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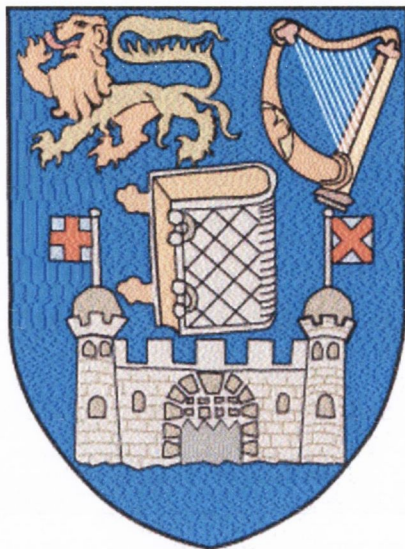
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Design and Synthesis of DMAP-derived Organocatalysts for Enantioselective Induction



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

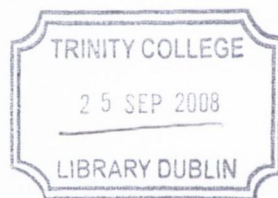
by

Ciarán Ó Dálaigh B. A. (Mod.)

Under the supervision of
Dr. Stephen Connon

July 2007

Trinity College Dublin



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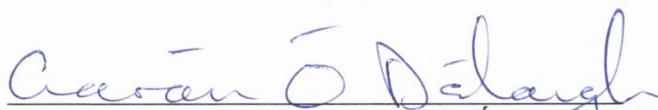
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Abstract

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*-dialkylaminopyridine acyl-transfer catalysts capable of exploiting both van der Waals (π) 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) π -pyridinium-ion interactions as playing a role in enantiodiscrimination for the (*S*)- α,α -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 1st 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	<i>tert</i> -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	<i>N,N'</i> -Dicyclohexylcarbodiimide
DIPAMP	Bis[(2-methoxyphenyl)phenylphosphino]ethane
DIPEA	<i>N,N'</i> -Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
E	Electrophile
EDCI	1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
EDTA	Ethylenediaminetetraacetic acid
<i>ee</i>	Enantioselective excess
Et	Ethyl
EWG	Electron withdrawing group
HATU	O-(7-azabenzotriazol-1-yl)- <i>N,N,N,N</i> -tetramethyluronium hexafluorophosphate
<i>het.</i>	heterocycle
IMD	Imidazole
IPA	<i>Iso</i> -propyl alcohol
IR	Infra red
k	Rate constant
<i>m</i>	Meta

<i>MCPBA</i>	<i>m</i> -Chloroperoxybenzoic acid
Me	Methyl
MVK	Methyl vinyl ketone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Np	Naphthyl
Nu	Nucleophile
<i>o</i>	Ortho
<i>p</i>	Para
PEG	Poly ethylene glycol
Ph	Phenyl
PMP	1,2,6-pentamethylpiperidine
PPY	Pyrrolidinated pyridine
<i>rac</i>	Racemic
RLS	Rate limiting step
RT	Room temperature
S	Selectivity factor
<i>sec</i>	Secondary
<i>t</i> -A. A	<i>tert</i> -Amyl alcohol
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBHP	<i>tert</i> -Butyl hydroperoxide
TBS	<i>tert</i> -Butylsilyl
TEM	Transmission electron microscopy
TES	Triethylsilyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TOCSY	Total Correlated Spectroscopy
Tol	Toluyll
TS	Transition state

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.¹ 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*)-Albuterol² is a β_2 -agonist used in the treatment of asthma, while (*S*)-Albuterol provokes airway constriction. Thus the synthesis of enantiopure 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.^{3,4,5}

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' epoxidation⁶ and

dihydroxylation⁷ catalysts and Noyori's hydrogenation⁸ 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, *etc.*).⁹

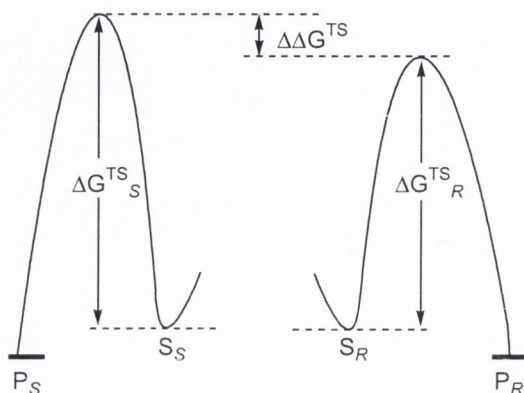
Pasteur's landmark discovery in 1848 *i.e.* the manual resolution of sodium ammonium tartrate crystals¹⁰ laid the foundations of stereochemistry. Today these observable phenomena are no longer merely elucidated but chemists are actively involved in the design and synthesis of truly synthetically useful 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 *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



$\Delta\Delta G^{\text{TS}}$ corresponds to the difference in activation energy between the transition states for the fast and slow [(R) and (S) respectively] reacting enantiomers [1.1].

$$\Delta\Delta G^{\text{TS}} = \Delta G^{\text{TS}}_R - \Delta G^{\text{TS}}_S \quad [1.1]$$

The magnitude of $\Delta\Delta G^{\text{TS}}$ 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].

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

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],

$$ee = \frac{([R] - [S])}{([R] + [S])} \times 100 \quad [1.3]$$

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)

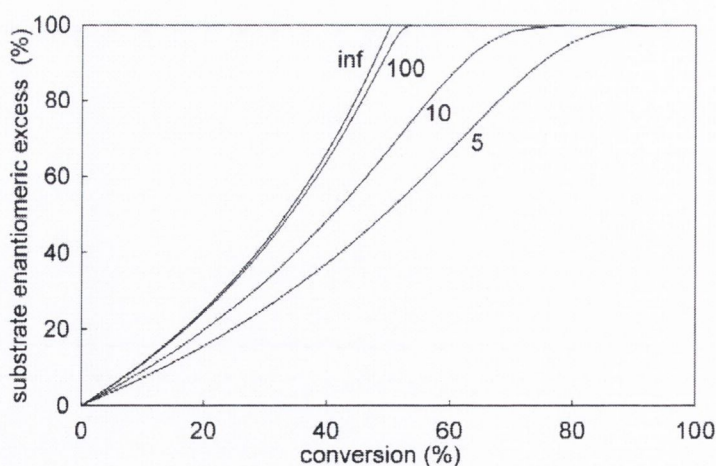
Thus the S value can be determined using the enantiomeric excess of the recovered substrate (ee) [1.4a] or the enantiomeric excess of the product (ee') [1.4b], achieved for a certain conversion, C i.e. $[ee/(ee + ee')]$.

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

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

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.

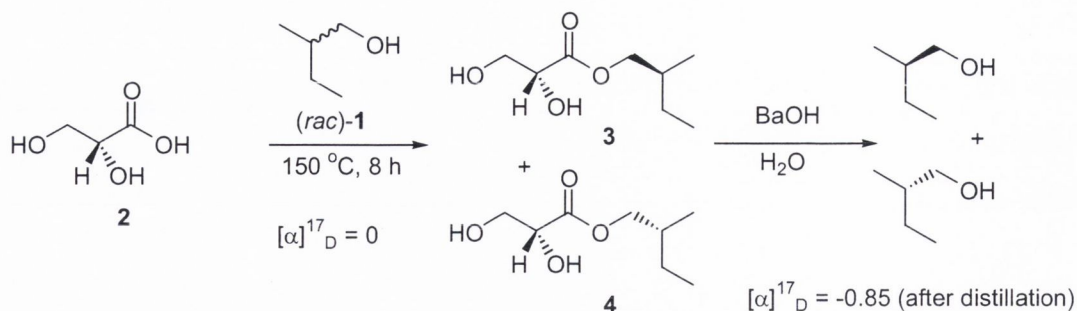
While it is assumed from equation [1.4a] that first-order kinetics are followed with regards to substrate, this is not always the case. In fact substrate kinetics can change over the course of a reaction,¹³ along with non-linear correlations between catalyst *ee* and product *ee*.¹⁴ Therefore k_{rel} 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.¹⁵ In this work he describes the selective reaction of (2*S*,3*S*)-tartaric acid, and the recovery of the previously unknown (2*R*,3*R*)-tartaric acid. This report represents the first enzymatic kinetic resolution performed in the laboratory. Further studies by Fischer¹⁶ 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.

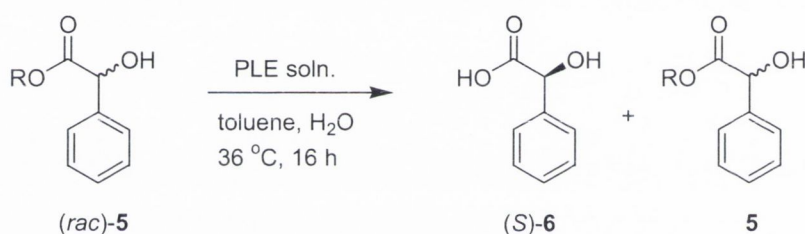
The first non-enzymatic and indeed catalytic kinetic resolutions were observed by Frankland and Price¹⁷ in 1897 with the acylation of racemic amyl alcohol **1** by (*R*)-glyceric acid (Scheme 1.1). (*S*)-**1** ($[\alpha]_{\text{D}}^{17} = -4.85$), was first racemised and subsequently an excess of **1** 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 McKenzie¹⁸ in 1899 and often cited¹⁹ as the first non-enzymatic kinetic resolution.

Scheme 1.1 Resolution of (*rac*)-amyl alcohol



Subsequently in 1903, Dakin published a pig liver esterase (PLE) catalysed hydrolysis of mandelic esters.²⁰ 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



R = Me, Et

Entry	R	Conv. (%)	$[\alpha]^{20}_{\text{D}}$	(<i>S</i>)-mandelic acid ^a (%)
1	Me	5.8	+39.9	25.5
2	Me	99.8	0	0
3	Et	5.2	+59.7	38.3
4	Et	93.6	+8.3	5.3

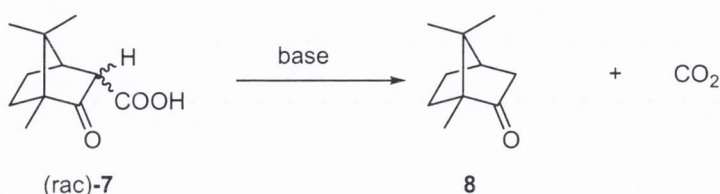
^a Determined as a percentage of pure dextro-mandelic acid

$[\alpha]^{20}_{\text{D}}$: +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 Bredig²¹ 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 work²² 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.

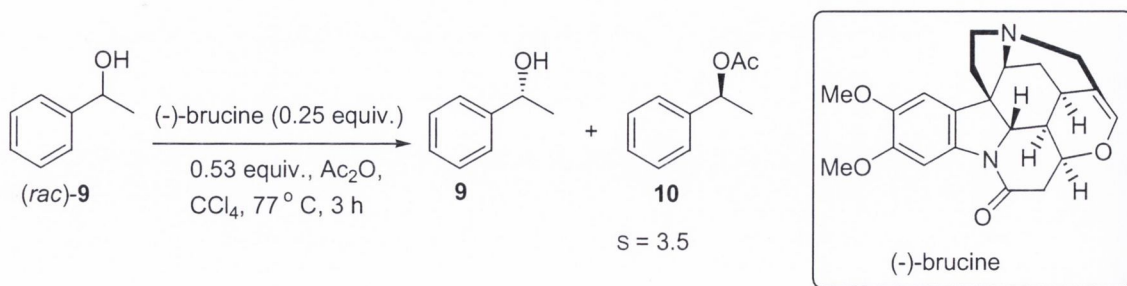


Entry	Base	$k_{(R)} : k_{(S)}^a$
1	nicotine	1.17 : 1
2	quinine	1 : 1.7
3	quinidine	1.7 : 1

^a $k_{(R)}$ and $k_{(S)}$ are the rate constants for the decarboxylation of the (*R*) and (*S*)-antipodes of the racemate respectively

Later in 1932, Wegler²³ 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



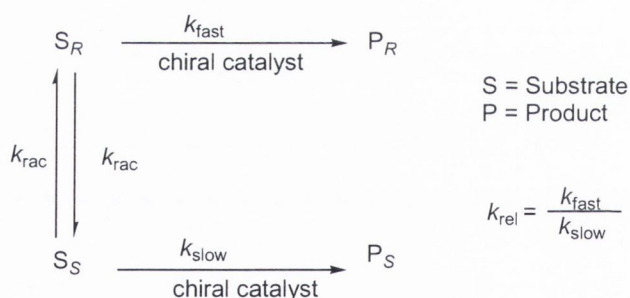
Although great strides had been made in a comparatively short period, the scientific community chose by enlarge to ignore these revelations for almost 60 years until the

advent of Sharpless' KR of racemic allylic alcohols²⁴ with a titanocene complex in 1981. Notably, organocatalysed resolution was not recognised for a further 15 years²⁵ 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)²⁶ 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_{rac} , is achieved more rapidly than k_{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.²⁷

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.

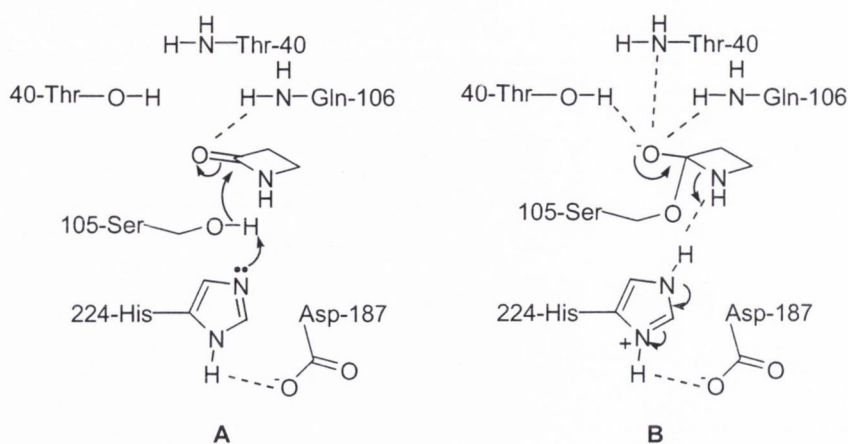
1.2.4.1 Enzyme mediated kinetic resolution

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 *Candida antarctica* is capable of catalysing the resolution of β -lactams²⁸ to afford enantiopure β -amino acids and unreacted β -lactam compounds. A wide array of β -lactams are medically 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.

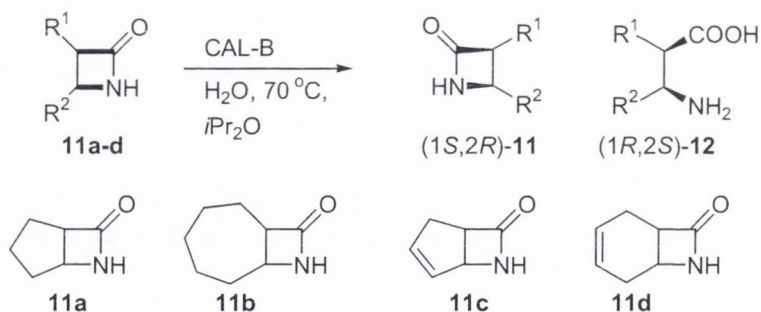
The mode of action of CAL-B has been intensively investigated, and has been found to involve the activation of Ser-105 by the Histidine-imidazole residue (His 224) with attendant H-bonding of the substrate to Gln-106 to activate the amide carbonyl towards nucleophilic attack (**A**) and to stabilise 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 selectivity²⁹ and conversion (entry 2, 3). Reaction has also been shown to proceed without the addition of water (thought to be present from enzyme preparation).³⁰

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

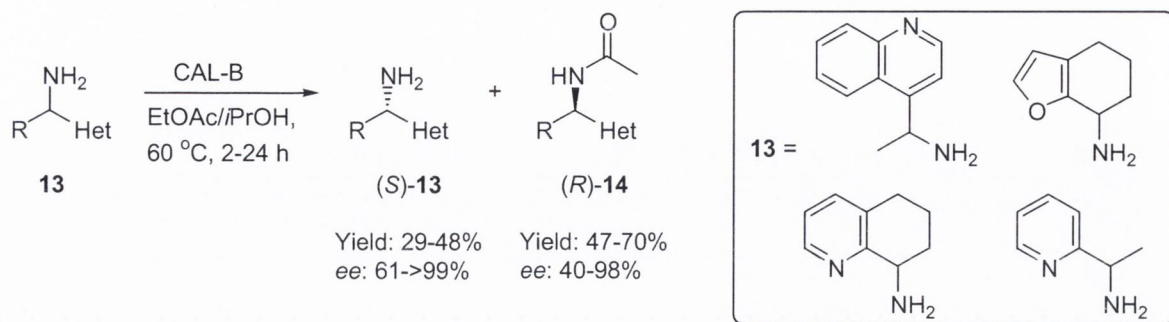


Entry	Substrate	H ₂ O (equiv.)	Time (h)	Conv. (%)	β-lactam (% <i>ee</i>)	β-amino acid (% <i>ee</i>)	S
1	11a	1	249	48	93	99	>200
2	11b	1	31	50	99	98	>200
3	11b	10	20	13	14	95	44
4	11c	1	5	51	99	96	>200
5	11d	1	7	51	99	99	>200

CAL-B has also been shown to effectively resolve 1-heteroaryl amines³¹ 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.³² 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



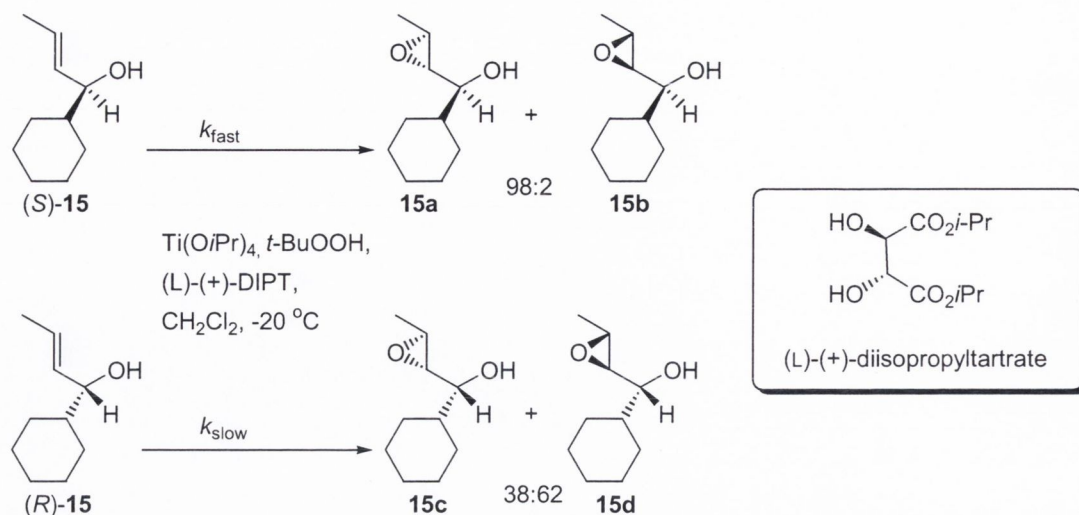
Adhering to Kazlauskas' rule,³³ (based on the steric difference of the R groups attached to the chiral centre) the lipase selects only for the (*R*)-enantiomer of **13**. The introduction of a saturated six-membered ring fusing the amine and the hetero-aryl moiety provided structural rigidity, leading 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 alcohols²⁴ 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 *et al.*²⁴ used the Ti(O*i*Pr)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).

Scheme 1.5 *Erythro-threo* ratio of enantiomers in the stereoselective epoxidation of **15**



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 $(+)\text{-diisopropyl tartrate}$ (DIPT) was used instead of $(+)\text{-dimethyl tartrate}$ (DMT)

Table 1.4 Selectivity of Sharpless kinetic resolution for allylic alcohols^a

Entry	Substrate	Time (h)	Config.	Alcohol (% <i>ee</i>)	k_{rel}	Epoxy alcohol product E/T ^b
1		288	<i>R</i>	>96	83	99/1
2		15	<i>R</i>	>96	104	97/3
3		15	<i>R</i>	>96	138	98/2

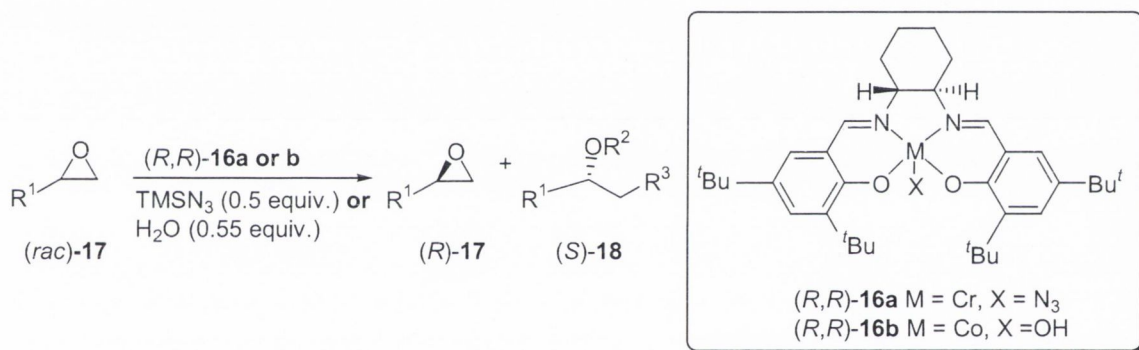
^a Conditions: 1 equiv. of $\text{Ti}(\text{O}i\text{Pr})_4$, 1.2 equiv. of DIPT and 1.0 eq. of alcohol in CH_2Cl_2 at $-20\text{ }^\circ\text{C}$, with subsequent addition of 0.6 equiv. of anhy. TBHP. The homogeneous reaction mixture was then left at $-20\text{ }^\circ\text{C}$ for the specified amount of time. ^b 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 experimentation³⁴ 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 TMSN_3 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 TMSN_3 ³⁵ (Table 1.5). Building on these results Jacobsen *et al.*³⁶ replaced the Cr^{III} with Co^{II} 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**



Entry	R ¹	R ²	R ³	Cat.	Yield (%)	Epoxide (%ee)
1	(CH ₂) ₃ CH ₃	MS	N ₃	16a	41	97
2	CH ₂ Cl	TMS	N ₃	16a	47	95
3	(CH ₂) ₂ CH=CH ₃	TMS	N ₃	16a	47	98
4	CH ₃	H	OH	16b	44	99
5	CH ₂ OTBS	H	OH	16b	47	>99
6	≡-TBS	H	OH	16b	41	>99
7	CH ₂ CO ₂ Et	H	OH	16b	43	>99

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 H₂O 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.

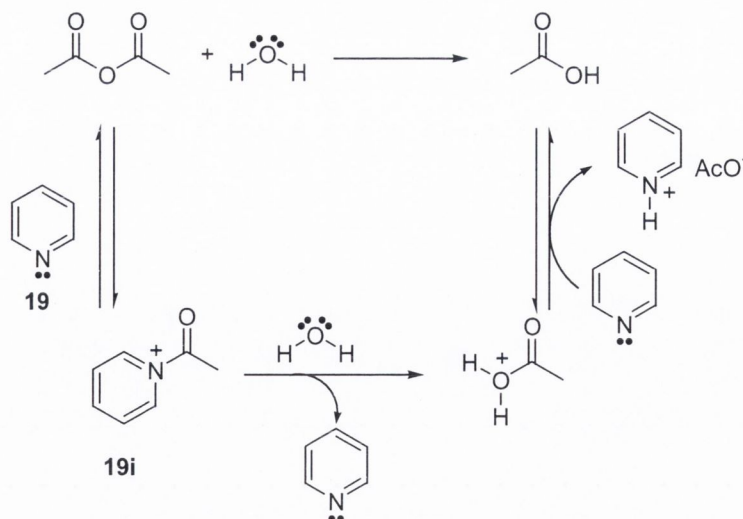
Enantiopure secondary alcohols are recognised by the synthetic community as a versatile class of substrate with their wide and varied applicability in the synthesis of natural products, chiral ligands and biologically active compounds. Enzymes (lipases and esterases) have traditionally been employed 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 amines⁴⁰/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 Hollandt⁴⁴ 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).

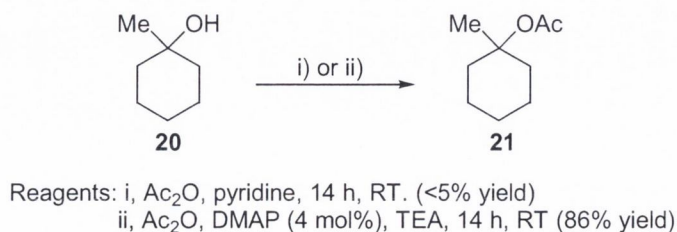
Scheme 1.6 Pyridine catalysed nucleophilic acyl transfer



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.⁴⁰

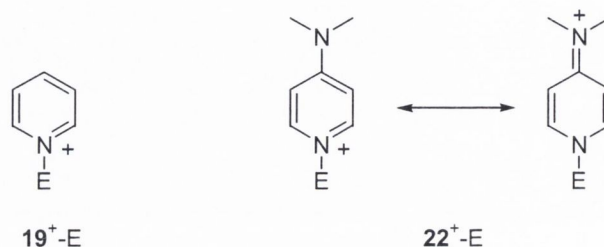
Scheme 1.7 Relative rates of reaction of **19** and DMAP



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).

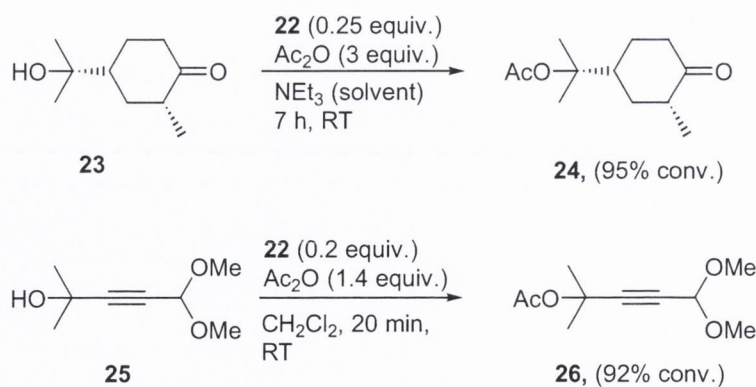
Figure 1.4 Stabilisation of pyridinium cation



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.

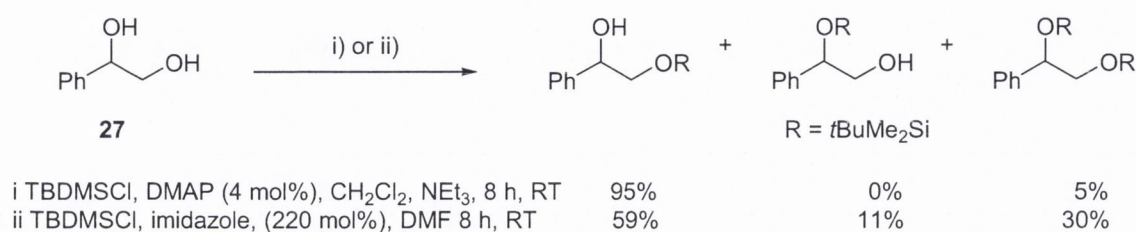
A diverse array of sterically hindered secondary and tertiary alcohols are acylated in the presence of catalytic amounts (0.05-0.25 equiv.) of **22**.⁴⁷ For example, using DMAP as a catalyst, **23** could be acylated without observable racemisation,⁴⁸ while **25** could be converted to **26** without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

Scheme 1.8 DMAP catalysed acylation of tertiary alcohols



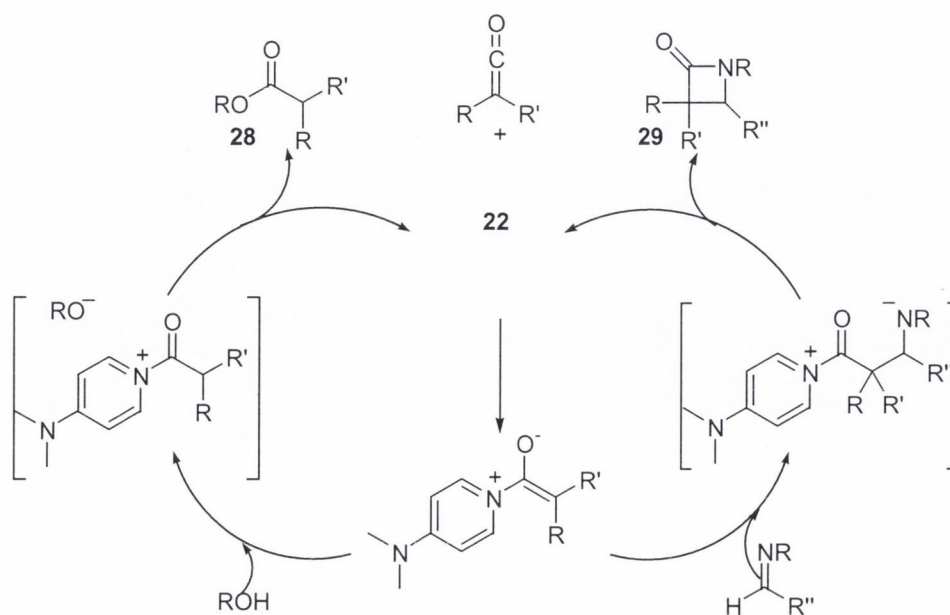
The regioselective silylation of a primary alcohol in the presence of a secondary alcohol is promoted by a catalytic amount of **22** (4 mol%); in contrast an imidazole-mediated alternative methodology afforded a mixture of products and required a greater than stoichiometric ‘catalyst’ loading (Scheme 1.9).⁴⁹

Scheme 1.9 Regioselective acylation of primary alcohols



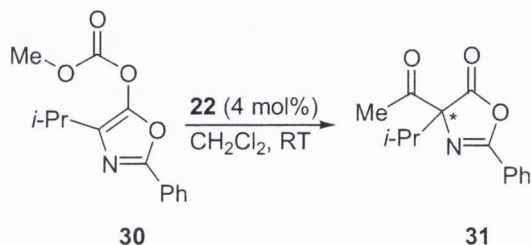
22 Is also capable of the catalysis of a wide range of other acyl-transfer processes. The alcoholysis of ketenes has been used to synthesise aryl propionic acids (precursors to a variety of pharmaceutically active substrates).⁵⁰ Reaction proceeds *via* a Zwitterionic intermediate formed by initial attack 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**.⁵¹ 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.⁵²

Scheme 1.10 Reactions of ketenes with imines and alcohols mediated by **22**



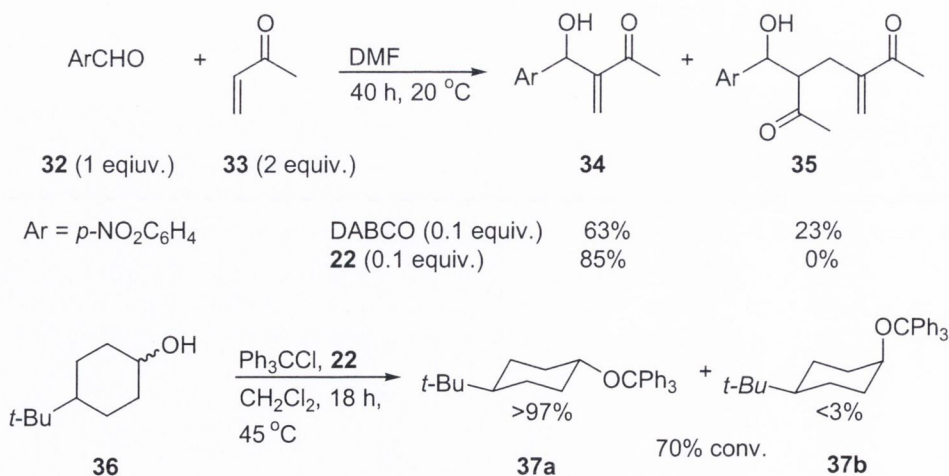
The rearrangement of *O*-acylated enolates such as **30** to form carbon-carbon bonds is of high synthetic utility, as a new quaternary centre is generated (Scheme 1.11).⁵³ Reaction with pyridine requires heating at 100 °C for six hours; however, rearrangement is complete in a matter of minutes at room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

Scheme 1.11 Rearrangement of *O*-acyloxyoxazole



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**).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).⁵⁶

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

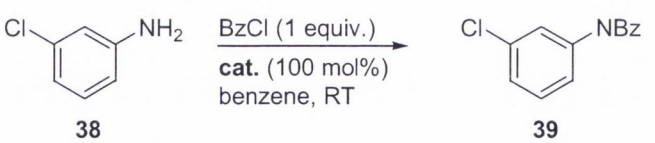


1.3.3 Substituted pyridine: Structure – activity relationship

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.⁵⁷ 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 benzylation of *m*-chloroaniline (entry 6). Recently, theoretical analysis by Zipse and Held⁵⁸ demonstrated that methyl substitution α to the active site led to a 22.0° distortion of the dihedral angle $\angle(O/C/N/C)$ out of the plane of the pyridine ring, that decreased the resonance stabilisation of the acylated intermediate by 16kJ/mol.

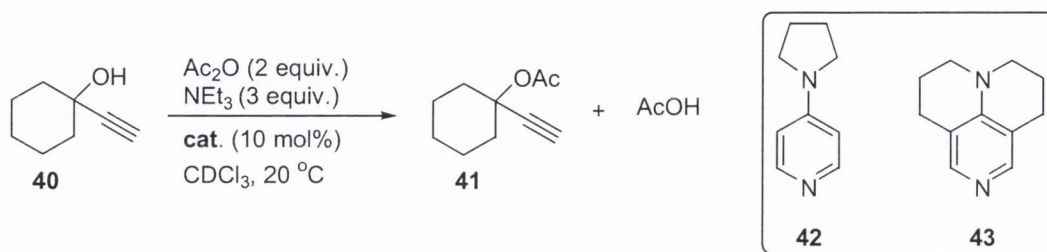
Table 1.6 Benzylation of *m*-chloroaniline promoted by substituted pyridines and NEt_3

			
Entry	Catalyst	pK_a^a	Rel. rate ^b
1	19	5.23	5.68
2	2-methylpyridine	5.96	29
3	4-methylpyridine	6.02	2.96×10^3
4	2,6-dimethylpyridine	6.72	8
5	22	9.70	3.14×10^6
6	NEt_3	10.65	21

^a Refers to $R_3N^+ -H$ at $25^\circ C$ in H_2O . ^b compared to reaction rate without added amine

Subsequent optimisation studies of the (4-dimethylamino)pyridine framework by Hassner *et al.*⁵⁹ found that 4-pyrrolidinopyridine **42** was the most effective analogue for catalysis of the acylation of 1-methylcyclohexanol. However, recently Steglich *et al.*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



Entry	Cat.	Rel. rate	$\delta(^1\text{H})$ $\beta\text{-H/ppm}$
1	22	1	6.48
2	42	2.4	6.38
3	43	6	-

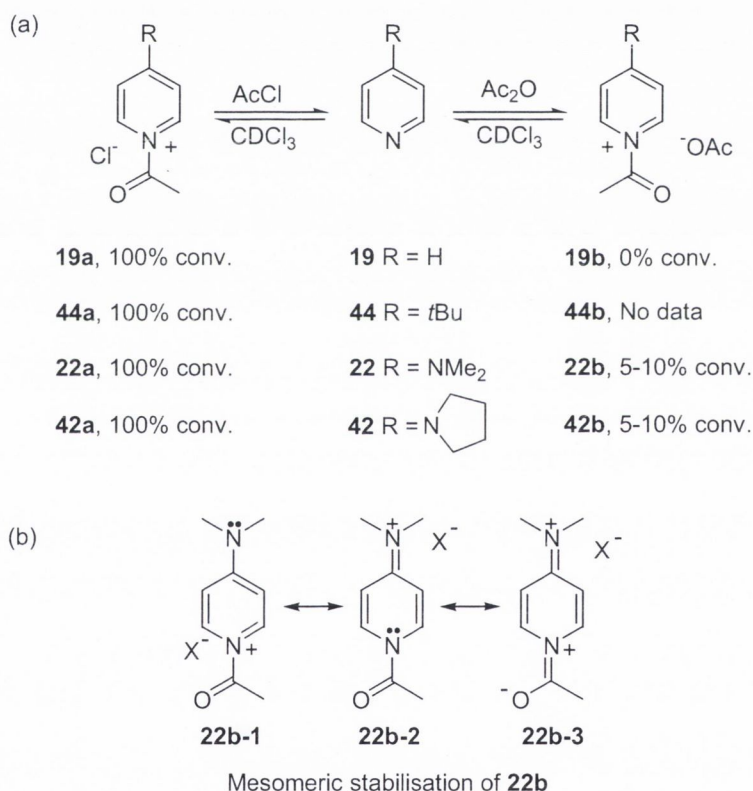
Hassner *et al.*⁵⁹ postulated that the catalytic activity of **22** and **42** could be correlated with the degree of shielding of the β -hydrogen (as demonstrated by ^1H NMR spectroscopic analysis: 6.48 and 6.38 ppm respectively), itself governed by the resonance stabilisation afforded to the acylated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

The mechanism of nucleophilic catalysis *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 auxillary 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_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**.



Evidence for the existence of the mesomeric effect can be found in the IR carbonyl stretching frequencies and ¹H 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, ^1H 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.

