s, 1H, CONHH), 5.66 (br s, 1H, CONHH), 5.18 (d, J = 12.0 Hz, 1H, OCHH), 5.13 (d, J = 12.0 Hz, 1H, OCHH), 4.42-4.25 (m, 1H, NCH), 3.61-3.35 (m, 2H, NCH_2), 2.43-1.83 (m, 4H, CH_2CH_2CH).

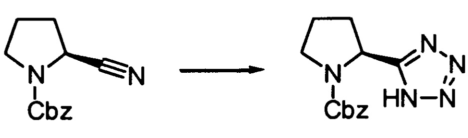
(*S*)-Benzyl 2-cyanopyrrolidine-1-carboxylate 336[183]



335 **336**

(*S*)-Benzyl 2-carbamoylpyrrolidine-1-carboxylate **335** (2.00 g, 8.1 mmol) was dissolved in *N*,*N*-dimethylformamide (30 mL) at 0 °C. Cyanuric chloride **338** (964 mg, 5.24 mmol) was added in one portion and the reaction was slowly allowed to warm to ambient temperature and stirring was continued for 20 hours. The reaction was quenched with water (40 mL) and the solution was excreted with ethyl acetate (3x30 mL). The organic layer was washed with water (5x30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The solid was dissolved in ethyl acetate:light petroleum 1:2 (120 mL) and run through a short plug of silica, followed by an equal amount of solvent with the same composition, to give the *title compound* **336** (1.17 g, 63%) as pale yellow oil with no further purification required; ^1H NMR was consistent with previously reported literature values;[181] ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.45-7.27 (m, 5H, ArH), 5.24-5.12 (m, 2H, OCH_2), 4.66-452 (m, 1H, CHCN), 3.66-3.34 (m, 2H, NCH_2), 2.34-1.99 (m, 4H, CH_2CH_2CH).

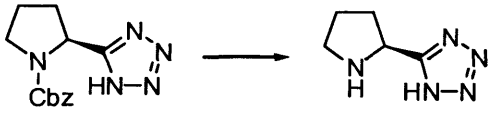
(*S*)-Benzyl 2-(1*H*-tetrazol-5-yl)pyrrolidine-1-carboxylate 337[181]



336 **337**

(*S*)-Benzyl 2-cyanopyrrolidine-1-carboxylate **336** (230 mg, 1.0 mmol), sodium azide (72 mg, 1.1 mmol) and ammonium chloride (58 mg, 1.1 mmol) were placed in nitrogen flushed flask and dry *N*,*N* dimethylformamide (1 mL) was added. The mixture was heated at 90-95 °C for 6 hours under an inert atmosphere. The mixture was poured onto ice and the pH was adjusted to 2 with diluted hydrochloric acid. The resulting aqueous solution was extracted with chloroform (3x10 mL). The organic layer was washed with water (3x10 mL), saturated with sodium chloride and dried (Na_2SO_4). The volatiles were evaporated *in vacuo* to afford crude product. Purification by flash column chromatography with ethyl acetate:light petroleum 1:1, afforded the *title compound* **337** (173 mg, 63%) as a colourless oil; ^1H NMR was consistent with previously reported literature values;[184] ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers with a ratio of 2:1 measured at 293 K) δ_H 7.33-7.15 (m, 4H, ArH), 6.99 (m, 1H, ArH), 5.38 (dd, J = 7.9, 3.2 Hz, 1H, CH_2CH, minor rot.), 5.20-4.13 (m, 2H, CH_2CH, major rot., OCHH, major rot.), 5.06 (d, J = 12.3 Hz, 1H, OCHH, major rot.), 5.02 (d, J = 12.5 Hz, 1H, OCHH, minor rot.), 4.98 (d, J = 12.6 Hz, 1H, OCHH, minor rot.), 3.65-3.47 (m, 2H, NCH_2), 2.57-1.87 (m, 4H, CH_2CH_2CH).

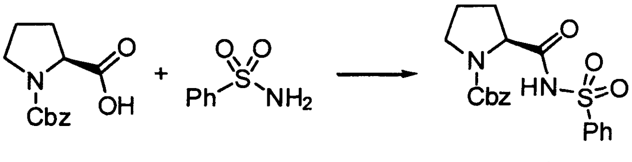
5-((*S*)-Pyrrolidin-2-yl)-1*H*-tetrazole 124[183]



337 **124**

(*S*)-Benzyl 2-(1*H*-tetrazol-5-yl)pyrrolidine-1-carboxylate **337** (440 mg, 1.61 mmol) and 10% Pd/C (184 mg, 176 μmol) in an mixture of acetic acid:H_2O 9:1 (24 mL) were stirred under an atmosphere of hydrogen at room temperature for 4 hours. The mixture was filtered through Celite® and the filtrate was reduced under reduced pressure. The resulting solid was recrystallised with a mixture of toluene and methanol to give the *title compound* **124** (192 mg, 86%) as a colourless solid. Spectroscopic data was in accordance to literature precedent;[183] ^1H NMR (400 MHz, d_6-DMSO) δ_H 4.75 (t, J = 7.6 Hz, 1H, CH), 3.33-3.14 (m, 2H, $NHCH_2$), 3.37-2-25 (m, 1H, CHCHH), 2.20-1.19 (m, 3H, $CHCHHCH_2$).

