Terms and Conditions of Use of Digitised Theses from Trinity College Library Dublin

Copyright statement

All material supplied by Trinity College Library is protected by copyright (under the Copyright and Related Rights Act, 2000 as amended) and other relevant Intellectual Property Rights. By accessing and using a Digitised Thesis from Trinity College Library you acknowledge that all Intellectual Property Rights in any Works supplied are the sole and exclusive property of the copyright and/or other IPR holder. Specific copyright holders may not be explicitly identified. Use of materials from other sources within a thesis should not be construed as a claim over them.

A non-exclusive, non-transferable licence is hereby granted to those using or reproducing, in whole or in part, the material for valid purposes, providing the copyright owners are acknowledged using the normal conventions. Where specific permission to use material is required, this is identified and such permission must be sought from the copyright holder or agency cited.

Liability statement

By using a Digitised Thesis, I accept that Trinity College Dublin bears no legal responsibility for the accuracy, legality or comprehensiveness of materials contained within the thesis, and that Trinity College Dublin accepts no liability for indirect, consequential, or incidental, damages or losses arising from use of the thesis for whatever reason. Information located in a thesis may be subject to specific use constraints, details of which may not be explicitly described. It is the responsibility of potential and actual users to be aware of such constraints and to abide by them. By making use of material from a digitised thesis, you accept these copyright and disclaimer provisions. Where it is brought to the attention of Trinity College Library that there may be a breach of copyright or other restraint, it is the policy to withdraw or take down access to a thesis while the issue is being resolved.

Access Agreement

By using a Digitised Thesis from Trinity College Library you are bound by the following Terms & Conditions. Please read them carefully.

I have read and I understand the following statement: All material supplied via a Digitised Thesis from Trinity College Library is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of a thesis is not permitted, except that material may be duplicated by you for your research use or for educational purposes in electronic or print form providing the copyright owners are acknowledged using the normal conventions. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.
Design and Synthesis of DMAP-derived Organocatalysts for Enantioselective Induction

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

by

Ciarán Ó Dálaigh B. A. (Mod.)

Under the supervision of
Dr. Stephen Connon

July 2007

Trinity College Dublin
DECLARATION

This thesis has not been submitted as an exercise for a degree at any other university. Except where stated, the work described therein was carried out by me alone.

I give permission for the Library to lend or copy this thesis upon request.

Signed: Ciaran O’Dalaigh
Declaration

I declare that this work has not been submitted as an exercise for degree at this or any other university, and that it is entirely my own work. Due acknowledgements and references are given to the work of others.

Ciarán Ó Dálaigh
# Contents

Acknowledgements.......................................................................................................................... vi
Abstract.................................................................................................................................................. vii
Abbreviations........................................................................................................................................ viii

1.1 General.................................................................................................................................................... 1
1.1.1 Synthesis of enantiopure compounds............................................................................................ 1

1.2 Kinetic resolution..................................................................................................................................... 2
1.2.1 Theoretical concepts.......................................................................................................................... 3
1.2.2 Historical perspective......................................................................................................................... 5
1.2.3 Dynamic kinetic resolution............................................................................................................... 8
1.2.4 Organocatalysed kinetic resolution reactions: A brief review.................................................. 9
1.2.4.1 Enzyme mediated kinetic resolution............................................................................................. 9
1.2.4.2 Metal-ion mediated kinetic resolution.......................................................................................... 11

1.3 Kinetic resolution processes involving acyl transfer........................................................................ 14
1.3.1 Nucleophilic catalysis – mode of action......................................................................................... 14
1.3.2 DMAP as an acylation catalysis....................................................................................................... 16
1.3.3 Substituted pyridine: Structure – activity relationship..................................................................... 19

1.4 Chiral DMAP analogues.................................................................................................................... 24
1.4.1 The first chiral DMAP derivative from Vedejs’ group................................................................. 24
1.4.2 Development of planar chiral catalysts by Fu.............................................................................. 26
1.4.3 Atropisomeric DMAP-derived catalysts....................................................................................... 29
1.4.4 Catalysts that employ remote chirality using an induced fit mechanism.................................. 32
1.4.5 Catalysts incorporating H-bond donors......................................................................................... 35
1.4.6 Alternative DMAP-based catalyst designs.................................................................................... 36

1.5 Non-pyridine based catalysts.............................................................................................................. 39
1.5.1 Aliphatic diamines............................................................................................................................ 39
1.5.2 Phosphines.......................................................................................................................................... 40
1.5.3 Carbenes............................................................................................................................................ 42
1.5.4 Catalysts incorporating an imidazole ring....................................................................................... 43

1.6 The Baylis-Hillman reaction: General............................................................................................... 49
1.6.1 Mechanism of the Baylis-Hillman reactions............................................................................... 50
1.6.2 Rate of reaction............................................................................................................................... 51
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6.3</td>
<td>Optimisation of the Lewis base catalysed Baylis-Hillman reaction</td>
<td>52</td>
</tr>
<tr>
<td>1.6.4</td>
<td>Enantioselective Baylis-Hillman synthesis</td>
<td>53</td>
</tr>
<tr>
<td>1.6.5</td>
<td>Overview of current asymmetric catalysts in the Baylis-Hillman reaction</td>
<td>54</td>
</tr>
<tr>
<td>1.6.6</td>
<td>Kinetic resolution of Baylis-Hillman adducts</td>
<td>58</td>
</tr>
<tr>
<td>1.6.7</td>
<td>Drawbacks associated with Baylis-Hillman reaction</td>
<td>60</td>
</tr>
<tr>
<td>1.7</td>
<td>DMAP functionalised nanoparticles: General</td>
<td>60</td>
</tr>
<tr>
<td>1.7.1</td>
<td>Homogeneous vs. heterogeneous catalysts</td>
<td>60</td>
</tr>
<tr>
<td>1.7.2</td>
<td>DMAP derived heterogeneous catalysts</td>
<td>62</td>
</tr>
<tr>
<td>1.7.3</td>
<td>Conclusions for DMAP supported catalysts</td>
<td>66</td>
</tr>
<tr>
<td>2.1</td>
<td>Guidelines for the successful design of a chiral DMAP catalyst</td>
<td>67</td>
</tr>
<tr>
<td>2.2</td>
<td>Synthesis of 1st generation chiral acyl-transfer catalyst</td>
<td>68</td>
</tr>
<tr>
<td>2.2.1</td>
<td>Mechanistic investigation of the 1st generation catalyst</td>
<td>70</td>
</tr>
<tr>
<td>2.3</td>
<td>Synthesis of 2nd generation catalyst</td>
<td>71</td>
</tr>
<tr>
<td>2.3.1</td>
<td>Solvent optimisation studies</td>
<td>74</td>
</tr>
<tr>
<td>2.3.2</td>
<td>Further investigation into the optimisation of catalyst framework</td>
<td>74</td>
</tr>
<tr>
<td>2.3.3</td>
<td>Optimisation of reaction conditions for KR of substrate 76b catalysed by 169</td>
<td>80</td>
</tr>
<tr>
<td>2.3.4</td>
<td>Comparison of catalysts 169 and 172 – 174 under optimised conditions</td>
<td>82</td>
</tr>
<tr>
<td>2.4</td>
<td>Investigation into the mode of action of catalysts 169 and 172</td>
<td>84</td>
</tr>
<tr>
<td>2.5</td>
<td>Investigation into the potential contribution of van der Waals (π) interactions to enantiodiscrimination in KR processes mediated by 169 and analogues</td>
<td>90</td>
</tr>
<tr>
<td>2.6</td>
<td>Conclusions for chapter 2</td>
<td>98</td>
</tr>
<tr>
<td>2.7</td>
<td>Enantioselective Steglich rearrangement</td>
<td>99</td>
</tr>
<tr>
<td>3.1</td>
<td>Baylis-Hillman: General</td>
<td>100</td>
</tr>
<tr>
<td>3.2</td>
<td>Design of 3rd generation catalysts, 219 – 222</td>
<td>101</td>
</tr>
<tr>
<td>3.2.1</td>
<td>Synthesis of catalysts 219 – 222</td>
<td>102</td>
</tr>
<tr>
<td>3.2.2</td>
<td>1H NMR analysis of catalysts 219 – 222</td>
<td>103</td>
</tr>
<tr>
<td>3.3</td>
<td>Synthesis of mono-protected trans-diol substrate 228</td>
<td>104</td>
</tr>
<tr>
<td>3.3.1</td>
<td>Evaluation of catalysts 219 – 222 in the KR of sec-alcohols</td>
<td>104</td>
</tr>
<tr>
<td>3.4</td>
<td>Synthesis of BH adducts for KR catalysed by 221</td>
<td>106</td>
</tr>
<tr>
<td>3.4.1</td>
<td>An investigation into the BH substrates kinetically resolved by acylation, catalysed by 169 and 221</td>
<td>106</td>
</tr>
<tr>
<td>3.5</td>
<td>One pot synthesis and resolution of BH adducts</td>
<td>109</td>
</tr>
</tbody>
</table>
3.6 Conclusion for chapter 3 ................................................................. 111
4.1 Solid-supported heterogeneous catalyst systems ........................................ 112
4.2 A nanoparticle supported heterogeneous catalyst system .......................... 112
4.3 Design of a nanoparticle-supported DMAP catalyst ............................... 113
4.3.1 Design of a 2nd generation nanoparticle-supported catalyst .................. 115
4.4 Evaluation of 248 as a recyclable catalyst ............................................... 117
4.4.1 Investigation into substrate scope of 248 ............................................ 119
4.5 Synthesis of non-silicon coated derivative of 248 i.e. 261 ....................... 121
4.5.1 Investigation into recyclability of 261 ................................................. 122
4.6 Conclusions for nanoparticle catalyst .................................................... 122
5.1 General ............................................................................................... 124
Acknowledgements

First and foremost I would like to offer my sincerest thanks to my supervisor Dr. Stephen Conn on for his advice, constant encouragement and friendship over the past few years and for making my studies a rewarding and enjoyable experience. His relentless pursuit of perfection and attention to detail made both the project and the writing of this thesis possible.

I am also deeply grateful to my colleagues, both past and present: Shay, Eimear, Dave, Con, Conor, Barbara, Sarah, Aldo, Jen, Ollie and Dave who enriched and shortened the hours spent in the lab. A special thank you to Eimear, Sarah, Barbara and Con for the early proof readings.

Special thanks is also in order for Dr. Mike Southern, Dr. Paul Evans and Dr. Matt O’Brien who could always be relied on for their knowledge and the occasional pint and thanks once again to Dr. Mike Southern for organising the football (the highlight of every week). I would also like to thank all of the technical staff who were always available when any analytical work needed taking care of; Dr. Martin Feeney (mass spectroscopy) and especially Dr. John O’ Brien and Dr. Manuel Ruether (NMR) for allowing me to jump the queue (I owe you a Mars bar).

Additionally I want to thank all my friends for providing me with a welcome distraction from the lab and for not allowing me to spend too many weekends in there. Finally, I wish to thank my family for all their support and for always giving me the confidence to pursue my goals.
Abstract

The development of small organic molecules capable of mimicking enzymatic action (in an asymmetric catalysis context) is a challenge that is receiving widespread attention in contemporary organic chemistry. Herein we report the design and synthesis of a new class of chiral 4-$N,N$-dialkyaminopyridine acyl-transfer catalysts capable of exploiting both van der Waals ($\pi$) and H-bonding interactions to allow remote chiral information to stereochemically control the kinetic resolution of a diverse range (both aromatic and aliphatic) sec-alcohols with moderate to excellent selectivity ($S = 6 - 30$). A combination of optimisation, substrate screening, catalyst modification, spectroscopic and computational studies have clearly identified both hydrogen bonding and (intra as well as possibly also intermolecular) $\pi$-pyridinium-ion interactions as playing a role in enantiodiscrimination for the ($S$)-$\alpha,\alpha$-diarylprolinol derived catalysts.

A succeeding generation of catalysts explored the influence of the steric and electronic properties of the aromatic substituents on catalyst performance, with a bis-trifluoromethyl substituted analogue promoting the greatest enantioselective acylations. A range of synthetically useful Baylis-Hillman adducts (derived from deactivated precursors) were also successfully kinetically resolved ($S = 3.5 - 13.1$, with $ee$ up to 97%), representing to the best of our knowledge the $1^{st}$ examples of effective non-enzymatic acylative KR of $sp^2$-$sp^2$ carbinols. A novel synthesis-kinetic resolution process involving a DBU-catalysed Baylis-Hillman reaction and subsequent catalyst/DBU-mediated enantioselective acylation has also been developed which allows the facile synthesis of enantioenriched adducts in one pot.

The synthesis of the first magnetic nanoparticle-supported nucleophilic organocatalyst is also reported. The immobilised heterogeneous catalyst is capable of efficiently promoting a range of reactions of high synthetic utility at loadings between 0.14 and 10 mol% and can be isolated from the reaction mixture by exposure to an external magnetic field. Using this recovery methodology the catalyst was recycled over 30 times across a range of reactions without any discernible loss of activity.
Abbreviations

Ac Acetyl
Ar Aryl
atm Atmosphere
Bn Benzyl
BOC tert-Butoxycarbonyl
Bu Butyl
Bz Benzoyl
cat. Catalyst
Conv. Conversion
COSY Correlation spectroscopy
Cp Cyclopentadienyl
CSP-HPLC Chiral stationary phase-high performance liquid chromatography
DABCO 1,4-Diazabicyclo[2.2.2]octane
DCC N,N'-Dicyclohexylcarbodiimide
DIPAMP Bis[(2-methoxyphenyl)phenylphosphino]ethane
DIPEA N,N'-Diisopropylethylamine
DMF Dimethylformamide
DMSO Dimethyl sulphoxide
E Electrophile
EDCI 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
EDTA Ethylenediaminetetraacetic acid
ee Enantioselective excess
Et Ethyl
EWG Electron withdrawing group
HATU O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate
het. heterocycle
IMD Imidazole
IPA Iso-propyl alcohol
IR Infra red
k Rate constant
m Meta
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCPBA</td>
<td><em>m</em>-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MVK</td>
<td>Methyl vinyl ketone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser effect</td>
</tr>
<tr>
<td>Np</td>
<td>Naphthyl</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>o</td>
<td>Ortho</td>
</tr>
<tr>
<td>p</td>
<td>Para</td>
</tr>
<tr>
<td>PEG</td>
<td>Poly ethylene glycol</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PMP</td>
<td>1,2,6-pentamethylpiperidine</td>
</tr>
<tr>
<td>PPY</td>
<td>Pyrrolidinated pyridine</td>
</tr>
<tr>
<td>rac</td>
<td>Racemic</td>
</tr>
<tr>
<td>RLS</td>
<td>Rate limiting step</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Selectivity factor</td>
</tr>
<tr>
<td>sec</td>
<td>Secondary</td>
</tr>
<tr>
<td>t-A. A</td>
<td>tert-Amyl alcohol</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-Butyl hydroperoxide</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butylsilyl</td>
</tr>
<tr>
<td>TEM</td>
<td>Transmission electron microscopy</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrhydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TOCSY</td>
<td>Total Correlated Spectroscopy</td>
</tr>
<tr>
<td>Tol</td>
<td>Toluyl</td>
</tr>
<tr>
<td>TS</td>
<td>Transition state</td>
</tr>
</tbody>
</table>
1.1 General

It is estimated that by the year 2008, drugs incorporating at least one chiral centre will account for greater than 40% of all global sales or a staggering €200 billion for the pharmaceutical industry. Demand for single enantiomer therapeutics is fuelled by the recognition that enantiomers of chiral compounds can have dramatically different biological activities. Examples of the remarkable differences of chiral drugs abound e.g. (R)-Albuterol is a \( \beta_2 \)-agonist used in the treatment of asthma, while (S)-Albuterol provokes airway constriction. Thus the synthesis of entantiopure molecules is of paramount importance for the success of the modern chemical industry. This has been recognised by academia, resulting in a three-fold increase in the number of chiral technology related papers in the last 10 years.

1.1.1 Synthesis of enantiopure compounds

The ideal conditions for an efficient and practical enantioselective synthesis (from either an industrial or an academic standpoint) include high stereoselectivity, operational simplicity, high rate and productivity, atom economy, cost efficiency and environmental compatibility. Unfortunately not all of these factors can be consistently fulfilled, therefore the most efficient strategy pertaining to a practical synthesis is utilised. Traditionally there are three approaches available for the synthesis of chiral compounds.

Chiral Pool: Synthesis using readily available enantiopure compounds as starting materials (chiral substrates or auxiliaries) including amino acids, carbohydrates and secondary metabolites that can easily be manipulated. However these are finite in number and the requisite starting material or enantiomer may not be readily available.

Asymmetric Synthesis: Enabling the synthesis of enantiopure compounds from prochiral or racemic precursors. This field encompasses biochemical methods, chiral auxiliaries and chemocatalysis. The scope of biocatalysis is limited due to its inherent single handed, lock-and-key specificity, whereas reactions utilising chiral auxiliaries require a stoichiometric amount of the chiral compound, often making them inconvenient for large scale synthesis. Chemocatalysis has been the subject of intense interest over the last four decades with the area dominated by transition-metal based catalysts and more recently by organocatalysis, the former exemplified by the Nobel Prize winning Sharpless' epoxidation and
dihydroxylation\textsuperscript{7} catalysts and Noyori’s hydrogenation\textsuperscript{8} catalyst. These metal-ligand complexes are easily modified in terms of steric bulk, electronic properties and lability, allowing both activity and selectivity to be fine-tuned to a considerable extent.

Resolution: Conventional separation of an equimolar mixture of enantiomers by either chemical or physical methods. Selected means for separation include chromatography, involving the use of a chiral stationary phase to selectively retard one enantiomer relative to the other. The formation of diastereoisomers, by reaction with a chiral acid or base, can facilitate the separation of enantiomers by the distinctive physical properties of their salts. Optically pure compounds can also be obtained by biochemical resolution whereby microorganisms (either whole cells or enzymes) degrade one antipode stereoselectively. Alternatively kinetic resolution can be employed to exploit the different reaction rates of enantiomers with chiral reaction partners or chiral catalysts.

These resolution strategies can also be applied to non-equimolar mixtures of enantiomers obtained through stereoselective synthesis, to further increase the enantiomeric excess of the desired substrate.

1.2 Kinetic Resolution

The definition of kinetic resolution as defined by IUPAC is: The achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, \textit{etc.}).\textsuperscript{9}

Pasteur’s landmark discovery in 1848 \textit{i.e.} the manual resolution of sodium ammonium tartrate crystals\textsuperscript{10} laid the foundations of stereochemistry. Today these observable phenomena are no longer merely elucidated but chemists are actively involved in the design and synthesis of truly synthetically useful chiral substrates for asymmetric induction.

Although it may seem that enantioselective synthesis is the most efficient methodology currently available to obtain enantioenriched compounds, by enlarge the ready availability of inexpensive racemates coupled with the easy application to virtually all chiral substrates ensures the position of kinetic resolution as \textit{the} premier synthetic strategy in obtaining optically pure substrates.
1.2.1 Theoretical concepts

In a catalytic kinetic resolution each antipode of substrate interacts with catalyst to form two diastereomeric transition states, Figure 1.1.

**Figure 1.1** Rate constants of enantiomers in Kinetic Resolution

\[ \Delta \Delta G^{TS} = \Delta G^{TS}_R - \Delta G^{TS}_S \]  
**[1.1]**

The magnitude of \( \Delta \Delta G^{TS} \) represents the ratio of the rate constants for the reaction of the substrate enantiomers and can be quantified by \( k_{rel} \) or the enantiomeric ratio, \( S \) **[1.2]**.

\[ S = k_{rel} = \frac{k_{fast}}{k_{slow}} = \Delta \Delta G^{TS} \]  
**[1.2]**

Alternatively the selectivity factor or \( S^{11} \) value can be calculated based on enantiomeric excess. The enantiomeric excess (\( ee \)) of a substrate is defined as the excess of one enantiomer over the other, expressed as a percentage of the whole, calculated by **[1.3]**.

\[ ee = \frac{([R]-[S])}{([R]+[S])} \times 100 \]  
**[1.3]**
with \([R]\) and \([S]\) representing the concentrations of each antipode (\(R\) being the dominant antipode in this case). Therefore in a racemic substrate the enantiomeric excess is zero, while for an enantiopure compound the enantiomeric excess is 1 (or 100% \(ee\)).

Thus the \(S\) value can be determined using the enantiomeric excess of the recovered substrate (\(ee\)) [1.4a] or the enantiomeric excess of the product (\(ee'\)) [1.4b], achieved for a certain conversion, \(C\) i.e. \([ee/(ee + ee')]\).

\[
S = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]}
\]  
[1.4a]

\[
S = \frac{\ln[1-C(1+ee')]}{\ln[1-C(1-ee')]} 
\]  
[1.4b]

One of the advantages of kinetic resolution (KR) is that the substrate can be recovered with the required \(ee\) by setting the necessary conversion regardless of selectivity as in Figure 1.2, as apposed to asymmetric synthesis where product is recovered with constant \(ee\). It is also pertinent to note that one can obtain significant amounts of enantioenriched product (>98% \(ee\), 45% yield) with selectivity values greater than 50.

**Figure 1.2**  Plot of substrate \(ee\) vs. conversion for different \(S\) values.\(^{12}\)

Unfortunately a problem arises at conversions approaching 50%, where selectivity for the desired antipode is hampered by the concentration of the slower reacting enantiomer. Due to this inherent build-up, the rate of selectivity for the less reactive antipode will increase,
known as mass action. This can be overcome if there is an exceptionally large difference in rate constant between enantiomers.

While it is assumed from equation [1.4a] that first-order kinetics are followed with regards to substrate, this is not always the case. In fact substrate kinetics can change over the course of a reaction, along with non-linear correlations between catalyst ee and product ee. Therefore $k_{rel}$ should be calculated for more than one conversion to verify that a deviation from the standard kinetics has not occurred. However as there is no alternative method to definitively correlate the expression of ee with conversion we will continue to apply $k_{rel}$ values for comparison of catalysts in kinetic resolution in this work.

### 1.2.2 Historical perspective

In 1858, Pasteur, prompted by his discovery of optical isomerism (section 1.2) published a seminal paper on the fermentation of racemic ammonium tartrate. In this work he describes the selective reaction of (25',35)-tartaric acid, and the recovery of the previously unknown (2R,3R)-tartaric acid. This report represents the first enzymatic kinetic resolution performed in the laboratory. Further studies by Fischer in 1890 as part of an investigation into the determination of the absolute configuration of sugars resulted in additional progress towards the utilisation of biological catalysts for the preparation of enantiopure molecules.

The first non-enzymatic and indeed catalytic kinetic resolutions were observed by Frankland and Price in 1897 with the acylation of racemic amyl alcohol 1 by (R)-glyceric acid (Scheme 1.1). (S)-1 ([α]$_D^{17}$ = -4.85), was first racemised and subsequently an excess of 1 was reacted with glyceric acid 2 to form the isomeric amylic glycerates 3 and 4, of 'unpleasant odour and taste'. Saponification with baryta water (aq. BaOH), followed by steam distillation and extraction with ether, yielded 1 with slight (S)-optical purity, although further purification was not undertaken. This predates the KR of epimeric mandelic acid by esterification with optically pure (-)-menthol reported by Marckwald and McKenzie in 1899 and often cited as the first non-enzymatic kinetic resolution.
Subsequently in 1903, Dakin published a pig liver esterase (PLE) catalysed hydrolysis of mandelic esters. In this study he clearly demonstrated a differential rate of hydrolysis for the antipodes of the ester (Table 1.1). Selection criteria for the esters were based on high optical activity so as to enable facile detection if resolution occurred (Table 1.1).

**Table 1.1** Kinetic resolution of mandelic ester analogues using Pig Liver Esterase

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conv. (%)</th>
<th>$[\alpha]^20_D$</th>
<th>(S)-mandelic acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>5.8</td>
<td>+39.9</td>
<td>25.5</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>99.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>5.2</td>
<td>+59.7</td>
<td>38.3</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>93.6</td>
<td>+8.3</td>
<td>5.3</td>
</tr>
</tbody>
</table>

*Determined as a percentage of pure dextro-mandelic acid

$[\alpha]^{20}_D: +156$

Dakin varied the amounts of enzyme added to obtain different conversions of hydrolysed product. He understood that partial hydrolysis liberated enantioenriched acid, but complete conversion gave optically inactive product, thereby concluding that differential rates of hydrolysis were involved for each antipode and that optically pure substrates could be obtained from inactive precursors.
In 1908, Fajans and Bredig\textsuperscript{21} reported the first example of organocatalytic KR of camphorcarboxylic acid (7) in the presence of optically active bases such as nicotine, quinine and quinidine. Previous work\textsuperscript{22} had shown that achiral bases promoted the decarboxylation of both antipodes of the racemic acid at the same rate. Fajans assumed (correctly) that the chiral bases used in this study act as catalysts – similar to enzymes – which decomposed one enantiomer to a greater extent (Table 1.2).

Table 1.2. Differential rates of decomposition of racemic camphorcarboxylic acid by optically active base.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>(k_{(R)} : k_{(S)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>nicotine</td>
<td>1.17 : 1</td>
</tr>
<tr>
<td>2</td>
<td>quinine</td>
<td>1 : 1.7</td>
</tr>
<tr>
<td>3</td>
<td>quinidine</td>
<td>1.7 : 1</td>
</tr>
</tbody>
</table>

\(k_{(R)}\) and \(k_{(S)}\) are the rate constants for the decarboxylation of the \((R)\) and \((S)\)-antipodes of the racemate respectively.

Later in 1932, Wegler\textsuperscript{23} reported the use of brucine as a means of resolving secondary alcohols, such as sec-phenylethanol, (9) and meso-dicarboxylic acids by esterification, further extending the field of organocatalytic kinetic resolution (Scheme 1.2).

Scheme 1.2 Resolution of sec-phenyl alcohol by (-)-brucine

Although great strides had been made in a comparatively short period, the scientific community chose by enlarge to ignore these revelations for almost 60 years until the
advent of Sharpless’ KR of racemic allylic alcohols with a titanocene complex in 1981. Notably, organocatalysed resolution was not recognised for a further 15 years as a valuable addition or useful alternative to the metal mediated methodologies.

1.2.3 Dynamic Kinetic Resolution

The inherent drawback associated with kinetic resolution is the theoretical maximum yield of 50% of the desired product. Various methodologies such as Dynamic Kinetic Resolution (DKR) have been developed to circumvent this impracticality. DKR involves a continuous racemisation of the reactant species during the course of reaction (Scheme 1.3), allowing for a theoretical yield of 100%, with the enantioselectivity determined by catalyst stereospecificity to a substrate enantiomer. A prerequisite for this reaction is that racemisation, $k_{\text{rac}}$, is achieved more rapidly than $k_{\text{rel}}$ thereby replenishing the faster reacting antipode, which allows for optimal catalyst activity. DKR has conventionally been achieved with either enzymes or metal catalysts or via a successful collaboration between the two.

Scheme 1.3 Dynamic Kinetic Resolution

DKR offers a readily available alternative to resolution, although the practical utility is questionable in terms of range of application. Racemisation of compounds is generally hard to effect and is limited to specific (usually acidic) substrates. While classical KR may be seen to have an ‘Achilles heel’ in terms of overall yield, its diverse substrate scope more than compensates for this in our view and as a consequence priority of discussion is afforded to KR over DKR hereafter.
1.2.4 Organocatalysed kinetic resolution reactions: A brief review

While enzymatic and metal mediated catalysis have been extensively investigated over the last 40 years, organocatalysed kinetic resolutions have recently been firmly established as genuine alternative methodologies. In this context a wide variety of organic small molecule catalysts capable of achieving high selectivities with low catalyst loading in a diverse range of resolutions have been developed. As such the main focus of this thesis will be on organic molecule mediated KR, predominantly acylation strategies, although a brief sampling of non-organic kinetic resolutions covering a selection of the major enantioselective strategies ensues to give a general perspective over the area.

1.2.4.1 Enzyme mediated kinetic resolution

Enzymes promote reactions with high chemo-, regio- and stereo-selectivity and form an important class of catalyst for kinetic resolution. Among these, lipases are perhaps the most versatile catalysts; capable of accepting a wide spectrum of non-natural substrates in the absence of a cofactor, with successful resolution realised in both aqueous and organic media.

CAL-B, a lipase obtained from *Candidia antarctica* is capable of catalysing the resolution of β-lactams\(^{28}\) to afford enantiopure β-amino acids and unreacted β-lactam compounds. A wide array of β-lactams are medicinally relevant scaffolds upon which several important antibiotic drug classes (*e.g.* penicillins and cephalosporins) can be constructed. Under normal circumstances CAL-B is unable to catalyse the hydrolysis of amide bonds; however, owing to the strained nature of the four membered β-lactam ring, there is a diminished resonance stabilisation of the amide bond which results in relatively high electrophilicity.

The mode of action of CAL-B has been intensively investigated, and has been found to involve the activation of Ser-105 by the Histidine-imidazole residue (His 224) with attendant H-bonding of the substrate to Gln-106 to activate the amide carbonyl towards nucleophilic attack (A) and to stabilise the subsequently formed tetrahedral intermediate (Figure 1.3) prior to formation of the enzyme β-amino ester (B). This is subsequently hydrolysed to yield the β-amino acid *via* a similar general acid and base catalysis pathway.
Figure 1.3  Mode of action of CAL-B mediated hydrolysis of β-lactam rings

As illustrated in Table 1.3, a range of β-lactams are compatible with CAL-B. Excessive water is deleterious to substrate selectivity and conversion (entry 2, 3). Reaction has also been shown to proceed without the addition of water (thought to be present from enzyme preparation).

Table 1.3  Selectivity of CAL-B for range of substrates 11a-d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>H₂O (equiv.)</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>β-lactam (% ee)</th>
<th>β-amino acid (% ee)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a</td>
<td>1</td>
<td>249</td>
<td>48</td>
<td>93</td>
<td>99</td>
<td>&gt;200</td>
</tr>
<tr>
<td>2</td>
<td>11b</td>
<td>1</td>
<td>31</td>
<td>50</td>
<td>99</td>
<td>98</td>
<td>&gt;200</td>
</tr>
<tr>
<td>3</td>
<td>11b</td>
<td>10</td>
<td>20</td>
<td>13</td>
<td>14</td>
<td>95</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>11c</td>
<td>1</td>
<td>5</td>
<td>51</td>
<td>99</td>
<td>96</td>
<td>&gt;200</td>
</tr>
<tr>
<td>5</td>
<td>11d</td>
<td>1</td>
<td>7</td>
<td>51</td>
<td>99</td>
<td>99</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

CAL-B has also been shown to effectively resolve 1-heteroaryl amines along with their corresponding acetamides using ethyl acetate as acyl donor and di-iso-propyl ether as solvent (Scheme 1.4). Successful resolution of β-substituted iso-propyl amines with CAL-B has also been reported. The inherent problem associated with amine resolution
(overcome in this instance) is that the amine is often of sufficient nucleophilicity to react with the acylating agent without catalysis.

**Scheme 1.4** CAL-B catalysed acylation of primary amines

\[
\begin{align*}
\text{NH}_2 & \quad \text{CAL-B} \\
& \quad \text{EtOAc/PrOH,} \\
& \quad 60 \, ^\circ \text{C, 2-24 h} \\
\end{align*}
\]

Adhering to Kazlauskas' rule,\(^{33}\) (based on the steric difference of the R groups attached to the chiral centre) the lipase selects only for the (R)-enantiomer of 13. The introduction of a saturated six-membered ring fusing the amine and the hetero-aryl moiety provided structural rigidity, leading to an increase in S values >500, however, augmentation of the size of the cycloalkyl ring led to a drastic decrease in selectivity. The (R)-antipode of 13 can be obtained although harsh conditions are required \(i.e\). hydrolysis of the acetamide (6N HCl, reflux).

### 1.2.4.2 Metal-ion mediated kinetic resolution

As alluded to earlier in Section 1.2, Sharpless' KR of allylic secondary alcohols\(^{24}\) reawakened the collective consciousness of the scientific community towards non-enzymatic KR. This work represented a continuation of the studies outlined in his seminal paper the year previous detailing the enantioselective epoxidation of allylic alcohols.\(^6\)

Sharpless \textit{et al.}\(^{24}\) used the Ti(OiPr)\(_4\)/diisopropyl tartrate catalyst complex to effect the resolution of a variety of secondary alcohols (Table 1.4), with S values as high as 138 with the same stereospecificity as that observed in the epoxidation reaction of \((E)\)-cyclohexylpropenylcarbinol, 15 with the erythro species predominating (Scheme 1.5).
An increase in steric bulk on both the tartrate ester and the titanium alkoxide ligand led to a manifest increase in rate constant, a ten-fold increase in $k_{rel}$ was realised when (+)-diisopropyl tartrate (DIPT) was used instead of (+)-dimethyl tartrate (DMT).

### Table 1.4

Selectivity of Sharpless kinetic resolution for allylic alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Config.</th>
<th>Alcohol (% ee)</th>
<th>$k_{rel}$</th>
<th>Epoxy alcohol product E/T&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$-Hexyl</td>
<td>288</td>
<td>$R$</td>
<td>&gt;96</td>
<td>83</td>
<td>99/1</td>
</tr>
<tr>
<td>2</td>
<td>$cC_{6}H_{11}$</td>
<td>15</td>
<td>$R$</td>
<td>&gt;96</td>
<td>104</td>
<td>97/3</td>
</tr>
<tr>
<td>3</td>
<td>$n$-Bu</td>
<td>15</td>
<td>$R$</td>
<td>&gt;96</td>
<td>138</td>
<td>98/2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 1 equiv. of Ti(OiPr)$_4$, 1.2 equiv. of DIPT and 1.0 eq. of alcohol in CH$_2$Cl$_2$ at -20 °C, with subsequent addition of 0.6 equiv. of anhy. TBHP. The homogeneous reaction mixture was then left at -20 °C for the specified amount of time. <sup>b</sup> E/T ratio = erythro versus threo.

As one can discern from Table 1.4, assay techniques for product enantioselectivity at the time were unable to quantify the exact ee i.e. >96%, where as the calculated ee was >99.99%. Only in recent years have more sensitive techniques been developed. While initially 25 mol% of catalyst was used in the resolution step with ($E$)-disubstituted allylic alcohols (the ideal substrates), subsequent experimentation revealed that the addition of
molecular sieves to remove water, allowed for the use of as little as 5 mol% catalyst loading without significant erosion of efficiency or selectivity.

Jacobsen, in a similar vein, but with an alternative catalyst reported the first efficient resolution of terminal epoxides. The relative inexpense and commercial availability of racemic terminal epoxides coupled with the lack of a readily available approach to their enantiopure synthesis made them ideal candidates for kinetic resolution. Initially resolution was achieved using TMSN₃ and a chiral Cr-Salen complex, 16a which facilitated the synthesis of a wide range of enantioenriched 1,2 amino alcohols (following desilylation and reduction), with S values ranging from 48-280, and near quantitative yields based on 0.5 equivalents of TMSN₃ (Table 1.5). Building on these results Jacobsen et al. replaced the Cr³⁺ with Co²⁺ in the chiral salen complex, allowing for the successful hydrolytic KR of propylene oxide with near perfect selectivity (S>500) (entry 4).

Table 1.5  KR of epoxides by 16

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Cat.</th>
<th>Yield (%)</th>
<th>Epoxide (%ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH₂)₂CH₃</td>
<td>MS</td>
<td>N₃</td>
<td>16a</td>
<td>41</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl</td>
<td>TMS</td>
<td>N₃</td>
<td>16a</td>
<td>47</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>(CH₂)₂CH=CH₃</td>
<td>TMS</td>
<td>N₃</td>
<td>16a</td>
<td>47</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>H</td>
<td>OH</td>
<td>16b</td>
<td>44</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>CH₂OTBS</td>
<td>H</td>
<td>OH</td>
<td>16b</td>
<td>47</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>-TBS</td>
<td>H</td>
<td>OH</td>
<td>16b</td>
<td>41</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>CH₂CO₂Et</td>
<td>H</td>
<td>OH</td>
<td>16b</td>
<td>43</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

Mechanistic studies have identified a second order dependence on catalyst, with one catalyst complex acting as a Lewis acid to activate the epoxide while another delivers the nucleophile to effect ring opening. The reaction is environmentally friendly: the catalyst has been shown to be recyclable (even after its immobilisation on solid support) with no discernable effect upon yield or selectivity. In general the reaction can be carried out in
aqueous solution, with H$_2$O acting as both solvent and nucleophile. Both product and unreacted starting material are synthetically useful and can be easily separated by fractional distillation. Recently this methodology has been applied to the synthesis of several natural products.$^{37}$

### 1.3 Kinetic resolution processes involving acyl transfer

Acyl transfer reactions are inherently useful in synthetic organic chemistry and play an active role in the KR of secondary alcohols. In general the redeeming features associated with these reactions are the ready availability of racemic alcohols, the inexpensive nature of acylating agents (with sterically hindered anhydrides often affording greatest selectivity) and the ease of separation of reactants and products.

Enantiopure secondary alcohols are recognised by the synthetic community as a versatile class of substrate with their wide and varied applicability in the synthesis of natural products, chiral ligands and biologically active compounds. Enzymes (lipases and esterases) have traditionally been employed and indeed have set the benchmark for the promotion of enantioselective acyl transfer.$^{38}$ However, over the last ten years, intensive interest has been focused on the development of non-enzymatic alternatives i.e. small chiral organic molecules that mimic enzymatic action. In this regard significant advancements have been made and chiral, Lewis basic, nucleophilic catalysts have emerged that rival and surpass (in certain cases) enzymes in terms of the range of substrate resolved and the selectivities achieved upon acylation.$^{39}$

Although acyl transfer reactions can be promoted by Brønsted acidic, Lewis acidic or Lewis basic mechanisms, the intention of this thesis is to focus exclusively on Lewis basic, nucleophilic methodologies, encompassing the use of tertiary amines$^{40}$/phosphines,$^{41}$ amidines,$^{42}$ carbenes and imidazoles.$^{43}$

### 1.3.1 Nucleophilic catalysis – mode of action

The origins of tertiary amine assisted acyl-transfer date back to Einhorn and Hollandt$^{44}$ in 1898, when the acetylation of sec-alcohols by AcCl was shown to be accelerated by pyridine. The mechanism was not properly elucidated until 1970,$^{45}$ when the hydrolysis of acetic anhydride in the presence of pyridine (19) was studied, (Scheme 1.6).
The reaction was shown to proceed through the formation of an acetylpyridinium ion intermediate 19i, with hydrolysis achieved by general base catalysis by either the acetate anion or excess pyridine. The formation of a Lewis adduct 19i, affords a higher energy intermediate which is more susceptible to nucleophilic attack than the anhydride. Hydrolysis of this acylated intermediate (regenerating the Lewis base) takes place several orders of magnitude faster than general base catalysed hydrolysis. As a result, nucleophilic catalysis allows for reactions to proceed under milder reaction conditions, preventing unwanted side reactions.

Unfortunately 19 is unable to efficiently catalyse the acylation of less reactive substrates, such as hindered tertiary alcohols (Scheme 1.7). However, the independent development of a ‘hypernucleophilic’ analogue of pyridine *i.e.* 4-*N*,*N*-dimethylaminopyridine (DMAP) in the late 1960’s by Steglich and Litvinenko resolved these activity issues.  

**Scheme 1.7** Relative rates of reaction of 19 and DMAP

<table>
<thead>
<tr>
<th>Reagents:</th>
<th>Reaction</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>AC₂O, pyridine, 14 h, RT. (&lt;5% yield)</td>
<td></td>
</tr>
<tr>
<td>ii</td>
<td>AC₂O, DMAP (4 mol%), TEA, 14 h, RT (86% yield)</td>
<td></td>
</tr>
</tbody>
</table>
1.3.2 DMAP as an acylation catalyst

The high degree of nucleophilicity attributed to DMAP (22) is due to the dialkylamino group allowing resonance electron donation to the ring nitrogen, thereby stabilising the pyridinium ion formed upon attack on the electrophile, this stabilisation mode is not available in the case of pyridine or alkylated pyridine derivatives (Figure 1.4).

Figure 1.4 Stabilisation of pyridinium cation

The utility of 22 as a nucleophilic catalyst has found widespread application.\(^{46}\) Outlined below is a selection of reactions mediated by 22, that represents either an improvement on an alternative methodology or a novel synthetic strategy where no catalytic alternative exists.

A diverse array of sterically hindered secondary and tertiary alcohols are acylated in the presence of catalytic amounts (0.05-0.25 equiv.) of 22.\(^ {47}\) For example, using DMAP as a catalyst, 23 could be acylated without observable racemisation,\(^ {48}\) while 25 could be converted to 26 without cleavage of the acid sensitive acetal functional group.

Scheme 1.8 DMAP catalysed acylation of tertiary alcohols
The regioselective silylation of a primary alcohol in the presence of a secondary alcohol is promoted by a catalytic amount of 22 (4 mol%); in contrast an imidazole-mediated alternative methodology afforded a mixture of products and required a greater than stoichiometric 'catalyst' loading (Scheme 1.9).

Scheme 1.9  Regioselective acylation of primary alcohols

\[
\begin{align*}
\text{OH} \quad \text{OH} \quad \text{OR} \\
\text{27} \quad \text{ii} \\
\text{TBDMSCI, DMAP (4 mol%), CH}_2\text{Cl}_2, \text{NEt}_3, \text{8 h, RT} \quad 95\% \\
\text{ii} \quad \text{TBDMSI, imidazole, (220 mol%), DMF 8 h, RT} \quad 59\% \\
\end{align*}
\]

22 is also capable of the catalysis of a wide range of other acyl-transfer processes. The alcoholysis of ketenes has been used to synthesise aryl propionic acids (precursors to a variety of pharmaceutically active substrates). Reaction proceeds via a Zwitterionic intermediate formed by initial attack of 22 on the ketene, with subsequent protonation and attack by alkoxide displacing 22 to form ester 28, (Scheme 1.10). The addition of an imine in place of an alcohol results in the formation of β-lactam rings of general type 29. Mono- and di-substituted ketenes can be employed in these reactions. β-Lactone formation is also possible if the imine is substituted for an aldehyde.

Scheme 1.10  Reactions of ketenes with imines and alcohols mediated by 22
The rearrangement of O-acylated enolates such as 30 to form carbon-carbon bonds is of high synthetic utility, as a new quaternary centre is generated (Scheme 1.11).\textsuperscript{53} Reaction with pyridine requires heating at 100 °C for six hours; however, rearrangement is complete in a matter of minutes at room temperature with 22. Nucleophilic attack by alcohol on the resulting aza-lactone leads to the formation of natural and unnatural amino acids.\textsuperscript{54}

**Scheme 1.11** Rearrangement of O-acyloxyoxazole

![Scheme 1.11 Rearrangement of O-acyloxyoxazole](image)

In addition to the acylation reactions and their variants cited above, further examples of transformations facilitated by 22 are reported. In the Baylis-Hillman reaction for example, 22 has been shown to be an effective catalyst, avoiding diadduct side product formation of 35 associated with the use of DABCO (Scheme 1.12) in Baylis-Hillman reactions involving methyl vinyl ketone (33).\textsuperscript{55} 22 Also promotes the stereoselective tritylation of a cis-trans mixture of 4-tert-butyl-cyclohexanol (36). Formation of the trans isomer, 37a predominates due to the steric bulk of the tert-butyl group inhibiting the cis-OH moiety attacking the alkylated pyridinium intermediate. (eq. 2, Scheme 1.12).\textsuperscript{56}

**Scheme 1.12** Baylis-Hillman and tritylation reactions catalysed by 22

![Scheme 1.12 Baylis-Hillman and tritylation reactions catalysed by 22](image)
1.3.3 Substituted pyridine: Structure – activity relationship

As illustrated in the reactions outlined in Section 1.3.2, 22 is a highly versatile nucleophilic catalyst with significant synthetic potential. Considerable attention has also recently been given to the design of asymmetric variants of 22—a topic that will be discussed fully in Section 1.4. Before this discussion begins it is perhaps useful to summarise the factors (in a structural context) which contribute to the high catalytic activity of DMAP-analogues.

The superior reactivity of 22 (22^+H, pK_a = 9.70) compared to pyridine (19^+H, pK_a = 5.29) could be attributed to their distinct basicities, however, experimentation has shown that pyridine and its derivatives act as nucleophilic bases rather than general base catalysts of acylation reactions. Litvinenko et al. demonstrated that alkyl substitution in the 2- and 6-position of the pyridine ring (entries 2 and 4, Table 1.6) leads to a dramatic decrease in catalytic activity while their relative pK_a show minimal alteration. Further substantiation is provided in the case of NEt_3 (pK_a = 10.65) where the considerable steric hinderance around the amine, results in negligible catalyst turnover in the benzoylation of m-chloroaniline (entry 6). Recently, theoretical analysis by Zipse and Held demonstrated that methyl substitution α to the active site led to a 22.0° distortion of the dihedral angle Θ(O/C/N/C) out of the plane of the pyridine ring, that decreased the resonance stabilisation of the acylated intermediate by 16kJ/mol.

Table 1.6 Benzoylation of m-chloroaniline promoted by substituted pyridines and NEt_3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>pK_a</th>
<th>Rel. rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>5.23</td>
<td>5.68</td>
</tr>
<tr>
<td>2</td>
<td>2-methylpyridine</td>
<td>5.96</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>4-methylpyridine</td>
<td>6.02</td>
<td>2.96 x 10^5</td>
</tr>
<tr>
<td>4</td>
<td>2,6-dimethylpyridine</td>
<td>6.72</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>9.70</td>
<td>3.14 x 10^6</td>
</tr>
<tr>
<td>6</td>
<td>NEt_3</td>
<td>10.65</td>
<td>21</td>
</tr>
</tbody>
</table>

a Refers to R_N-H at 25 °C in H_2O. b compared to reaction rate without added amine
Subsequent optimisation studies of the (4-dimethylamino)pyridine framework by Hassner et al.\textsuperscript{59} found that 4-pyrrolidinopyridine 42 was the most effective analogue for catalysis of the acylation of 1-methylcyclohexanol. However, recently Steglich et al.\textsuperscript{60} have shown that the conformationally restricted tricyclic aminopyridine 43, possesses even greater catalytic activity.

**Table 1.7** Relative rates of reaction for DMAP derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Rel. rate</th>
<th>$\delta(^1H)$</th>
<th>$\beta$-H/ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>1</td>
<td>6.48</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>2.4</td>
<td>6.38</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>6</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Hassner et al.\textsuperscript{59} postulated that the catalytic activity of 22 and 42 could be correlated with the degree of shielding of the $\beta$-hydrogen (as demonstrated by $^1$H NMR spectroscopic analysis: 6.48 and 6.38 ppm respectively), itself governed by the resonance stabilisation afforded to the acylated pyridinium ion by the lone pair of electrons on the exocyclic amine.

The mechanism of nucleophilic catalysis \textit{i.e.} acylation of alcohol/water (Scheme 1.6) by the formation of an $N$-acyl pyridinium salt, with subsequent alcoholysis and concomitant deprotonation fails to explain a number of significant observations; namely: 1) the counterintuitive solvent dependency of 22, with limited Lewis adduct formation in apolar solvents that affords optimal catalyst turnover, 2) the variable rate of acylation achieved with acid chlorides and anhydrides and 3) the ability of the auxiliary base to augment the rate of reaction. An investigation of these anomalies follows.