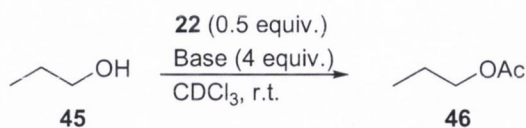
Table 1.8 Comparison of **22** and **44** as catalysts for the acetylation of **40** with both acetyl chloride and acetic anhydride.

$\text{40} + \text{CH}_3\text{COX} \xrightarrow[\text{CDCl}_3, 27^\circ\text{C}]{\text{Base (3 equiv.)}} \text{41}$ 2 equiv.				
Entry	Base	Conc. (mol%)	X	$t_{1/2}$ (min)
1	22	0.6	OCOCH ₃	7
2	22	0.6	Cl	20
3	44	0.6	Cl	60

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 Kattnig⁶¹ found that acylation of 1-propanol **45** in the presence of a heterogeneous base (K_2CO_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 ($\text{AcO}^- > \text{Cl}^-$) and is rate determining; a theory further supported by the observation of even faster acylation using acetyl cyanide (HCN , $\text{pK}_a = 9.4$), 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



Entry	Base	Acylating agent	pK _a ^a of anion	T _{1/2} (min)
1	K ₂ CO ₃	Ac ₂ O	4.75	3.2
2	K ₂ CO ₃	AcCl	-1.7	35
3	K ₂ CO ₃	AcCN	9.4	1.3

^a Refers to the pK_a 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 performed 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.

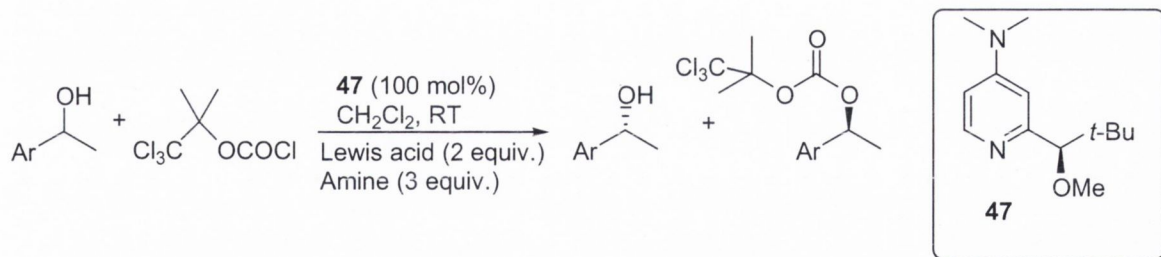
1.4 Chiral DMAP analogues

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 Vedejs⁶⁴ and Fu⁶⁵ 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 α -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 α - 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.

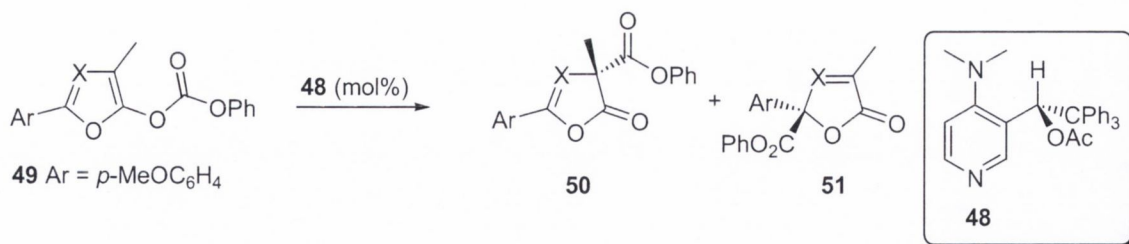
1.4.1 The first chiral DMAP derivative from Vedejs' group

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 *ca.* 90% *ee*, equating to selectivities in the range of 12-53 (Table 1.10). It was hypothesised⁶⁴ that enantiodiscrimination was achieved by the rotation of the benzylic substituents placing the *t*-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 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**

Entry	Ar	Lewis acid	Amine	Time (h)	Conv. (%)	ArOH (%ee)	Ester (%ee)	S
1	1-Np	MgBr ₂	NEt ₃	17	54	87	84	48
2	2-Np	ZnCl ₂	NEt ₃	52	24	30	94	45
3	2-Tol	ZnCl ₂	PMP	43	39	59	93	53
4	Ph	ZnCl ₂	NEt ₃	40	25	NA	93	38

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**

Entry	Cat. (mol%)	X	Time (h)	Yield (%)	50:51	(%ee)
1	1	N	12 ^a	95	100:0	91
2	10	C	24 ^b	83 ^c	10:1	90

^a Reaction carried out at 0 °C, in *t*-A.A. ^b Reaction carried out in THF at RT

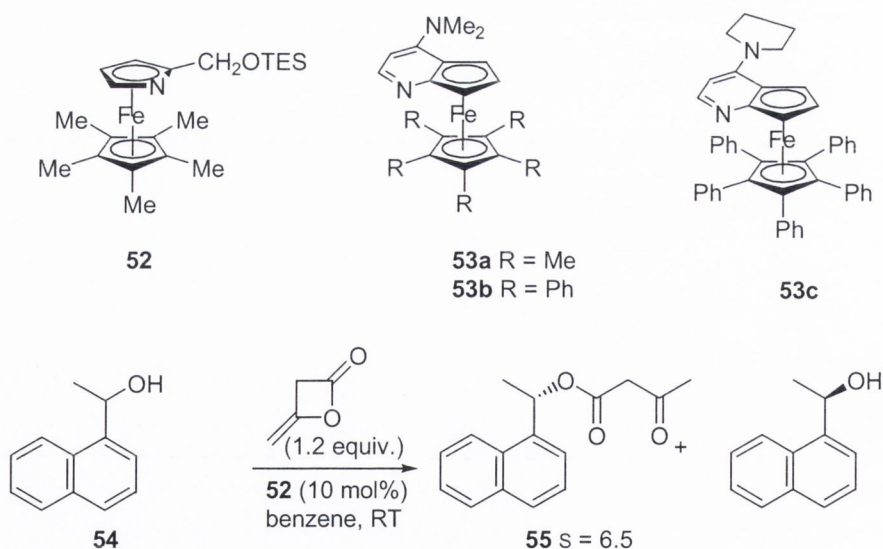
^c 7% yield of **51** with 80% ee

1.4.2 Development of planar chiral catalysts by Fu

Independently in the same year Fu⁶⁵ reported the synthesis of (π -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. π -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**

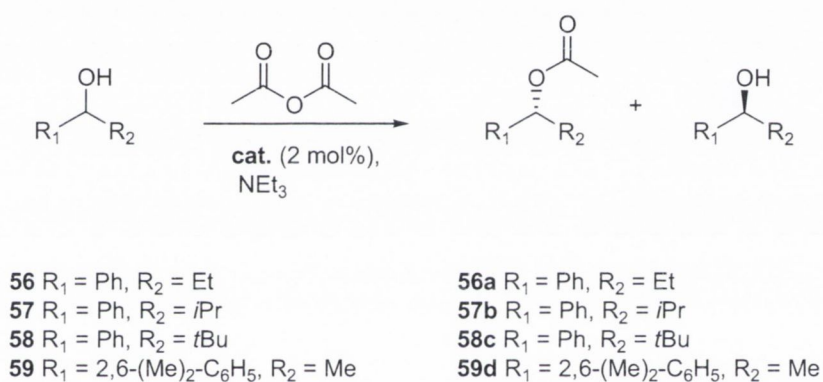


In designing the second generation catalyst, Fu took inspiration from the activity associated with **53a** and surmised that an increase in the steric environment around the ferrocene moiety would promote greater enantiodiscrimination. The use of the ferrocene moiety was an excellent choice on two fronts; 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%).⁶⁹ 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**⁷⁰ (entries 3-8, Table 1.12).

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

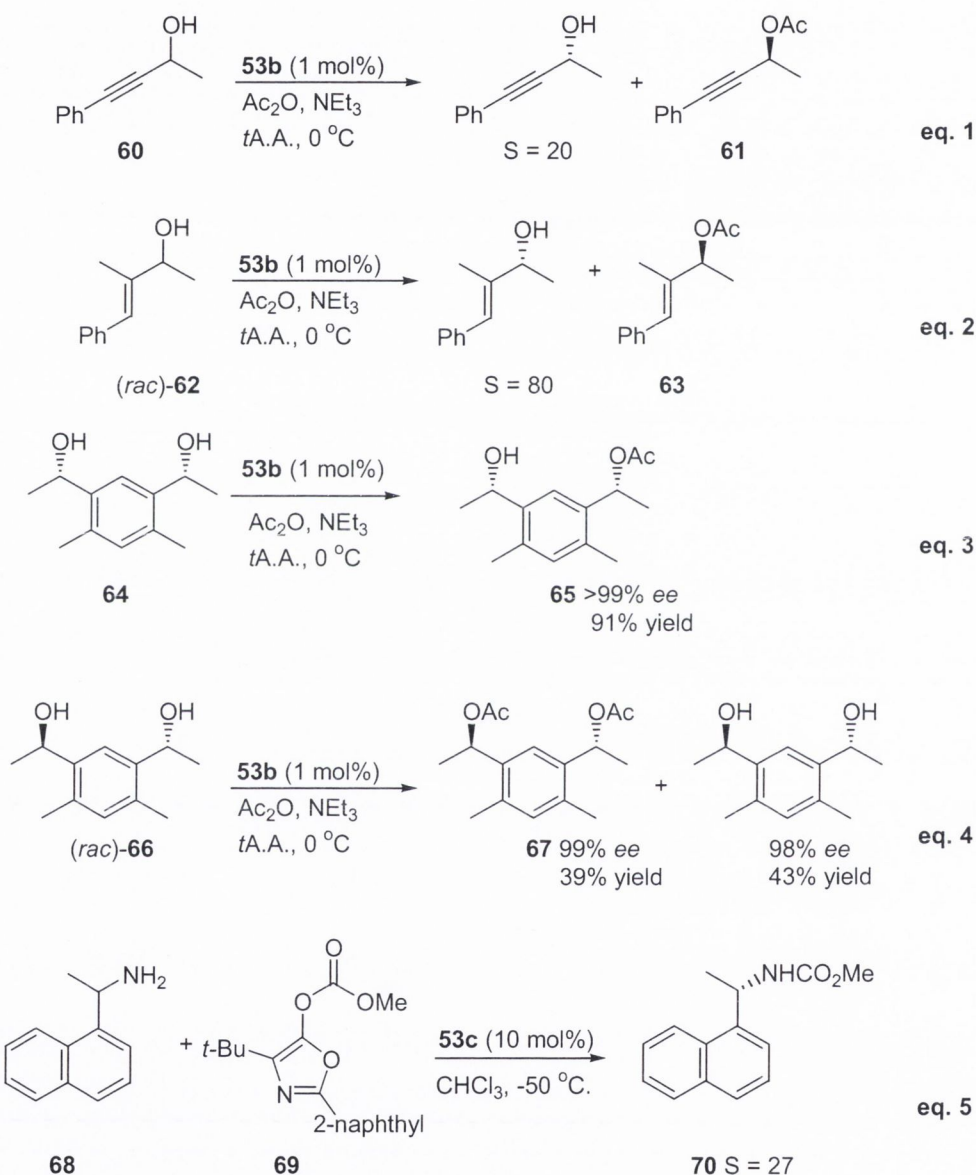


Entry	Cat.	Substrate	T (°C)	Conv. (%)	Solvent	Alcohol <i>ee</i> (%)	S
1	53a	9	RT	67.5	Et ₂ O	26.7	1.7
2	53b	9	RT	61.2	Et ₂ O	95.2	13.6
3	53b	9	0	55	<i>t</i> -A.A	99	43
4	53b	56	0	54	<i>t</i> -A.A	99	59
5	53b	57	0	52	<i>t</i> -A.A	97	87
6	53b	58	0	51	<i>t</i> -A.A	96	95
7	53b	54	0	52	<i>t</i> -A.A	95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

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).⁷¹ Allylic alcohols proved to be superior substrates (S = 5-107) (eq. 2).⁷² 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).⁷³

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



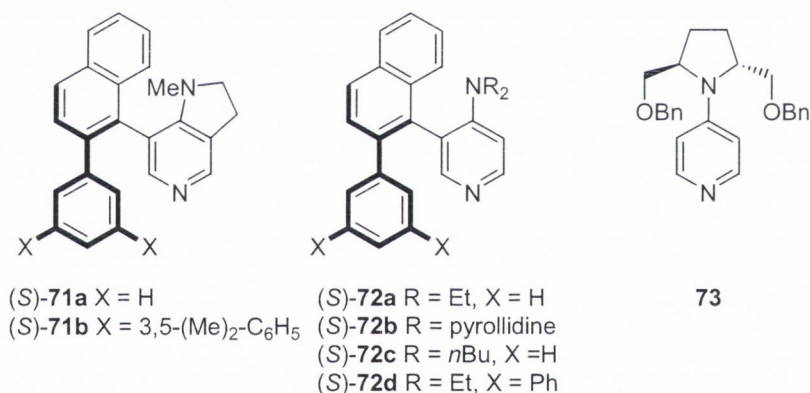
Expansion of the substrate scope to include further nucleophile catalysed reactions has resulted in the asymmetric synthesis of β -lactams⁷⁴ and β -lactones⁷⁵ via the addition of imines and aldehydes to ketenes respectively and also from the DKR of *aza*-lactones⁷⁶ and the C-acylation of silyl ketene acetals⁷⁷ and imines.⁷⁸

53b 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 Spivey⁷⁹ 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-interconvertible enantiomeric conformations *i.e.* atropisomers (Figure 1.5). Initial acylation studies using the standard tertiary alcohol 1-methylcyclohexanol (**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 $k_{\text{rel}} = 2.5$ (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 ($k_{\text{rel}} = 4.7$) (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**.⁸⁰ Subsequent KR of **54** generated a two fold increase on the previous optimum selectivity factor ($k_{\text{rel}} = 9.7$) (entry 3).⁸¹

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 ($k_{\text{rel}} = 29$) (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**

$\text{R}^1\text{-CH(OH)-R}^2 \xrightarrow[\text{cat. (1 mol\%), toluene, -78 }^\circ\text{C}]{(\text{R}'\text{CO})_2\text{O, NEt}_3} \text{R}^1\text{-CH(O-CO-R')-R}^2 + \text{R}^1\text{-CH(OH)-R}^2$

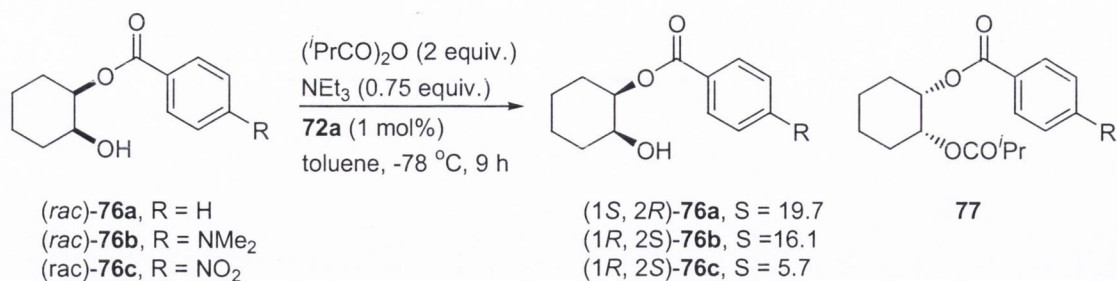
74a $\text{R}^1 = 2\text{-Me-C}_6\text{H}_4$, $\text{R}^2 = \text{Me}$ **(S)-75a** **(R)-74a**
74b $\text{R}^1 = 2,6\text{-(Me)}_2\text{-C}_6\text{H}_3$, $\text{R}^2 = \text{Me}$ **(S)-75b** **(R)-74b**

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

^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 ($k_{\text{rel}} = 5.5$ -19.7, Scheme 1.16) no obvious trend with regards to the sense of stereinduction promoted by **72a** *i.e.* **76a** (1*S*,2*R*) and **76b** (1*R*,2*S*) or the electronic nature of the benzoates was observed.⁸² In addition the successful KR of a purely aliphatic substrate *i.e.* 1-cyclohexylethanol was promoted by **72a** in moderate selectivity ($k_{\text{rel}}=8.4$).

Scheme 1.16 KR of monobenzoates of cis-cyclohexane-1,2-diol by **72a**



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.⁸³ 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 ($S = 39$)⁸⁴ 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 PPh_3 as an achiral additive⁸⁵ was found to successfully mediate the KR of **54** in 30 min with $S = 15.5$.

A C_2 -symmetric PPY catalyst (**73**) was also synthesised by Spivey *et al.*⁸⁶ 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 ($k_{\text{rel}} = 1.8$) 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

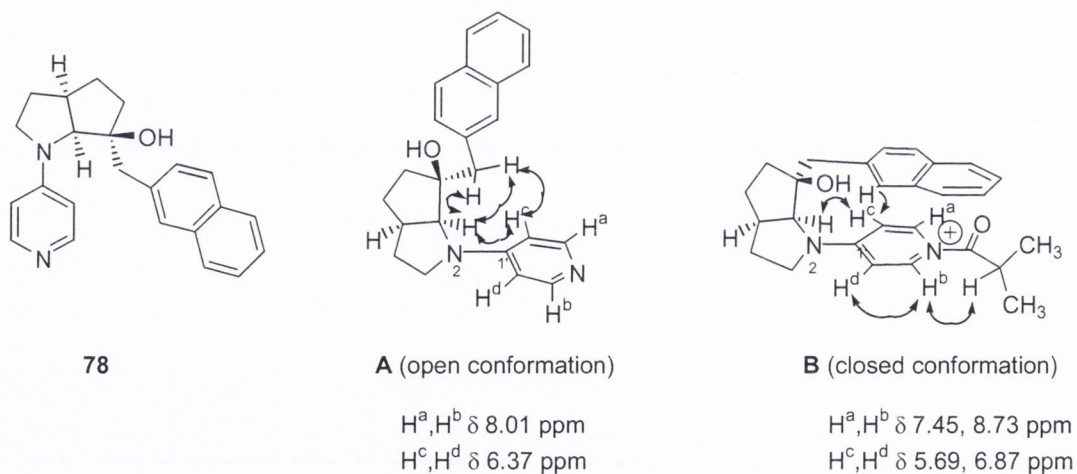
of a variety of *sec*-alcohols and with the addition of PPh_3 , viable selectivities ($S > 10$) are achieved at ambient temperatures.⁸⁴

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 ($\text{H}^c \delta 5.69 \text{ ppm}$ in comparison to $\text{H}^d \delta 6.87 \text{ ppm}$) 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.

79a X = O, R = <i>t</i> -Bu 79b X = O, R = <i>p</i> -NO ₂ C ₆ H ₄ 79c X = NH, R = <i>t</i> -Bu 79d X = NH, R = <i>p</i> -NMe ₂ C ₆ H ₄				80a X = O, R = <i>t</i> -Bu 80b X = O, R = <i>p</i> -NO ₂ C ₆ H ₄ 80c X = NH, R = <i>t</i> -Bu 80d X = NH, R = <i>p</i> -NMe ₂ C ₆ H ₄			
Entry	Substrate	Solvent	Time (h)	Cat. (mol%)	Conv. (%)	<i>ee</i> _A	S
1	79a	toluene	4	5	68	94	8.3
2	79b	toluene	5	5	73	54	2.4
3	76b	toluene	3	5	72	>99	>10.1 ^a
4	79c	CHCl ₃	24	5	69	72	4.0
5	79d	CHCl ₃	9	5	63	>99	>18
6	79d	CHCl ₃	24	0.5	66	>99	>15

^a At 65% conversion the substrate was present in 97% *ee*, *i.e.* S= 12.3.

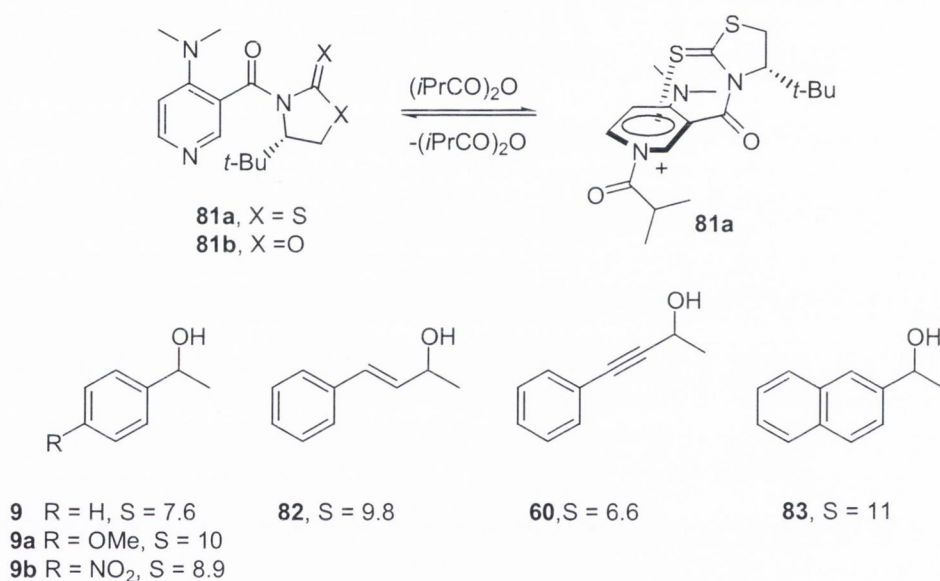
The enantioselectivity generated by resolution of the amino alcohol derivative **79d** (entry 5) was found to increase significantly on KR at -40 °C (*S* = 54). Regardless, due to the tedious catalyst synthesis involved and a lack of modifiable groups to improve activity, the practical application of 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 π -cation complex,⁸⁹ 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.⁹⁰

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 ¹H 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



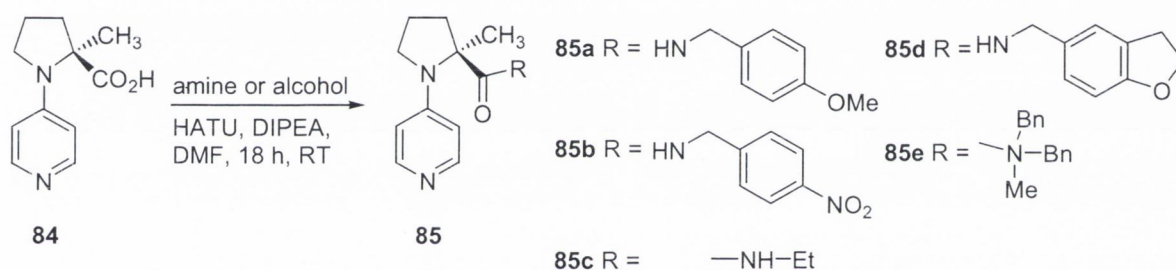
As a catalyst for the acylative KR of *sec*-alcohols, **81a** proved remarkably insensitive to substrate steric bulk or electronic character (Scheme 1.17), affording the (*S*)-enantiomer of the unreacted alcohol in each case. Optimum selectivity was achieved using *iso*-butyric anhydride and *t*-BuOMe 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 α -methyl proline, **84**.⁹²

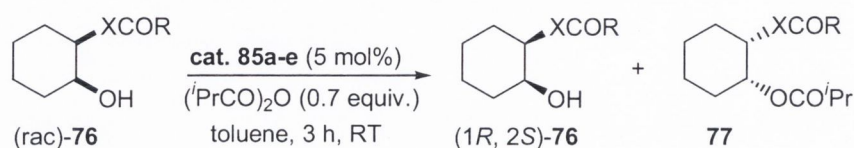
Scheme 1.18 Synthesis of analogues of **85**



A small family of catalysts based on an *N*-4'-pyridinyl- α -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.* *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**



Entry	Substrate	Cat	Conv. (%)	ee_A	S
1	76b	85a	64	93	10.1
2	76b	85b	62	88	9.2
3	76b	85c	64	89	8.4
4	76b	85d	62	95	13.2
5	76b	85e	51	32	2.5
6	76b	85d	44	14	1.6 ^a
7	79d	85d	59	96	18.8

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

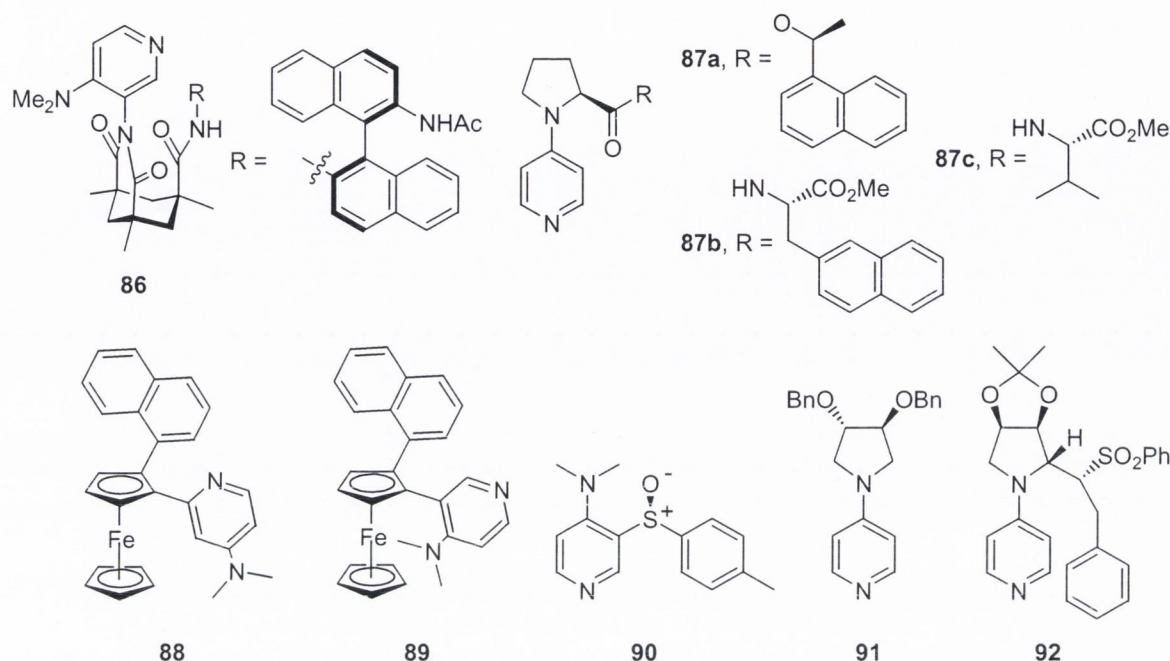
While an improvement in the level of asymmetric induction over that achieved by Fuji was not obtained, a definite insight into the mode of action for catalysis was provided. This is proof positive that catalyst-substrate H-bonding interactions can be an effective means of bringing about enantiodiscrimination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

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).

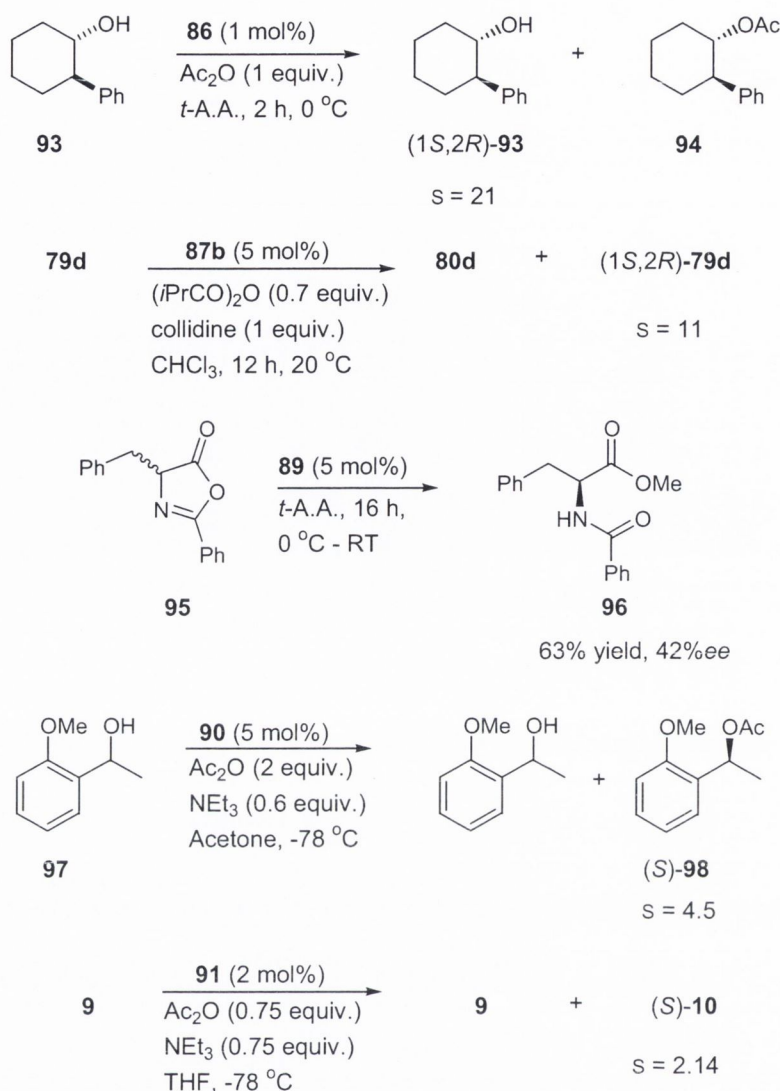
Figure 1.7 KR catalysts **86** – **92**



Investigations by Kim *et al.*⁹⁴ 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 triacid⁹⁵ coupled to an axially chiral binaphthyl moiety affords a nucleophilic catalyst with promising enantiobias. A range of aryl-alkyl alcohols were resolved in *t*-amyl alcohol with k_{rel} increasing with increased alkyl substitution (Me < *t*-Bu, $S = 4.4$ and 13.3 respectively). The acylation of *trans*-2-phenyl cyclohexanol (**93**) in the presence of **86** afforded optimum selectivity ($S = 21$) with the (1*S*,2*R*) enantiomer of the racemate recovered after reaction (entry 1, Table 1.15).

In 2003, a collaboration between Fuji and Kawabata⁹⁶ generated a library of substituted chiral *N*-(4-pyridinyl)prolines of which **87b** proved to be the most efficacious promoter of the enantioselective acylation of the amino alcohol **79d** (1*S*,2*R*) ($S = 11$, entry 2). H-bonding and π -stacking appeared to play pivotal roles in enantiodiscrimination as ester **87a** ($S = 1.1$) and *iso*-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**



Johannsen *et al.* synthesised 2- and 3-substituted ferrocene based planar chiral DMAP analogues (**88** and **89**).⁹⁷ 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-workers⁹⁸ prepared a novel catalyst in a single step utilising a Knochel substitution⁹⁹ 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.

Díez *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**).¹⁰⁰ 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.

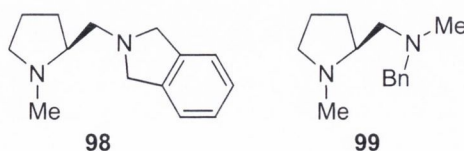
1.5 Non-pyridine based catalysts

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.¹⁰¹ 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 investigation¹⁰² found that the addition of an achiral amine *i.e.* NEt₃ (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.¹⁰³

Figure 1.8 Proline derived catalysts **98** and **99**



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 ^1H 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**

Entry	Substrate	Cat.	Yield. ^a (%)	ee_A (%)	S
1	93	99^b	48	97	200
2	93	98	49	95	160
3	9	98	43	67	9
4	74a	98	45	78	20

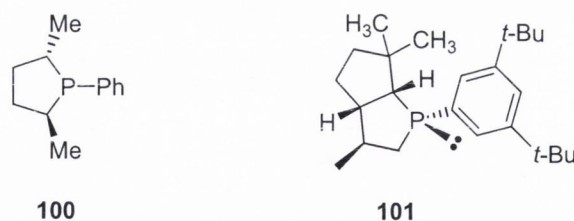
^a Isolated yield. ^b 5 mol% cat. used in reaction

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

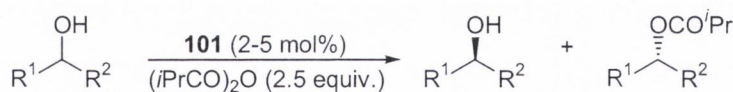
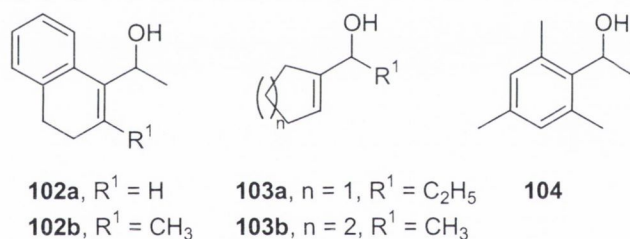
In addition to the previously reported (Section 1.4.1) chiral DMAP analogue **47**, a chiral phosphine **100** capable of catalysing asymmetric acylations was developed by Vedejs in 1996.²⁵ Selectivities of the order $S = 12$ -15 were obtained for phenyl *tert*-butyl carbinol **58** at room temperature with *m*-chlorobenzoic anhydride as acylating agent.

Figure 1.9 Vedejs' chiral, nucleophilic phosphine catalysts.