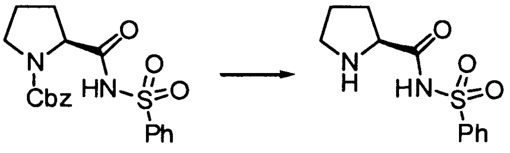
(2*S*)-2-Benzenesulfonylaminocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester 340[184]



334 **336** **340**

To a stirred solution of (*S*)-carbobenzyloxy proline **334** (5.00 g, 20.1 mmol) in dichloromethane (150 mL) were added benzenesulfonamide **336** (3.16 g, 20.1 mmol), DMAP **144** (400 mg, 3.28 mol), EDCI **341** (3.85 g, 20.1 mmol). The resulting mixture was stirred at room temperature for 2 days before being partitioned in ethyl acetate (250 mL) and 1 M aqueous hydrochloric acid (100 mL). The organic layer was washed with half-saturated brine, dried ($MgSO_4$) and the volatiles were removed under reduced pressure. The residue was treated with dichloromethane and the resulting white solid was filtered. The filtrate was reduced *in vacuo* and purified by flash column chromatography, eluting with dichloromethane:ethyl acetate 7:3, to give the *title compound* **340** (4.76 g, 61%) as a colourless solid. Spectroscopic data was in accordance to literature precedent;[184] ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers with a ratio of 3:2 measured at 293 K) δ_H 8.02 (d, *J* = 7.0, 2H, Ar**H**, major rot.), 7.92 (d, *J* = 7.0 Hz, 2H, Ar**H**, minor rot.), 7.65-7.21 (m, 8H, Ar**H**), 5.26-5.10 (m, 2H, $OC\mathbf{H}_2$), 4.44-4.36 (m, 1H, NC**H**, minor rot.), 4.32-4.16 (m, 1H, NC**H**, major rot.), 3.66-3.27 (m, 2H, $NC\mathbf{H}_2$), 2.39-1.75 (m, 4H, $CHC\mathbf{H}_2C\mathbf{H}_2$).

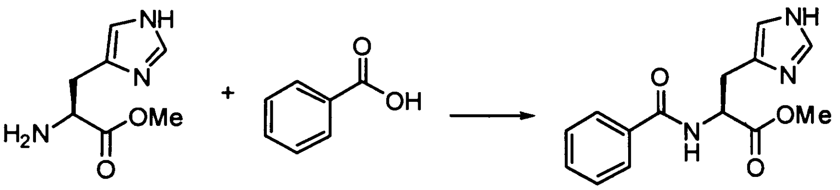
(2*S*)-*N*-(2-Pyrrolidine-2-carbonyl)-benzenesulfonamide 328[184]



340 **328**

To a solution of (2*S*)-2-benzenesulfonylaminocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester **340** (5.85 g, 15.0 mmol) in methanol (300 mL) was added 10% Pd/C (900 mg, 1.5 mmol). The mixture was stirred at room temperature for 20 hours under an atmosphere of hydrogen. The reaction was filtered through Celite® and silica gel (1 cm) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography, eluting with dichloromethane:methanol 8:2, afforded the *title compound* **328** (3.43 g, 90%) as a colourless solid. ^{1}H NMR was consistent with previously reported literature values;[184] ^{1}H NMR (500 MHz, d_6-DMSO) δ_H 8.50 (br s, 2H, SN**H**), 7.77 (dd, *J* = 10.3, 2.6 Hz, 2H, Ar**H**), 7.47-7.32 (m, 3H, Ar**H**), 3.81 (dd, *J* = 8.3, 6.7 Hz, 1H, NHC**H**), 3.21-3.07 (m, 1H, NHCH**H**), 3.15-2.91 (m, 1H, NHC**H**H), 2.10-1.67 (m, 4H, $CHC\mathbf{H}_2C\mathbf{H}_2$).

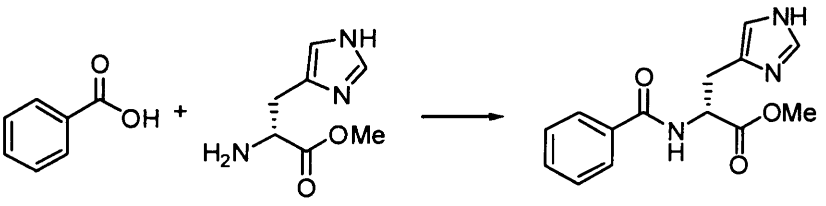
(*S*)-Methyl 2-(benzamido)-3-(1*H*-imidazol-4-yl)propanoate 345



2xHCl **348** **346** **345**

The *title compound* **345** was prepared according to the general procedure **G**, from benzoic acid **346** (503 mg, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate then methanol, afforded the *title compound* **345** (924 mg, 82%) as a pale yellow solid; mp (methanol) = 155-157 °C; IR (nujol mull) 3277, 3178, 1757, 1735, 1644, 1576, 1537, 1462 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.37 (d, J = 7.1 Hz, 1H, NHCH), 7.80 (d, J = 7.3 Hz, 2H, ArH), 7.48 (s, 1H, ImH-2), 7.43 (t, J = 7.5 Hz, 1H, ArH), 7.35 (dd, J = 7.5, 7.3 Hz, 2H, ArH), 6.75 (s, 1H, ImH-5), 4.88 (dd, J = 8.9, 6.0 Hz, 1H, NHCH), 3.60 (s, 3H, CH_3), 3.17 (dd, J = 15.0, 6.0 Hz, 1H, CHCHH), 3.13 (dd, J = 15.0, 8.9 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 171.8 (s), 167.5 (s), 135.1 (d), 134.2 (s), 133.3 (s), 131.5 (d), 128.3 (d), 126.9 (d), 115.3 (d), 53.1 (d), 52.0 (q), 28.7 (t); LRMS (APCI, $[M+H]^+$) *m/z* 274 (100%), 214 (30); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{14}H_{16}N_3O_3$) requires *m/z* 274.1186, found *m/z* 274.1186; $[\alpha]_D^{20}$ = -24.4 (*c* = 1, methanol).