The formation of $N$-acyl pyridinium salts is a reversible reaction, with the equilibrium dependent on the stability of the acylated intermediate. Steglich found that acetylation of 19, 22, 42 and 44 (a $t$Bu derivative of 19) with acetyl chloride in CDCl\textsubscript{3} resulted in
complete conversion to their respective salts (Scheme 1.13a), although the N-acetylpyridinium chloride salt of 19 proved to be insoluble in aprotic solvent and therefore of limited synthetic utility. Reaction of acetic anhydride with 19, 22 and 42 led to 5-10% formation of the pyridinium acetates of 22b and 42b with no detectable formation of the N-acetylpyridinium acetate of 19. The superior stability of the chloride salts over the acetate salts is attributed to the higher nucleofugacity associated with chloride anions which tightly bind to the cation, while the increased resonance stabilisation (mesomeric effect) of the substituted pyridines 22b and 42b accounts for the preferential formation of their pyridinium acetates over the unsubstituted pyridine 19. (Scheme 1.13b).

**Scheme 1.13**  (a) Formation of acyl-pyridinium chloride and acetate salts (b) mesomeric effect on 22.

![Scheme 1.13](image)

Evidence for the existence of the mesomeric effect can be found in the IR carbonyl stretching frequencies and $^1$H NMR chemical shifts of the acetyl methyl signal. In the case of 22a and 22b resonance stabilisation affords an apparently less reactive intermediate (1755 cm$^{-1}$, δ 3.04) than 44a (1800 cm$^{-1}$, δ 3.53) with the positive charge localised on the pyridine ring nitrogen.
From the analysis of the data (IR, $^1$H NMR and conversion) it would appear that in solution 44a would be most susceptible to nucleophilic attack. However as clearly illustrated in Table 1.8, 22a promotes the acylation of the hindered alcohol three times faster than the apparently more activated 44a. In this instance the mesomeric stabilisation of the acylated intermediate affords a wider ion pair i.e. 22b-2 or -3, mediating a less hindered attack on the pyridinium ion.

**Table 1.8** Comparison of 22 and 44 as catalysts for the acetylation of 40 with both acetyl chloride and acetic anhydride.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conc. (mol%)</th>
<th>X</th>
<th>$t_{1/2}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>0.6</td>
<td>OCOCH$_3$</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>0.6</td>
<td>Cl</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>0.6</td>
<td>Cl</td>
<td>60</td>
</tr>
</tbody>
</table>

Rate acceleration is also observed on changing the acylating agent from acetyl chloride to acetic anhydride in CDCl$_3$ (entries 1 and 2, Table 1.8). This is remarkable given that a maximum of 10% of 22b is present in solution compared to 100% of 22a, alluding to strong anion dependence on catalytic turnover in a non-polar solvent.

Based on this data an assumption is made that the anion acts as a general base in a concerted deprotonation of the alcohol as it attacks the acylated intermediate, therefore to maximise rate, a loosely bound, basic ion would be advantageous. Investigation by Albert and Kattwig$^{61}$ found that acylation of 1-propanol 45 in the presence of a heterogeneous base (K$_2$CO$_3$) proceeded with a 10 fold increase in efficiency when acetic anhydride was used in place of acetyl chloride (Table 1.9). This indicates that the deprotonation of the alcohol in the transition state is dependent on the basicity of the anion (AcO$^-$ > Cl$^-$) and is rate determining; a theory further supported by the observation of even faster acylation using acetyl cyanide (HCN, pK$_a$ = 9.4), promoting faster reaction. Albert et al.$^{61}$ also noted that in the presence of 19 the relative reaction times for acetyl chloride and acetic anhydride reversed, with 19 acting predominantly as an auxiliary base.
Table 1.9  
Rates of acylation of 45 catalysed by 22 with three different acylating agents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Acylating agent</th>
<th>pKₐ* of anion</th>
<th>T₁/₂ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>Ac₂O</td>
<td>4.75</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃</td>
<td>AcCl</td>
<td>-1.7</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃</td>
<td>AcCN</td>
<td>9.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*a Refers to the pKₐ of the conjugate acid (H₂O, 25 °C) of the anion liberated on attack of 22 on the acylating agent

The formation of a salt from neutral species generally necessitates a polar solvent to solvate the resultant ions in order to prevent back reaction to the starting materials. Conversely, Hassner *et al.*⁵⁹ demonstrated that acylation of 1,1-diphenylethanol in the presence of either 22 or 42 proceeded with greater efficacy in non-polar solvents than in polar solvents. Recently confirmation of the requirement for a non-polar solvent system was obtained by Zipse *et al.*⁶² Theoretical calculations preformed on the reaction of acetic anhydride with *tert*-butanol catalysed by 22 found that polar solvents raise the barrier to reaction *via* solvation of the reactants.

An increase in the rate of reaction of 19 over 22 is observed in protic solvents, with the rate of hydrolysis of *N*-acetylpyridinium chloride 2000 times faster than that of the dimethylamino derivative.⁶³ This result correlates with the observed spectral data, with the respective pyridinium cations reacting independently of the solvated anions *i.e.* general base catalysis of the alcoholysis is less favoured.

In conclusion, a number of factors can influence the rate of acylation reactions catalysed by 22 and related analogues. Mesomeric stabilisation of the *N*-acyl pyridinium salt is clearly important, as is the use of an acylating agent which generates an anion of sufficient basicity to act as a general base catalyst for the deprotonation of the alcohol upon addition to the pyridinium ion intermediate and the use of a non solvating apolar solvent system.

23
1.4 Chiral DMAP analogues

As a consequence of the synthetic utility and commercial availability of 22 (Section 1.3.2 and 1.3.3), several thousand patents and papers pertaining to 22 and its derivatives have materialised since its discovery in the late 1960s. In light of this versatility and reactivity it is surprising that the first examples of a chiral DMAP catalyst appeared as recently as 1996 when Vedejs and Fu both independently reported chiral analogues of 22 that promoted asymmetric acyl transfer.

In designing chiral DMAP analogues, one would assume that the same activity constraints are encountered as in their achiral counterparts. As discussed in Section 1.3.3, substitution in the 2- or 6-position results in poor nucleophilicity; consequently hyper-nucleophilic achiral derivatives lack \( \alpha \)-substitution. Unfortunately when designing a chiral catalyst it is desirable to place the stereochemical information as close to the active site as possible to maximise its influence on the stereochemical outcome of the reaction. Herein lays an activity-selectivity conundrum: bulky substituents \( \alpha \)-to the ring nitrogen facilitate enantio-discrimination while simultaneously attenuating catalyst activity. Therefore a successful catalyst design must represent a compromise between these opposing constraints. Thus over the last decade, several groups have endeavoured to synthesise asymmetric variants of 22 and a summary of their work follows.

1.4.1 The first chiral DMAP derivative from Vedejs' group

In 1996 Vedejs published a pioneering paper on the KR of secondary alcohols utilising the first chiral DMAP based reagent 47. A range of alkyl aryl carbinols were isolated with 20-44% yield and \( \text{ca. 90\% ee} \), equating to selectivities in the range of 12-53 (Table 1.10). It was hypothesised that enantiodiscrimination was achieved by the rotation of the benzylic substituents placing the \( \tau \)-butyl and methoxy substituents on opposing sides of the pyridine ring plane. Unfortunately the decision to tether the selectivity determining steric bulk to the 2 position resulted in stoichiometric amounts of 47 being required in addition to a Lewis acid (2 equiv.) and a tertiary amine (3 equiv.) to activate the acylated intermediate.
Table 1.10  
Acylation of sec-alcohols catalysed by 47

\[
\text{Ar}^+ \text{OH} + \text{Cl}_3\text{C} \text{OOC} \text{Cl} \xrightarrow{\text{47} \text{ (100 mol\%)} \ \text{CH}_2\text{Cl}_2, \text{RT}} \text{Lewis acid (2 equiv.)} \ \text{Amine (3 equiv.)} \xrightarrow{} \text{Ar}^+ \text{OH} + \text{Cl}_3\text{C} \text{C}_\text{OOC} \text{Ar}^+ \text{Cl}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Lewis acid</th>
<th>Amine</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>ArOH (%ee)</th>
<th>Ester (%ee)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-Np</td>
<td>MgBr₂</td>
<td>NEt₃</td>
<td>17</td>
<td>54</td>
<td>87</td>
<td>84</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>2-Np</td>
<td>ZnCl₂</td>
<td>NEt₃</td>
<td>52</td>
<td>24</td>
<td>30</td>
<td>94</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>2-Tol</td>
<td>ZnCl₂</td>
<td>PMP</td>
<td>43</td>
<td>39</td>
<td>59</td>
<td>93</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>ZnCl₂</td>
<td>NEt₃</td>
<td>40</td>
<td>25</td>
<td>NA</td>
<td>93</td>
<td>38</td>
</tr>
</tbody>
</table>

Refining the initial reagent design based on activity considerations led to the subsequent synthesis of 48, a C-3 substituted chiral-DMAP catalyst capable of achieving significantly better catalyst turnover due to the removal of steric hinderance in the vicinity of the nucleophilic ring nitrogen. However the attempted KR of secondary alcohols with 48 ended in relative failure with an optimum selectivity factor of 4.4 achieved for sec-naphthyl ethanol.⁶⁶ Undeterred, Vedejs et al. successfully employed 48 as a catalyst for the Steglich rearrangement of oxazolyl and furanyl enol carbonates,⁶⁷ generating enantioenriched aza-lactones incorporating quaternary chiral centres with potential use as precursors to chiral lactam derivatives and lactone synthesis in addition to natural products.⁶⁸

Table 1.11  
Steglich rearrangement catalysed by 48

\[
\text{Ar} = p-\text{MeOC}_6\text{H}_4
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>X</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>50:51 (%ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>N</td>
<td>12⁴</td>
<td>95</td>
<td>100:0</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>C</td>
<td>24⁵</td>
<td>83⁶</td>
<td>10:1</td>
</tr>
</tbody>
</table>

⁴ Reaction carried out at 0 °C, in t-A.A. ⁵ Reaction carried out in THF at RT ⁶ 7% yield of 51 with 80% ee
1.4.2 Development of planar chiral catalysts by Fu

Independently in the same year Fu\(^6\) reported the synthesis of (\(\pi\)-heterocycle) FeCp complexes 52 and 53a as nucleophilic catalysts for a range of transformations including the acylation of secondary alcohols with diketene (Scheme 1.14). Activity studies indicated that catalytic turnover was greatest for 53a, however initial investigations into KR of secondary alcohols concluded that 52 was the more selective and could catalyse the KR of 1-naphthylethanol (54) at 10 mol\% loading with a selectivity factor of 6.5 in the presence of diketene (Scheme 1.4).

The catalyst design was based on the robust and versatile nature of 22 with the introduction of asymmetry requiring the destruction of the two mirror planes \(i.e.\) one in the plane of the pyridine ring and the other running perpendicular through the two nitrogen atoms. \(\pi\)-Complexation of an iron cyclopentadienyl group to the heterocycle provided top/bottom selectivity \(i.e.\) FeCp vs. nothing, while alkyl substitution in the 2-position resulted in left/right differentiation \(i.e.\) alkyl vs. H. In the case of 52, a five membered heterocycle was favoured in place of the pyridine ring to generate a more stable 18-electron complex.

Scheme 1.14 Fu’s chiral heterocyclic metal catalysts and KR of 54

In designing the second generation catalyst, Fu took inspiration from the activity associated with 53a and surmised that an increase in the steric environment around the ferrocene moiety would promote greater enantiodiscrimination. The use of the ferrocene moiety was an excellent choice on two fronts; firstly it was electron rich, increasing the
nucleophilicity of the catalyst and counteracting the decrease in activity associated with fusing a cyclopentyl ring to 22. Secondly the steric environment is easily tuneable by modifying the steric bulk of the cyclopentadienyl rings.

Catalyst 53b was later shown to be capable of promoting the acylation of a diverse range of aryl-alkyl carbinols with high levels of selectivity at low catalyst loadings (2 mol%). Selectivity was shown to increase upon substrate alkyl substitution, with maximum selectivity achieved for the t-butyl analogue. Subsequent optimisation studies found that reaction at 0 °C in t-amyl alcohol afforded greatest selectivity for 53b (entries 3-8, Table 1.12).

Table 1.12 KR of a variety of sec-alcohols catalysed by 53a, b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Substrate</th>
<th>T (°C)</th>
<th>Conv. (%)</th>
<th>Solvent</th>
<th>Alcohol ee (%)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53a</td>
<td>9</td>
<td>RT</td>
<td>67.5</td>
<td>Et2O</td>
<td>26.7</td>
<td>1.7</td>
</tr>
<tr>
<td>2</td>
<td>53b</td>
<td>9</td>
<td>RT</td>
<td>61.2</td>
<td>Et2O</td>
<td>95.2</td>
<td>13.6</td>
</tr>
<tr>
<td>3</td>
<td>53b</td>
<td>9</td>
<td>0</td>
<td>55</td>
<td>t-A.A</td>
<td>99</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>53b</td>
<td>56</td>
<td>0</td>
<td>54</td>
<td>t-A.A</td>
<td>99</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>53b</td>
<td>57</td>
<td>0</td>
<td>52</td>
<td>t-A.A</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>53b</td>
<td>58</td>
<td>0</td>
<td>51</td>
<td>t-A.A</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>53b</td>
<td>54</td>
<td>0</td>
<td>52</td>
<td>t-A.A</td>
<td>95</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>53b</td>
<td>59</td>
<td>0</td>
<td>51</td>
<td>t-A.A</td>
<td>99</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

Further classes of alcohols were identified as suitable to be resolved under these optimised conditions. KR of propargylic alcohols such as 60 promoted by 53b generated moderate selectivities (S = 8-20) (eq 1, Scheme 1.15). Allylic alcohols proved to be superior substrates (S = 5-107) (eq. 2). Racemic diols (>98% ee) and meso-diols could also be effectively desymmetrised in high yield and selectivity (eq. 3, 4). Fu also accomplished the
resolution of amines. The KR of these substrates had proved elusive due to the inherent nucleophilicity of the amines, with acylation occurring in the absence of catalyst. Resolution was carried out by the use of an O-acylated azalactone that would not react with the amine in an uncatalysed reaction. The acylative resolution of 68 promoted by 53c proceeded with synthetically useful selectivity (eq. 5).\textsuperscript{73}

Scheme 1.15  Sample of substrates resolved in presence of 53b and 53c

Expansion of the substrate scope to include further nucleophile catalysed reactions has resulted in the asymmetric synthesis of β-lactams\textsuperscript{74} and β-lactones\textsuperscript{75} via the addition of imines and aldehydes to ketenes respectively and also from the DKR of azo-lactones\textsuperscript{76} and the C-acylation of silyl ketene acetals\textsuperscript{77} and imines.\textsuperscript{78}
Has been shown to be a versatile catalyst, promoting a wide range of reactions enantioselectively with efficient catalytic turnover; no more than 1-2 mol% is generally required. The catalyst is also readily recyclable and is air and moisture insensitive with reactions exposed to air catalysed by 53b affording identical enantioselectivities. However synthesis of 53b is non-trivial and requires an expensive resolution step, coupled with long reaction times (20-40 h).

1.4.3 Atropisomeric DMAP derived catalysts

In 1998 Spivey reported the synthesis of ‘axially chiral’ analogues of 22, i.e. 71a, with chirality resulting from the restricted rotation about the biaryl bond at C-5 on the pyridine ring, resulting in two non-interconvertable enantiomeric conformations i.e. atropisomers (Figure 1.5). Initial acylation studies using the standard tertiary alcohol 1-methylecyclohexanol (20) and Ac₂O indicated a catalytic activity comparable to 22.

Figure 1.5 A selection of Spivey’s atropisomeric catalysts.

Owing to the inherent activity of 71a, enantioselective acylations could be performed with 1 mol% catalyst at low temperatures, allowing for greater selectivity. Unfortunately, the KR of 54 at -78 °C was only moderately selective with \( k_{rel} = 2.5 \) (Table 1.13, entry 1). It was felt that insufficient top/bottom differentiation was responsible for the limited selectivity, thus catalyst 71b was synthesised. This generated a slight increase in selectivity \( (k_{rel} = 4.7) \) (entry 2) not appreciable enough to regard it as ‘practically useful’. Further deliberations led to Spivey et al. postulating that left/right differentiation was lacking as both meta positions relative to the ring nitrogen had carbon substituents. This pseudo symmetry promoted an almost equivalent rate of nucleophilic attack on the open face of the pyridinium salt. Therefore 72a was envisioned as a more chirally distinct catalyst with
a configurational stability far in excess of that associated with 71b. Subsequent KR of 54 generated a two fold increase on the previous optimum selectivity factor ($k_{rel} = 9.7$) (entry 3).

Optimisation studies were carried out which determined that the non-polar toluene was the solvent of choice with a sterically more hindered acylating agent i.e. iso-butyric anhydride. Use of these optimised conditions afforded a trebling of selectivity ($k_{rel} = 29$) (entry 4). A range of alcohols were tested with selectivity markedly improved by ortho-substitution (entries 5 and 6).

Table 1.13  KR of a range of sec-alcohols catalysed by 71a, b, 72a, b, c, d and 73

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Substrate</th>
<th>R'</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>ee$_A$ (%)</th>
<th>ee$_E$ (%)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71a</td>
<td>54</td>
<td>Me</td>
<td>2</td>
<td>18.3</td>
<td>9</td>
<td>40.1</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>71b</td>
<td>54</td>
<td>Me</td>
<td>2</td>
<td>17.6</td>
<td>13.1</td>
<td>61.2</td>
<td>4.7</td>
</tr>
<tr>
<td>3</td>
<td>72a</td>
<td>54</td>
<td>Me</td>
<td>2</td>
<td>5.7</td>
<td>4.9</td>
<td>80.5</td>
<td>9.7</td>
</tr>
<tr>
<td>4</td>
<td>72a</td>
<td>54</td>
<td>i-Pr</td>
<td>8</td>
<td>22.3</td>
<td>26.3</td>
<td>91.4</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>72a</td>
<td>74a</td>
<td>i-Pr</td>
<td>9.5</td>
<td>41.4</td>
<td>60.7</td>
<td>86</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>72a</td>
<td>74b</td>
<td>i-Pr</td>
<td>8</td>
<td>19.0</td>
<td>21.3</td>
<td>90.7</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>72b</td>
<td>54</td>
<td>i-Pr</td>
<td>9</td>
<td>70</td>
<td>67.5</td>
<td>28.5</td>
<td>3.5</td>
</tr>
<tr>
<td>8</td>
<td>72c</td>
<td>54</td>
<td>i-Pr</td>
<td>14.2</td>
<td>37</td>
<td>53.6</td>
<td>90.8</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>72d</td>
<td>54</td>
<td>i-Pr</td>
<td>6.6</td>
<td>15</td>
<td>16.8</td>
<td>94.1</td>
<td>39</td>
</tr>
<tr>
<td>10</td>
<td>73a</td>
<td>9</td>
<td>Me</td>
<td>2</td>
<td>45.8</td>
<td>18</td>
<td>14.5</td>
<td>1.8</td>
</tr>
</tbody>
</table>

$^a$ ee$_A$ = ee of recovered alcohol, ee$_E$ = ee of ester product. $^b$ Reaction carried out at -93 °C. $^c$ 2 mol% catalyst used.

The role of π-systems in the selectivity determining step between the acylated pyridinium intermediate and benzoates of cis-cyclohexane-1,2-diols was explored. Although they proved to be useful substrates ($k_{rel} = 5.5 -19.7$, Scheme 1.16) no obvious trend with regards to the sense of stereoinduction promoted by 72a i.e.76a (1S,2R) and 76b (1R,2S) or the electronic nature of the benzoates was observed. In addition the successful KR of a purely aliphatic substrate i.e. 1-cyclohexylethanol was promoted by 72a in moderate selectivity ($k_{rel} =8.4$).
Scheme 1.16 KR of monobenzoates of cis-cyclohexane-1,2-diol by 72a

\[
\begin{align*}
\text{OH} & \quad \text{O} \quad \text{O} \\
\text{R} & \quad \text{R} & \quad \text{PrCO}_2 \text{O} (2 \text{ equiv.)} \\
\text{NEt}_3 (0.75 \text{ equiv.)} & \quad \text{72a} (1 \text{ mol%}) \\
toluene, -78^\circ \text{C}, 9 \text{ h} & \quad (\text{rac})-76a, \text{ R} = \text{H} \\
& \quad (\text{rac})-76b, \text{ R} = \text{NMe}_2 \\
& \quad (\text{rac})-76c, \text{ R} = \text{NO}_2
\end{align*}
\]

(1S, 2R)-76a, S = 19.7 \\
(1R, 2S)-76b, S = 16.1 \\
(1R, 2S)-76c, S = 5.7

The design of the next generation of catalyst relied on the X-ray crystal structure of 72a, this showed that the diethylamino group adopted a chiral confirmation due to the ortho chiral naphthyl moiety. Spivey et al. postulated that the alkyl group influenced the positioning of the counter ion of the pyridinium salt and therefore played an active role in determining selectivity. Affirmation of this hypothesis was given on synthesis of the pyrrolidine derivative 72b and the n-butyl derivative 72c. Use of 72b resulted in a significant attenuation in selectivity whereas 72c proved to be the most selective catalyst owing to the chirally distinct alkyl moieties. Unfortunately due to the increased alkyl substitution, solubility proved to be an issue resulting in poor catalyst activity.

Recently a third generation atropisomeric catalyst 72d has been developed by the same group which synergistically employs the increased facial selectivity afforded by 71b and the left/right differentiation associated with 72a facilitating a moderate increase in selectivity (S = 39) while decreasing catalytic activity. These results persuaded Spivey et al. to investigate a more practical catalytic system capable of operating at room temperature. Thus the highly active and readily available 72a (1 mol%), in conjunction with 2,6-di-(t-Bu)-pyridine in t-amyl alcohol and PPh3 as an achiral additive was found to successfully mediate the KR of 54 in 30 min with S = 15.5.

A C2-symmetric PPY catalyst (73) was also synthesised by Spivey et al. with the aromatic moiety expected to π-π stack with the electron deficient acylated pyridinium ring intermediate providing enantiodiscrimination. The selectivities however were truly modest (krel = 1.8) and further elaboration of catalyst design was subsequently discontinued.

Spivey et al. have synthesised an active acylation catalyst that is readily available in three steps including resolution (34% overall yield). 72a Could be effectively utilised in the KR.
of a variety of sec-alcohols and with the addition of PPh₃, viable selectivities (S > 10) are achieved at ambient temperatures.⁸⁴

1.4.4 Catalysts that employ remote chirality using an induced fit mechanism

In 1997, Fuji reported the synthesis of a novel nucleophilic catalyst 78 based on the PPY structural motif with stereochemical information installed at the C-4 position. 78 was employed in the KR of a range of mono protected diols⁸⁷ and cyclic amino alcohol⁸⁸ derivatives at ambient temperature (S = 4.7 – 21).

The mode of action of 78 was based on an ‘induced fit’ mechanism (Figure 1.6) elucidated by ¹H NMR and NOE studies. In the unacylated form (conformation A) the catalyst lies open and unhindered with the naphthyl group free to rotate in space; NOE studies show no interaction of the naphthyl moiety with the pyridine ring. However, on acylation (conformation B) it is proposed that the catalyst blocks the si face of the acylated pyridinium intermediate by a π-cation interaction between the naphthyl group and the positively charged pyridinium ring, resulting in stereoselective addition.

Figure 1.6 Catalyst 78 in both open and closed conformations, with arrows indicating observed NOEs.

However, in Fuji’s appraisal of the catalyst’s mode of action a number of possible points of contention remain. The ¹H NMR data suggests an uneven distribution of electron density on the acyl-pyridinium ion (Hₜ δ 5.69 ppm in comparison to Hₜ δ 6.87 ppm) implying a less than perfect π-π alignment or a pseudo side on conformation. Fuji also neglected the potential H-bonding ability of the hydroxyl group, which is interesting in view of the
increase in selectivity observed for substrates with more pronounced Lewis basic carbonyl moieties.

The KR of mono protected diols proceeded preferentially with electron rich aromatic substituents over alkyl groups (entry 1-3, Table 1.13). A similar trend was observed for the amino alcohol derivatives with protection of the amine functionality affording a means of resolving these challenging substrates (entries 4-6).

**Table 1.13**  KR of substituted cyclohexyl diols and amino alcohols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Cat. (mol%)</th>
<th>Conv. (%)</th>
<th>ee ( e )</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79a</td>
<td>toluene</td>
<td>4</td>
<td>5</td>
<td>68</td>
<td>94</td>
<td>8.3</td>
</tr>
<tr>
<td>2</td>
<td>79b</td>
<td>toluene</td>
<td>5</td>
<td>5</td>
<td>73</td>
<td>54</td>
<td>2.4</td>
</tr>
<tr>
<td>3</td>
<td>76b</td>
<td>toluene</td>
<td>3</td>
<td>5</td>
<td>72</td>
<td>&gt;99</td>
<td>&gt;10.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>79c</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>5</td>
<td>69</td>
<td>72</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>79d</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>9</td>
<td>5</td>
<td>63</td>
<td>&gt;99</td>
<td>&gt;18</td>
</tr>
<tr>
<td>6</td>
<td>79d</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>0.5</td>
<td>66</td>
<td>&gt;99</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>

<sup>a</sup> At 65% conversion the substrate was present in 97% ee, i.e. S = 12.3.

The enantioselectivity generated by resolution of the amino alcohol derivative 79d (entry 5) was found to increase significantly on KR at -40 °C (S = 54). Regardless, due to the tedious catalyst synthesis involved and a lack of modifiable groups to improve activity, the practical application of this catalyst is not feasible, although this catalyst is certainly interesting from a mechanistic point of view.

In a similar vein to Fuji's 'induced-fit' catalyst and independent of our own experimentation (Section 2.1), Yamada, building on initial investigations into an intramolecular \( \pi \)-cation complex, recently reported a 'conformation switch system' 81a.
(Scheme 1.17) based on a chiral C-3 substituted analogue of 22 capable of resolving a variety of sec-alcohols at ambient temperature with 0.5 mol% catalyst.\(^9\)

The π-pyridinium interaction occurs upon formation of an acyl pyridinium ion derived from the unhindered \(81a\) and is based on an attractive interaction between the thiocarbonyl moiety and the aforementioned heterocyclic ion (a theory supported by \(^1\)H NMR studies on a methylated derivative of \(81a\)). This effectively provides top/bottom differentiation with left/right discrimination speculated to arise from the steric repulsion of the amide functionality in the thiazolidine-2-thione.

**Scheme 1.17** ‘Conformation switch system’ catalyst \(81a\) and its use in the KR of sec-alcohols

As a catalyst for the acylative KR of sec-alcohols, \(81a\) proved remarkably insensitive to substrate steric bulk or electronic character (Scheme 1.17), affording the \((S)\)-enantiomer of the unreacted alcohol in each case. Optimum selectivity was achieved using \(iso\)-butyric anhydride and \(\text{-BuOMe}\) as the acylating agent and solvent respectively. Substitution of the thiazolidine-2-thione (\(81a\)) for an oxazolidine-2-one analogue (\(81b\)) led to a dramatic decrease in selectivity for the KR of \(83\) (\(81a\), \(S = 11\) and \(81b\), \(S = 2.7\)).
1.4.5 Catalysts incorporating H-bond donors

In 2002 Campbell and fellow researchers at GlaxoSmithKline synthesised a library of readily available catalysts, again taking inspiration from Fuji’s enzyme mimic design. Mono-protected cis-diols were chosen as substrates for KR as they had already proven to be excellent substrates in KR reactions using catalyst 78. $K_{rel}$ values as high as 18.8 were achieved for the most selective catalysts at ambient temperature.$^{91}$

The design of the catalyst series relied on the facile modification of the final synthetic step to afford catalysts tuneable to substrate demands. A total of 31 compounds were prepared in a concise manner via the coupling of amine or alcohol to the carboxylic acid group of $\alpha$-methyl proline, 84.$^{92}$

**Scheme 1.18 Synthesis of analogues of 85**

A small family of catalysts based on an N-4'-pyridinyl-$\alpha$-methyl proline framework i.e. 85, were synthesised and employed in catalysing the KR of 76b. Catalysts 85a and 85b incorporating electron rich and electron poor aromatic moieties respectively promoted reactions with comparable enantioselectivities (entries 1 and 2, Table 1.14), while catalyst 85d with a tetrahydrofuran moiety fused to a phenyl ring promoted the most selective resolution (entry 4, $s = 13.2$). Non aromatic moieties i.e. $\mathrm{t}$-Bu and Et (85c, entry 3) were similarly effective at resolving alcohol 76b by acylation, suggesting an alternative mode of action to 78, further supported by the failure of tertiary amines (85e, entry 5) or esters to promote selective reactions. This implicated H-bonding of the amide functionality in the mediation of enantioselective acyl transfer. Solvent studies reaffirmed this postulate with non-solvating apolar solvents such as toluene generating greatest selectivity in conjunction with iso-butyric anhydride.
Subsequent investigations into the use of alternative sec-alcohols found that amino alcohol derivatives (entry 7) were superior substrates to mono-protected diols and that substrates possessing cis-relative stereochemistry underwent more selective acylation than their corresponding trans isomers (entry 6). It was also found that 85a-e did not promote highly enantioselective acylation of substrates lacking carbonyl moieties in close proximity to the hydroxyl group.

Table 1.14  KR of mono-protected diols and amino alcohol derivatives by 85a-e

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Cat</th>
<th>Conv. (%)</th>
<th>ee&lt;sub&gt;A&lt;/sub&gt;</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76b</td>
<td>85a</td>
<td>64</td>
<td>93</td>
<td>10.1</td>
</tr>
<tr>
<td>2</td>
<td>76b</td>
<td>85b</td>
<td>62</td>
<td>88</td>
<td>9.2</td>
</tr>
<tr>
<td>3</td>
<td>76b</td>
<td>85c</td>
<td>64</td>
<td>89</td>
<td>8.4</td>
</tr>
<tr>
<td>4</td>
<td>76b</td>
<td>85d</td>
<td>62</td>
<td>95</td>
<td>13.2</td>
</tr>
<tr>
<td>5</td>
<td>76b</td>
<td>85e</td>
<td>51</td>
<td>32</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>76b</td>
<td>85d</td>
<td>44</td>
<td>14</td>
<td>1.6*</td>
</tr>
<tr>
<td>7</td>
<td>79d</td>
<td>85d</td>
<td>59</td>
<td>96</td>
<td>18.8</td>
</tr>
</tbody>
</table>

*a Selectivity obtained in the acylation of trans-76b.

While an improvement in the level of asymmetric induction over that achieved by Fuji was not obtained, a definite insight into the mode of action for catalysis was provided. This is proof positive that catalyst-substrate H-bonding interactions can be an effective means of bringing about enantiodiscrimination between fast and slow reacting substrate antipodes. A solid supported analogue of 85 with similar k<sub>rel</sub> values has also been recently reported by Campbell et al.<sup>93</sup>

1.4.6  Alternative DMAP-based catalyst designs

As the examples outlined above indicate, significant advances in catalyst design have enabled the kinetic resolution of a range of racemic substrates, with some catalyst systems approaching the levels of efficiency/selectivity normally associated with enzymatic systems. However, limitations still abound in terms of practical applicability, i.e. substrate specificity, laborious catalyst syntheses (sometimes involving inefficient resolution steps)
and catalyst instability. Therefore the field continues to generate interest with a host of alternative catalytic systems continually emerging (Figure 1.7).

Figure 1.7  KR catalysts 86 – 92

Investigations by Kim <i>et al.</i><sup>94</sup> led to the design of 86. To induce enantiodiscrimination and to avoid steric inhibition of catalytic activity C-3-substitution of 22 by Kemp’s triacid<sup>95</sup> coupled to an axially chiral binaphthyl moiety affords a nucleophilic catalyst with promising enantiobias. A range of aryl-alkyl alcohols were resolved in <i>t</i>-amyl alcohol with <i>k</i> increasing with increased alkyl substitution (Me < <i>t</i>-Bu, S = 4.4 and 13.3 respectively). The acylation of <i>trans</i>-2-phenyl cyclohexanol (93) in the presence of 86 afforded optimum selectivity (S = 21) with the (1<i>S</i>,2<i>R</i>) enantiomer of the racemate recovered after reaction (entry 1, Table 1.15).

In 2003, a collaboration between Fuji and Kawabata<sup>96</sup> generated a library of substituted chiral <i>N</i>-(4-pyridinyl)prolines of which 87b proved to be the most efficacious promoter of the enantioselective acylation of the amino alcohol 79d (1<i>S</i>,2<i>R</i>) (S = 11, entry 2). H-bonding and π-stacking appeared to play pivotal roles in enantiodiscrimination as ester 87a (S = 1.1) and <i>iso</i>-propyl derivative 87c (S = 1.6) failed to promote acylative KR reactions with high selectivity.
Table 1.15  Range of substrates resolved by catalysts 86-92

\[
\begin{align*}
\text{Ph} \quad 86 \quad \text{(1 mol\%)} \\
\text{Ac}_2\text{O} \quad (1 \text{ equiv.)} \\
t-\text{A.A.}, 2 \text{ h, 0 °C} \\
\text{Ph} \quad 87b \quad (5 \text{ mol\%)} \\
(\text{iPrCO})_2\text{O} \quad (0.7 \text{ equiv.)} \\
collidine \quad (1 \text{ equiv.)} \\
\text{CHCl}_3, 12 \text{ h, 20 °C} \\
\text{Ph} \quad 89 \quad (5 \text{ mol\%)} \\
t-\text{A.A.}, 16 \text{ h, 0 °C - RT} \\
\text{Ph} \quad 90 \quad (5 \text{ mol\%)} \\
\text{Ac}_2\text{O} \quad (2 \text{ equiv.)} \\
\text{NEt}_3 \quad (0.6 \text{ equiv.)} \\
\text{Acetone, -78 °C} \\
\text{Ph} \quad 91 \quad (2 \text{ mol\%)} \\
\text{Ac}_2\text{O} \quad (0.75 \text{ equiv.)} \\
\text{NEt}_3 \quad (0.75 \text{ equiv.)} \\
\text{THF, -78 °C} \\
\end{align*}
\]

Johannsen et al. synthesised 2-and 3-substituted ferrocene based planar chiral DMAP analogues (88 and 89). Resolution of sec-phenylethanol proved unsuccessful, due to a lack of catalyst activity. However the DKR of azalactone 95 via alcoholysis was possible using 89 as catalysts (entry 3). An X-ray crystal structure and molecular modelling studies indicated that the steric shielding environment around the catalyst active site was insufficient, leading Johannsen to propose that a more hindered aryl substituent would be essential in future catalyst designs of this type.

Levacher and co-workers prepared a novel catalyst in a single step utilising a Knochel substitution to generate enantiopure 90 in 60% yield from commercially available 3-bromo-4-(dimethylamino)pyridine. Modest selectivity and catalytic turnover were achieved at -78 °C in the acylation of optimum substrate 97 (entry 4) by acetic anhydride.
Diez et al. produced two novel catalysts, the first a C-2 symmetric material 91 closely related to Spivey’s original design (catalyst 73) and the second a C-2’ substituted PPY (92). Although the chiral information in 91 is further removed from the catalytic centre than in 73, a slightly more selective KR of 9 at -78 °C (S = 2.14) was achieved.

1.5 Non-pyridine based catalysts

Organocatalysed kinetic resolutions are not solely confined to chiral analogues of DMAP or PPY. Alternative methods incorporating proline derivatives, phosphines, carbenes, imidazoles and biomimetic approaches have been investigated and successfully employed in the KR of primary, secondary and tertiary alcohols along with the desymmetrisation of meso-diols. Similar activities and $k_{rel}$ values surpassing those of 47 and 53b (in some instances) have been obtained for non-pyridine based catalysts. An overview of the most relevant catalysts in terms of selectivity and/or mode of action ensues.

1.5.1 Aliphatic diamines

In 1998 Oriyama reported a proline-derived chiral diamine 98 for the asymmetric acylation of meso-1,2-cyclohexandiol. A stoichiometric amount of 98 was required in order to achieve efficient conversion. In the presence of BzCl and molecular sieves as an effective additive a yield of 62% of the monobenzylated adduct in 95% ee at -78 °C was obtained, with concomitant generation of the dibenzylated adduct (12% yield). Subsequent investigation found that the addition of an achiral amine i.e. NEt$_3$ (100 mol%) allowed the use of a catalytic amount of 99 while increasing the yield of the monobenzoate to 92% (97% ee) without production of the bis-product. Oriyama also reported the desymmetrisation of the more difficult primary 1,3-diols.

![Proline derived catalysts 98 and 99](image)

98 and 99 also catalysed the KR of epimeric sec-alcohols. Initial resolution of 93 with 99 (5 mol%) and BzCl was exceptionally selective (S = 200), 98 proved slightly less effective.
(S = 160) but showed remarkable activity, allowing for 0.3 mol% to catalyse the reaction in 3 h. Subsequently a range of cyclic (5-8 membered rings) and acyclic alcohols were successfully resolved by 98 (0.3 mol%) with moderate to excellent enantioselectivity (S = 4-170).\(^{104}\) Based on \(^1\)H NMR chemical shift analysis, Oriyama proposed a mode of action of 98 and 99 involving the synergistic chelation of the diamine to the carbon of the acylating agent in a bidentate manner prior to nucleophilic attack (ROH), thereby mediating enantioselective acyl transfer.\(^{105}\)

Table 1.16 Kinetic resolution of sec-alcohols by 98 and 99

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Cat.</th>
<th>Yield,(^a) (%)</th>
<th>ee(_A) (%)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>99</td>
<td>48</td>
<td>97</td>
<td>200</td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>98</td>
<td>49</td>
<td>95</td>
<td>160</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>98</td>
<td>43</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>74a</td>
<td>98</td>
<td>45</td>
<td>78</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield.  \(^b\) 5 mol% cat. used in reaction

Oriyama’s diamines 98 and 99 represent very efficient catalytic structures and are readily synthesised from (S)-proline in enantiopure form. They exhibit excellent catalytic turnover (0.3 mol%) and facilitate asymmetric acylations for a range of meso-diols and sec-alcohols and have recently been shown to promote the KR of primary alcohols.\(^{106}\) As a direct result 98 and 99 are considered model catalytic systems.

1.5.2 Phosphines

In addition to the previously reported (Section 1.4.1) chiral DMAP analogue 47, a chiral phosphine 100 capable of catalysing asymmetric acylations was developed by Vedejs in 1996.\(^{25}\) Selectivities of the order S = 12-15 were obtained for phenyl tert-butyl carbinol 58 at room temperature with \(m\)-chlorobenzoic anhydride as acylating agent.
Figure 1.9  Vedejs’ chiral, nucleophilic phosphine catalysts.

\[
\begin{array}{c}
\text{Me} & \text{Me} \\
\text{P-Ph} \quad \text{H,C} & \text{f-Bu} \\
100 \\
\end{array}
\]

The next generation catalyst 101 based on the ‘PBO’ motif \textit{i.e.} 2-phosphabicyclo-[3.3.0]octane was synthesised in enantiopure form (99.7 \% \textit{ee}).\textsuperscript{107} A >100 fold increase in catalytic turnover was observed using 101 as compared to 100. Increased reactivity allowed for the incorporation of less reactive anhydrides and lower reaction temperatures in an effort to maximise selectivity (entries 1 and 2, Table 1.17). Reactivity could also be improved through the efficient exclusion of \textit{O}_2, with \textit{H} NMR analysis indicating a 15-30\% oxidation of 101 to the corresponding phosphine oxide at the end of the reaction.

Table 1.17  KR of a range of allylic and alky carbino1 alcohols catalysed by 101

\[
\begin{array}{cccccc}
\text{Entry} & \text{Substrate} & \text{Temp} & \text{Time} & \text{Conv.} & \text{ee}_A \\
& & (\degree \text{C}) & (\text{h}) & (\%) & (\%) \\
1 & 54 & RT. & 5 & 41 & 50.2 & 10 \\
2 & 54 & -40 & 14 & 50.4 & 89.8 & 49 \\
3 & 74a & -40 & 4 & 50.1 & 95.3 & 145 \\
4 & 74a & -40 & 4 & 50.7 & 98.0 & 188 \\
5 & 104 & -40 & 16 & 44.4 & 78.8 & 369 \\
6 & 102a & -40 & 72 & 52.6 & 96.1 & 55 \\
7 & 102b & -40 & 25 & 40.3 & 64.2 & 82 \\
8 & 103a & -40 & 14 & 50.4 & 89.8 & 52 \\
9 & 103b & -40 & 46 & 37.7 & 56.4 & 52 \\
\end{array}
\]

Vedejs found an increase in catalyst optical purity from 99.7\% \textit{ee} to \textgreater99.99\% \textit{ee} by recrystallisation afforded a measured increase in selectivity (entries 3 and 4). Subsequent
reaction of methyl mesityl carbinol 104 with recrystallised 101 in the presence of iso-
butyric anhydride proceeded with exceptional enantiodiscrimination (S = 369) at -40 °C.\textsuperscript{39}
Allylic alcohols were also investigated, with the acylation of unsaturated substituted
cycloalkyl alcohols by 101 promoting greatest selectivity.\textsuperscript{108}

101 Has also exhibited excellent activity and enantioselectivity in the acylative
desymmetrisation of diols.\textsuperscript{109} Unfortunately 101 is air sensitive and its precise mode of
action is unclear, with modification of the PBO backbone or synthesis of a range of
alternative catalysts failing as yet to result in catalysts which surpass the exceptional
selectivity achieved in KR reactions promoted by 101.\textsuperscript{110}

1.5.3 Carbenes

Suzuki\textsuperscript{111} and Maruoka\textsuperscript{112} independently reported the first N-heterocyclic carbene (NHC)
for use in the KR of aryl alkyl carbinols and allylic alcohols with high selectivity (S ≤ 80).
Previous to this, studies by Hedrick\textsuperscript{113} and Nolan\textsuperscript{114} had concluded that achiral NHCs
catalysed acylation/transesterification reactions. The NHC imidazolium precursor salts are
readily prepared in a single step from chiral amines, paraformaldehyde, glyoxal and
tetrafluourboric acid. Generation of the nucleophilic carbene requires reaction with
potassium \textit{tert}-butoxide.

Suzuki synthesised a number of C-2 symmetric aryl- and cycloalkylethyl substituted NHCs
to explore the steric environment necessary for successful enantioselective acyl transfer of
\textit{sec}-alcohols. The 1-naphthyl analogue promoted greatest selectivity and interestingly the
cyclohexyl derivative selected for the opposite antipode with reduced enantioselectivity.

Maruoka also prepared catalysts 105a-b and initial attempts to resolve 9 with methyl
acetate as acylating agent yielded racemic alcohol. Subsequent investigation found that
resolution of 9 by the more reactive and hindered diphenyl vinyl acetate resulted in optimal
selectivity (S = 80). A diverse range of \textit{sec}-alcohols including allylic substrates were
selectively resolved under these reaction conditions with 105b promoting a more selective
resolution than 105a.
Table 1.18  KR of sec-alcohols catalysed by 105a-d

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat</th>
<th>Substrate</th>
<th>R¹, R³</th>
<th>Conditions (°C, h)</th>
<th>Yield * (%)</th>
<th>eeE (%)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>105b</td>
<td>54</td>
<td>Me, Me</td>
<td>0, 24</td>
<td>33</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>105c</td>
<td>54</td>
<td>Me, Me</td>
<td>RT, 18</td>
<td>27</td>
<td>49</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>105a</td>
<td>9</td>
<td>Ph₂CH, (vinyl)</td>
<td>-78, 3</td>
<td>33</td>
<td>93</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>105b</td>
<td>9</td>
<td>Ph₂CH, (vinyl)</td>
<td>-78, 3</td>
<td>32</td>
<td>96</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>105b</td>
<td>9a</td>
<td>Ph₂CH, (vinyl)</td>
<td>-40, 3</td>
<td>30</td>
<td>94</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>105b</td>
<td>106</td>
<td>Ph₂CH, (vinyl)</td>
<td>-78, 4</td>
<td>39</td>
<td>91</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>105a</td>
<td>82</td>
<td>Ph₂CH, (vinyl)</td>
<td>-78, 3.5</td>
<td>27</td>
<td>84</td>
<td>16</td>
</tr>
</tbody>
</table>

* Isolated yield

1.5.4 Catalysts incorporating an imidazole ring

Miller *et al.* developed a small molecule biomimetic catalyst 107 *i.e.* a synthetic peptide for kinetic resolution reactions consisting of the minimal environment required for asymmetric induction and rate enhancement. An L-histidine residue was incorporated into a peptide framework with a β-turn structure enabling efficient communication between the nucleophilic imidazole and the chiral environment of the peptide during catalysis.

trans-2-(N-Acetylamino)-cyclohexan-1-ol (108) was chosen as a suitable substrate for KR with Miller speculating that a H-bonding interaction between substrate and catalyst would be advantageous for selectivity (S = 3). Non-polar solvents facilitated rigidification of the peptide structure through the facilitation of intramolecular H-bonding thereby further increasing $k_{rel}$ (entry 1, Table 1.19). Under these optimised conditions the corresponding acetate ester of 107 (lacking H-bond donor capability) failed to promote selective acyl transfer comparable to that observed using aryl alkyl carbinol substrates.

Further development of the first generation catalyst led to the synthesis of 109 and 110. A marked difference in selectivity and a reversal of stereoinduction was observed between the two; with 109 containing an L-proline residue (S = 3.1) and 110 a D-proline residue (S = 43...
28. $^1$H NMR analysis showed an intramolecular H-bond in 109 facilitated by the β-turn, while a similar analysis of 110 identified an additional H-bond interaction and thus a more rigid structure, leading to greater selectivity. Subsequent investigation concluded that a single stereogenic centre controlled the sense of stereoinduction in catalysis.$^{117}$

**Figure 1.10** Miller’s KR catalysts

Inspired by 110, a D-proline based octapeptide 111 (known to exhibit four intramolecular H-bonds)$^{118}$ was prepared and the analogous L-proline derivative was also synthesised for comparison. 111 Exhibited a significant increase in selectivity ($S > 50$) while the L-proline-derived analogue was moderate at best ($S = 7$).$^{119}$ However a covalently linked analogue of 111 with a further increase in conformational rigidity also promoted a less selective transformation ($S = 12$), suggesting that a degree of flexibility is required for productive asymmetric induction.

Kinetic studies were performed in an effort to understand the mode of action of catalysis, with reaction found to be first order in both catalyst and substrate. A comparison of the relative rates of acylation found octapeptide 111 to be the most active catalyst, even outperforming 22.$^{119}$
Subsequent implementation of a combinatorial approach towards the design of selective catalysts for the KR of aryl alkyl carbinols led to a need for an assay procedure to quantitatively assign catalytic activity and consequently selectivity. A fluorescence based assay was employed to evaluate catalytic turnover,\textsuperscript{120} with acetic acid, a by-product of resolution with acetic anhydride, mediating proton-activated fluorescence. Octapeptide 112 was identified as being the most selective catalyst promoting the resolution of a range of \textit{sec}-alcohols. The combinatorial-fluorescence approach was later successfully applied to the KR of tertiary alcohols.\textsuperscript{121}

**Table 1.19**  KR of \textit{sec}-alcohols by catalysts 107, 109-112

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Substrate</th>
<th>T (°C)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>108</td>
<td>0</td>
<td>12.6\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>107</td>
<td>113</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>109</td>
<td>108</td>
<td>25</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>110</td>
<td>108</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>111</td>
<td>108</td>
<td>25</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>112</td>
<td>9</td>
<td>-65</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>112</td>
<td>54</td>
<td>-65</td>
<td>&gt;50</td>
</tr>
<tr>
<td>8</td>
<td>112</td>
<td>93</td>
<td>-65</td>
<td>&gt;50</td>
</tr>
<tr>
<td>9</td>
<td>112</td>
<td>58</td>
<td>-65</td>
<td>30</td>
</tr>
</tbody>
</table>

\textsuperscript{a} S = 17 at higher dilution and at 25 °C.