The next generation catalyst **101** based on the 'PBO' motif *i.e.* 2-phosphabicyclo-[3.3.0]octane was synthesised in enantiopure form (99.7 % *ee*).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 O₂, with ¹H 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 carbinol alcohols catalysed by **101**



Entry	Substrate	Temp (°C)	Time (h)	Conv. (%)	ee _A (%)	S
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

Vedejs found an increase in catalyst optical purity from 99.7% *ee* to >99.99% *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 $-40\text{ }^{\circ}\text{C}$.³⁹ Allylic alcohols were also investigated, with the acylation of unsaturated substituted cycloalkyl alcohols by **101** promoting greatest selectivity.¹⁰⁸

101 Has also exhibited excellent activity and enantioselectivity in the acylative desymmetrisation of diols.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**.¹¹⁰

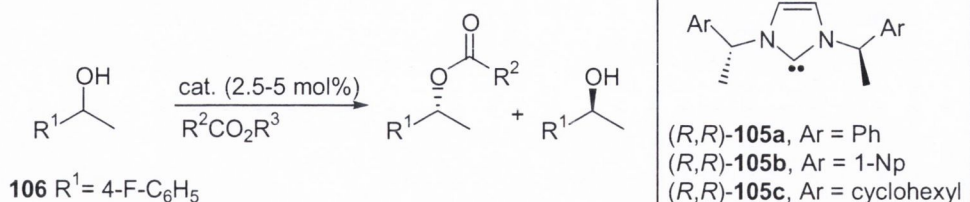
1.5.3 Carbenes

Suzuki¹¹¹ and Maruoka¹¹² independently reported the first *N*-heterocyclic carbene (NHC) for use in the KR of aryl alkyl carbinols and allylic alcohols with high selectivity ($S \leq 80$). Previous to this, studies by Hedrick¹¹³ and Nolan¹¹⁴ 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 tetrafluoroboric acid. Generation of the nucleophilic carbene requires reaction with potassium *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 *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 *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**



Entry	Cat	Substrate	R^2, R^3	Conditions ($^{\circ}\text{C}$, h)	Yield ^a (%)	ee_E (%)	S
1	105b	54	Me, Me	0, 24	33	45	-
3	105c	54	Me, Me	RT, 18	27	49	-
4	105a	9	Ph_2CH , (vinyl)	-78, 3	33	93	46
5	105b	9	Ph_2CH , (vinyl)	-78, 3	32	96	80
6	105b	9a	Ph_2CH , (vinyl)	-40, 3	30	94	48
7	105b	106	Ph_2CH , (vinyl)	-78, 4	39	91	42
8	105a	82	Ph_2CH , (vinyl)	-78, 3.5	27	84	16

^a Isolated yield

1.5.4 Catalysts incorporating an imidazole ring

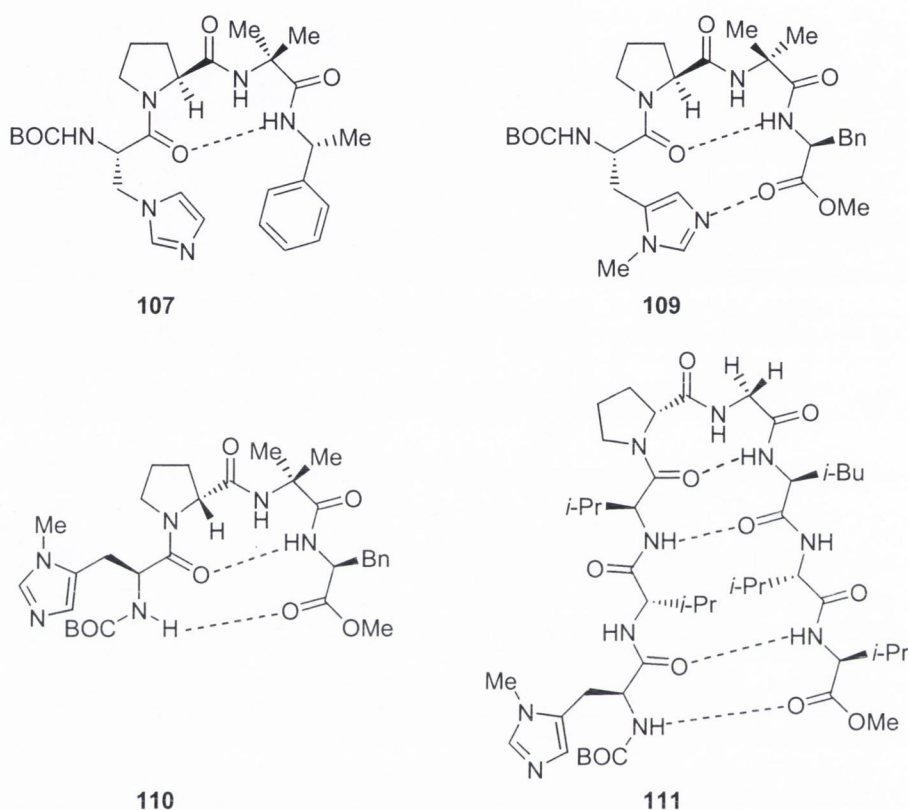
Miller *et al.* developed a small molecule biomimetic catalyst **107** *i.e.* a synthetic peptide for kinetic resolution reactions consisting of the minimal environment required for asymmetric induction and rate enhancement.¹¹⁵ An L-histidine residue was incorporated into a peptide framework with a β -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**.¹¹⁶ A marked difference in selectivity and a reversal of stereinduction was observed between the two; with **109** containing an L-proline residue ($S = 3.1$) and **110** a D-proline residue ($S =$

28). ^1H 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

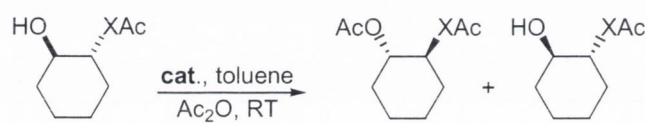
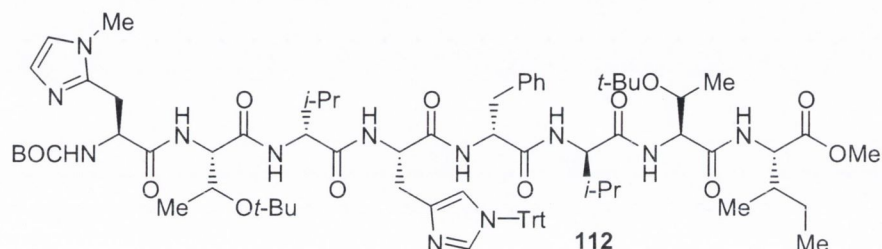


Inspired by **110**, a D-proline based octapeptide **111** (known to exhibit four intramolecular H-bonds)¹¹⁸ was prepared and the analogous L-proline derivative was also synthesised for comparison. **111** Exhibited a significant increase in selectivity ($S > 50$) while the L-proline-derived analogue 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,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 *sec*-alcohols. The combinatorial-fluorescence approach was later successfully applied to the KR of tertiary alcohols.¹²¹

Table 1.19 KR of *sec*-alcohols by catalysts **107**, **109-112**



(*rac*)-**108**, X = NH

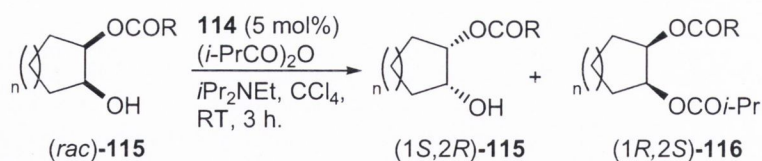
(*rac*)-**113**, X = O

Entry	Cat.	Substrate	T (°C)	S
1	107	108	0	12.6 ^a
2	107	113	0	1.4
3	109	108	25	3.1
4	110	108	25	28
5	111	108	25	51
6	112	9	-65	20
7	112	54	-65	>50
8	112	93	-65	>50
9	112	58	-65	30

^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.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**



115a $n = 2$, $\text{R} = \text{Me}_2\text{N}$

115b $n = 2$, $\text{R} = (\text{CH}_2\text{CH}_2)_2\text{N}$

115c $n = 1$, $\text{R} = (\text{CH}_2\text{CH}_2)_2\text{N}$

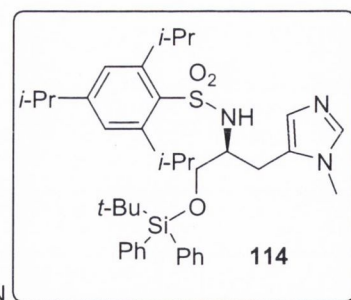
115d $n = 3$, $\text{R} = (\text{CH}_2\text{CH}_2)_2\text{N}$

116a $n = 2$, $\text{R} = \text{Me}_2\text{N}$

116b $n = 2$, $\text{R} = (\text{CH}_2\text{CH}_2)_2\text{N}$

116c $n = 1$, $\text{R} = (\text{CH}_2\text{CH}_2)_2\text{N}$

116d $n = 3$, $\text{R} = (\text{CH}_2\text{CH}_2)_2\text{N}$

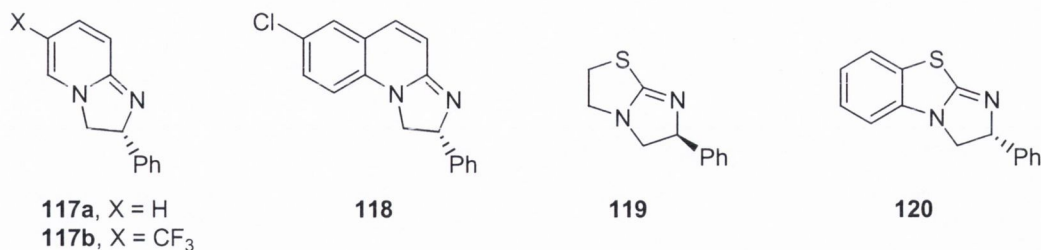


Entry	Substrate	Conv. (%)	ee _A (%)	S
1	76b	49	81	27
2	115a	53	96	42
3	115b	52	97	87
4	115c	49	90	93
5	115d	50	93	83

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 ($S \leq 93$). 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 (1*R*,2*S*) 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).¹²³ The nucleophilicity of the reactive amidine nitrogen was tuneable *via* substitution on the pyridine ring, with a CF_3 substituent promoting maximum stereinduction while still generating appreciable catalytic turnover.

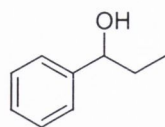
Figure 1.11. Birman's acylation catalysts.



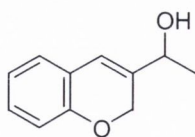
An additional class of *sec*-alcohols *i.e.* allylic alcohols were investigated owing to their π -stacking ability (entry 5). Modest selectivities were achieved ($S = 11 - 26$) as the π - π interaction was less effective with the olefin while the aromatic moiety of the alcohol was further removed from 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_{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_{rel} for aryl alkyl alcohols (entry 7) was also achieved.¹²⁵

A commercially available and enantiomerically pure substituted tetrahydroimidazothiazole (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.

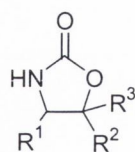
Table 1.21 Range of alcohol KR by catalysts **117-120**



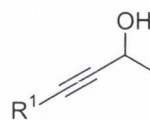
121



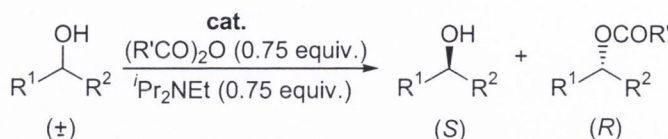
122



123, R¹ = 1-Np, R² = R³ = Me
124, R¹ = 1-Np, R² = R³ = H



125, R¹ = 1-hexynyl
126, R¹ = acetyl



Entry	Cat (mol%)	Substrate	R'	Time (h)	Conv. (%)	S
1	117a (20)	121	Me	1 ^a	21	3.3
2	117b (20)	121	Me	1 ^a	38	14
3	117b (20)	121	Et	8 ^b	39	36
4	117b (20)	58	Et	52 ^b	48	85
5	117b (20)	122	Et	8 ^b	50	26
6	118 (20)	122	Et	4 ^b	55	57
7	118 (20)	58	Et	8 ^b	42	117
8	119 (10)	121	Et	6 ^b	53	31
9	119 (10)	82	Et	8 ^b	45	4.9
10	120 (4)	74a	Et	33 ^b	50	209
11	120 (4)	74a	<i>i</i> Pr	33 ^b	48	355
12	120 (4)	9	<i>i</i> Pr	33 ^b	46	104
13	120 (4)	58	<i>i</i> Pr	48 ^b	31	192
14	120 (4)	104	Et	24 ^b	20	2.5
15	120 (4)	123	<i>i</i> Pr	7 ^a	45	520
16	120 (4)	124	<i>i</i> Pr	21 ^a	42	450
17	120 (4)	125	Et	2 ^a	52	32
18	120 (4)	126	Et	1.5 ^a	55	26

^a Reaction carried out at RT. ^b Reaction 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 CDCl₃ 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).

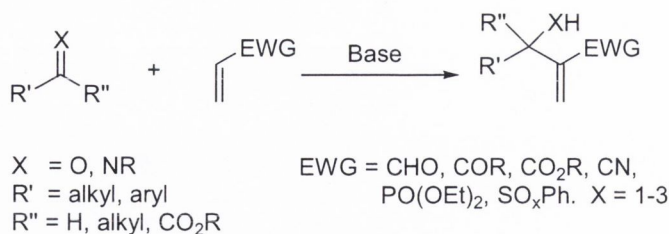
Birman has designed a catalyst of genuine synthetic utility that can be synthesised in enantiopure form from commercially available reagents in three steps. The small molecule catalyst **120** promotes the KR of a wide array of substrates under mild conditions, some of which are useful as chiral building 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 sp^2 hybridised carbon electrophile, Scheme 1.19.

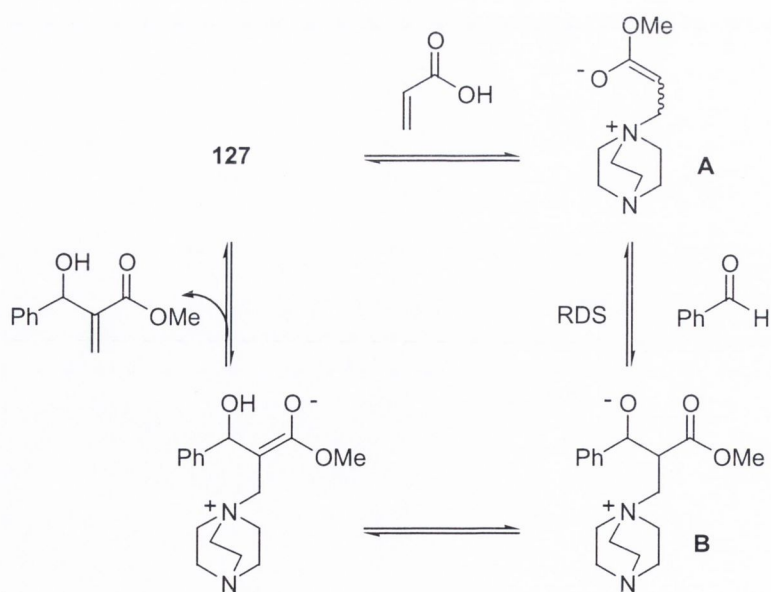
Scheme 1.19 Overview of activated alkenes and electrophiles in the BH



1.6.1 Mechanism of the Baylis-Hillman reaction

The widely accepted mechanism proffered by Hill *et al.*¹²⁷ based on pressure dependence, rate and kinetic isotope data has been independently supported by a multitude of kinetic and mechanistic investigations^{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.¹³⁰

$$\text{rate} = k_{\text{obs}} [\text{alkene}][\text{aldehyde}][\text{amine}] \quad \text{eq.1}$$

However, recent studies have called into question the validity of the above mechanism. McQuade¹³¹ 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).¹³² Subsequent investigations by Leitner *et al.*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

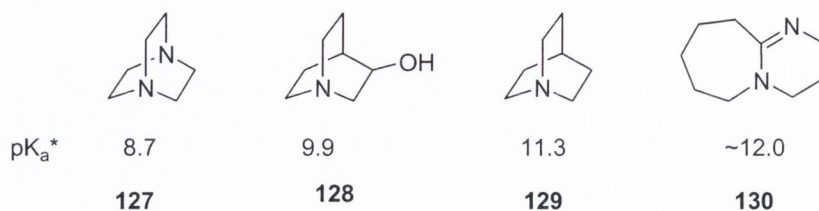
In order that the BH adducts be regarded as synthetically useful, short reaction times along with high yields are a priority. Unfortunately the reaction of activated alkenes with electrophiles tends to be a tedious endeavour, with protracted reaction times at room temperature. A number of strategies have been devised to combat this inherent problem. Hydrogen bonding by the introduction of MeOH¹³⁴ or AcOH¹³⁵ 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 catalyst¹³⁶ or substrate¹³⁷ 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 α 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.¹³⁸ However in some instances elevated temperatures have promoted dimerisation of the alkene substrates.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_a of tertiary amines in BH reaction¹⁴⁰

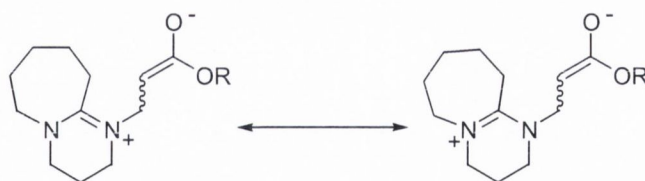


* Refers to $^+NHR_3$ at 25 °C in H_2O

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.*¹⁴¹ observed that 3-hydroxyquinuclidine (**128**) outperformed **127** and **127** was superior to quinuclidine (**129**), with the assumption that **128** stabilised the enolate **A** *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.¹⁴² **130** is the antithesis of the nucleophilic and unhindered bases **127** and **128**. Previous attempts to incorporate α -substituents into a tertiary amine framework to catalyse the BH reaction had proved deleterious to catalytic activity.¹⁴³ Schuurman proposed that α -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 β -ammonium enolate resulting in an increased equilibrium concentration (Figure 1.13).

Figure 1.13 Resonance stabilisation of the Zwitterionic intermediate



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.¹⁴⁴

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

131	132	133	
Catalyst		Rate (%/min)	pK_a^a k_{rel}
quinuclidine, 129		1.8	11.3 9.0
3-hydroxyquinuclidine, 128		8.8×10^{-1}	9.9 4.3
DABCO, 127		2.1×10^{-1}	8.7 1

^a Refers to the pK_a of the corresponding conjugate acid in H_2O 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.¹⁴⁵ The synthesis of enantiopure BH adducts can in theory be accomplished by the incorporation of chiral information into one of the reaction components *i.e.* alkene, electrophile or catalyst. While moderate success has been achieved utilising optically pure chiral auxiliaries *e.g.* activated alkenes and electrophiles,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).¹⁴⁷ 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

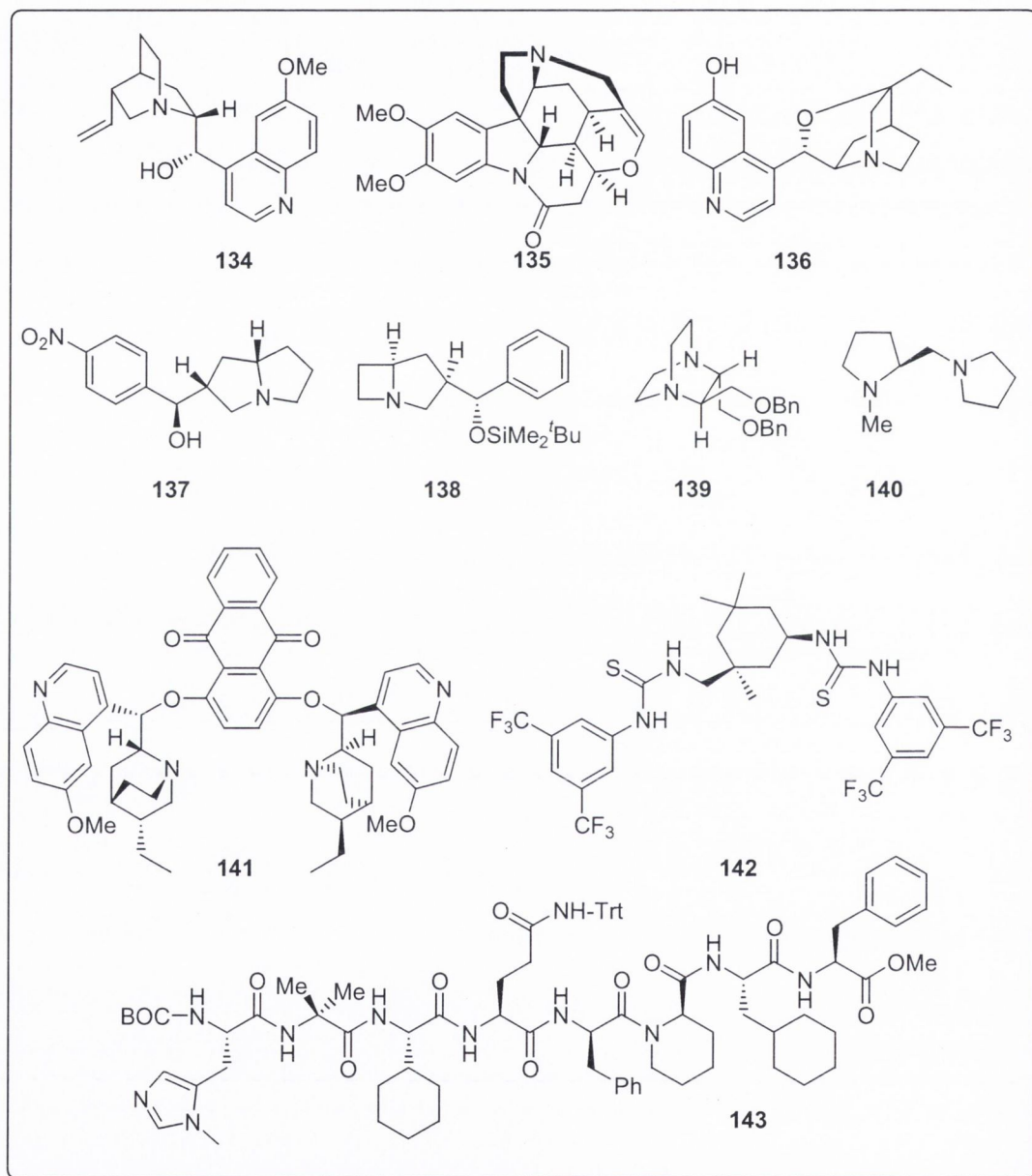
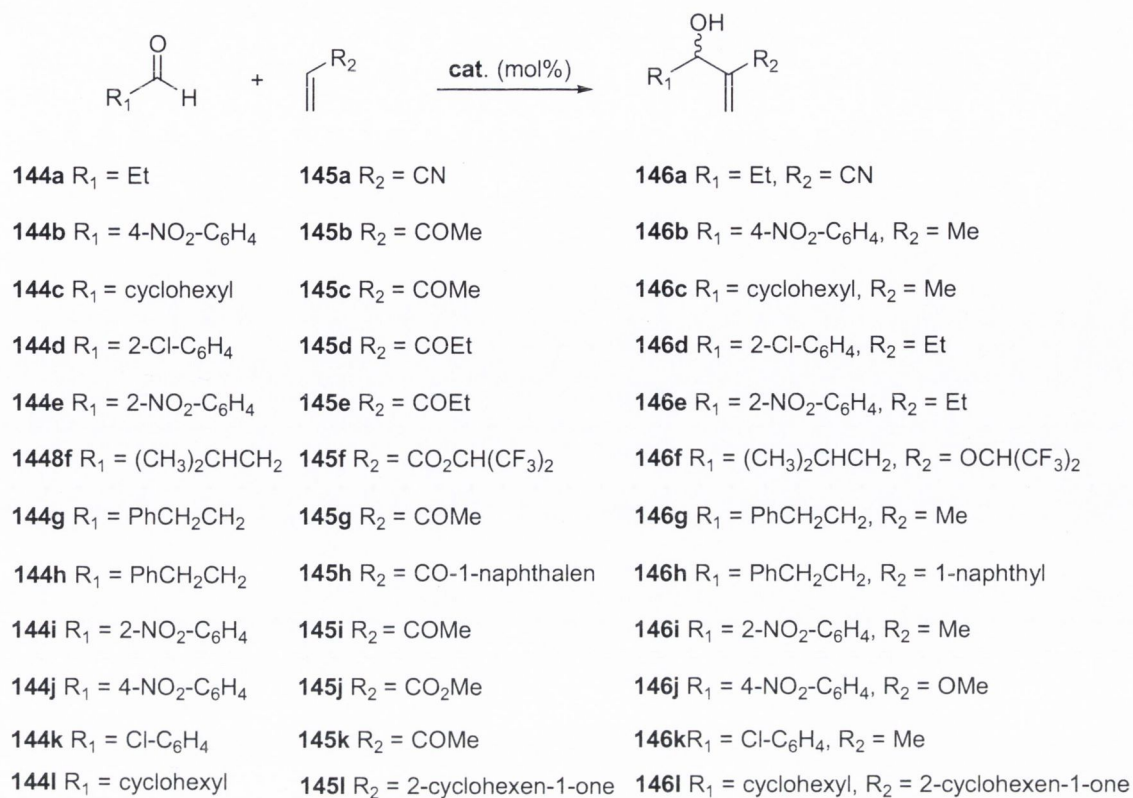


Table 1.23 Overview of reactions catalysed by **134** - **143**


Entry	Cat.	Loading (mol%)	Temp (°C)	Product	Time (h)	Yield (%)	ee (%)
1	134	10	25	146a	-	-	20
2	139	15	30	146b	12	45	47
3	134	10	25	146c	-	45	45
4	137	10	-40	146d	14	58	72
5	138	10	-30	146e	1.5	70	26
6	136	10	-55	146f	4	51	99
7	136	10	-30	146g	60	69	49
8	136	10	-20	146h	120	17	92
9	143	100	25	146i	16	81	78
10	141	10	-	146j	17 d	11	62
11	140	30	0	146k	3	72	75
12	142	20	10	146l	72	75	96

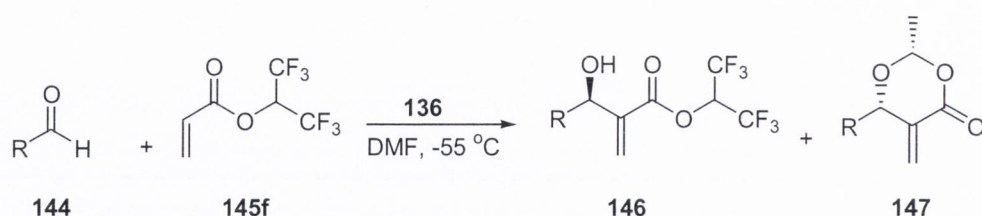
Initial attempts to catalyse the synthesis of enantiopure BH analogues employed the naturally occurring cinchona alkaloid quinidine (**134**) and brucine (**130**). However, very modest enantioselectivities *i.e.* a maximum of 20% *ee*, were achieved in reactions catalysed by **134** (entry 1, Table 1.23).^{129,146,148} In 1995, Hirama and co-workers, encouraged by these preliminary studies, reported a C₂-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*.¹⁴⁹ 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.¹⁵⁰

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%)¹⁵¹ 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.¹⁵² The enantioselective synthesis of medicinally relevant epropromycin B and (-)-mycestericin E mediated by **136** has also been reported.¹⁵³

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.¹⁵⁴ 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, Shi¹⁵⁵ and Hatakeyama,¹⁵⁶ 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.*¹⁵⁷ 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-workers¹⁵⁸ investigated the catalytic competence of the Sharpless ligand (DHQD)₂AQN, **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).¹⁵⁹ 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,¹⁶⁰ developed a chiral *bis*-(thio)urea analogue of isophoronediamine, *i.e.* **142**.¹⁶¹ In combination with tetra

methyated 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.

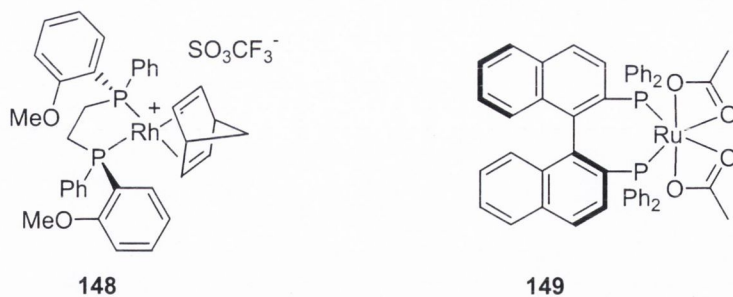
Unfortunately, the asymmetric BH syntheses reported thus far are limited in both scope and synthetic utility; with success confined to reactions where at least one component is activated and a catalyst incorporating at least one hydrogen-bond donating moiety is required. Furthermore, no useful enantioselective 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 epoxidation¹⁶² and diastereomeric crystallisations,¹⁶³ with hydrogenation¹⁶⁴ and biocatalytic acylations¹⁶⁵ proving most effective.

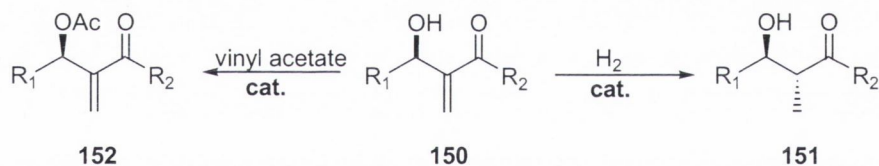
α -Methylene- β -hydroxycarbonyl compounds are ideal substrates for Rh-catalysed asymmetric hydrogenation, with a polar hydroxyl moiety in close proximity to the olefin functionality controlling enantioselective hydrogen transfer. Brown *et al.* demonstrated the synthetic utility of DIPAMP–Rh catalyst **148**; selective hydrogenation of **150a** 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 **150b** employing a BINAP-Ru(II) catalyst **149**. Reaction (25 °C, 4 atm, H₂) amassed unreacted (*S*)-**150b** in >99% *ee* at 76% conversion (entry 2). A range of (α -aminoalkyl)acrylates have also been resolved by stereoselective hydrogenation.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.

Figure 1.15 Hydrogenation catalysts for the KR of BH adducts



An alternative strategy involves chemoenzymatic methodologies. Burgess *et al.*¹⁶⁷ employed a crude *Pseudomonas* AK preparation (Amano) that effectively catalysed the acylation of both α -(hydroxyalkyl)-acrylates and vinyl ketones in good yield and enantioselectivity (entries 3 and 4). Hayashi later demonstrated the exceptional k_{rel} values obtained upon acylation of acrylate-derived BH adducts utilising Lipase PS (*Pseudomonas* sp.) (entry 5).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*).¹⁶⁸

Table 1.24 KR of BH adducts



150a $R_1 = \text{Ph}$, $R_2 = \text{OEt}$
150b $R_1 = \text{Me}$, $R_2 = \text{OCH}_3$
150c $R_1 = \text{Me}$, $R_2 = \text{OBu}$
150d $R_1 = \text{Me}$, $R_2 = \text{Bu}$
150e $R_1 = \text{Et}$, $R_2 = \text{Et}$

Entry	Cat	Substrate	Conditions	Conv. (%)	<i>ee</i> _A	S
1	148	150a	THF, 0 °C	70 ^a	90 (<i>S</i>)	-
2	149	150b	MeOH, 11 h, 25 °C	24 ^{a,b}	99 (<i>S</i>)	16
3	Pseudo. Ak	150c	Hex, 48 h, 25 °C	50	>95 (<i>S</i>)	>56
4	Pseudo. Ak	150d	Hex, 12 h, 25 °C	52	>95 (<i>S</i>)	>56
5	Lipase PS	150e	CH ₃ CN, 7 d, 35 °C	41	70 (<i>S</i>) ^c	>424

^a Product predominantly *anti* (>98%). ^b 24% yield. ^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)

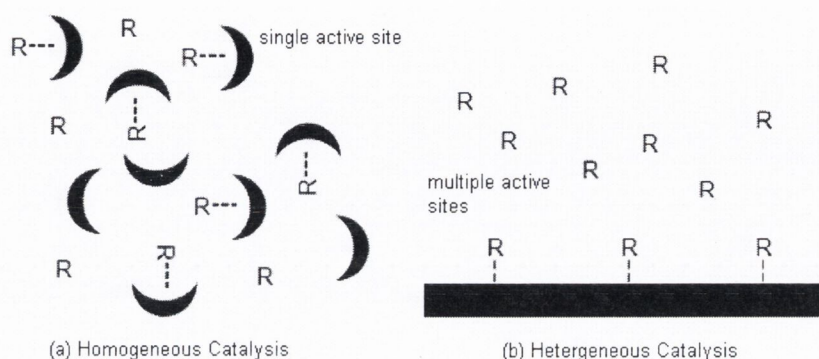
Nanotechnology has received unprecedented interest over the last decade and is expected to become one of the main platforms for technological innovation in the 21st century. Research and development into the synthesis of nanoparticle catalysts is currently the main focus of endeavour,¹⁶⁹ and a host of 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



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.

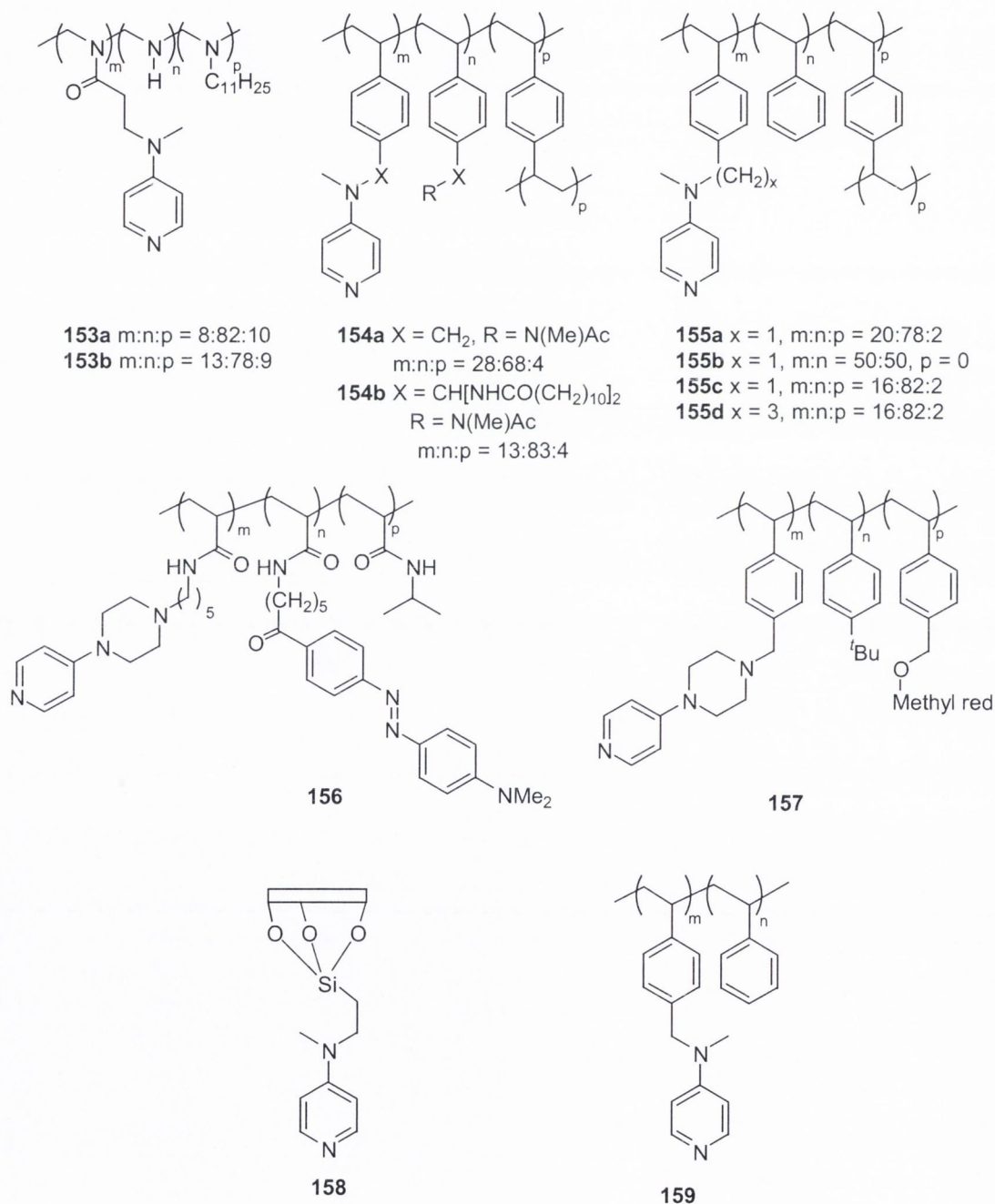
Immobilisation of catalysts involves the formation of a covalent bond with an inorganic or polymer (predominantly polystyrene) support. Non-covalent strategies include ion-pairing of cationic or anionic complexes or encapsulation within mesoporous silicates or zeolites. The support material is required 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 diminution 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 candidate¹⁷¹ for immobilisation on a solid support and several groups have developed plausible strategies (Figure 1.17) for same.

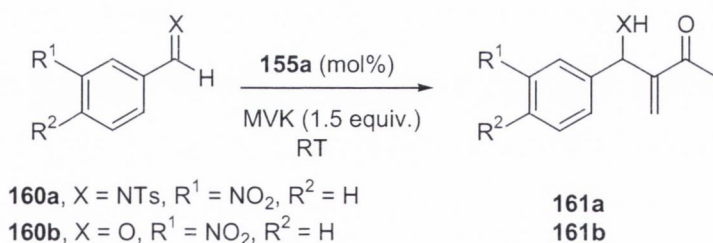
Figure 1.17 Supported DMAP catalysts



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 Shinkai¹⁷³ 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 adducts¹⁷⁵ 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**



Entry	Substrate	Cat. (mol%)	Solvent	Time (h)	Yield (%)
1	144b	100	DMF	24	81
2	144b	100	DMF	24	78
3	160a	20	CH ₂ Cl ₂	72	25
4	160b	20	<i>t</i> -A.A.	24	91
5	160b	20	<i>t</i> -A.A.	24	91

Independently, Shi and Huang¹⁷⁶ utilised **155a** to catalyse the *aza*-Baylis-Hillman reaction of *N*-tosylimines and MVK (entry 3). Reaction required three days and afforded products in 47 – 58% yield. **155a** Proved more efficient in the catalysis of aromatic aldehydes and MVK, with *t*-A.A. as solvent. **155a** Was recovered by filtration and resubjected to the reaction of *m*-NO₂-benzaldehyde and MVK with no discernable loss in reactivity after five cycles (entries 4 and 5).

Insoluble catalyst **155b**, synthesised by Menger *et al.*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 **155b** with subsequent removal of the catalyst by filtration. Although the equivalent DMAP promoted reactions realised only moderately better yields, no attempt to recycle **155b** was made.

Catalysts **155c** and **155d**, closely resembling **155b** were synthesised by Fréchet *et al.*¹⁷⁸ A comparison of activity between **155c** and **155d** employed the hindered alcohol **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 **22**). The introduction of 4-vinylpyridine spacer units in place of polystyrene proved deleterious to catalytic activity. A comparable result was obtained when **19** was employed as solvent in place of toluene.

A soluble polyacrylamide bound catalyst **156**, with a covalently bound azo-dye that allowed for visual monitoring of catalyst recovery, was reported by Bergbreiter and co-workers.¹⁷⁹ Acylation of **20** was effected at room temperature with moderate efficiency (60% conv., 6 h) (entry 4) as compared to **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 **156** remained in solution). **156** was recovered and resubmitted to the acylation of **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

$$\text{ROH} \xrightarrow{\text{Cat.}} \text{ROX}$$

162a R = 2,6-(CH₃)₂-C₆H₃ X = Ac, TBDMS
162b R = CH₂CH₂CH₂C₆H₅

Entry	Cat. (mol%)	Substrate	X	Temp. (°C)	Yield (%)
1	155b (4.1)	20	Ac	20	45
2	155c (5)	20	Ac	60	87
3	155d (5)	20	Ac	60	92
4	156 (5)	20	Ac	25	60 ^a
5	157 (1)	162a	Ac	25	94.6 ^b
6	158 (7.5)	54	Ac	60	93
7	158 (7.5)	40	Ac	60	54
8	158 (6.0)	162b	TBDMS	25	96
9	158 (6.0)	54	TBDMS	25	35
10	159 (0.5)	9	Ac	-	91

^a Conversion as compared to **22**. ^b Yield of run 5

Recently poly(4-*tert*-butylstyrene) was identified by Bergbreiter as a suitable framework for a supported DMAP homogeneous catalyst **157**.¹⁸⁰ 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 methodology¹⁸¹ were developed by Lin and coworkers.¹⁸² **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.

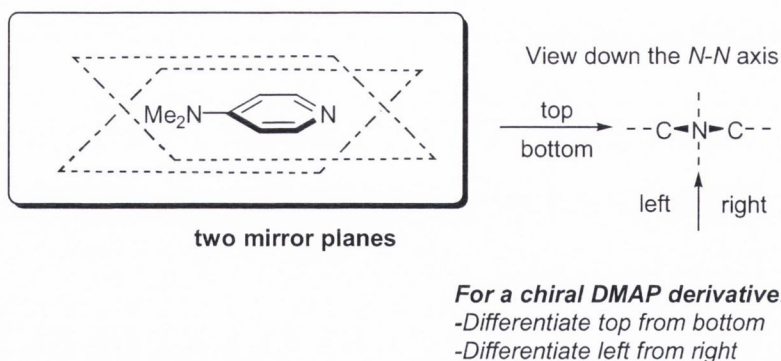
2.1. Guidelines for the successful design of a chiral DMAP catalyst

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 π -pyridinium cation aromatic interaction.