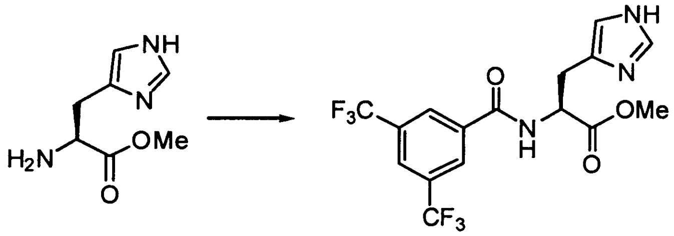
(*R*)-Methyl 2-(benzamido)-3-(1*H*-imidazol-4-yl)propanoate 351



346 2xHCl **350** **351**

The *title compound* **351** was prepared according to the general procedure **G**, from benzoic acid **346** (352 mg, 2.89 mmol) and (*S*)-histidine methyl ester dihydrochloride **350** (700 mg, 2.89 mmol). Purification by flash column chromatography, eluting with ethyl acetate then methanol, afforded the *title compound* **351** (315 mg, 40%) as a pale yellow solid; mp (methanol) = 148-150 °C; IR (nujol mull) 3275, 1757, 1729, 1642, 1568, 1534, 1461, 1377 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ_H 7.84-7.80 (m, 2H, ArH), 7.64 (s, 1H, ImH-2), 7.55 (t, J = 7.6 Hz, 1H, ArH), 7.49-7.44 (m, 2H, ArH), 6.93 (s, 1H, ImH-5), 4.90 (dd, J = 8.8, 5.3 Hz, 1H, NHCH), 3.75 (s, 3H, CH_3), 3.27 (dd, J = 14.6, 5.3 Hz, 1H, CHCHH), 3.17 (dd, J = 14.6, 8.8 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, MeOD) δ_C 173.5 (s), 170.1 (s), 136.4 (d), 135.0 (s), 134.9 (s), 132.9 (d), 129.3 (d), 128.4 (d), 117.9 (d), 54.6 (d), 52.7 (q), 29.7 (t); LRMS (ES, $[M+H]^+$) *m/z* 274 (100%), 214 (90), 135 (15); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{14}H_{16}N_3O_3$) requires *m/z* 274.1186, found *m/z* 274.1185; $[\alpha]_D^{20}$ = +36.0 (*c* = 1, methanol).

(*S*)-Methyl 2-(3,5-bis(trifluoromethyl)benzamido)-3-(1*H*-imidazol-4-yl)propanoate 354



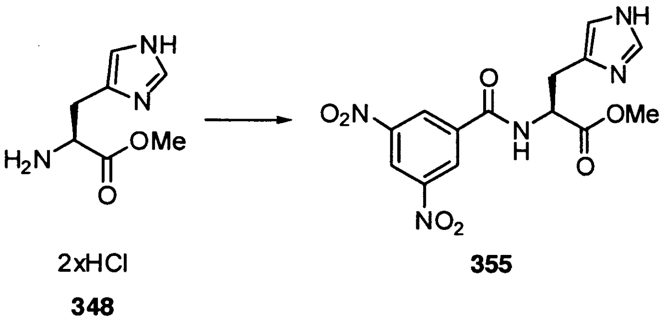
2xHCl

348

354

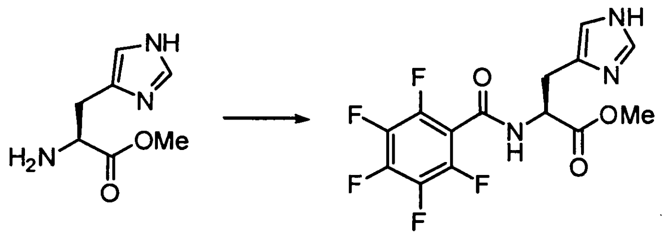
The *title compound* **354** was prepared according to the general procedure **G**, from 3,5-bis(trifluoromethyl)benzoic acid (1.07 g, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate:light petroleum 1:1 then ethyl acetate, afforded the *title compound* **354** (770 mg, 46%) as a colourless solid; mp (ethyl acetate) = 146-148 °C; IR (nujol mull) 3159, 1735, 1652, 1610, 1565 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ_H 8.43 (s, 2H, ArH), 8.19 (s, 1H, ArH), 7.63 (s, 1H, ImH-2), 6.94 (s, 1H, ImH-5), 5.00-4.89 (m, 1H, NHCH), 3.77 (s, 3H, CH_3), 3.29 (dd, J = 14.8, 5.1 Hz, 1H, CHCHH), 3.18 (dd, J = 14.6, 8.9 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, MeOD) δ_C 173.5 (s), 166.7 (s), 137.4 (s), 136.5 (s), 136.4 (d), 133.0 (q, $^{2}J_{C\text{-}F}$ = 33 Hz), 129.1 (d), 126.1 (d), 124.5 (q, ${}^{1}J_{C\text{-}F}$ = 272 Hz), 115.9 (d), 55.0 (d), 52.9 (q), 29.8 (t); LRMS (ES, [M+H]$^+$) m/z 410 (100%), 182 (10); HRMS (ES, [M+H]$^+$) exact mass calcd for ($C_{16}H_{14}N_3O_3F_6$) requires m/z 410.0934, found m/z 410.0935; $[\alpha]_D^{20}$ = -22.6 (*c* = 1, methanol);

(*S*)-Methyl 2-(3,5-dinitrobenzamido)-3-(1*H*-imidazol-4-yl)propanoate 355



The *title compound* **355** was prepared according to the general procedure **G**, from 3,5-dinitrobenzoic acid (876 mg, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, afforded the *title compound* **355** (350 mg, 23%) as an orange solid; mp (ethyl acetate/methanol) = 89-91 °C; IR (nujol mull) 3183, 3088, 1742, 1661, 1539, 1344 cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ_H 9.11 (t, ${}^4J$ = 1.9 Hz, 1H, ArH), 9.11 (d, ${}^4J$ = 1.9 Hz, 2H, ArH), 7.61 (s, 1H, ImH-2), 6.92 (s, 1H, ImH-5), 4.91 (dd, *J* = 9.1, 5.2 Hz, 1H, NHCH), 3.74 (s, 3H, CH$_3$), 3.26 (dd, *J* = 14.7, 5.2 Hz, 1H, CHCHH), 3.16 (dd, *J* = 14.7, 9.1 Hz, 1H, CHCHH); ^{13}C NMR (100 MHz, MeOD) δ_C 172.5 (s), 166.0 (s), 150.6 (s), 138.8 (s), 136.1 (d), 135.9 (s), 129.3 (d), 122.4 (d), 118.2 (d), 55.6 (d), 53.7 (q), 30.7 (t); LRMS (APCI, [M+H]$^+$) m/z 364 (100%); HRMS (ES, [M+H]$^+$) exact mass calcd for ($C_{14}H_{14}N_5O_7$) requires m/z 364.0888, found m/z 364.0890; $[\alpha]_D^{20}$ = -26.8 (*c* = 1, methanol).