In 2004, Isihara, prompted by the success of Miller’s peptidic catalysts, reported an artificial acylase, (114) derived from L-histidine.\textsuperscript{122} The design rationale for the catalyst focused on the incorporation of a sulphonamide functionality to act as a H-bond donor and a substituted imidazole to provide high catalytic turnover.
Table 1.20 KR of alcohols by 114

114 proved selective in the KR of monoprotected diol 76b (entry 1, Table 1.20), utilising iso-butyric anhydride as acylating agent. Ishihara postulated that an increase in the Lewis basicity of a substrate would afford a stronger H-bond interaction with a concomitant increase in selectivity. Thus 115a and 115b (entries 2 and 3) were subjected to KR catalysed by 114 and an increase in asymmetric induction was duly observed. A range of pyrrolidinated cycloalkyl diols and amino alcohols were similarly found to be amenable to resolution (S ≤ 93). Ishihara proposed a transition state based on X-ray crystal structure analysis of 114, where H-bonding of the sulphonamido group to the substrate allowed for selective attack by the (1R,2S) antipode of 76b on the acylimidazolium ion.

Birman et al. initially reported a class of readily-modified acyl transfer catalysts (117) based on 2,3-dihydroimidazo[1,2-a]pyridine, (DHIP). The nucleophilicity of the reactive amidine nitrogen was tuneable via substitution on the pyridine ring, with a CF3 substituent promoting maximum stereoinduction while still generating appreciable catalytic turnover.
An additional class of sec-alcohols \textit{i.e.} allylic alcohols were investigated owing to their \(\pi\)-stacking ability (entry 5). Modest selectivities were achieved \((S = 11 - 26)\) as the \(\pi-\pi\) interaction was less effective with the olefin while the aromatic moiety of the alcohol was further removed from the cation preventing successful communication\(^{124}\). A second generation of catalyst was envisioned to extend the electronic influence of the catalyst system, thus a phenyl group was fused to the pyridine ring forming a 1,2-dihydroimidazo[1,2-a]quinoline (DHIQ) framework. 118 was prepared in a complimentary two step procedure to DHIP 117, starting from \((R)\)-phenylglycinol and 2,6-dichloroquinoline. A two-fold increase in \(k_{\text{rel}}\) along with a significant rate enhancement was achieved using 118 in the KR of allylic alcohols (entry 6), a considerable aggrandisement in rate and \(k_{\text{rel}}\) for aryl alkyl alcohols (entry 7) was also achieved\(^{125}\).

A commercially available and enantiomerically pure substituted tetrahydroimidазothiazole (tetramisole, 119) afforded an opportunity to analyse the influence the pyridine ring exerted on the catalytic system. Direct comparison of 119 against 117 and 118 under optimised conditions with a variety of benzyl carbinols gave similar selectivities with reduced activities (entry 8), however cinnamyl alcohols proved less receptive (entry 9). Therefore the presence of a pyridinium ring was not a prerequisite for the catalytic system.
Table 1.21  Range of alcohol KR by catalysts 117-120

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat (mol%)</th>
<th>Substrate</th>
<th>R'</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>117a (20)</td>
<td>121</td>
<td>Me</td>
<td>1⁰</td>
<td>21</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>117b (20)</td>
<td>121</td>
<td>Me</td>
<td>1¹</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>117b (20)</td>
<td>121</td>
<td>Et</td>
<td>8⁰</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>117b (20)</td>
<td>121</td>
<td>Et</td>
<td>5⁲</td>
<td>48</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>117b (20)</td>
<td>122</td>
<td>Et</td>
<td>8⁰</td>
<td>50</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>118 (20)</td>
<td>122</td>
<td>Et</td>
<td>4⁰</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>118 (20)</td>
<td>58</td>
<td>Et</td>
<td>8⁰</td>
<td>42</td>
<td>117</td>
</tr>
<tr>
<td>8</td>
<td>119 (10)</td>
<td>121</td>
<td>Et</td>
<td>6⁰</td>
<td>53</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>119 (10)</td>
<td>82</td>
<td>Et</td>
<td>8⁰</td>
<td>45</td>
<td>4.9</td>
</tr>
<tr>
<td>10</td>
<td>120 (4)</td>
<td>74a</td>
<td>Et</td>
<td>33⁰</td>
<td>50</td>
<td>209</td>
</tr>
<tr>
<td>11</td>
<td>120 (4)</td>
<td>74a</td>
<td>tPr</td>
<td>33⁰</td>
<td>48</td>
<td>355</td>
</tr>
<tr>
<td>12</td>
<td>120 (4)</td>
<td>9</td>
<td>tPr</td>
<td>33⁰</td>
<td>46</td>
<td>104</td>
</tr>
<tr>
<td>13</td>
<td>120 (4)</td>
<td>58</td>
<td>tPr</td>
<td>48⁰</td>
<td>31</td>
<td>192</td>
</tr>
<tr>
<td>14</td>
<td>120 (4)</td>
<td>104</td>
<td>Et</td>
<td>24⁰</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>15</td>
<td>120 (4)</td>
<td>123</td>
<td>tPr</td>
<td>7⁰</td>
<td>45</td>
<td>520</td>
</tr>
<tr>
<td>16</td>
<td>120 (4)</td>
<td>124</td>
<td>tPr</td>
<td>21⁰</td>
<td>42</td>
<td>450</td>
</tr>
<tr>
<td>17</td>
<td>120 (4)</td>
<td>125</td>
<td>Et</td>
<td>2²</td>
<td>52</td>
<td>32</td>
</tr>
<tr>
<td>18</td>
<td>120 (4)</td>
<td>126</td>
<td>Et</td>
<td>1.5⁴</td>
<td>55</td>
<td>26</td>
</tr>
</tbody>
</table>

* R eaction carried out at RT. ¹ R eaction carried out at 0 °C.

Nonetheless, inspired by the previous optimisation of asymmetric induction achieved by fusing a phenyl ring to the catalyst framework, 120 was synthesised, resulting in a two fold increase in selectivity. Further optimisation studies included the reduction in reaction temperature to 0 °C and the addition of Na₂SO₄ (to prevent hydrolysis of the acyl intermediate). Iso-butyric anhydride was also found to promote greater enantiodifferentiation although reaction rates decreased due to the increase in steric bulk in comparison to propionic anhydride. Resolution of aryl alkyl carbinols proceeded with exceptional selectivity. Increasing the steric bulk of the alkyl group led to an appreciable increase in selectivity, while ortho substitution of the aryl moiety also afforded excellent
selectivity (entries 11-13). However, sec-mesitylethanol was resolved with surprisingly low selectivity (entry 14).

Recent work by Birman and co-workers has included the first KR of 2-oxazolidinones via N-acylation and the KR of propargylic alcohols catalysed by 120. In the former the selectivities reported include the highest yet achieved for any KR promoted by organocatalysts (S = 520). A range of C-4 and C-5 aryl substituted oxazolidinones underwent KR in CDC13 at room temperature with iso-butyric anhydride as the acylating agent (entries 15 and 16). The KR of propargylic alcohols with 120, while not as selective as the benzyl carbinols, still provides the most selective non-enzymatic approach to date and unlike 53 a range of substituted propargylic alcohols undergo selective resolution in a realistic time frame (as opposed to up to 3 weeks, entries 17 and 18).

Birman has designed a catalyst of genuine synthetic utility that can be synthesised in enantiopure form from commercially available reagents in three steps. The small molecule catalyst 120 promotes the KR of a wide array of substrates under mild conditions, some of which are useful as chiral building blocks.

1.6 The Baylis-Hillman reaction: General

C-C bond formation is of paramount importance in the synthesis of organic molecules, with the discovery and development of new synthetic methods vital for the evolution of modern organic chemistry. The Baylis-Hillman reaction is one such method, affording the selective (chemo- and regio-) formation of densely functionalised carbon frameworks from simple precursors with atom economy.

Originally discovered by A. B. Baylis and M. E. D. Hillman in 1972,126 this reaction lay dormant in the literature for almost a decade until its synthetic utility became apparent. The Baylis-Hillman (BH) reaction is a base (tertiary amine, phosphine) catalysed reaction involving the formation of an α-methylene-β-hydroxycarbonyl compound from an α-functionalised electron deficient alkene and an sp2 hybridised carbon electrophile, Scheme 1.19.
Scheme 1.19 Overview of activated alkenes and electrophiles in the BH

\[ \begin{align*}
X = &\ O, \ NR \\
R' = &\ \text{alkyl, aryl} \\
R'' = &\ H, \ \text{alkyl, } CO_2R \\
EWG = &\ CHO, \ COR, \ CO_2R, \ CN, \ PO(OEt)_2, \ SO_xPh. \ X = 1-3
\end{align*} \]

1.6.1 Mechanism of the Baylis-Hillman reaction

The widely accepted mechanism proffered by Hill et al.\textsuperscript{127} based on pressure dependence, rate and kinetic isotope data has been independently supported by a multitude of kinetic and mechanistic investigations\textsuperscript{128,129} (Scheme 1.20). A DABCO (127) catalysed reaction of benzaldehyde with methyl acrylate is taken as a representative example. The mechanism involves the reversible Michael addition of the nucleophilic amine catalyst to the electron deficient alkene resulting in the formation of a Zwitterionic intermediate A. Subsequent aldol reaction with nucleophilic attack of the enolate on the aldehyde forms a second Zwitterionic intermediate B. Intramolecular proton transfer followed by elimination of the catalyst affords the desired β-hydroxy-α,β-unsaturated ester with concomitant regeneration of the tertiary amine.

Scheme 1.20 Mechanism of the Baylis-Hillman reaction
Kinetic studies have also shown that the rate determining step (RDS) is formation of B enolate, with the reaction exhibiting third order kinetics (eq.1) or pseudo second order kinetics if the relative concentration of the amine is considered to remain constant.  

\[ \text{rate} = k_{\text{obs}} \text{[alkene]} \text{[aldehyde]} \text{[amine]} \]  

However, recent studies have called into question the validity of the above mechanism. McQuade\textsuperscript{131} recently found a second order rate dependence on the aldehyde component and Aggarwal has suggested that proton transfer can be rate limiting in aprotic solvents at low reaction conversions (at higher conversion this step is catalysed by the product and the aldol-type addition step becomes rate limiting).\textsuperscript{132} Subsequent investigations by Leitner \textit{et al.}\textsuperscript{133} have substantiated Aggarwal's rate determining step assertion in an aza-Baylis-Hillman system, however no autocatalysis was observed.

1.6.2 Rate of reaction

In order that the BH adducts be regarded as synthetically useful, short reaction times along with high yields are a priority. Unfortunately the reaction of activated alkenes with electrophiles tends to be a tedious endeavour, with protracted reaction times at room temperature. A number of strategies have been devised to combat this inherent problem. Hydrogen bonding by the introduction of MeOH\textsuperscript{134} or AcOH\textsuperscript{135} was envisioned to afford rate enhancement via either stabilisation of enolate A or activation of aldehyde. The presence of a hydroxyl moiety in either the catalyst\textsuperscript{136} or substrate\textsuperscript{137} also greatly enhanced rate. Increasing the amount of catalyst is another plausible alternative.

The electronic and steric composition of activated alkenes and electrophiles asserts the greatest influence on rate. Electron withdrawing groups activate both alkene and electrophile towards reaction, whereas electron donating groups or steric hindrance \( \sigma \) to the key functional groups leads to a dramatic attenuation in rate. The utilisation of high pressure and microwave assisted techniques has also enabled significant rate enhancements in otherwise slow reactions.\textsuperscript{138} However in some instances elevated temperatures have promoted dimerisation of the alkene substrates.\textsuperscript{139}
1.6.3 Optimisation of the Lewis base catalysed Baylis-Hillman reaction

Many attempts have been made to optimise the base catalysed BH reaction and a number of investigations have reported alternative amines as promoting optimal activity.

**Figure 1.12** pK\textsubscript{a} of tertiary amines in BH reaction\textsuperscript{140}

\[
\begin{array}{cccc}
\text{pK}_{a}^* & 8.7 & 9.9 & 11.3 \\
127 & 128 & 129 & 130 \\
\end{array}
\]

* Refers to $^\text{*}\text{NHR}_3$ at 25 °C in H\textsubscript{2}O

127 was utilised by Baylis and Hillman in their initial patent as the amine of choice for the BH reaction. The nucleophilic and non-hindered nature of 127 was responsible for the superior rates and conversions achieved in comparison to alternative tertiary amines. Subsequent investigation by Drewes et al.\textsuperscript{141} observed that 3-hydroxyquinuclidine (128) outperformed 127 and 127 was superior to quinuclidine (129), with the assumption that 128 stabilised the enolate A \textit{via} intermolecular H-bonding which mediates greater conversion.

Surprisingly, in 1999 Aggarwal reported the hindered, non nucleophilic base 1,8-diazabicyclo[5.4.0]undecen-7-ene (DBU, 130) as promoting optimum conversion in the BH reaction of benzaldehyde and methyl acrylate.\textsuperscript{142} 130 is the antithesis of the nucleophilic and unhindered bases 127 and 128. Previous attempts to incorporate $\alpha$-substituents into a tertiary amine framework to catalyse the BH reaction had proved deleterious to catalytic activity.\textsuperscript{143} Schuurman proposed that $\alpha$-substitution hindered attack of the nucleophile on the activated alkene. Aggarwal postulated that the enhanced rate of reaction using 130 in place of 127 was due to the resonance stabilisation of the $\beta$-ammonium enolate resulting in an increased equilibrium concentration (Figure 1.13).
Later Aggarwal et al. compared catalyst basicity with catalyst efficacy in reactions promoted by 127-129. Contrary to the previous assertions by Drewes, Aggarwal noted a direct correlation between conversion and basicity, with a reversal in the order of activity of amines 129 and 127. A significant rate enhancement was also observed for 129 on addition of protic solvents; MeOH was preferred due to its solubilising ability and ease of evaporation.\textsuperscript{144}

**Table 1.22**  Rate of BH reaction catalysed by bases 127-129

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Rate (%/min)</th>
<th>pK\textsubscript{a} \textsuperscript{a}</th>
<th>k\textsubscript{rel}</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinuclidine, 129</td>
<td>1.8</td>
<td>11.3</td>
<td>9.0</td>
</tr>
<tr>
<td>3-hydroxyquinuclidine, 128</td>
<td>8.8 x 10\textsuperscript{-1}</td>
<td>9.9</td>
<td>4.3</td>
</tr>
<tr>
<td>DABCO, 127</td>
<td>2.1 x 10\textsuperscript{-1}</td>
<td>8.7</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Refers to the pK\textsubscript{a} of the corresponding conjugate acid in H\textsubscript{2}O at 25°C.

### 1.6.4 Enantioselective Baylis-Hillman synthesis

Highly functionalised allylic alcohols derived from the BH reaction are amenable to further synthetic elaboration and in enantiopure form can be employed in natural product synthesis.\textsuperscript{145} The synthesis of enantiopure BH adducts can in theory be accomplished by the incorporation of chiral information into one of the reaction components \textit{i.e.} alkene, electrophile or catalyst. While moderate success has been achieved utilising optically pure chiral auxillaries \textit{e.g.} activated alkenes and electrophiles,\textsuperscript{146} the main focus of endeavour has been on the development of chiral base catalysts, particularly tertiary amines (tertiary phosphines have also mediated asymmetric synthesis but will not be discussed in this
work). The synthesis of chiral allylic amines via the analogous aza-Baylis-Hillman reaction has likewise been comprehensively investigated, however this falls outside the boundaries of our study and will not be discussed in detail.

1.6.5 Overview of current asymmetric catalysts in the Baylis-Hillman reaction

Figure 1.14 Chiral Baylis-Hillman catalysts reported in the literature
Initial attempts to catalyse the synthesis of enantiopure BH analogues employed the naturally occurring cinchona alkaloid quinidine (134) and brucine (130). However, very modest enantioselectivities i.e. a maximum of 20% ee, were achieved in reactions catalysed by 134 (entry 1, Table 1.23).\textsuperscript{129,146,148} In 1995, Hirama and co-workers, encouraged by these preliminary studies, reported a C\textsubscript{2}-symmetric chiral DABCO analogue 139, capable of promoting the asymmetric synthesis of BH adducts in up to 47% ee at high
pressure (entry 2). Subsequently, Markó et al. also observed a marked pressure dependence on 134 catalysed asymmetric BH reactions of aliphatic aldehydes with MVK. Under optimised conditions 45% ee was obtained at 3 Kbar (entry 3).

In 1998, Barrett et al. designed a proline-derived enantiopure hydroxypyrrolizidine catalyst 137, that mediated the synthesis of asymmetric BH adducts in 21-47% ee. NaBF₄ was employed as a Lewis acidic co-catalyst which led to a significant increase in reaction rate and selectivity. Enantioselectivities up to 72% ee were achieved (entry 4) in the reaction of electron deficient aldehydes with ethyl vinyl ketone. A second generation catalyst 138 proved to be less selective (entry 5), although a 10-fold amplification in catalytic activity was observed.

Hatakeyama and co-workers investigated a range of cinchona alkaloid derivatives for the selective catalysis of the BH reaction. β-isocupreidine (136), proved most efficient, promoting the reaction of alkyl and aryl aldehydes alike with the highly activated alkene 1,1,1,3,3,3-hexafluoroisopropylacrylate (145f) in excellent enantioselectivities (91 – 99% ee) (entry 6). Unfortunately moderate yields (31 – 58%) were achieved due to the concomitant formation of an unwanted side product, dioxane 147 (Scheme 1.21). An increase in both asymmetric induction and catalytic turnover was achieved on recrystallisation of 136, which was suggested to be due to the removal of bound H₂O.

The enantioselective synthesis of medicinally relevant eproptomycin B and (-)-mycestericin E mediated by 136 has also been reported.

Scheme 1.21  Synthesis of BH adduct (146) and dioxane side product (147)

The substrate dependency of 136 was later explored by Shi et al., who coupled aryl aldehydes to MVK and α-naphthyl acrylates. Selectivities up to 49 and 92% were generated respectively (entries 7, 8), while the introduction of either Li salts or proline as co-catalysts failed to enhance catalytic activity or enantiomeric excess significantly. The
by-product formation of dioxane also persisted with a 59% yield of 147 as compared to 17% yield of the desired product for the most selective reaction (entry 8).

Unfortunately, the asymmetric BH syntheses reported are limited in both scope and synthetic utility, with success confined to reactions where at least one component is activated and a proton donor (in general) is required. Furthermore, no useful enantioselective reactions have been reported with either or both deactivated Michael acceptors or aldehydes.

Later, Shi and Hatakeyama, independently explored the asymmetric synthesis of aza-BH adducts for a range of substituted aldehydes and activated alkene with both realising synthetically useful yields and high enantioselectivities.

Miller et al. influenced by Shi, employed an N-methyl imidazole (NMI) based peptide 143 in conjunction with proline as a co-catalyst to effect the BH reaction. Asymmetric induction increased with peptide chain length up to an optimal octamer, however the individual amino acid-derived substituents remained unoptimised. A range of highly electron deficient aromatic aldehydes were coupled with MVK in the presence of 143 to give Baylis-Hillman adducts with consistently high enantioselectivity (63 – 81% ee) in good yields (81 – 95%) (entry 9), although a stoichiometric amount of 143 was required.

Warner and co-workers investigated the catalytic competence of the Sharpless ligand (DHQD)$_2$AQN, 141, in the presence of an equivalent amount of acid. High levels of asymmetric induction (> 77% ee) were observed, however the prohibitively slow catalyst turnover i.e. maximum 11% conversion after 17 days (entry 10), negated any further investigation.

A diamine catalyst 140 derived from proline promoted the reaction of MVK with aryl aldehydes in moderate to good enantioselectivity (44 – 75% ee) with fast reaction times (> 6 h). Optimisation studies found that an excess of either aldehyde or MVK, in the presence of a protic solvent were required for highly enantioselective reactions (entry 11).

Recently, while our investigations were ongoing, Berkessel et al., inspired by a symmetric (thio)urea catalyst previously synthesised in our laboratory, developed a chiral bis-(thio)urea analogue of isophoronediamine, i.e. 142. In combination with tetra
methylated IPDA (142) (20 mol%) a range of aromatic and aliphatic aldehydes were coupled to cyclohexen-1-one in modest to high yields (28 - 79%) and enantioselectivities (34 – 96% ee) (entry 12). Attempts to utilise methyl acrylate as the Michael acceptor gave racemic products.

Unfortunately, the asymmetric BH syntheses reported thus far are limited in both scope and synthetic utility; with success confined to reactions were at least one component is activated and a catalyst incorporating at least one hydrogen-bond donating moiety is required. Furthermore, no useful enantioselective reactions have been reported with either or both deactivated Michael acceptors or aldehydes.

1.6.6 Kinetic resolution of Baylis-Hillman adducts

An alternative approach to the enantioselective synthesis of BH adducts is KR. Various strategies have been employed to effect resolution, including epoxidation\textsuperscript{162} and diastereomeric crystallisations,\textsuperscript{163} with hydrogenation\textsuperscript{164} and biocatalytic acylations\textsuperscript{165} proving most effective.

\(\alpha\)-Methylene-\(\beta\)-hydroxycarbonyl compounds are ideal substrates for Rh-catalysed asymmetric hydrogenation, with a polar hydroxyl moiety in close proximity to the olefin functionality controlling enantioselective hydrogen transfer. Brown \textit{et al.} demonstrated the synthetic utility of DIPAMP –Rh catalyst 148; selective hydrogenation of 150\textsuperscript{a} allowed for the recovery of the (S)-antipode of the starting material in >90% ee with conversions in excess of 70% (entry 1, Table 1.24). Subsequently, Noyori reported the KR of allylic alcohol 150\textsuperscript{b} employing a BINAP-Ru(II) catalyst 149. Reaction (25 °C, 4 atm, H\textsubscript{2}) amassed unreacted (S)-150\textsuperscript{b} in >99% ee at 76% conversion (entry 2). A range of (\(\alpha\)-aminoalkyl)acrylates have also been resolved by stereoselective hydrogenation.\textsuperscript{166} However, the air sensitivity of the catalysts and the susceptibility of other functional groups to reduction inhibit the hydrogenation protocol as a versatile means of resolution.
An alternative strategy involves chemoenzymatic methodologies. Burgess et al.\textsuperscript{167} employed a crude \textit{Pseudomonas} AK preparation (Amano) that effectively catalysed the acylation of both $\alpha$-(hydroxyalkyl)-acrylates and vinyl ketones in good yield and enantioselectivity (entries 3 and 4). Hayashi later demonstrated the exceptional $k_{\text{rel}}$ values obtained upon acylation of acrylate-derived BH adducts utilising Lipase PS (\textit{Pseudomonas} sp.) (entry 5).\textsuperscript{165} Hydrolysis of the acylated BH substrates by pig liver acetone powder (PLAP) generated optically active alcohols in moderate yields (19 – 37%) and selectivities (46 - 86% ee).\textsuperscript{168}

### Table 1.24 KR of BH adducts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Conv. (%)</th>
<th>$ee_A$</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>148</td>
<td>150a</td>
<td>THF, 0 °C</td>
<td>70\textsuperscript{a}</td>
<td>90 (S)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>149</td>
<td>150b</td>
<td>MeOH, 11 h, 25 °C</td>
<td>24\textsuperscript{b}</td>
<td>99 (S)</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>Pseudo. Ak</td>
<td>150c</td>
<td>Hex, 48 h, 25 °C</td>
<td>50</td>
<td>$&gt;$95 (S)</td>
<td>$&gt;$56</td>
</tr>
<tr>
<td>4</td>
<td>Pseudo. Ak</td>
<td>150d</td>
<td>Hex, 12 h, 25 °C</td>
<td>52</td>
<td>$&gt;$95 (S)</td>
<td>$&gt;$56</td>
</tr>
<tr>
<td>5</td>
<td>Lipase PS</td>
<td>150e</td>
<td>CH$_3$CN, 7 d, 35 °C</td>
<td>41</td>
<td>70 (S)\textsuperscript{c}</td>
<td>$&gt;$424</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Product predominantly \textit{anti} (>98%). \textsuperscript{b} 24% yield. \textsuperscript{c} The acylated product was isolated in >99% ee.
1.6.7 Drawbacks associated with Baylis-Hillman reaction

The synthetic utility of BH adducts is undoubted; with each adduct invariably offering three distinctive functional groups in addition to a chiral centre. However the BH reaction suffers from notoriously slow reaction rates, requiring high catalyst loadings and long reaction times for the coupling of deactivated alkenes and electrophiles. Attempts to optimise conversion through chemical (co-catalysts, protic solvents) or physical stimuli (microwave irradiation, high pressure), have frequently increased side product formation or dimerisation.

Asymmetric synthesis has also proved difficult, with 136 the only notable exception to date. Nonetheless, attempts to elaborate on the substrate scope of 136 (highlighted by Shi with respect to the activated alkene) and other nucleophilic catalysts has proven less than successful and thus the synthetic practicality of the established catalytic systems warrants improvement.

1.7 DMAP functionalised nanoparticles (General)

Nanotechnology has received unprecedented interest over the last decade and is expected to become one of the main platforms for technological innovation in the 21st century. Research and development into the synthesis of nanoparticle catalysts is currently the main focus of endeavour,169 and a host of reviews have been dedicated to their design and the reactions they promote,170 with our specific interest pertaining to the immobilisation of DMAP on magnetic nanoparticles for nucleophilic catalysis with subsequent recovery and reuse.

1.7.1 Homogeneous vs. heterogeneous catalysis

Traditionally, the field of chemical catalysis has been split into two distinct categories, i.e. homogeneous- and heterogeneous catalysis. Homogeneous catalysis involves reactions that proceed in solution, whereas heterogeneous catalysis takes place at the surface interface. The inherent differences between the two classes can be appreciated by examining the activity profiles; where homogeneous catalysis occurs on the molecular level with a single active site, under mild conditions, with greater selectivity and (in general) higher catalytic turnover, (Figure 1.16a). In comparison, heterogeneous catalysis takes place on the surface
of a large aggregation of atoms possessing multiple active sites, with a poor surface to area ratio, often requiring elevated temperatures and/or pressures for diffusion and adsorption onto the reactant surface, Figure 1.16 (b).

**Figure 1.16** Homo- vs. Heterogeneous catalysed reactions

![Figure 1.16](image)

Nonetheless, heterogeneous catalysts are employed more frequently in industrial processes owing to their ease of separation and cost effectiveness. Heterogeneous organocatalysts are preferred to metal-based supported catalysts, as they display increased bench stability, are more amenable to immobilisation and avoid the inherent problem of leaching, contaminating the resulting product.

Immobilisation of catalysts involves the formation of a covalent bond with an inorganic or polymer (predominantly polystyrene) support. Non-covalent strategies include ion-pairing of cationic or anionic complexes or encapsulation within mesoporous silicates or zeolites. The support material is required to be structurally inert with a high surface to area ratio (or suitable pore size), facilitating ease of access to the catalyst active site. Unfortunately, the local environment of a heterogeneous catalyst can be more sterically hindered and of different polarity (due to the influence of the solid support) than an unsupported counterpart; this can lead to a diminuation of control (in a design context) over catalyst conformation, a decrease in catalytic activity and an attenuation in selectivity in the case of chiral catalysts.

The ideal situation involves a combination of *hetero* and *homo*-geneous based methodologies *i.e.* the high catalytic activity associated with homogeneous catalysts coupled with the lower cost and efficient catalyst recovery associated with heterogeneous catalyst systems.
1.7.2 DMAP derived heterogeneous catalysts

As discussed earlier in Section 1.3, DMAP (22) is an active, commercially available 'hypernucleophilic' promoter of a diverse range of synthetically useful transformations susceptible to nucleophilic catalysis. Thus, 22 is an ideal candidate for immobilisation on a solid support and several groups have developed plausible strategies (Figure 1.17) for same.

**Figure 1.17** Supported DMAP catalysts
Klotz et al. reported the first poly(ethyleneimine) derived DMAP catalysts (153a and 153b) in 1979, that promoted the successful hydrolysis of \( p \)-nitrophenyl esters. Interestingly, at pH 7.3 the polymer supported catalysts reacted 50 – 2000 fold faster than the unbound catalysts.\(^{172}\) Later Shinkai\(^{173}\) synthesised polystyrene supported 154a and 154b to facilitate the DCC coupling of MeOH and benzoic acid, however both 154a (65\% yield, 24 h) and 154b (53\%, 24 h) reacted significantly slower than 22 (100\%, 1 h). 154a was recovered by filtration and promoted a second cycle with a slight decrease in yield (53\%).

In 1982, Tomoi and co-workers developed catalyst 155a and applied it to the acylation of hindered tertiary alcohols.\(^{174}\) The catalytic turnover of 155a was moderately lower than 22 with diffusion into the support pores and the electron withdrawing nature of the \( N \)-benzyl group as compared to the \( N \)-methyl group of 22 purported to reduce activity. Recently 155a was applied to the synthesis of BH adducts\(^{175}\) and promoted the coupling of 144b and MVK in DMF at 20 °C. A reduction in activity was observed upon recycling, with the formation of a Zwitterionic Michael addition product responsible for deactivation. Hydrolysis of the Zwitterion with NaOH reinvigorated the catalyst and subsequent reaction led to comparable yields (entries 1 and 2, Table 1.25)

**Table 1.25** Synthesis of BH adducts catalysed by 155a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>144b</td>
<td>100</td>
<td>DMF</td>
<td>24</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>144b</td>
<td>100</td>
<td>DMF</td>
<td>24</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>160a</td>
<td>20</td>
<td>CH(_2)Cl(_2)</td>
<td>72</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>160b</td>
<td>20</td>
<td>( t )-A.A.</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>160b</td>
<td>20</td>
<td>( t )-A.A.</td>
<td>24</td>
<td>91</td>
</tr>
</tbody>
</table>
Independently, Shi and Huang\textsuperscript{176} utilised \textbf{155a} to catalyse the \textit{aza}-Baylis-Hillman reaction of \(N\)-tosylimines and MVK (entry 3). Reaction required three days and afforded products in 47 – 58% yield. \textbf{155a} Proved more efficient in the catalysis of aromatic aldehydes and MVK, with \(t\)-A.A. as solvent. \textbf{155a} Was recovered by filtration and resubjected to the reaction of \(m\)-NO\(_2\)-benzaldehyde and MVK with no discernable loss in reactivity after five cycles (entries 4 and 5).

Insoluble catalyst \textbf{155b}, synthesised by Menger \textit{et al}..\textsuperscript{177} promoted a range of acetylations of hindered secondary and tertiary alcohols (entry 1, Table 1.26), in addition to indole. TBDMS protection of a steroidal alcohol and the hydrolysis of an ester were also effected by \textbf{155b} with subsequent removal of the catalyst by filtration. Although the equivalent DMAP promoted reactions realised only moderately better yields, no attempt to recycle \textbf{155b} was made.

Catalysts \textbf{155c} and \textbf{155d}, closely resembling \textbf{155b} were synthesised by Fréchet \textit{et al}.\textsuperscript{178} A comparison of activity between \textbf{155c} and \textbf{155d} employed the hindered alcohol \textbf{20} (entries 2 and 3) and found that an elongation of the \(N\)-alkyl chain attached to the active heterocycle promoted greater catalytic turnover (98% as efficient as that associated with \textbf{22}). The introduction of 4-vinylpyridine spacer units in place of polystyrene proved deleterious to catalytic activity. A comparable result was obtained when \textbf{19} was employed as solvent in place of toluene.

A soluble polyacrylamide bound catalyst \textbf{156}, with a covalently bound azo-dye that allowed for visual monitoring of catalyst recovery, was reported by Bergbreiter and co-workers.\textsuperscript{179} Acylation of \textbf{20} was effected at room temperature with moderate efficiency (60% conv., 6 h) (entry 4) as compared to \textbf{22} (100% conv., 6 h). The catalyst was successfully recovered by precipitation on addition of hexanes with subsequent filtration (UV – vis spectroscopy determined < 0.1% of \textbf{156} remained in solution). \textbf{156} was recovered and resubmitted to the acylation of \textbf{20} on a further 4 occasions without loss of activity.
Table 1.26  Comparison of DMAP supported catalysts for the acylation and silylation of alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>Substrate</th>
<th>X</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>155b (4.1)</td>
<td>20</td>
<td>Ac</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>155c (5)</td>
<td>20</td>
<td>Ac</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>155d (5)</td>
<td>20</td>
<td>Ac</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>156 (5)</td>
<td>20</td>
<td>Ac</td>
<td>25</td>
<td>60&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>157 (1)</td>
<td>162a</td>
<td>Ac</td>
<td>25</td>
<td>94.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>158 (7.5)</td>
<td>54</td>
<td>Ac</td>
<td>60</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>158 (7.5)</td>
<td>40</td>
<td>Ac</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>158 (6.0)</td>
<td>162b</td>
<td>TBDMS</td>
<td>25</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>158 (6.0)</td>
<td>54</td>
<td>TBDMS</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>159 (0.5)</td>
<td>9</td>
<td>Ac</td>
<td>-</td>
<td>91</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conversion as compared to 22.  <sup>b</sup> Yield of run 5

Recently poly(4-tert-butylstyrene) was identified by Bergbreiter as a suitable framework for a supported DMAP homogeneous catalyst 157. BOC protection of 2,6-dimethylphenol 162a, was catalysed in a homogeneous solvent system (heptane:EtOH (1:1)) by 157. Water (<10% vol.) was added after 24 hours to induce the formation of a biphasic system with 157 and product partitioned between heptane and EtOH/water layers respectively. However the product was slightly soluble in heptane and as a result a low yield (34.6%) of protected alcohol was obtained. Separation and recycling of the heptane phase containing 157 led to a saturation of product in the organic layer, which resulted in an increased concentration of product in the aqueous phase. A near quantitative yield of product (93%) was obtained on average, for twenty iterative runs (entry 5).

The first reported DMAP functionalised mesoporous silica nanospheres, 158 (average diameter of 400nm) synthesised via a novel alkoxysilane co-condensation methodology were developed by Lin and coworkers. 158 (30 mol%) Promoted the synthesis of BH adducts via coupling of substituted aryl aldehydes with MVK in moderate to quantitative yields (25 – 99%) over 24 h at 50 °C. Silylation of a range of primary and secondary
alcohols was catalysed by 158, unfortunately the increased steric hindrance associated with secondary alcohols proved detrimental to catalytic turnover (entries 8 and 9).

158 Also proved useful in the acylation of secondary and tertiary alcohols at elevated temperatures (7.5 mol%, 2.5 h, 60 °C) (entries 6 and 7). Attempts at recycling utilised 54 as the substrate of choice, with 158 recovered by suction filtration which allowed the catalyst to be recycled 10 times without any measurable loss of activity. However, a significant background reaction (33% conversion under reaction conditions) was reported in the absence of 158.

McQuade et al. recently reported a soluble DMAP supported linear polystyrene entrapped within a heterogeneous microcapsule 159,\(^{183}\) that promoted the acetylations of 9 at very low loadings (ca. 0.5 mol%) (entry 10). The rate of reaction of 159 was 3 fold lower than that of 22, although 159 could be recycled 3 times with a small loss (5%) in efficiency.

1.7.3 Conclusions for DMAP supported catalysts

Remarkable progress has been made in recent years in the successful design and synthesis of a diverse array of immobilised heterogeneous DMAP analogues. However, the activity of these derivatives is often inconveniently lower than that of DMAP itself. Furthermore while catalyst recycle and reuse has been demonstrated, at present, no DMAP analogue has combined operational efficiency at ambient temperature and low loadings (ca. 5 mol%) in a readily recyclable catalyst i.e. >10 times, without significant loss of activity. Thus the goal of designing a highly active and recoverable immobilised catalyst remains a significant challenge.
2.1. Guidelines for the successful design of a chiral DMAP catalyst

Successful designs for asymmetric DMAP based catalysts represent a practical compromise between reactivity and selectivity i.e. as chirality is moved closer to the nucleophilic ring heteroatom, stereoselectivity increases while catalytic activity decreases. As alluded to in Section 1.4, a number of groups have endeavoured to solve this activity-selectivity conundrum and as a result a range of highly selective chiral catalysts have emerged for use in the KR of sec-alcohols and other enantioselective acyl-transfer processes.

With the knowledge acquired from these previous attempts at designing chiral DMAP catalysts it was decided to set down guidelines for the preparation of a conceptually novel generation of chiral DMAP derivatives that would improve upon the best literature systems in terms of ease of synthesis, activity and selectivity in a range of enantioselective acyl-transfer reactions.

(1) Firstly, as illustrated in Scheme 2.1, 22 is a planar molecule with 2 planes of symmetry, a mirror plane in the plane of the pyridine ring and another mirror plane perpendicular to the first passing through the two nitrogen atoms, therefore functionality must be introduced which imparts good top/bottom and left/right differentiation for enantioselectivity to occur.

Scheme 2.1 Desymmetrisation of 22

(2) To facilitate catalyst synthesis and ease of modification, the synthetic route to the catalyst should be concise and based on readily available, inexpensive starting materials. Coupling procedures must also be efficient.
(3) No substitution should be present immediately adjacent to the ring nitrogen at C-2 or C-6, as substitution hinders the approach of the electrophile to the pyridine heteroatom and the substrate to the acylated intermediate.

(4) The catalyst’s chiral substituents should be drawn from inexpensive derivatives of the chiral pool, thereby eliminating the need for inefficient resolution steps.

(5) The catalyst’s asymmetry must ideally be based on tetrahedral chirality, due to other sources of asymmetry being relatively ineffective.

(6) In general, the enantioselective step of the catalytic cycle involves attack of the substrate on the acylated pyridinium ion intermediate. Therefore, the catalytic efficiency may be improved if the group which imparts top/bottom differentiation does so on this pyridinium intermediate only and not on its neutral precursor. Thus the initial attack on the acylating agent (or electrophile) will not be obstructed, allowing an increase in reactivity without impeding enantioselectivity. Consequently a chiral substituent is required which will chemoselectively interact with a pyridinium cation e.g. via a \( \pi \)-pyridinium cation aromatic interaction.

(7) Finally the catalyst should structurally resemble 22, with only ring functionalisation present that is relevant to catalyst function.

2.2 Synthesis of 1st generation chiral acyl-transfer catalyst

Catalyst 163 represents our group’s preliminary attempts to design a chiral acyl-transfer catalyst based on the criteria outlined above. The original synthesis of 163 was carried out in our laboratory by Dr. Declan Maher, in the months preceeding the start of these doctoral studies. However, subsequent synthesis, testing and elucidation of catalyst mode of action formed part of the initial research for this thesis. The choice of structure 163 stems from a report by Yamada\(^90\) which disclosed that the 3-substituted pyridine 164 exhibited a \( \pi-\pi \) stacking interaction upon acylation/alkylation\(^184\) which both rigidified the structure and effectively shielded one face of the resultant pyridinium cation, allowing subsequent enantioselective attack of a nucleophile at C-4 (164a, Figure 2.1).
We therefore reasoned that a 4-pyrrolidino analogue of 164 (likely to be of increased nucleophilicity) was a promising lead structure, with the advantages that it could be easily assembled and modified and was potentially capable of operating \textit{via} an 'induced-fit’ mechanism.

**Figure 2.1** 1\textsuperscript{st} generation catalyst 163, Yamada’s substituted pyridine 164 and acylated pyridinium ion 164a.

The synthesis of catalyst 163 was carried out as outlined in Scheme 2.1. Treatment of 4-chloropyridine-3-carboxylic acid (165) with thionyl chloride furnished the corresponding acid chloride hydrochloride, which was then coupled with the oxazolidine 166 (derived from (S)-phenylalaninol)\textsuperscript{185} to afford amide 167 in reasonable yield. Conversion of 167 to 163 was achieved \textit{via} a nucleophilic aromatic substitution reaction with excess pyrrolidine.

**Scheme 2.1** Synthesis of catalyst 163

Unfortunately, \textsuperscript{1}H NMR analysis (CDCl\textsubscript{3}, RT) of 163 revealed the presence of two rotameric species in a 1:1 ratio, with only one rotamer conceivably conducive to the intramolecular \(\pi-\pi\) stacking presumed to be required for enantioselective acyl-transfer (a time-averaged single conformer was obtained when the \textsuperscript{1}H NMR experiment was carried
out at 50 °C). Nonetheless, it was decided to evaluate the catalyst in the KR of sec-phenyl ethanol (9), (Scheme 2.2).

**Scheme 2.2** KR of 9 catalysed by 163

![Scheme 2.2](image)

A chiral shift reagent, Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorate] Eu(hfc)₃ was used to determine the enantiomeric excess in ¹H NMR experiments as a suitable chiral HPLC column was unavailable to the group at that time. The lanthanide shift reagent (a Lewis acid) coordinates with the substrate enantiomers to form diastereomeric complexes with distinguishable chemical shifts. The resultant ¹H NMR signals were split in the ratio of their antipodes and a modest 9% ee was obtained with the catalyst preferentially selecting for the (S)-enantiomer.

**2.2.1 Mechanistic investigation of the 1st generation catalyst**

Alkylation experiments were undertaken in an attempt to elucidate the conformational preference of 163 during acylation (Figure 2.2). Upon methylation of 163 (monitored by ¹H NMR spectroscopy) two rotameric pyridinium ion species were detected which slowly equilibrated to a single rotamer 168 over 12 h. It is of interest that the resonances associated with H-2 and H-6 shifted to lower and higher field respectively on alkylation of 163. This is consistent with a π-stacked conformation, as proposed by Yamada.

In view of the slow equilibration, it seemed likely that both rotamers of the acylated pyridinium intermediate in the KR processes mediated by 163 would possess independent catalytic profiles. We propose that the low level of selectivity observed in acylation reactions promoted by 163 is due (at least in part) to the similar steric bulk of the amide alkyl substituents which form part of the oxazolidine ring. This lack of a steric discrepancy gives rise to two rotameric forms, of which only one is capable of enantioselective catalysis. Therefore, in order to better control the catalyst’s conformational preference and augment the potential for π-pyridinium ion interactions the oxazolidine moiety needed to be replaced.
2.3 Synthesis of 2nd generation catalyst

A new catalyst design was proposed taking into account the improvement in structural rigidity required if selectivity was to be enhanced. Catalyst 169 was prepared in a similar fashion to 163 using commercially available enantiopure (S)-α,α-diphenylprolinol (170). An additional aromatic substituent was introduced alpha to the quaternary centre in an attempt to increase the potential for π-pyridinium ion interactions and concomitantly reduce the number of conformations available to the catalyst. The amide moiety was also envisioned to promote the preferred catalyst conformation with a large steric discrepancy between the N-alkyl substituents (a methylene group on one side and a bulky methane group on the other). A hydroxyl group was also introduced into the catalysts’ framework as both Campbell92 and Miller115 had implicated H-bonding in promoting enantioselective acyl transfer.
Gratifyingly, $^1$H NMR analysis of 169 showed only one rotamer present. Catalyst 169 was evaluated in the KR of 9 as per catalyst 163 in Scheme 2.2, resulting in a marked improvement in selectivity at room temperature. 169 Also exhibited excellent activity, with reaction complete after 13 minutes in the presence of 1 mol% catalyst. The resultant mixture of starting material (9) and product (10) was separated via flash chromatography (100% CH$_2$Cl$_2$). 10 Was isolated and the enantiomeric excess (31% ee at 59% conversion) determined by $^1$H NMR spectroscopy after complexation with (+)-Eu(hfc)$_3$.  

Scheme 2.3  Synthesis of catalyst 169
Figure 2.3  Determination of the ee of 10 by $^1$H NMR spectroscopy using a chiral lanthanide shift reagent. Top: Isolated 10. Bottom: $^1$H NMR spectrum of 10 after the addition of 1.5 equiv. of Eu(hfc)$_3$. 

![NMR Spectra](image)
2.3.1 Solvent optimisation studies

Solvent optimisation studies were undertaken to investigate the effect of solvent polarity on catalytic enantiodiscrimination. In accordance with the findings of Cambpell and co-workers, less polar solvents promoted a more efficient enantioselective acyl-transfer reaction, with the highest S factor obtained using CH$_2$Cl$_2$. Unfortunately, attempts at KR involving the use of the less polar hexane failed due to a lack of catalyst solubility.

### Table 2.1 Determination of the contribution of solvent polarity to selectivity

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conv. (%)$^a$</th>
<th>$ee$ (%)$^{b,c}$</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>59.3</td>
<td>31</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>63.0</td>
<td>21</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>58.0</td>
<td>22</td>
<td>2.0</td>
</tr>
<tr>
<td>4</td>
<td>Et$_2$O</td>
<td>58.0</td>
<td>17</td>
<td>1.7</td>
</tr>
<tr>
<td>5</td>
<td>t-A.A.</td>
<td>9.0</td>
<td>17</td>
<td>1.4</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>57.2</td>
<td>9</td>
<td>1.3</td>
</tr>
</tbody>
</table>

$^a$ Conversion which could be determined by $^1$H NMR spectroscopy $^b$Refers to the $ee$ of the ester product. $^c$% ee from ester. Determined by $^1$H NMR spectroscopy using a (+)-Eu(hfc)$_3$ chiral shift reagent

2.3.2 Further investigation into the optimisation of catalyst framework

Subsequently, the influence of each of the catalyst’s components on enantioselectivity was probed through the synthesis and systematic evaluation of variant catalyst structures. The modular nature of the synthesis outlined for 169 in Scheme 2.3 afforded a direct route for the facile alteration of catalyst structure (Figure 2.4).
A 2-naphthyl analogue of 167, i.e. 172 was synthesised in order to extend the range of influence of the pendant aromatic groups (which we postulated would be crucial in view of their ability to participate in π-pyridinium ion interactions). Synthesis of the (S)-α,α-di(2-naphthyl)prolinol precursor required the preformation of a proline-\(N\)-carboxy anhydride, 176 according to the procedure of Mathre et al.\(^{186}\) outlined in Scheme 2.4. Phosgene was added dropwise to a suspension of (S)-proline (177) in CH\(_2\)Cl\(_2\) at 0 °C under an atmosphere of argon, followed by heating at 35 °C for 2 h to promote formation of intermediate 178. Addition of NEt\(_3\) facilitated the cyclisation of 178 to form 176, with concomitant formation of the insoluble NEt\(_3\).HCl salt. The THF solution of (S)-176 was filtered and used immediately.
Scheme 2.4  Synthesis of (S)-α,α-di(2-naphthyl)prolinol, 179

(S)-176 Was added dropwise to a solution of 2-naphthylmagnesium bromide (180) in THF at -20 °C generating the sulphate salt of 179 after acidic workup with H2SO4. Conversion of the salt to the free base required reaction with 2M NaOH in THF to afford 179 in 48% yield.

Subsequent synthesis of 172 was accomplished via an identical procedure to that outlined in Scheme 2.3, coupling the amino alcohol 179 to the acid chloride derivative of 165, followed by pyrrolidination of the resultant chloropyridine 181, (Scheme 2.5).

Scheme 2.5  Synthesis of 172

Further to this, a naphthyl amide analogue, 173 was prepared from the commercially available proline naphthyl amide hydrochloride salt in order to deduce what effects the steric bulk of the phenyl and naphthyl groups had on stereoselectivity. A bis-methyl analogue of 169 would have been ideal, however literature precedent had ruled out a convenient synthesis due to racemisation of the prolinol’s acidic precursors.
Additionally, in order to determine the contribution of the catalyst hydroxyl group to the enantioselection process the reduced analogues of 169 and 172 (174 and 175 respectively) were prepared. The amine precursor of 174 i.e. 185 was synthesised via a literature procedure from (S)-proline. The synthesis of a 2-naphthyl derivative, 186 required the substitution of the phenyl Grignard used in the preparation of 174 for a 2-naphthyl Grignard reagent.

Reaction of (S)-177 with ethyl chloroformate and K₂CO₃ in methanol furnished 182 in a respectable isolated yield (73%). Addition of 182 to a solution of Grignard (Ph- or 2-Np-MgBr) in THF at 0 °C afforded 183 and 184 respectively. Hydrogenation of the pyrrolo-oxazolones 183 and 184 employing palladium on carbon as the catalyst yielded the corresponding substituted pyrrolidines 185 (82%) and 186 (68%).