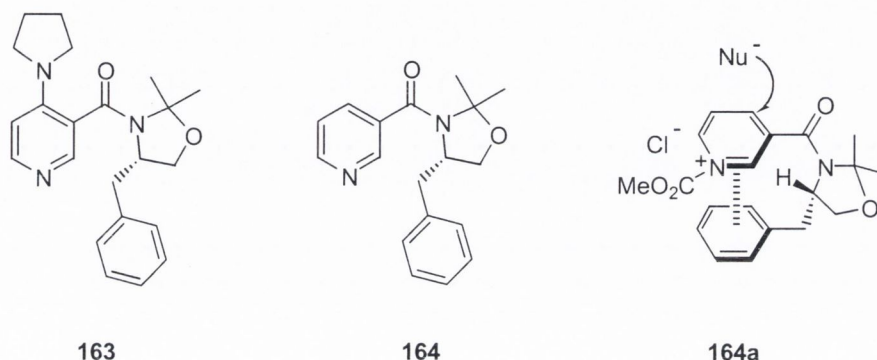
(7) Finally the catalyst should structurally resemble **22**, with only ring functionalisation present that is relevant to catalyst function.

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 Yamada⁹⁰ which disclosed that the 3-substituted pyridine **164** exhibited a π - π stacking interaction upon acylation/alkylation¹⁸⁴ 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).

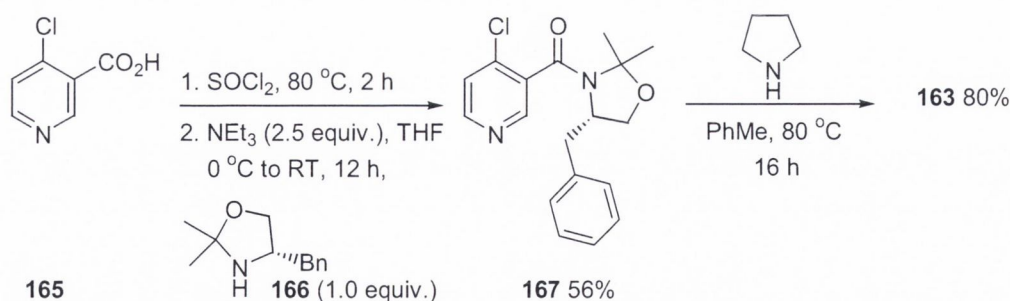
We therefore reasoned that a 4-pyrrolidino analogue of **164** (likely to be of increased nucleophilicity) was a promising lead structure, with the advantages that it could be easily assembled and modified and was potentially capable of operating *via* an ‘induced-fit’ mechanism.

Figure 2.1 1st 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)¹⁸⁵ to afford amide **167** in reasonable yield. Conversion of **167** to **163** was achieved *via* a nucleophilic aromatic substitution reaction with excess pyrrolidine.

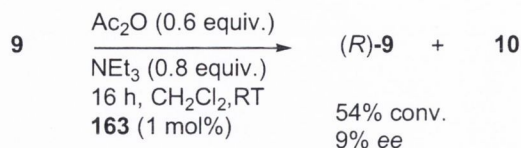
Scheme 2.1 Synthesis of catalyst **163**



Unfortunately, ¹H NMR analysis (CDCl₃, RT) of **163** revealed the presence of two rotameric species in a 1:1 ratio, with only one rotamer conceivably conducive to the intramolecular π - π stacking presumed to be required for enantioselective acyl-transfer (a time-averaged single conformer was obtained when the ¹H 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**



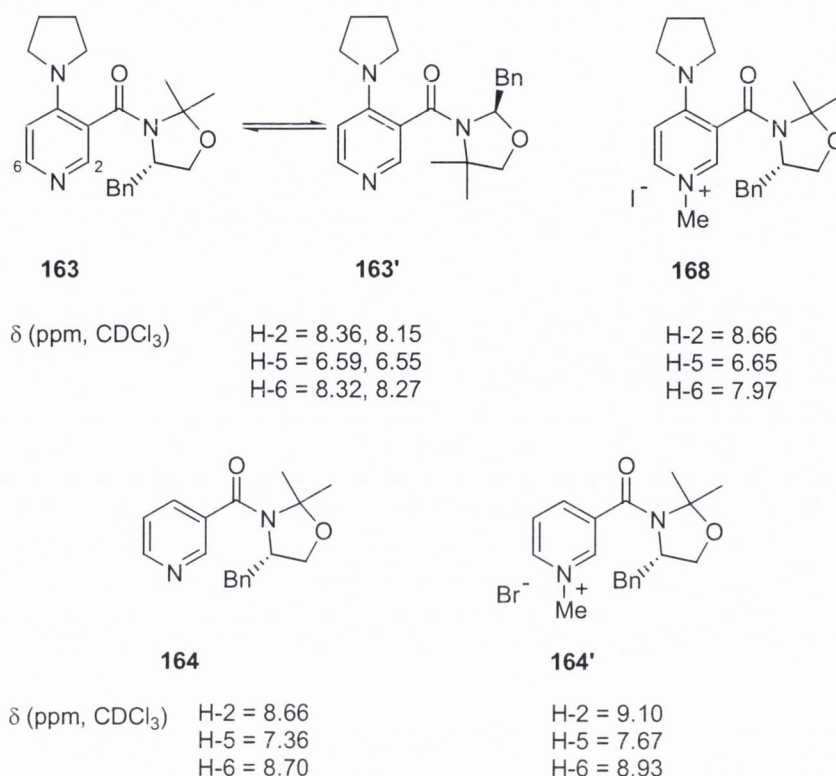
A chiral shift reagent, Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] Eu(hfc)₃ was used to determine the enantiomeric excess in ¹H NMR experiments as a suitable chiral HPLC column was unavailable to the group at that time. The lanthanide shift reagent (a Lewis acid) coordinates 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.⁸⁹

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.

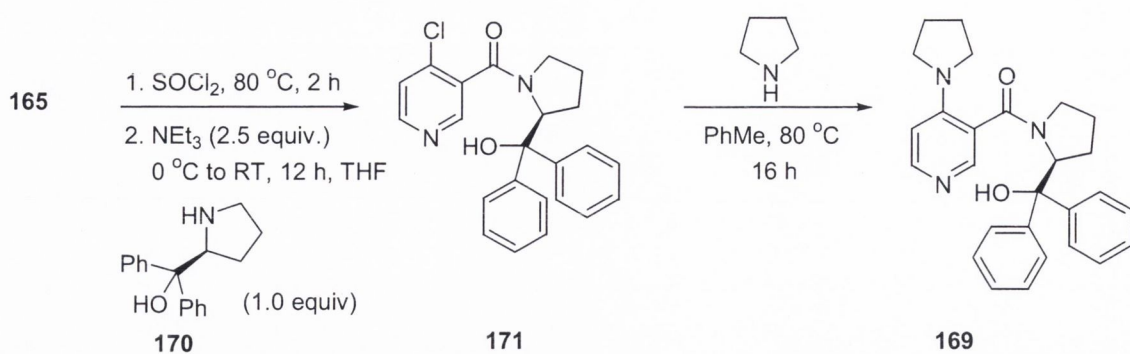
Figure 2.2 ^1H NMR chemical shifts of **163** and **168**



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.

Scheme 2.3 Synthesis of catalyst **169**

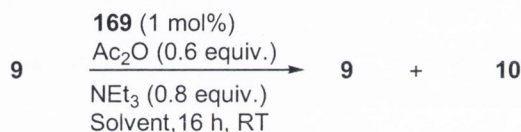


Gratifyingly, ^1H NMR analysis of **169** showed only one rotamer present. Catalyst **169** was evaluated in the KR of **9** as per catalyst **163** in Scheme 2.2, resulting in a marked improvement in selectivity at room temperature. **169** Also exhibited excellent activity, with reaction complete after 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_2Cl_2). **10** Was isolated and the enantiomeric excess (31% *ee* at 59% conversion) determined by ^1H NMR spectroscopy after complexation with (+)- $\text{Eu}(\text{hfc})_3$.

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 Campbell and co workers,⁹² less polar solvents promoted a more efficient enantioselective acyl-transfer reaction, with the highest S factor obtained using CH₂Cl₂. 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



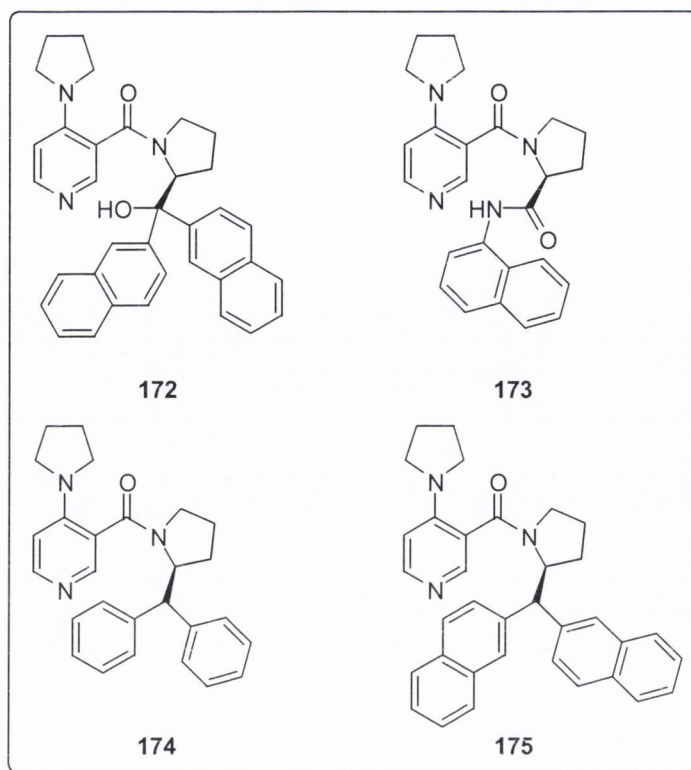
Entry	Solvent	Conv. (%) ^a	ee (%) ^{b,c}	S
1	CH ₂ Cl ₂	59.3	31	2.9
2	PhMe	63.0	21	2.1
3	THF	58.0	22	2.0
4	Et ₂ O	58.0	17	1.7
5	<i>t</i> -A.A.	9.0	17	1.4
6	DMSO	57.2	9	1.3

^a Conversion which could be determined by ¹H NMR spectroscopy ^bRefers to the ee of the ester product. %ee from ester. ^c Determined by ¹H NMR spectroscopy using a (+)-Eu(hfc)₃ chiral shift reagent

2.3.2 Further investigation into the optimisation of catalyst framework

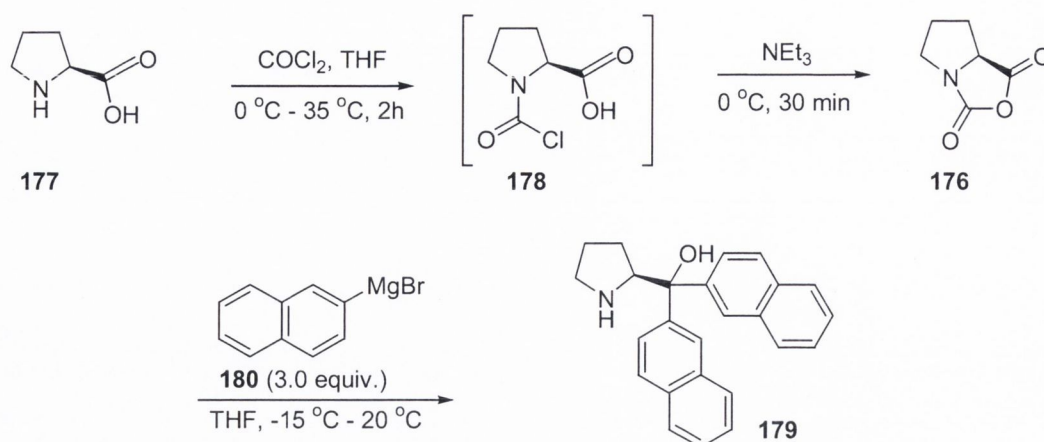
Subsequently, the influence of each of the catalyst's components on enantioselectivity was probed through the synthesis and systematic evaluation of variant catalyst structures. The modular nature of the synthesis outlined for **169** in Scheme 2.3 afforded a direct route for the facile alteration of catalyst structure (Figure 2.4).

Figure 2.4 Chiral analogues of catalyst **169**



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_2Cl_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 $\text{NEt}_3\cdot\text{HCl}$ salt. The THF solution of (*S*)-**176** was filtered and used immediately.

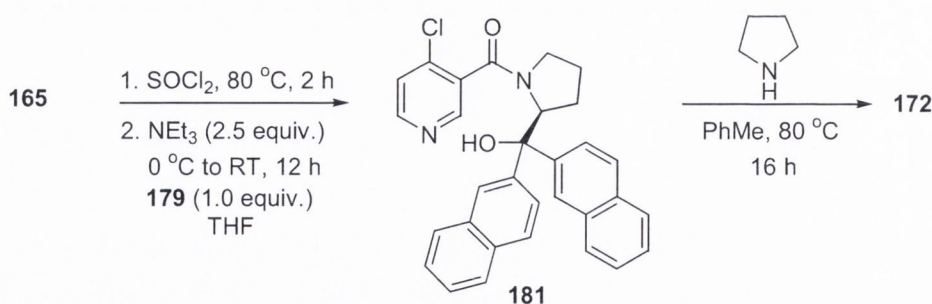
Scheme 2.4 Synthesis of (*S*)- α,α -di(2-naphthyl)prolinol, **179**



(*S*)-**176** Was added dropwise to a solution of 2-naphthylmagnesium bromide (**180**) in THF at $-20\text{ }^\circ\text{C}$ generating the sulphate salt of **179** after acidic workup with H_2SO_4 . 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**

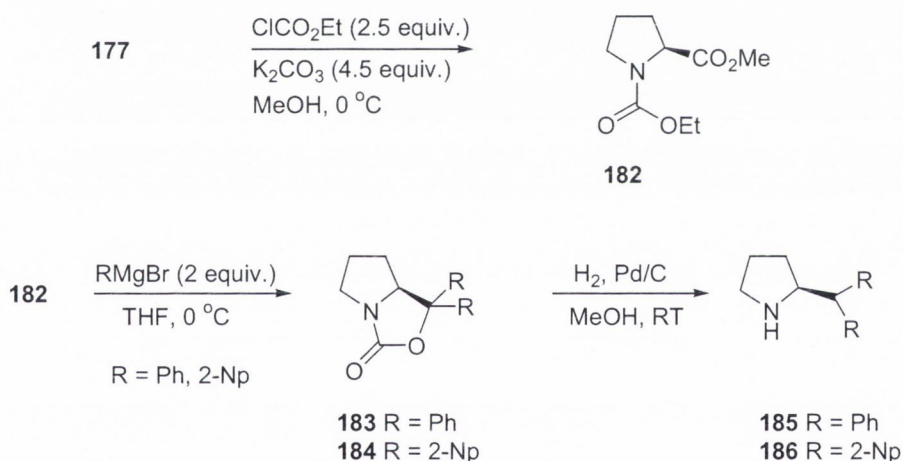


Further to this, a naphthyl amide analogue, **173** was prepared from the commercially available proline naphthyl amide hydrochloride salt in order to deduce what effects the steric bulk of the phenyl and naphthyl groups had on stereoselectivity. A *bis*-methyl analogue of **169** would have been ideal, however literature precedent¹⁸⁶ 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.¹⁸⁷ 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.

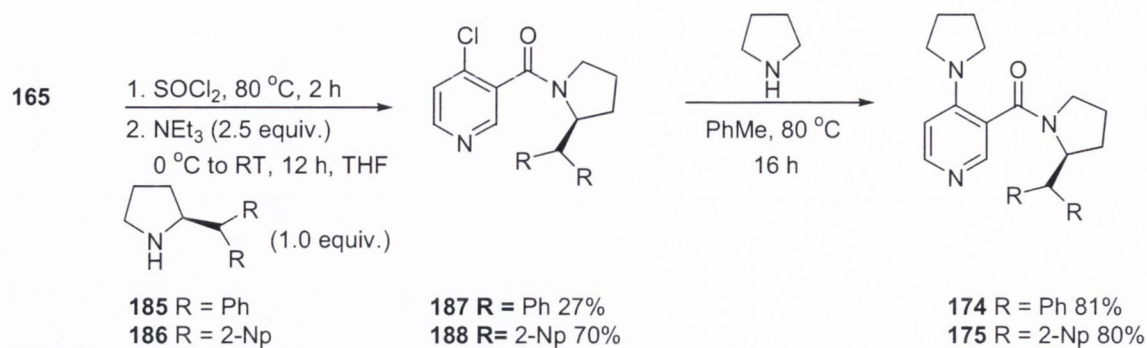
Reaction of (*S*)-**177** with ethyl chloroformate and K₂CO₃ in methanol furnished **182** in a respectable isolated yield (73%). Addition of **182** to a solution of Grignard (Ph- or 2-Np-MgBr) in THF at 0 °C afforded **183** and **184** respectively. Hydrogenation of the pyrrolo-oxazolones **183** 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**



^1H 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**

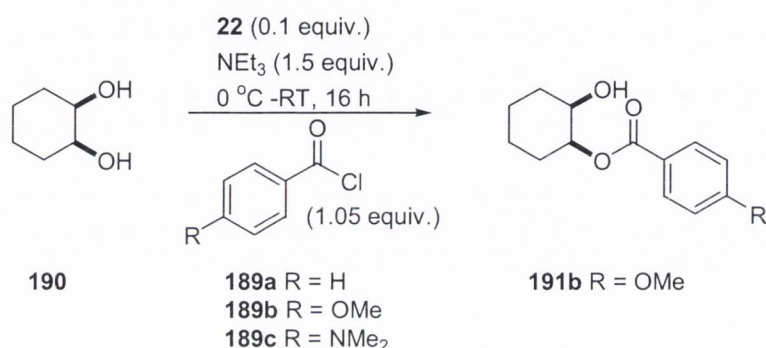
$ \begin{array}{c} \text{cat. (1 mol\%)} \\ \text{Ac}_2\text{O (0.55 equiv.)} \\ \text{NEt}_3 (0.6 \text{ equiv.}) \\ \text{CH}_2\text{Cl}_2, 16 \text{ h, RT} \end{array} \xrightarrow{\quad} \begin{array}{c} \text{9} \\ + \\ \text{10} \end{array} $						
Entry	Cat.	Conv. ^a (%)	ee _A ^b (%)	ee _E ^b (%)	S	Absol. config ^b
1	172	48.2	32	34	2.7	(R)
2	173	50.5	16	15	1.6	(R)
3	174	48.6	7	7	1.2	(S)
4	175	54.9	4	3	1.1	(S)

^a Conversion which could be determined (with excellent agreement) either by ^1H NMR spectroscopy or using chiral HPLC, where $C = 100 \times ee_{\text{alcohol}} / (ee_{\text{alcohol}} + ee_{\text{ester}})$. ^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 stereinduction 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 Fuji⁸⁷ 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).

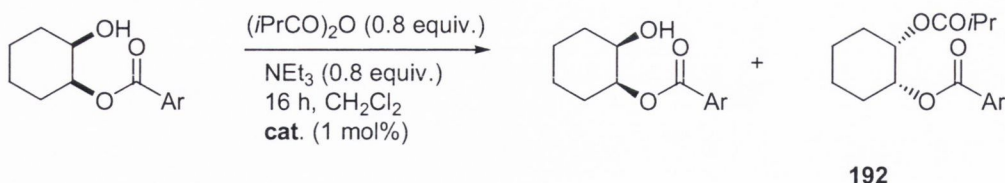
Scheme 2.8 Synthesis of mono-protected *cis*-diols



Both literature⁸³ 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_3 as the general base in anhydrous CH_2Cl_2 under an inert atmosphere of argon.

Table 2.3 KR of mono-protected diols **76a,b** and **191b** by catalysts **169** and **172**



Entry	Cat	ROH	Temp. (°C)	Conv. ^a (%)	ee _A ^b (%)	S	Absol. config. ^c
1	169	76b	25	78	93	4.9	(1 <i>S</i> , 2 <i>R</i>)
2	169	76b	-78	69 ^d	97	9.4	(1 <i>S</i> , 2 <i>R</i>)
3	169	191b	25	68	74	4.3	(1 <i>S</i> , 2 <i>R</i>) ^e
4	172	76b	25	73.5	90	5.4	(1 <i>S</i> , 2 <i>R</i>)
5	172	191b	25	71	80	4.4	(1 <i>S</i> , 2 <i>R</i>) ^e
6	172	76a	25	88	95	3.5	(1 <i>S</i> , 2 <i>R</i>) ^e

^a Refers to conversion, which could be determined (with excellent agreement) either by ¹H NMR spectroscopy or using chiral HPLC, where conv. = 100 x ee_{alcohol}/(ee_{alcohol} + ee_{ester}). ^b ee of alcohols **76a,b** and **191b** 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.⁹¹ ^d 1.5 equiv. (iPrCO)₂, 8 h. ^e Tentative assignment assuming that the elution order is identical to that of **76b**.

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-naphthyl 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)⁸⁷ 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 preformed 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 auxillary 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 preformed on the KR of **76b** catalysed by **169**

76b <math>\xrightarrow[\text{base (0.7 equiv.) 16 h, solvent, RT 169 (1 mol\%)}]{(i\text{PrCO})_2\text{O (0.7 equiv.)}}</math> 77b						
Entry	Solvent	Base	Conv. ^a (%)	ee _A ^b (%)	S	Absol. config. ^c
1	CH ₂ Cl ₂	DIPEA	64	70	4.6	(1 <i>S</i> , 2 <i>R</i>)
2	CH ₂ Cl ₂	DABCO	61	63	4.4	(1 <i>S</i> , 2 <i>R</i>)
3	CH ₂ Cl ₂	Imidazole	19	6	1.9	(1 <i>S</i> , 2 <i>R</i>) ^d
4	CH ₂ Cl ₂	DBU	38.5	28	3.4	(1 <i>S</i> , 2 <i>R</i>)
5	CH ₂ Cl ₂	Na ₂ CO ₃	61	58	3.7	(1 <i>S</i> , 2 <i>R</i>) ^d
6	CH ₂ Cl ₂	NEt ₃	64	70	4.6	(1 <i>S</i> , 2 <i>R</i>) ^d
7	CDCl ₃	NEt ₃	69	77	4.4	(1 <i>S</i> , 2 <i>R</i>)
8	PhMe	NEt ₃	67	67	3.7	(1 <i>S</i> , 2 <i>R</i>)
9	THF	NEt ₃	63	55	3.1	(1 <i>S</i> , 2 <i>R</i>)
10	Et ₂ O	NEt ₃	64	26	1.7	(1 <i>S</i> , 2 <i>R</i>)
11	DMSO	NEt ₃	66	20	1.5	(1 <i>S</i> , 2 <i>R</i>)

^a Refers to conversion, which could be determined (with excellent agreement) either by ¹H NMR spectroscopy or using chiral HPLC, where conv. = 100 x ee_{alcohol}/(ee_{alcohol} + ee_{ester}). ^b ee of alcohol **76b** 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.⁹¹ ^d 1.5 equiv. (iPrCO)₂, 8 h.

The auxiliary amines were chosen to represent a range of basicities (pK_as 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.

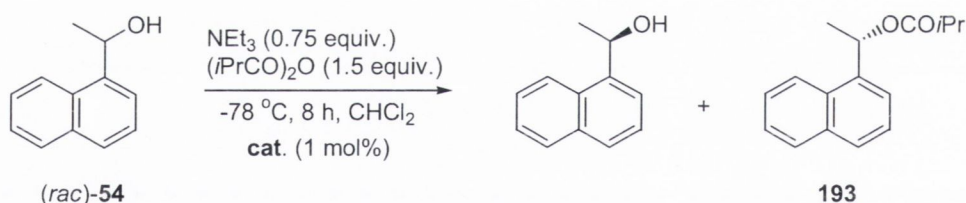
DIPEA and NEt_3 promoted the most stereoselective KR under these reaction conditions. NEt_3 was preferred as the base of choice owing to its relative inexpensive and lower boiling point which enables its facile removal under reduced pressure after reaction.

The influence of the solvent system was again revisited, with each solvent regardless of polarity promoting successful conversion to product. Protic 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 *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**



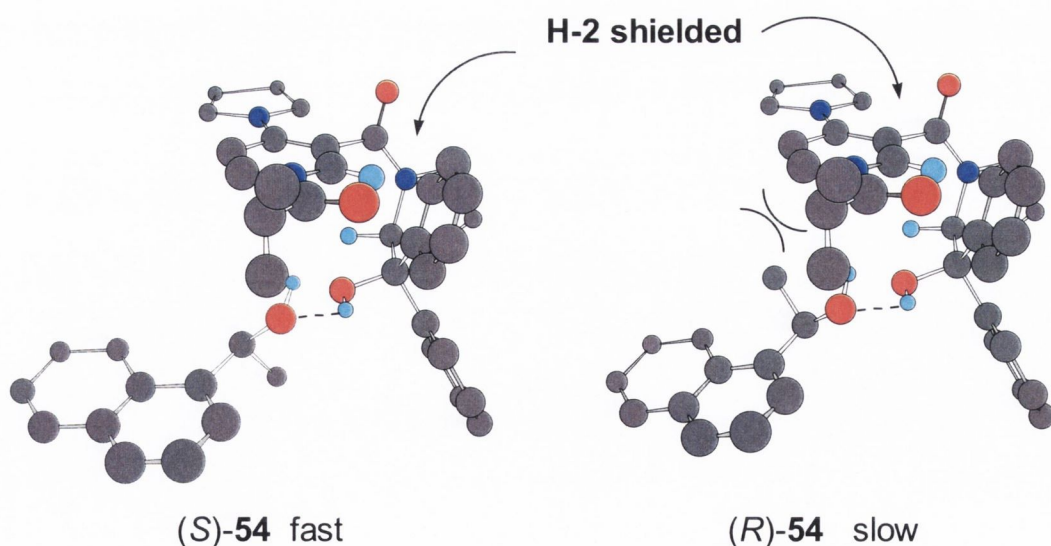
Entry	Cat.	Conv. ^a (%)	<i>ee</i> _A ^b (%)	<i>ee</i> _E ^b (%)	S	Absol. config. ^c
1	169	72	93	29	6.3	(<i>R</i>)
2	172	43 ^d	51	63	8.7	(<i>R</i>)
3	174	36	22	36	2.8	(<i>S</i>)
4	175	43	30	38	3.0	(<i>S</i>)

^a Conversion: which could be determined (with excellent agreement) either by ^1H NMR spectroscopy or using chiral HPLC, where $C = 100 \times ee_{\text{alcohol}} / (ee_{\text{alcohol}} + ee_{\text{ester}})$. ^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.⁸³ ^d 0.80 equiv. $(i\text{PrCO})_2\text{O}$, 8 h.

The results are in agreement with those in Table 2.2, with an inversion in the sense of stereoreduction 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 π -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 plane 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.

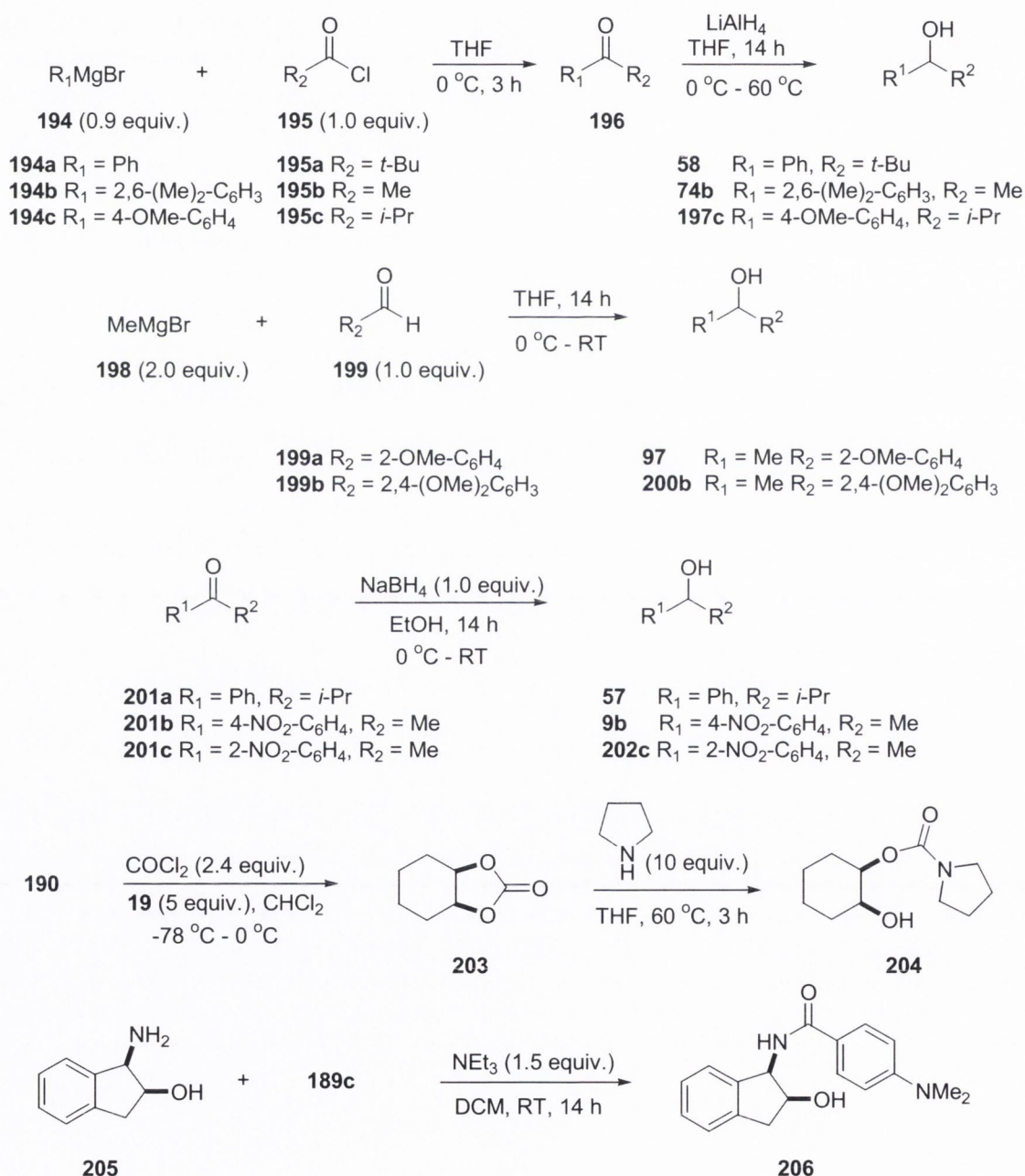
Figure 2.5 Possible pre-TS-assemblies for the acylation of **54** by $(i\text{PrCO})_2\text{O}$ catalysed by **169**



2.4 Investigation into the mode of action of catalysts 169 and 172

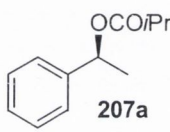
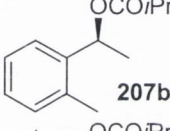
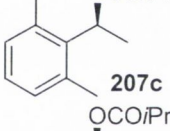
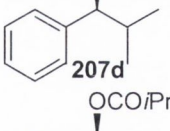
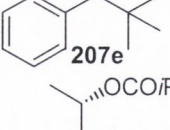
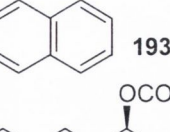
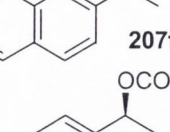
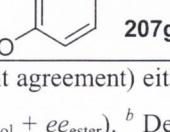
In order to garner further insight into the mode of action of catalysts **169** and **172**, attention then turned to the question of substrate scope. Catalyst **169** was favoured in place of the 2-naphthyl analogue, **172**, due to the commercial availability of the prolinol precursor **170**. **169** 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**



The *sec*-alcohols were subjected to the optimised conditions outlined in Section 2.3.3; acylation by *iso*-butyric anhydride in CH₂Cl₂ with NEt₃ 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

$ \begin{array}{c} \text{OH} \\ \\ \text{R}^1\text{---CH---R}^2 \\ (\text{rac}) \end{array} \xrightarrow[\text{169 (1 mol\%)}]{\begin{array}{c} \text{NEt}_3 \text{ (0.75 equiv.)} \\ (\text{iPrCO})_2\text{O (0.75 equiv.)} \\ -78\text{ }^\circ\text{C, 6 h, CH}_2\text{Cl}_2 \end{array}} \begin{array}{c} \text{OCO/iPr} \\ \\ \text{R}^1\text{---CH---R}^2 \end{array} + \begin{array}{c} \text{OH} \\ \\ \text{R}^1\text{---CH---R}^2 \end{array} $						
Entry	Substrate	Conv. ^a (%)	ee _A ^b (%)	Ester	S	Absol. config. ^c
1	9	27.5	25	 207a	6.3	<i>R</i>
2	74a	17	14	 207b	6.0	<i>R</i>
3	74b	14.6	1	 207c	1.1	<i>R</i>
4	57	19	19	 207d	13.5	<i>R</i>
5	58	4.1	1.6	 207e	2.2	<i>R</i>
6	54	22.5	20	 193	6.6	<i>R</i>
7	83	37	40	 207f	7.6	<i>R</i>
8	9a	20	19	 207g	9.1	<i>R</i>

^a Conversion which could be determined (with excellent agreement) either by ¹H NMR spectroscopy or using chiral HPLC, where C = 100 x ee_{alcohol}/(ee_{alcohol} + 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. ^{81,83,124,188,189}

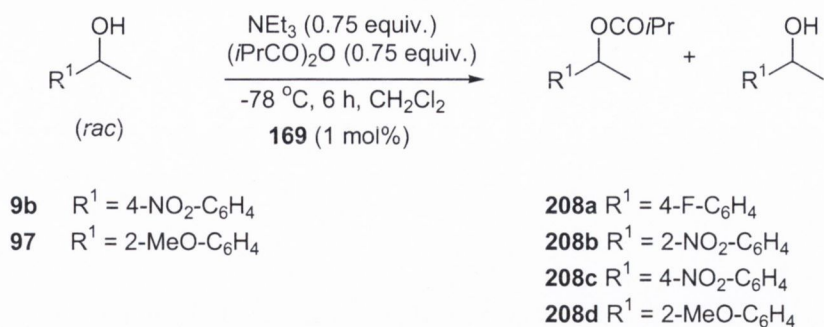
Moderate conversions to the corresponding *iso*-propyl ester (14.6 – 37%) were observed under the reaction conditions (-78 °C, 6 h). In the case of the benzyl alcohols **9**, **74a** and **74b**, a distinct decrease in conversion was observed upon increased *ortho*-substitution of the aromatic moiety (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 Fu⁷⁰ and Spivey⁸³ 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



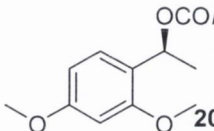
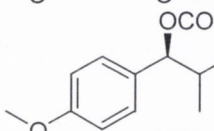
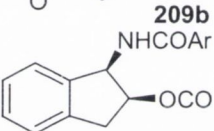
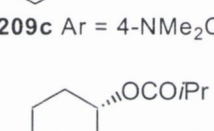
Entry	Substrate	Conv. ^a (%)	ee _A ^b (%)	S	Absol. config. ^c
1	97	18	18	11.4	<i>R</i>
2	9b	27	6	1.4	<i>R</i>
3	202c	28	6	1.5	<i>R</i>
4	106^d	33	-	-	nd

^a Conversion which could be determined (with excellent agreement) either by ¹H NMR spectroscopy or using chiral stationary phase HPLC, where $C = 100 \times ee_{\text{alcohol}} / (ee_{\text{alcohol}} + ee_{\text{ester}})$. ^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 or optical rotation data.^{188, 190, 191} ^d Failed to resolve substrate by Chiral HPLC analysis.