(*S*)-Methyl 2-(2,3,4,5,6-pentafluorobenzamido)-3-(1*H*-imidazol-4-yl)propanoate 356

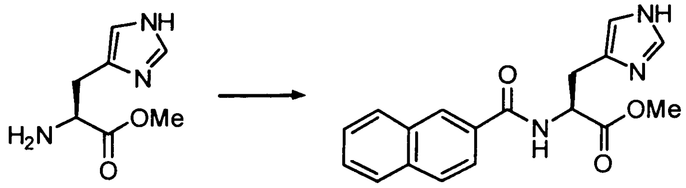


2xHCl
348

356

The *title compound* **356** was prepared according to the general procedure **G**, from 2,3,4,5,6-pentafluorobenzoic acid (876 mg, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate, afforded the *title compound* **356** (330 mg, 22%) as a pale orange solid; mp (ethyl acetate) = 181-183 °C; IR (nujol mull) 3268, 3178, 1747, 1665, 1571, 1499 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ_H 7.63 (s, 1H, ImH-2), 6.93 (s, 1H, ImH-5), 4.93 (dd, J = 9.2, 5.1 Hz, 1H, NHCH), 3.79 (s, 3H, CH$_3$), 3.25 (dd, J = 14.9, 5.1 Hz, 1H, CHCHH), 3.08 (dd, J = 14.9, 9.2 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, MeOD) δ_C 173.8 (s), 160.0 (s), 145.2 (d, $^{1}J_{C\text{-}F}$ = 246.1 Hz), 143.4 (d, $^{1}J_{C\text{-}F}$ = 253.0 Hz), 138.8 (d, $^{1}J_{C\text{-}F}$ = 252.7 Hz), 136.1 (d), 134.5 (s), 117.9 (d), 113.1 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz), 55.1 (d), 53.0 (q), 30.7 (t); LRMS (ES, [M+H]$^+$): *m/z* 364 (100%), 146 (15); HRMS (ES, [M+H]$^+$): exact mass calcd for ($C_{14}H_{11}N_3O_3F_5$) requires *m/z* 364.0715, found *m/z* 364.0716; $[\alpha]_D^{20}$ = -13.0 (*c* = 1, methanol).

(*S*)-Methyl 2-(2-naphthamido)-3-(1*H*-imidazol-4-yl)propanoate 357

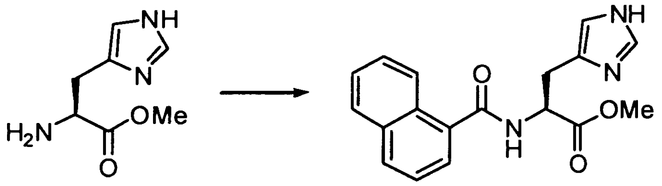


2xHCl
348

357

The *title compound* **357** was prepared according to the general procedure **G**, from 2-naphthoic acid (710 mg, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, afforded the *title compound* **357** (980 mg, 73%) as a colourless solid; mp (ethyl acetate/methanol) = 193-195 °C; IR (nujol mull) 3201, 1748, 1667, 1530, 1208 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ_H 11.91 (br s, 1H, NHCHN), 9.10 (d, *J* = 9.1 Hz, 1H, NHCH), 8.47 (s, 1H, ArH), 8.07-7.89 (m, 4H, ArH), 7.65-7.56 (m, 3H, ImH-2, ArH), 6.91 (br s, 1H, ImH-5), 4.76 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 1H, NHCH), 3.64 (s, 3H, CH_3), 3.11 (dd, *J* = 7.1, 7.1 Hz, 2H, $CHCH_2$); ^{13}C NMR (100 MHz, d_6-DMSO) δ_C 172.5 (s), 166.1 (s), 135.4 (d), 134.7 (s), 133.6 (s), 132.5 (s), 131.4 (s), 129.3 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.3 (d), 124.5 (d), 113.9 (d), 53.6 (d), 52.4 (q), 29.6 (t); LRMS (ES, $[M+H]^+$) *m/z* 324 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{18}H_{18}N_3O_3$) requires *m/z* 324.1343, found *m/z* 324.1344; $[\alpha]_D^{20}$ = -34.2 (*c* = 1, methanol).

(*S*)-Methyl 2-(1-naphthamido)-3-(1*H*-imidazol-4-yl)propanoate 358

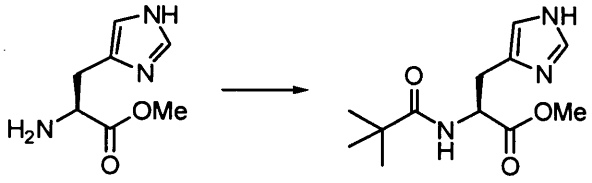


2xHCl **358**

348

The *title compound* **358** was prepared according to the general procedure **G**, from 1-naphthoic acid (710 mg, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, afforded the *title compound* **358** (842 mg, 63%) as a colourless solid; mp (ethyl acetate/methanol) = 117-119 °C; IR (nujol mull) 3208, 1741, 1637, 1520 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ_H 8.04-7.90 (m, 3H, ArH), 7.69 (s, 1H, ImH-2), 7.58-7.49 (m, 5H, ArH), 6.96 (s, 1H, ImH-5), 5.05 (dd, *J* = 9.7, 5.0 Hz, 1H, NHCH), 3.83 (s, 3H, CH_3), 3.31 (dd, *J* = 14.8, 5.0 Hz, 1H, CHCHH), 3.13 (dd, *J* = 14.8, 9.7 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, MeOD) δ_C 174.0 (s), 172.9 (s), 137.4 (d), 135.8 (s), 135.6 (s), 135.4 (s), 132.1 (d), 131.9 (s), 129.8 (d), 128.4 (d), 128.0 (d), 127.0 (d), 126.9 (d), 124.4 (d), 118.9 (d), 55.6 (d), 53.5 (q), 30.5 (t); LRMS (ES, $[M+H]^+$) m/z 324 (100%), 288 (10); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{14}H_{15}N_3O_3$) requires m/z 324.1343, found m/z 324.1343; $[\alpha]_D^{20}$ = -22.4 (*c* = 1, methanol).