Scheme 2.6  Synthesis of amines 185 and 186

Finally the synthesis of 174 (81%) and 175 (80%) was effected by coupling the amines 185 and 186 to 165 with subsequent pyrrolidination of the chloropyridines 187 and 188, Scheme 2.7.
Scheme 2.7  Synthesis of catalysts 174 and 175

\[ \text{[Chemical Reaction]} \]

\[ 1. \text{SOCl}_2, 80 ^\circ \text{C}, 2 \text{ h} \]
\[ 2. \text{NET}_3 (2.5 \text{ equiv.}) \]
\[ 0 ^\circ \text{C to RT}, 12 \text{ h}, \text{THF} \]
\[ \text{[Chemical Structure]} \]

185 \( R = \text{Ph} \)

186 \( R = 2-\text{Np} \)

187 \( R = \text{Ph} \) 27%

188 \( R = 2-\text{Np} \) 70%

174 \( R = \text{Ph} \) 81%

175 \( R = 2-\text{Np} \) 80%

\(^{1}H\) NMR analysis of each of the newly prepared catalysts showed the presence of only one rotamer. Catalysts 172 – 175 were then evaluated in the KR of 9 (Table 2.2)

Table 2.2  KR of 9 catalysed by catalysts 172 - 175

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Conv.(^a) (%)</th>
<th>( ee_A ^b ) (%)</th>
<th>( ee_Y ^b ) (%)</th>
<th>S</th>
<th>Absol. config(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>172</td>
<td>48.2</td>
<td>32</td>
<td>34</td>
<td>2.7</td>
<td>(R)</td>
</tr>
<tr>
<td>2</td>
<td>173</td>
<td>50.5</td>
<td>16</td>
<td>15</td>
<td>1.6</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>174</td>
<td>48.6</td>
<td>7</td>
<td>7</td>
<td>1.2</td>
<td>(S)</td>
</tr>
<tr>
<td>4</td>
<td>175</td>
<td>54.9</td>
<td>4</td>
<td>3</td>
<td>1.1</td>
<td>(S)</td>
</tr>
</tbody>
</table>

\(^a\) Conversion which could be determined (with excellent agreement) either by \(^{1}H\) NMR spectroscopy or using chiral HPLC, where \( C = 100 \times \frac{\text{ee}_{\text{alcohol}}}{(\text{ee}_{\text{alcohol}} + \text{ee}_{\text{ester}})} \)^\(^b\) Determined by chiral HPLC using a chiralcel OD-H column (4.6 x 250 mm). \(^c\) Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times.\(^{81}\)

The results of these experiments were instructive; in general, the level of selectivity achieved in the above reactions was modest, however a clear trend emerged with catalysts 172 and 173 (as in catalyst 169) incorporating functionality capable of donating H-bonds promoting reactions with the greatest stereocontrol (entries 1 and 2). Interestingly 174 and 175 (which are incapable of efficient H-bond donation) gave the opposite sense of stereoinduction while no noticeable effect on catalyst activity was observed in the reaction.
On consideration of these results it was decided to concentrate our efforts on the more selective catalysts. Therefore catalysts 169 and 172 were evaluated in the KR of the mono-protected diols in the presence of iso-butyric anhydride. These alcohols had been previously identified by Fuji\textsuperscript{87} as providing high enantioselectivities on acylation and were readily synthesised by coupling the appropriate acid chloride (189a – c) with cis-1,2-cyclohexanediol (190), (Scheme 2.8).

**Scheme 2.8** Synthesis of mono-protected cis-diols

Both literature\textsuperscript{83} and our own preliminary investigations had shown that a more enantioselective reaction was promoted by the presence of iso-butyric anhydride across a wide range of substrates, compared with acetic anhydride. The sterically demanding iso-propyl moiety reduces reaction rates and helps bias the conformational preferences of the acylated intermediate.

The initial reaction conditions included the treatment of racemic alcohols 76a, b and 191b with 1 mol\% of the active catalysts at ambient temperature, with iso-butyric anhydride as acylating agent and NEt\textsubscript{3} as the general base in anhydrous CH\textsubscript{2}Cl\textsubscript{2} under an inert atmosphere of argon.
As expected catalysts 169 and 172 promoted the smooth acylation of 76a,b and 191b at low catalyst loadings, with synthetically useful selectivity possible at low temperature (entry 2). It is noteworthy that the exchange of the phenyl substituents of catalyst 169 for 2-naphtyl moieties (catalyst 172) resulted in a marginal improvement in performance (entries 1 and 4), and that a decrease in the substrate carbonyl Lewis-basicity led to an attenuation of enantioselectivity (entries 4-6). This suggested the possible involvement of H-bonding in determining the preference of the acylated catalyst for one antipode of the racemic substrate. However it should also be noted that a possible π-π interaction between the substrate and the acylated pyridinium ion (as postulated by Fuji) could also be responsible for the superiority of 76a over 76b and 191b.

2.3.3 Optimisation of reaction conditions for KR of substrate 76b catalysed by 169

Subsequently, a control experiment in the absence of catalyst was performed using alcohol 191b; under these conditions a moderate background conversion of 8% was observed after 16 h. Although the conversion of mono-protected cis-diol to 192 is significantly
accelerated by catalysts 169 and 172, the uncatalysed racemic acylation impinges considerably on the enantioselectivities achieved during the catalysed reaction. In an effort to reduce the level of background reaction, a study was initiated to investigate the effect of a diverse array of auxiliary bases on the outcome of the KR of substrate 76b. Given that 76b was the substrate most susceptible to enantiodifferentiation in KR processes catalysed by 169 (entries 1 and 2, Table 2.3), it was chosen as the substrate for these studies so that the effect of the base on the enantioselectivity of the acylation could be conveniently determined.

Table 2.4  Optimisation studies performed on the KR of 76b catalysed by 169

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Conv. (%)</th>
<th>eeA (%)</th>
<th>S</th>
<th>Absol. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>DIPEA</td>
<td>64</td>
<td>70</td>
<td>4.6</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>DABCO</td>
<td>61</td>
<td>63</td>
<td>4.4</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>Imidazole</td>
<td>19</td>
<td>6</td>
<td>1.9</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>DBU</td>
<td>38.5</td>
<td>28</td>
<td>3.4</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>Na₂CO₃</td>
<td>61</td>
<td>58</td>
<td>3.7</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>NEt₃</td>
<td>64</td>
<td>70</td>
<td>4.6</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>NEt₃</td>
<td>69</td>
<td>77</td>
<td>4.4</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>8</td>
<td>CH₂Cl₂</td>
<td>NEt₃</td>
<td>67</td>
<td>67</td>
<td>3.7</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>9</td>
<td>CH₂Cl₂</td>
<td>NEt₃</td>
<td>63</td>
<td>55</td>
<td>3.1</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>NEt₃</td>
<td>66</td>
<td>20</td>
<td>1.5</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>11</td>
<td>DMSO</td>
<td>NEt₃</td>
<td>66</td>
<td>20</td>
<td>1.5</td>
<td>(1S, 2R)</td>
</tr>
</tbody>
</table>

Refer to conversion, which could be determined (with excellent agreement) either by ¹H NMR spectroscopy or using chiral HPLC, where conv. = 100 x eelcohol/(eealcohol + eester). ee of alcohol 76b determined by chiral HPLC using a Chiralcel OD-H column (4.6 x 250 mm). Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times. The auxiliary amines were chosen to represent a range of basicities (pKₐs of conjugate acids ranging from 7 (imidazole) to ~12 (DBU)). With the exception of the reactions involving imidazole and DBU, acylation proceeded to near completion within 16 h (entries, 1, 2, 5 and 6). However, no discernable correlation between the auxiliary base structure and the level of enantioselectivity achieved on acylation were identified.
DIPEA and NEt₃ promoted the most stereoselective KR under these reaction conditions. NEt₃ was preferred as the base of choice owing to its relative inexpense and lower boiling point which enables its facile removal under reduced pressure after reaction.

The influence of the solvent system was again revisited, with each solvent regardless of polarity promoting successful conversion to product. Proti solvents or aromatic solvents (e.g. toluene) resulted in lower selectivity.

2.3.4 Comparison of catalysts 169 and 172 – 174 under optimised conditions

The newly optimised conditions afforded us an opportunity to effectively compare the performance of our acyl-transfer catalysts with those reported in the literature. Racemic 1-(naphthyl)ethanol (54) was chosen as a suitable substrate for comparison as the majority of the synthetically useful literature catalysts \textit{i.e.} 47, 53 and 72, had employed 54 in successful KR processes (Sections 1.4 and 1.5), (Table 2.5).

**Table 2.5** Evaluation of catalysts 169, 172, 174 and 175 in the KR of 54

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Conv. ( (%) )</th>
<th>( ee_A ) ( (%) )</th>
<th>( ee_E ) ( (%) )</th>
<th>S</th>
<th>Absol. config.(^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>169</td>
<td>72</td>
<td>93</td>
<td>29</td>
<td>6.3</td>
<td>(R)</td>
</tr>
<tr>
<td>2</td>
<td>172</td>
<td>43 (^d)</td>
<td>51</td>
<td>63</td>
<td>8.7</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>174</td>
<td>36</td>
<td>22</td>
<td>36</td>
<td>2.8</td>
<td>(S)</td>
</tr>
<tr>
<td>4</td>
<td>175</td>
<td>43</td>
<td>30</td>
<td>38</td>
<td>3.0</td>
<td>(S)</td>
</tr>
</tbody>
</table>

\(^a\) Conversion: which could be determined (with excellent agreement) either by \(^1\)H NMR spectroscopy or using chiral HPLC, where \( C = 100 \times \frac{ee_{alcohol}}{(ee_{alcohol} + ee_{ester})} \). \(^b\) Determined by chiral HPLC using a Chiralcel OD-H column (4.6 x 250 mm). \(^c\) Absolute configuration of recovered alcohol (major enantiomer) as determined by comparison with literature retention times. \(^d\) 0.80 equiv. \((\text{PrCO})_2\text{O}\), 8 h.
The results are in agreement with those in Table 2.2, with an inversion in the sense of stereoinduction observed using reduced analogues of 169 and 172 (i.e. 174 and 175 respectively). It is noteworthy that hydroxyl substituted catalyst 169 proved considerably more active than its reduced analogue (174) and promoted the acylation of 54 twice as efficiently under identical reaction conditions. We would posit that this indicates the hydroxyl group not only contributes to enantioselectivity, but accelerates the reaction (entries 1, 3 and 4). While both 169 and 172 promoted the KR of 54 with selectivities approaching synthetically useful levels (entries 1 and 2) catalyst 172, with larger aromatic moieties than 169 promoted a moderately more selective resolution.

On the basis of the enantioselective acylations observed in Tables 2.3 – 2.5 we proposed a preliminary model for the acylative KR of 54 catalysed by 169 (Figure 2.5). The proximity of H-2 to the \(\pi\)-cloud of one of the phenyl substituents forces the iso-propyl group to occupy the distal side of the N-N pyrrolidinated pyridine-axis. The N-iso-propyl moiety is conjugated with and lies in the plain of the pyridine ring with the hydroxyl moiety (through H-bonding) controlling the angle of attack of 54 (assuming that the naphthyl group avoids the acylated catalyst). Therefore, the (R)-54 antipode reacts relatively slowly due to catalyst-methyl group repulsion as the substrate approaches.

**Figure 2.5** Possible pre-TS-assemblies for the acylation of 54 by (iPrCO)\(_2\)O catalysed by 169.
In order to garner further insight into the mode of action of catalysts 169 and 172, attention then turned to the question of substrate scope. Catalyst 169 was favoured in place of the 2-naphthyl analogue, 172, due to the commercial availability of the prolinol precursor 170. 169 was prepared on a gram scale and a range of substrates were chosen to systematically probe the catalyst’s sensitivity to substrate steric, electronic and hydrogen-bond donating/accepting characteristics. These substrates were prepared as outlined in Scheme 2.9.

**Scheme 2.9** Synthesis of substrates for KR catalysed by 169

\[
\begin{align*}
R_1\text{MgBr} & \quad R_2\text{Cl} \quad \text{THF} \quad 0^\circ C, 3 \, \text{h} \quad \text{LiAlH}_4 \quad \text{THF, 14 h} \\
194 & \quad (0.9 \, \text{equiv.}) \quad 195 & \quad (1.0 \, \text{equiv.}) \quad 196 \quad (0^\circ C - 60^\circ C) \quad R_1 R_2 \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
194a \quad R_1 = \text{Ph} & \quad 195a \quad R_2 = \text{t-Bu} \\
194b \quad R_1 = 2,6-(\text{Me})_2-\text{C}_6\text{H}_3 & \quad 195b \quad R_2 = \text{Me} \\
194c \quad R_1 = 4-\text{OMe}-\text{C}_6\text{H}_4 & \quad 195c \quad R_2 = \text{i-Pr}
\end{align*}
\]

\[
\begin{align*}
\text{MeMgBr} & \quad R_2\text{H} \quad \text{THF, 14 h} \\
198 & \quad (2.0 \, \text{equiv.}) \quad 199 & \quad (1.0 \, \text{equiv.})
\end{align*}
\]

\[
\begin{align*}
199a \quad R_2 = 2-\text{OMe}-\text{C}_6\text{H}_4 & \quad 197 \quad R_1 = \text{Me} \quad R_2 = 2-\text{OMe}-\text{C}_6\text{H}_4 \\
199b \quad R_2 = 2,4-(\text{OMe})_2-\text{C}_6\text{H}_3 & \quad 200b \quad R_1 = \text{Me} \quad R_2 = 2,4-(\text{OMe})_2-\text{C}_6\text{H}_3
\end{align*}
\]

\[
\begin{align*}
\text{R}_1\text{R}_2 & \quad \text{NaBH}_4 \quad (1.0 \, \text{equiv.)} \quad \text{EtOH, 14 h} \quad 0^\circ C - \text{RT} \\
201a \quad R_1 = \text{Ph} \quad R_2 = \text{i-Pr} & \quad 57 \quad R_1 = \text{Ph} \quad R_2 = \text{i-Pr} \\
201b \quad R_1 = 4-\text{NO}_2-\text{C}_6\text{H}_4, R_2 = \text{Me} & \quad 9b \quad R_1 = 4-\text{NO}_2-\text{C}_6\text{H}_4, R_2 = \text{Me} \\
201c \quad R_1 = 2-\text{NO}_2-\text{C}_6\text{H}_4, R_2 = \text{Me} & \quad 202c \quad R_1 = 2-\text{NO}_2-\text{C}_6\text{H}_4, R_2 = \text{Me}
\end{align*}
\]

\[
\begin{align*}
190 \quad \text{COCl}_2 \quad (2.4 \, \text{equiv.)} \quad 19 \quad (5 \, \text{equiv.)}, \text{CHCl}_2 \\
-78^\circ C - 0^\circ C & \quad \text{piperidine} \quad (10 \, \text{equiv.)} \quad \text{THF, 60 °C, 3 h}
\end{align*}
\]

\[
\begin{align*}
205 & \quad \text{NH}_2 \quad \text{NMe}_2 \quad \text{NET}_3 \quad (1.5 \, \text{equiv.)} \quad \text{DCM, RT, 14 h}
\end{align*}
\]

84
The sec-alcohols were subjected to the optimised conditions outlined in Section 2.3.3; acylation by iso-butyric anhydride in CH$_2$Cl$_2$ with NEt$_3$ as the auxiliary base catalysed by 169 (1 mol%) at low temperature (-78 °C), under an inert atmosphere of argon. The results of these studies are presented in Table 2.6.

Table 2.6  Substrate scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conv.$^a$ (%)</th>
<th>$ee_A^b$ (%)</th>
<th>Ester</th>
<th>S</th>
<th>Absol. config.$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>27.5</td>
<td>25</td>
<td>OCO/Pr</td>
<td>6.3</td>
<td>$R$</td>
</tr>
<tr>
<td>2</td>
<td>74a</td>
<td>17</td>
<td>14</td>
<td>OCO/Pr</td>
<td>6.0</td>
<td>$R$</td>
</tr>
<tr>
<td>3</td>
<td>74b</td>
<td>14.6</td>
<td>1</td>
<td>OCO/Pr</td>
<td>1.1</td>
<td>$R$</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>19</td>
<td>19</td>
<td>OCO/Pr</td>
<td>13.5</td>
<td>$R$</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>4.1</td>
<td>1.6</td>
<td>OCO/Pr</td>
<td>2.2</td>
<td>$R$</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>22.5</td>
<td>20</td>
<td>OCO/Pr</td>
<td>6.6</td>
<td>$R$</td>
</tr>
<tr>
<td>7</td>
<td>83</td>
<td>37</td>
<td>40</td>
<td>OCO/Pr</td>
<td>7.6</td>
<td>$R$</td>
</tr>
<tr>
<td>8</td>
<td>9a</td>
<td>20</td>
<td>19</td>
<td>OCO/Pr</td>
<td>9.1</td>
<td>$R$</td>
</tr>
</tbody>
</table>

$^a$ Conversion which could be determined (with excellent agreement) either by $^1$H NMR spectroscopy or using chiral HPLC, where $C = 100 \times e_{ee_{alcohol}}/(e_{ee_{alcohol}} + e_{ee_{ester}})$. $^b$ Determined by chiral stationary phase HPLC using a Chiralcel OD-H column (4.6 x 250 m). $^c$ Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data.
Moderate conversions to the corresponding iso-propyl ester (14.6 – 37%) were observed under the reaction conditions (-78 °C, 6 h). In the case of the benzyl alcohols 9, 74a and 74b, a distinct decrease in conversion was observed upon increased ortho-substitution of the aromatic moiety (entries 2 and 3), while a more dramatic attenuation in conversion accompanied augmentation of the alkyl substituent bulk (entries 1, 4 and 5).

However, contrary to literature precedents set by Fu\textsuperscript{70} and Spivey\textsuperscript{83} regarding the beneficial effects of augmenting alkyl- and aromatic substituent bulk on enantioselectivity being additive (in a qualitative sense), selectivity failed to increase accordingly. Enlargement of the aliphatic substituent bulk from methyl to iso-propyl proved favourable, with a two fold increase in selectivity (entries 1 and 4), unfortunately, a further increase in steric bulk to the tert-butyl derivative resulted in a major reduction in enantiodiscrimination. The aggrandisement of the steric requirement of the aromatic substituent was poorly tolerated by the catalyst (entries 2-3 and 6-7), with an almost racemic product afforded upon the acylation of 74b catalysed by 169. These results strongly imply that the steric nature of both the aromatic and aliphatic substituents is critical for the efficient KR of benzyl alcohols promoted by 169.

A preliminary investigation into the electronic requirements of the benzyl alcohols was also undertaken, with 1-(4-methoxy-phenyl)-ethanol (9a) resolved by acylation in the presence of 169. 9a proved clearly superior to the unsubstituted parent alcohol in terms of the selectivities achieved upon acylation (entries 1 and 8).

Subsequently, further attempts were made to elucidate catalyst sensitivity to the electronic characteristics of the aromatic sec-alcohol. sec-Phenyl ethanol derivatives substituted with electron donating and withdrawing groups in the ortho and para-positions were prepared and evaluated under identical conditions to those used in the KR of the benzyl alcohols in Table 2.6 (Table 2.7).
Table 2.7  Contribution of electronic groups to enantioselectivity

\[
\begin{align*}
\text{NEt}_3 (0.75 \text{ equiv.}) & \quad (\text{PrCO}_2\text{O} (0.75 \text{ equiv.}) \\
-78 \, ^\circ\text{C}, 6 \, \text{h}, \text{CH}_2\text{Cl}_2 & \quad \rightarrow \quad \text{OCOPr} \\
\text{rac} & \quad \downarrow I \quad ^\uparrow R \\
\end{align*}
\]

-78 °C, 6 h, CH$_2$Cl$_2$

\[\text{NEt}_3 (0.75 \text{ equiv.})\ (\text{PrCO}_2\text{O} (0.75 \text{ equiv.}) \quad \rightarrow \quad \text{OCOPr} \quad + \quad \text{OH}\]

\begin{align*}
\text{9b} & \quad R^1 = 4-\text{NO}_2-\text{C}_6\text{H}_4 \\
\text{97} & \quad R^1 = 2-\text{MeO}-\text{C}_6\text{H}_4
\end{align*}

\begin{align*}
\text{208a} & \quad R^1 = 4-\text{F}-\text{C}_6\text{H}_4 \\
\text{208b} & \quad R^1 = 2-\text{NO}_2-\text{C}_6\text{H}_4 \\
\text{208c} & \quad R^1 = 4-\text{NO}_2-\text{C}_6\text{H}_4 \\
\text{208d} & \quad R^1 = 2-\text{MeO}-\text{C}_6\text{H}_4
\end{align*}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conv. (%)</th>
<th>$ee_A$ (%)</th>
<th>S</th>
<th>Absolut. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97</td>
<td>18</td>
<td>18</td>
<td>11.4</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>27</td>
<td>6</td>
<td>1.4</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>202c</td>
<td>28</td>
<td>6</td>
<td>1.5</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>106d</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>nd</td>
</tr>
</tbody>
</table>

\[a\text{ Conversion which could be determined (with excellent agreement) either by } ^1\text{H NMR spectroscopy or using chiral stationary phase HPLC, where } C = 100 \times \frac{ee_{\text{alcohol}}}{(ee_{\text{alcohol}} + ee_{\text{ester}})}. \]

\[b\text{ Determined by chiral HPLC using a Chiralcel OD-H column (4.6 x 250 mm).} \]

\[c\text{ Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data.}^{188, 190, 191} \]

Interestingly, the presence of an electron donating methoxy substituent in the ortho-position resulted in a comparable level of enantiodiscrimination to the para-MeO analogue, 9a (entry 1, Table 2.7 and entry 7, Table 2.6). In comparison, substrates 9b and 202c, with electron withdrawing groups incorporated in the 2- and 4-positions performed poorly. These results appeared to indicate that the increased Lewis basicity of the methoxy substituted secondary alcohols facilitated greater enantiodiscrimination possibly through a H-bonding interaction with the hydroxyl group of the acylated pyridinium intermediate of 169.

It was clear at this juncture that both the steric and electronic makeup of the substrate alkyl and aromatic substituents influenced the efficacy of enantioselective acylation using catalyst 169. Substrates were subsequently prepared to investigate these observed phenomena further. A comprehensive review of the literature also unearthed two other potential optimal substrates 206 and 93.
Table 2.8 Contribution of substrate aromatic groups to enantioselectivity

\[
\begin{align*}
\text{Entry} & \quad \text{Substrate} & \quad \text{Conv.}^a \quad \text{ee}_A^b & \quad \text{Ester} & \quad S & \quad \text{Absol. config.}^c \\
1 & 200b & 27.5 & 25 & \text{OCO/iPr} & 6.3 & \text{R} \\
2 & 197c & 15 & 14 & \text{OCO/iPr} & 9.5 & \text{R} \\
3 & 206 & 23 & 11 & \text{OCO/iPr} & 2.3 & \text{IR,2S} \\
4 & 93 & 19 & 22 & \text{OCO/iPr} & 30 & \text{IR,2S} \\
\end{align*}
\]

\text{**Conversion which could be determined (with excellent agreement) either by }^1\text{H NMR spectroscopy or using chiral stationary phase HPLC, where } C = 100 \times \text{ee}_{\text{alcohol}} / (\text{ee}_{\text{alcohol}} + \text{ee}_{\text{ester}}).^a \text{ Determined by chiral HPLC using a Chiralcel OD-H column (4.6 x 250 mm).}^b \text{ Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data.}^c

Surprisingly, the increased electron density associated with substrate 200b failed to improve enantiodiscrimination further (entry 1). Additionally the combined electronic and steric contributions from the optimal substrates 9a and 57 respectively, were not additive (substrate 197c, entry 2), even though 169 promoted the preferential acylation of the same (S)-antipode of 197c as 9a and 57.

206 appeared to be an excellent choice of substrate for KR (considering the obvious compatibility of 76b with 169), unfortunately 206 underwent acylation with poor selectivity (entry 3). In hindsight a number of factors potentially contribute to make 206 a poor substrate for KR using 169; the presence of two substrate aromatic moieties, the conformational preference of the amide (relative to the ester functionality of substrate
the relative planarity of the benzo-fused five membered ring and the presence of a second potentially hydrogen bond donating group (amide N-H). In contrast, the KR of trans-2-phenylcyclohexanol (93) using 169 proceeded with superb enantioselectivity (entry 4 and Figure 2.6).

In view of the considerable sensitivity of the catalyst to the nature of the substrate aromatic group, aliphatic carbamate 204 was synthesised and subsequently acylated in the presence of 169 under standard conditions (Scheme 2.8). The resolution of this substrate with relatively good selectivity (S = 8.6) demonstrates the broad scope of catalyst 169 and indicates that an aromatic substituent is not an absolute requirement for selectivity in this system.

On analysis of the data in Tables 2.3-2.8, a picture emerges in which a confluence of contributions from the catalyst hydroxyl group/aromatic substituents (Tables 2.3 – 2.5) and substrate aliphatic/aromatic components (Table 2.6 – 2.8) seem responsible for selectivity in KR processes using catalyst 169.
2.5 Investigation into the potential contribution of van der Waals (π) interactions to enantiodiscrimination in KR processes mediated by 169 and analogues

A control catalyst (211), lacking a quaternary centre, with no aryl or hydroxyl substituents was synthesised to accurately assign the ¹H NMR chemical shifts of the pyridine ring i.e. H-2, -5 and -6, in the absence of the functional groups that facilitate enantiodiscrimination. 211 Was prepared via a double pyrrolidination of the acid chloride of 165 (Scheme 2.9). H-5 appeared at 6.47 ppm, while the more deshielded H-2 and H-6 resonated further downfield at 8.16 and 8.19 ppm respectively (Figure 2.7).

**Scheme 2.9  Synthesis of control catalyst 211**

\[
\begin{align*}
165 & \xrightarrow{1. \text{SOCl}_2, 80^\circ \text{C}, 2 \text{ h}} \xrightarrow{2. \text{0}^\circ \text{C} - \text{RT, 4 h, THF}} \xrightarrow{(5.0 \text{ equiv.})} \xrightarrow{70^\circ \text{C}, 12 \text{ h}} \xrightarrow{(2.0 \text{ equiv.})} 211 \\
\end{align*}
\]

**Figure 2.7 ¹H NMR of control catalyst 211**
In an attempt to detect possible aryl-pyridinium ion π-stacking interactions, the $^1$H NMR spectra of catalysts 169, 172, 174, 175 and control material 211 were compared to that of their corresponding products on methylation with iodomethane (Table 2.9). These experiments were informative; while little evidence was found to support a ‘face-face’ π-π stacking interaction as reported by Fuji and Yamada (Figure 2.1), a strong upfield shift associated with H-2 upon methylation of 169, 172, 174 and 175 (which is absent on methylation of 211) was observed, the magnitude and localisation of which indicates that an interaction between the substituted edge of the pyridinium cation (or H-2 itself) and one of the pendant aryl moieties takes place.

Table 2.9 $^1$H NMR data for 169, 172, 174, 175, 211 and methylated analogues

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>$\delta$ H-2&lt;sup&gt;±,κ&lt;/sup&gt;</th>
<th>$\delta$ H-5&lt;sup&gt;±,κ&lt;/sup&gt;</th>
<th>$\delta$ H-6&lt;sup&gt;±,κ&lt;/sup&gt;</th>
<th>$\delta$ CH&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>169</td>
<td>7.33</td>
<td>6.45</td>
<td>8.09</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>169a</td>
<td>6.52 (-0.81)</td>
<td>6.80 (0.45)</td>
<td>8.04 (-0.05)</td>
<td>3.88</td>
</tr>
<tr>
<td>3</td>
<td>172</td>
<td>7.51</td>
<td>6.45</td>
<td>8.09</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>172a</td>
<td>5.99 (-1.52)</td>
<td>6.70 (0.25)</td>
<td>7.88 (-0.21)</td>
<td>3.33</td>
</tr>
<tr>
<td>5</td>
<td>174</td>
<td>7.73</td>
<td>6.42</td>
<td>8.12</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>174a</td>
<td>6.68 (-1.05)</td>
<td>6.79 (0.37)</td>
<td>8.10 (-0.02)</td>
<td>4.02</td>
</tr>
<tr>
<td>7</td>
<td>175</td>
<td>7.93</td>
<td>6.42</td>
<td>8.11</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>175a</td>
<td>6.39 (-1.54)</td>
<td>6.66 (0.24)</td>
<td>7.88 (-0.23)</td>
<td>3.49</td>
</tr>
<tr>
<td>9</td>
<td>211</td>
<td>8.19</td>
<td>6.47</td>
<td>8.16</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>211a</td>
<td>8.17 (-0.02)</td>
<td>6.90 (0.43)</td>
<td>8.21 (0.05)</td>
<td>4.21</td>
</tr>
</tbody>
</table>

$^\text{±}$ Is quoted in ppm in CDCl<sub>3</sub> as solvent. $^\text{κ}$ Value in parenthesis represents $\Delta\delta$: the change in chemical shift of the proton indicated on methylation (in ppm), a negative value for $\Delta\delta$ indicates an upfield shift. $^\text{κ}$ All pyridine ring proton resonances were unambiguously assigned by NMR spectroscopy ($^1$H-$^1$H COSY, $^1$H-$^13$C COSY, NOE and 1-D TOCSY experiments).
This effect is more dramatic in the case of the naphthyl-substituted 172a and 175a, where even the pyridinium methyl protons are significantly shielded relative to the corresponding 211a methyl group. Clear illustration of the upfield shift of H-2, H-5 and H-6 associated with methylation is observed in the $^1$H NMR spectra of 174 and 174a (Figure 2.8). It is also noteworthy that $\delta$ H-2 is observed at considerably higher field in the cases of 169 and 172 than for 211, which we propose demonstrates that the aforementioned interaction is also a feature of the solution-state structure of these materials.

**Figure 2.8** $^1$H NMR spectra of catalyst 174 and methylated derivative 174a

Attempts to obtain an x-ray crystal structure of 169a met with failure, however, fortunately the corresponding benzylated catalyst 212 was amenable to recrystallisation and an X-ray structure was obtained (Figure 2.9)
The amide moiety is in an \textit{s-cis} conformation with the diaryl tertiary alcohol substituent orientated towards H-2 and the nucleophilic ring-nitrogen: consistent with the proposed \(\pi\)-interactions and observed catalytic importance of the hydroxyl group. While an upfield shift of the H-2 resonance was observed in 212 (Figure 2.6), this was less pronounced than in the case of the methylated compound 169a, which may be related to steric repulsion between the \(N\)-benzyl and pendant phenyl substituents.

Subsequently, the \textit{acylation} of 169 and 211 was undertaken to determine whether a corresponding shift in proton resonance (as observed on methylation, Table 2.10) would be observed. The initial acylation was performed using distilled acetyl chloride (1 equiv.) in CDCl\(_3\). Unfortunately the acetylated intermediate hydrolysed rapidly and the resultant acid protonated the catalyst, causing the formation of supplementary proton resonances which prevented the unambiguous assignment of the acylated intermediate proton chemical shifts.

\textit{iso}-Butyric acid chloride was successfully employed as an acylating agent and afforded a more stable intermediate with readily observable proton chemical shifts. No upfield shift of the H-2 resonance was observed upon acylation of 169, this is perhaps unsurprising, in view of the powerful (anisotropic) electron withdrawing ability of the carbonyl moiety.
Scheme 2.10 $^1$H NMR acylation studies of 169 and 211

Figure 2.10 $^1$H NMR spectra of catalyst 169 and acylated derivative 213
However, it is noteworthy that H-2 of acylated catalyst 213 resonates at considerably higher field (ca. 0.5 ppm) than that of acylpyridinium chloride 214 (and even resonates at higher field than the corresponding proton of either 211 or 211a) and that there is a greater difference between δ H-2 and δ H-6 in pyridinium ion 213 (1.04 ppm) than in the case of 214 (0.5 ppm), Scheme 2.10.

These results indicate that in the case of both 213 and 214 (contrary to what might be expected from first principles but in agreement with reports from Spivey and Yamada) the bulky iso-propyl moiety is located on the same side of the N-N axis as the catalyst amide substituent (i.e. as depicted above in Scheme 2.10) and that while the stark conformational change observed on methylation of 169 is difficult to detect when the same catalyst is acylated, nonetheless considerable shielding at H-2 consistent with the aforementioned ‘edge to face’ π-pyridinium ion interaction is observed.

The results in Table 2.3 – 2.9 indicate that the ability of 169 and 172 to serve as active and enantioselective acyl-transfer catalysts is due to a unique combination of several factors including aryl-pyridinium ion π-π (or π-H) and substrate-catalyst H-bonding and possibly also π-π interactions.

To better understand the origins of enantiodiscrimination using 169 and 172 we enlisted the aid of Prof. Graeme Watson to help examine the conformational preferences of 169a and 215 (the N-acetyl analogue of 213) using B3LYP hybrid density functional theory (Gaussian 03, 6-31G* basis set). We postulated that two conformational features would have particularly strong influence on catalyst performance: 1) isomerism of the C-3 amide linkage (i.e. s-cis vs. s-trans) and crucially, 2) the preferred conformation of the acyl-moiety in 213.

Therefore we calculated the gas-phase energetics of methylated and acetylated analogues of 169 (Table 2.10 and 1-IV, Figure 2.8) with respect to these parameters. The results of these calculations are presented in Table 2.10. An examination of the relative energies for the s-cis vs. s-trans chiral amide conformation reveals a strong preference for the s-cis rotamer (entries 1-2, Table 2.10), which is consistent with the X-ray crystal structure obtained for 212.
Table 2.10  Calculated relative energies of I-IV

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Conformation</th>
<th>Amide rotamer</th>
<th>N-acetyl rotamer</th>
<th>Relative energy (kJ mol(^{-1}))(^{a,b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>169a</td>
<td>I</td>
<td>s-cis</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>169a</td>
<td>II</td>
<td>s-trans</td>
<td>-</td>
<td>44.9</td>
</tr>
<tr>
<td>3</td>
<td>215</td>
<td>III</td>
<td>s-cis</td>
<td>s-trans</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>215</td>
<td>IV</td>
<td>s-cis</td>
<td>s-cis</td>
<td>4.2</td>
</tr>
</tbody>
</table>

\(^a\) Calculated relative energies. \(^b\) Does not account for the influence of the counter ion

Calculated minimum energy conformers of 169a and 215
Interestingly, these studies also indicate (somewhat counter-intuitively but consistent with the findings of the NMR studies – see Scheme 2.10) that the conformer of 215 (s-cis C-3 amide) in which the methyl group resides on the more hindered catalyst hemisphere (III) is more stable than the corresponding conformer where the smaller carbonyl group is directed towards the chiral amide substituent (IV – entries 3-4, Table 2.10). Since this phenomenon does not seem to be sterically driven, it may, by analogy with a suggestion made by Spivey,\textsuperscript{195} be related to partial conjugation with the C-3 substituent, although like Spivey we have no evidence to support this claim.

Interestingly, a C\textsubscript{2}-symmetric analogue of 169 (216, Scheme 2.11) designed to circumvent potential problems associated with N-acyl isomerism and synthesised by Dr. Stephen J. Hynes in our group, proved to be a completely inactive acylation catalyst.

**Scheme 2.11** C\textsubscript{2}-symmetric catalyst 216

```
Based on the available data, a revised rationale for the selectivity observed in the acylation of aromatic substrate 57 catalysed by 169 in non-polar solvents is shown in Figure 2.10. H-2 is located in the vicinity of the π-cloud of one of the phenyl substituents (Tables 2.9 and 2.10), with the second phenyl moiety orientated into the solvent. In this conformation the hydroxyl group can control the Burgi-Dunitz trajectory of 57 by H-bonding (Tables 2.1, 2.3 and 2.5), assuming that the incoming substrate maximises both face-face π-π interactions with the pyridinium ring (Tables 2.6 and 2.7) and hydrogen bonding interactions with the catalyst hydroxyl substituent. The (R)-57 antipode reacts relatively slowly due to steric repulsion between the substrate iso-propyl group and the catalyst as the substrate approaches (Figure 2.11).
```
2.6 Conclusions for chapter 2

In summary, we have developed a new class of active, chiral 4-(pyrrolidino)-pyridine derivatives (169 and 172) for the kinetic resolution of an exceptionally wide range (both aromatic and aliphatic) of sec-alcohols with synthetically useful selectivity. These proline-derived promoters are readily prepared from simple, readily available starting materials without the need for resolution steps. A combination of optimisation (Table 2.3 and 2.4), substrate screening (Table 2.3 – 2.8), catalyst modification (Table 2.5), spectroscopic (Table 2.9, Figure 2.7 and Scheme 2.10) and computational (Table 2.10) studies have clearly identified both hydrogen bonding and (intra as well as possibly also intermolecular) π-pyridinium-ion interactions as playing a role in enantiodiscrimination, and have provided insight into the conformational preferences of the key acylated catalytic intermediates in these reactions.

To the best of our knowledge 169 and 172 represent the first chiral 4-\(N,N\)-dialkylaminopyridine catalysts to synergistically employ both van der Waals (π) interactions and hydrogen bonding to allow remote chirality to exert stereochemical influence on an acylation reaction, and while the levels of enantiodiscrimination possible are lower than those associated with the benchmark literature catalysts, nonetheless, synthetically useful (\(S > 10\)) KR processes promoted by 169 have been demonstrated (up to a maximum of \(S = 30\)). Furthermore, the ready accessibility of these materials combined with the demonstrable influence of three independent, tunable catalyst properties
(hydrogen bond accepting/donating ability, aromatic substituent steric and electronic characteristics) on enantioselectivity provides considerable scope for subsequent catalyst development.

2.7 Enantioselective Steglich rearrangement

Previous investigations by Vedejs\(^7\) and Fu\(^{197}\) (Section 1.41 and 1.42 respectively) had demonstrated that enol carbonates were suitable substrates for enantioselective Steglich rearrangement reactions. Thus, in an attempt to further expand the reaction scope of our proline derived catalysts, 169 was employed to catalyse the azalactone acyl migration of substrate 217 at 0 °C in CH\(_2\)Cl\(_2\), Scheme 2.12. 217 Was chosen as a suitable substrate for reaction as both 48 and 53b had successfully catalysed its enantioselective rearrangement (89% ee and 91% ee respectively).

Scheme 2.12 Steglich rearrangement of 217 catalysed by 169

The reaction was monitored by \(^1\)H NMR and was complete in 10 mins with the catalyst then deactivated by addition of MeI (MeOH was originally employed, however methanolysis of the product azalactone occurred). The product, 218 was isolated by flash chromatography (100% CH\(_2\)Cl\(_2\)) and the enantiomeric excess determined by CSP-HPLC. Unfortunately, 169 failed to promote a stereoselective rearrangement to the C-acylated isomer 218 and no further investigation into Steglich rearrangements was undertaken.
The three-component nucleophile-catalysed Baylis-Hillman reaction is a synthetically important carbon-carbon bond forming process which can furnish chiral products of high utility from relatively simple achiral starting materials. Two significant limitations associated with these transformations are slow reaction rates and a general dearth of catalyst systems (relative to that of other Michael/aldol type processes) capable of promoting asymmetric BHRs of wide substrate scope.

While a number of solutions have been found to the reactivity issue which has resulted in a significant expansion of reaction scope, the pace of progress towards the development of the corresponding catalytic asymmetric methodologies has been relatively slow. The magnitude of this catalyst-design challenge is amplified by a complex mechanistic picture in which the identity of the rate-limiting step has yet to be fully substantiated. A number of chiral catalyst systems have been developed which can efficiently promote BHRs in which at least one reaction component (either aldehyde or Michael acceptor) is highly electrophilic with good enantioselectivity (>70% ee) (Section 1.6.5), however less activated aldehydes (e.g. anisaldehydes) and deactivated Michael acceptors (simple acrylates, acrylamides etc.) are generally extremely poor partners from both efficiency and enantioselectivity standpoints. Thus, for the synthesis of enantiopure/enantioenriched BH adducts not currently compatible with benchmark catalyst technology kinetic resolution (KR) is a viable alternative with several KR approaches reported to date (Table 1.24).

In the last decade, several highly active non-enzymatic small molecule nucleophilic organocatalysts capable of the acylative KR of sec-alcohols with excellent selectivity have been developed, however their application in the resolution of BH adducts has not yet been reported. This is due (at least in part) to the fact that the stereogenic center of an aldehyde-derived BH adduct is flanked by two planar sp\(^2\)-hybridised substituents which are very difficult for the acylated catalyst to distinguish in the enantio-discriminating acylation event - to the best of our knowledge no examples of the effective enantioselective acylation of any such substrate promoted by a small-molecule nucleophilic catalyst is known.

Therefore, encouraged by the highly active catalyst -developed for the acylative kinetic resolution of sec-alcohols- exhibiting an unusually strong preference for substrates
containing either electron rich carbonyl- or aromatic moieties, and encouraged by the broad substrate scope of 169 with respect to the KR of the alkyl-alkyl sec-carbinol 204, we were attracted to the asymmetric catalysis of BHRs involving electron rich substrates (either Michael acceptor or aldehyde) and the catalytic challenge of the non-enzymatic KR of sp²-sp² sec-carbinols outlined above. As a result we decided to evaluate 169 (and analogues) as a promoter of the KR of BH adducts difficult to synthesize in high enantiopurity using current benchmark catalytic methods.

3.2 Design of 3rd generation catalysts, 219-222

In previous studies investigating the mode of action of 169 we demonstrated that both the catalyst hydroxyl group and pendant aromatic moieties are required for high catalyst selectivity. A π-π interaction between the phenyl and pyridine rings (which strengthens considerably on either N-alkylation or N-acylation of 169) was also detected, however, it’s bearing on the stereochemical outcome of the acylation event was not fully explored. Given the inherent unsuitability of BHR adducts as substrates in acylative KR processes (vide supra) we decided to first investigate the influence of the steric and electronic properties of the aromatic substituents on catalyst performance so that an optimal catalyst structure could be identified for later application in the KR of BHR adducts (Figure 3.1).

Figure 3.1 Chiral analogues of 169, catalysts 219-222
3.2.1 Synthesis of catalysts 219-222

The synthesis of the prolinol precursors of catalysts 219-222 required the preparation of the corresponding Grignard reagents 223a-c (223d was commercially available). 223a And 223b were prepared via the addition of 224a and 224b respectively to a suspension of Mg dust in THF and heated under reflux. While 223c was prepared via a Knochel substitution, with addition of iso-propyl magnesium bromide to 3,5-bis(trifluoromethyl)bromobenzene 225 in THF at -10 °C. Addition of arylmagnesium bromides 223a-d to anhydride 176 furnished the required α,α-diarylprolinols 226a-d

Scheme 3.1 Synthesis of di-aryl prolinols 226a-d

Catalysts 219-222 were designed to examine the influence of the steric bulk and the electronic nature of the aromatic substituents on the π-pyridinium cation interaction and to concomitantly investigate the H-bonding contribution of the catalyst hydroxyl moiety (dependent on the electronic nature of the aromatic substituents) to the enantioselection process. 219-222 Were prepared as outlined in Scheme 3.2, in a superior overall yield to that of their precursors (Schemes 2.1, 2.3, 2.5 and 2.7), due to a reduction in the
temperature (80 °C - 65 °C) upon removal of SOCl₂ by distillation under reduced pressure which prevented the sublimation of the acid chloride hydrochloride.

Scheme 3.2  Synthesis of catalysts 219-222

1. SOCl₂, 65 - 80 °C, 2 h
2. NEt₃ (2.5 equiv.) 0 °C to RT, 12 h
   THF

226 (0.85 equiv.)

165

R = Ph 56%
R = OMe 57%
R = CF₃ 44%
R = Me 38%

226

227a

227a R = Ph 56%
227b R = OMe 57%
227c R = CF₃ 44%
227d R = Me 38%

Scheme 3.3  Rotameric ratio of catalysts 219-222

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Ratio of rotamers major:minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>219</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>220</td>
<td>17:3</td>
</tr>
<tr>
<td>3</td>
<td>221</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>222</td>
<td>4:1</td>
</tr>
</tbody>
</table>

Unfortunately, ¹H NMR analysis of each of the catalysts (219-222) revealed the presence of rotamers, with only one rotamer conceivably conducive to the intramolecular π-π stacking presumed to be required for enantioselective acyl-transfer (Scheme 3.3). This notwithstanding, it was decided to evaluate 219-222 as catalysts in the KR of a range of sec-alcohols.
3.3 Synthesis of mono-protected trans-diol substrate 228

The successful kinetic resolution of the mono-protected cis-diol 76b and of the trans-alcohol 93 combined with the reported excellent selectivity achieved upon the catalysed acylation of mono-protected trans-diol 228, led to our subsequent interest in 228 as a potential optimal substrate for resolution by our catalytic system. 228 was synthesised by coupling acid chloride 189c with trans-cyclohexane diol 229, Scheme 3.4.

Scheme 3.4 Synthesis of 228

3.3.1 Evaluation of catalysts 219-222 in the KR of sec-alcohols

Catalysts 219-222 were evaluated as promoters of the KR of sec-alcohols 57, 76b and 228 (Table 3.1). It was expected that significant augmentation of the steric bulk of the aromatic substituents (i.e. catalyst 222) would lead to a more enantioselective acylation (entries 1-2
and 6-7) in view of the proposed contribution of a π-pyridinium cation interaction to selectivity in reactions catalysed by 169. However, the clear (reproducible) superiority of the catalyst equipped with electron-withdrawing trifluoromethyl substituents (221, entries 5 and 10) over more electron rich analogues (219 and 220, entries 3-4 and 8-9) was somewhat surprising. It should be noted that the electronic character of the aromatic substituents also influences the hydrogen-bond donating/accepting characteristics of the hydroxyl group which is known to play a pivotal role in the enantioselection process (Section 2.3.4).

Table 3.1 Evaluation of catalysts 169 and 219-222 as enantioselective acylation catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Substrate</th>
<th>T (°C)</th>
<th>C (%)</th>
<th>eeR (%)</th>
<th>eeS (%)</th>
<th>S absolute config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>169</td>
<td>57</td>
<td>0</td>
<td>35</td>
<td>50</td>
<td>27</td>
<td>3.9 (R)</td>
</tr>
<tr>
<td>2</td>
<td>222</td>
<td>57</td>
<td>0</td>
<td>63</td>
<td>44</td>
<td>74</td>
<td>5.3 (R)</td>
</tr>
<tr>
<td>3</td>
<td>220</td>
<td>57</td>
<td>0</td>
<td>62</td>
<td>40</td>
<td>65</td>
<td>4.4 (R)</td>
</tr>
<tr>
<td>4</td>
<td>219</td>
<td>57</td>
<td>0</td>
<td>56</td>
<td>31</td>
<td>40</td>
<td>2.7 (R)</td>
</tr>
<tr>
<td>5</td>
<td>221</td>
<td>57</td>
<td>0</td>
<td>61</td>
<td>44</td>
<td>69</td>
<td>5.1 (R)</td>
</tr>
<tr>
<td>6</td>
<td>169</td>
<td>76b</td>
<td>0</td>
<td>57</td>
<td>54</td>
<td>71</td>
<td>6.9 (1S,2R)</td>
</tr>
<tr>
<td>7</td>
<td>222</td>
<td>76b</td>
<td>0</td>
<td>59</td>
<td>57</td>
<td>82</td>
<td>9.0 (1S,2R)</td>
</tr>
<tr>
<td>8</td>
<td>220</td>
<td>76b</td>
<td>0</td>
<td>61</td>
<td>50</td>
<td>77</td>
<td>6.6 (1S,2R)</td>
</tr>
<tr>
<td>9</td>
<td>219</td>
<td>76b</td>
<td>0</td>
<td>58</td>
<td>50</td>
<td>87</td>
<td>3.9 (1S,2R)</td>
</tr>
<tr>
<td>10</td>
<td>221</td>
<td>76b</td>
<td>0</td>
<td>60</td>
<td>58</td>
<td>87</td>
<td>10.1 (1S,2R)</td>
</tr>
<tr>
<td>11</td>
<td>221</td>
<td>76b</td>
<td>-78</td>
<td>66</td>
<td>50</td>
<td>96</td>
<td>10.8 (1S,2R)</td>
</tr>
<tr>
<td>12</td>
<td>221</td>
<td>228</td>
<td>-78</td>
<td>77</td>
<td>30</td>
<td>&gt;99</td>
<td>20.0 nd</td>
</tr>
</tbody>
</table>

Conversion: which could be determined (with excellent agreement) either by 1H NMR spectroscopy or chiral HPLC, where C = 100 × ee_alcohol/(ee_alcohol + ee_ester). ee determined by chiral HPLC using a Chiralcel OD-H column (4.6 x 250 mm), ee_E = ee of the ester product, ee_A = ee of the recovered alcohol. 's = enantioselectivity (k_fast/k_slow, see ref. 11). Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data. '6 h reaction time. '24 h reaction time.