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{array}{c} \text{OH} \\ \\ \text{R}^1\text{---CH---R}^2 \\ (\text{rac}) \end{array} \xrightarrow[\text{169 (1 mol\%)}]{\text{NEt}_3 \text{ (0.75 equiv.)} \\ (\text{iPrCO})_2\text{O (0.75 equiv.)} \\ -78\text{ }^\circ\text{C, 6 h, CH}_2\text{Cl}_2} \begin{array}{c} \text{OCO iPr} \\ \\ \text{R}^1\text{---CH---R}^2 \\ (\text{S})\text{-209} \end{array} + \begin{array}{c} \text{OH} \\ \\ \text{R}^1\text{---CH---R}^2 \end{array} $						
Entry	Substrate	Conv. ^a (%)	ee _A ^b (%)	Ester	S	Absol. config. ^c
1	200b	27.5	25		6.3	<i>R</i>
2	197c	15	14		9.5	<i>R</i>
3	206	23	11	 209c Ar = 4-NMe ₂ C ₆ H ₄	2.3	<i>1R,2S</i>
4	93	19	22		30	<i>1R,2S</i>

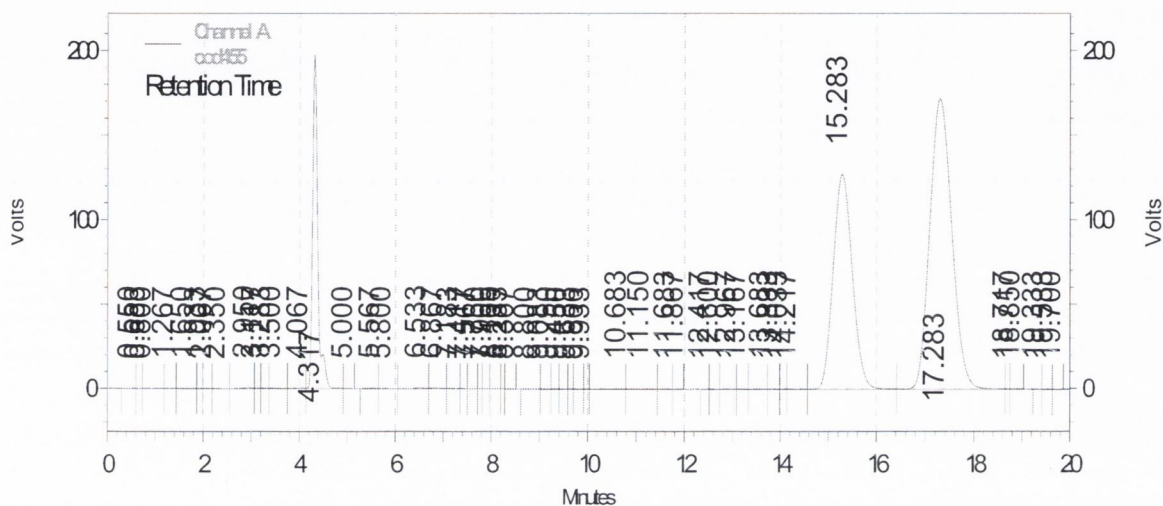
^a Conversion which could be determined (with excellent agreement) either by ¹H NMR spectroscopy or using chiral stationary phase HPLC, where $C = 100 \times ee_{\text{alcohol}} / (ee_{\text{alcohol}} + ee_{\text{ester}})$. ^b Determined by chiral HPLC using a Chiralcel OD-H column (4.6 x 250 mm). ^c Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data.^{88, 192, 193}

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

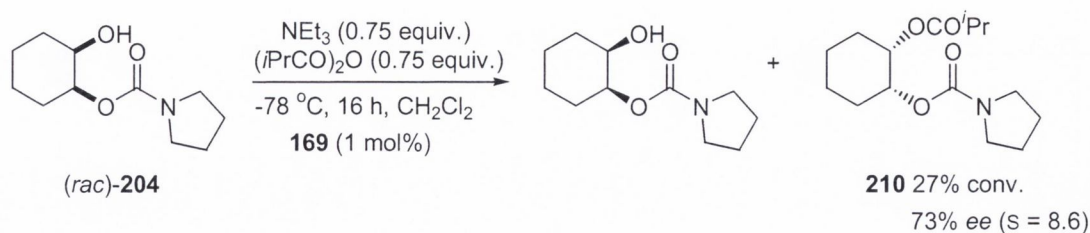
76b), the relative planarity of the benzo-fused five membered ring and the presence of a second potentially hydrogen bond donating group (amide N-H). In contrast, the KR of *trans*-2-phenylcyclohexanol (**93**) using **169** proceeded with superb enantioselectivity (entry 4 and Figure 2.6).

Figure 2.6 CSP-HPLC trace for the separation of (-) and (+) **93**



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.

Scheme 2.8 Kinetic resolution of aliphatic carbamate **204**



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**

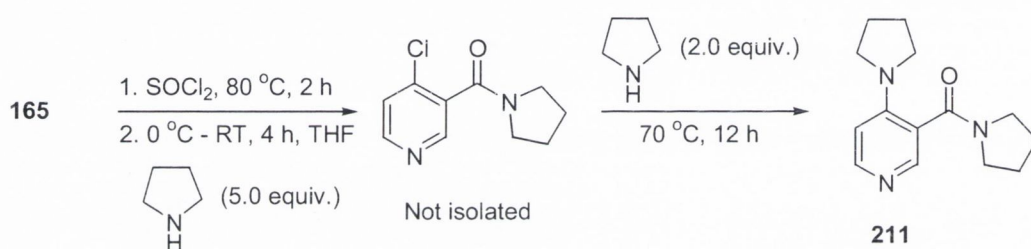
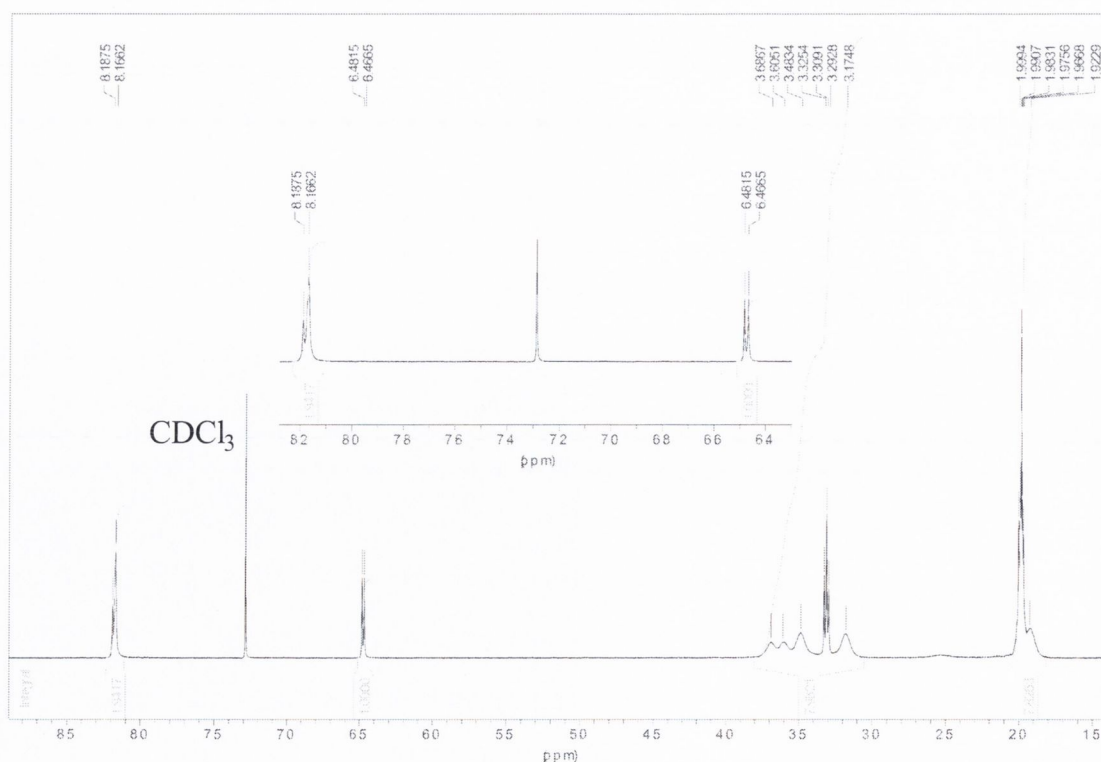
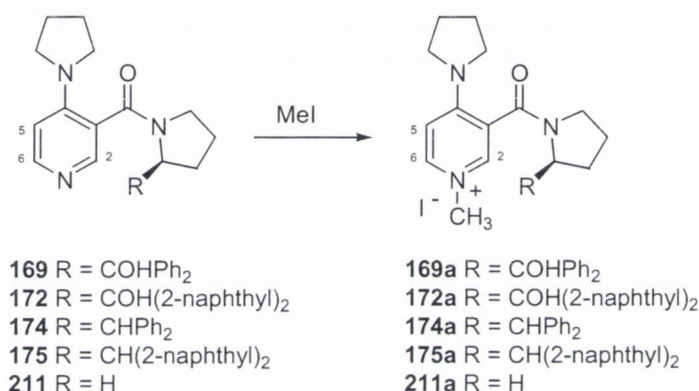


Figure 2.7 ^1H NMR of control catalyst **211**



In an attempt to detect possible aryl-pyridinium ion π -stacking interactions, the ^1H 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).⁸⁹ These experiments were informative; while little evidence was found to support a ‘face-face’ π - π stacking interaction as reported by Fuji⁸⁷ and Yamada¹⁸⁴ (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.¹⁹⁴

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

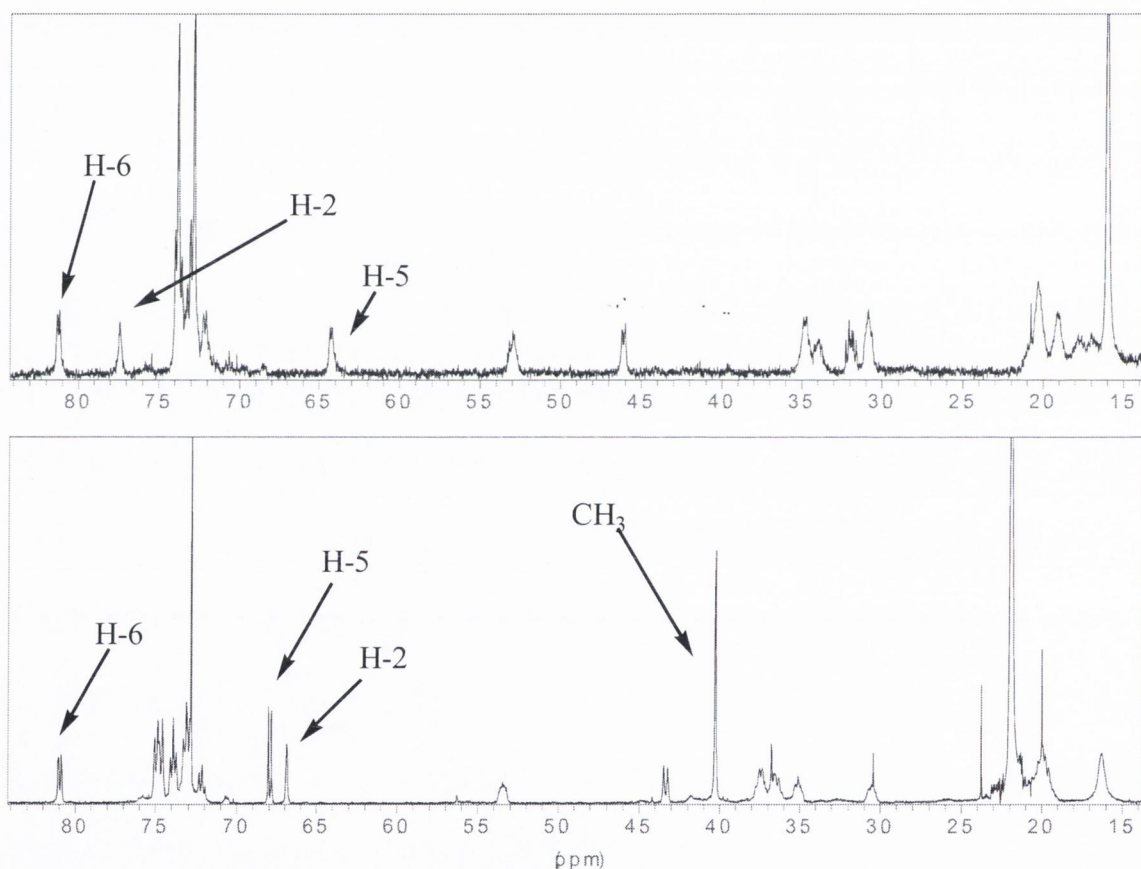


Entry	Cat.	δ H-2 ^{a,b,c}	δ H-5 ^{a,b,c}	δ H-6 ^{a,b,c}	δ CH ₃
1	169	7.33	6.45	8.09	-
2	169a	6.52 (-0.81)	6.80 (0.45)	8.04 (-0.05)	3.88
3	172	7.51	6.45	8.09	-
4	172a	5.99 (-1.52)	6.70 (0.25)	7.88 (-0.21)	3.33
5	174	7.73	6.42	8.12	-
6	174a	6.68 (-1.05)	6.79 (0.37)	8.10 (-0.02)	4.02
7	175	7.93	6.42	8.11	-
8	175a	6.39 (-1.54)	6.66 (0.24)	7.88 (-0.23)	3.49
9	211	8.19	6.47	8.16	-
10	211a	8.17 (-0.02)	6.90 (0.43)	8.21 (0.05)	4.21

^a δ Is quoted in ppm in CDCl₃ as solvent. ^bValue 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. ^cAll pyridine ring proton resonances were unambiguously assigned by NMR spectroscopy (^1H - ^1H COSY, ^1H - ^{13}C COSY, NOE and 1-D TOCSY experiments).

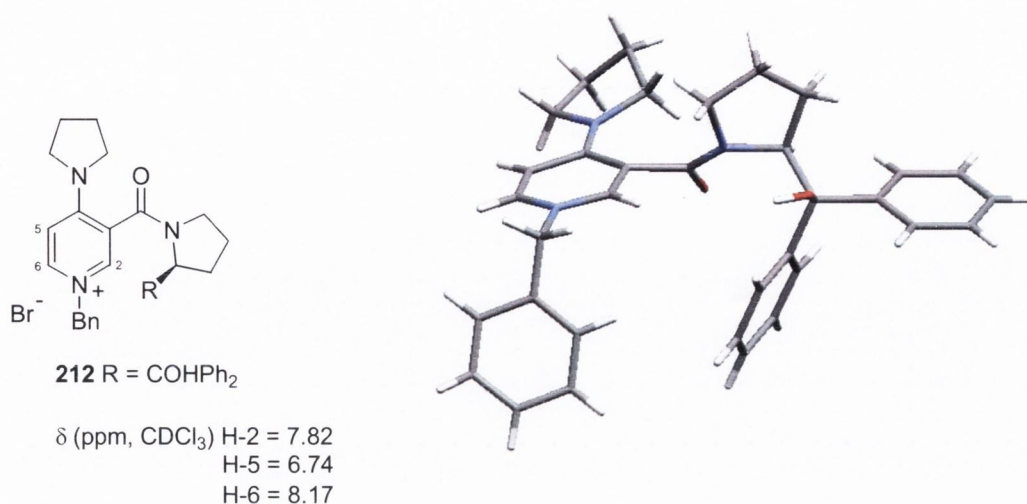
This effect is more dramatic in the case of the naphthyl-substituted **172a** and **175a**, where even the pyridinium methyl protons are significantly shielded relative to the corresponding **211a** methyl group. Clear illustration of the upfield shift of H-2, H-5 and H-6 associated with methylation is observed in the ^1H NMR spectra of **174** and **174a** (Figure 2.8). It is also noteworthy that δ 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 ^1H 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)

Figure 2.9 X-ray crystal structure of benzylated catalyst **212** (bromide counter ion omitted)



The amide moiety is in an *s-cis* conformation with the diaryl tertiary alcohol substituent orientated towards H-2 and the nucleophilic ring-nitrogen: consistent with the proposed π -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 *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 CDCl₃. 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.

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 ^1H NMR acylation studies of **169** and **211**

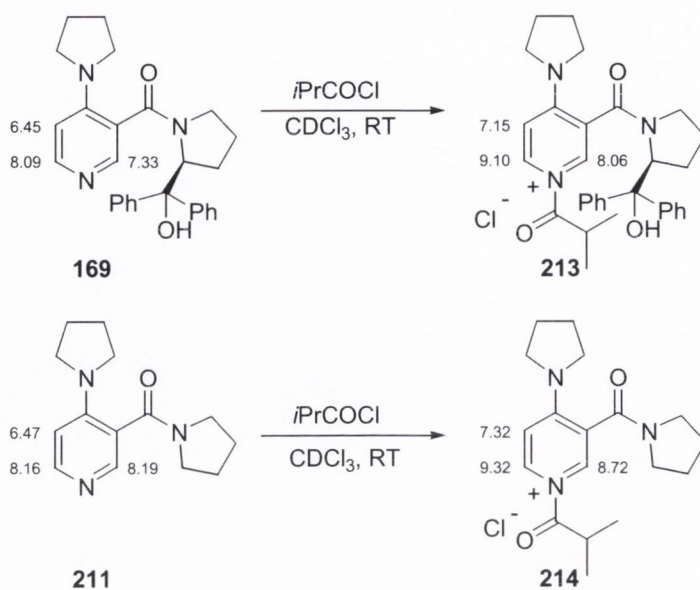
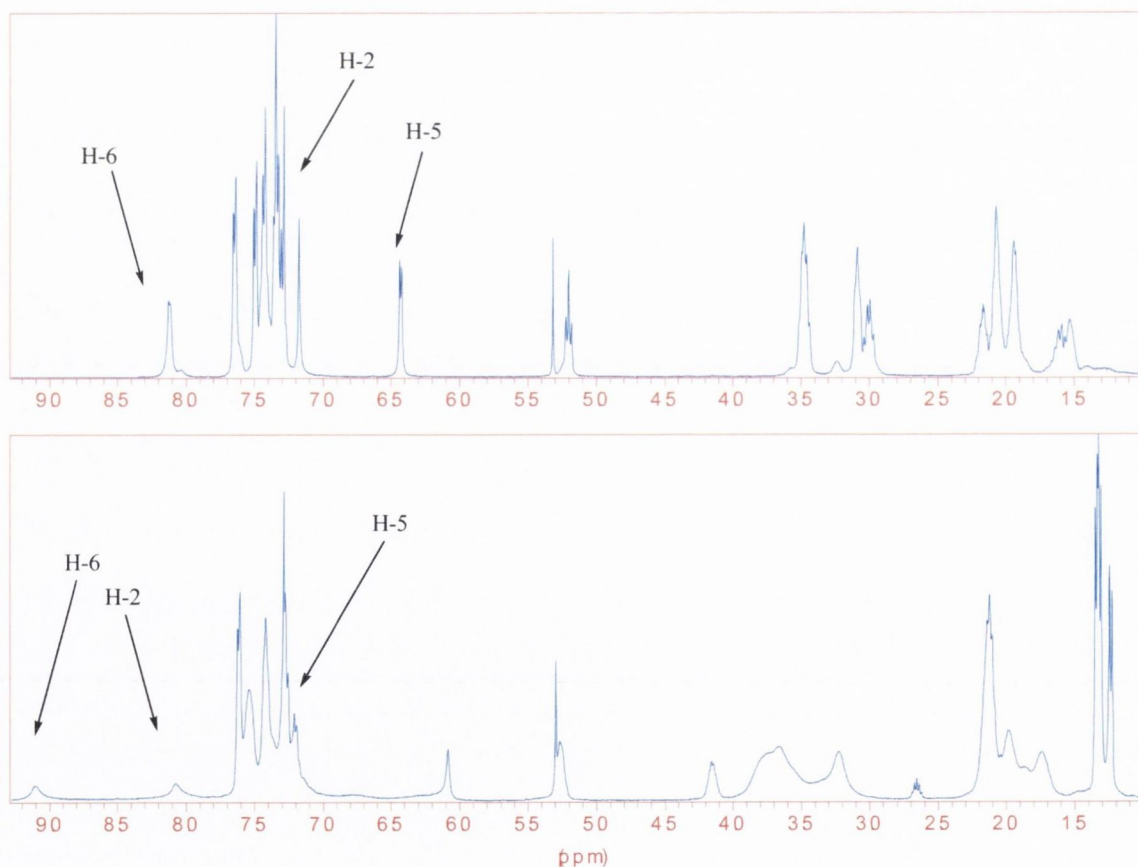


Figure 2.10 ^1H NMR spectra of catalyst **169** and acylated derivative **213**



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.

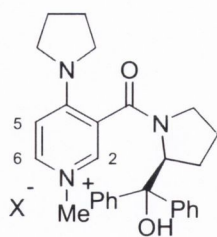
These results indicate that in the case of both **213** and **214** (contrary to what might be expected from first principles but in agreement with reports from Spivey¹⁹⁵ and Yamada⁹⁰) the bulky *iso*-propyl moiety is located on the same side of the *N-N* axis as the catalyst amide substituent (*i.e.* 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.

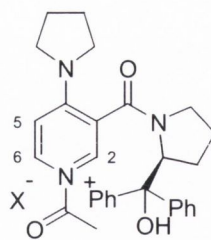
To better understand the origins of enantiodiscrimination using **169** and **172** we enlisted the aid of Prof. Graeme Watson to help examine the conformational preferences of **169a** and **215** (the *N*-acetyl analogue of **213**) using B3LYP hybrid density functional theory (Gaussian 03, 6-31G* basis set).¹⁹⁶ 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 **I-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**



169a

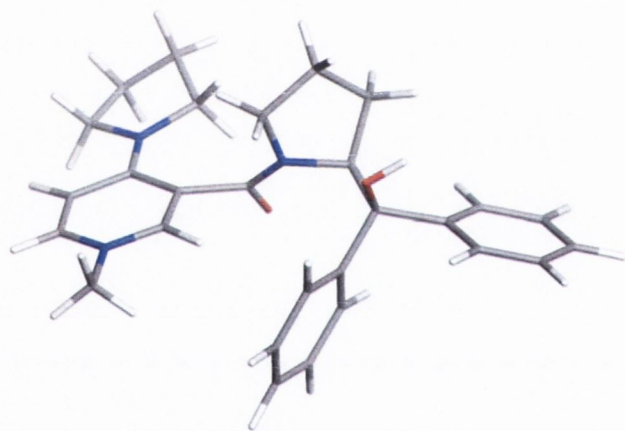


215

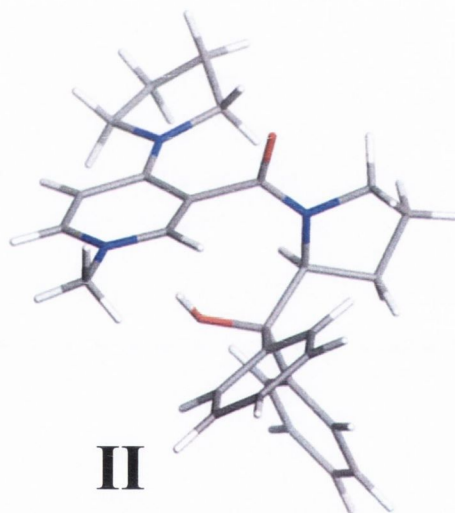
Entry	Cat.	Conformation	Amide rotamer	N-acetyl rotamer	Relative energy (kJ mol ⁻¹) ^{a,b}
1	169a	I	<i>s-cis</i>	-	0
2	169a	II	<i>s-trans</i>	-	44.9
3	215	III	<i>s-cis</i>	<i>s-trans</i>	0
4	215	IV	<i>s-cis</i>	<i>s-cis</i>	4.2

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

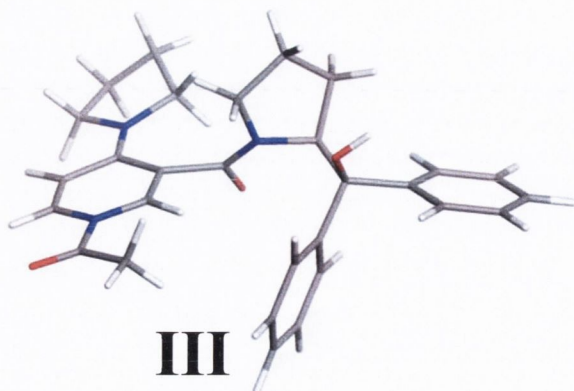
Calculated minimum energy conformers of **169a** and **215**



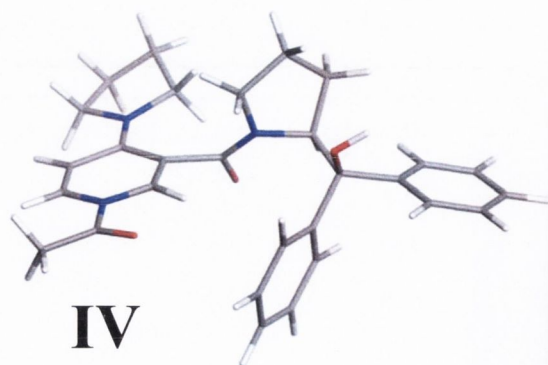
I



II



III

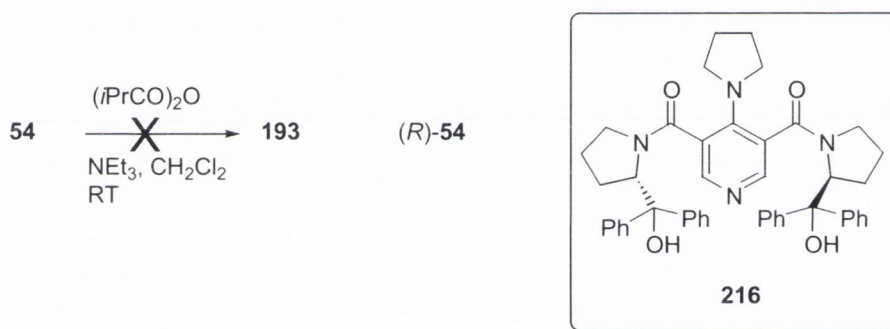


IV

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,¹⁹⁵ be related to partial conjugation with the C-3 substituent, although like Spivey we have no evidence to support this claim.

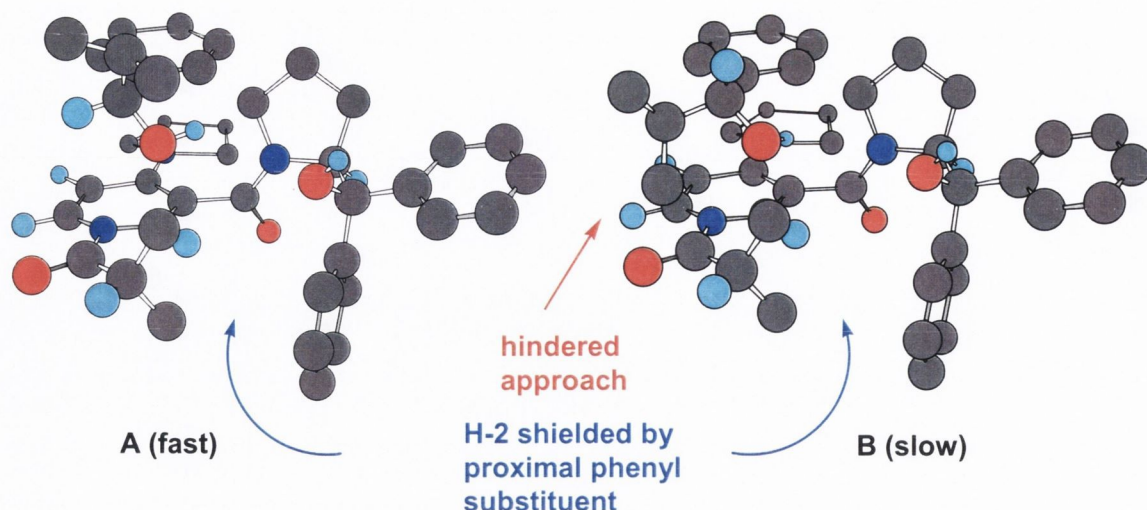
Interestingly, a C₂-symmetric analogue of **169** (**216**, Scheme 2.11) designed to circumvent potential problems associated with *N*-acyl isomerism and synthesised by Dr. Stephen J. Hynes in our group, proved to be a completely inactive acylation catalyst.

Scheme 2.11 C₂-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).

Figure 2.11 Possible pre-TS-assemblies for the acylation of **57** by **215**. A: (*S*)-**57** by **215**. B: acylation of (*R*)-**57** by **215**



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.

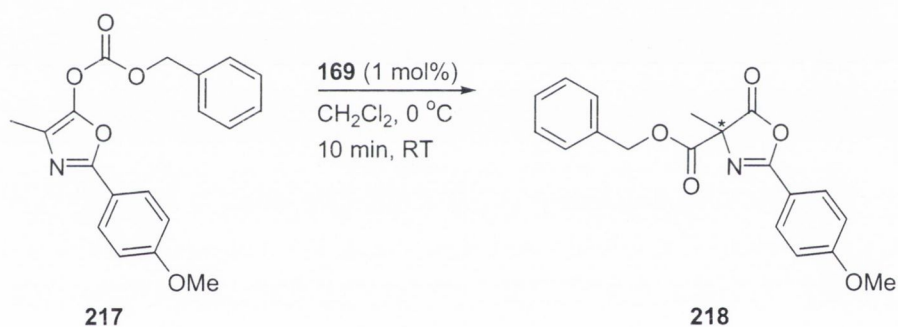
To the best of our knowledge **169** and **172** represent the first chiral 4-*N,N*-dialkylaminopyridine catalysts to synergistically employ both van der Waals (π) interactions and hydrogen bonding to allow remote chirality to exert stereochemical influence on an acylation reaction, and while the levels 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 Vedejs⁶⁷ and Fu¹⁹⁷ (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 CH₂Cl₂, 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 ¹H 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% CH₂Cl₂) 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.

3.1 Baylis-Hillman: General

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.^{131, 132, 198}

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,¹⁹⁹ 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.

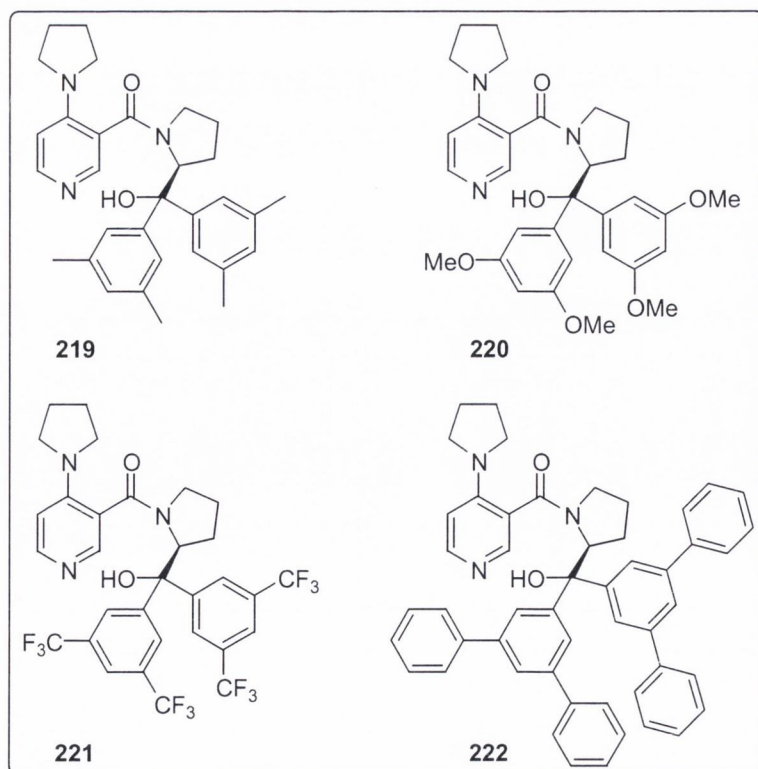
Therefore, encouraged by the highly active catalyst **169** -developed for the acylative kinetic resolution of *sec*-alcohols- exhibiting an unusually strong preference for substrates

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 sp^2 - sp^2 *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).

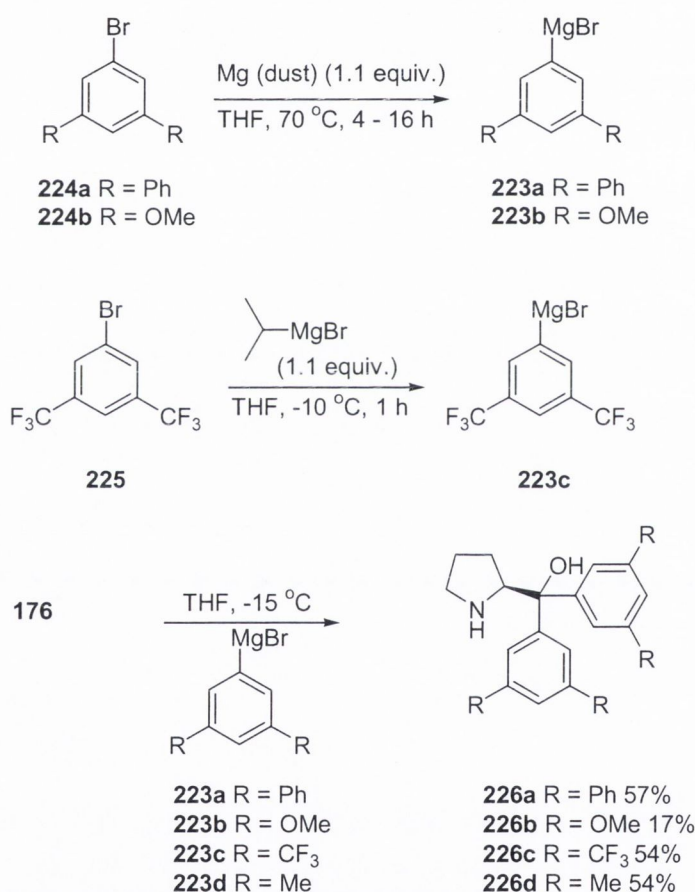
Figure 3.1 Chiral analogues of 169, catalysts 219-222



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,²⁰⁰ 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**

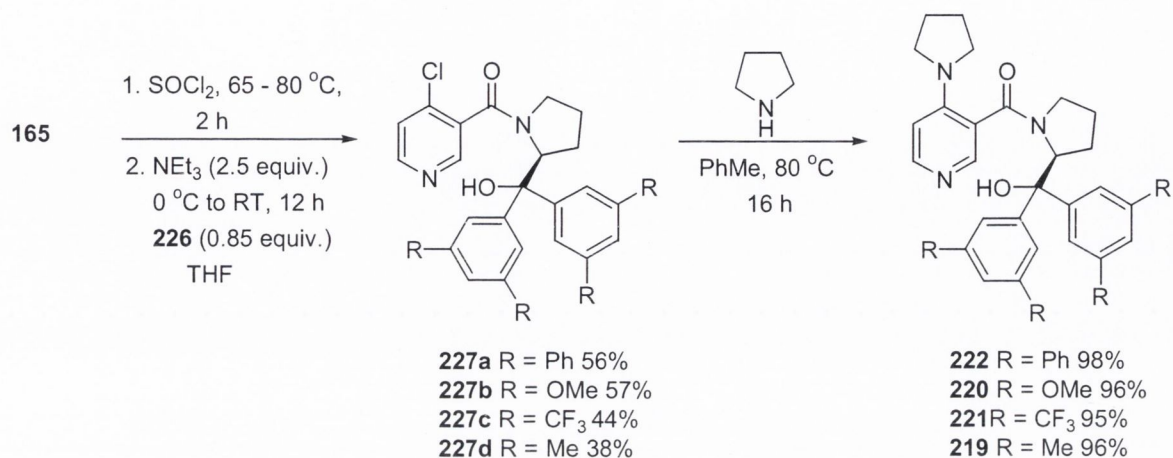
Scheme 3.1 Synthesis of di-aryl prolinols **226a-d**



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.