(*S*)-Methyl 3-(1*H*-imidazol-4-yl)-2-(pivalamido)propanoate 359

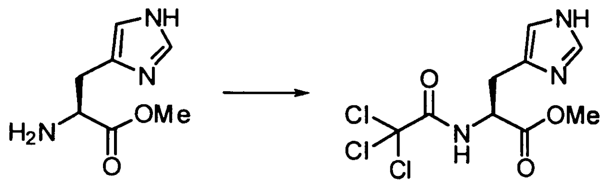


2xHCl
348

359

The *title compound* **359** was prepared according to the general procedure **G**, from pivalic acid (421 mg, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, afforded the *title compound* **359** (425 mg, 41%) as a colourless solid; mp (ethyl acetate/methanol) = 142-144 °C; IR (nujol mull) 3311, 3253, 1735, 1665, 1570 1443 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ_H 7.63 (s, 1H, ImH-2), 6.88 (s, 1H, ImH-5), 4.65 (dd, *J* = 8.7, 5.3 Hz, 1H, NHCH), 3.72 (s, 3H, OCH_3), 3.16 (dd, *J* = 14.9, 5.3 Hz, 1H, CHCHH), 3.08 (dd, *J* = 14.9, 8.7 Hz, 1H, CHCHH), 1.16 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, MeOD) δ_C 181.5 (s), 173.6 (s), 136.4 (d), 135.0 (s), 117.9 (d), 54.8(s), 54.1 (d), 52.7 (q), 29.7 (t), 27.6 (q); LRMS (ES, $[M+H]^+$) m/z 254 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{12}H_{20}N_3O_3$) requires m/z 254.1499, found m/z 254.1500; $[\alpha]_D^{20}$ = -24.6 (*c* = 1, methanol).

(*S*)-Methyl 2-(2,2,2-trichloroacetamido)-3-(1*H*-imidazol-4-yl)propanoate 360



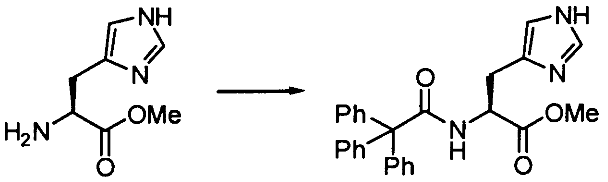
2xHCl

348

360

The *title compound* **360** was prepared according to the general procedure **G**, from 2,2,2-trichloroacetic acid (675 mg, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate, afforded the *title compound* **360** (297 mg, 23%) as a colourless solid; mp (ethyl acetate) = 108-110 °C; IR (nujol mull) 3322, 3263, 1725, 1689, 1625, 1561 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ_H 7.59 (s, 1H, ImH-2), 6.88 (s, 1H, ImH-5), 4.70 (dd, J = 9.1, 4.9 Hz, 1H, NHCH), 3.72 (s, 3H, CH_3), 3.23 (dd, J = 14.8, 4.9 Hz, 1H, CHCH**H**), 3.14 (dd, J = 14.8, 9.1 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, MeOD) δ_C 172.5 (s), 163.7 (s), 136.4 (d), 134.6 (s), 117.5 (d), 93.4 (s), 55.6 (d), 53.0 (q), 29.2 (t); LRMS (ES, $[M+H]^+$) *m/z* 319 (5), 318 (30), 316 (95), 314 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_9H_{11}N_3O_3Cl_3$) requires *m/z* 313.9861, found *m/z* 313.9861; $[\alpha]_D^{20}$ = -25.2 (*c* = 1, methanol).

(*S*)-Methyl 2-(2,2,2-triphenylacetamido)-3-(1*H*-imidazol-4-yl)propanoate 361



2xHCl

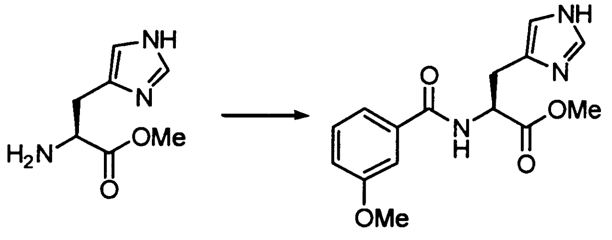
348

361

The *title compound* **361** was prepared according to the general procedure **G**, from 2,2,2-triphenylacetic acid (1.19 g, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, afforded the *title compound* **361** (842 mg, 47%) as a colourless solid;

mp (ethyl acetate/methanol) = 70-72 °C; IR (nujol mull) 3405, 3144, 1742, 1660, 1490, 1447 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ_H 7.96 (s, 1H, ImH-2), 7.33-7.15 (m, 15H, ArH), 6.69 (s, 1H, ImH-5), 4.84 (dd, J = 9.3, 4.7 Hz, 1H, NHCH), 3.77 (s, 3H, CH$_3$), 3.19 (dd, J = 15.0, 4.7 Hz, 1H, CHCHH), 3.06 (dd, J = 15.0, 9.3 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, MeOD) δ_C 175.5 (s), 172.8 (s), 144.5 (s), 136.0 (d), 131.6 (d), 128.8 (d), 128.0 (d), 117.9 (d), 62.4 (s), 53.9 (d), 52.9 (q), 28.7 (t); LRMS (ES, [M+H]$^+$) m/z 440 (100%); HRMS (ES, [M+H]$^+$) exact mass calcd for ($C_{27}H_{26}N_3O_3$) requires m/z 440.1969, found m/z 440.1975; $[\alpha]_D^{20}$ = -16.6 (c = 1, methanol).