Gratifyingly, the readily prepared catalyst 221 proved capable of resolving substrates containing Lewis-basic carbonyl moieties with synthetically useful selectivity (s >10, entries 10-12) at either 0 or -78 °C, which allowed the recovery of either enantioenriched or enantiopure (87-99.9% ee) alcohols with reasonable efficiency (23-40%).

105
3.4 Synthesis of BH adducts for KR catalysed by 221

With a superior catalyst (to 169) in hand, attention now turned to the question of the KR of BHR adducts. To examine the potential utility of the proposed KR strategy we decided to focus on the resolution of adducts currently difficult to synthesize in high enantiopurity using direct catalytic asymmetric BHRs. Bearing this in mind we selected BH adducts 232a-d as candidates, these are derived from the coupling of Michael acceptor substrates which (to the best of our knowledge) do not readily participate in highly enantioselective organocatalytic asymmetric BHR - i.e. methyl acrylate and acrylonitrile - with challenging, deactivated aromatic aldehydes (benzaldehyde and o-anisaldehyde). The synthesis of these BH adducts is outlined in Scheme 3.4, with the addition of the Michael acceptor substrates to the aldehyde in PEG catalysed by DABCO.

**Scheme 3.4  Synthesis of BH adducts 232a-d**

![Scheme 3.4](image)

(1.5 equiv.)

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅</td>
<td>CO₂Me</td>
<td>232a R₁ = C₆H₅, R₂ = CO₂Me 68%</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>CN</td>
<td>232b R₁ = C₆H₅, R₂ = CN 70%</td>
</tr>
<tr>
<td>2-OCH₃-C₆H₄</td>
<td>CO₂Me</td>
<td>232c R₁ = 2-OCH₃-C₆H₄, R₂ = CO₂Me 59%</td>
</tr>
<tr>
<td>2-OCH₃-C₆H₄</td>
<td>CN</td>
<td>232d R₁ = 2-OCH₃-C₆H₄, R₂ = CN 65%</td>
</tr>
</tbody>
</table>

3.4.1 An investigation into the BH substrates kinetically resolved by acylation, catalysed by 169 and 221

These BH adducts were subsequently subjected to the previously optimised conditions outlined in Section 3.3.2 for the KR of sec-alcohols (Table 3.2).
We were pleased to find that both 169 and 221 were compatible with these aryl-vinyl carbinol substrates - treatment of acrylate 232a with substoichiometric loadings of isobutyric anhydride and amine base in the presence of 169 or 221 (1 mol%) at low temperature followed by column chromatography furnished resolved 232a in moderate to good levels of enantioselectivity (entries 3 and 4, Table 3.2) and isolated yield (ca. 30%, max. = 50%). While the selectivity of these acylation processes was unsurprisingly (given the planar nature of the substituents at the substrate’s stereogenic center) moderate (S = 3.7 using catalyst 221), it was of sufficient magnitude to allow 232a to be isolated with excellent enantiomeric purity (95% ee) if the reaction was allowed to proceed to higher conversion (entry 3).

In line with our earlier findings regarding the particular aptitude of 169 for the resolution of sec-alcohols bearing electron-rich aromatic moieties (Table 2.6 and 2.7), the methoxy-substituted adduct 232c - which is outside the scope of current asymmetric BHR
nucleophilic catalyst technology - proved an outstanding substrate which could be resolved with excellent selectivity (S >10) using either 169 or 221 (Figure 3.3). Thus 232c could be isolated in respectable yields (for a KR process - 35-40%) and excellent enantioselectivity (up to 97% ee). It is noteworthy that the highly selective acylation observed in these reactions (entries 4-6) also allows the isolation of the acylated ester product 233c in >50% enantiomeric excess. While it was expected that the relatively unhindered, less Lewis basic acrylonitrile-derived adducts 232b and 232d would prove more difficult to resolve, their acylation catalysed by 221 was sufficiently selective to allow 232d and 232g to be recovered in high enantiopurity at high reaction conversion (entries 8 and 10).

Figure 3.3 CSP-HPLC trace for the separation of (S)- and (R)-233c and (R)- and (S)-
232c respectively catalysed by 221

<table>
<thead>
<tr>
<th>Peak No</th>
<th>Result (%)</th>
<th>Ret. Time (min)</th>
<th>Time Offset (min)</th>
<th>Area (counts)</th>
<th>Rel Ret Time</th>
<th>Sep. Code</th>
<th>Width (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.4026</td>
<td>8.280</td>
<td>0.000</td>
<td>17787792</td>
<td>0.00</td>
<td>VP</td>
<td>12.3</td>
</tr>
<tr>
<td>2</td>
<td>49.1853</td>
<td>20.741</td>
<td>0.000</td>
<td>60746008</td>
<td>0.00</td>
<td>PB</td>
<td>35.0</td>
</tr>
<tr>
<td>3</td>
<td>35.2724</td>
<td>35.2724</td>
<td>0.000</td>
<td>43562972</td>
<td>0.00</td>
<td>VB</td>
<td>58.3</td>
</tr>
<tr>
<td>4</td>
<td>0.5718</td>
<td>41.209</td>
<td>0.000</td>
<td>706221</td>
<td>0.00</td>
<td>VB</td>
<td>96.1</td>
</tr>
<tr>
<td>Totals</td>
<td>99.4321</td>
<td>0.000</td>
<td>12280293</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An investigation into the scope of potential BH adducts amenable to KR catalysed by 221 led to the synthesis of electron rich Michael acceptor and aldehyde (acrylamide- and furan-2-carbaldehyde respectively) derived substrates 236a-d (Scheme 3.5). Substrates 236a-d were subjected to the identical reactions conditions as outlined in Table 3.2. Unfortunately,
the catalysed acylative resolution of 236a-b failed to yield either product or starting material with good levels of enantioselectivity (Scheme 3.6).

**Scheme 3.5 Synthesis of BH substrates 236a-d**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furan</td>
<td>CO2Me</td>
<td>235a</td>
<td>56%</td>
</tr>
<tr>
<td>Furan</td>
<td>CN</td>
<td>235b</td>
<td>63%</td>
</tr>
<tr>
<td>C6H5</td>
<td>CONH2</td>
<td>235c</td>
<td>45%</td>
</tr>
<tr>
<td>2-OCH3-C6H4</td>
<td>CONH2</td>
<td>235d</td>
<td>36%</td>
</tr>
<tr>
<td>R1 = Furan</td>
<td>R2 = CO2Me</td>
<td>236a</td>
<td>56%</td>
</tr>
<tr>
<td>R1 = Furan</td>
<td>R2 = CN</td>
<td>236b</td>
<td>63%</td>
</tr>
<tr>
<td>R1 = C6H5</td>
<td>R2 = CONH2</td>
<td>236c</td>
<td>45%</td>
</tr>
<tr>
<td>R1 = 2-OCH3-C6H4</td>
<td>R2 = CONH2</td>
<td>236d</td>
<td>36%</td>
</tr>
</tbody>
</table>

The resolution of acrylamide substrate 236c and 236d under the optimised conditions proved somewhat more successful, although initially the KR reaction was inhibited due to the insolubility of 236c and 236d in CH2Cl2 at -78 °C. Attempts to resolve the substrates at -20 °C also failed. A further elevation of the reaction temperature to 0 °C allowed for the successful resolution of 236c (78% ee), however 236d was again insoluble.

**Scheme 3.6 KR of BH adducts 236a-d catalysed by 221**

Given the key roles that tertiary amines often play in both BHRs (as nucleophilic catalysts) and acylation reactions (as bases) we were intrigued by the possibility that a dual catalyst...
system could be developed whereby a single nucleophilic amine could first serve as a
catalyst for a challenging BHR process and then as a base in a subsequent acylative
resolution reaction, thereby providing a potentially useful, one-pot route to enantioenriched
Baylis-Hillman products difficult to prepare using direct asymmetric catalysis.

In 1999 Aggarwal et al. reported that DBU (somewhat unexpectedly) served as a highly
active BHR catalyst compatible with a wide range of substrates including deactivated
aldehydes and Michael acceptors. Interestingly (given its high nucleophilicity in the
BHR) we have previously reported (Table 2.4) that DBU does not compete to any great
extent with 169 as a catalyst in the acylation of alcohols by anhydride and as such it
seemed possible that DBU and 221 could act as orthogonal nucleophilic catalysts in a one-
pot BHR-acylative KR operation.

To test this hypothesis, o-anisaldehyde (230c) was reacted with methyl acrylate (231c) in
the presence of DBU followed by cooling to −78 °C and addition of iso-butryic anhydride
and 221. Using this novel tandem synthesis-kinetic resolution methodology 232c could be
isolated with high enantioselectivity i.e. 89% ee and 25% yield (Scheme 3.5). A similar
one-pot process furnished enantioenriched 232a from benzaldehyde and methyl acrylate.

Scheme 3.5 One pot synthesis and acylative resolution of BH adducts promoted by
DBU and 221

![Scheme 3.5](image-url)
In summary catalyst 169 and its optimised analogue 221 promote the synthetically useful KR of Baylis-Hillman adducts 232a-d and 236c derived from deactivated precursors (difficult to synthesise using catalytic asymmetric BHRs) — allowing the convenient preparation of 232a-d and 236c in 78-97% ee. To the best of our knowledge this study also represents the first examples of effective non-enzymatic acylative KR of sp²-sp² carbinols. A novel BHR-KR process which complements contemporary asymmetric BHR catalyst technology has also been developed in which DBU serves both as a nucleophilic promoter of the BHR and a base in the KR reaction without competing effectively with 221 as an acylation catalyst. Using this strategy 232a and 232c can be readily prepared in appreciable yield from their aldehyde and methyl acrylate precursors with high levels of enantiomeric excess in a convenient one-pot process.
4.1 Solid-supported heterogeneous catalyst systems

A successful design for any useful heterogeneous catalyst system \( (i.e. \) highly active and recoverable) for which the corresponding unsupported (soluble) catalyst is known to be active and stable must meet three criteria: 1) substrate access to the catalytically active sites must be maximised, 2) the heterogeneous support must be as robust as possible to prevent degradation on use/recycle and should not interact with the catalyst moieties or otherwise interfere (destructively) with activity and 3) the support must be compatible with a facile (relatively free of mechanical loss) recovery methodology.

To date the most successful heterogeneous catalyst system is the Wang resin-supported quinine catalyst \( 238 \), designed by Leckta\(^\text{201} \). \( 238 \) Promoted the enantioselective Staudinger \( \beta \)-lactam reaction in moderate yield (60% average) and high enantioselectivity (90% \( ee \)) through a total of 60 cycles without a reduction in efficiency. However the ‘catalyst’ was present in more than stoichiometric amounts and required recycling 5 – 10 times to attain consistent results (due to initial leaching of quinine), Scheme 4.1.

Scheme 4.1  Enantioselective \( \beta \)-lactam synthesis catalysed by \( 238 \)

4.2 A nanoparticle supported heterogeneous catalyst system

Recently, magnetic nanoparticles have emerged as viable alternatives to porous materials as robust, readily available high surface area heterogeneous catalyst supports for use in metal-catalysed transformations, that possess the added advantage of being magnetically recoverable, thereby eliminating the requirement for either solvent swelling before or catalyst filtration after reaction respectively.\(^{202} \)
Surprisingly, at the outset of this study no examples of a nanoparticle-supported organocatalyst system had been reported, despite the potential inherent stability and activity of such a (metal-free) species. Thus, we were intrigued at the possibility of applying nanotechnology to the design of a novel, active, recyclable and magnetically recoverable DMAP-derivative for the first time. However, subsequently an example of an achiral magnetic nanoparticle-supported quaternary ammonium salt-based phase transfer catalyst (242) for the butylation of sodium phenoxide at 100 °C appeared. The catalyst was active at 4 mol% loadings and could be recycled four times with only a 5% reduction in yield, Scheme 4.2.

Scheme 4.2  Catalysed butylation of sodium phenoxide by 242

Our initial design for a supported DMAP analogue employed an alkyl-siloxy linker to tether the silicon coated magnetite to PPY. Magnetite (Fe₃O₄) nanoparticles of 9.6 nm average diameter (calculated from XRD analysis by Ms Serena Corr, using the Debye-Scherrer equation) were prepared via the coprecipitation technique. In a departure from conventional catalyst loading strategies, the particles were then coated with a silica layer by preliminary dispersion in aqueous tetramethylammonium hydroxide followed by exposure to sodium silicate (carried out by Ms. Serena Corr), Scheme 4.3.

Scheme 4.3  Synthesis of silicon coated magnetite
The potential advantages associated with this novel (in a catalyst-support context) modification are: it a) prevents potential interactions between the iron oxide particle core and the organocatalyst moiety/reaction intermediates (possible ammonium cation binding to the uncoated Fe$_3$O$_4$ nanoparticles), and b) provides a stable, relatively inert shell onto which a triethoxysilane-substituted organocatalyst moiety can be installed.

Ms Serena Corr in the Gun’ko laboratory carried out the initial synthesis of 245, by coupling 165 to 3-aminopropyltriethoxysilane (246) in dry DMF with EDCl, followed by immediate reaction with magnetite and subsequent pyrrolidination to afford the desired catalyst 245 (Scheme 4.4). Although the catalyst loading was unknown IR analysis confirmed the presence of an amide bond.

**Scheme 4.4 Synthesis of 245**

245 Was evaluated as a promoter in the acylation of 57 by acetic anhydride with mechanical agitation for 18 h at RT followed with quenching by the addition of MeOH. $^1$H NMR analysis revealed only a moderate catalytic turnover (32.4 % conversion). The catalyst was separated by exposure of the reaction vessel to an external magnet (Figure 4.1) and decantation of the reaction solution, followed by washing of the nanoparticles with THF, drying under vacuum and subsequently resubjecting 245 to identical reaction conditions, which lead to a slight improvement in conversion (34.4%). A control experiment, in the absence of catalyst, resulted in a very low background reaction (<4% conv.), Scheme 4.5.
While 245 demonstrated the synthetic utility of a nanoparticle supported DMAP catalyst system, two inherent problems needed to be addressed in order to realise the catalytic system’s potential and to make a viable alternative to the established/reported supported DMAP analogues (Section 1.7.2): 1) the lack of a quantifiable catalyst loading strategy and 2) the modest conversions achieved upon acylation.

4.3.1 Design of a 2\textsuperscript{nd} generation nanoparticle-supported catalyst

A second generation catalyst was designed with substitution on the exocyclic DMAP nitrogen to avoid any potential steric hindrance to the catalyst active site and to avoid the necessity for the use of an electron withdrawing amide linker. The supported DMAP analogue 248 was prepared via a concise route outlined in Scheme 4.6. Triethoxysilane derivative 249 (Figure 4.2) was prepared by coupling commercially available 4-N-methylpyridine (250) and (3-chloropropyl)triethoxysilane (251) and purified via flash chromatography (CH\textsubscript{2}Cl\textsubscript{2}-NE\textsubscript{3}, 95:5, distilled). Immediate treatment of the silica coated nanoparticles with an excess of triethoxysilane derivative 249 in THF at reflux followed by reaction with N-propyltrimethoxysilane to cap remaining (acidic) surface silanol groups afforded catalyst 248.
Figure 4.2  $^1$H NMR of triethoxysilane derivative 249

Scheme 4.6  Synthesis of the second generation catalyst 248

It is noteworthy that only a single catalyst-loading step is necessary. The loading process proceeded cleanly and was quantitatively and conveniently monitored (loading 0.20 mmol g$^{-1}$, consistent between batches) by $^1$H NMR spectroscopy in the presence of (E)-stilbene.
as an internal standard. TEM analysis (Figure 4.3) illustrated the core-shell structure of the particles and confirmed the presence of the silica coating.

**Figure 4.3** TEM images of silica-coated magnetite nanoparticle aggregates (248). Inset shows a single particle

---

**4.4 Evaluation of 248 as a recyclable catalyst**

Nanoparticle-supported catalyst 248 was first evaluated as a promoter of the acetylation of 1-phenylethanol (9) by acetic anhydride. Gratifyingly, 248 (at 5 mol% loading) exhibited high catalytic activity, allowing the smooth conversion of 9 to the acetyl analogue 10 in quantitative conversion at ambient temperature with mechanical agitation (entry 1, Table 4.1).

The catalyst was easily separated from the products by exposure of the reaction vessel to an external magnet and to decantation of the reaction solution. The remaining catalyst was washed with THF to remove residual product and dried under high vacuum. This material was then subsequently reused in 13 further iterative cycles, furnishing the acylated product with 90-100% conversion in each case (entries 2 – 14). The excellent activity and recyclability of 248 in this reaction is illustrated by the finding that the 14th consecutive acylation cycle was 97% complete after only 1 h reaction time (entry 14). The
corresponding reaction in the absence of 248 (under otherwise identical conditions) gave only 3% conversion to 10.

Table 4.1  Evaluation of 248 as a recyclable catalyst for the acetylation of 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycle</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>16</td>
<td>&gt;98</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>16</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>16</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>16</td>
<td>&gt;98</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>16</td>
<td>&gt;98</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>16</td>
<td>&gt;98</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>16</td>
<td>&gt;98</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>16</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>16</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>16</td>
<td>97</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>16</td>
<td>&gt;98</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>16</td>
<td>&gt;98</td>
</tr>
<tr>
<td>13</td>
<td>13</td>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
<td>1</td>
<td>97</td>
</tr>
</tbody>
</table>

"Determined by $^1$H NMR spectroscopy. $^b$ 2.0 Equiv. of Ac$_2$O employed. $^c$ 1.2 Equiv. of NEt$_3$ employed.

This same catalyst material was subsequently found to be active when employed at considerably lower loadings - 10 could be prepared from 9 in excellent isolated yield using as little as 0.2 mol% (Scheme 4.7).

Scheme 4.7  Acetylation of 9 at low catalyst loadings (cycle 15)
4.4.1 Investigation into substrate scope of 248

Encouraged by the results of the preliminary acylation study, attention then turned to the issue of reaction scope. We tested the same batch of 248 used to promote the 14 acylation experiments outlined in Table 4.1 as a catalyst for a number of distinct transformations susceptible to nucleophilic catalysis of high synthetic utility (Table 4.2). 252, 253 and 254 were commercially available, while 228 had been previously prepared (Scheme 3.4). 255 was prepared as outlined in Scheme 4.8 from the previously synthesised oxazolone 256.197

Scheme 4.8 Synthesis of substrate 255

![Scheme 4.8](image)

Employing the same catalyst recovery methodology as before, it was found that 248 (in as little as 1 mol% loading) could promote the *bis*-hydroalkoxylation of alkyne 252 by a methodology recently-developed in our laboratory208 to give the mono-protected-1,3-dicarbonyl product 257 (a formal alkyne oxidation) in excellent isolated yield in each of three consecutive cycles (entries 1-3, Table 4.2).

The robust nature and excellent activity of this catalyst was further underlined by its subsequent ability to efficiently promote challenging, yet synthetically useful reactions which (to the best of our knowledge) had not been previously catalysed by a heterogeneous nucleophilic promoter, such as the room temperature peracetylation of D-glucose (253) – requiring the catalyst to mediate five separate acylation events per glucose molecule (which was also initially insoluble under the reaction conditions) – and the nucleophile-catalysed BOC-protection of indole (254) (no reaction occurred in the absence of 248). The catalyst was also compatible with the hindered acylating agent *iso*-butyric anhydride (allowing the esterification of mono-protected diol 228) and promoted the rearrangement of O-acyl enolate 255 to afford an *aza*-lactone (260) with a quaternary stereogenic centre.
Table 4.2  Application of 248 in reactions of synthetic interest

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycle</th>
<th>Substrate</th>
<th>Product</th>
<th>Loading (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>252</td>
<td>257</td>
<td>1</td>
<td>16</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>252</td>
<td>257</td>
<td>1</td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>252</td>
<td>257</td>
<td>1</td>
<td>16</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>253</td>
<td>258</td>
<td>10</td>
<td>16</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>253</td>
<td>258</td>
<td>10</td>
<td>16</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>253</td>
<td>258</td>
<td>10</td>
<td>15</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>254</td>
<td>259</td>
<td>10</td>
<td>15</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>254</td>
<td>259</td>
<td>10</td>
<td>15</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>254</td>
<td>259</td>
<td>10</td>
<td>15</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>228</td>
<td>228a</td>
<td>5</td>
<td>20</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>26</td>
<td>228</td>
<td>228a</td>
<td>5</td>
<td>20</td>
<td>91</td>
</tr>
<tr>
<td>12</td>
<td>27</td>
<td>228</td>
<td>228a</td>
<td>5</td>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td>13</td>
<td>28</td>
<td>255</td>
<td>260</td>
<td>1</td>
<td>8</td>
<td>94</td>
</tr>
<tr>
<td>14</td>
<td>29</td>
<td>255</td>
<td>260</td>
<td>1</td>
<td>8</td>
<td>97</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>255</td>
<td>260</td>
<td>1</td>
<td>8</td>
<td>93</td>
</tr>
</tbody>
</table>

^a Isolated yield.
No catalyst degradation (physical or chemical) was discernable after 30 consecutive catalyst cycles (Tables 4.1 and 4.2). To demonstrate that 248 had retained high catalytic activity at this juncture the acylation of 9 with 0.2 mol% loading (Scheme 4.7) was repeated. Pleasingly 10 could be isolated in excellent yield in a comparable time (Scheme 4.8).

**Scheme 4.8** Repeat of the acetylation of 9 at low catalyst loading (cycle 31)

\[
\begin{align*}
9 & \xrightarrow{\text{Ac}_2\text{O} \text{ (2.0 equiv.)}} \quad 10 \ (79\%)
\end{align*}
\]

NEt\(_3\) (1.5 equiv.)
CH\(_2\)Cl\(_2\) (0.4 M), RT
248 (0.2 mol%) 36 h

4.5 Synthesis of non-silicon coated derivative of 248 *i.e.* 261

A non-silicon coated analogue of catalyst 248 *i.e.* 261 was synthesised in an attempt to ascertain the potential benefit of silicon coating the magnetite in affording an efficient and recyclable catalytic system. Catalyst 261 was synthesised in an identical manner to 248 (Scheme 4.9). The loading process proceeded cleanly and was again quantitatively and conveniently monitored (loading 0.16 mmol g\(^{-1}\)) by \(^1\)H NMR spectroscopy in the presence of (E)-stilbene as an internal standard.

**Scheme 4.9** Synthesis of catalyst 261

261 (0.2 mol%) was initially used to catalyse the acylation of 9 under identical conditions to those in Scheme 4.8 for catalyst 248. Surprisingly 261 (89% yield) was marginally more efficient than 248 in promoting the acylation of 9.
4.5.1 Investigation into recyclability of 261

An investigation into the recyclability of 261 followed, with 261 subjected to the BOC protection of indole (as per entries 7–9, Table 4.2). In these experiments 259 could be prepared from 254 with quantitative conversion in each of 5 consecutive cycles (Table 4.3).

Table 4.3 BOC protection of indole catalysed by 261

<table>
<thead>
<tr>
<th>Entry</th>
<th>Loading (mol%)</th>
<th>Time (h)</th>
<th>Conv*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>15</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>15</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>15</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>15</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>15</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

*Quantified by $^1$H NMR analysis using (E)-stilbene as an internal standard

A final catalysed acetylation of 9 was performed by 261, again under identical conditions to those in Scheme 4.8. After 36 h a sample was taken from the reaction mixture and analysed by $^1$H NMR spectroscopy, which revealed a 94% conversion to the ester 10. Thus the non-silicon coated catalyst retained its original activity through seven cycles.

4.6 Conclusions for nanoparticle catalyst

In summary, we have developed the first magnetic nanoparticle-supported DMAP-analogues for use as robust heterogeneous nucleophilic catalysts of unprecedented activity and recyclability. The catalysts are readily prepared via a concise route from inexpensive commercially available starting materials using standard laboratory techniques, readily (quantifiably) loaded onto a support in a single step and are capable of promoting a range of synthetically useful reactions at room temperature with loadings (as low as 0.2 mol%) not generally associated with heterogeneous organocatalysis.
Recovery of the catalysts by decantation of the reaction is both convenient and efficient, which, combined with the intrinsic stability of both the organic- and nanoparticle-catalyst components, allows 248 to be recycled over 30 times (261 has only verifiably been recycled 7 times) in a number of transformations without any discernable loss in activity.
5.1 General

Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in CDCl₃ referenced relative to residual CHCl₃ (δ = 7.26 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F₂₅₄ slides, and visualised by either UV irradiation or KMnO₄ staining. Specific rotation measurements were made on a Rudolph research analytical Autopol IV instrument, and are quoted in units of 10⁻¹ degcm²g⁻¹. Anhydrous diethylether and THF were distilled over sodium-benzophenone ketyl radical before use. Methylene chloride, toluene and triethylamine were distilled from calcium hydride. Analytical CSP-HPLC was preformed using Daicel CHIRALCEL OD-H (4.6 mm x 25 cm) and CHIRALPAK AS (4.6 mm x 25 cm) columns. Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. All reactions were carried out in oven dried glassware under an atmosphere of nitrogen or argon unless otherwise stated.

5.2.1 Experimental data for Section 2.2

5.2.1.1 Kinetic resolution of 9 catalysed by (S)-163, as in Scheme 2.2

\[ \text{A} \quad \text{1 mL reaction vessel charged with catalyst (1 mg, 2.34 \, \mu\text{mol}) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of 9 (29 \, \mu\text{L}, 0.234 \, \text{mmol}) and NEt₃ (26 \, \mu\text{L}, 0.187 \, \text{mmol}) in CH₂Cl₂ (500 \, \mu\text{L}). The resulting solution was left to stir for 30 minutes. Acetic anhydride (13 \, \mu\text{L}, 0.14 \, \text{mmol}) was subsequently added via syringe. After 16 h at room temperature the reaction was quenched by the addition of MeOH (200 \, \mu\text{L}). Solvents were removed in vacuo. The alcohol and its} \]

\[ \text{OH} \quad \text{Ac₂O (0.6 equiv.)} \quad \text{NEt₃ (0.8 equiv.)} \quad 16 \text{ h, CH₂Cl₂, RT} \quad 163 \quad (1 \text{ mol%}) \]

\[ \text{OH} \quad (R)-9 \quad 54\% \text{ conv.} \quad 9\% \text{ ee} \quad \text{10} \]
ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

\(^1\)H NMR of 10:

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.56 (d, 3H, J 6.8, \text{CH}_3), 2.10 (s, 3H, \text{CH}_3), 5.90 (q, 1H, J 6.8, \text{H-1}), 7.30-7.38 (m, 5H, \text{Ar-H}). \]

\(^1\)H NMR of 9:

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.46 (d, 3H, J 6.8, \text{CH}_3), 4.84 (q, 1H, J 6.8, \text{H-1}), 7.19-7.25 (m, 5H, \text{Ar-H}). \]

5.2.1.2 Procedure A: General procedure for determining ee using a chiral shift reagent, (+)-Eu(hfc)_3

A stock solution of (+)-Eu(hfc)_3 (43 mg, 0.36 mmol) was prepared in CDCl₃ (400 μL) and 20 μL volumes were added via syringe to a solution of 10 (3 μL, 0.18 mmol) in CDCl₃ (200 μL). \(^1\)H NMR analysis followed each addition of Eu(hfc)_3. The enantiomeric excess was determined by integration of the methyl peaks upon resolution of the (R) and (S) antipodes of 10.

5.2.1.2.1 Determination of the enantiomeric excess of 10

Procedure A was followed using chiral product 10 from the reaction of 9 with acetic anhydride catalysed by 163. Analysis of the resulting methyl peaks showed a 9% ee for the (R)-antipode.

5.2.1.3 Procedure B: General procedure for the methylation of catalysts

To a 5 mL round bottom flask charged with catalyst (0.07 mmol) in CH₂Cl₂ (500 μL) was added iodomethane (0.7 mmol) via syringe and the resulting solution stirred at room temperature. After TLC analysis indicated complete conversion of the starting material, the resulting solution was concentrated in vacuo, taken up in CDCl₃ (400 μL) and analysed by \(^1\)H NMR spectroscopy.
5.2.1.3.1 Methylation of catalyst (S)-163

![Chemical structure of (S)-163]

Procedure B was followed using catalyst 163 (25.6 mg, 0.07 mmol) in CH$_2$Cl$_2$ (500 µL), with the addition of iodomethane (44 µL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (168) in CDCl$_3$ by $^1$H NMR spectroscopy.

5.2.2 Experimental data for Section 2.3

5.2.2.1 Procedure C: Synthesis of (4-chloro-pyridin-3-yl)-[2-(hydroxyl-diphenyl-ethyl)-pyrrolidine-1-yl]-methanone (S)-(171)

![Chemical structure of (S)-(171)]

A 10 mL round bottom flask charged with 165 (315 mg, 2.0 mmol) and SOCl$_2$ (1.45 mL, 20.0 mL) was fitted with a reflux condenser and heated under reflux for 1 hour. Removal of SOCl$_2$ by distillation gave 4-chloronicotinic acid chloride.HCl as a yellow solid, which was placed under an atmosphere of Ar, cooled to 0 °C and THF (10 mL) added via syringe. Subsequently a solution of (S)-α,α-diphenylprolinol (506 mg, 2.0 mmol) and NEt$_3$ (550 µL, 4.0 mmol) in THF (20 mL) was added via syringe. The yellow solution was left to stir overnight. CH$_2$Cl$_2$ (80 mL) was then added and the resulting solution washed with NaHCO$_3$ (2 x 40 mL) and brine (2 x 40 mL). The organic extracts were separated, dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography (9:1 CH$_2$Cl$_2$-EtOAc, R$_f$ = 0.2) gave 171 (627 mg, 80%) as a white solid. M.p. 64-66 °C. [α]$_D^{20}$ = -95 (c 0.11, CHCl$_3$).
\[ \delta_H (400 \text{ MHz, } \text{CDCl}_3): \] 1.74 (m, 2H, H-9, H-10), 2.05 (m, 1H, H-11), 2.22 (m, 1H, H-12), 2.90 (m, 1H, H-7), 3.10 (m, 1H, H-8), 5.30 (app. t, 1H, J 5.5, H-13), 6.48 (s, 1H, OH), 7.22-7.60 (m, 11H, Ar-H, H-5), 8.10 (bs, 1H, H-2), 8.52 (d, 1H, J 5.6, H-6).

\[ \delta_C (100 \text{ MHz, } \text{CDCl}_3): \] 23.9, 30.1, 50.5, 68.2, 81.8 (q), 124.5, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 132.7 (q), 140.0 (q), 142.7 (q), 145.2 (q), 148.1, 150.9, 167.2 (C=O).

\[ \nu_{\max} (\text{film})/\text{cm}^{-1}: \] 3281, 1615, 1431, 1155, 699.

HRMS (m/z - ES): Found 415.1200 (M^+ + Na. C_{23}H_{21}N_{2}O_{2}ClNa Requires: 415.1189)

5.2.2.2 Procedure D: Synthesis of [2-(hydroxy-diphenyl-methyl)-pyrrolidin-1-yl]-(4-pyrrolidine-1-yl-pyridin-3-yl)-methanone (S)-(169)

A 10 mL round bottom flask was charged with 171 (160 mg, 0.41 mmol) and toluene (4 mL) with stirring. To this was added pyrrolidine (2 mL, 28.2 mmol) and the resulting solution heated under reflux at 86 °C overnight. CH_2Cl_2 (20 mL) was then added and the solution was washed with NaHCO_3 (2 x 30 mL) and brine (2 x 30 mL). The organic layer was separated, dried (MgSO_4) and the solvent removed in vacuo. Purification by column chromatography (8:2 EtOAc-CH_2Cl_2, R_f = 0.3), gave 169 (171 mg, 98%) as a white solid. M.p. 144-146. [\alpha]_D^{20} = -98 (c 0.96, CHCl_3).

\[ \delta_H (400 \text{ MHz, } \text{CDCl}_3): \] 0.95-1.18 (m, 2H, H-17, H-19), 1.80-2.20 (m, 6H, H-9, H-10, H-11, H-12, H-18, H-20), 2.90-3.15 (m, 3H, H-7, H-8, H-13), 3.40-3.55 (m, 3H, H-14, H-15, H-16), 5.20 (dd, 1H, J 9.0, 8.5, H-21),

127
6.45 (d, 1H, J 6.0, H-5), 7.25-7.38 (m, 5H, Ar-H), 7.41-7.60 (m, 6H, Ar-H, H-2), 8.09 (d, 1H, J 6.0, H-6).

δC (100 MHz, CDCl₃): 23.3, 25.1, 30.2, 48.8, 51.6, 68.3, 81.5 (q), 108.1, 116.2 (q), 127.0, 127.1, 127.2, 127.3, 127.4, 127.6, 142.1 (q), 144.6 (q), 146.6 (q), 147.6, 148.5, 170.4 (C=O).

νmax (film)/cm⁻¹: 3179, 2854, 1590, 1304, 971.

HRMS (m/z - ES): Found 428.2328 (M⁺ + H). C₂₇H₃₀N₃O₂ Requires: 428.2338

5.2.2.3 Determination of the enantiomeric excess of 10 (Figure 2.3)

Procedure A was followed using chiral product 10 from the reaction of 9 with acetic anhydride catalysed by 169. Analysis of the resulting methyl peaks showed a 31% ee for the (S)-antipode.

5.2.2.4 Kinetic resolution of 9 catalysed by (S)-169 (Table 2.1)

\[
\text{Ac}_2\text{O} (0.6 \text{ equiv.}) \\
\text{NET}_3 (0.8 \text{ equiv.}) \\
16 \text{ h}, \text{CH}_2\text{Cl}_2, \text{RT} \\
\text{169} (1 \text{ mol%}) \\
\]

A 1 mL reaction vessel charged with catalyst (2.34 µmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of 9 (29 µL, 0.234 mmol) and NEt₃ (26 µL, 0.187 mmol) in solvent (500 µL). The resulting solution was left to stir for 30 minutes. Acetic anhydride (13 µL, 0.14 mmol) was subsequently added via syringe. After 16 h at room temperature the reaction was quenched by the addition of MeOH (200 µL). Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.
A 100 mL three-necked round bottom flask fitted with an Ar inlet tube, 50 mL addition funnel and a Teflon-coated thermocouple probe, containing dry THF (15 mL) was charged with (S)-proline (177) (1.15 g, 10 mmol) under an atmosphere of Ar. To the well-stirred, cooled (15-20 °C) suspension was added a solution of triphosgene (1.04 g, 3.5 mmol) in THF (10 mL) over a 30 min period, maintaining the internal temperature at 15-20 °C. The mixture was warmed to 30-40 °C and aged for 30 min. Once homogeneous, the reaction mixture was aged an additional 30 min at 30-35 °C and then cooled to 15-20 °C. While maintaining the internal temperature at 15-20 °C, the reaction mixture was concentrated in vacuo to 10% of the original volume. The residue was dissolved in dry THF (22.5 mL) and the solution was cooled to 0-5 °C. With good agitation, dry NEt₃ (1.53 mL, 11 mmol) was added over 15 min while maintaining the internal temperature at 0-5 °C. After the addition was complete, the mixture was aged for 30 min at 0-5 °C and then filtered through an enclosed, medium frit, sintered-glass funnel. The resultant cake of NEt₃.HCl was washed with THF (10 mL). The filtrate and THF washes were combined to afford a solution containing (S)-176 (ca. 9.5-10.0 mmol) that was used immediately without further purification.

5.2.2.6 Procedure E: Synthesis of (S)-α,α-(2-naphthyl)prolinol (S)-(179)

A 100 mL three-necked flask fitted with a 50 mL addition funnel containing the THF solution of (S)-176 (6.52 mmol in 40 mL THF) and a stirrer was charged with a solution of 2-naphthylmagnesium bromide (180) (0.5 M in THF, 22.5 mmol) and cooled to -15 °C. The THF solution of (S)-176 was added over a 1 h period while maintaining the internal temperature at -10 to -15 °C. After the addition was complete, the mixture was allowed to
warm to room temperature and stirred for 16 h. The reaction was quenched with the addition of 2 M aqueous H$_2$SO$_4$ (25 mmol), over a 0.5-1.0 h period, while maintaining the internal temperature below 20 °C. During the quench a thick white precipitate of MgSO$_4$ formed. The mixture was agitated for 1 h at 0 °C and filtered through a medium-frit, sintered-glass funnel. The MgSO$_4$ cake was washed free of residual product with THF (3 x 10 mL). The filtrate and THF washes were combined and concentrated at atmospheric pressure to 10% of the original volume. The product as its sulfate salt precipitated during the concentration. The mixture was cooled to 0-5 °C, aged for 1 h and filtered. The cake was washed with H$_2$O (2 x 40 mL) to remove excess H$_2$SO$_4$, with EtOAc (3 x 40 mL) and dried in vacuo, affording (2.56 g, 69%) of (S)-179 sulphate as a white solid.

A portion of the sulfate salt was converted to the free base as follows: to a stirred solution of THF (2.0 mL) and 2 M NaOH (2.0 mL, 4.0 mmol) at 20 °C was added (S)-179 sulfate (600 mg, 1.0 mmol). The mixture was stirred at 20 °C until all solids dissolved and was then diluted with toluene (10 mL). The two-phase mixture was filtered through a medium-frit sintered-glass funnel, partitioned, and the organic layer was washed with H$_2$O (10 mL). The organic layer was concentrated in vacuo, affording (240 mg, 48%) of (S)-179 as a colourless oil that crystallized on standing. M.p. 78-80 °C (lit., 78-79 °C).

δ$_H$ (400 MHz, CDCl$_3$): 1.61-1.89 ( m, 4H, H-3, H-4, H-5, H-6), 3.02 (m, 1H, H-1), 3.08 (m, 1H H-2), 4.54 (app.t, 1H, J 8.0, H-7), 7.45-8.04 (m, 12H, Ar-H), 8.20 (s, 2H, 1').

5.2.2.7 Synthesis of (4-chloro-pyridin-3-yl)-[2[(hydroxyl-dinapthyl-methyl)-pyrrolidin-1-yl]-methanone (S)-(181)

Procedure C was followed using 165 (330 mg, 2.10 mmol), SOCl$_2$ (1.5 mL, 21.0 mmol), THF (5 + 4 mL), (S)-179 (740 mg, 2.10 mmol) and NEt$_3$ (870 µL, 6.28 mmol).
Purification by column chromatography (9:1 CH₂Cl₂-EtOAc, \( R_f = 0.3 \)) gave 181 (350 mg, 34%) as a white solid. M.p. 140-142 °C. \([\alpha]_D^{20} = -84 \text{ (c 0.1, CHCl}_3)\).

\( \delta_H (400 \text{ MHz, CDCl}_3): 1.61-1.94 \text{ (m, 2H, H-11, H-12)}, 2.18-2.42 \text{ (m, 2H, H-9, H-10)}, 2.92 \text{ (m, 1H, H-7)}, 3.11 \text{ (m, 1H, H-8)}, 5.61 \text{ (dd, 1H, J 7.0, 7.5, H-13)}, 6.62 \text{ (s, 1H, OH)}, 7.3-7.91 \text{ (m, 15H, Ar-H, H-5)}, 8.20 \text{ (s, 1H, H-2)}, 8.47 \text{ (d, 1H, J 5.6, H-6)}. \)

\( \delta_C (100 \text{ MHz, CDCl}_3): 23.5, 29.6, 49.9, 67.5, 81.7 \text{ (q), 124.1}, 125.3, 125.5, 125.7, 125.8, 125.9, 126.2, 126.7, 126.9, 127.1, 127.7, 127.9, 128.0, 132.2 \text{ (q), 132.3 (q), 132.4 (q), 132.5 (q), 139.6 (q), 139.7 (q), 142.2 (q), 145.1 (q), 147.7, 150.5, 167.1 (C=O)}. \)

\( \nu_{\text{max (film)/cm}^{-1}}: 3371, 1612, 1377, 1155, 721. \)

HRMS \( (m/z - \text{ES}): \) Found 493.1681 (\( \text{M}^+ + \text{H. C}_{31}\text{H}_{28}\text{N}_2\text{O}_2\text{Cl} \)) Requires: 493.1683

5.2.2.7.1 Synthesis of [2-(hydroxy-di-naphthalen-2-yl-methyl)-pyrrolidin-1-yl]-
(4-pyrrolidinin-1-yl-pyridin-3-yl)-methanone (S)-(172)

Procedure D was followed using 181 (71.5 mg, 0.15 mmol), toluene (4 mL) and pyrrolidine (2 mL, 24.0 mmol). Purification by column chromatography (9:1 EtOAc-CH₂Cl₂, \( R_f = 0.2 \)), gave 172 (55 mg, 72%) as a white solid. M.p. 146-148. \([\alpha]_D^{20} = -65 \text{ (c 0.11, CHCl}_3)\).

\( \delta_H (400 \text{ MHz, CDCl}_3): 1.34-1.62 \text{ (m, 2H, H-17, H-19)}, 1.88-2.27 \text{ (m, 6H, H-9, H-10, H-11, H-12, H-18, H-20)}, 2.92-3.15 \text{ (m, 3H, H-7, H-8, H-13)}, 3.35-3.53 \text{ (m, 3H, H-14, H-15, H-16)}, 5.43 \text{ (dd, 1H, J 8.0, 8.5, H-21)}, \)
6.40 (d, 1H, J 6.0, H-5), 7.41-7.56 (m, 5H, Ar-H, H-2), 7.64-7.94 (m, 9H, Ar-H), 8.07 (d, 1H, J 5.0, H-6), 8.16 (s, 1H, Ar-H).

\[ \delta_C \text{ (100 MHz, CDCl}_3\text{):} 23.3, 25.2, 30.0, 48.6, 51.4, 67.4, 82.0 \text{ (q), 108.1, 116.2 \text{ (q), 125.8, 125.9, 126.0, 126.1, 126.3, 126.6, 127.0, 127.1, 127.2, 127.4, 127.5, 127.9, 128.3, 128.4, 132.3 \text{ (q), 132.4 \text{ (q), 132.5 \text{ (q), 132.7 \text{ (q), 140.2 \text{ (q), 142.6 \text{ (q), 148.2, 148.3 \text{ (q), 149.4, 171.5 \text{ (C=O).}}}}}

v_{\text{max}} \text{ (film)} / \text{cm}^{-1}: 3369, 1588, 1539, 1505, 1123, 721.

HRMS \text{ (m/z - ES):} \text{ Found 528.2673 (M}^+ \text{ + H. C}_{35}\text{H}_{34}\text{N}_{3}\text{O}_{2} \text{ Requires: 528.2651).}

5.2.2.8 Synthesis of pyrrolidine-1,2-dicarboxylic acid 1-ethyl ester 2-methyl ester (S)-(182)

To a 25 mL round bottom flask charged with 177 (1.00 g, 8.7 mmol) and MeOH (10 mL) was added K$_2$CO$_3$ (5.4 g, 39.0 mmol) and the resulting solution was left to stir at 0 °C for 30 min. Ethyl chloroformate (2.01 mL, 21.70 mmol) was subsequently added via syringe. After 16 h the reaction was diluted with CH$_2$Cl$_2$ (25 mL), washed with NaHCO$_3$ (2 x 30 mL) and brine (2 x 30 mL). The organic extracts were separated, dried (MgSO$_4$) and the solvent removed in vacuo to give 182 (1.27 g, 72.7%) as a colourless liquid. $^1$H NMR spectral data is consistent with literature precedent.$^{187}$

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{):} 1.18 \text{ (t, 3H, J 8.0, CH}_3\text{), 1.86-2.30 \text{ (m, 4H, H-3, H-4, H-5, H-6), 3.45-3.62 \text{ (m, 2H, H-1, H-2), 3.75 \text{ (s, 3H, OCH}_3\text{), 4.06-4.21 \text{ (m, H, CH}_2\text{), 4.32-4.40 \text{ (m, 1H, H-7).}}}}

132
Procedure F: Synthesis of 1, 1-diphenyl-tetrahydro-pyrrolo[1, 2-c]oxazol-3-one (S)-(183)

A 10 mL round bottom flask charged with a solution of phenylmagnesium bromide (3.0 M in THF, 7.96 mmol) with and a stirring bar was placed under an atmosphere of Ar and cooled to 0 °C. A solution of 182 (640 mg, 3.2 mmol) in THF (3 mL) was added slowly via syringe and left to stir at 0 °C for 45 min, warmed to room temperature and then heated under reflux for 3 h. The reaction mixture was then added to an ice cold solution of NH₄Cl and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The organic extracts were separated, dried (MgSO₄) and the solvent removed *in vacuo.* Purification by flash chromatography (CH₂Cl₂, *Rf* = 0.3) gave 183 (474 mg, 53%) as white solid. M.p. 147-148 °C (lit., 148-149 °C).

δH (400 MHz, CDCl₃): 1.41-1.62 (m, 2H, H-3, H-5), 1.95-2.20 (m, 2H, H-4, H-6) 2.88 (m, 1H, H-1), 3.29 (m, 1H, H-2), 5.39 (app.t, 1H, J 8.0, H-7), 7.20-7.68 (m, 10H, Ar-H).

Synthesis of 1, 1-dinapthyl-tetrahydro-pyrrolo[1, 2-c]oxazol-3-one (S)-(184)

Procedure F was followed using 2-naphthylmagnesium bromide (0.5 M in THF, 5.47 mmol) and 182 (550 mg, 2.74 mmol) in THF (5 mL). Purification by flash chromatography (CH₂Cl₂, *Rf* = 0.8), gave 184 (630 mg, 61%) as a white solid. M.p. 108-110 °C. [α]_D^20 = -88 (c 0.01, CHCl₃).
δ_H (400 MHz, CDCl_3):  1.24 (m, 1H, H-3), 1.78-2.09 (m, 3H, H-4, H-5, H-6), 3.36 (m, 1H, H-1), 3.81 (m, 1H, H-2), 4.82 (dd, 1H, J 5.5, 8.5, H-7), 7.35-8.15 (m, 14H, Ar-H).

δ_C (100 MHz, CDCl_3):  24.6, 28.7, 45.7, 68.3, 85.8 (q), 123.3, 123.8, 124.1, 124.4, 126.0, 126.1, 126.2, 126.3, 127.1, 127.2, 127.7, 127.9, 128.0, 128.3, 132.1 (q), 132.3 (q), 132.4 (q), 132.6 (q), 137.0 (q), 139.6 (q), 160.0 (C=O).

ν_{max} (film)/cm^{-1}:  2924, 1746, 1497, 1458, 1377, 1053.