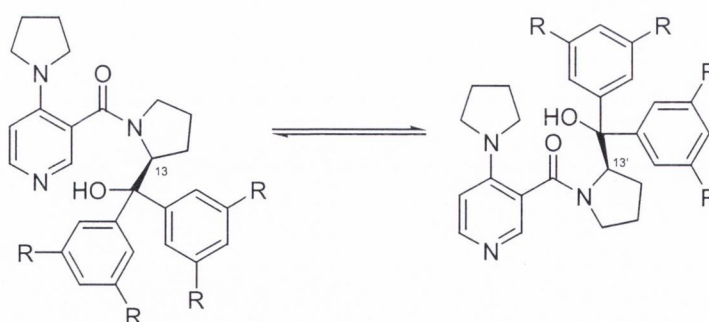
Scheme 3.2 Synthesis of catalysts **219-222**



3.2.2 ¹H NMR analysis of catalysts **219-222**

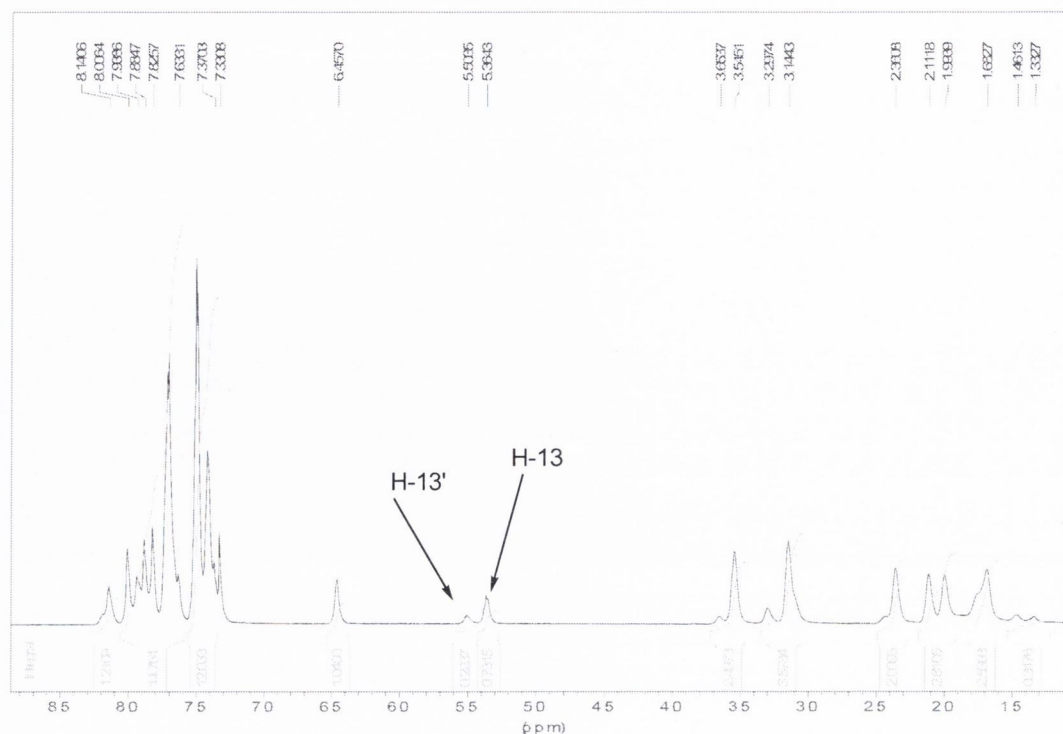
Unfortunately, ¹H NMR analysis of each of the catalysts (**219-222**) revealed the presence of rotamers, with only one rotamer conceivably conducive to the intramolecular π - π stacking presumed to be required for enantioselective acyl-transfer (Scheme 3.3). This notwithstanding, it was decided to evaluate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

Scheme 3.3 Rotameric ratio of catalysts **219-222**



Entry	Cat.	Ratio of rotamers major:minor
1	219	3:1
2	220	17:3
3	221	4:1
4	222	4:1

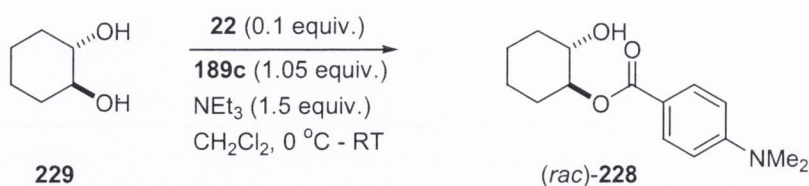
Figure 3.2 ^1H NMR of catalyst **222** at RT with both rotamers present



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**

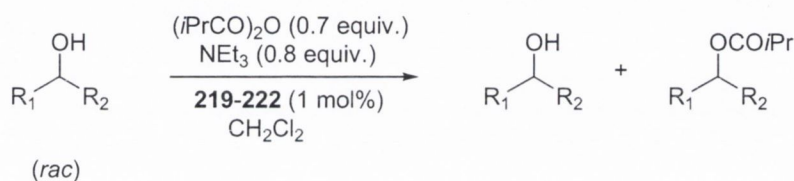


3.3.1 Evaluation of catalysts **219-222** in the KR of *sec*-alcohols

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



Entry	Cat.	Substrate	T (°C)	C (%) ^a	ee _E (%) ^b	ee _A (%) ^b	S ^c	absolute config. ^d
1 ^e	169	57	0	35	50	27	3.9	(R)
2 ^e	222	57	0	63	44	74	5.3	(R)
3 ^e	220	57	0	62	40	65	4.4	(R)
4 ^e	219	57	0	56	31	40	2.7	(R)
5 ^e	221	57	0	61	44	69	5.1	(R)
6 ^e	169	76b	0	57	54	71	6.9	(1 <i>S</i> ,2 <i>R</i>)
7 ^e	222	76b	0	59	57	82	9.0	(1 <i>S</i> ,2 <i>R</i>)
8 ^e	220	76b	0	61	50	77	6.6	(1 <i>S</i> ,2 <i>R</i>)
9 ^e	219	76b	0	58	40	55	3.9	(1 <i>S</i> ,2 <i>R</i>)
10 ^e	221	76b	0	60	58	87	10.1	(1 <i>S</i> ,2 <i>R</i>)
11 ^f	221	76b	-78	66	50	96	10.8	(1 <i>S</i> ,2 <i>R</i>)
12 ^f	221	228	-78	77	30	>99	20.0	nd

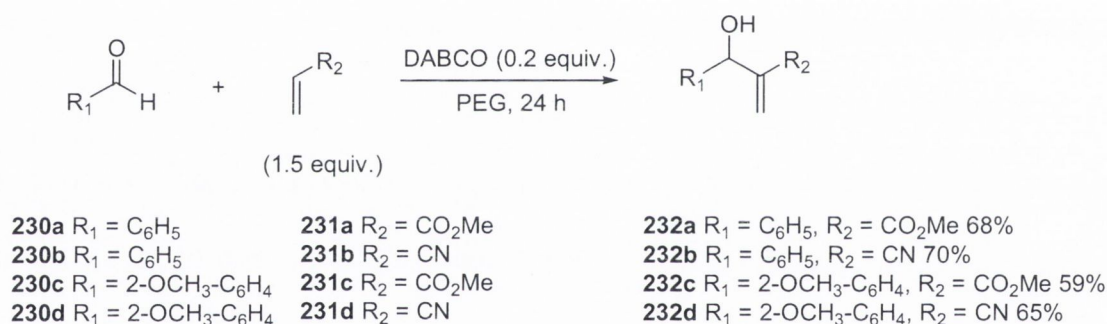
^aConversion: which could be determined (with excellent agreement) either by ¹H NMR spectroscopy or chiral HPLC, where C = 100 x ee_{alcohol}/(ee_{alcohol} + ee_{ester}). ^bee determined by chiral HPLC using a Chiralcel OD-H column (4.6 x 250 mm), ee_E = ee of the ester product, ee_A = ee of the recovered alcohol. ^cs = enantioselectivity (k_{fast}/k_{slow}, see ref. 11). ^dAbsolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data ^e6 h reaction time. ^f24 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%).

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.

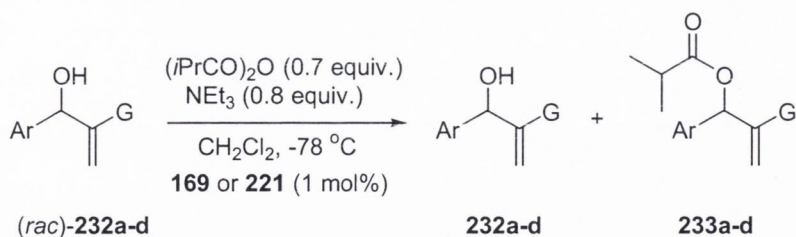
Scheme 3.4 Synthesis of BH adducts **232a-d**



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).

Table 3.2 KR of BH adducts catalysed by **169** and **221**



Entry	Cat.	Substrate	Conv. (%) ^a	S ^b	ee _E (%)	ee _A (%) ^c	Yield (%) ^d	absolute config. ^e
1	169	232a	70	3.1	27	62	29	(+)-(S)
2	221	232a	72	3.7	29	74	27	(+)-(S)
3	221	232a	83	3.8	20	95	16	(+)-(S)
4	169	232c	61	10.9	57	90	36	(+)-(S)
5	221	232c	56	11.0	64	82	40	(+)-(S)
6	221	232c	64	13.1	55	97	35	(+)-(S)
7	221	232b	51	3.5	-	41	45	nd
8	221	232b	85	3.6	-	93	13	nd
9	221	232d	32	4.0	-	25	64	(+)-(R) ⁱ
10	221	232d	78	3.5	-	82	19	(+)-(R) ⁱ

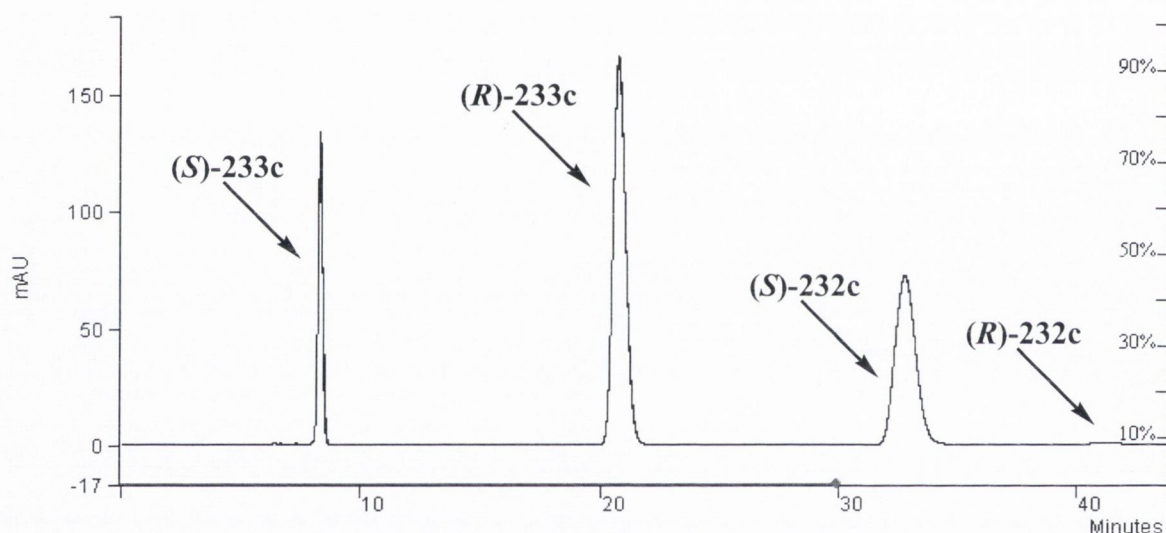
^aConversion: determined by CSP-HPLC, where $C = 100 \times ee_{\text{alcohol}} / (ee_{\text{alcohol}} + ee_{\text{ester}})$. ^d_S = enantioselectivity ($k_{\text{fast}}/k_{\text{slow}}$, see ref. 11). ^eee of the recovered alcohol determined by CSP-HPLC using a Chiralcel OD-H column (4.6 x 250 mm). ^dRefers to isolated yield of the recovered alcohol after chromatography. ^eAbsolute configuration of the alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data. ^f0.85 equiv. isobutyric anhydride, 0.95 equiv. NEt₃, 24 h. ^g0.70 equiv. (iPrCO)₂O, 0.80 equiv. NEt₃, 24 h. ^h1.50 equiv. (iPrCO)₂O, 0.80 equiv. NEt₃, 8h. ⁱNote that due to a priority change, the label of the stereogenic centre changes in (+)-**232d** from (S) to (R).

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 *iso*-butyric 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**

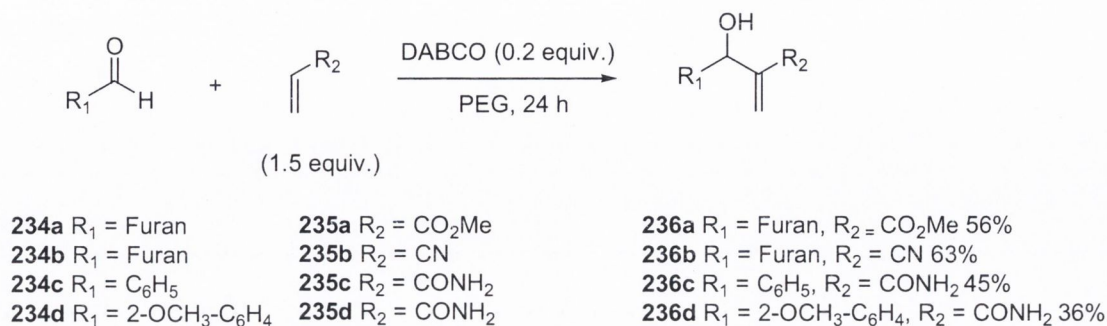


Peak No	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)
1	14.4026	8.280	0.000	17787792	0.00	VP	12.3
2	49.1853	20.741	0.000	60746008	0.00	PB	35.0
3	35.2724	35.2724	0.000	43562972	0.00	VB	58.3
4	0.5718	41.209	0.000	706221	0.00	VB	96.1
Totals	99.4321		0.000	122802993			

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,

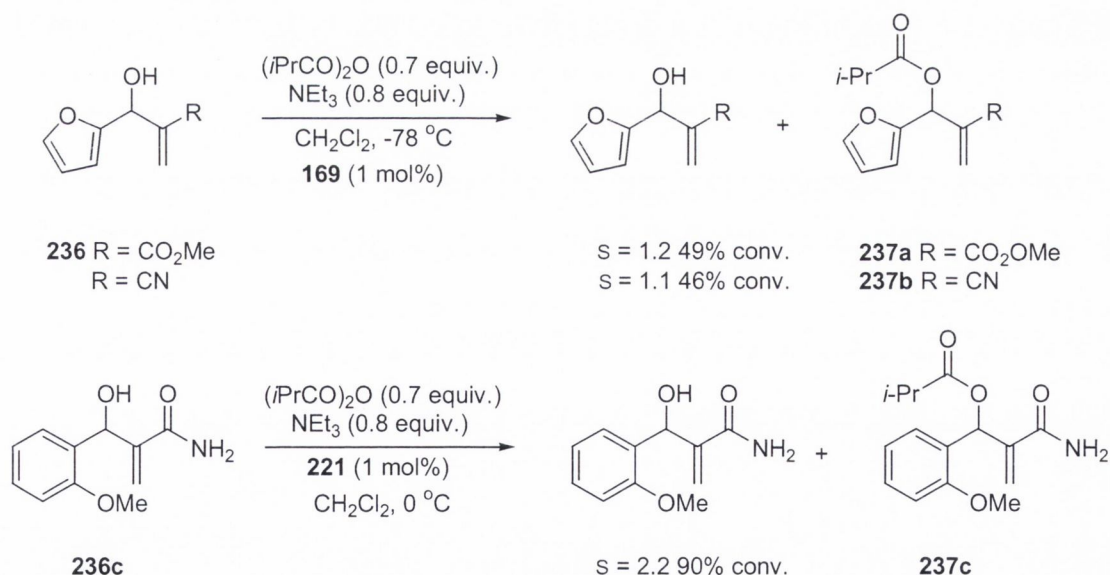
the catalysed acylative resolution of **236a-b** failed to yield either product or starting material with good levels of enantioselectivity (Scheme 3.6).

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



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 CH_2Cl_2 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**



3.5 One pot synthesis and resolution of BH adducts

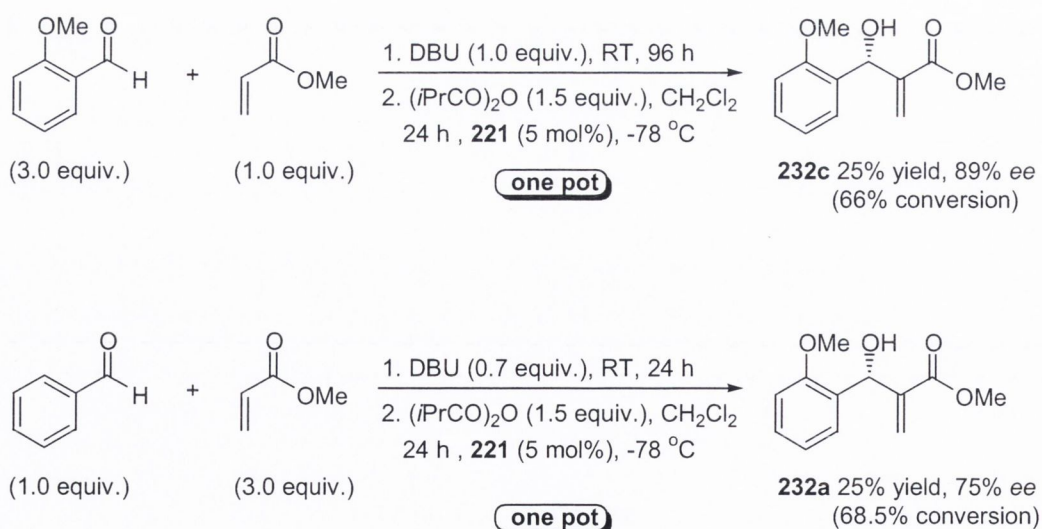
Given the key roles that tertiary amines often play in both BHRs (as nucleophilic catalysts) and acylation reactions (as bases) we were intrigued by the possibility that a dual catalyst

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.¹⁴² 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 $-78\text{ }^{\circ}\text{C}$ and addition of *iso*-butyric 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



3.6 Conclusion for chapter 3

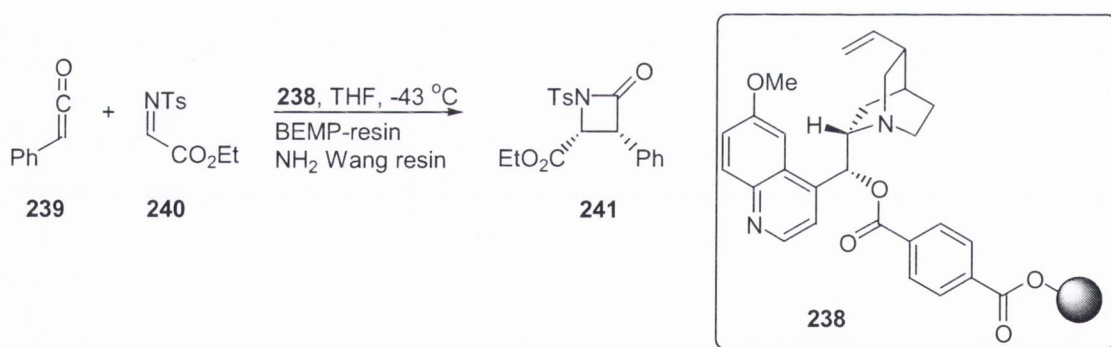
In summary catalyst **169** and its optimised analogue **221** promote the synthetically useful KR of Baylis-Hillman adducts **232a-d** and **236c** derived from deactivated precursors (difficult to synthesise using catalytic asymmetric BHRs) – allowing the convenient preparation of **232a-d** and **236c** in 78-97% *ee*. To the best of our knowledge this study also represents the first examples of effective non-enzymatic acylative KR of sp^2 - sp^2 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.²⁰¹ **238** Promoted the enantioselective Staudinger β -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 β -lactam synthesis catalysed by **238**

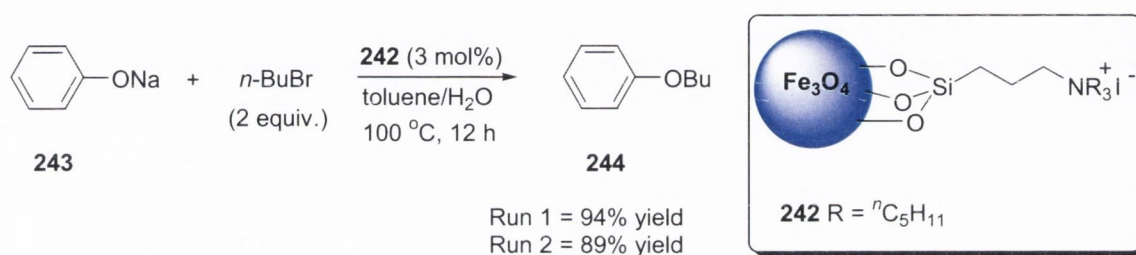


4.2 A nanoparticle supported heterogeneous catalyst system

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 4.2.²⁰³

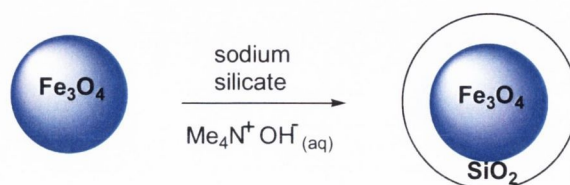
Scheme 4.2 Catalysed butylation of sodium phenoxide by **242**



4.3 Design of a nanoparticle supported DMAP catalyst

Our initial design for a supported DMAP analogue employed an alkyl-siloxy linker to tether the silicon coated magnetite to PPY. Magnetite (Fe_3O_4) nanoparticles of 9.6 nm average diameter (calculated from XRD analysis by Ms Serena Corr, using the Debye-Scherrer equation)²⁰⁴ were prepared *via* the coprecipitation technique.²⁰⁵ In a departure from conventional catalyst loading strategies, the particles were then coated with a silica layer²⁰⁶ by preliminary dispersion in aqueous tetramethylammonium hydroxide followed by exposure to sodium silicate (carried out by Ms. Serena Corr), Scheme 4.3.

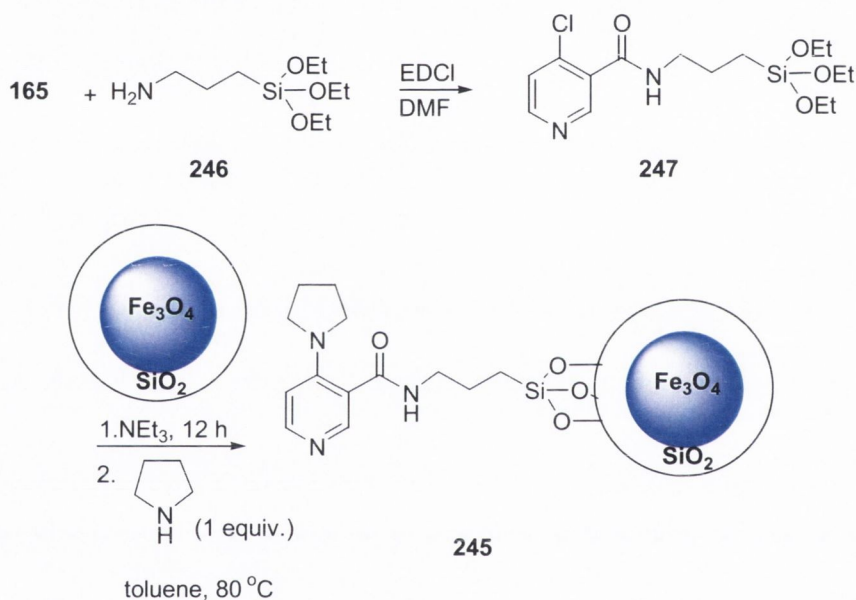
Scheme 4.3 Synthesis of silicon coated magnetite



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 Fe₃O₄ nanoparticles),²⁰⁷ and b) provides a stable, relatively inert shell onto which a triethoxysilane-substituted organocatalyst moiety can be installed.

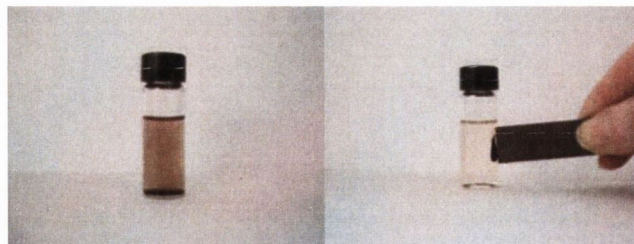
Ms Serena Corr in the Gun'ko laboratory carried out the initial synthesis of **245**, by coupling **165** to 3-aminopropyltriethoxysilane (**246**) in dry DMF with EDCI, followed by immediate reaction with magnetite and subsequent pyrrolidination to afford the desired catalyst **245** (Scheme 4.4). Although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

Scheme 4.4 Synthesis of **245**

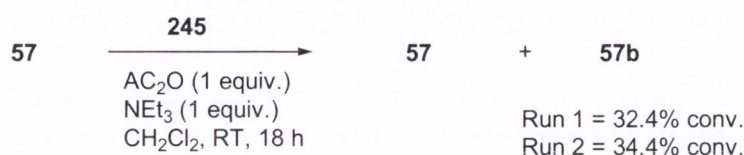


245 Was evaluated as a promoter in the acylation of **57** by acetic anhydride with mechanical agitation for 18 h at RT followed with quenching by the addition of MeOH. ¹H NMR analysis revealed only a moderate catalytic turnover (32.4 % conversion). The catalyst was separated by exposure of the reaction 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.

Figure 4.1 Removal of magnetic nanoparticles



Scheme 4.5 Acetylation of **57** promoted by **245**

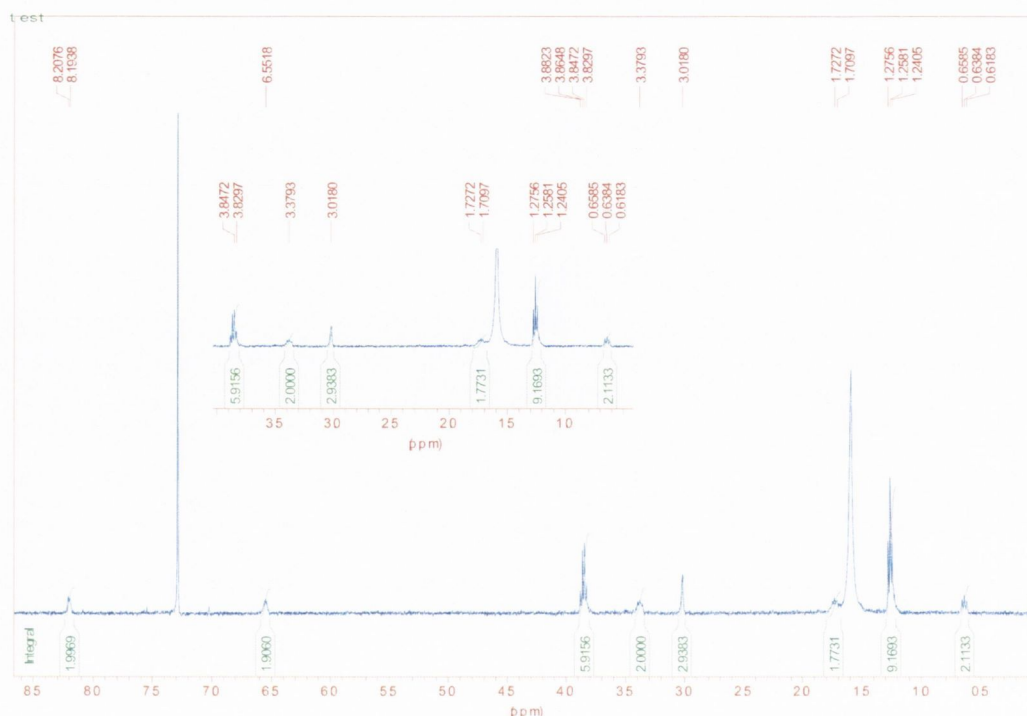


While **245** demonstrated the synthetic utility of a nanoparticle supported DMAP catalyst system, two inherent problems needed to be addressed in order to realise the catalytic system's potential and to make a viable alternative to the established/reported supported DMAP analogues (Section 1.7.2): 1) the lack of a quantifiable catalyst loading strategy and 2) the modest conversions achieved upon acylation.

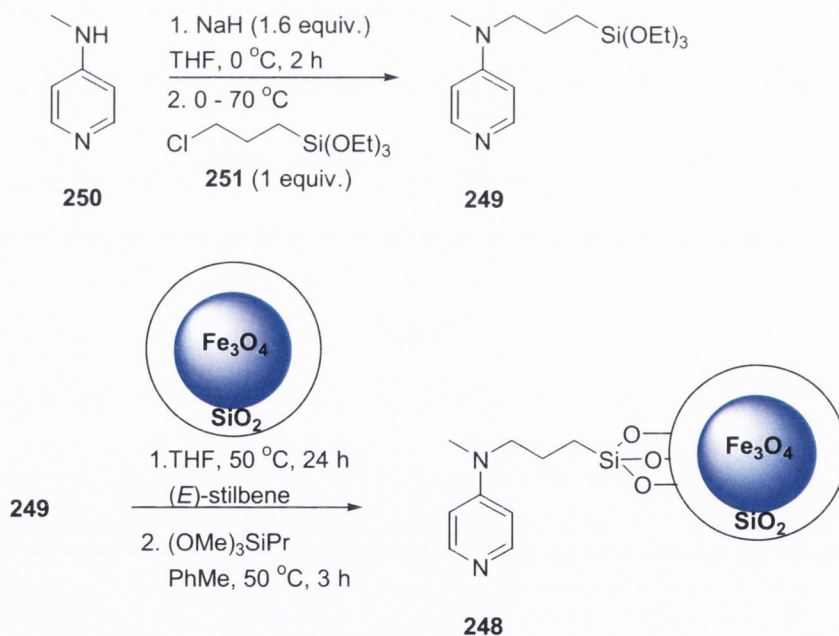
4.3.1 Design of a 2nd generation nanoparticle-supported catalyst

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 (CH₂Cl₂-NEt₃, 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 ^1H NMR of triethoxysilane derivative **249**



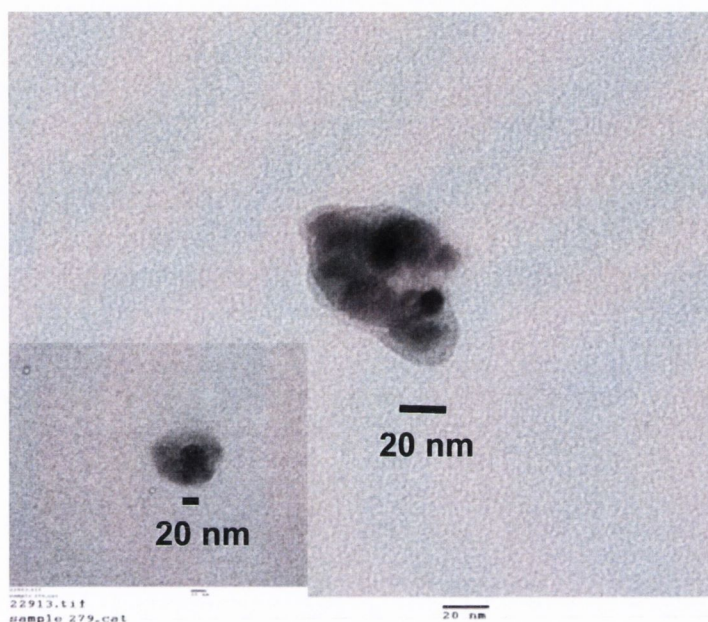
Scheme 4.6 Synthesis of the second generation catalyst **248**



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 ^1H 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**

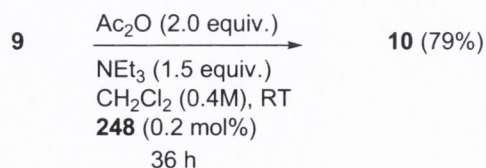
$$\begin{array}{ccc}
 \mathbf{9} & \xrightarrow[\substack{\text{NEt}_3 \text{ (1-1.5 equiv.)} \\ \text{CH}_2\text{Cl}_2 \text{ (0.4M), RT} \\ \mathbf{248} \text{ (5 mol\%)} }]{\text{Ac}_2\text{O (1.5 equiv.)}} & \mathbf{10}
 \end{array}$$

Entry	Cycle	Time (h)	Conv. (%) ^a
1	1	16	>98
2	2	16	94
3	3	16	97
4	4	16	>98
5	5	16	>98
6	6	16	>98
7	7	16	>98
8	8	16	97
9	9	16	98
10	10	16	97
11 ^b	11	16	>98
12 ^b	12	16	>98
13 ^c	13	3	94
14	14	1	97

^aDetermined by ¹H NMR spectroscopy. ^b 2.0 Equiv. of Ac₂O employed. ^c 1.2 Equiv. of NEt₃ 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).

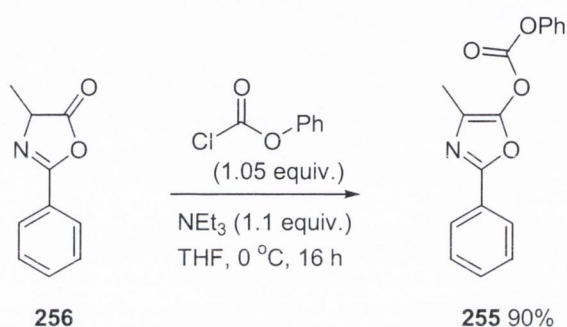
Scheme 4.7 Acetylation of **9** at low catalyst loadings (cycle 15)



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

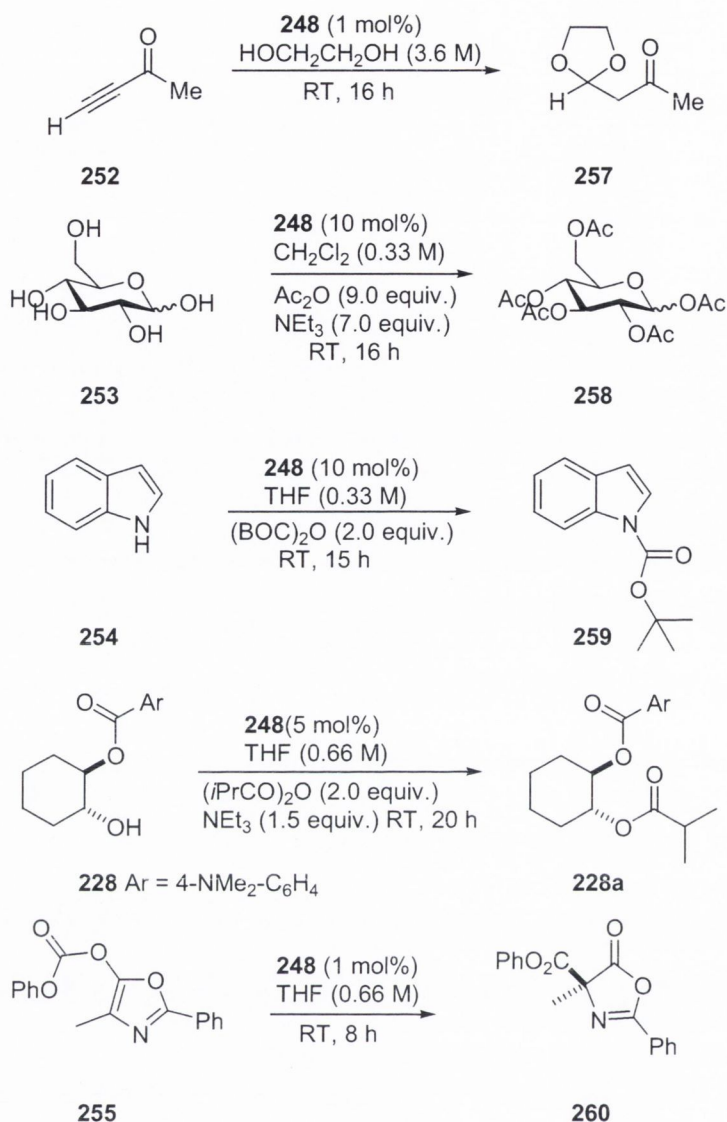
Scheme 4.8 Synthesis of substrate **255**



Employing the same catalyst recovery methodology as before, it was found that **248** (in as little as 1 mol% loading) could promote the *bishydroalkoxylation* 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

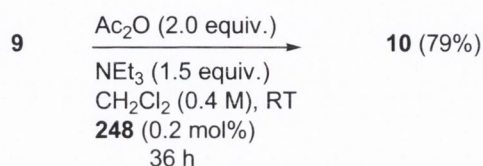


Entry	Cycle	Substrate	Product	Loading (mol%)	Time (h)	Yield (%) ^a
1	16	252	257	1	16	91
2	17	252	257	1	16	90
3	18	252	257	1	16	88
4	19	253	258	10	16	96
5	20	253	258	10	16	95
6	21	253	258	10	16	96
7	22	254	259	10	15	97
8	23	254	259	10	15	98
9	24	254	259	10	15	98
10	25	228	228a	5	20	91
11	26	228	228a	5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

^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).

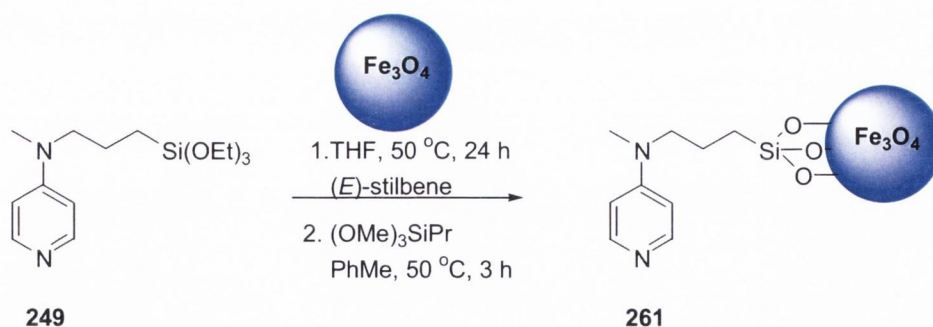
Scheme 4.8 Repeat of the acetylation of **9** at low catalyst loading (cycle 31)



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 ¹H 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**

254	261 (10 mol%) BOC ₂ O (2.0 equiv.) THF (0.33 M) 15 h, RT, (<i>E</i>)-stilbene	259	
Entry	Loading (mol%)	Time (h)	Conv ^a
1	10	15	>99
2	10	15	>99
3	10	15	>99
4	10	15	>99
5	10	15	>99

^aQuantified by ¹H 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 ¹H 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.

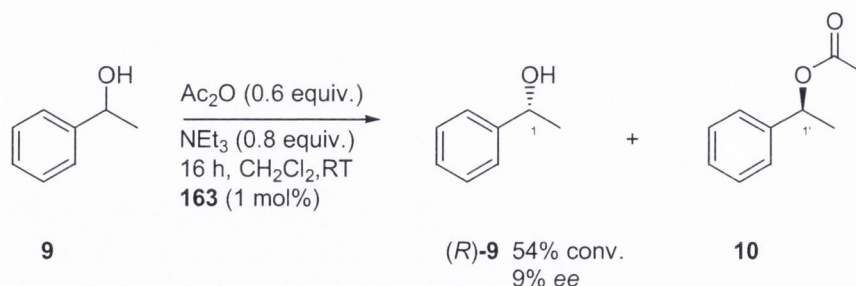
Recovery of the catalysts by decantation of the reaction is both convenient and efficient, which, combined with the intrinsic stability of both the organic- and nanoparticle-catalyst components, allows **248** to be recycled over 30 times (**261** has only verifiably been recycled 7 times) in a number of transformations without any discernable loss in activity.

5.1 General

Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in CDCl_3 referenced relative to residual CHCl_3 ($\delta = 7.26$ 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 KMnO_4 staining. Specific rotation measurements were made on a Rudolph research analytical Autopol IV instrument, and are quoted in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. 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 performed 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



A 1 mL reaction vessel charged with catalyst (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 **9** (29 μL , 0.234 mmol) and NEt_3 (26 μL , 0.187 mmol) in CH_2Cl_2 (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 (CH_2Cl_2) through a pad of silica gel.