(*S*)-Methyl 2-(3-methoxybenzamido)-3-(1*H*-imidazol-4-yl)propanoate 362



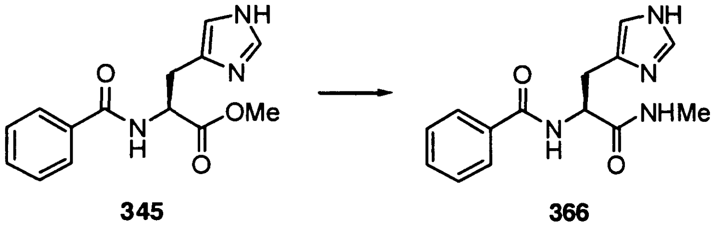
2xHCl

348

362

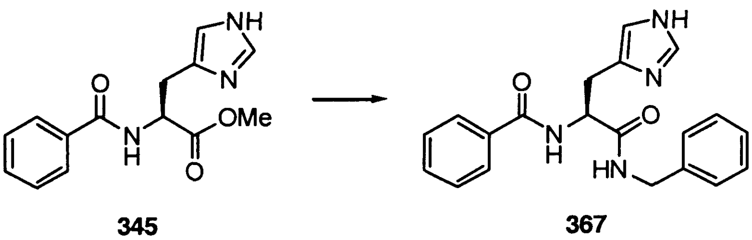
The *title compound* **362** was prepared according to the general procedure **G**, from 3-methoxybenzoic acid (630 mg, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348**. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, afforded the *title compound* **362** (888 mg, 71%) as a pale yellow solid; mp (ethyl acetate/methanol) = 133-135 °C; IR (nujol mull) 3266, 3197, 1754, 1644, 1585, 1546 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ_H 8.33 (d, J = 7.1 Hz, 1H, NHCH), 7.49 (s, 1H, ImH-2), 7.41-7.36 (m, 2H, ArH), 7.29 (dd, J = 8.0, 7.8 Hz, 1H, ArH), 7.00 (d, J = 8.0, 1H, ArH), 6.75 (s, 1H, ImH-5), 4.89 (ddd, J = 7.1, 5.5, 4.8 Hz, 1H, NHCH), 3.76 (s, 3H, ArOCH$_3$), 3.63 (s, 3H, OCH$_3$), 3.19 (dd, J = 14.8, 5.5 Hz, 1H, CHCHH), 3.14 (dd, J = 14.8, 4.8 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, CDCl$_3$) δ_C 172.0 (s), 167.1 (s), 159.7 (s), 135.4 (d), 135.0 (s), 134.9 (s), 129.6 (d), 119.1 (d), 118.0 (d), 115.2 (d), 112.4 (d), 55.6 (q), 53.2 (d), 52.6 (q), 29.0 (t); LRMS (ES, [M+H]$^+$) m/z 304 (100%); HRMS (ES, [M+H]$^+$) exact mass calcd for ($C_{15}H_{18}N_3O_4$) requires m/z 304.1292, found m/z 304.1293; $[\alpha]_D^{20}$ = -33.8 (c = 1, methanol).

N-((*S*)-1-(Methylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethyl)benzamide 366[11]



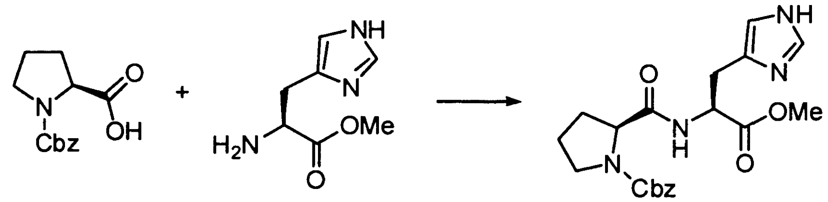
To a solution of *N*-menthylamine in methanol (8 M, 7.53 g; 243.0 mmol, 10.0 mL) was added (*S*)-methyl 2-(benzamido)-3-(1*H*-imidazol-4-yl)propanoate **345** (500 mg, 1.83 mmol). The resulting solution was stirred at room temperature for 24 hours until the amino ester was consumed by TLC. The volatiles were removed under reduced pressure. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, provided the *title compound* **366** (448 mg, 90%) as a colourless solid; mp (ethyl acetate/methanol) = 203-205 °C; IR (nujol mull) 3361, 3159, 1644, 1572, 1521, 1310 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ_H 7.85-7.81 (m, 2H, ArH), 7.63 (s, 1H, ImH-2), 7.55 (t, J = 7.3 Hz, 1H, ArH), 7.49-7.44 (m, 2H, ArH), 6.92 (s, 1H, ImH-5), 4.80 (dd, J = 8.7, 5.6 Hz, 1H, NHCH), 3.21 (dd, J = 14.7, 5.6 Hz, 1H, CHCHH), 3.10 (dd, J = 14.7, 8.7 Hz, 1H, CHCHH) 2.75 (s, 3H, CH$_3$); ^{13}C NMR (125 MHz, MeOD) δ_C 174.5 (s), 170.1 (s), 136.4 (d), 135.0 (s), 134.9 (s), 132.8 (d), 129.5 (d), 128.4 (d), 118.0 (d), 55.6 (d), 30.7 (t), 26.3 (q); LRMS (ES, [M+H]$^+$) *m/z* 273 (100%), 242 (25), 214 (35); HRMS (ES, [M+H]$^+$) exact mass calcd for ($C_{14}H_{17}N_4O_2$) requires *m/z* 273.1346, found *m/z* 273.1348; $[\alpha]_D^{20}$ = -4.4 (*c* = 1, methanol)

N-((*S*)-1-(Benzylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethyl)benzamide 367[11]