HRMS (m/z - ES):  Found 336.1764 (M^+ + H – CO_2. C_{26}H_{21}NO_2 Requires: 379.1684)

5.2.2.10 Procedure G: Synthesis of (S)-2(diphenylmethyl)pyrrolidine (S)-(185)

A 25 mL round bottom flask charged with 183 (730 mg, 2.6 mmol), MeOH (15 mL) and a stirring bar was placed under Ar. Pd/C (250 mg) (10%) was slowly added. The flask was flushed with H_2 at room temperature for 72 h. The catalyst was filtered off and the solvent removed in vacuo. Purification by flash chromatography (60:35:5, Hexane-EtOAc-NEt_3, R_f = 0.4) gave 185 (510 mg, 82%) as a colourless oil. Spectral data for this compound is consistent with that in the literature.^{187}

δ_H (400 MHz, CDCl_3):  1.50-1.89 (m, 4H, H-3, H-4, H-5, H-6), 2.87 (m, 1H, H-1), 3.02 (m, 1H, H-2), 3.98 (m, 2H, H-7, H-8), 7.15-7.45 (m, 10H, Ar-H).

δ_C (100 MHz, CDCl_3):  23.8, 30.1, 45.4, 49.7, 62.1, 126.3, 126.4, 127.4, 127.7, 128.2, 128.4, 141.8 (q), 142.0 (q).
5.2.2.10.1 Synthesis of (S)-2(dinapthylmethyl)pyrrolidine (S)-(186)

Procedure G was followed using (S)-184 (300 mg, 0.80 mmol) and Pd/C (80 mg) (10%) in MeOH (10 mL). Purification by flash chromatography (85:10:5, Hexane-EtOAc-NEt₃, Rᵣ = 0.4) gave 186 (180 mg, 68%) as a white solid. M.p. 46-48 °C. [α]ᵣ⁰⁻¹ = -118 (c 0.005, CHCl₃).

δₓ (400 MHz, CDCl₃): 1.55 (m, 1H, H-3), 1.85 (m, 3H, H-4, H-5, H-6), 2.88 (m, 1H, H-1), 3.06 (m, 1H, H-2), 4.15 (m, 2H, H-7, H-8), 7.38-7.60 (m, 6H, Ar-H), 7.70-8.00 (m, 8H, Ar-H).

δₓ (100 MHz, CDCl₃): 24.3, 30.2, 45.7, 57.9, 61.5, 125.1, 125.2, 125.5, 125.6, 125.9, 126.0, 126.3, 126.4, 127.0, 127.1, 127.3, 127.4, 127.7, 127.9, 131.8 (q), 131.9 (q), 133.0 (q), 133.1 (q), 140.3 (q), 140.4 (q).

vₚₑₑₑₑₑₑₑₑₑₑₑₑₑₑ (film)/cm⁻¹: 2922, 1505, 1108, 855.

HRMS (m/z - ES): Found 338.1897 (M⁺ + H. C₂₅H₂₅N Requires: 338.1909)

5.2.2.11 Synthesis of (2-benzhydryl-pyrrolidin-1-yl)-(4-chloro-pyridin-3-yl)-methanone (S)-(187)
Procedure C was followed using **165** (300 mg, 1.90 mmol), SOCl₂ (1.2 mL, 17.1 mmol), THF (5 + 6 mL), **(S)-185** (450 mg, 1.90 mmol) and NEt₃ (660 μL, 4.70 mmol). Purification by column chromatography (1:1 Hexane-EtOAc, R₁ = 0.3) gave **187** (190 mg, 27%) as a white solid. M.p. 56-58 °C. [α]D²⁰ = -93 (c 0.1, CHCl₃).

**Major Rotamer:**

δₜ (400 MHz, CDCl₃): 1.97-2.21 (m, 4H, H-9, H-10, H-11, H-12), 3.01-3.18 (m, 2H, H-7, H-8), 4.57 (d, 1H, J 8.0, H-14), 5.36 (dd, 1H, J 3.5, 4.0, H-13), 6.87 (d, 1H, J 7.0, H-5), 7.11-7.42 (m, 10H, Ar-H), 8.22 (s, 1H, H-2), 8.49 (d, 1H, J 7.0, H-6).

**Major and minor rotamers:**

δₜ (400 MHz, CDCl₃): 1.71-2.21 (m, 4H, H-9, H-10, H-11, H-12), 3.01-3.18 (m, 1.5H, H-7, H-8), 3.60 (m, 0.25H, H-7), 3.95 (m, 0.25H, H-8), 4.15 (m, 0.25H, H-14), 4.30 (m, 0.25H, H-13), 4.57 (d, 0.75H, J 8.0, H-14), 5.36 (dd, 0.75H, J 7.5, 8.0, H-13), 6.87 (d, 1H, J 7.0, H-5), 7.11-7.42 (m, 10H, Ar-H), 8.22 (s, 0.75H, H-2), 8.38 (s, 0.25H, H-2), 8.49 (d, 1H, J 7.0, H-6).

δₜ (100 MHz, CDCl₃): 23.2, 27.8, 47.6, 52.8, 59.4, 124.2, 126.1, 126.5, 127.7, 128.1, 128.4, 129.0, 139.8 (q), 140.1 (q), 141.0 (q), 141.3 (q), 148.1, 150.1, 164.0 (C=O).

**Minor resonances found:**

δₜ (100 MHz, CDCl₃): 21.1, 29.6, 44.2, 53.4, 63.0, 126.4, 126.7, 128.2, 128.3, 128.5, 131.9, 132.9, 140.6, 149.6, 164.2 (C=O).

νₘ₉ₐₓ (film)/cm⁻¹: 3480, 1628, 1390, 1187, 933, 683.

HRMS (m/z - ES): Found 399.1227 (M⁺ + Na. C₂₃H₂₁N₂OClNa Requires: 399.1240)
5.2.2.11.1 Synthesis of (4-chloro-pyridin-3-yl)-[2-(di-naphthalen-2-yl-methyl)-pyrrolidin-1-yl]-methanone (S)-(188)

Procedure C was followed using 165 (74 mg, 0.47 mmol), SOCl₂ (340 µL, 4.70 mmol), THF (2 + 3 mL), (S)-186 (160 mg, 0.47 mmol) and NEt₃ (164 µL, 1.19 mmol). Purification by column chromatography (1:3 Hexane-EtOAc, Rf = 0.3) gave 188 (158 mg, 70%) as a white solid. M.p. 92-94 °C. [α]d° = -72 (c 0.12, CHCl₃).

Major rotamers:
δₑ (400 MHz, CDCl₃): 1.59-1.80 (m, 1H, H-11), 1.94-2.18 (m, 3H, H-9, H-10, H-12), 2.91-3.12 (m, 2H, H-7, H-8), 4.93 (d, 1H, J 8.0, H-14), 5.51 (dd, 1H, J 4.5, 5.0, H-13), 7.33 (d, 1H, J 5.8, H-5), 7.43-7.95 (m, 14 H), 8.22 (s, 1H, H-2), 8.52 (d, 1H, J = 5.8, H-6).

Major and minor rotamer:
δₑ (400 MHz, CDCl₃): 1.59-1.80 (m, 1H, H-11), 1.94-2.18 (m, 3H, H-9, H-10, H-11), 2.91-3.12 (m, 1.5H, H-7, H-8), 3.60 (m, 0.25H, H-7), 4.10 (m, 0.25H, H-8), 4.31 (d, 0.25H, J 8.5, H-14), 4.93 (d, 0.75H, J 8.0, H-14), 5.51 (dd, 1H, J 7.5, 8.0, H-13), 6.86 (d, 0.25H, J 9.0, Ar-H), 7.33 (d, 1H, J 5.8, H-5), 7.43-7.95 (m, 13.75H, Ar-H), 8.22 (s, 1H, H-2), 8.52 (d, 1H, J 5.8, H-6).

δₑ (100 MHz, CDCl₃): 24.0, 28.3, 48.4, 53.1, 59.9, 124.7, 125.8, 126.0, 126.2, 126.4, 127.0, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.9, 131.0, 132.4 (q), 132.6 (q), 133.3 (q), 133.4 (q), 133.5 (q), 138.9 (q), 139.4 (q), 140.4 (q), 148.6, 150.8, 164.3 (C=O).
Minor resonances found:

\( \delta_C \) (100 MHz, CDCl\(_3\)): 23.9, 29.1, 54.5, 63.2, 126.1, 126.5, 126.6, 127.1, 128.6, 128.8, 132.4, 150.3.

\( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 1574, 1497, 1122, 825, 721.

HRMS (\( m/z \) - ES): Found 477.1751 (\( M^+ + H \). C\(_{31}\)H\(_{26}\)N\(_2\)OCl Requires: 477.1734)

5.2.2.12 **Synthesis of (2-benzhydryl-pyrrolidin-1-yl)-(4-pyrrolidin-1-yl-pyridin-3-yl)-methanone (S)-(174)**

Procedure D was followed using (S)-187 (130 mg, 0.35 mmol), toluene (4 mL) and pyrrolidine (2 mL, 24.0 mmol). Purification by column chromatography (98:2 EtOAc-NEt\(_3\), \( R_f = 0.2 \)), gave 174 (115 mg, 81%) as a white solid. M.p. 177-178. \( [\alpha]_D^{20} = -81 \) (c 0.12, CHCl\(_3\)).

\( \delta_H \) (400 MHz, CDCl\(_3\)): 1.62-2.15 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 3.04-3.22 (m, 3H, H-7, H-8, H-13), 3.32-3.54 (m, 3H, H-14, H-15, H-16), 4.60 (d, 1H, J 8.0, H-22), 5.29 (m, 1H, H-21), 6.42 (d, 1H, J 6.0, H-5), 7.19-7.42 (m, 10H, Ar-H), 7.74 (s, 1H, H-2), 8.12 (d, 1H, J 6.0, H-6).

\( \delta_C \) (100 MHz, CDCl\(_3\)): 23.1, 25.1, 27.9, 48.5, 48.9, 52.8, 59.0, 108.0, 117.1 (q), 126.2, 126.4, 127.7, 128.1, 128.3, 129.0, 141.0 (q), 141.4 (q), 148.5, 148.6 (q), 148.9, 168.2 (C=O).

\( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 1628, 1591, 1403, 1303, 1243, 977, 794

HRMS (\( m/z \) - ES): Found 412.2393 (\( M^+ + H \). C\(_{27}\)H\(_{30}\)N\(_2\)O Requires: 412.2392)
5.2.2.12.1 Synthesis of 2-(di-naphthalen-2-yl-methyl)-pyrrolidin-1-yl)-(4-pyrrolidin-1-yl-pyridin-3-yl)-methanone (S)-(175)

Procedure D was followed using (S)-188 (130 mg, 0.273 mmol), toluene (4 mL) and pyrrolidine (2 mL, 24.0 mmol). Purification by column chromatography (98:2 EtOAc-NEt$_3$, $R_f=0.3$), gave 175 (111 mg, 80%) as a white solid. M.p. 123-124. $[a]_D^{20} = -53$ (c 0.15, CHCl$_3$).

Note: 175 exists in two rotameric forms in the $^1$H NMR and $^{13}$C NMR time-frame. All discernable resonances from both rotameric forms are included.

Major rotamer:
$\delta_H$ (400 MHz, CDCl$_3$): 1.48-2.12 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 3.02-3.22 (m, 3H, H-7, H-8, H-13), 3.32-3.53 (m, 3H, H-14, H-15, H-16), 5.05 (d, 1H, J 8.0, H-22), 5.49 (m, 1H, H-21), 6.42 (d, 1H, J 6.0, H-5), 7.18-7.42 (m, 14H, Ar-H), 7.71 (s, 1H, H-2), 8.12 (d, 1H, J 6.0, H-6).

Major and minor rotamers:
$\delta_H$ (400 MHz, CDCl$_3$): 1.48-2.12 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 3.02-3.22 (m, 3H, H-7, H-8, H-13), 3.32-3.53 (m, 3H, H-14, H-15, H-16), 5.05 (d, 1H, J 8.0, H-22), 5.49 (m, 0.9H, H-21), 5.63 (m, 0.1H, H-21), 6.38 (m, 0.1H, H-5), 6.42 (d, 0.9H, J 6.0, H-5), 7.18-7.42 (m, 14H, Ar-H), 7.71 (s, 1H, H-2), 8.12 (d, 1H, J 6.0, H-6).

$\delta_C$ (100 MHz, CDCl$_3$): 23.3, 25.2, 27.9, 48.5, 49.1, 52.4, 59.0, 108.0, 117.2 (q), 125.1, 125.4, 125.5, 125.6, 125.8, 125.9, 126.3, 126.9, 127.1, 127.2,
127.3, 127.6, 127.7, 127.8, 131.8 (q), 131.9 (q), 132.8 (q), 132.9 (q), 138.4 (q), 139.0 (q), 148.3, 148.5 (q) 148.9, 168.5 (C=O).

Minor resonances Found:
\[ \delta_c \text{ (100 MHz, CDCl}_3\text{): } 21.2, 24.1, 29.2, 43.9, 47.6, 54.7, 61.9, 108.9, 125.0, 125.9, 128.4, 131.8, 132.7, 133.0, 138.3, 139.4, 167.6 (C=O). \]

\[ \nu_{\text{max}} \text{ (film)/cm}^{-1}: \] 1620, 1586, 1303, 1199, 975, 811, 722.

HRMS \( m/z - \text{ES): \} \) Found 512.2692 (M\(^+\) + H. C\(_{35}\)H\(_{34}\)N\(_3\)O Requires: 512.2702)

### 5.2.2.13 Kinetic resolution of 9 catalysed by 172 – 175 (Table 2.2)

\[
\begin{array}{c|c c}
\text{Ac}_2\text{O (0.55 equiv.)} & \text{NEt}_3 (0.6 \text{ equiv.)} & (R)-9 + 10 \\
16 \text{ h, CH}_2\text{Cl}_2, \text{RT} & \text{cat. (1 mol%)} & \\
\end{array}
\]

A 1 mL reaction vessel charged with catalyst (2.34 µmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of 9 (29 µL, 0.234 mmol) and NEt\(_3\) (26 µL, 0.187 mmol) in solvent (500 µL). The resulting solution was left to stir for 30 minutes. Acetic anhydride (13 µL, 0.129 mmol) was subsequently added via syringe. After 16 h at room temperature the reaction was quenched by the addition of MeOH (200 µL). Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH\(_2\)Cl\(_2\)) through a pad of silica gel.

\(^1\text{H NMR of 10:}\

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{): } 1.56 \text{ (d, 3H, J 6.8, CH}_3\text{), 2.10 \text{ (s, 3H, CH}_3\text{), 5.90 \text{ (q, 1H, J 6.8, H-1) 7.30-7.38 \text{ (m, 5H, Ar-H).}} \]

\(^1\text{H NMR of 9:}\

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{): } 1.46 \text{ (d, 3H, J 6.8, CH}_3\text{), 4.84 \text{ (q, 1H, J 6.8, H-1), 7.19-7.25 \text{ (m, 5H, Ar-H).}} \]
HPLC data for recovered alcohol 9:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 99/1, 1.0 mL min\(^{-1}\), RT, UV detection at 220 nm, retention times: 29.0 min (\(R\)) major and 40.3 min (\(S\)) minor.

5.2.2.14 Procedure H: Synthesis of (rac)-(cis)-benzoic acid 2-hydroxy-cyclohexyl ester (76a)

A 50 mL three-necked round bottom flask fitted with a 50 mL addition funnel containing a solution of benzoyl chloride (189a) (530 µL, 4.5 mmol) in CH\(_2\)Cl\(_2\) (9 mL) was charged with 190 (500 mg, 4.3 mmol), NEt\(_3\) (900 µL, 6.5 mmol), CH\(_2\)Cl\(_2\) (8 mL) and a stirring bar was placed under an atmosphere of Ar and cooled to 0 °C. The acid chloride solution was added slowly over a 45 min period and the resulting solution was allowed to warm to room temperature and stirred for 16 h. CH\(_2\)Cl\(_2\) (20 mL) was then added and the resulting solution washed with Na\(_2\)CO\(_3\) (2 x 40 mL) and NaHCO\(_3\) (2 x 40 mL). The organic extracts were separated, dried (MgSO\(_4\)) and the solvent removed in vacuo. Purification by column chromatography (CH\(_2\)Cl\(_2\), R\(_f\) = 0.3), gave 77a (498 mg, 53%) as a colourless oil. Spectral data for this compound is consistent with that in the literature.

\(\delta\)\(_H\) (400 MHz, CDCl\(_3\)): 1.40-1.66 (m, 2H, H-5, H-7), 1.68-2.09 (m, 6H, H-3, H-4, H-6, H-8, H-9, H-10), 3.99 (m, 1H, H-1), 5.24 (m, 1H, H-2), 7.48 (dd, 2H, J 7.5, 7.0 H-2’), 7.59 (app.t, 1H, J 7.5, H-3’), 8.08 (d, 2H, J 7.0, H-1’).

5.2.2.14.1 Synthesis of (rac)-(cis)-4-methoxy-benzoic acid 2-hydroxy-cyclohexyl ester (191)
Procedure H was followed using anisoyl chloride (189b) (771 mg, 4.5 mmol), 190 (500 mg, 4.3 mmol), NEt3 (900 μL, 6.5 mmol) in CH2Cl2 (9 + 8 mL). Purification by column chromatography (9:1, CH2Cl2-EtOAc, Rf = 0.3), gave 191 (351 mg, 33%) as a white solid. M.p 80-81 °C. Spectral data for this compound is consistent with that in the literature.87

δH (400 MHz, CDCl3): 1.38-1.54 (m, 2H, H-5, H-7), 1.63-2.08 (m, 6H, H-3, H-4, H-6, H-8, H-9, H-10), 3.89 (s, 3H, OCH3), 3.99 (m, 1H, H-1), 5.21 (m, 1H, H-2), 6.95 (d, 2H, J 8.5, H-2’), 8.03 (d, 2H, J 8.5, H-1’)

5.2.2.14.2 Synthesis of (rac)-(cis)-4-dimethylamino-benzoic acid 2-hydroxy-cyclohexyl ester (76b)

![Chemical structure](image)

Procedure H was followed using 4-dimethylamino-benzoyl chloride (189c) (1.66 g, 9.1 mmol), 190 (1 g, 8.6 mmol), NEt3 (1.8 mL, 13.0 mmol) in CH2Cl2 (18 + 15 mL). Purification by column chromatography (CH2Cl2, Rf = 0.2), gave 77b (990 mg, 44%) as a white solid. M.p 120-121 °C, (lit.,87 120-122 °C).

δH (400 MHz, CDCl3): 1.36-1.54 (m, 2H, H-5, H-7), 1.62-2.15 (m, 6H, H-3, H-4, H-6, H-8, H-9, H-10), 3.08 (s, 6H, NMe2), 3.98 (m, 1H, H-1), 5.19 (m, 1H, H-2) 6.72 (d, 2H, J 9.0, H-2’), 7.95 (d, 2H, J 9.0, H-1’).

5.2.2.15 Procedure I: general procedure for the KR of mono-benzylated cis-diol as in Table 2.3

![Chemical structure](image)

A 1 mL reaction vessel charged with catalyst (2.34 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of alcohol (0.234 mmol) and NEt3 (26 μL, 0.187 mmol) in CH2Cl2 (500 μL). The resulting solution was left
to stir for 30 minutes. *Iso*-butyric anhydride (31 μL, 0.187 mmol) was subsequently added *via* syringe. After 16 h the reaction was quenched by the addition of MeOH (200 μL). Solvents were removed *in vacuo*. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

**5.2.2.15.1 (cis)-4-Dimethylamino-benzoic acid 2-isobutyloxy-cyclohexyl ester (77b)**

Procedure I was followed using (S)-169 (1 mg, 2.34 μmol) and 76b (61.5 mg, 0.234 mmol) at room temperature. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

HPLC Data for recovered alcohol 76b:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 17.3 min (1R,2S) minor and 34.4 min (1S,2R) major.⁹¹
Procedure I was followed using (S)-169 (1 mg, 2.34 μmol) and 76b (61.5 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

5.2.2.15.3 (cis)-4-Methoxy-benzoic acid 2-isobutyloxy-cyclohexyl ester (190)

\[
\text{Procedure I was followed using (S)-169 (1 mg, 2.34 μmol) and 189 (61.5 mg, 0.234 mmol) at room temperature. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.}
\]

\[\text{H NMR of 77b} \]

\[
\delta_\text{H} (400 MHz, CDCl₃): 1.13 (d, 3H, J 6.5, CH₃), 1.15 (d, 3H, J 6.5, CH₃), 1.40-1.50 (m, 2H, H-5, H-7), 1.60-2.05 (m, 6H, H-3, H-4, H-6, H-8, H-9, H-10), 2.50 (app. hept, 1H, CH(CH₃)₂), 3.84 (s, 3H, OCH₃), 5.10 (m, 1H, H-2), 5.22 (m, 1H, H-1), 6.89 (d, 2H, J 9.0, H-2'), 7.95 (d, 2H, J 9.0, H-1')
\]

HPLC Data for recovered alcohol 191:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 10.7 min (1R,2S) minor and 14.6 min (1S,2R) major.⁹¹

5.2.2.15.4 (cis)-4-Dimethylamino-benzoic acid 2-isobutyloxy-cyclohexyl ester (77b)
Procedure I was followed using (S)-172 (1.2 mg, 2.34 μmol) and 76b (61.5 mg, 0.234 mmol) at room temperature. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

5.2.2.15.5 (cis)-4-methoxy-benzoic acid 2-isobutryloxy-cyclohexyl ester (190)

Procedure I was followed using (S)-172 (1.2 mg, 2.34 μmol) and 189 (61.5 mg, 0.234 mmol) at room temperature. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

5.2.2.15.6 (cis)-Benzoic acid 2-isobutryloxy-cyclohexyl ester (77a)

Procedure I was followed using (S)-172 (1.2 mg, 2.34 μmol) and 76a (51.5 mg, 0.234 mmol) at room temperature. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

$^1$H NMR of 77a

$\delta$H (400 MHz, CDCl$_3$): 1.14 (d, 3H, J 6.5, CH$_3$), 1.16 (d, 3H, J 6.5, CH$_3$), 1.45-1.55 (m, 2H, H-5, H-7), 1.65-2.05 (m, 6H, H-3, H-4, H-6, H-8, H-9, H-10), 2.51 (app. hept, 1H, CH(CH$_3$)$_2$), 5.12 (m, 1H, H-2), 5.28 (m, 1H, H-1), 7.43 (dd, 2H, J 7.0, H-2'), 7.54 (app. t, 1H, J 7.0, H-3'), 8.01 (d, 2H, J 7.0, H-1').
HPLC Data for recovered alcohol 76a:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 6.7 min (1R,2S) minor and 7.4 min (1S,2R) major.²

5.2.2.16 Procedure for optimisation studies preformed on the KR of 76b catalysed by 169 (Table 2.4)

A 1mL reaction vessel charged with (S)-169 (1 mg, 2.34 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of 76b (61.5 mg, 0.234 mmol) and base (0.164 mmol) in solvent (500 μL). The resulting solution was left to stir for 30 minutes. Iso-butyric anhydride (27 μL, 0.164 mmol) was subsequently added via syringe. After 16 h the reaction was quenched by the addition of MeOH (200 μL). Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

5.2.2.17 General procedure for the KR of 54 catalysed by 169, 172 and 174-175 (Table 2.5)

A 1mL reaction vessel charged with catalyst (2.34 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of 54 (40.3 mg, 0.234 mmol) and NEt₃ (24μL, 0.176 mmol) in CH₂Cl₂ (500 μL). The resulting solution was cooled to -78 °C and left to stir for 30 minutes. Iso-butyric anhydride (58 μL, 0.351 mmol) was subsequently added via syringe. After 8 h at -78 °C the reaction was quenched by the addition of MeOH (200 μL) and allowed to warm to ambient temperature. Solvents were
removed *in vacuo*. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

$^1$H NMR of 54

δ$_H$ (400 MHz, CDCl$_3$): 1.63 (d, 3H, J 6.5, CH$_3$), 5.69 (q, 1H, J 6.5, H-1'), 7.47-7.55 (m, 3H, H-3', H-7', H-8'), 7.70 (d, 1H, J 7.0, H-2'), 7.79 (d, 1H, J 8.0, H-4'), 7.89 (d, 1H, J 7.5, H-6'), 8.13 (d, 1H, J 8.5, H-9').

$^1$H NMR of 193

δ$_H$ (400 MHz, CDCl$_3$): 1.13 (d, 3H, J 6.5, CH$_3$), 1.16 (d, 3H, J 6.5, CH$_3$), 1.68 (d, 3H, J 6.5, CH$_3$), 2.61 (app. hept, 1H, CH(CH$_3$)$_2$), 6.61 (q, 1H, J 6.5, H-1), 7.43-7.54 (m, 3H, H-3', H-7', H-8'), 7.58 (d, 1H, J 7.0, H-2'), 7.77 (d, 1H, J 8.0, H-4'), 7.85 (d, 1H, J 7.5, H-6'), 8.06 (d, 1H, J 8.5, H-9').

HPLC Data for ester 193:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min$^{-1}$, RT, UV detection at 220 nm, retention times: 4.0 min ($R$) minor and 5.4 min ($S$) major.$^{83}$

HPLC Data for recovered alcohol 54:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min$^{-1}$, RT, UV detection at 220 nm, retention times: 9.4 min ($S$) minor and 13.9 min ($R$) major.$^{83}$

5.2.3 Experimental data for Section 2.4

5.2.3.1 Procedure J: Synthesis of 2,2-dimethyl-1-phenyl-propan-1-one 196a
A 50 mL round bottom flask charged with 195a (2.6 ml, 21.0 mmol), THF (10 mL) and a stirrer was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 10 mins. 194a (33.2 mL, 18.4 mmol, 0.5 M) was subsequently added via syringe over a 15 min period, with the resulting solution allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by the addition of H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (2 x 20 mL). The resulting organic extracts were combined and washed with NaHCO$_3$ (2 x 40 mL) and brine (2 x 40 mL). The organic extracts were separated, dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography (CH$_2$Cl$_2$, R$_f$ = 0.6) gave 196a (1.163 g, 39%) as a colourless oil.

$^1$H NMR of 196a:

$\delta_H$ (400 MHz, CDCl$_3$): 1.31 (s, 9H, CH$_3$), 7.45-7.70 (m, 5H, Ar-H).

5.2.3.1.1 1-(2,6-Dimethyl-phenyl)-ethanone 196b

Procedure J was followed using 195b (1.42 ml, 20.0 mmol), 194b (37.8 ml, 18.0 mmol, 0.5 M) and THF (10 mL) at 0 °C. Purification by column chromatography (1:1 Hex-CH$_2$Cl$_2$, R$_f$ = 0.4) gave 196b (1.43 g, 53.6%) as a colourless oil.

$^1$H NMR of 196b:

$\delta_H$ (400 MHz, CDCl$_3$): 2.27 (s, 6H, CH$_3$), 2.50 (s, 3H, CH$_3$), 7.05 (m, 2H, H-1'), 7.17 (m, 1H, H-2').

5.2.3.1.2 1-(4-Methoxy-phenyl)-2-methyl-propan-1-one 196c

$\delta_H$ (400 MHz, CDCl$_3$): 2.35 (s, 3H, CH$_3$), 6.85-7.00 (m, 3H, Ar-H), 3.85 (s, 3H, OCH$_3$), 2.60 (s, 3H, CH$_3$), 7.05 (m, 2H, H-1'), 7.12 (m, 1H, H-2').
Procedure J was followed using **195c** (1.0 ml, 9.5 mmol), **194c** (17.2 ml, 8.6 mmol, 0.5 M) and THF (4 mL) at 0 °C. Purification by column chromatography (1:4 Hex-CH₂Cl₂, Rₖ = 0.2) gave **196c** (1.01 g, 66%) as a colourless oil.

¹H NMR of **196c**:

δₕ (400 MHz, CDCl₃): 1.22 (d, 6H, J 7.0, CH₃), 3.54 (app. hept, 1H, H-1), 3.89 (s, 3H, OCH₃), 6.96 (d, 2H, J 9.0, H-2'), 7.97 (d, 2H, J 9.0, H-1').

5.2.3.2 Procedure K: Synthesis of 2,2-dimethyl-1-phenyl-propan-1-ol (58) by reduction with LiAlH₄

A 25 mL round bottom flask charged with LiAlH₄ (703 mg, 18.5 mmol), THF (5 mL) and a stirring bar was placed under an atmosphere of N₂, cooled to 0 °C and left to stir for 10 mins. Subsequently a solution of **196a** (1.5 g, 9.3 mmol) in THF (5 mL) was added via syringe and the resulting solution was heated at reflux overnight. The reaction was quenched by the addition of 2M NaOH and extracted with CH₂Cl₂ (2 x 20 mL). The organic extracts were separated, dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography (1:1 Hex-CH₂Cl₂, Rₖ = 0.3) gave **58** (1.23 g, 81%) as a colourless oil.

¹H NMR of **58**:

δₕ (400 MHz, CDCl₃): 0.95 (s, 9H, CH₃), 4.43 (s, 1H, H-1), 7.28-7.35 (m, 5H, Ar-H).

5.2.3.2.1 1-(2,6-Dimethyl-phenyl)-ethanol (74b)
Procedure K was followed using LiAlH$_4$ (180 mg, 4.7 mmol), 196b (350 mg, 2.3 mmol) and THF (10 mL). Purification by column chromatography (CH$_2$Cl$_2$, $R_f = 0.3$) gave 74b (226 mg, 64%) as a colourless oil.

$^1$H NMR of 74b:

$\delta_H$ (400 MHz, CDCl$_3$): 1.45 (d, 3H, J 6.5, CH$_3$), 2.45 (s, 6H, CH$_3$), 5.36 (q, 1H, J 6.5, H-1), 7.03 (d, 2H, J 7.3, H-1'), 7.17 (app. t, 1H, J 7.3, H-2').

5.2.3.2.2 1-(4-Methoxy-phenyl)-2-methyl-propanol (197c)

Procedure K was followed using LiAlH$_4$ (304 mg, 8.0 mmol), 196c (705 mg, 3.96 mmol) and THF (15 mL). Purification by column chromatography (CH$_2$Cl$_2$, $R_f = 0.3$) gave 197c (226 mg, 64%) as a colourless oil.

$^1$H NMR of 196c:

$\delta_H$ (400 MHz, CDCl$_3$): 0.79 (d, 3H, J 7.0, CH$_3$), 1.03 (d, 3H, J 7.0, CH$_3$), 1.95 (app. hept, 1H, H-2), 3.83 (s, 3H, OCH$_3$), 4.32 (d, 1H, J 7.0, H-1), 6.90 (d, 2H, J 8.5, H-2'), 7.26 (d, 2H, J 8.5, H-1').

5.2.3.3  Procedure L: Synthesis of 1-(2-methoxy-phenyl)-ethanol (97)

A 25 mL round bottom flask charged with 199a (1.00 g, 7.34 mmol), THF (10 mL) and a stirrer was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 10 mins. Methyl Grignard (198) (10.5 ml, 14.7 mmol, 1.4 M) was subsequently added via syringe over a 15 min period, with the resulting solution allowed to warm to room temperature and stirred for 14 h. The reaction was quenched by the addition of H$_2$O (10 mL) and extracted
with CH₂Cl₂ (2 x 20 mL). The resulting organic extracts were combined and washed with NaHCO₃ (2 x 40 mL) and brine (2 x 40 mL). The organic extracts were separated, dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography (CH₂Cl₂, R_val = 0.2) gave 97 (692 mg, 62%) as a colourless oil.

¹H NMR of 97:

δ_H (400 MHz, CDCl₃): 1.53 (d, 3H, J 6.5, CH₃), 3.80 (s, 3H, OCH₃), 4.94 (q, 1H, J 6.5, H-1), 7.06 (m, 4H, Ar-H).

5.2.3.3.1 1-(2,4-Dimethoxy-phenyl)-ethanol (200b)

Procedure L was followed using 199b (1.0 g, 6.0 mmol), 198 (8.57 mL, 12.0 mmol, 1.4 M) and THF (10 mL) at 0 °C. Purification by column chromatography (CH₂Cl₂, R_val = 0.1) gave 200b (598 mg, 55%) as a colourless oil.

¹H NMR of 200b:

δ_H (400 MHz, CDCl₃): 1.51 (d, 3H, J 6.5, CH₃), 2.53 (s, 1H, OH), 3.83 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 5.06 (q, 1H, J 6.5, H-1), 6.50 (m, 2H, H-1', H-3'), 7.27 (m, 1H, H-4').

5.2.3.4 Procedure M: Synthesis of 2-Methyl-1-phenyl-propan-1-ol (57) by reduction with NaBH₄

A 25 mL round bottom flask charged with NaBH₄ (126.1 mg, 3.33 mmol), EtOH (6 mL) and a stirring bar was cooled to 0 °C and left to stir for 10 mins. Subsequently a solution of 201a (500 mg, 3.33 mmol) in THF (4 mL) was added via syringe with the resulting
solution allowed to warm to room temperature and left to stir for 14 h. CH₂Cl₂ (20 mL) was then added and the resulting solution washed with NaHCO₃ (2 x 20 mL) and brine (2 x 20 mL) The organic extracts were separated, dried (MgSO₄) and the solvent removed in vacuo. Complete conversion gave 57 (500 mg, 99%) as a colourless oil.

¹H NMR of 57:

δH (400 MHz, CDCl₃):  0.82 (d, 3H, J 7.0, CH₃), 1.03 (d, 3H, J 7.0, CH₃), 2.01 (app. hept, 1H, H-2), 4.39 (q, 1H, J 7.0, H-1), 7.30-7.39 (m, 5H, Ar-H).

5.2.3.4.1 1-(4—Nitro-phenyl)-ethanol (9b)

Procedure M was followed using NaBH₄ (229 mg, 6.05 mmol), 200b (1.0 g, 6.05 mmol) and EtOH (12 mL). Purification by column chromatography (CH₂Cl₂, Rf = 0.1) gave 9b (497 mg, 49%) as a colourless oil.

¹H NMR of 9b:

δH (400 MHz, CDCl₃):  1.58 (d, 3H, J 6.5, CH₃), 5.39 (q, 1H, J 6.5, H-1), 7.39 (d, 2H, J 6.5, H-1'), 8.09 (d, 2H, J 6.5, H-2')

5.2.3.4.2 1-(2—Nitro-phenyl)-ethanol (202c)

Procedure M was followed using NaBH₄ (229 mg, 6.05 mmol), 201c (1.0 g, 6.05 mmol) and EtOH (12 mL). Purification by column chromatography (CH₂Cl₂, Rf = 0.1) gave 202c (628 mg, 62%) as a colourless oil.
\(^1\)H NMR of 202c:

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.61 (d, 3H, J 6.0, CH₃), 2.30 (s, 1H, OH), 5.45 (q, 1H, J 6.0, H-1), 7.45 (app.t, 1H, J 8.5, H-3'), 7.68 (app. t, 1H, J 8.0, H-2'), 7.87 (d, 1H, J 8.0, H-4'), 7.92 (d, 1H, J 8.5, H-1'). \]

5.2.3.5 Procedure for the synthesis of hexahydrobenzo[1,3]dioxol-2-one (203)

\[
\text{O} \quad \text{O}
\]

A 50 ml round bottom flask charged with 190 (1 g, 11.2 mmol), CH₂Cl₂ (25 mL), and a stirring bar was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 10 mins. 19 (4.53 mL, 56.0 mmol) was added via syringe and the resulting solution was cooled further to -78 °C. Subsequently a solution of triphosgene (2.66 g, 8.96 mmol) in CH₂Cl₂ (25 mL) was added via syringe with the resulting solution allowed to warm to 0 °C and left to stir for 1 h. The reaction was quenched by the addition of NH₄Cl and extracted with CH₂Cl₂ (x 2). CH₂Cl₂ was then added and the resulting solution washed with NaHCO₃ (x 2) and brine (x 2) The organic extracts were separated, dried (Na₂SO₄) and the solvent removed in vacuo. Purification by column chromatography (CH₂Cl₂, \(R_f = 0.4\)) gave 203 (567 mg, 38%) as a colourless oil.

\(^1\)H NMR of 203:

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.45 (m, 2H, H-5, H-7), 1.65 (m, 2H, H-6, H-8), 1.92 (m, 4H, H-3, H-4, H-9, H-10), 4.70 (m, 2H, H-1, H-2). \]

5.2.3.6 Procedure for the synthesis of 1-cyclopentyl-2-(2-hydroxy-cyclohexyl)-ethanone (204)

\[
\text{OH} \quad \text{O}
\]

153
A 25 mL round bottom flask charged with 202 (567 mg, 3.99 mmol), THF (20 mL) and a stirring bar was placed under an atmosphere of Ar and left to stir for 10 mins. Subsequently pyrrolidine (3.33 mL, 40.0 mmol) was added via syringe and the resulting solution was heated under reflux for 3 h. CH₂Cl₂ (50 mL) was then added and the solution was washed with NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL). The organic extracts were separated, dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography (CH₂Cl₂, Rf = 0.2) gave 203 (720 mg, 85%) as a colourless oil.

¹H NMR of 203:

δH (400 MHz, CDCl₃): 1.25-2.15 (m, 12H, H-3, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-13, H-14, H-15, H-16), 2.58 (s, 1H, OH), 3.42 (m, 4H, H-11, H-12, H-17, H-18), 3.82 (m, 1H, H-2), 4.93 (m, 1H, H-1).

5.2.3.7 Procedure for the synthesis of 4-dimethylamino N-(2-hydroxy-indan-1-yl)-benzamide (206)

A 50 mL three-necked round bottom flask fitted with a 25 mL addition funnel containing a solution of 189c (1.29 g, 7.04 mmol) in CH₂Cl₂ (20 mL) was charged with 205 (1.0 g, 6.70 mmol), NEt₃ (1.4 mL, 10.0 mmol), CH₂Cl₂ (15 mL) and a stirring bar was placed under an atmosphere of Ar and cooled to 0 °C. The acid chloride solution was added slowly over a 45 min period and the resulting solution was allowed to warm to room temperature and stirred for 16 h. CH₂Cl₂ (20 mL) was then added and the resulting solution washed with Na₂CO₃ (2 x 60 mL) and NaHCO₃ (2 x 60 mL). The organic extracts were separated, dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography (CH₂Cl₂, Rf = 0.1) gave 206 (1.31 g, 66%) as a white solid. M.p. 180-182 °C (lit. 181-182 °C).
$^1$H NMR of 206:

$\delta_H$ (400 MHz, CDCl₃): 2.23 (bs, 1H, OH), 3.04 (m, 1H, H-3), 3.05 (s, 6H, NMe₂), 3.26 (m, 1H, H-4), 4.77 (m, 1H, H-2), 5.63 (m, 1H, H-1), 6.61 (d, 1H, J 7.8, H-6), 6.70 (d, 2H, J 8.8, H-2’), 7.26-7.31 (m, 2H, H-7, H-8), 7.38 (d, 1H, J 6.8, H-9), 7.77 (d, 2H, J 8.8, H-1’).

5.2.3.8 Procedure N: General procedure for the kinetic resolution of sec-alcohols in Table 2.6, 2.7 and 2.8

A 1mL reaction vessel charged with catalyst (2.34 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of alcohol (0.234 mmol) and NEt₃ (24.0 μL, 0.176 mmol) in CH₂Cl₂ (500 μL). The resulting solution was cooled to -78 °C and left to stir for 30 minutes. Iso-butyric anhydride (29.0 μL 0.176 mmol) was subsequently added via syringe. After 8 h at -78 °C the reaction was quenched by the addition of MeOH (200 μL) and allowed to warm to ambient temperature. Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel. The selectivity of the kinetic resolution was then established by CSP-HPLC.

5.2.3.8.1 Iso-butyric acid-1-phenyl ethyl ester (207a)

![Iso-butyric acid-1-phenyl ethyl ester](image)

Procedure N was followed using 169 (1 mg, 2.34 μmol) and 9 (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.
$^1$H NMR of 207a:

$\delta_H$ (400 MHz, CDCl$_3$): 1.19 (d, 3H, J 7.3, CH$_3$), 1.21 (d, 3H, J 7.3, CH$_3$), 1.54 (d, 3H, J 6.8, CH$_3$), 2.58 (app. hept, 1H, CH(CH$_3$)$_2$), 5.89 (q, 1H, J 6.8, H-1), 7.29-7.41 (m, 5H, Ar-H).

$^1$H NMR of 9:

$\delta_H$ (400 MHz, CDCl$_3$): 1.44 (d, 3H, J 6.8, CH$_3$), 4.93 (q, 1H, J 6.8, H-1), 7.17-7.34 (m, 5H, Ar-H).

HPLC data for recovered alcohol 9:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min$^{-1}$, RT, UV detection at 220 nm. Retention times: 29.0 min ($R$) major and 40.3 min ($S$) minor.$^8$

5.2.3.8.2 *Iso*-butyric acid-1-phenyl ethyl ester (207b)

![Iso-butyric acid-1-phenyl ethyl ester (207b)]

Procedure N was followed using 169 (1 mg, 2.34 μmol) and 74a (31.9 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

$^1$H NMR of 207b:

$\delta_H$ (400 MHz, CDCl$_3$): 1.18 (d, 3H, J 7.0, CH$_3$), 1.20 (d, 3H, J 7.0, CH$_3$), 1.51 (d, 3H, J 6.4, CH$_3$), 2.39 (s, 3H, CH$_3$), 2.60 (app. hept, 1H, CH(CH$_3$)$_2$), 6.07 (q, 1H, J 6.4, H-1), 7.18-7.27 (m, 3H, Ar-H), 7.40 (d, 1H, J 7.6, H-1’).
\(^1\)H NMR of 74a:

\[ \delta_H (400 \text{ MHz, CDCl}_3) : 1.49 (d, 3H, J 6.4, \text{CH}_3), \ 2.37 (s, 3H, \text{CH}_3), \ 5.16 (q, 1H, J 6.4, H-1), \ 7.14-7.26 (m, 3H, Ar-H), \ 7.54 (d, 1H, J 7.6, H-1'). \]

HPLC data for recovered alcohol 74a:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min\(^{-1}\), RT, UV detection at 220 nm. Retention times: 27.7 min (R) major and 29.6 min (S) minor.\(^{188}\)

5.2.3.8.3  Iso-butyric acid-1-(2,6-dimethyl-phenyl)-ethyl ester (207c)

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{O} & \quad \text{C}
\end{align*}
\]

Procedure N was followed using 169 (1 mg, 2.34 \(\mu\)mol) and 74b (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH\(_2\)Cl\(_2\)) through a pad of silica gel.

\(^1\)H NMR of 207c:

\[ \delta_H (400 \text{ MHz, CDCl}_3) : 1.17 (d, 3H, J 7.0, \text{CH}_3), \ 1.19 (d, 3H, J 7.0, \text{CH}_3), \ 1.48 (d, 3H, J 6.5, \text{CH}_3), \ 2.44 (s, 6H, \text{CH}_3), \ 2.62 (\text{app. hept, } 1H, \text{CH(CH}_3)_2), \ 6.29 (q, 1H, J 6.5, H-1), \ 7.02 (d, 2H, J 7.3, H-1'), \ 7.17 (\text{app t, } 1H, J 7.3, H-2'). \]

\(^1\)H NMR of 74b:

\[ \delta_H (400 \text{ MHz, CDCl}_3) : 1.45 (d, 3H, J 6.5, \text{CH}_3), \ 2.45 (s, 6H, \text{CH}_3), \ 5.36 (q, 1H, J 6.5, H-1), \ 7.03 (d, 2H, J 7.3, H-1'), \ 7.17 (\text{app t, } 1H, J 7.3, H-2'). \]
HPLC data for recovered alcohol 74b:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min⁻¹, RT, UV detection at 220 nm. Retention times: 20.9 min (R) major and 28.1 min (S) minor.⁸³

5.2.3.8.4  Iso-butyric acid-2-methyl-1-phenyl-proyl ester (207d)

Procedure N was followed using 169 (1 mg, 2.34 μmol) and 57 (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

¹H NMR of 207d:

δ_H (400 MHz, CDCl₃): 0.83 (d, 3H, J 7.0, CH₃), 0.98 (d, 3H, J 7.0, CH₃), 1.18 (d, 3H, J 6.8, CH₃), 1.22 (d, 3H, J 6.8, CH₃), 2.12 (app. hept, 1H, H-2), 2.61 (app. hept, 1H, CH(CH₃)₂), 3.39 (m, 1H, H-2) 5.48 (d, 1H, J 7.0, H-1), 7.27-7.36 (m, 5H, Ar-H).

¹H NMR of 57:

δ_H (400 MHz, CDCl₃): 0.82 (d, 3H, J 7.0, CH₃), 1.03 (d, 3H, J 7.0, CH₃), 2.01 (app. hept, 1H, H-2), 4.39 (q, 1H, J 7.0, H-1), 7.30-7.39 (m, 5H, Ar-H).

HPLC data for recovered alcohol 57:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min⁻¹, RT, UV detection at 220 nm. Retention times: 21.2 min (R) major and 22.8 min (S) minor.¹²⁴
Procedure N was followed using 169 (1 mg, 2.34 μmol) and 58 (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CHCl₂) through a pad of silica gel.

\(^1\)H NMR of 207e:

\[ \delta_H (400 \text{ MHz, CDCl}_3): 0.95 (s, 9H, CH\textsubscript{3}), 1.19 (d, 3H, J 6.8, CH\textsubscript{3}), 1.21 (d, 3H, J 6.8, CH\textsubscript{3}), 2.61 (\text{app. hept, } 1H, \text{ CH(CH}_3\textsubscript{2})\text{)}, 5.49 (s, 1H, H-1), 7.27-7.36 (m, 5H, Ar-H). \]

\(^1\)H NMR of 58:

\[ \delta_H (400 \text{ MHz, CDCl}_3): 0.95 (s, 9H, CH\textsubscript{3}), 4.43 (s, 1H, H-1), 7.28-7.35 (m, 5H, Ar-H). \]

HPLC data for recovered alcohol 58:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min\(^{-1}\), RT, UV detection at 220 nm. Retention times: 16.4 min (R) major and 21.8 min (S) minor.\(^{124}\)

5.2.3.8.6 Iso-butyric acid 1-naphthalen-1-yl ethyl ester (193)

Procedure N was followed using 169 (1 mg, 2.34 μmol) and 54 (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH\textsubscript{2}Cl\textsubscript{2}) through a pad of silica gel.
\[ \text{H N M R of 193:} \]

\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.13 \text{ (d, 3H, J 6.5, CH}_3 \text{)}, 1.16 \text{ (d, 3H, J 6.5, CH}_3 \text{)}, 1.68 \text{ (d, 3H, J 6.5, CH}_3 \text{)}, 2.61 \text{ (app. hept, 1H, CH(CH}_3)_2 \text{)}, 6.61 \text{ (q, 1H, J 6.5, H-1)}, 7.43-7.54 \text{ (m, 3H, H-3', H-7', H-8')}, 7.58 \text{ (d, 1H, J 7.0, H-2')}, 7.77 \text{ (d, 1H, J 8.0, H-4')}, 7.85 \text{ (d, 1H, J 7.5, H-6')}, 8.06 \text{ (d, 1H, J 8.5, H-9')}. \]

\[ \text{H N M R of 54} \]

\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.63 \text{ (d, 3H, J 6.5, CH}_3 \text{)}, 5.69 \text{ (q, 1H, J 6.5, H-1)} 7.47-7.55 \text{ (m, 3H, H-3', H-7', H-8')}, 7.70 \text{ (d, 1H, J 7.0, H-2')}, 7.79 \text{ (d, 1H, J 8.0, H-4')}, 7.89 \text{ (d, 1H, J 7.5, H-6')}, 8.13 \text{ (d, 1H, J 8.5, H-9')}. \]

HPLC data for recovered alcohol 54:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/IPA, 90/10, 1mL min\(^{-1}\), RT, UV detection at 220 nm. Retention times: 9.4 min (S) minor and 13.9 min (R) major.\(^{83}\)

\[ \text{5.2.3.8.7 Iso-butyric acid 1-naphthalen-2-yl ethyl ester (207f)} \]

![iso-butyric acid 1-naphthalen-2-yl ethyl ester (207f)](image)

Procedure N was followed using 169 (1 mg, 2.34 \(\mu\)mol) and 83 (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH\(_2\)Cl\(_2\)) through a pad of silica gel.

\[ \text{H N M R of 207f:} \]

\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.18 \text{ (d, 3H, J 7.0, CH}_3 \text{)}, 1.20 \text{ (d, 3H, J 7.0, CH}_3 \text{)}, 1.63 \text{ (d, 3H, J 6.5, CH}_3 \text{)}, 2.62 \text{ (app. hept, 1H, CH(CH}_3)_2 \text{)}, 6.06 \text{ (q, 1H, J 6.5, H-}\]
1), 7.45-7.53 (m, 3H, H-3', H-7', H-8'), 7.81-7.88 (m, 4H, H-1', H-4', H-6', H-8').