^1H NMR of **10**:

δ_{H} (400 MHz, CDCl_3): 1.56 (d, 3H, J 6.8, CH_3), 2.10 (s, 3H, CH_3), 5.90 (q, 1H, J 6.8, H-1'), 7.30-7.38 (m, 5H, Ar-H).

^1H NMR of **9**:

δ_{H} (400 MHz, CDCl_3): 1.46 (d, 3H, J 6.8, CH_3), 4.84 (q, 1H, J 6.8, H-1), 7.19-7.25 (m, 5H, 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 CDCl_3 (400 μL) and 20 μL volumes were added *via* syringe to a solution of **10** (3 μL , 0.18 mmol) in CDCl_3 (200 μL). ^1H 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**.

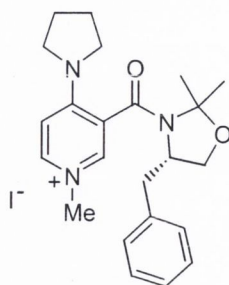
5.2.1.2.1 Determination of the enantiomeric excess of **10**

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 CH_2Cl_2 (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 CDCl_3 (400 μL) and analysed by ^1H NMR spectroscopy.

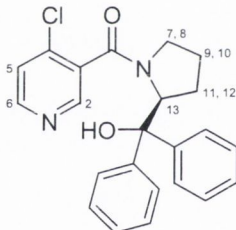
5.2.1.3.1 Methylation of catalyst (*S*)-163



Procedure B was followed using catalyst **163** (25.6 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 (**168**) in CDCl₃ by ¹H 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)



A 10 mL round bottom flask charged with **165** (315 mg, 2.0 mmol) and SOCl₂ (1.45 mL, 20.0 mL) was fitted with a reflux condenser and heated under reflux for 1 hour. Removal of SOCl₂ 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 NEt₃ (550 μL, 4.0 mmol) in THF (20 mL) was added *via* syringe. The yellow solution was left to stir overnight. CH₂Cl₂ (80 mL) was then added and the resulting solution 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 (9:1 CH₂Cl₂-EtOAc, R_f = 0.2) gave **171** (627 mg, 80%) as a white solid. M.p. 64-66 °C. [α]_D²⁰ = -95 (c 0.11, CHCl₃).

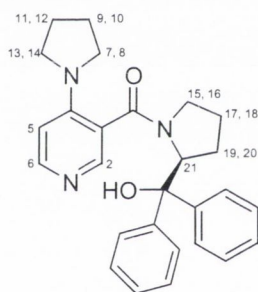
δ_{H} (400 MHz, CDCl_3): 1.74 (m, 2H, H-9, H-10), 2.05 (m, 1H, H-11), 2.22 (m, 1H, H-12), 2.90 (m, 1H, H-7), 3.10 (m, 1H, H-8), 5.30 (app. t, 1H, J 5.5, H-13), 6.48 (s, 1H, OH), 7.22-7.60 (m, 11H, Ar-H, H-5), 8.10 (bs, 1H, H-2), 8.52 (d, 1H, J 5.6, H-6).

δ_{C} (100 MHz, 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).

ν_{max} (film)/ cm^{-1} : 3281, 1615, 1431, 1155, 699.

HRMS (m/z - ES): Found 415.1200 ($\text{M}^+ + \text{Na}$. $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_2\text{ClNa}$ 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. $[\alpha]_{\text{D}}^{20}$ = -98 (c 0.96, CHCl_3).

δ_{H} (400 MHz, 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),

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).

δ_C (100 MHz, $CDCl_3$): 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).

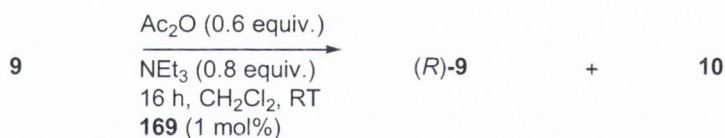
ν_{max} (film)/ cm^{-1} : 3179, 2854, 1590, 1304, 971.

HRMS (m/z - ES): Found 428.2328 ($M^+ + H$. $C_{27}H_{30}N_3O_2$ Requires: 428.2338)

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

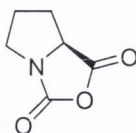
Procedure A was followed using chiral product **10** from the reaction of **9** with acetic anhydride catalysed by **169**. Analysis of the resulting methyl peaks showed a 31% *ee* for the (*S*)-antipode.

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



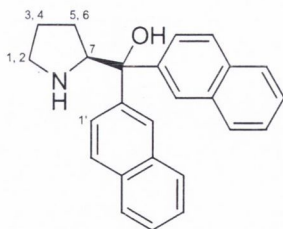
A 1 mL reaction vessel charged with catalyst (2.34 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of **9** (29 μL , 0.234 mmol) and NEt_3 (26 μL , 0.187 mmol) in solvent (500 μL). The resulting solution was left to stir for 30 minutes. Acetic anhydride (13 μL , 0.14 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 (CH_2Cl_2) through a pad of silica gel.

5.2.2.5 Synthesis of tetrahydro-pyrrol[1,2-*c*]oxazole-1,3-dione (*S*)-(176)¹⁸⁶



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)



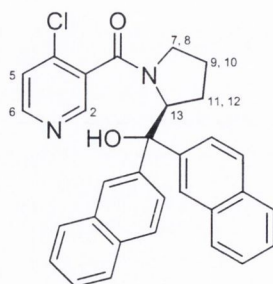
A 100 mL three-necked flask fitted with a 50 mL addition funnel containing the THF solution of (*S*)-**176** (6.52 mmol in 40 mL THF) and a stirrer was charged with a solution of 2-naphthylmagnesium bromide (**180**) (0.5 M in THF, 22.5 mmol) and cooled to -15 °C. The THF solution of (*S*)-**176** was 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 H₂SO₄ (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 MgSO₄ formed. The mixture was agitated for 1 h at 0 °C and filtered through a medium-frit, sintered-glass funnel. The MgSO₄ 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 H₂O (2 x 40 mL) to remove excess H₂SO₄, 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 H₂O (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.,²⁰⁹ 78-79 °C).

δ_{H} (400 MHz, CDCl₃): 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-dinaphthyl-methyl)-pyrrolidin-1-yl]-methanone (**S**)-(181)



Procedure C was followed using **165** (330 mg, 2.10 mmol), SOCl₂ (1.5 mL, 21.0 mmol), THF (5 + 4 mL), (**S**)-**179** (740 mg, 2.10 mmol) and NEt₃ (870 μ L, 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. $[\alpha]_D^{20} = -84$ (c 0.1, CHCl₃).

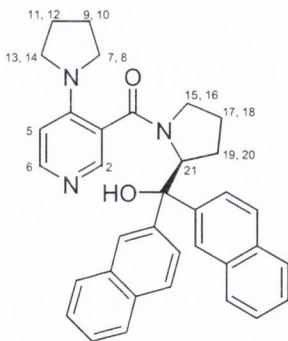
δ_H (400 MHz, CDCl₃): 1.61-1.94 (m, 2H, H-11, H-12), 2.18-2.42 (m, 2H, H-9, H-10), 2.92 (m, 1H, H-7), 3.11 (m, 1H, H-8), 5.61 (dd, 1H, J 7.0, 7.5, H-13), 6.62 (s, 1H, OH) 7.3-7.91 (m, 15H, Ar-H, H-5), 8.20 (s, 1H, H-2), 8.47 (d, 1H, J 5.6, H-6).

δ_C (100 MHz, CDCl₃): 23.5, 29.6, 49.9, 67.5, 81.7 (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 (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).

ν_{max} (film)/cm⁻¹: 3371, 1612, 1377, 1155, 721.

HRMS (*m/z* - ES): Found 493.1681 (M⁺ + H. C₃₁H₂₆N₂O₂Cl Requires: 493.1683)

5.2.2.7.1 Synthesis of [2-(hydroxy-di-naphthalen-2-yl-methyl)-pyrrolidin-1-yl]-(4-pyrrolidin-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. $[\alpha]_D^{20} = -65$ (c 0.11, CHCl₃).

δ_H (400 MHz, CDCl₃): 1.34-1.62 (m, 2H, H-17, H-19), 1.88-2.27 (m, 6H, H-9, H-10, H-11, H-12, H-18, H-20), 2.92-3.15 (m, 3H, H-7, H-8, H-13), 3.35-3.53 (m, 3H, H-14, H-15, H-16), 5.43 (dd, 1H, J 8.0, 8.5, H-21),

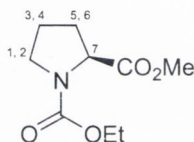
6.40 (d, 1H, J 6.0, H-5), 7.41-7.56 (m, 5H, Ar-H, H-2), 7.64-7.94 (m, 9H, Ar-H), 8.07 (d, 1H, J 5.0, H-6), 8.16 (s, 1H, Ar-H).

δ_C (100 MHz, $CDCl_3$): 23.3, 25.2, 30.0, 48.6, 51.4, 67.4, 82.0 (q), 108.1, 116.2 (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 (q), 132.4 (q), 132.5 (q), 132.7 (q), 140.2 (q), 142.6 (q), 148.2, 148.3 (q), 149.4, 171.5 (C=O).

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

HRMS (m/z - ES): Found 528.2673 ($M^+ + H$, $C_{35}H_{34}N_3O_2$ Requires: 528.2651).

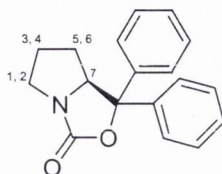
5.2.2.8 Synthesis of pyrrolidine-1,2-dicarboxylic acid 1-ethyl ester 2-methyl ester (*S*)-(182)



To a 25 mL round bottom flask charged with **177** (1.00 g, 8.7 mmol) and MeOH (10 mL) was added K_2CO_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_2Cl_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. 1H NMR spectral data is consistent with literature precedent.¹⁸⁷

δ_H (400 MHz, $CDCl_3$): 1.18 (t, 3H, J 8.0, CH_3), 1.86-2.30 (m, 4H, H-3, H-4, H-5, H-6), 3.45-3.62 (m, 2H, H-1, H-2), 3.75 (s, 3H, OCH_3), 4.06-4.21 (m, H, CH_2), 4.32-4.40 (m, 1H, H-7).

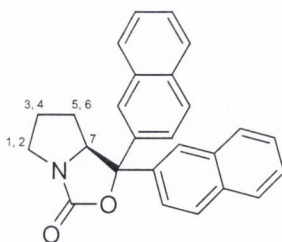
5.2.2.9 Procedure F: Synthesis of 1, 1-diphenyl-tetrahydro-pyrrolo[1, 2-c]oxazol-3-one (*S*)-(183)



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, R_f = 0.3) gave **183** (474 mg, 53%) as white solid. M.p. 147-148 °C (lit.,¹⁸⁷ 148-149 °C).

δ_H (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).

5.2.2.9.2 Synthesis of 1, 1-dinaphthyl-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, R_f = 0.8), gave **184** (630 mg, 61%) as a white solid. M.p. 108-110 °C. [α]_D²⁰ = -88 (c 0.01, CHCl₃).

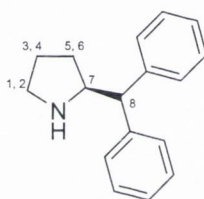
δ_{H} (400 MHz, CDCl_3): 1.24 (m, 1H, H-3), 1.78-2.09 (m, 3H, H-4, H-5, H-6), 3.36 (m, 1H, H-1), 3.81 (m, 1H, H-2), 4.82 (dd, 1H, J 5.5, 8.5, H-7), 7.35-8.15 (m, 14H, Ar-H).

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 ($\text{M}^+ + \text{H} - \text{CO}_2$. $\text{C}_{26}\text{H}_{21}\text{NO}_2$ Requires: 379.1684)

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

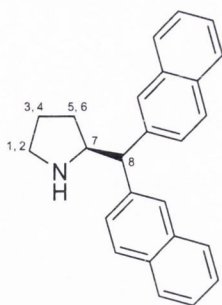


A 25 mL round bottom flask charged with **183** (730 mg, 2.6 mmol), MeOH (15 mL) and a stirring bar was placed under Ar. Pd/C (250 mg) (10%) was slowly added. The flask was flushed with H_2 at room temperature for 72 h. The catalyst was filtered off and the solvent removed *in vacuo*. Purification by 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-(dinaphthylmethyl)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, R_f = 0.4) gave **186** (180 mg, 68%) as a white solid. M.p. 46-48 °C. $[\alpha]_D^{20} = -118$ (c 0.005, CHCl₃).

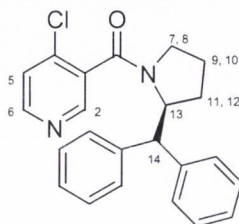
δ_H (400 MHz, CDCl₃): 1.55 (m, 1H, H-3), 1.85 (m, 3H, H-4, H-5, H-6), 2.88 (m, 1H, H-1), 3.06 (m, 1H, H-2), 4.15 (m, 2H, H-7, H-8), 7.38-7.60 (m, 6H, Ar-H), 7.70-8.00 (m, 8H, Ar-H).

δ_C (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).

ν_{max} (film)/cm⁻¹: 2922, 1505, 1108, 855.

HRMS (*m/z* - ES): Found 338.1897 (M⁺ + H. C₂₅H₂₄N 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, R_f = 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:

δ_H (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:

δ_H (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).

δ_C (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).

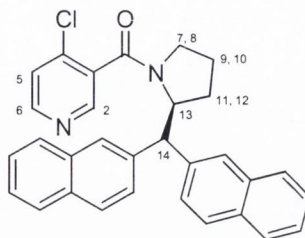
Minor resonances found:

δ_C (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).

ν_{max} (film)/cm⁻¹: 3480, 1628, 1390, 1187, 933, 683.

HRMS (*m/z* - ES): Found 399.1227 (M⁺ + Na. C₂₃H₂₁N₂OCINa 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), SOCl_2 (340 μL , 4.70 mmol), THF (2 + 3 mL), (**S**)-**186** (160 mg, 0.47 mmol) and NEt_3 (164 μL , 1.19 mmol). Purification by column chromatography (1:3 Hexane-EtOAc, R_f = 0.3) gave **188** (158 mg, 70%) as a white solid. M.p. 92-94 $^\circ\text{C}$. $[\alpha]_D^{20}$ = -72 (c 0.12, CHCl_3).

Major rotamers:

δ_{H} (400 MHz, CDCl_3): 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:

δ_{H} (400 MHz, CDCl_3): 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).

δ_{C} (100 MHz, CDCl_3): 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).

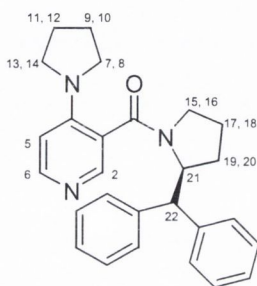
Minor resonances found:

δ_{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.

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

HRMS (m/z - ES): Found 477.1751 ($\text{M}^+ + \text{H}$. $\text{C}_{31}\text{H}_{26}\text{N}_2\text{OCl}$ 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. $[\alpha]_{\text{D}}^{20}$ = -81 (c 0.12, CHCl_3).

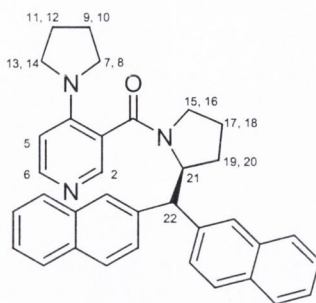
δ_{H} (400 MHz, CDCl_3): 1.62-2.15 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 3.04-3.22 (m, 3H, H-7, H-8, H-13), 3.32-3.54 (m, 3H, H-14, H-15, H-16), 4.60 (d, 1H, J 8.0, H-22), 5.29 (m, 1H, H-21), 6.42 (d, 1H, J 6.0, H-5), 7.19-7.42 (m, 10H, Ar-H), 7.74 (s, 1H, H-2), 8.12 (d, 1H, J 6.0, H-6).

δ_{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).

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

HRMS (m/z - ES): Found 412.2393 ($\text{M}^+ + \text{H}$. $\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}$ 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-NEt₃, R_f = 0.3), gave **175** (111 mg, 80%) as a white solid. M.p. 123-124. [α]_D²⁰ = -53 (c 0.15, CHCl₃).

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

Major rotamer:

δ_H (400 MHz, CDCl₃): 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:

δ_H (400 MHz, CDCl₃): 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).

δ_C (100 MHz, CDCl₃): 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).

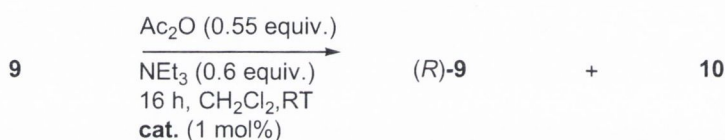
Minor resonances Found:

δ_C (100 MHz, $CDCl_3$): 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).

ν_{max} (film)/ cm^{-1} : 1620, 1586, 1303, 1199, 975, 811, 722.

HRMS (m/z - ES): Found 512.2692 ($M^+ + H$, $C_{35}H_{34}N_3O$ Requires: 512.2702)

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



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_2Cl_2) through a pad of silica gel.

^1H NMR of **10**:

δ_H (400 MHz, $CDCl_3$): 1.56 (d, 3H, J 6.8, CH_3), 2.10 (s, 3H, CH_3), 5.90 (q, 1H, J 6.8, H-1) 7.30-7.38 (m, 5H, Ar-H).

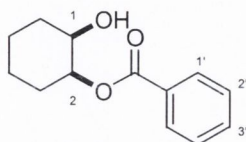
^1H NMR of **9**:

δ_H (400 MHz, $CDCl_3$): 1.46 (d, 3H, J 6.8, CH_3), 4.84 (q, 1H, J 6.8, H-1), 7.19-7.25 (m, 5H, Ar-H).

HPLC data for recovered alcohol **9**:

Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 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.

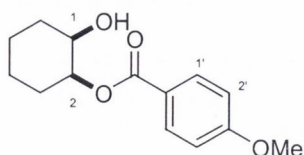
5.2.2.14 Procedure H: Synthesis of (*rac*)-(*cis*)-benzoic acid 2-hydroxy-cyclohexyl ester (**76a**)



A 50 mL three-necked round bottom flask fitted with a 50 mL addition funnel containing a solution of benzoyl chloride (**189a**) (530 μ L, 4.5 mmol) in CH₂Cl₂ (9 mL) was charged with **190** (500 mg, 4.3 mmol), NEt₃ (900 μ L, 6.5 mmol), CH₂Cl₂ (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. CH₂Cl₂ (20 mL) was then added and the resulting solution washed with Na₂CO₃ (2 x 40 mL) and NaHCO₃ (2 x 40 mL). The organic extracts were separated, dried (MgSO₄) and the solvent removed *in vacuo*. Purification by column chromatography (CH₂Cl₂, 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.⁸⁷

δ_H (400 MHz, CDCl₃): 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').

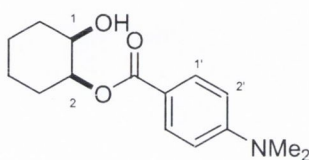
5.2.2.14.1 Synthesis of (*rac*)-(*cis*)-4-methoxy-benzoic acid 2-hydroxy-cyclohexyl ester (**191**)



Procedure H was followed using anisoyl chloride (**189b**) (771 mg, 4.5 mmol), **190** (500 mg, 4.3 mmol), NEt₃ (900 μ L, 6.5 mmol) in CH₂Cl₂ (9 + 8 mL). Purification by column chromatography (9:1, CH₂Cl₂-EtOAc, R_f = 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

δ_H (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')

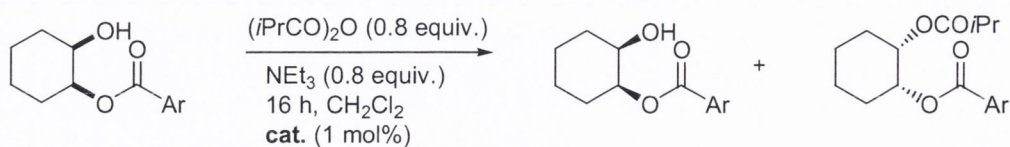
5.2.2.14.2 Synthesis of (*rac*)-(*cis*)-4-dimethylamino-benzoic acid 2-hydroxy-cyclohexyl ester (**76b**)



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, R_f = 0.2), gave **77b** (990 mg, 44%) as a white solid. M.p 120-121 °C, (lit.,⁸⁷ 120-122 °C).

δ_H (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').

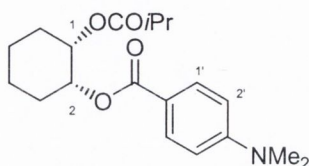
5.2.2.15 Procedure I: general procedure for the KR of mono-benzylated *cis*-diol as in Table 2.3



A 1 mL reaction vessel charged with catalyst (2.34 μ mol) 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 μ L, 0.187 mmol) in CH₂Cl₂ (500 μ L). The resulting solution was left

to stir for 30 minutes. *Iso*-butyric anhydride (31 μ L, 0.187 mmol) was subsequently added *via* syringe. After 16 h the reaction was quenched by the addition of MeOH (200 μ L). Solvents were removed *in vacuo*. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel.

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



Procedure I was followed using (**S**)-**169** (1 mg, 2.34 μ mol) 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_2Cl_2) through a pad of silica gel.

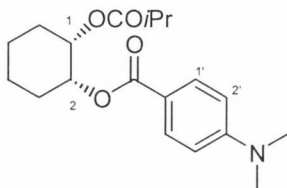
^1H NMR of **77b**

δ_{H} (400 MHz, CDCl_3): 1.12 (d, 3H, J 6.5, CH_3), 1.14 (d, 3H, J 6.5, CH_3), 1.40-1.50 (m, 2H, H-5, H-7), 1.60-2.00 (m, 6H, H-3, H-4, H-6, H-8, H-9, H-10), 2.50 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 3.00 (s, 6H, NMe_2), 5.07 (m, 1H, H-2), 5.20 (m, 1H, H-1), 6.61 (d, 2H, J 9.0, H-2'), 7.87 (d, 2H, J 9.0, H-1').

HPLC Data for recovered alcohol **76b**:

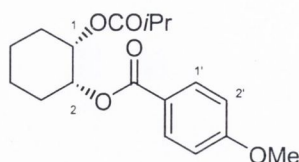
Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 90/10, 1.0 mL min^{-1} , RT, UV detection at 220 nm, retention times: 17.3 min (1*R*,2*S*) minor and 34.4 min (1*S*,2*R*) major.⁹¹

5.2.2.15.2 (*cis*)-4-Dimethylamino-benzoic acid 2-isobutryloxy-cyclohexyl ester (**77b**)



Procedure I was followed using **(S)-169** (1 mg, 2.34 μmol) and **76b** (61.5 mg, 0.234 mmol) at $-78\text{ }^{\circ}\text{C}$. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel.

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



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 (CH_2Cl_2) through a pad of silica gel.

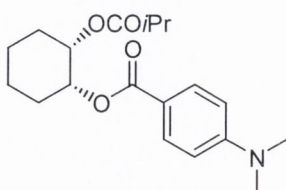
^1H NMR of **77b**

δ_{H} (400 MHz, CDCl_3): 1.13 (d, 3H, J 6.5, CH_3), 1.15 (d, 3H, J 6.5, CH_3), 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, $\text{CH}(\text{CH}_3)_2$), 3.84 (s, 3H, OCH_3), 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**:

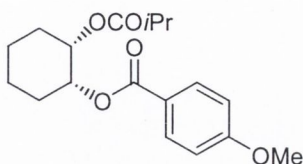
Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 90/10, 1.0 mL min^{-1} , RT, UV detection at 220 nm, retention times: 10.7 min (1*R*,2*S*) minor and 14.6 min (1*S*,2*R*) major.⁹¹

5.2.2.15.4 (cis)-4-Dimethylamino-benzoic acid 2-isobutryloxy-cyclohexyl ester (**77b**)



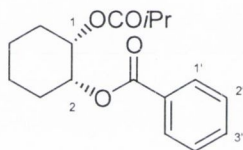
Procedure I was followed using (**S**)-**172** (1.2 mg, 2.34 μ mol) and **76b** (61.5 mg, 0.234 mmol) at room temperature. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel.

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 μ mol) 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_2Cl_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 μ mol) 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_2Cl_2) through a pad of silica gel.

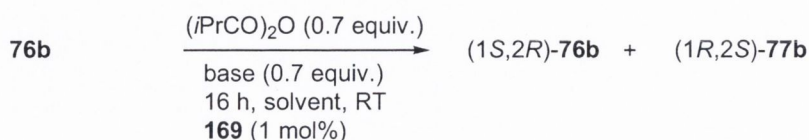
^1H NMR of **77a**

δ_{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, $\text{CH}(\text{CH}_3)_2$), 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**:

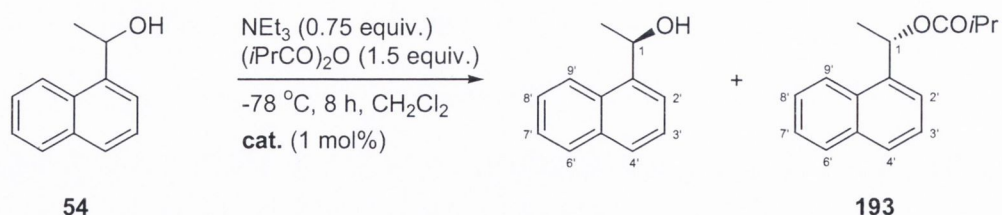
Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 6.7 min (1*R*,2*S*) minor and 7.4 min (1*S*,2*R*) major.⁹¹

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 (24 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 (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_2Cl_2) through a pad of silica gel.

^1H 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').

^1H 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, $\text{CH}(\text{CH}_3)_2$), 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**:

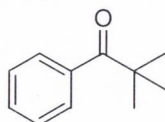
Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 90/10, 1.0 mL min^{-1} , RT, UV detection at 220 nm, retention times: 4.0 min (*R*) minor and 5.4 min (*S*) major.⁸³

HPLC Data for recovered alcohol **54**:

Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 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**

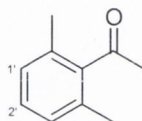


A 50 mL round bottom flask charged with **195a** (2.6 ml, 21.0 mmol), THF (10 mL) and a stirrer was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 10 mins. **194a** (33.2 mL, 18.4 mmol, 0.5 M) was subsequently added *via* syringe over a 15 min period, with the resulting solution allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by the addition of H₂O (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_f = 0.6) gave **196a** (1.163 g, 39%) as a colourless oil.

¹H NMR of **196a**:

δ_H (400 MHz, CDCl₃): 1.31 (s, 9H, CH₃), 7.45-7.70 (m, 5H, Ar-H).

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

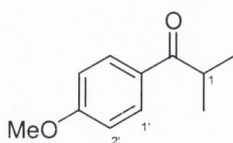


Procedure J was followed using **195b** (1.42 ml, 20.0 mmol), **194b** (37.8 ml, 18.0 mmol, 0.5 M) and THF (10 mL) at 0 °C. Purification by column chromatography (1:1 Hex-CH₂Cl₂, R_f = 0.4) gave **196b** (1.43 g, 53.6%) as a colourless oil.

¹H NMR of **196b**:

δ_H (400 MHz, CDCl₃): 2.27 (s, 6H, CH₃), 2.50 (s, 3H, CH₃), 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**

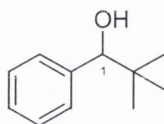


Procedure J was followed using **195c** (1.0 ml, 9.5 mmol), **194c** (17.2 ml, 8.6 mmol, 0.5 M) and THF (4 mL) at 0 °C. Purification by column chromatography (1:4 Hex-CH₂Cl₂, R_f = 0.2) gave **196c** (1.01 g, 66%) as a colourless oil.

¹H NMR of **196c**:

δ_H (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

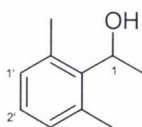


A 25 mL round bottom flask charged with LiAlH₄ (703 mg, 18.5 mmol), THF (5 mL) and a stirring bar was placed under an atmosphere of N₂, cooled to 0 °C and left to stir for 10 mins. Subsequently a solution of **196a** (1.5 g, 9.3 mmol) in THF (5 mL) was added *via* syringe and the resulting solution was 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, R_f = 0.3) gave **58** (1.23 g, 81%) as a colourless oil.

¹H NMR of **58**:

δ_H (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**)

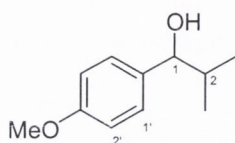


Procedure K was followed using LiAlH_4 (180 mg, 4.7 mmol), **196b** (350 mg, 2.3 mmol) and THF (10 mL). Purification by column chromatography (CH_2Cl_2 , $R_f = 0.3$) gave **74b** (226 mg, 64%) as a colourless oil.

^1H NMR of **74b**:

δ_{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**)

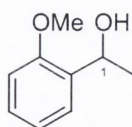


Procedure K was followed using LiAlH_4 (304 mg, 8.0 mmol), **196c** (705 mg, 3.96 mmol) and THF (15 mL). Purification by column chromatography (CH_2Cl_2 , $R_f = 0.3$) gave **197c** (226 mg, 64%) as a colourless oil.

^1H NMR of **196c**:

δ_{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**)



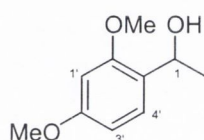
A 25 mL round bottom flask charged with **199a** (1.00 g, 7.34 mmol), THF (10 mL) and a stirrer was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 10 mins. Methyl Grignard (**198**) (10.5 ml, 14.7 mmol, 1.4 M) was subsequently added *via* syringe over a 15 min period, with the resulting solution allowed to warm to room temperature and stirred for 14 h. The reaction was quenched by the addition of H_2O (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_f = 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**)

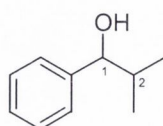


Procedure L was followed using **199b** (1.0 g, 6.0 mmol), **198** (8.57 mL, 12.0 mmol, 1.4 M) and THF (10 mL) at 0 °C. Purification by column chromatography (CH₂Cl₂, R_f = 0.1) gave **200b** (598 mg, 55%) as a colourless oil.

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-propanol-1-ol (**57**) by reduction with NaBH₄



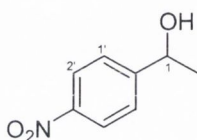
A 25 mL round bottom flask charged with NaBH₄ (126.1 mg, 3.33 mmol), EtOH (6 mL) and a stirring bar was cooled to 0 °C and left to stir for 10 mins. Subsequently a solution of **201a** (500 mg, 3.33 mmol) in THF (4 mL) was added *via* syringe with the resulting

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**:

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).

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

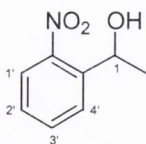


Procedure M was followed using NaBH₄ (229 mg, 6.05 mmol), **200b** (1.0 g, 6.05 mmol) and EtOH (12 mL). Purification by column chromatography (CH₂Cl₂, R_f = 0.1) gave **9b** (497 mg, 49%) as a colourless oil.

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')

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

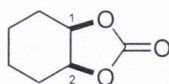


Procedure M was followed using NaBH₄ (229 mg, 6.05 mmol), **201c** (1.0 g, 6.05 mmol) and EtOH (12 mL). Purification by column chromatography (CH₂Cl₂, R_f = 0.1) gave **202c** (628 mg, 62%) as a colourless oil.

¹H NMR of **202c**:

δ_{H} (400 MHz, CDCl₃): 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)

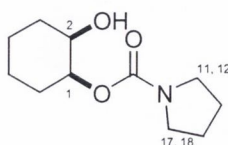


A 50 ml round bottom flask charged with **190** (1 g, 11.2 mmol), CH₂Cl₂ (25 mL), and a stirring bar was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 10 mins. **19** (4.53 mL, 56.0 mmol) was added *via* syringe and the resulting solution was cooled further to -78 °C. Subsequently 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.

¹H NMR of **203**:

δ_{H} (400 MHz, CDCl₃): 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)

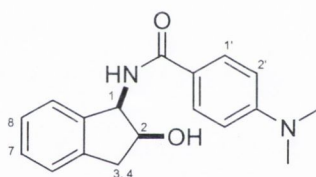


A 25 mL round bottom flask charged with **202** (567 mg, 3.99 mmol), THF (20 mL) and a stirring bar was placed under an atmosphere of Ar and left to stir for 10 mins. Subsequently pyrrolidine (3.33 mL, 40.0 mmol) was added *via* syringe and the resulting solution was heated under reflux for 3 h. CH₂Cl₂ (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, R_f = 0.2) gave **203** (720 mg, 85%) as a colourless oil.²¹⁰

¹H NMR of **203**:

δ_H (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, R_f = 0.1) gave **206** (1.31 g, 66%) as a white solid. M.p. 180-182 °C (lit.⁸⁸ 181-182 °C).

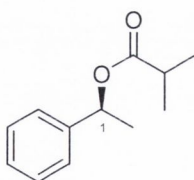
¹H NMR of **206**:

δ_{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 μ mol) 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 μ L, 0.176 mmol) in CH₂Cl₂ (500 μ L). The resulting solution was cooled to -78 °C and left to stir for 30 minutes. *Iso*-butyric anhydride (29.0 μ L 0.176 mmol) was subsequently added *via* syringe. After 8 h at -78 °C the reaction was quenched by the addition of MeOH (200 μ L) 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**)



Procedure N was followed using **169** (1 mg, 2.34 μ mol) 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.

^1H NMR of **207a**:

δ_{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, $\text{CH}(\text{CH}_3)_2$), 5.89 (q, 1H, J 6.8, H-1), 7.29-7.41 (m, 5H, Ar-H).

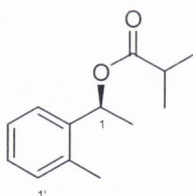
^1H NMR of **9**:

δ_{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/*i*PrOH, 99/1, 1 mL min^{-1} , RT, UV detection at 220 nm. Retention times: 29.0 min (*R*) major and 40.3 min (*S*) minor.⁸¹

5.2.3.8.2 *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 $-78\text{ }^\circ\text{C}$. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel.

^1H NMR of **207b**:

δ_{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, $\text{CH}(\text{CH}_3)_2$), 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').

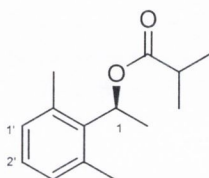
^1H NMR of **74a**:

δ_{H} (400 MHz, CDCl_3): 1.49 (d, 3H, J 6.4, CH_3), 2.37 (s, 3H, 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/*i*PrOH, 99/1, 1 mL 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**)



Procedure N was followed using **169** (1 mg, $2.34\text{ }\mu\text{mol}$) and **74b** (28.6 mg, 0.234 mmol) at $-78\text{ }^\circ\text{C}$. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel.

^1H NMR of **207c**:

δ_{H} (400 MHz, CDCl_3): 1.17 (d, 3H, J 7.0, CH_3), 1.19 (d, 3H, J 7.0, CH_3), 1.48 (d, 3H, J 6.5, CH_3), 2.44 (s, 6H, CH_3), 2.62 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 6.29 (q, 1H, J 6.5, H-1), 7.02 (d, 2H, J 7.3, H-1'), 7.17 (app t, 1H, J 7.3, H-2').

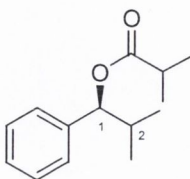
^1H NMR of **74b**:

δ_{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').

HPLC data for recovered alcohol **74b**:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/*i*PrOH, 99/1, 1 mL 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).

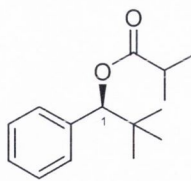
¹H NMR of **57**:

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/*i*PrOH, 99/1, 1 mL min⁻¹, RT, UV detection at 220 nm. Retention times: 21.2 min (*R*) major and 22.8 min (*S*) minor.¹²⁴

5.2.3.8.5 *Iso*-butyric acid-2,2-dimethyl-1-phenyl-propyl ester (**207e**)



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 (CHCl_2) through a pad of silica gel.

^1H NMR of **207e**:

δ_{H} (400 MHz, CDCl_3): 0.95 (s, 9H, CH_3), 1.19 (d, 3H, J 6.8, CH_3), 1.21 (d, 3H, J 6.8, CH_3), 2.61 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 5.49 (s, 1H, H-1), 7.27-7.36 (m, 5H, Ar-H).

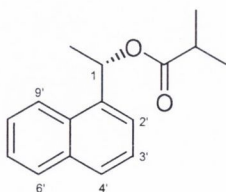
^1H NMR of **58**:

δ_{H} (400 MHz, CDCl_3): 0.95 (s, 9H, CH_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/*i*PrOH, 99/1, 1 mL 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_2Cl_2) through a pad of silica gel.

^1H 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, $\text{CH}(\text{CH}_3)_2$), 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').

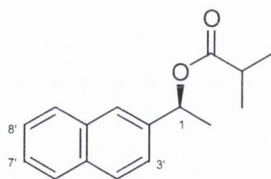
^1H NMR of **54**

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').

HPLC data for recovered alcohol **54**:

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

5.2.3.8.7 *Iso*-butyric acid 1-naphthalen-2-yl ethyl ester (**207f**)



Procedure N was followed using **169** (1 mg, 2.34 μmol) 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_2Cl_2) through a pad of silica gel.

^1H NMR of **207f**:

δ_{H} (400 MHz, CDCl_3): 1.18 (d, 3H, J 7.0, CH_3), 1.20 (d, 3H, J 7.0, CH_3), 1.63 (d, 3H, J 6.5, CH_3), 2.62 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 6.06 (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').