To a solution of benzylamine in methanol (2.75 M, 2.94 g, 27.5 mmol, 10.0 mL) was added (*S*)-methyl 2-(benzamido)-3-(1*H*-imidazol-4-yl)propanoate **345** (500 mg, 1.83 mmol). The resulting solution was stirred at room temperature for 48 hours until the amino ester was consumed by TLC. The volatiles were concentrated under reduced pressure. Purification by flash column chromatography, eluting with ethyl acetate then ethyl acetate:methanol 9:1, provided the *title compound* **367** (413 mg, 65% yield) as a colourless solid; mp (ethyl acetate/methanol) = 185-187 °C; IR (nujol mull) 3354, 3163, 1644, 1630, 1566, 1455 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ_H 7.87-7.82 (m, 2H, ArH), 7.62 (s, 1H, ImH-2), 7.55 (t, $J = 7.4$ Hz, 1H, ArH), 7.49-7.43 (m, 2H, ArH), 7.33-7.28 (m, 2H, ArH), 7.27-7.19 (m, 3H, ArH), 6.88 (s, 1H, ImH-5), 4.88 (dd, J = 8.2, 6.1 Hz, 1H, NHCH), 4.42 (d, J = 15.0 Hz, 1H, NHCHHAr), 4.37 (d, J = 15.0, Hz, 1H, NHCHHAr) 3.22 (dd, J = 14.8, 6.1 Hz, 1H, CHCHH), 3.13 (dd, J = 14.8, 8.2 Hz, 1H, CHCHH); ^{13}C NMR (125 MHz, MeOD) δ_C 173.5 (s), 169.9 (s), 139.8 (s), 136.4 (d), 135.0 (s), 133.5 (s), 132.9 (d), 129.6 (d), 129.5 (d), 128.6 (d), 128.5 (d), 128.2 (d), 116.5 (d), 55.6 (d), 44.7 (t), 30.7 (t); LRMS (ES, $[M+H]^+$) m/z 349 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{20}H_{21}N_4O_2$) requires m/z 349.1659 found m/z 349.1654; $[\alpha]_D^{20}$ = -4.0 (c = 4, methanol).

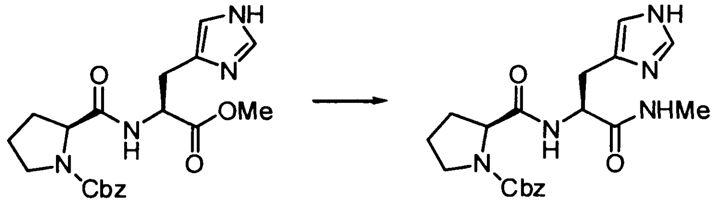
(*S*)-Benzyl 2-((*S*)-1-(methoxycarbonyl)-2-(1*H*-imidazol-4-yl)ethylcarbamoyl)pyrroledine-1-carboxylate 371



334 2xHCl **348** **371**

The *title compound* **371** was prepared according to the general procedure **G**, from (*S*)-carbobenzyloxy proline **334** (1.00 g, 4.13 mmol) and (*S*)-histidine methyl ester dihydrochloride **348** (972 mg, 4.02 mmol). Purification by flash column chromatography, eluting with ethyl acetate: light petroleum 1:1, gave the *title compound* **371** (980 mg, 61%) as a viscous oil; IR (nujol mull) 3275, 1757, 1729, 1642, 1568, 1534, 1461, 1377 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers with a ratio of 7:3 mesured at 293 K) δ_H 7.96 (br s, 1H, NHCH), 7.46 (s, 1H, ImH-2, major rot.), 7.41 (s, 1H, ImH-2, minor rot.), 7.36-7.14 (m, 5H, ArH), 6.70 (s, 1H, ImH-5, major rot.), 6.68 (s, 1H, ImH-5, minor rot.), 5.17 (d, *J* = 12.9 Hz, 1H, ArCHHO, major rot.), 5.12 (d, *J* = 13.2 Hz, 1H, ArCHHO, minor rot.), 5.06 (d, *J* = 12.9 Hz, 1H, ArCHHO, major rot.), 5.01 (d, *J* = 13.2 Hz, 1H, ArCHHO), 4.81-4.65 (m, 1H, NHCH), 4.39-4.14 (m, 1H, NCH), 3.71 (s, 3H, CH_3, major rot.), 3.54 (s, 3H, CH_3, minor rot.), 3.65-3.46 (m, 2H, CH_2NCH), 3.23 (dd, *J* = 14.8, 4.3 Hz, 1H, NHCHCHH, major rot.), 3.06 (dd, *J* = 15.0, 4.5 Hz, 1H, NHCHCHH, minor rot.), 3.13 (dd, *J* = 14.8, 4.1 Hz, 1H, NHCHCHH, major rot.), 2.93 (dd, *J* = 15.0, 4.2 Hz, 1H, NHCHCHH, minor rot.), 2.24-1.77 (m, 4H, CH_2CH_2CH); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers with a ratio of 7:3 mesured at 293 K) δ_C 172.4 (s), 171.7 (s), 171.6 (s) 171.1 (s), 155.1 (s), 154.9 (s), 145.5 (s), 136.5 (s), 136.3 (s), 135.6 (d), 135.2 (d), 128.5 (d), 128.3 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.6 (d), 115.1 (d), 67.4 (t), 67.0 (t), 60.7 (d), 53.1 (d), 52.5 (d), 52.3 (q), 52.0 (q), 47.3 (t), 47.0 (t), 29.8 (t), 29.0 (t), 27.5 (t), 24.6 (t), 23.4 (t); LRMS (APCI, $[M+H]^+$) *m/z* 401 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{20}H_{15}N_4O_5$) requires *m/z* 401.1819, found *m/z* 401.1820; $[\alpha]_D^{20}$ = -33.2 (*c* = 1, methanol).

(*S*)-Benzyl 2-((*S*)-1-(methylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethylcarbamoyl)pyrroledine-1-carboxylate 370[11]