$^1$H NMR of 83:

$\delta_H$ (400 MHz, CDCl$_3$): 1.61 (d, 3H, J 6.5, CH$_3$), 5.10 (q, 1H, J 6.5, H-1), 7.48-7.55 (m, 3H, H-3', H-7', H-8'), 7.85-7.88 (m, 4H, H-1', H-4', H-6', H-8')

HPLC data for recovered alcohol 83:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 90/10, 1mL min$^{-1}$, RT, UV detection at 220 nm. Retention times: 15.8 min (S) minor and 17.1 min (R) major.$^{124}$

5.2.3.8.8 Iso-butyric acid-1-(4-methoxy-phenyl)-ethyl ester (207g)

$^1$H NMR of 207g:

$\delta_H$ (400 MHz, CDCl$_3$): 1.17 (d, 3H, J 7.0, CH$_3$), 1.19 (d, 3H, J 7.0, CH$_3$), 1.52 (d, 3H, J 6.5, CH$_3$), 2.54 (app. hept, 1H, CH(CH$_3$)$_2$), 3.82 (s, 3H, OCH$_3$), 5.85 (q, 1H, J 6.5, H-1), 6.89 (d, 2H, J 8.5, H-2'), 7.30 (d, 2H, J 8.5, H-1').
1H NMR of 9a:

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 1.51 (d, 3H, J 6.5, CH\textsubscript{3}), 3.83 (s, 3H, OCH\textsubscript{3}), 4.88 (q, 1H, J 6.5, H-1), 6.91 (d, 2H, J 8.5, H-2'), 7.33 (d, 2H, J 8.5, H-1').

HPLC data for recovered alcohol 9a:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1 mL min\textsuperscript{-1}, RT, UV detection at 220 nm. Retention times: 53.1 min (R) major and 59.7 min (S) minor.\textsuperscript{189}

5.2.3.8.9  
*Iso*-butyric acid-1-(4-fluoro-phenyl)-ethyl ester (208a)

\[
\text{O} \\
\text{F} \\
\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \\
\text{H} \\
\text{C}_6\text{H}_4\text{F} \\
\text{H}
\]

Procedure N was followed using 169 (1 mg, 2.34 μmol) and 106 (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH\textsubscript{2}Cl\textsubscript{2}) through a pad of silica gel.

1H NMR of 208a:

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 1.19 (d, 3H, J 7.0, CH\textsubscript{3}), 1.21 (d, 3H, J 7.0, CH\textsubscript{3}), 1.52 (d, 3H, J 6.4, CH\textsubscript{3}), 2.57 (app. hept, 1H, CH(CH\textsubscript{3})\textsubscript{2}), 5.86 (q, 1H, J 6.4, H-1), 7.04 (m, 2H, H-2'), 7.36 (m, 2H, H-1').

1H NMR of 106:

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 1.50 (d, 3H, J 6.4, CH\textsubscript{3}), 4.91 (q, 1H, J 6.4, H-1), 7.05 (m, 2H, H-2'), 7.35 (m, 2H, H-1').
HPLC data for recovered alcohol 106:


5.2.3.8.10  *Iso*-butyric acid-1-(2-nitro-phenyl)-ethyl ester (208b)

![Structural formula of 208b]

Procedure N was followed using 169 (1 mg, 2.34 \(\mu\)mol) and 202c (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH\(_2\)Cl\(_2\)) through a pad of silica gel.

\(^1\)H NMR of 208b:

\(\delta_H (400 MHz, CDCl_3)\):

1.19 (d, 3H, J 7.0, CH\(_3\)), 1.21 (d, 3H, J 7.0, CH\(_3\)), 1.63 (d, 3H, J 6.0, CH\(_3\)), 2.60 (app. hept, 1H, CH(CH\(_3\))\(_2\)), 6.38 (q, 1H, J 6.0, H-1), 7.43 (app. t, 1H, J 8.5, H-3'), 7.67 (app. t, 1H, J 8.0, H-2'), 7.86 (d, 1H, J 8.0, H-1'), 7.92 (d, 1H, J 8.5, H-4').

\(^1\)H NMR of 202c:

\(\delta_H (400 MHz, CDCl_3)\):

1.61 (d, 3H, J 6.0, CH\(_3\)), 2.30 (s, 1H, OH), 5.45 (q, 1H, J 6.0, H-1), 7.45 (app. t, 1H, J 8.5, H-3'), 7.68 (app. t, 1H, J 8.0, H-2'), 7.87 (d, 1H, J 8.0, H-1'), 7.92 (d, 1H, J 8.5, H-4').

HPLC data for recovered alcohol 202c:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min\(^{-1}\), RT, UV detection at 220 nm. Retention times: 49.5 min (\(R\)) major and 52.7 min (\(S\)) minor. \([\alpha]_D^{20} = -3.5\) (c 0.14, CHCl\(_3\)).\(^{188}\)
Procedure N was followed using 169 (1 mg, 2.34 µmol) and 9b (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

¹H NMR of 208c:

δ_H (400 MHz, CDCl₃): 1.19 (d, 3H, J 7.0, CH₃), 1.21 (d, 3H, J 7.0, CH₃), 1.57 (d, 3H, J 6.5, CH₃), 2.62 (app. hept, 1H, CH(CH₃)₂), 6.31 (q, 1H, J 6.5, H-1), 7.41 (d, 2H, J 6.5, H-1’), 8.11 (d, 2H, J 6.5, H-2’).

¹H NMR of 9b:

δ_H (400 MHz, CDCl₃): 1.58 (d, 3H, J 6.5, CH₃), 5.39 (q, 1H, J 6.5, H-1), 7.39 (d, 2H, J 6.5, H-1’), 8.09 (d, 2H, J 6.5, H-2’)

HPLC data for recovered alcohol 9b:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 90/10, 1mL min⁻¹, RT, UV detection at 220 nm. Retention times: 18.9 min (R) major and 24.4 min (S) minor. [α]D²⁰ = -4.4 (c 0.1, CHCl₃).

5.2.3.8.12 Iso-butyric acid-1-(4-methoxy-phenyl)-ethyl ester (208d)
Procedure N was followed using 169 (1 mg, 2.34 μmol) and 97 (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

¹H NMR of 208d:

δ_H (400 MHz, CDCl₃): 1.19 (d, 3H, J 7.0, CH₃), 1.21 (d, 3H, J 7.0, CH₃), 1.55 (d, 3H, J 6.5, CH₃), 2.62 (app. hept, 1H, CH(CH₃)₂), 3.79 (s, 3H, OCH₃), 5.88 (q, 1H, J 6.5, H-1), 7.06 (m, 4H, Ar-H).

¹H NMR of 97:

δ_H (400 MHz, CDCl₃): 1.53 (d, 3H, J 6.5, CH₃), 3.80 (s, 3H, OCH₃), 4.94 (q, 1H, J 6.5, H-1), 7.06 (m, 4H, Ar-H).

HPLC data for recovered alcohol 97:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min⁻¹, RT, UV detection at 220 nm. Retention times: 29.6 min (S) minor and 31.8 min (R) major.¹⁹⁰

5.2.3.8.13  _Iso_-butyric acid-l-(2,4-dimethoxy-phenyl)-ethyl ester (209a)

Procedure N was followed using 169 (1 mg, 2.34 μmol) and 200b (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

¹H NMR of 209a:

δ_H (400 MHz, CDCl₃): 1.18 (d, 3H, J 7.0, CH₃), 1.20 (d, 3H, J 7.0, CH₃), 1.47 (d, 3H, J 6.5, CH₃), 2.57 (app. hept, 1H, CH(CH₃)₂), 3.87 (s, 6H, OCH₃),
6.17 (q, 1H, J 6.5, H-1), 6.45 (m, 2H, H-2', H-4'), 7.27 (m, 1H, H-1').

$^1$H NMR of 200b:

$\delta_H$ (400 MHz, CDCl$_3$): 1.51 (d, 3H, J 6.5, CH$_3$), 3.82 (s, 6H, OCH$_3$), 5.06 (q, 1H, J 6.5, H-1), 6.45-6.51 (m, 2H, H-2', H-4'), 7.27 (m, 1H, H-1').

HPLC data for recovered alcohol 200b:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 98/2, 1mL min$^{-1}$, RT, UV detection at 220 nm. Retention times: 28.6 min ($S$) minor and 48.6 min ($R$) major. $[\alpha]_D^{20} = +4$ (c 0.1, CHCl$_3$).$^{193}$

5.2.3.8.14 Iso-butyric acid-1-(4-methoxy-phenyl)-2-methyl-propyl ester (209b)

![Chemical structure]

Procedure N was followed using 169 (1 mg, 2.34 $\mu$mol) and 197c (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

$^1$H NMR of 209b:

$\delta_H$ (400 MHz, CDCl$_3$): 0.80 (d, 3H, J 7.0, CH$_3$), 0.98 (d, 3H, J 7.0, CH$_3$), 1.15 (d, 3H, J 7.0, CH$_3$), 1.18 (d, 3H, J 7.0, CH$_3$), 2.09 (app. hept, 1H, H-2), 2.58 (app. hept, 1H, CH(CH$_3$)$_2$), 3.81 (s, 3H, OCH$_3$), 5.41 (d, 1H, J 7.0, H-1), 6.87 (d, 2H, J 8.5, H-2'), 7.22 (d, 2H, J 8.5, H-1').
H NMR of 197c:

δ₁H (400 MHz, CDCl₃): 0.79 (d, 3H, J 7.0, CH₃), 1.03 (d, 3H, J 7.0, CH₃), 1.95 (app. hept, 1H, H-2), 3.83 (s, 3H, OCH₃), 4.32 (d, 1H, J 7.0, H-1), 6.90 (d, 2H, J 8.5, H-2'), 7.26 (d, 2H, J 8.5, H-1').

HPLC data for recovered alcohol 197c:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min⁻¹, RT, UV detection at 220 nm. Retention times: 28.5 min (R) major and 31.1 min (S) minor. [α]D²⁰ = +8.2 (c 0.3, CHCl₃). Absolute configuration is tentatively assigned based on a comparison of CSP-HPLC retention times with that of 208d.

5.2.3.8.15 Iso-butyric acid-1-(4-dimethylamino-benzoylamino)-inden-2-yl ester (209c)

Procedure N was followed using 169 (1 mg, 2.34 μmol) and 206 (28.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

H NMR of 209c:

δ₁H (400 MHz, CDCl₃): 1.18 (d, 3H, J 6.8, CH₃), 1.22 (d, 3H, J 6.8, CH₃), 2.56 (app. hept, 1H, CH(CH₃)₂), 3.20 (m, 1H, H-3), 3.05 (s, 6H, NMe₂), 3.32 (m, 1H, H-4), 5.66 (m, 1H, H-2'), 5.94 (m, 1H, H-1), 6.43 (d, 1H, J 9.0, H-6), 6.70 (d, 2H, J 9.0, H-2'), 7.24-7.31 (m, 2H, H-7, H-8), 7.37 (d, 1H, J 7.0, H-9), 7.73 (d, 2H, J 9.0, H-1').
$^1$H NMR of 206:

$\delta$$_H (400$ MHz, CDCl$_3$): 2.23 (bs, 1H, OH), 3.04 (m, 1H, H-3), 3.05 (s, 6H, NMe$_2$), 3.26 (m, 1H, H-4), 4.77 (m, 1H, H-2), 5.63 (m, 1H, H-1), 6.61 (d, 1H, J 7.8, H-6), 6.70 (d, 2H, J 8.8, H-2'), 7.26-7.31 (m, 2H, H-7, H-8), 7.38 (d, 1H, J 6.8, H-9), 7.77 (d, 2H, J 8.8, H-1').

HPLC data for recovered alcohol 206:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99/1, 1mL min$^{-1}$, RT, UV detection at 220 nm. Retention times: 57.2 min (1R,2S) major and 61.7 min (1S,2R) minor. $[\alpha]$$_D^{20}$ = +12 (c 0.2, CHCl$_3$).

5.2.3.8.16 Iso-butyric acid-2-phenyl-cyclohexyl ester (209d)

![Iso-butyric acid-2-phenyl-cyclohexyl ester structure]

Procedure N was followed using 169 (1 mg, 2.34 µmol) and 93 (28.6 mg, 0.234 mmol) at -78 $^\circ$C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

$^1$H NMR of 209d:

$\delta$$_H (400$ MHz, CDCl$_3$): 1.18 (d, 3H, J 7.0, CH$_3$), 1.20 (d, 3H, J 7.0, CH$_3$), 1.35-1.55 (m, 4H, H-5, H-6, H-7, H-8), 1.79-1.91 (m, 2H, H-9, H-10), 2.15-2.35 (m, 2H, H-3, H-4), 2.55 (app. hept, 1H, CH(CH$_3$)$_2$), 2.70 (m, 1H, H-2), 4.98 (m, 1H, H-1). 7.17-7.39 (m, 5H, Ar-H).
$^1$H NMR of 93:

$\delta$H (400 MHz, CDCl$_3$): 1.33-1.56 (m, 4H, H-5, H-6, H-7, H-8), 1.77-1.89 (m, 2H, H-9, H-10), 2.10-2.30 (m, 2H, H-3, H-4), 2.45 (m, 1H, H-2), 3.68 (m, 1H, H-1), 7.17-7.38 (m, 5H, Ar-H).

HPLC data for recovered alcohol 93:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 99.5/0.5, 1mL min$^{-1}$, RT, UV detection at 220 nm. Retention times: 15.7 min (1S,2R) major and 18.2 min (1R,2S) minor.$^{192}

5.2.4 Experimental data for Section 2.5

5.2.4.1 Synthesis of pyrrolidine-1-yl-(4-pyrrolidin-1-yl-pyridin-3-yl)-methanone (211)

A 10 mL round bottom flask charged with 165 (90 mg, 0.57 mmol) and SOCl$_2$ (500 µL, 5.7 mmol) was fitted with a reflux condenser and under reflux for 1 hour. Removal of SOCl$_2$ by distillation gave 4-chloronicotinic acid chloride hydrochloride as a yellow solid, which was placed under an atmosphere of Ar, cooled to 0 °C and THF (4 mL) added via syringe. Pyrrolidine (238 µL, 2.85 mmol) was added via syringe and the yellow solution was left to stir for 4 h. Subsequently, extra pyrrolidine (95 µL, 1.14 mmol) was added and the resulting solution was left to heat under reflux overnight. CH$_2$Cl$_2$ (25 mL) was then added and the resulting solution washed with NaHCO$_3$ (x 2) and brine (x 2). The organic extracts were separated, dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography gave 211 (95 mg, 68%) as a white solid. M.p. 126-128 °C. $[\alpha]_D^{20} = -34.8$ (c 0.12, CHCl$_3$).
$^1$H NMR of 211:


$^{13}$C NMR of 211:


$\nu_{max}$ (film)/cm$^{-1}$: 3356, 2289, 1590, 1261, 792

HRMS (m/z - ES): Found 246.1605 (M$^+$ + H. C$_{14}$H$_{20}$N$_3$O Requires: 246.1606)

5.2.4.2. Methylolation of catalyst (S)-169 as in Table 2.9

![Chemical Structure](image-url)

Procedure B was followed using catalyst 169 (30 mg, 0.07 mmol) in CH$_2$Cl$_2$ (500 µL), with the addition of iodomethane (44 µL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (169a) in CDCl$_3$ by $^1$H NMR spectroscopy.
5.2.4.2.1 Methylation of catalyst (S)-172 as in Table 2.9

Procedure B was followed using catalyst 172 (37 mg, 0.07 mmol) in CH$_2$Cl$_2$ (500 µL), with the addition of iodomethane (44 µL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (172a) in CDCl$_3$ by $^1$H NMR spectroscopy.

5.2.4.2.2 Methylation of catalyst (S)-174 as in Table 2.9

Procedure B was followed using catalyst 174 (29 mg, 0.07 mmol) in CH$_2$Cl$_2$ (500 µL), with the addition of iodomethane (44 µL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (174a) in CDCl$_3$ by $^1$H NMR spectroscopy.

5.2.4.2.3 Methylation of catalyst (S)-175 as in Table 2.9
Procedure B was followed using catalyst 175 (36 mg, 0.07 mmol) in CH₂Cl₂ (500 μL), with the addition of iodomethane (44 μL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (175a) in CDCl₃ by ¹H NMR spectroscopy.

5.2.4.2.4 Methylation of catalyst 211 as in Table 2.9

![Chemical structure of catalyst 211]

Procedure B was followed using catalyst 211 (17 mg, 0.07 mmol) in CH₂Cl₂ (500 μL), with the addition of iodomethane (44 μL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (211a) in CDCl₃ by ¹H NMR spectroscopy.

5.2.4.3 Procedure for the benzylation of catalyst (S)-169 as in Figure 2.8

![Chemical structure of catalyst 169 and product 212]

A 5 mL round bottom flask charged with 169 (100 mg, 0.23 mmol), toluene (2 mL) and a stirring bar was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 5 min. Subsequently BnBr (28 μL, 0.23 mmol) was added slowly via syringe and the reaction was left to stir for 3 h. After TLC analysis indicated complete conversion of the starting material, the resulting solution was concentrated in vacuo and recrystallised (Hex-CH₂Cl₂) to give 212 (96 mg, 68.6%) as colourless crystals.
**1H NMR of 212:**

δ<sub>H</sub> (400 MHz, CDCl₃): 1.89-2.18 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 2.98 (m, 1H, H-15), 3.45-3.76 (m, 4H, H-7, H-8, H-13, H-14), 4.02 (m, 1H, H-16), 5.30 (app. t, 1H, J 7.3, H-21), 5.48 (d, 1H, J 14.5, H-1'), 5.77 (d, 1H, J 14.5, H-1'), 5.98 (s, 1H, OH), 6.74 (d, 1H, J 7.0, H-5), 7.16-7.70 (m, 15H, Ar-H), 7.82 (s, 1H, H-2), 8.17 (d, 1H, J 7.0, H-6).

### 5.2.4.4 Procedure O: General procedure for the acylation of catalysts

**Note:** These intermediates are relatively unstable and decompose rapidly in the presence of adventitious water. Under anhydrous conditions these materials are stable enough to be analysed by ¹H NMR spectroscopy over a period of several hours.

A solution of the pyridine (0.07 mmol) in CDCl₃ (400 µL, freshly distilled and stored for short periods under Ar over 4 Å mol sieves) was added to a screw-cap-NMR tube under an atmosphere of Ar. To this was added iso-butyric acid chloride (0.07 mmol) via syringe. The NMR tube was shaken for 10 seconds and the resulting mixture analysed by ¹H NMR spectroscopy.

### 5.2.4.4.1 3-[2-(Hydroxy-diphenyl-methyl)-pyrrolidine-1-carbonyl]-1-isobutyryl-4-pyrrolidin-1-yl-pyridinium;chloride (213)

![Chemical Structure](attachment:image.png)

Procedure O was followed using 169 (30 mg, 0.07 mmol) in CDCl₃ (500 µL).
5.2.4.2 3-(pyrrolidine-1-carbonyl)-1-isobutyryl-4-pyrrolidin-1-yl-pyridinium; chloride (214)

![Chemical Structure Image]

Procedure O was followed using 211 (17 mg, 0.07 mmol) in CDCl₃ (500 µL).

5.2.4.5 Synthesis of carbonic acid benzyl ester 2-(4-methoxy-phenyl)-4-methyl-oxazol-5-yl ester (217)

![Chemical Structure Image]

A 25 mL round bottom flask charged with 2-(4-methoxy-phenyl)-4-methyl-4\textsubscript{H}-oxazol-5-one\textsuperscript{197} (765 mg, 3.73 mmol), NEt₃ (570 µL, 4.1 mmol), THF (10 mL) and a stirring bar was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 20 mins. Subsequently benzoyl chloride (530 µL, 3.73 mmol) was added via syringe over a 10 min period. The resulting solution was allowed to warm to room temperature and left to stir overnight. The reaction was quenched by the addition of H₂O (10 mL) and extracted with Et₂O (2 x 20 mL). The resulting organic solution was washed with 1M HCl (2 x 25 mL), NaHCO₃ (2 x 25 mL) and brine (2 x 25 mL). The organic extracts were separated, dried (MgSO₄) and the solvent removed in vacuo. Purification by recrystallisation (2:3 Et₂O-Hex) gave 217 (360 mg, 29%) as a white solid. M.p 82-84 (lit.,\textsuperscript{197} 82-83 °C)
$^1$H NMR of 217:

$\delta$H (400 MHz, CDCl$_3$): 2.13 (s, 3H, CH$_3$), 3.87 (s, 3H, OCH$_3$), 5.34 (s, 2H, CH$_2$), 6.95 (d, 2H, J 9.0, H-2), 7.45 (m, 5H, Ar-H), 7.89 (d, 2H, J 9.0, H-1).

5.2.4.5.1 Synthesis of carbonic acid benzyl ester 2-(4-methoxy-phenyl)-4-methyl-oxazol-5-yl ester (218) catalysed by 169.

A 5 mL reaction vessel charged with 169 (1 mg, 2.34 µmol), CH$_2$Cl$_2$ (500 µL) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of 217 (26.4 mg, 0.078 mmol) in CH$_2$Cl$_2$ (500 µL). The resulting solution was left to stir for 3 h and subsequently quenched by the addition of Mel (10 µL). Solvents were removed in vacuo. 217 and 218 were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

$^1$H NMR of 218:

$\delta$H (400 MHz, CDCl$_3$): 1.80 (s, 3H, CH$_3$), 3.90 (s, 3H, OCH$_3$), 5.26 (s, 2H, CH$_2$), 7.00 (d, 2H, J 9.0, H-2), 7.33 (m, 5H, Ar-H), 7.98 (d, 2H, J 9.0, H-1).

HPLC data for recovered alcohol 218:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 90/10, 1 mL min$^{-1}$, RT, UV detection at 220 nm. Retention times: 11.7 min and 15.0 min (both peaks were equivalent, therefore the product was racemic).
5.3.1 Experimental data for Section 3.2

5.3.1.1 Synthesis of 5-bromo-m-terphenyl (224a)

\[
\begin{array}{c}
\text{Br} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array}
\]

A 150 mL round bottom flask charge with 1,3,5-tribromobenzene (4.2 g, 13.4 mmol) and Pd(PPh\textsubscript{3})\textsubscript{4} (500 mg, 0.4 mmol) was placed under an atmosphere of Ar. Subsequently, a solution of phenylboronic acid (3.5 g, 28.5 mmol) in toluene (60 mL) and a 1M Na\textsubscript{2}CO\textsubscript{3} solution (50 mL, degassed) were added to the reaction vessel via syringe and the mixture was heated under reflux for 48 h. The reaction mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude liquid was partitioned between CH\textsubscript{2}Cl\textsubscript{2}-H\textsubscript{2}O (1:1, 100 mL). The organic extract was separated, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated in vacuo. Purification by column chromatography (Hexane) gave 224a (2.11 g, 51.0 %) as a white solid.

\[^{1}\text{H} \text{NMR of 218:}\]

\[\delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 7.43 \text{ (app. t, 2H, J 6.0, H-1'''), 7.50 (app. t, 4H, J 7.5, H-2'''), 7.64 (d, 4H, J 5.0, H-3'''), 7.74 (s, 3H, H-1', H-3').}\]

5.3.1.2 Procedure P: synthesis of m-terphenyl magnesium bromide (223a) (Figure 3.1)

\[
\begin{array}{c}
\text{MgBr} \\
\end{array}
\]

A round bottom flask charged with Mg (dust) (152.3 mg, 6.27 mmol), THF (5 mL) and a stirring bar was place under an atmosphere of Ar. Subsequently a solution of 224a (1.76 g, 5.7 mmol) in THF (5 mL) was slowly added via syringe. The resulting mixture was heated
under reflux for 4 h with a colour change (colourless to dark red) upon the disappearance of Mg. The solution was cooled to -15 °C and used immediately.

5.3.1.2.2 (3,5-Dimethoxyphenyl)magnesium bromide (223b)

![Structural formula of (3,5-Dimethoxyphenyl)magnesium bromide](image)

Procedure P was followed using Mg (dust) (230 mg, 9.5 mmol), 224b (1.88 g, 8.64 mmol) in THF (50 mL) and the reaction heated under reflux for 16 h.

5.3.1.3 Synthesis of 3,5-[bis(trifluoromethyl)phenyl]magnesium bromide (223c)

![Structural formula of 3,5-[bis(trifluoromethyl)phenyl]magnesium bromide](image)

A 50 mL round bottom flask charged with 225 (5.17 mL, 30 mmol), THF (20 mL) and a stirring bar was placed under an atmosphere of Ar, cooled to -15 °C. A solution of isopropyl magnesium bromide (16.5 mL, 2M in THF) was slowly added via syringe. The resulting solution was allowed to stir at -10 °C for 1 h and used immediately.

5.3.1.4 Synthesis of pyrrolidine-2-yil-bis-[1,1',3',1'']terphenyl-5'-yl-methanol (S)-(226a)

![Structural formula of pyrrolidine-2-yil-bis-[1,1',3',1'']terphenyl-5'-yl-methanol (S)-(226a)](image)

Procedure E was followed with the addition of (S)-176 (1.6 mmol in 30 mL THF) to m-terphenylmagnesium bromide, (223a) (5.7 mmol) in THF (10 mL). The product as its
sulphate salt failed to precipitate from solution. The crude mixture was basified with 2M NaOH (4 mL, 8 mmol) and diluted with CH₂Cl₂ (25 mL). The organic layer was washed with H₂O (2 x 25 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography (99:1 CH₂Cl₂-NEt₃) gave 226a (512 mg, 57 %) as a white solid. M.p. 92-94 °C. [α]D²⁰ = -62.2 (c 0.143, CHCl₃).

²H NMR of 226a:

δH (400 MHz, CDCl₃): 1.70-1.92 (m, 4H, H-3, H-4, H-5, H-6), 2.96 (m, 2H, H-1, H-2), 4.56 (m, 1H, H-7), 7.36-7.40 (m, 4H, H-3’’), 7.41-7.49 (m, 8H, H-2’’), 7.60 (10H, H-1’’, H-3’’), 7.80 (s, 2H, H-1’), 7.90 (s, 2H, H-1’).

¹³C NMR of 226a:

δH (100 MHz, CDCl₃): 25.2, 26.5, 46.6, 64.7, 77.4 (q), 123.3, 123.7, 124.4, 124.7, 127.2, 127.3, 128.5, 128.6, 141.0 (q), 141.2 (q), 141.4 (q), 141.8 (q), 145.9 (q).

ν_max (film)/cm⁻¹: 3356, 2968, 2869, 2299, 1594, 1428, 1264

HRMS (m/z - ES): Found 558.2791 (M⁺ + H. C₄₁H₃₆NO Requires: 558.2797)

5.3.1.4.1 Synthesis of bis-(3,5-bis-dimethoxy-phenyl)-pyrrolidin-2-yl-methanol (S)-(226b)

Procedure E was followed with the addition of (S)-176 (2.88 mmol in 20 mL THF) to 223b (8.64 mmol) in THF (40 mL). The product as its sulphate salt failed to precipitate from
solution. The crude mixture was basified with 2M NaOH (4 mL, 8 mmol) and diluted with CH₂Cl₂ (60 mL). The organic layer was washed with H₂O (2 x 50 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography (99:1 EtOAc-NEt₃, Rᵣ = 0.2) gave 226b (185 mg, 17%) as a colourless oil. [α]ᵣ²⁰° = -81 (c 0.12, CHCl₃).

¹H NMR of 226b:

δ_H (400 MHz, CDCl₃): 1.57-1.78 (m, 4H, H-3, H-4, H-5, H-6), 2.98 (m, 2H, H-1, H-2), 3.78 (s, 6H, OCH₃), 3.79 (s, 6H, OCH₃), 4.19 (dd, 1H, J 7.5, 7.5, H-7), 6.30 (s, 2H, H-3'), 6.69 (s, 2H, H-1'), 6.77 (s, 2H, H-1').

¹³C NMR of 226b:

δ_C (100 MHz, CDCl₃): 24.8, 25.8, 46.2, 54.8, 54.9, 64.2, 76.8 (q), 97.8, 98.0, 103.3, 103.8, 159.9 (q), 160.2 (q).

ν_max(film)/cm⁻¹: 3344, 2936, 2837, 1592, 1425, 1203, 1152

HRMS (m/z - ES): Found 396.1923 (M⁺+Na. C₂₁H₂₇NO₅Na Requires: 396.1927)

5.3.1.4.2 Synthesis of bis-(3,5-bis-trifluoromethyl-phenyl)-pyrrolidin-2-yl-methanol (S)-(226c)

Procedure E was followed with the addition of (S)-176 (8.68 mmol in 20 mL THF) to 223c (33.0 mmol) in THF (30 mL). The product as its sulphate salt failed to precipitate from solution. The crude mixture was basified with 2M NaOH (4 mL, 8.0 mmol) and diluted with CH₂Cl₂ (50 mL). The organic layer was washed with H₂O (2 x 40 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography (99:1 EtOAc-
\( \text{NEt}_3, R_t = 0.3 \) gave 226c (2.45 g, 54 %) as a white solid. M.p 110-112 °C. Spectral data for this compound is consistent with that in the literature.\(^{211}\)

\(^1\)H NMR of 226c:

\[
\delta_H (400 \text{ MHz, CDCl}_3): \quad 1.51-1.61 \text{ (m, 2H, H-5, H-6), 1.72 (m, 1H, NH), 1.77-1.86 (m, 2H, H-3, H-4), 3.09 (m, 2H, H-1, H-2), 4.37 (dd, 1H, J 7.5, 7.5, H-7), 7.79 (s, 2H, H-3’), 7.98 (s, 2H, H-1’), 8.06 (s, 2H, H-1’).}
\]

5.3.1.4.3 Synthesis of bis-(3,5-bis-dimethyl-phenyl)-pyrrolidin-2-yl-methanol (S)-(226d)

Procedure E was followed with the addition of (S)-176 (6.52 mmol in 20 mL THF) to 223d (19.55 mmol) in THF (40 mL). The product as its sulphate salt failed to precipitate from solution. The crude mixture was basified with 2M NaOH (4 mL, 8 mmol) and diluted with CH\(_2\)Cl\(_2\) (60 mL). The organic layer was washed with \( \text{H}_2\text{O} \) (2 x 50 mL), dried (MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography (98:2 CH\(_2\)Cl\(_2\)-NEt\(_3\), \( R_t = 0.3 \)) gave 226d (1.10 g, 54 %) as a white solid. M.p 96-98 °C (lit.,\(^{186}\) 97.5-98 °C)

\(^1\)H NMR of 226d:

\[
\delta_H (400 \text{ MHz, CDCl}_3): \quad 1.55-1.78 \text{ (m, 4H, H-3, H-4, H-5, H-6), 2.29 (s, 6H, CH\(_3\)), 2.30 (s, 6H, CH\(_3\)), 2.92-3.08 \text{ (m, 2H, H-1, H-2), 4.24 (dd, 1H, J 8.0, 7.5, H-7), 6.81 (s, 2H, H-3’), 7.12 (s, 2H, H-1’), 7.19 (s, 2H, H-1’).}
\]
5.3.1.5 Synthesis of (4-Chloro-pyridin-3-yl)-[2-(hydroxyl-bis-[1,1';3',1''])
terphenyl-5'-yl-methyl)-pyrrolidin-1-yl]-methanone (S)-(227a)

Procedure C was followed using 165 (68 mg, 0.43 mmol), SOCl\textsubscript{2} (1.0 mL), CH\textsubscript{2}Cl\textsubscript{2} (3 + 5 mL), (S)-226a (200 mg, 0.36 mmol) and NEt\textsubscript{3} (200 µL, 1.44 mmol). Purification by column chromatography (9:1 CH\textsubscript{2}Cl\textsubscript{2}-EtOAc, R\textsubscript{f} = 0.3) gave 227a (141 mg, 56%) as a white solid. M.p. 136-137 °C. [\(\alpha\)]\textsubscript{D}\textsuperscript{20} = -117.5 (c 0.143, CHCl\textsubscript{3}).

\(^1\)H NMR of 227a:

\[\begin{align*}
\delta_H (400 \text{ MHz, CDC\textsubscript{13}}): & \quad 1.38-1.59 (m, 1H, H-11), 1.62-1.78 (m, 1H, H-12), 2.28-2.40 (m, 2H, H-9, H-10), 2.91-3.12 (m, 2H, H-7, H-8), 5.57 (dd, 1H, J 7.0, 7.0, H-13), 6.72 (s, 1H, OH), 7.30-7.41 (m, 5H, H-2, \ldots, H-3'''), 7.45-7.49 (m, 9H, H-5, H-2'''), 7.67 (m, 8H, H-1'''), 7.80-7.85 (m, 4H, H-1''), 7.92 (s, 2H, H-3'''), 8.50 (bs, 1H, H-6). 
\end{align*}\]

\(^{13}\)C NMR of 227a:

\[\begin{align*}
\delta_C (100 \text{ MHz, CDC\textsubscript{13}}): & \quad 23.9, 30.4, 50.4, 68.4, 82.2 (q), 125.5, 125.6, 125.7, 125.8, 127.2, 127.3, 127.4, 127.5, 127.6, 128.8, 128.9, 129.0 (q), 141.0 (q), 141.2 (q), 141.4 (q), 141.6 (q), 143.8 (q), 146.2 (q), 147.8, 150.4 (q), 150.5, 167.5 (C=O). 
\end{align*}\]

\(v_{\text{max}}\) (film)/cm\textsuperscript{-1}:

3275, 2962, 2245, 1575, 1427, 1185, 1030.

HRMS (m/z - ES): Found 697.2640 (M\textsuperscript{+} + H. C\textsubscript{47}H\textsubscript{38}N\textsubscript{2}O\textsubscript{2}Cl Requires: 697.2622)
5.3.1.5.1 Synthesis of \{2-[bis-(3,5-dimethoxy-phenyl)-hydroxy-methyl]-pyrrolidin-1-yl\}-(4-chloro-pyridin-3-yl)-methanone (S)-(227b)

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{HO} & \quad \text{MeO} \\
\text{OMe} & \quad \text{OMe}
\end{align*}
\]

Procedure C was followed using 165 (86 mg, 0.547 mmol), SOCl₂ (1.0 mL), CH₂Cl₂ (3 + 5 mL), (S)-226b (170 mg, 0.456 mmol) and NEt₃ (253 µL, 1.82 mmol). Purification by column chromatography (1:2 CH₂Cl₂-EtOAc, Rᵣ = 0.3) gave 227b (132 mg, 57%) as a white solid. M.p. 70-72 °C. [α]D²⁰ = -98 (c 0.126, CHCl₃).

\(^1\text{H} \text{NMR of} \ 227\text{b}:

\[\begin{align*}
\delta_H (400 \text{ MHz, CDCl}_3): & \quad 1.48-1.73 \ (m, \ 2\text{H, H-11, H-12}), \ 2.14 \ (m, \ 2\text{H, H-9, H-10}), \ 3.17 \ (m, \ 2\text{H, H-7, H-8}), \ 3.79 \ (s, \ 6\text{H, OCH}_3), \ 3.80 \ (s, \ 6\text{H, OCH}_3), \ 5.19 \ (dd, \ 1\text{H, J 7.5, 8.0, H-13}), \ 6.41 \ (s, \ 1\text{H, OH}), \ 6.46 \ (s, \ 1\text{H, H-3'}), \ 6.61 \ (s, \ 1\text{H, H-3'}), \ 6.67 \ (s, \ 2\text{H, H-1'}), \ 6.78 \ (s, \ 2\text{H, H-1'}), \ 7.37 \ (d, \ 1\text{H, J 5.0, H-5}), \ 8.15-8.30 \ (bs, \ 1\text{H, H-2}), \ 8.53 \ (d, \ 1\text{H, J 5.0, H-6}).
\end{align*}\]

\(^{13}\text{C} \text{NMR of} \ 227\text{b}:

\[\begin{align*}
\delta_C (100 \text{ MHz, CDCl}_3): & \quad 23.5, \ 29.9, \ 49.2, \ 54.9, \ 55.0, \ 68.4, \ 81.2 \ (q), \ 98.6, \ 98.7, \ 105.7, \ 105.9, \ 124.5, \ 131.4 \ (q), \ 139.1 \ (q), \ 144.6, \ 146.8 \ (q), \ 147.0 \ (q), \ 149.7, \ 159.8 \ (q), \ 159.9 \ (q), \ 166.4 \ (C=O).
\end{align*}\]

\[\nu_{\text{max}} \ (\text{film})/\text{cm}^{-1}: \quad 3275, \ 2938, \ 2837, \ 1594, \ 1425, \ 1203, \ 1060.\]

\[\text{HRMS (m/z - ES):} \quad \text{Found 513.1805 (M}^+ + \text{H, C}_{27}\text{H}_{39}\text{N}_2\text{O}_6\text{Cl Requires: 513.1792)}\]
5.3.1.5.2 Synthesis of \{2-[bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-
pyrrolidin-1-yl\}-(4-chloro-pyridin-3-yl)-methanone (S)-(227c)

Procedure C was followed using 165 (144 mg, 0.914 mmol), SOCl₂ (1.0 mL), CH₂Cl₂ (3 +
5 mL), (S)-226c (400 mg, 0.762 mmol) and NEt₃ (540 μL, 3.90 mmol). Purification by
column chromatography (1:1 CH₂Cl₂-EtOAc, R₂ = 0.3) gave 227c (222 mg, 44%) as a
white solid. M.p. 78-80 °C. [α]D²⁰ = -67.5 (c 0.157, CHCl₃).

¹H NMR of 227c:

δH (400 MHz, CDCl₃): 1.50 (m, 1H, H-11), 1.76 (m, 1H, H-12), 1.97 (m, 1H, H-9), 2.20
(m, 1H, H-10), 3.08 (m, 1H, H-7), 3.28 (m, 1H, H-8), 5.31 (dd,
1H, J 8.0, 8.0, H-13), 7.17 (s, 1H, OH), 7.37 (d, 1H, J 5.5, H-5),
7.89 (s, 3H, H-1’, H-3’), 7.96 (s, 1H, H-3’), 8.08 (s, 2H, H-
1’),8.22-8.40 (bs, 1H, H-2) 8.55 (d, 1H, J 5.5, H-6).

¹³C NMR of 227c:

δC (100 MHz, CDCl₃): 23.5, 29.7, 50.0, 67.7, 80.1 (q), 121.8, 121.9, 122.6 (q, J 271.4),
122.7 (q, J 271.4), 124.2, 127.0, 127.4, 131.2 (q, J 34.0), 131.3 (q,
J 34.0), 131.4 (q), 139.6 (q), 144.2, 146.0 (q), 147.4 (q), 151.1,
167.9 (C=O).

νmax (film)/cm⁻¹: 3368, 2923, 2853, 1623, 1462, 1277, 1130.

HRMS (m/z - ES): Found 665.0881 (M+ + H. C₂₇H₁₈N₂O₂F₁₂Cl Requires: 665.0865)
5.3.1.5.3 Synthesis of \(2\)-[bis-(3,5-dimethyl-phenyl)-hydroxy-methyl]-pyrrolidin-1-yl]-\(4\)-chloro-pyridin-3-yl]-methanone \((S)-(227d)\)

Procedure C was followed using \(165\) (440 mg, 2.79 mmol), \(\text{SOCl}_2\) (2.0 mL), \(\text{CH}_2\text{Cl}_2\) (6 + 10 mL), \((S)-226d\) (720 mg, 2.32 mmol) and \(\text{NEt}_3\) (1.29 mL, 9.28 mmol). Purification by column chromatography (1:1 \(\text{CH}_2\text{Cl}_2\)-EtOAc, \(R_f = 0.4\)) gave \(227d\) (394 mg, 38%) as a white solid. M.p. 73-75 °C. \([\alpha]_D^{20} = -117.5\) (c 0.143, CHCl₃).

\(^1\)H NMR of \(227d\):

\(\delta_H (400\text{ MHz, }\text{CDCl}_3)\): 1.34 (m, 1H, H-11), 1.60 (m, 1H, H-12), 2.11 (m, 1H, H-9), 2.25 (m, 1H, H-10), 2.32 (s, 6H, \(\text{CH}_3\)), 2.35 (s, 6H, \(\text{CH}_3\)), 2.85 (m, 1H, H-7), 3.08 (m, 1H, H-8), 5.35 (dd, 1H, \(J = 6.5, 6.5\), H-13), 6.20 (s, 1H, OH), 6.95 (s, 1H, H-3’), 6.99 (s, 1H, H-3’), 7.08 (s, 2H, H-4’), 7.21 (s, 2H, H-3’), 7.37 (d, 1H, \(J = 5.0, H-5\)), 8.20 (bs, 1H, H-2), 8.52 (d, 1H, \(J = 5.0, H-6\)).

\(^1\)C NMR of \(227d\):

\(\delta_C (100\text{ MHz, }\text{CDCl}_3)\): 21.1, 21.2, 23.4, 29.5, 49.9, 67.3, 81.4 (q), 124.2, 125.0, 125.3, 128.6, 132.5, 136.6 (q), 136.9 (q), 139.7 (q), 139.8 (q), 142.4 (q), 144.9 (q), 147.7, 150.5, 166.5 (C=O).

\(v_{max}\) (film)/cm\(^{-1}\): 3303, 2917, 2245, 1619, 1576, 1435, 1156.

HRMS \((m/z - \text{ES})\): Found 471.1824 (\(M^+ + \text{Na}\). \text{C}_{27}\text{H}_{29}\text{N}_{2}\text{O}_{2}\text{NaCl}\) Requires: 471.1815)
5.3.1.6 Synthesis of \{2-[bis-(3,5-dimethyl-phenyl)-hydroxy-methyl]-pyrrolidin-1-yl\}-(4-pyrrolidin-1-yl-pyridin-3-yl)-methanone (5)-(219)

Procedure D was followed using 227d (80 mg, 0.179 mmol), toluene (2 mL) and pyrrolidine (2 mL, 24.0 mmol). Purification by recrystallisation (1:1 Hex-CH$_2$Cl$_2$), gave 219 (83 mg, 96%) as a white solid. M.p. 179-180. $[\alpha]_D^{20}$ = -50.3 (c 0.171, CHCl$_3$).

Note: 219 exists in two rotameric forms in the $^1$H NMR and $^{13}$C NMR time-frame. All discernable resonances from both rotameric forms are included.

$^1$H NMR of 219:

Major rotamer

$\delta_H$ (400 MHz, CDCl$_3$): 1.52-2.26 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 2.32 (s, 6H, CH$_3$), 2.39 (s, 6H, CH$_3$), 2.94 (m, 1H, H-7), 3.11 (m, 2H, H-8, H-13), 3.50 (m, 3H, H-14, H-15, H-16), 5.20 (dd, 1H, J 5.3, 5.3, H-21), 6.45 (d, 1H, J 4.0, H-5), 6.86 (s, 1H, OH), 6.94 (s, 1H, H-3'), 7.06 (s, 1H, H-3'), 7.11 (s, 2H, H-1'), 7.25 (s, 2H, H-1'), 7.45 (s, 1H, H-2), 8.14 (d, 1H, J 4.0, H-6).

Major and minor rotamer

$\delta_H$ (400 MHz, CDCl$_3$): 1.52-2.26 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 2.32 (s, 6H, CH$_3$), 2.39 (s, 6H, CH$_3$), 2.94 (m, 1H, H-7), 3.11 (m, 2H, H-8, H-13), 3.33 (m, 0.2H, H-15), 3.50 (m, 2.8H, H-14, H-15, H-16), 5.20-5.26 (dd, 1H, J 5.3, 5.3, H-21), 6.45 (d, 1H, J 4.0, H-5), 6.85-6.96 (m, 2H, H-3', OH) 7.06-7.16 (m, 3H, H-1', H-3'), 7.25 (s, 2H, H-1'), 7.45 (s, 1H, H-2), 8.14 (d, 1H, J 4.0, H-6).
$^{13}$C NMR of 219:

$\delta_{C}$ (100 MHz, CDCl$_3$): 21.4, 21.5, 23.6, 25.5, 30.4, 48.8, 51.8, 68.2, 82.1 (q), 108.3, 116.7 (q), 125.4, 125.5, 128.8, 128.9, 136.9 (q), 137.2 (q), 142.5 (q), 145.0 (q), 148.3 (q), 148.4, 149.4, 171.2 (C=O).

Rotamer peaks found: 22.5, 25.6, 29.9, 49.0, 68.8, 82.1, 125.7, 171.5 (C=O).

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 3244, 2970, 1587, 1415, 749.

HRMS (m/z - ES): Found 484.2964 (M$^+$ + H. C$_{31}$H$_{38}$N$_3$O$_2$ Requires: 484.2964)

*Anal. calcd. for C$_{31}$H$_{37}$N$_3$O$_2$: C, 76.98; H, 7.71; N, 8.69. Found: C, 76.84; H, 7.73; N, 8.53.*

5.3.1.6.1 Synthesis of $\{2$-[bis-(3,5-dimethoxy-phenyl)-hydroxy-methyl]-pyrrolidin-1-yl$\}$(4-pyrrolidin-1-yl-pyridin-3-yl)-methanone (S)-(220)

Procedure D was followed using $227b$ (77.0 mg, 0.150 mmol), toluene (2 mL) and pyrrolidine (2 mL, 24.0 mmol). Purification by recrystallisation (1:1 Hex-CH$_2$Cl$_2$), gave 220 (79 mg, 96%) as a white solid. M.p. 227-229. [a]$_D^{20}$ = -78.3 (c 0.143, CHCl$_3$).

Note: 220 exists in two rotameric forms in the $^1$H NMR and $^{13}$C NMR time-frame. All discernable resonances from both rotameric forms are included.
\(^1\)H NMR of 220:

**Major rotamer**

\(\delta_H (400 \text{ MHz, CDCl}_3):\) 1.58-2.28 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 3.09-3.28 (m, 3H, H-7, H-8, H-13), 3.50 (m, 3H, H-14, H-15, H-16), 3.80 (s, 6H, OCH\(_3\)), 3.82 (s, 6H, OCH\(_3\)), 5.07 (dd, 1H, J 5.0, 5.5, H-21), 6.39-6.52 (m, 3H, H-5 (J 4.0), H-3'), 6.70 (s, 2H, H-1'), 6.82 (s, 2H, H-1'), 7.21 (s, 1H, OH), 7.54 (s, 1H, H-2), 8.15 (d, 1H, J 4.0, H-6).

**Major and minor rotamer**

\(\delta_C (400 \text{ MHz, CDCl}_3):\) 1.58-2.28 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 2.91 (m, 0.3H, H-7, H-13), 3.09-3.28 (m, 3H, H-7, H-8, H-13, H-14, H-15), 3.50 (m, 2.55 H, H-14, H-15, H-16), 3.65 (m, 0.15H, H-16), 3.80 (s, 6H, OCH\(_3\)), 3.82 (s, 6H, OCH\(_3\)), 5.07 (dd, 1H, J 5.0, 5.5, H-21), 6.39-6.52 (m, 3H, H-5, H-3'), 6.70 (s, 2H, H-1'), 6.82 (s, 2H, H-1'), 7.21 (s, 1H, OH), 7.54-7.58 (m, 1H, H-2), 8.15 (d, 1H, J 4.0, H-6).