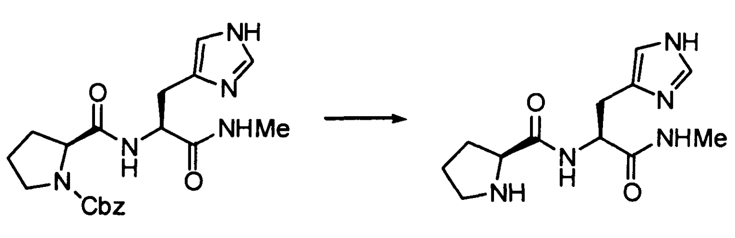


371 **370**

To a solution of *N*-methylamine in methanol (8 M, 7.53 g, 243.0 mmol, 10.0 mL) was added (*S*)-benzyl 2-((*S*)-1-(methoxycarbonyl)-2-(1*H*-imidazol-4-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate **371** (1.08 g, 2.71 mmol). The resulting solution was stirred at room temperature for 24 hours until the amino ester was consumed by TLC. The volatiles were removed under reduced pressure. Purification by flash column chromatography, using ethyl acetate then ethyl acetate:methanol 9:1, afforded the *title compound* **370** (670 mg, 62% yield) as a colourless solid; mp (ethyl acetate/methanol) = 81-83 °C; IR (nujol mull) 3338, 1660, 1537, 1417, 1358 cm^{-1}; ^1H NMR (500 MHz, MeOD, mixture of rotamers with a ratio of 6:4

mesured at 293 K) δ_H 7.59 (s, 1H, ImH-2), 7.45-7.19 (m, 5H, ArH), 6.89 (s, 1H, ImH-5, major rot.), 6.84 (s, 1H, ImH-5, minor rot.), 5.16 (d, J = 12.7 Hz, 1H, ArCHHO, major rot.), 5.06 (d, J = 13.0 Hz, 1H, ArCHHO, minor rot.), 5.14 (d, J = 12.7 Hz, 1H, ArCHHO, major rot.), 5.01 (d, J = 13.1 Hz, 1H, ArCHHO, minor rot.), 4.62 (dd, J = 8.2, 4.8 Hz, 1H, NHCH, major rot.), 4.57 (dd, J = 7.9, 4.6 Hz, 1H, NHCH, minor rot.), 4.34 (dd, J = 7.9, 3.4 Hz, NCH, major rot.), 4.26 (dd, J = 8.0, 3.5 Hz, NCH, minor rot.), 3.68-3.44 (m, 2H, CH_2NCH), 3.16 (dd, J = 15.1, 4.8 Hz, 1H, NHCHCHH, major rot.), 2.97 (dd, J = 14.6, 6.3 Hz, 1H, NHCHCHH, minor rot.), 3.03 (dd, J = 15.1, 8.2 Hz, 1H, NHCHCHH, major rot.), 2.87 (dd, J = 14.9, 8.2 Hz, 1H, NHCHCHH, minor rot.), 2.69 (s, 3H, CH_3, major rot.), 2.63 (s, 3H, CH_3, minor rot.), 2.46-2.11 (m, 4H, CH_2CH_2CH, major rot.), 1.95-1.61 (m, 4H, CH_2CH_2CH, minor rot.); ^{13}C NMR (125 MHz, MeOD, mixture of rotamers with a ratio of 6:4 mesured at 293 K) δ_C 174.9 (s), 174.8 (s), 173.6 (s), 173.5 (s), 157.5 (s), 156.3 (s), 137.8 (s), 137.7 (s), 136.2 (d), 136.1 (d), 134.6 (s), 134.4 (s), 129.5 (d), 129 4 (d), 129.1 (d), 128.9 (d), 128.8 (d), 128.5 (d), 118.3 (d), 118.0 (d), 68.4 (t), 68.1 (t), 62.4 (d), 61.4 (d), 54.7 (d), 54.6 (d), 48.5 (t), 48.1 (t), 32.3 (t), 31.1 (t), 30.5 (t), 29.5 (t), 26.3 (q), 26.2 (q), 25.3 (t), 24.4 (t); LRMS (ES, $[M+H]^+$) m/z 400 (100%); HRMS (ES, $[M+H]^+$) exact mass calcd for ($C_{20}H_{26}N_5O_4$) requires m/z 400.1979, found m/z 400.1981; $[\alpha]_D^{20}$ = -49.0 (c = 1, methanol).

(2*S*)-*N*-((*S*)-1-(methylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethyl)pyrrolidine-2-carboxamide 369


370 **369**

To a solution of (*S*)-benzyl 2-((*S*)-1-(methylcarbamoyl)-2-(1*H*-imidazol-4-yl)ethylcarbamoyl)pyrroledine-1-carboxylate **370** (521 mg, 1.3 mmol) in methanol (26 mL) was added 10% Pd/C (78 mg, 0.13 mmol). The mixture was stirred at room temperature for 20 hours under an atmosphere of hydrogen. The reaction was filtered through Celite® and and the filtrate was concentrated under reduced pressure to provide the *title compound* **369** (324 mg, 94%) as a colourless solid with no further purification required; mp (methanol) = 90-92 °C; IR (nujol mull) 3318, 3165, 1642, 1526, 1494, 1406 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ_H 7.61 (s, 1H, ImH-2), 6.88 (s, 1H, ImH-5), 4.57 (dd, J = 8.7, 5.4 Hz, 1H, CONHCH), 3.69 (dd, J = 8.9, 5.3 Hz, 1H, CH_2NHCH), 3.10 (dd, J = 14.8, 5.4 Hz, 1H, ImCHH), 3.00-2.84 (m, 3H, ImCHH, CH_2CH_2NH), 2.74 (s, 3H, CH_3), 2.15-2.02 (m, 1H, CH_2CHHCH), 1.77-1.54 (m, 3H, CH_2CHHCH); ^{13}C NMR (125 MHz, MeOD) δ_C 177.5 (s), 173.1 (s), 136.3 (d), 134.0 (s), 118.3 (d), 61.4 (d), 54.6 (d), 47.7 (t), 31.7 (t), 30.7 (t), 26.7 (t), 26.3 (q); LRMS (APCI, $[M+H]^+$): m/z 266 (100%), 235 (30), 169 (45); HRMS (ES, $[M+H]^+$): exact mass calcd for ($C_{12}H_{20}N_5O_2$) requires m/z 266.1612, found m/z 266.1616; $[\alpha]_D^{20}$ = -31.0 (c = 2, methanol).

Appendix: solvent purification methods

Acetonitrile

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

Cyclopentadiene

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

Dichloromethane

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

Diethyl ether

Diethyl ether was obtained by distillation from sodium benzophenone ketyl.

N,N-Dimethylformamide

N,N-Dimethylformamide was dried by stirring over phosphorus pentoxide for 48 h followed by distillation from calcium hydride.

Ethyl acetate

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

Methanol

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

Tetrahydrofuran

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

Triethylamine

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

Toluene

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

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