\(^{13}\)C NMR of 220:

\(\delta_C (100 \text{ MHz, CDCl}_3):\) 23.6, 25.5, 30.7, 48.8, 52.1, 55.2, 55.3, 68.9, 81.7 (q), 99.0, 99.1, 106.1, 106.2, 108.3, 116.7 (q), 144.8 (q), 147.3 (q), 148.4, 148.5 (q) 149.6, 160.1 (q), 160.3 (q), 171.7 (C=O).

Rotamer peaks found: 22.5, 31.4, 51.4, 70.4, 80.9, 98.8, 105.8, 145.1, 146.9, 149.2, 172.9 (C=O).

\(v_{\text{max (film)}}/\text{cm}^{-1}:\) 3217, 2955, 2332, 1592, 1424, 1153.

HRMS (m/z - ES): Found 548.2775 (M\(^+\) + H. C\(_{31}\)H\(_{38}\)N\(_3\)O\(_6\) Requires: 548.2761)

*Anal. calcd. for C\(_{31}\)H\(_{37}\)N\(_3\)O\(_6\): C, 67.99; H, 6.81; N, 7.67. Found: C, 67.78; H, 6.78; N, 7.48.*
5.3.1.6.2 Synthesis of {2-[bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidin-1-yl}-(4-pyrrolidin-1-yl-pyridin-3-yl)-methanone (S)-(221)

Procedure D was followed using 227c (55 mg, 0.08 mmol), toluene (2 mL) and piperidine (2 mL, 24.0 mmol). Purification by recrystallisation (1:1 Hex-CH₂Cl₂), gave 221 (55 mg, 95%) as a white solid. M.p. 120-122. \( [\alpha]_D^{20} = -54 \) (c 0.1, CHCl₃).

Note: 221 exists in two rotameric forms in the \(^1\text{H NMR}\) and \(^{13}\text{C NMR}\) time-frame. All discernable resonances from both rotameric forms are included.

\(^1\text{H NMR of 221:}\)

Major and minor rotamer
\[ \delta_\text{H} \text{ (400 MHz, CDCl₃): } 1.65-2.28 \text{ (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20)}, \ 2.91-3.28 \text{ (m, 3H, H-7, H-8, H-15)}, \ 3.49 \text{ (m, 2H, H-13, H-14)}, \ 3.68 \text{ (m, 1H, H-16)}, \ 5.05-5.24 \text{ (m, 1H, H-21)}, \ 6.49 \text{ (d, 1H, J 5.5, H-5)}, \ 7.44 \text{ (s, 1H, H-2)}, \ 7.83-8.22 \text{ (m, 7H, H-6 (J 5.5), Ar-H)}. \]

\(^{13}\text{C NMR of 221:}\)

\[ \delta_\text{C} \text{ (100 MHz, CDCl₃): } 23.7, 25.4, 31.2, 49.1, 52.2, 68.9, 80.4 \text{ (q)}, \ 108.6, 115.6 \text{ (q)}, \ 122.0, \ 122.1, 123.0 \text{ (q, J 180.8)}, \ 123.1 \text{ (q, J 180.8)}, \ 127.4, 127.5, 131.6 \text{ (q, J 22.6)}, \ 131.7 \text{ (q, J 22.6)}, \ 144.5 \text{ (q)}, \ 146.3 \text{ (q)}, \ 147.9, 148.6 \text{ (q)}, \ 149.9, 172.4 \text{ (C=O)}. \]

Rotamer peaks found: 22.5, 29.5, 30.4, 50.9, 68.7, 80.2, 147.3, 149.6, 173.1 (C=O).
\[ \nu_{\text{max}} (\text{film})/\text{cm}^{-1}: \quad 3240, 2928, 2298, 1642, 1371, 1132, 682. \]

HRMS (m/z - ES): Found 700.1835 (M$^+$ + H. C$_{31}$H$_{26}$F$_{12}$N$_3$O$_2$ Requires: 700.1833)

Anal. calcd. for C$_{31}$H$_{25}$F$_{12}$N$_3$O$_2$: C, 53.23; H, 3.60; F, 32.59; N, 6.01. Found: C, 53.07; H, 3.71; F, 32.29, N, 5.72.

5.3.1.6.3 Synthesis of [2-(hydroxy-bis-[1,1’;3’,1’’]terphenyl-5’-yl-methyl)-pyrrolidin-1-yl]-(4-pyrrolidin-1-yl-pyridin-3-yl)-methanone (S)-(222)

Procedure D was followed using 227a (121 mg, 0.170 mmol), toluene (2 mL) and pyrrolidine (2 mL, 24.0 mmol). Purification by column chromatography (1:1 Hex-CH$_2$Cl$_2$, R$_f$ = 0.2), gave 222 (124 mg, 98%) as a white solid. M.p. 253-254. $\left[\alpha\right]_{\text{D}}^{20} = -37$ (c 0.1, CHCl$_3$).

Note: 222 exists in two rotameric forms in the $^1$H NMR and $^{13}$C NMR time-frame. All discernable resonances from both rotameric forms are included.

$^1$H NMR of 222:

Major rotamer

$\delta$ (400 MHz, CDCl$_3$): 1.50-1.70 (m, 2H, H-17,H-19,), 1.96 (m, 2H, H-18, H-20), 2.08 (m, 2H, H-9, H-11), 2.32 (m, 2H, H-10 H-12), 3.11 (m, 3H, H-7, H-13, H-15), 3.51 (m, 3H, H-8, H-14, H-16), 5.32 (m, 1H, H-21), 6.43 (d, 1H, J 3.0, H-5), 7.32-8.02 (m, 27H, Ar-H, H-2), 8.10 (d, 1H, J 3.0, H-6).
Major and minor rotamer

δH (400 MHz, CDCl₃): 1.30-1.43 (m, 0.5H, H-17, H-19), 1.50-1.70 (m, 2.5H, H-9, H-11, H-17, H-18, H-19, H-20), 1.96 (m, 1.5H, H-18, H-20), 2.08 (m, 1.5H, H-9, H-11), 2.30-2.48 (m, 2H, H-10, H-12), 3.01-3.16 (m, 3H, H-7, H-10, H-11), 3.27 (m, 0.5H, H-7, H-10), 3.51 (m, 2.25H, H-7, H-10, H-11), 3.63 (m, 0.25H, H-11), 5.32 (m, 0.75H, H-14), 5.47 (m, 0.25H, H-14), 6.43 (d, 1H, J 3.0, H-5), 7.32-8.02 (m, 26.75H, Ar-H, H-2), 8.10 (d, 1H, J 3.0, H-6), 8.12 (m, 0.25H, Ar-H)

13C NMR of 222:

δC (100 MHz, CDCl₃): 23.7, 25.5, 31.4, 48.9, 52.1, 69.6, 82.1 (q), 108.3, 116.5 (q), 125.3, 125.4, 125.6, 125.8, 127.1, 127.2, 127.3, 127.4, 128.6, 128.7, 141.0 (q), 141.2 (q), 141.3 (q), 141.5 (q), 143.4 (q), 146.0 (q), 148.4, 148.5 (q), 149.7, 171.8 (C=O).

Rotamer peaks found: 23.5, 30.4, 50.9, 69.2, 81.5, 144.9, 147.3, 148.1, 149.4, 172.7 (C=O).

νmax (film)/cm⁻¹: 3210, 2972, 1589, 1412, 1144, 696.

HRMS (m/z - ES): Found 732.3610 (M⁺ + H. C₅₁H₄₆N₃O₂ Requires: 732.3590)

Anal. calcd. for C₅₁H₄₅N₃O₂: C, 83.69; H, 6.20; N, 5.74. Found: C, 83.50; H, 6.23; N, 5.78.

5.3.2 Experimental data for Section 3.3

5.3.2.1 Synthesis of (trans)-4-dimethylamino-benzoic acid 2-hydroxy-cyclohexyl ester (228)

\[
\begin{align*}
\text{229} \quad \text{OH} & \quad \text{OH} \\
\text{22} \quad (0.1 \text{ equiv.}) & \quad \text{189c} \quad (1.05 \text{ equiv.}) \\
\text{NEt₃} \quad (1.5 \text{ equiv.}) & \quad \text{CH₂Cl₂, 0 °C - RT} \\
\end{align*}
\]

(rac)-228
Procedure H was followed using anilinoyl chloride (189c) (1.16 g, 6.33 mmol), 229 (700 mg, 6.03 mmol), NEt₃ (1.25 mL, 9.04 mmol) in THF (12 + 8 mL). Purification by column chromatography (CH₂Cl₂, Rf = 0.2), gave 228 (684 mg, 43%) as a white solid. M.p 120-121. Spectral data for this compound is consistent with that in the literature.¹¹

¹H NMR of 228:

δ_H (400 MHz, CDCl₃): 1.29-1.48 (m, 4H, H-5, H-6, H-7, H-8), 1.77 (m, 2H, H-9, H-10), 2.15 (m, 2H, H-3, H-4), 2.51 (s, 1H, OH), 3.08 (s, 6H, N(CH₃)₂), 3.73 (m, 1H, H-1), 4.80 (m, 1H, H-2), 6.72 (d, 2H, J 8.5, H-2'), 7.95 (d, 2H, J 8.5, H-1')

5.3.2.2 Procedure Q: KR of (trans)-4-Dimethylamino-benzoic acid 2-isobutyryloxy-cyclohexyl ester (228a)

A 1mL reaction vessel charged with 221 (1.6 mg, 2.34 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of 228 (61.5 mg, 0.234 mmol) and NEt₃ (26 μL, 0.187 mmol) in CH₂Cl₂ (500 μL). The resulting solution was cooled to 0 °C and left to stir for 30 minutes. Iso-butyric anhydride (27 μL, 0.164 mmol) was subsequently added via syringe. The reaction was quenched by the addition of MeOH (200 μL). Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

¹H NMR of 228a:

δ_H (400 MHz, CDCl₃): 1.19 (d, 3H, J 7.0, CH₃), 1.23 (d, 3H, J 7.0, CH₃), 1.32-1.57 (m, 4H, H-5, H-6, H-7, H-8), 1.77 (m, 2H, H-9, H-10), 2.05-2.18 (m, 2H, H-3, H-4), 2.62 (app. hept, 1H, CH(CH₃)₂), 3.05 (s, 6H,
N(CH$_3$)$_2$), 4.96-5.08 (m, 2H, H-1, H-2), 6.64 (d, 2H, J 8.5, H-2'), 7.88 (d, 2H, J 8.5, H-1').

HPLC data for recovered alcohol 228:

Chiralpak AS-H (4.6 mm x 25 cm), hexanes/iPrOH, 90/10, 1.0 mL min$^{-1}$, RT, UV detection at 220 nm. Retention times: 12.2 min minor and 25.8 min major.

HPLC data for recovered ester 228a:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/iPrOH, 90/10, 1 mL min$^{-1}$, RT, UV detection at 220 nm. Retention times: 11.9 min major and 14.7 min minor.

5.3.3 Experimental data for Section 3.4

5.3.3.1 Procedure R: Synthesis of 2-(hydroxyl-phenyl-methyl)-acrylic acid methyl ester (232a)

\[
\text{OH} \quad \text{O} \\
\text{OMe} \quad \text{O}
\]

A 5 mL round bottom flask charged with 230a (500 mg, 4.7 mmol), 231a (634 µL, 7.05 mmol), PEG (1 mL) and a stirring bar was placed under an atmosphere of Ar. Subsequently DABCO (115.1 mg, 0.94 mmol) was added and the resulting solution was left to stir at room temperature for 24 h. The solution was then washed with Et$_2$O (2 x 5 mL). The organic layer was separated, dried (MgSO$_4$) and the solvent removed *in vacuo*. Purification by column chromatography (CH$_2$Cl$_2$, R$_f$ = 0.2), gave 232a (614.3 mg, 68%) as a colourless oil.$^{212}$

$^1$H NMR of 231a:

$\delta$ (400 MHz, CDCl$_3$): 3.75 (s, 3H, OCH$_3$), 5.59 (s, 1H, H-3), 5.86 (s, 1H, H-2), 6.37 (s, 1H, H-1), 7.31-7.40 (m, 5H, Ar-H).
5.3.3.1.2 Synthesis of 2-(hydroxyl-phenyl-methyl)-acrylonitrile (232b)

Procedure R was followed using $230b$ (500 mg, 4.7 mmol), $231b$ (309 µL, 7.05 mmol), PEG (av. Mw. 200) (1 mL) and DABCO (115.1 mg, 0.94 mmol). Purification by column chromatography ($\text{CH}_2\text{Cl}_2$, $R_f = 0.2$), gave $232b$ (523.7 mg, 70%) as a colourless oil.$^{212}$

$^1\text{H NMR of } 232b$: 

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$):  2.31 (s, 1H, OH), 5.35 (s, 1H, H-3), 6.08 (s, 1H, H-2), 6.16 (s, 1H, H-1), 7.43 (m, 5H, Ar-H).

5.3.3.1.3 Synthesis of 2-[hydroxyl-(2-methoxy-phenyl)-methyl]-acrylic acid methyl ester (232c)

Procedure R was followed using $230c$ (500 mg, 3.67 mmol), $231c$ (454 µL, 5.51 mmol), PEG (1 mL) and DABCO (82.4 mg, 0.73 mmol). Purification by column chromatography ($\text{CH}_2\text{Cl}_2$, $R_f = 0.1$), gave $232c$ (481.2 mg, 59%) as a colourless oil.$^{142}$

$^1\text{H NMR of } 232c$: 

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$):  3.77 (s, 3H, OCH$_3$'), 3.85 (s, 3H, OCH$_3$), 5.74 (s, 1H, H-3), 5.89 (s, 1H, H-2), 6.33 (s, 1H, H-1), 6.90 (d, 1H, J 8.0, H-1'), 6.99 (app. t, 1H, J 8.0, H-3'), 7.29 (app. t, J 8.0, H-2'), 7.37 (d, 1H, J 8.0, H-4').
5.3.3.1.4 Synthesis of 2-[hydroxyl-(2-methoxy-phenyl-)methyl]-acrylonitrile (232d)

Procedure R was followed using 230d (500 mg, 3.67 mmol), 231d (363 µL, 5.51 mmol), PEG (1 mL) and DABCO (82.4 mg, 0.73 mmol). Purification by column chromatography (CH$_2$Cl$_2$, $R_f = 0.1$), gave 232d (694.4 mg, 63%) as a colourless oil.$^{213}$

$^1$H NMR of 231d:

$\delta_H$ (400 MHz, CDCl$_3$): 3.89 (s, 3H, OCH$_3$), 5.52 (s, 1H, H-3), 6.05 (s, 2H, H-1, H-2), 6.95 (d, 1H, J 8.0, H-1′), 7.04 (app. t, 1H, J 7.5, H-3′), 7.37 (m, 2H, H-2′, H-4′).

5.3.3.2 Procedure S: General procedure for the KR of BH adducts

A 1 mL reaction vessel charged with catalyst (2.34 µmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of alcohol (0.234 mmol) and NEt$_3$ (26 µL, 0.187 mmol) in CH$_2$Cl$_2$ (500 µL). The resulting solution was cooled to -78 °C and left to stir for 30 minutes. Iso-butyric anhydride (27 µL, 0.164 mmol) was subsequently added via syringe. The reaction was quenched after 8 - 24 h by the addition of MeOH (200 µL). Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.

5.3.3.2.1 2-(Iso-butyryloxy-phenyl-methyl)-acrylic acid methyl ester (232a)
Procedure S was followed using 221 (1.6 mg, 2.34 μmol) and 232a (45 mg, 0.234 mmol), at -78 °C. The alcohol, its ester and the catalyst were separated and isolated by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel to give 233a (40.8 mg, 66%) as a colourless oil. [α]D²⁰ = -33 (c 0.16, CHCl₃) and 232a (12.2 mg, 29%)

¹H NMR of 233a

δH (400 MHz, CDCl₃): 1.17-1.22 (m, 6H, CH₃), 2.63 (app. hept, 1H, J 7.0, H-4), 3.74 (s, 3H, OCH₃), 5.86 (s, 1H, H-2), 6.41 (s, 1H, H-1), 6.69 (s, 1H, H-3), 7.30-7.42 (m, 5H, Ar-H).

¹³C NMR of 233a:

δC (100 MHz, CDCl₃): 18.6, 18.8, 33.9, 51.8, 72.6, 125.6, 127.4, 128.1, 128.3, 137.9 (q), 139.9 (q), 165.4 (C=O), 175.2 (C=O).

νmax (film)/cm⁻¹: 2975, 1729, 1495, 1249, 1140.

HRMS (m/z - ES): Found 285.1115 (M⁺ + Na, C₁₃H₁₈O₄Na Requires: 285.1103)

HPLC Data for recovered ester 233a:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 6.0 min (S) minor and 6.7 min (R) major.

HPLC Data for recovered alcohol 232a:

Chiralcel AS-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 7.8 min (R) minor and 14.9 min (S) major.

Absolute configuration of the major isomer determined by comparision of optical rotation²¹⁴ and CSP-HPLC data with that in the literature.²¹⁵
Procedure S was followed using 221 (1.6 mg, 2.34 μmol) and 232b (37.3 mg, 0.234 mmol), at -78 °C. The alcohol, its ester and the catalyst were separated and isolated by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel to give 233b (24.8 mg, 46%) as a colourless oil. [α]₂⁰ = -14.2 (c 0.29, CHCl₃) and 232b (16.9 mg, 45%)

¹H NMR of 233b

δH (400 MHz, CDCl₃): 1.22-1.28 (m, 6H, CH₃), 2.71 (app. hept, 1H, J 7.0, H-4), 6.01 (s, 1H, H-2), 6.10 (s, 1H, H-1), 6.35 (s, 1H, H-3), 7.30-7.42 (m, 5H, Ar-H).

¹³C NMR of 233b:

δC (100 MHz, CDCl₃): 18.3, 18.4, 33.5, 73.6, 115.7 (q), 123.0 (q), 126.4, 128.5, 128.7, 131.5, 135.3 (q), 174.9 (C=O).

νmax (film)/cm⁻¹: 2976, 2228, 1739, 1496, 1243.

HRMS (m/z - ES): Found 252.1009 (M⁺ + Na. C₁₄H₁₅NO₂Na Requires: 252.1000)

HPLC Data for recovered ester 233b:

HPLC Data for recovered alcohol 232b:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 13.2 min (minor) and 14.0 min (major).

5.3.3.2.3 2-[Iso-butyroyloxy-(2-methoxy-phenyl)-methyl]-acrylic acid methyl ester (233c)

Procedure S was followed using 221 (1.6 mg, 2.34 μmol) and 232c (52 mg, 0.234 mmol), at -78 °C. The alcohol, its ester and the catalyst were separated and isolated by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel to give 233c (34.9 mg, 51%) as a colourless oil. [α]D²⁰ = -62 (c 0.1, CHCl₃) and 232c (20.9 mg, 40%)

¹H NMR of 233c

δH (400 MHz, CDCl₃): 1.18-1.22 (m, 6H, CH₃), 2.63 (app. hept, 1H, J 7.0, H-4), 3.76 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 5.61 (s, 1H, H-2), 6.41 (s, 1H, H-1), 6.90 (d, 1H, J 8.0, H-1’), 6.96 (app. dd, 1H, J 7.5, H-3’), 7.05 (s, 1H, H-3), 7.27-7.34 (m, 2H, H-2’, H-4’).

¹³C NMR of 232b:

δC (100 MHz, CDCl₃): 18.4, 18.5, 33.6, 51.5, 56.0, 67.2, 110.3, 119.9, 125.7(q), 126.8, 127.1, 129.0, 138.8 (q), 156.5 (q), 165.4 (C=O), 175.0 (C=O).

νmax (film)/cm⁻¹: 2973, 2840, 1725, 1492, 1246.

HRMS (m/z - ES): Found 315.1216 (M⁺ + Na. C₁₅H₂₀O₅Na Requires: 315.1208)
HPLC Data for recovered ester 233c:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 98/2, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 8.5 min (S) minor and 22.3 min (R) major.

HPLC Data for recovered alcohol 232c:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 98/2, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 34.8 min (S) major and 45.0 min (R) minor. Absolute configuration is tentatively assigned based on a comparison of CSP-HPLC retention times and optical rotation data with that of (S)-232a.

5.3.3.2.4 2-[(S)-3-butyryloxy-(2-methoxy-phenyl)-methyl]-acrylonitrile (233d)

Procedure S was followed using 221 (1.6 mg, 2.34 µmol) and 232d (44.3 mg, 0.234 mmol), at -78 °C. The alcohol, its ester and the catalyst were separated and isolated by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel to give 233d (41.3 mg, 68%) as a colourless oil. [α]D²⁰ = -11.9 (c 0.26, CHCl₃) and 232d (7.5 mg, 17%)

¹H NMR of 233d

δH (400 MHz, CDCl₃): 1.23-1.28 (m, 6H, CH₃), 2.71 (app. hept, 1H, J 7.0, H-4), 3.87 (s, 3H, OCH₃), 6.00 (s, 1H, H-2), 6.03 (s, 1H, H-1), 6.73 (s, 1H, H-3), 6.92 (d, 1H, J 8.0, H-1'), 7.04 (app. dd, 1H, J 8.0, H-3'), 7.35 (app dd, 1H, J 8.0, H-2'), 7.48 (d, 1H, J 8.0, H-4').
$^{13}$C NMR of 233d:

$\delta$C (100 MHz, CDCl$_3$): 18.4, 18.5, 33.6, 55.0, 68.2, 110.2, 115.9 (q), 120.5, 122.2 (q), 123.9 (q), 126.4, 129.7, 131.5, 155.8 (q), 174.9 (C=O).

$v_{\text{max}}$ (film)/cm$^{-1}$: 2975, 2841, 2228, 1740, 1492, 1247, 1142.

HRMS (m/z - ES): Found 282.1118 (M$^+$ + Na). C$_{13}$H$_{17}$NO$_3$Na Requires: 282.1106

HPLC Data for recovered ester 233d:


HPLC Data for recovered alcohol 232d:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min$^{-1}$, RT, UV detection at 220 nm, retention times: 11.3 min ($R$) major and 12.6 min ($S$) minor.

Note that due to a priority change, the label of the stereogenic centre changes in 232d from (S) to (R) $[\alpha]_D^{20} = +31.8$ (c 0.08, CHCl$_3$). Absolute configuration of the major isomer determined by comparison of optical rotation data with that in the literature.$^{216}$

5.3.3.3 Synthesis of 2-(furan-2-yl-hydroxy-methyl)-acrylic acid methyl ester (236a)

![Structure of 236a](image-url)

Procedure R was followed using 234a (500 mg, 5.20 mmol), 235a (703 $\mu$L, 7.81 mmol), PEG (1 mL) and DABCO (116.7 mg, 1.04 mmol). Purification by column chromatography (CH$_2$Cl$_2$, $R_f = 0.1$), gave 236a (530 mg, 56%) as a colourless oil.
$^1$H NMR of 236a

$\delta$H (400 MHz, CDCl$_3$): 3.05 (bs, 1H, OH), 3.79 (s, 3H, OCH$_3$), 5.61 (s, 1H, H-3), 5.97 (s, 1H, H-2), 6.29 (d, 1H, J 3.5, H-1'), 6.36 (m, 1H, H-2'), 6.42 (s, 1H, H-1), 7.40 (m, 1H, H-3').

5.3.3.3.1 Synthesis of 2-(furan-2-yl-hydroxy-methyl)-acrylonitrile (236b)

![Structure of 236b]

Procedure R was followed using 234b (500 mg, 5.20 mmol), 235b (514 μL, 7.81 mmol), PEG (1 mL) and DABCO (116.7 mg, 1.04 mmol). Purification by column chromatography (CH$_2$Cl$_2$, R$_f$ = 0.2), gave 236b (489 mg, 63%) as a colourless oil.

$^1$H NMR of 236b

$\delta$H (400 MHz, CDCl$_3$): 5.39 (s, 1H, H-3), 6.17 (s, 1H, H-2), 6.22 (d, 1H, J 3.5, H-1'), 6.42 (m, 1H, H-2'), 6.47 (s, 1H, H-1), 7.47 (d, 1H, J 5.5, H-3').

5.3.3.3.2 Synthesis of 2-(hydroxyl-phenyl-methyl)-acrylamide (236c)

![Structure of 236c]

Procedure R was followed using 234c (500 mg, 4.71 mmol), 235c (502 mg, 7.06 mmol), PEG (1 mL) and DABCO (115.1 mg, 0.94 mmol). Purification by column chromatography (CH$_2$Cl$_2$, R$_f$ = 0.1), gave 236c (376 mg, 45%) as a white solid. M.p. 98-100 °C (lit. 217 97-99 °C).
\textsuperscript{1}H NMR of 236c

$\delta_H$ (400 MHz, DMSO-$d_6$): 5.49 (d, 1H, J 4.5, H-2), 5.60 (s, 1H, H-3), 5.69 (d, 1H, J 4.5, H-1), 5.79 (s, 1H, OH), 6.98 (s, 1H, NH), 7.22-7.30 (m, 5H, Ar-H), 7.47 (s, 1H, NH).

5.3.3.3.3 Synthesis of 2-[hydroxyl-(2-methoxyphenyl)methyl]acrylamide (236d)

\begin{center}
\begin{tikzpicture}
\draw[thick] (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\draw[thick] (0.5,0.5) -- (0.5,1) -- (0,1) -- cycle;
\end{tikzpicture}
\end{center}

Procedure R was followed using 234d (500 mg, 3.67 mmol), 235d (167 mg, 5.51 mmol), PEG (1 mL) and DABCO (89.7 mg, 0.73 mmol). Purification by column chromatography (CH$_2$Cl$_2$, $R_f = 0.1$), gave 236d (273.8 mg, 36%) as a white solid. M.p. 164-166 °C (lit.\textsuperscript{217} 164-166 °C).

\textsuperscript{1}H NMR of 236c

$\delta_H$ (400 MHz, DMSO-$d_6$): 3.75 (s, 3H, OCH$_3$), 5.30 (s, 1H, H-2), 5.38 (s, 1H, H-1), 5.75 (s, 1H, H-3), 5.78 (s, 1H, OH), 6.93 (m, 3H, H-1', H-3', NH), 7.21 (m, 2H, H-2', H-4'), 7.45 (s, 1H, NH).

5.3.3.4 2-(Furan-2-yl-iso-butyryloxy-methyl)-acrylic acid methyl ester (237a)

\begin{center}
\begin{tikzpicture}
\draw[thick] (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\draw[thick] (0.5,0.5) -- (0.5,1) -- (0,1) -- cycle;
\end{tikzpicture}
\end{center}

Procedure S was followed using 169 (1.0 mg, 2.34 \textmu mol) and 236a (42.6 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH$_2$Cl$_2$) through a pad of silica gel.
\(^1\text{H NMR of 237a}\)

\[\delta^H (400 \text{ MHz, CDCl}_3): 1.18 (d, 3H, J 7.0, \text{CH}_3), 1.20 (d, 3H, J 7.0, \text{CH}_3), 2.55 \text{ (app. hept, } 1\text{H, CH(CH}_3\text{)_2}), 3.77 \text{ (s, 3H, OCH}_3\text{), 6.00 \text{ (s, 1H, H-2), 6.36 \text{ (m, 2H, H-1', H-2')}, 6.49 \text{ (s, 1H, H-3), 6.76 \text{ (s, 1H, H-1), 7.41 \text{ (d, 1H, J 5.5, H-3')}\}.}]

HPLC Data for recovered ester 237a:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min\(^{-1}\), RT, UV detection at 220 nm, retention times: 18.1 min (minor) and 21.2 min (major).

HPLC Data for recovered alcohol 236a:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min\(^{-1}\), RT, UV detection at 220 nm, retention times: 10.6 min (major) and 11.8 min (minor).

5.3.3.4.1. \textit{Iso}-butyric acid 2-cyano-1-furan-2-yl-allyl ester (237b)

![Chemical Structure](image)

Procedure S was followed using 169 (1.0 mg, 2.34 \mu mol) and 236b (34.9 mg, 0.234 mmol) at -78 \degree C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH\(_2\)Cl\(_2\)) through a pad of silica gel.

\(^1\text{H NMR of 237b}\)

\[\delta^H (400 \text{ MHz, CDCl}_3): 1.19 (d, 3H, J 7.0, \text{CH}_3), 1.21 (d, 3H, J 7.0, \text{CH}_3), 2.52 \text{ (app. hept, } 1\text{H, CH(CH}_3\text{)_2}), 6.10 \text{ (s, 1H, H-2), 6.18 \text{ (d, 1H, J 3.5, H-1')}, 6.42 \text{ (m, 2H, H-2', H-3), 6.52 \text{ (s, 1H, H-1), 7.47 \text{ (m, 1H, H-3')}\}.}]}
HPLC Data for recovered ester 237b:


HPLC Data for recovered alcohol 236b:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 95/5, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 24.0 min (major) and 27.5 min (minor).

5.3.3.4.2  *Iso*-butyric acid 2-carbamoyl-1-phenyl-allyl ester (237c)

![Chemical structure of 237c](image)

Procedure S was followed using 221 (1.6 mg, 2.34 µmol) and 236c (41.5 mg, 0.234 mmol) at -78 °C. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel.

¹H NMR of 237c

δH(400 MHz, CDCl₃): 1.19 (d, 3H, CH₃), 1.21 (d, 3H, CH₃), 2.55 (app. hept, 1H, CH(CH₃)₂), 5.67 (s, 1H, H-2), 6.13 (s, 1H, H-1), 6.71 (s, 1H, H-3), 7.32-7.39 (m, 5H, Ar-H).

HPLC Data for recovered ester 237c:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 10.1 min (major) and 11.7 min (minor).
HPLC Data for recovered alcohol 236c:

Chiralcel OD-H (4.6 x 250 mm), hexane/iPrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 12.9 min (minor) and 16.0 min (major).

5.3.4 Experimental data for Section 3.5

5.3.4.1 One pot synthesis and resolution of 232a

A 1 mL reaction vessel charged with 221 (12.7 mg, 18.2 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added 230a (370 μL, 0.364 mmol), DBU (380 μL, 0.255 mmol) and 231a (985 μL, 1.09 mmol) via syringe and the resulting homogeneous solution stirred at room temperature for 24 h. CH₂Cl₂ (500 μL) was then added via syringe and the solution was cooled to -78 °C and left to stir for 30 minutes. Iso-butyric anhydride (91 μL, 0.546 mmol) was subsequently added via syringe. After 24 h at -78 °C the reaction was quenched by the addition of MeOH (200 μL) and allowed to warm to ambient temperature. Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel. The selectivity of the kinetic resolution \( s = 4.3 \) was then established by CSP-HPLC. The alcohol was then isolated by column chromatography (CH₂Cl₂) to give \((S)-232a\) (17.6 mg, 25%, 75% ee) as a colorless oil. \([\alpha]_D^{20} = +47.3\) (c 0.1, CHCl₃).

5.3.4.2 One pot synthesis and resolution of 232c

A 1 mL reaction vessel charged with 221 (4.3 mg, 6.14 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added 230c (50 mg, 0.368 mmol), DBU (18 μL, 0.123 mmol) and 231c (11 μL, 0.123 mmol) via syringe and the resulting homogeneous solution stirred at room temperature for 96 h. CH₂Cl₂ (500 μL) was then added via syringe and the solution was cooled to -78 °C and left to stir for 30 minutes. Iso-butyric anhydride (16 μL, 0.98 mmol) was subsequently added via syringe. After 24 h at -78 °C the reaction was quenched by the addition of MeOH (200 μL) and allowed to warm to ambient temperature. Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH₂Cl₂) through a pad of silica gel. The selectivity of the kinetic resolution \( s = 7.6 \) was then
established by CSP-HPLC. The alcohol was then isolated by column chromatography (CH$_2$Cl$_2$) to give (S)-232c (6.9 mg, 25%, 89% ee) as a colorless oil [$\alpha$]$_D^{20}$ = +83 (c 0.1, CHCl$_3$). Absolute configuration is tentatively assigned based on a comparison of CSP-HPLC retention times and optical rotation data with that of (S)-232a.

5.4.1 Experimental data for Section 4.1

5.4.1.1 Nanoparticle synthesis and subsequent silica coating

Stock solutions of 25 mL of each of 1 M FeCl$_3$.6H$_2$O (6.56 g, 0.024 mol), 0.5 M FeCl$_2$.4H$_2$O (2.48 g, 0.012 mol), and 0.4 M HCl were made up with Millipore water. NaOH solution (0.5 M, 250 mL) was heated to 80°C and the iron solution was added dropwise. After 1 h of stirring with heat, the black magnetic nanoparticles were washed with Millipore water (5 x 20 mL) until neutral. A sample of the nanoparticles (1 g) was dispersed in tetramethylammonium hydroxide (30 mL) and made up to 570 mL with Millipore water. 0.58% activated sodium silicate (430 mL) was added to the nanoparticle suspension. The sodium silicate was activated by passing through a regenerated cation exchange resin. After 2 h stirring, the magnetic fluid was transferred into dialysis tubing and dialysed against Millipore water, brought to pH 10 by the addition of tetramethylammonium hydroxide. The dialysis tubing was prepared by boiling tubing of the required length in 2% (w/v) sodium bicarbonate (100 mL) and 1mM EDTA (100 mL) at pH 8.0 for 10 min. The tubing was rinsed with Millipore water then boiled for 10 min in 1mM EDTA followed by Millipore water rinsing. After 24 h dialysis, the solution was brought to pH 8.0 by the addition of dilute HCl. The particles (98 % yield) were washed and finally dried under vacuum.
5.4.1.2 Synthesis of 249

4-(Methylamino)pyridine (250) (500 mg, 4.62 mmol) was dissolved in dry THF (10mL). This solution was added dropwise at 0°C under Ar to a suspension of sodium hydride (177 mg, 7.39 mmol) in THF (5 mL). The resulting suspension was stirred for 2 h. 3-Chloropropyltriethoxysilane (1.11 mL, 4.62 mmol) in 1 mL THF was added dropwise to the suspension at 0°C. The reaction mixture was heated to 70°C for 8 h and a colour change from pale yellow to brown was noted. Purification by flash chromatography (CHCl₃-NEt₃, 95:5, distilled) gave 249 as colourless oil (42%). Note: 249 is susceptible to hydrolysis, we found it best to prepare this compound for immediate use.

'H NMR of 249

δ_H (400 MHz, CDCl₃): 0.63 (t, 2H, J 8.0, H-3), 1.25 (t, 9H, J 7.0, CH₃), 1.71 (m, 2H, J 7.0, H-2), 3.01 (s, 3H, CH₃), 3.37 (m, 2H, H-1), 3.84 (q, 6H, J 7.0, CH₂), 6.55 (d, 2H, J 5.0, H-2'), 8.20 (d, 2H, J 5.0, H-1').

5.4.1.3 Procedure T: General procedure for catalyst loading

A 5 mL reaction vial charged with magnetite nanoparticles (100 mg) was placed under an atmosphere of Ar (balloon). To this was added a solution of 249 (1 equiv.) and (E)-stilbene (1 equiv.) in THF (2 mL) via syringe. A sample of this solution was taken for 'H NMR spectral analysis (t = 0). The resulting mixture was heated to 50°C for 24 h under mechanical agitation. The vessel was then placed in the vicinity of an external magnet and the reaction solution was decanted (a sample was again removed for 'H NMR analysis (t = 24 h)). The remaining magnetite was washed repeatedly with THF and dried under vacuum. Catalyst loading was then determined by 'H NMR spectral analysis. A comparison of the integrals for the 'H resonances of the pyridine ring in 249 relative to the 'H resonances of the ethylene moiety in (E)-stilbene at t = 0 and t = 24 h revealed the extent of catalyst loading.
5.4.1.3.1 Synthesis of 248

![Diagram of 248]

Procedure T was followed using 249 (55 mg, 0.177 μmol) and (E)-stilbene (0.177 mmol) in THF.

Capping of any unreacted silanol moieties was subsequently carried out. The vessel containing the nanoparticles was placed under an atmosphere of Ar (balloon). To this was added a solution of N-propyltriethoxysilane (990 μL, 4.3 mmol) in toluene (2 mL) and heated at 50 °C for 2 h. The vessel was then placed in the vicinity of an external magnet, the reaction solution was decanted and the remaining magnetite washed repeatedly with THF and dried under vacuum.

5.4.2 Experimental data for Section 4.4

5.4.2.1 Evaluation of 248 as a recyclable catalyst for the acetylation of 9

A 5 mL round bottom flask charged with 248 (70 mg, 0.0164 mmol) was placed under an atmosphere of Ar (balloon). To this was added a solution of 9 (0.327 mmol) and NEt₃ (68 μL, 0.491 mmol) in CH₂Cl₂ (1.5 mL). The resulting suspension was shaken (mechanical agitation) for 5 min. Acetic anhydride (0.491 mmol) was subsequently added via syringe. After 16 h the reaction was quenched by the addition of MeOH (200 μL). The vessel was then placed in the vicinity of an external magnet, the reaction solution was decanted off. The remaining magnetite was washed repeatedly with THF and dried under vacuum. The combined organic extracts were concentrated in vacuo and the product isolated by flash chromatography (CH₂Cl₂).
5.4.2.2 Synthesis of 2-phenyl-4-methyloxazolone (256).

A round bottom flask charged with 2-benzoylamino-propionic acid (1.0g, 5.18 mmol), prepared according to literature precedent\textsuperscript{218} from alanine methyl ester hydrochloride, was placed under an atmosphere of Ar (balloon). To this was added acetic anhydride (3.1 mL, 32.8 mmol) and heated to 65 °C for 3 h. The resulting solution was then cooled to ambient temperature and concentrated (aspirator), with residual acetic acid/anhydride removed by addition of toluene followed by further concentration. The residue was purified by flash chromatography (Hex-CHCl\textsubscript{3}, 1:1, R\textsubscript{f} = 0.3) to give 2-phenyl-4-methyloxazolone as white solid (650 mg, 72%). M.p. 39.5-40.5 °C (lit.,\textsuperscript{219} 38-39 °C).

\textsuperscript{1}H NMR of 256

\[ \delta_{\text{H}} \text{(400 MHz, CDCl}_3\text{):} \] 1.45 (d, 3H, J 7.5, CH\textsubscript{3}), 4.70 (q, 1H, J 7.0, H-1), 7.56 (m, 2H, H-2'), 7.65 (m, 1H, H-3'), 7.93 (d, 2H, J 8.5, H-1').

5.4.2.3 Synthesis of 5-phenoxycarbonyl-methyl-2-phenyl-oxazole (255)

A 5 mL round bottom flask charged with 256 (600 mg, 3.43 mmol) was placed under an atmosphere of Ar (balloon). To this was added NEt\textsubscript{3} (524 μL, 3.77 mmol) in THF (3 mL) via syringe and the resulting solution was cooled to 0 °C. Phenyl chloroformate (452 μL, 3.60 mmol) was added causing a white precipitate to form. The mixture was allowed to stir overnight, then poured into H\textsubscript{2}O (5 mL) and extracted with Et\textsubscript{2}O (2 x 10 mL). The combined organic extracts were washed with 1M HCl (2 x 20 mL), sat. NaHCO\textsubscript{3} (2 x 20
mL), brine (2 x 20 mL) and dried over MgSO₄. The residue was purified by flash chromatography (Hex-DCM, 1:1, Rₜ = 0.2) to yield 255 as a white solid (915 mg, 90.3%).

\[ ^{1} \text{H NMR of 255} \]
\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 2.26 (s, 3H, CH₃), 7.30-7.35 (m, 3H, H-4', H-6'), 7.46-7.49 (m, 5H, H-2', H-3', H-5'), 8.04 (m, 2H, H-1'). \]

\[ ^{13} \text{C NMR of 255} \]
\[ \delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 10.2, 120.4, 120.8, 125.8, 126.7, 126.9, 128.6, 129.6, 130.3, 145.7, 149.9, 150.6, 154.9. \]

\[ \nu_{\text{max}} (\text{film})/\text{cm}^{-1}: \]
\[ 1784, 1495, 1222 \]

HRMS (m/z - ES): Found 296.0912 (M⁺ + H, C₁₇H₁₄NO₄Na Requires: 296.0912)

5.4.2.4 Synthesis of 1-[1,3]dioxolan-2-yl-propan-2-one (257)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & 
\end{align*}
\]

A 5 mL round bottom flask charged with 248 (82 mg, 0.0164 mmol) was placed under an atmosphere of Ar (balloon). Ethylene glycol (454 µL, 3.6 M) was added via syringe and the reaction cooled to 0 °C. 252 (127 µL, 1.64 mmol) was subsequently added and the reaction raised to rt. After 16 h crude product was separated from 248 by placing the reaction vessel in the vicinity of an external magnet, the reaction solution was decanted off. The remaining magnetite was washed repeatedly with THF and dried under vacuum. Purification by flash chromatography (CH₂Cl₂-EtOAc, 9:1) gave 57 as colourless oil. 257 Exhibited spectral characteristics consistent with those in the literature.\[220\]

\[ ^{1} \text{H NMR of 257} \]
\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 2.2.4 (s, 3H, CH₃), 2.83 (d, 2H, J 5.0, H-2), 3.76-4.03 (m, 4H, H-3, H-4), 5.25 (t, 1H, J 5.0, H-1). \]

209
5.4.2.4.1 Synthesis of acetic acid 4,5,6-triacetoxy-2-acetoxymethyl-tetrahydro-pyran-3-yl ester (258)

A 5 mL round bottom flask charged with 248 (82 mg, 0.0164 mmol) and D-glucose (29.5 mg, 0.164 mmol) was placed under an atmosphere of Ar. To this was added a solution of NEt₃ (204 µL, 1.47 mmol) in CH₂Cl₂ (0.5 mL). The resulting suspension was shaken (mechanical agitation) for 5 min. Acetic anhydride (108 µL, 1.14 mmol) was subsequently added via syringe. After 16 h crude product was separated from 248 by placing the reaction vessel in the vicinity of an external magnet, the reaction solution was decanted off. The remaining magnetite was washed repeatedly with THF and dried under vacuum. Purification by flash chromatography (CH₂Cl₂) gave 258 as white solid (α-/β-anomers 62.6:37.4). 258 Exhibited spectral characteristics consistent with those in the literature.*

¹H NMR of 258

δ_H (400 MHz, CDCl₃): 2.04, 2.05, 2.06, 2.07, 2.11, 2.12, 2.14, 2.21 (8s, 15H, CH₃), 4.10-4.16 (m, 2H, CH₂), 4.27-4.32 (m, 1H, H-4), 5.11-5.19 (m, 2H, H-2, H-3), 5.47-5.52 (m, 1H, H-5), 5.74 (d, 1H, H-1), 6.35 (d, 1H, J 3.6, α-anomer, H-1).

5.4.2.4.2 Synthesis of indole-1-carboxylic acid tert-butyl ester (259)

A 5 mL round bottom flask charged with 248 (82 mg, 0.0164 mmol) and 254 (19 mg, 0.164 mmol) was placed under an atmosphere of Ar (balloon). To this was added a solution of (BOC)₂O (71.4 mg, 0.327 mmol) in THF (0.5 mL). The resulting suspension was shaken (mechanical agitation). After 16 h crude product was separated from 248 by
placing the reaction vessel in the vicinity of an external magnet, the reaction solution was decanted off. The remaining magnetite was washed repeatedly with THF and dried under vacuum. Purification by flash chromatography (CH$_2$Cl$_2$) gave 259 as colourless oil. 259 Exhibited spectral characteristics consistent with those in the literature.$^{222}$

$^1$H NMR of 259

$\delta_h$ (400 MHz, CDCl$_3$): 1.69 (s, 9H, CH$_3$), 6.58 (d, 1H, J 4.0, H-2), 7.22-7.32 (m, 2H, H-5, H-6), 7.57-7.61 (m, 2H, H-1, H-7), 8.12-8.15 (m, 1H, H-4).

5.4.2.4.3 Synthesis of 228a

A 5 mL round bottom flask charged with 248 (82 mg, 0.0164 mmol) was placed under an atmosphere of Ar (balloon). To this was added a solution of 228 (0.327 mmol) and NEt$_3$ (68\,$\mu$L, 0.491 mol) in THF (0.5 mL). The resulting suspension was shaken (mechanical agitation) for 5 min. Iso-butyric anhydride (108\,$\mu$L, 0.654 mmol) was subsequently added via syringe. After 20 h the crude product was separated from 248 by placing the reaction vessel in the vicinity of an external magnet and the reaction solution was decanted off. The remaining magnetite was washed repeatedly with THF and dried under vacuum. Purification by flash chromatography (CH$_2$Cl$_2$) gave product as colourless oil. 228a Exhibited spectral characteristics consistent with those in the literature.$^{223}$

5.4.2.4.4 Synthesis of 4-methyl-5-oxo-2-phenyl-4,5-dihydro-oxazolo-4-carboxylic acid phenyl ester (260)
A 5 mL round bottom flask charged with 248 (16 mg, 0.00327 mmol) and 255 (96.5 mg, 0.327 mmol) was placed under an atmosphere of Ar (balloon). To this was added THF (0.5 mL) and the resulting suspension was shaken (mechanical agitation). After 15 h crude product was separated from 248 by placing the reaction vessel in the vicinity of an external magnet and the reaction solution was decanted off. The remaining magnetite was washed repeatedly with THF and dried under vacuum. Purification by flash chromatography (Hex-CH₂Cl₂, 1:1) gave 260 as a colourless oil.

¹H NMR of 260

δₜ (400 MHz, CDCl₃): 1.91 (s, 3H, CH₃), 7.13 (d, 2H, J 8.0, H-4'), 7.27 (m, 1H, H-6'), 7.40 (app. t, 2H, J 5.0, H-5'), 7.56 (app. t, 2H, J 8.0, H-2'), 7.66 (app. t, 1H, J 7.0, H-3'), 8.11 (d, 2H, J 8.0, H-1').

¹³C NMR of 260

δₗ (100 MHz, CDCl₃): 20.0, 72.5, 120.6, 124.7, 126.1, 127.9, 128.5, 129.1, 133.1 (q), 149.7 (q), 163.3 (q), 164.2, 174.4.

vₘₐₓ (film)cm⁻¹: 1769, 1648, 1492.

5.4.3 Experimental data for Section 4.5

5.4.3.1 Synthesis of non-silicon coated catalyst 261

Procedure T was followed using non-silicon coated nanoparticles (50 mg), 249 (20 mg, 0.064 mmol) and (E)-stilbene (11.5 mg, 0.064 mmol) in THF (2 mL).

Capping of any unreacted silanol moieties was subsequently carried out. The vessel containing the nanoparticles was placed under an atmosphere of Ar (balloon). To this was
added a solution of N-propyltriethoxysilane (990 µL, 4.3 mmol) in toluene (2 mL) and heated at 50 °C for 2 h. The vessel was then placed in the vicinity of an external magnet, the reaction solution was decanted and the remaining magnetite washed repeatedly with THF and dried under vacuum.

5.4.3.2 Testing the recyclability of 261 by the synthesis of 278

A 5 mL round bottom flask charged with 261 (50 mg, 0.0163 mmol) and 254 (19.1 mg, 0.164 mmol) was placed under an atmosphere of Ar (balloon). To this was added a solution of (BOC)₂O (71.4 mg, 0.326 mmol) in THF (0.5 mL) and (E)-stilbene (29.3 mg, 0.163 mmol) (to act as an internal standard). The resulting suspension was shaken (mechanical agitation). After 15 h the crude product was separated from 261 by placing the reaction vessel in the vicinity of an external magnet, the reaction solution was decanted off. The remaining magnetite was washed repeatedly with THF and dried under vacuum. Purification by flash chromatography (CH₂Cl₂) gave 259 as colourless oil. 259 Exhibited spectral characteristics consistent with those in the literature.²²²
References


Published Work