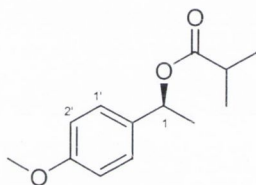
¹H NMR of **83**:

δ_{H} (400 MHz, CDCl₃): 1.61 (d, 3H, J 6.5, CH₃), 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/*i*PrOH, 90/10, 1 mL 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**)



Procedure N was followed using **169** (1 mg, 2.34 μ mol) and **9a** (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 **207g**:

δ_{H} (400 MHz, CDCl₃): 1.17 (d, 3H, J 7.0, CH₃), 1.19 (d, 3H, J 7.0, CH₃), 1.52 (d, 3H, J 6.5, CH₃), 2.54 (app. hept, 1H, CH(CH₃)₂), 3.82 (s, 3H, OCH₃), 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').

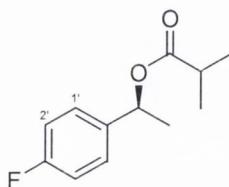
^1H NMR of **9a**:

δ_{H} (400 MHz, CDCl_3): 1.51 (d, 3H, J 6.5, CH_3), 3.83 (s, 3H, OCH_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/*i*PrOH, 99/1, 1 mL min^{-1} , RT, UV detection at 220 nm. Retention times: 53.1 min (*R*) major and 59.7 min (*S*) minor.¹⁸⁹

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



Procedure N was followed using **169** (1 mg, 2.34 μmol) and **106** (28.6 mg, 0.234 mmol) at $-78\text{ }^\circ\text{C}$. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel.

^1H NMR of **208a**:

δ_{H} (400 MHz, CDCl_3): 1.19 (d, 3H, J 7.0, CH_3), 1.21 (d, 3H, J 7.0, CH_3), 1.52 (d, 3H, J 6.4, CH_3), 2.57 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 5.86 (q, 1H, J 6.4, H-1), 7.04 (m, 2H, H-2'), 7.36 (m, 2H, H-1').

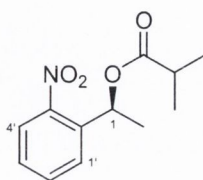
^1H NMR of **106**:

δ_{H} (400 MHz, CDCl_3): 1.50 (d, 3H, J 6.4, CH_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**:

Could not be resolved by CSP-HPLC using Chiralcel OD-H, Chiralcel AS-H or Chiralpak AD-H columns.

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



Procedure N was followed using **169** (1 mg, 2.34 μ 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_2Cl_2) through a pad of silica gel.

^1H NMR of **208b**:

δ_{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, $\text{CH}(\text{CH}_3)_2$), 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').

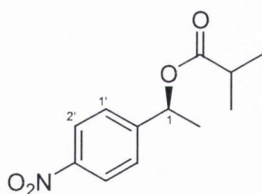
^1H NMR of **202c**:

δ_{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/*i*PrOH, 99/1, 1 mL min^{-1} , RT, UV detection at 220 nm. Retention times: 49.5 min (*R*) major and 52.7 min (*S*) minor. $[\alpha]_{\text{D}}^{20} = -3.5$ (c 0.14, CHCl_3).¹⁸⁸

5.2.3.8.11 *Iso*-butyric acid-1-(4-nitro-phenyl)-ethyl ester (208c)



Procedure N was followed using **169** (1 mg, 2.34 μ mol) 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 (CH_2Cl_2) through a pad of silica gel.

^1H NMR of **208c**:

δ_{H} (400 MHz, CDCl_3): 1.19 (d, 3H, J 7.0, CH_3), 1.21 (d, 3H, J 7.0, CH_3), 1.57 (d, 3H, J 6.5, CH_3), 2.62 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 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').

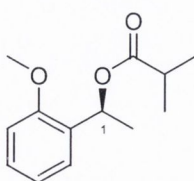
^1H NMR of **9b**:

δ_{H} (400 MHz, CDCl_3): 1.58 (d, 3H, J 6.5, CH_3), 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/*i*PrOH, 90/10, 1 mL min^{-1} , RT, UV detection at 220 nm. Retention times: 18.9 min (*R*) major and 24.4 min (*S*) minor. $[\alpha]_{\text{D}}^{20} = -4.4$ (c 0.1, CHCl_3).¹⁹¹

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 (CH_2Cl_2) through a pad of silica gel.

^1H NMR of **208d**:

δ_{H} (400 MHz, CDCl_3): 1.19 (d, 3H, J 7.0, CH_3), 1.21 (d, 3H, J 7.0, CH_3), 1.55 (d, 3H, J 6.5, CH_3), 2.62 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 3.79 (s, 3H, OCH_3), 5.88 (q, 1H, J 6.5, H-1), 7.06 (m, 4H, Ar-H).

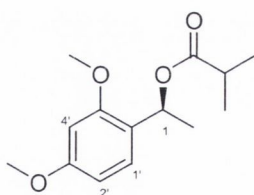
^1H NMR of **97**:

δ_{H} (400 MHz, CDCl_3): 1.53 (d, 3H, J 6.5, CH_3), 3.80 (s, 3H, OCH_3), 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/*i*PrOH, 99/1, 1 mL 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-1-(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 (CH_2Cl_2) through a pad of silica gel.

^1H NMR of **209a**:

δ_{H} (400 MHz, CDCl_3): 1.18 (d, 3H, J 7.0, CH_3), 1.20 (d, 3H, J 7.0, CH_3), 1.47 (d, 3H, J 6.5, CH_3), 2.57 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 3.87 (s, 6H, OCH_3),

6.17 (q, 1H, J 6.5, H-1), 6.45 (m, 2H, H-2', H-4'), 7.27 (m, 1H, H-1').

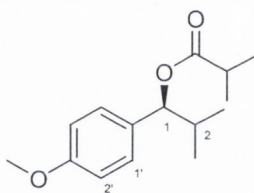
¹H NMR of **200b**:

δ_H (400 MHz, CDCl₃): 1.51 (d, 3H, J 6.5, CH₃), 3.82 (s, 6H, OCH₃), 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/*i*PrOH, 98/2, 1mL min⁻¹, RT, UV detection at 220 nm. Retention times: 28.6 min (*S*) minor and 48.6 min (*R*) major. [α]_D²⁰ = +4 (c 0.1, CHCl₃).¹⁹³

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



Procedure N was followed using **169** (1 mg, 2.34 μmol) 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 (CH₂Cl₂) through a pad of silica gel.

¹H NMR of **209b**:

δ_H (400 MHz, CDCl₃): 0.80 (d, 3H, J 7.0, CH₃), 0.98 (d, 3H, J 7.0, CH₃), 1.15 (d, 3H, J 7.0, CH₃), 1.18 (d, 3H, J 7.0, CH₃), 2.09 (app. hept, 1H, H-2), 2.58 (app. hept, 1H, CH(CH₃)₂), 3.81 (s, 3H, OCH₃), 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').

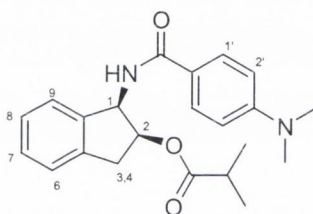
¹H NMR of **197c**:

δ_{H} (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/*i*PrOH, 99/1, 1mL min⁻¹, RT, UV detection at 220 nm. Retention times: 28.5 min (*R*) major and 31.1 min (*S*) minor. $[\alpha]_{\text{D}}^{20} = +8.2$ (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)-indan-2-yl ester (**209c**)



Procedure N was followed using **169** (1 mg, 2.34 μ mol) 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.

¹H NMR of **209c**:

δ_{H} (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').

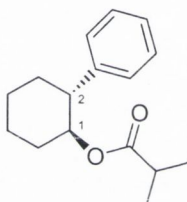
^1H NMR of **206**:

δ_{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/*i*PrOH, 99/1, 1 mL min^{-1} , RT, UV detection at 220 nm. Retention times: 57.2 min (1*R*,2*S*) major and 61.7 min (1*S*,2*R*) minor. $[\alpha]_{\text{D}}^{20} = +12$ (c 0.2, CHCl_3).⁸⁸

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



Procedure N was followed using **169** (1 mg, 2.34 μmol) and **93** (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_2Cl_2) through a pad of silica gel.

^1H NMR of **209d**:

δ_{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, $\text{CH}(\text{CH}_3)_2$), 2.70 (m, 1H, H-2), 4.98 (m, 1H, H-1). 7.17-7.39 (m, 5H, Ar-H).

^1H NMR of **93**:

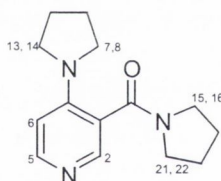
δ_{H} (400 MHz, CDCl_3): 1.33-1.56 (m, 4H, H-5, H-6, H-7, H-8), 1.77-1.89 (m, 2H, H-9, H-10), 2.10-2.30 (m, 2H, H-3, H-4), 2.45 (m, 1H, H-2), 3.68 (m, 1H, H-1), 7.17-7.38 (m, 5H, Ar-H).

HPLC data for recovered alcohol **93**:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/*i*PrOH, 99.5/0.5, 1 mL min^{-1} , RT, UV detection at 220 nm. Retention times: 15.7 min (1*S*,2*R*) major and 18.2 min (1*R*,2*S*) 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 $^{\circ}\text{C}$ 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_2Cl_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 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} = -34.8$ (c 0.12, CHCl_3).

^1H NMR of **211**:

δ_{H} (400 MHz, CDCl_3): 1.92-1.99 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 3.17-3.68 (m, 8H, H-7, H-8, H-13, H-14, H-15, H-16, H-21, H-22), 6.47 (d, 1H, J 6.0, H-5), 8.17 (m, 2H, H-2, H-6).

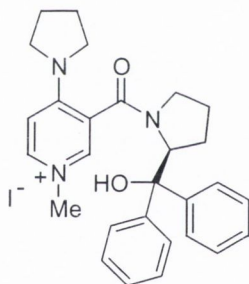
^{13}C NMR of **211**:

δ_{H} (100 MHz, CDCl_3): 24.2, 25.1, 25.3, 45.3, 48.2, 48.3, 107.9, 117.7, 148.2, 148.5 (q), 149.2, 168.4 (C=O).

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

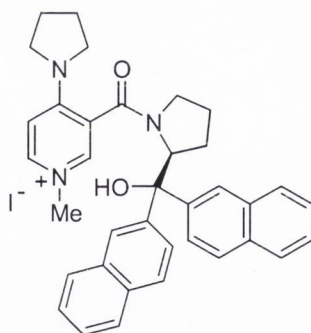
HRMS (m/z - ES): Found 246.1605 ($\text{M}^+ + \text{H}$, $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}$ Requires: 246.1606)

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



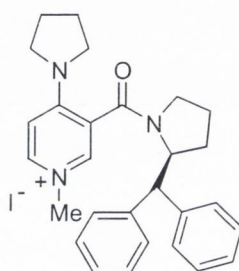
Procedure B was followed using catalyst **169** (30 mg, 0.07 mmol) in CH_2Cl_2 (500 μL), with the addition of iodomethane (44 μL , 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (**169a**) in CDCl_3 by ^1H NMR spectroscopy.

5.2.4.2.1 Methylation of catalyst (*S*)-172 as in Table 2.9



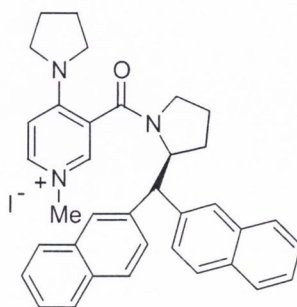
Procedure B was followed using catalyst **172** (37 mg, 0.07 mmol) in CH₂Cl₂ (500 μL), with the addition of iodomethane (44 μL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (**172a**) in CDCl₃ by ¹H NMR spectroscopy.

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



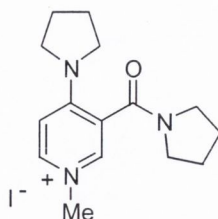
Procedure B was followed using catalyst **174** (29 mg, 0.07 mmol) in CH₂Cl₂ (500 μL), with the addition of iodomethane (44 μL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (**174a**) in CDCl₃ by ¹H NMR spectroscopy.

5.2.4.2.3 Methylation of catalyst (*S*)-175 as in Table 2.9



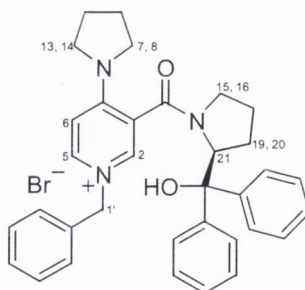
Procedure B was followed using catalyst **175** (36 mg, 0.07 mmol) in CH₂Cl₂ (500 μL), with the addition of iodomethane (44 μL, 0.7 mmol), followed by concentration of the resultant solution and analysis of the product (**175a**) in CDCl₃ by ¹H NMR spectroscopy.

5.2.4.2.4 Methylation of catalyst **211** as in Table 2.9



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



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**:

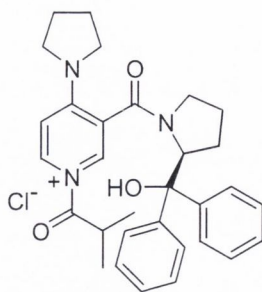
δ_{H} (400 MHz, CDCl_3): 1.89-2.18 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 2.98 (m, 1H, H-15), 3.45-3.76 (m, 4H, H-7, H-8, H-13, H-14), 4.02 (m, 1H, H-16), 5.30 (app. t, 1H, J 7.3, H-21), 5.48 (d, 1H, J 14.5, H-1'), 5.77 (d, 1H, J 14.5, H-1'), 5.98 (s, 1H, OH), 6.74 (d, 1H, J 7.0, H-5), 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.

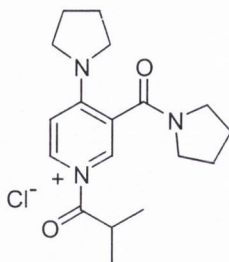
A solution of the pyridine (0.07 mmol) in CDCl_3 (400 μL , freshly distilled and stored for short periods under Ar over 4 Å mol sieves) was added to a screw-cap-NMR tube under an atmosphere of Ar. To this was added *iso*-butyric acid chloride (0.07 mmol) *via* syringe. The NMR tube was shaken for 10 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**)



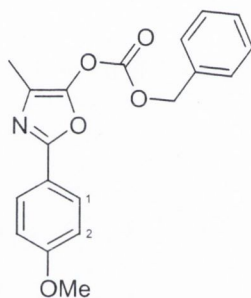
Procedure O was followed using **169** (30 mg, 0.07 mmol) in CDCl_3 (500 μL).

5.2.4.4.2 3-(pyrrolidine-1-carbonyl)-1-isobutyryl-4-pyrrolidin-1-yl-pyridinium; chloride (214)



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)

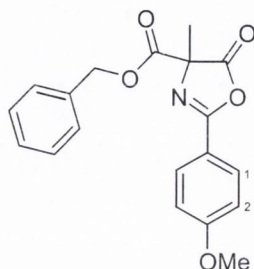


A 25 mL round bottom flask charged with 2-(4-methoxy-phenyl)-4-methyl-4*H*-oxazol-5-one¹⁹⁷ (765 mg, 3.73 mmol), NEt₃ (570 μL, 4.1 mmol), THF (10 mL) and a stirring bar was placed under an atmosphere of Ar, cooled to 0 °C and left to stir for 20 mins. Subsequently benzoyl chloride (530 μL, 3.73 mmol) 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.,¹⁹⁷ 82-83 °C)

^1H NMR of **217**:

δ_{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_2Cl_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_2Cl_2 (500 μL). The resulting solution was left to stir for 3 h and subsequently quenched by the addition of MeI (10 μL). Solvents were removed *in vacuo*. **217** and **218** were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel.

^1H NMR of **218**:

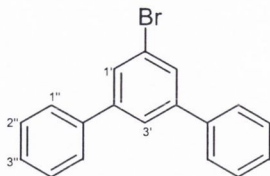
δ_{H} (400 MHz, CDCl_3): 1.80 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 5.26 (s, 2H, CH_2), 7.00 (d, 2H, J 9.0, H-2), 7.33 (m, 5H, Ar-H), 7.98 (d, 2H, J 9.0, H-1).

HPLC data for recovered alcohol **218**:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/*i*PrOH, 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**)

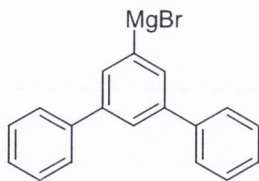


A 150 mL round bottom flask charge with 1,3,5-tribromobenzene (4.2 g, 13.4 mmol) and $\text{Pd(PPh}_3)_4$ (500 mg, 0.4 mmol) was placed under an atmosphere of Ar. Subsequently, a solution of phenylboronic acid (3.5 g, 28.5 mmol) in toluene (60 mL) and a 1M Na_2CO_3 solution (50 mL, degassed) were added 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_2Cl_2 - H_2O (1:1, 100 mL). The organic extract was separated, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (Hexane) gave **224a** (2.11 g, 51.0 %) as a white solid.

^1H NMR of **218**:

δ_{H} (400 MHz, CDCl_3): 7.43 (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').

5.3.1.2.1 5.3.1.2 Procedure P: synthesis of *m*-terphenyl magnesium bromide (**223a**) (Figure 3.1)



A round bottom flask charged with Mg (dust) (152.3 mg, 6.27 mmol), THF (5 mL) and a stirring bar was placed 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

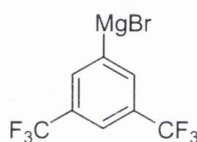
under reflux for 4 h with a colour change (colourless to dark red) upon the disappearance of Mg. The solution was cooled to -15 °C and used immediately.

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



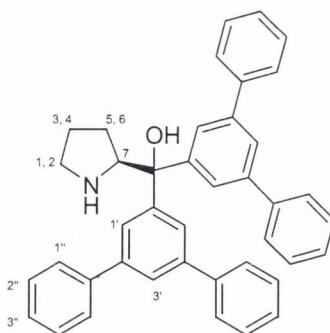
Procedure P was followed using Mg (dust) (230 mg, 9.5 mmol), **224b** (1.88 g, 8.64 mmol) in THF (50 mL) and the reaction heated under reflux for 16 h.

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



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 *iso*-propyl 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-yl-bis-[1,1',3',1'']terphenyl-5'-yl-methanol (*S*)-(**226a**)



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. $[\alpha]_D^{20} = -62.2$ (c 0.143, CHCl₃).

¹H NMR of **226a**:

δ_H (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').

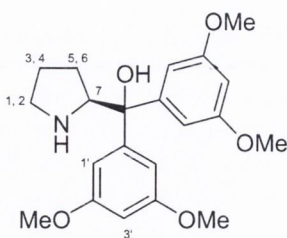
¹³C NMR of **226a**:

δ_H (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).

$\nu_{\max}$ (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, R_f = 0.2) gave **226b** (185 mg, 17 %) as a colourless oil. $[\alpha]_D^{20} = -81$ (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').

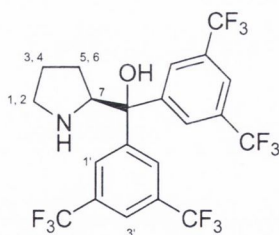
¹³C NMR of **226b**:

δ_H (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).

$\nu_{\max}$ (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)



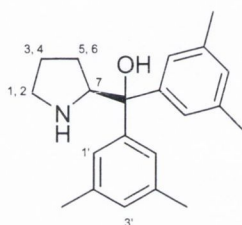
Procedure E was followed with the addition of (*S*)-**176** (8.68 mmol in 20 mL THF) to **223c** (33.0 mmol) in THF (30 mL). The product as its sulphate salt failed to precipitate from solution. The crude mixture was basified with 2M NaOH (4 mL, 8.0 mmol) and diluted with CH₂Cl₂ (50 mL). The organic layer was washed with H₂O (2 x 40 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (99:1 EtOAc-

NEt₃, R_f = 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

¹H NMR of **226c**:

δ_H (400 MHz, CDCl₃): 1.51-1.61 (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)

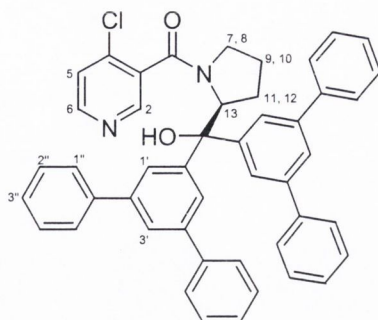


Procedure E was followed with the addition of (*S*)-**176** (6.52 mmol in 20 mL THF) to **223d** (19.55 mmol) in THF (40 mL). The product as its sulphate salt failed to precipitate from solution. The crude mixture was basified with 2M NaOH (4 mL, 8 mmol) and diluted with CH₂Cl₂ (60 mL). The organic layer was washed with H₂O (2 x 50 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (98:2 CH₂Cl₂-NEt₃, R_f = 0.3) gave **226d** (1.10 g, 54 %) as a white solid. M.p 96-98 °C (lit.,¹⁸⁶ 97.5-98 °C)

¹H NMR of **226d**:

δ_H (400 MHz, CDCl₃): 1.55-1.78 (m, 4H, H-3, H-4, H-5, H-6), 2.29 (s, 6H, CH₃), 2.30 (s, 6H, CH₃), 2.92-3.08 (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), SOCl₂ (1.0 mL), CH₂Cl₂ (3 + 5 mL), (*S*)-**226a** (200 mg, 0.36 mmol) and NEt₃ (200 μL, 1.44 mmol). Purification by column chromatography (9:1 CH₂Cl₂-EtOAc, R_f = 0.3) gave **227a** (141 mg, 56%) as a white solid. M.p. 136-137 °C. [α]_D²⁰ = -117.5 (c 0.143, CHCl₃).

¹H NMR of **227a**:

δ_H (400 MHz, CDCl₃): 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, 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).

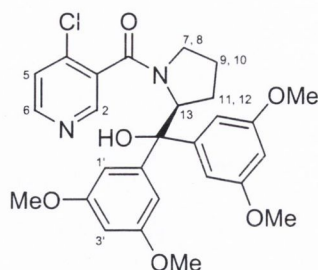
¹³C NMR of **227a**:

δ_C (100 MHz, CDCl₃): 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).

ν_{max} (film)/cm⁻¹: 3275, 2962, 2245, 1575, 1427, 1185, 1030.

HRMS (*m/z* - ES): Found 697.2640 (M⁺ + H. C₄₇H₃₈N₂O₂Cl 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)



Procedure C was followed using **165** (86 mg, 0.547 mmol), SOCl_2 (1.0 mL), CH_2Cl_2 (3 + 5 mL), (*S*)-**226b** (170 mg, 0.456 mmol) and NEt_3 (253 μL , 1.82 mmol). Purification by column chromatography (1:2 CH_2Cl_2 -EtOAc, R_f = 0.3) gave **227b** (132 mg, 57%) as a white solid. M.p. 70-72 $^\circ\text{C}$. $[\alpha]_D^{20}$ = -98 (c 0.126, CHCl_3).

^1H NMR of **227b**:

δ_{H} (400 MHz, CDCl_3): 1.48-1.73 (m, 2H, H-11, H-12), 2.14 (m, 2H, H-9, H-10), 3.17 (m, 2H, H-7, H-8), 3.79 (s, 6H, OCH_3), 3.80 (s, 6H, OCH_3), 5.19 (dd, 1H, J 7.5, 8.0, H-13), 6.41 (s, 1H, OH), 6.46 (s, 1H, H-3'), 6.61 (s, 1H, H-3'), 6.67 (s, 2H, H-1'), 6.78 (s, 2H, H-1') 7.37 (d, 1H, J 5.0, H-5), 8.15-8.30 (bs, 1H, H-2), 8.53 (d, 1H, J 5.0, H-6).

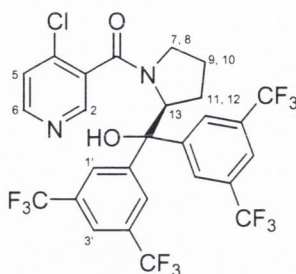
^{13}C NMR of **227b**:

δ_{C} (100 MHz, CDCl_3): 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).

ν_{max} (film)/ cm^{-1} : 3275, 2938, 2837, 1594, 1425, 1203, 1060.

HRMS (m/z - ES): Found 513.1805 ($\text{M}^+ + \text{H}$. $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_6\text{Cl}$ 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, R_f = 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**:

δ_{H} (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).

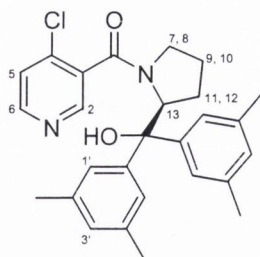
¹³C NMR of **227c**:

δ_{C} (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).

ν_{max} (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), SOCl₂ (2.0 mL), CH₂Cl₂ (6 + 10 mL), (*S*)-**226d** (720 mg, 2.32 mmol) and NEt₃ (1.29 μL, 9.28 mmol). Purification by column chromatography (1:1 CH₂Cl₂-EtOAc, R_f = 0.4) gave **227d** (394 mg, 38%) as a white solid. M.p. 73-75 °C. [α]_D²⁰ = -117.5 (c 0.143, CHCl₃).

¹H NMR of **227d**:

δ_H (400 MHz, CDCl₃): 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, CH₃), 2.35 (s, 6H, CH₃), 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-1'), 7.21 (s, 2H, H-1'), 7.37 (d, 1H, J 5.0, H-5), 8.20 (bs, 1H, H- 2), 8.52 (d, 1H, J 5.0, H-6).

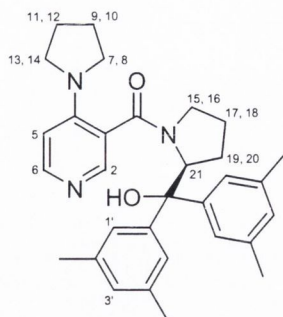
¹³C NMR of **227d**:

δ_C (100 MHz, CDCl₃): 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).

ν_{max} (film)/cm⁻¹: 3303, 2917, 2245, 1619, 1576, 1435, 1156.

HRMS (*m/z* - ES): Found 471.1824 (M⁺ + Na. C₂₇H₂₉N₂O₂NaCl 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 (*S*)-(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-CH₂Cl₂), gave **219** (83 mg, 96%) as a white solid. M.p. 179-180. $[\alpha]_D^{20} = -50.3$ (c 0.171, CHCl₃).

Note: **219** exists in two rotameric forms in the ¹H NMR and ¹³C NMR time-frame. All discernable resonances from both rotameric forms are included.

¹H NMR of **219**:

Major rotamer

δ_H (400 MHz, CDCl₃): 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, CH₃), 2.39 (s, 6H, CH₃), 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

δ_H (400 MHz, CDCl₃): 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, CH₃), 2.39 (s, 6H, CH₃), 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**:

δ_{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).

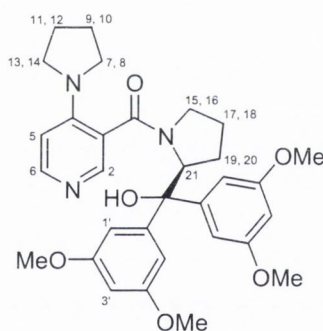
Rotamer peaks found: 22.5, 25.6, 29.9, 49.0, 68.8, 82.1, 125.7, 171.5 (C=O).

ν_{max} (film)/ cm^{-1} : 3244, 2970, 1587, 1415, 749.

HRMS (m/z - ES): Found 484.2964 ($\text{M}^+ + \text{H}$. $\text{C}_{31}\text{H}_{38}\text{N}_3\text{O}_2$ Requires: 484.2964)

Anal. calcd. for $\text{C}_{31}\text{H}_{37}\text{N}_3\text{O}_2$: 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_2Cl_2), gave **220** (79 mg, 96%) as a white solid. M.p. 227-229. $[\alpha]_{\text{D}}^{20} = -78.3$ (c 0.143, CHCl_3).

Note: **220** exists in two rotameric forms in the ^1H NMR and ^{13}C NMR time-frame. All discernable resonances from both rotameric forms are included.

¹H NMR of **220**:

Major rotamer

δ_H (400 MHz, CDCl₃): 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, OCH₃), 3.82 (s, 6H, OCH₃), 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

δ_C (400 MHz, CDCl₃): 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, OCH₃), 3.82 (s, 6H, OCH₃), 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).

¹³C NMR of **220**:

δ_C (100 MHz, CDCl₃): 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).

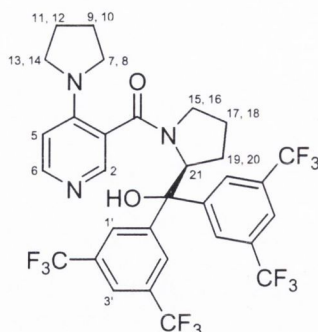
Rotamer peaks found: 22.5, 31.4, 51.4, 70.4, 80.9, 98.8, 105.8, 145.1, 146.9, 149.2, 172.9 (C=O).

ν_{max} (film)/cm⁻¹: 3217, 2955, 2332, 1592, 1424, 1153.

HRMS (*m/z* - ES): Found 548.2775 (M⁺ + H. C₃₁H₃₈N₃O₆ Requires: 548.2761)

Anal. calcd. for C₃₁H₃₇N₃O₆: 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 pyrrolidine (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 ¹H NMR and ¹³C NMR time-frame. All discernable resonances from both rotameric forms are included.

¹H NMR of **221**:

Major and minor rotamer

δ_H (400 MHz, CDCl₃): 1.65-2.28 (m, 8H, H-9, H-10, H-11, H-12, H-17, H-18, H-19, H-20), 2.91-3.28 (m, 3H, H-7, H-8, H-15), 3.49 (m, 2H, H-13, H-14), 3.68 (m, 1H, H-16), 5.05-5.24 (m, 1H, H-21), 6.49 (d, 1H, J 5.5, H-5), 7.44 (s, 1H, H-2), 7.83-8.22 (m, 7H, H-6 (J 5.5), Ar-H).

¹³C NMR of **221**:

δ_C (100 MHz, CDCl₃): 23.7, 25.4, 31.2, 49.1, 52.2, 68.9, 80.4 (q), 108.6, 115.6 (q), 122.0, 122.1, 123.0 (q, J 180.8), 123.1 (q, J 180.8), 127.4, 127.5, 131.6 (q, J 22.6), 131.7 (q, J 22.6), 144.5 (q), 146.3 (q), 147.9, 148.6 (q), 149.9, 172.4 (C=O).

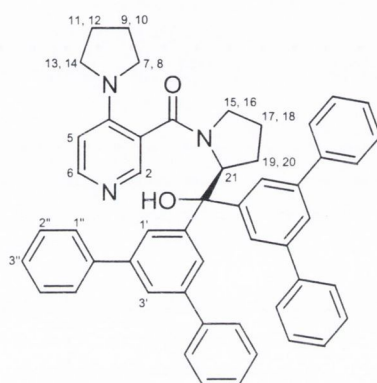
Rotamer peaks found: 22.5, 29.5, 30.4, 50.9, 68.7, 80.2, 147.3, 149.6, 173.1 (C=O).

$\nu_{\max}$ (film)/ cm^{-1} : 3240, 2928, 2298, 1642, 1371, 1132, 682.

HRMS (m/z - ES): Found 700.1835 ($M^+ + H$, $C_{31}H_{26}N_3F_{12}O_2$ Requires: 700.1833)

Anal. calcd. for $C_{31}H_{25}F_{12}N_3O_2$: 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_2Cl_2 , R_f = 0.2), gave **222** (124 mg, 98%) as a white solid. M.p. 253-254. $[\alpha]_D^{20}$ = -37 (c 0.1, CHCl_3).

Note: **222** exists in two rotameric forms in the ^1H NMR and ^{13}C NMR time-frame. All discernable resonances from both rotameric forms are included.

^1H NMR of **222**:

Major rotamer

δ_{H} (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

δ_{H} (400 MHz, CDCl_3): 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)

^{13}C NMR of **222**:

δ_{C} (100 MHz, CDCl_3): 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).

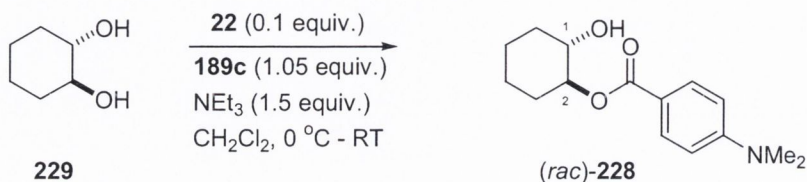
ν_{max} (film)/ cm^{-1} : 3210, 2972, 1589, 1412, 1144, 696.

HRMS (m/z - ES): Found 732.3610 ($\text{M}^+ + \text{H}$, $\text{C}_{51}\text{H}_{46}\text{N}_3\text{O}_2$ Requires: 732.3590)

Anal. calcd. for $\text{C}_{51}\text{H}_{45}\text{N}_3\text{O}_2$: 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**)

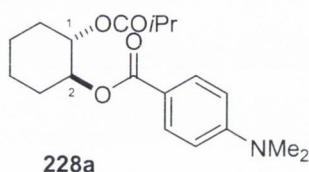


Procedure H was followed using anilinoyl chloride (**189c**) (1.16 g, 6.33 mmol), **229** (700 mg, 6.03 mmol), NEt₃ (1.25 mL, 9.04 mmol) in THF (12 + 8 mL). Purification by column chromatography (CH₂Cl₂, R_f = 0.2), gave **228** (684 mg, 43%) as a white solid. M.p 120-121. Spectral data for this compound is consistent with that in the literature.⁹¹

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,

$\text{N}(\text{CH}_3)_2$), 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**:

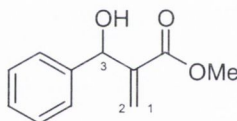
Chiralpak AS-H (4.6 mm x 25 cm), hexanes/*i*PrOH, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm. Retention times: 12.2 min minor and 25.8 min major.

HPLC data for recovered ester **228a**:

Chiralcel OD-H (4.6 mm x 25 cm), hexanes/*i*PrOH, 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**)

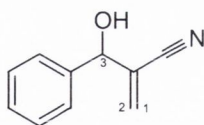


A 5 mL round bottom flask charged with **230a** (500 mg, 4.7 mmol), **231a** (634 μ L, 7.05 mmol), PEG (1 mL) and a stirring bar was placed under an atmosphere of Ar. Subsequently DABCO (115.1 mg, 0.94 mmol) was added and the resulting solution was left to stir at room temperature for 24 h. The solution was then washed with Et₂O (2 x 5 mL). The organic layer was separated, dried (MgSO₄) and the solvent removed *in vacuo*. Purification by column chromatography (CH₂Cl₂, R_f = 0.2), gave **232a** (614.3 mg, 68%) as a colourless oil.²¹²

¹H NMR of **231a**:

δ_{H} (400 MHz, CDCl₃): 3.75 (s, 3H, OCH₃), 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**)

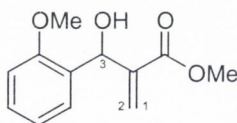


Procedure R was followed using **230b** (500 mg, 4.7 mmol), **231b** (309 μ L, 7.05 mmol), PEG (av. Mw. 200) (1 mL) and DABCO (115.1 mg, 0.94 mmol). Purification by column chromatography (CH_2Cl_2 , $R_f = 0.2$), gave **232b** (523.7 mg, 70%) as a colourless oil.²¹²

^1H NMR of **232b**:

δ_{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**)

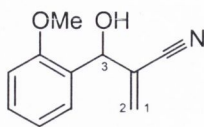


Procedure R was followed using **230c** (500 mg, 3.67 mmol), **231c** (454 μ L, 5.51 mmol), PEG (1 mL) and DABCO (82.4 mg, 0.73 mmol). Purification by column chromatography (CH_2Cl_2 , $R_f = 0.1$), gave **232c** (481.2 mg, 59%) as a colourless oil.¹⁴²

^1H NMR of **232c**:

δ_{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 μ L, 5.51 mmol), PEG (1 mL) and DABCO (82.4 mg, 0.73 mmol). Purification by column chromatography (CH_2Cl_2 , $R_f = 0.1$), gave **232d** (694.4 mg, 63%) as a colourless oil.²¹³

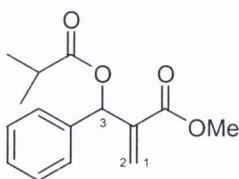
^1H NMR of **231d**:

δ_{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 μ mol) 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 μ L, 0.187 mmol) in CH_2Cl_2 (500 μ L). The resulting solution was cooled to -78°C and left to stir for 30 minutes. *Iso*-butyric anhydride (27 μ L, 0.164 mmol) was subsequently added *via* syringe. The reaction was quenched after 8 - 24 h by the addition of MeOH (200 μ L). Solvents were removed *in vacuo*. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_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 μ mol) 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 (CH_2Cl_2) through a pad of silica gel to give **233a** (40.8 mg, 66%) as a colourless oil. $[\alpha]_{\text{D}}^{20} = -33$ (c 0.16, CHCl_3) and **232a** (12.2 mg, 29%)

^1H NMR of **233a**

δ_{H} (400 MHz, CDCl_3): 1.17-1.22 (m, 6H, CH_3), 2.63 (app. hept, 1H, J 7.0, H-4), 3.74 (s, 3H, OCH_3), 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).

^{13}C NMR of **233a**:

δ_{C} (100 MHz, CDCl_3): 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).

ν_{max} (film)/ cm^{-1} : 2975, 1729, 1495, 1249, 1140.

HRMS (m/z - ES): Found 285.1115 ($\text{M}^+ + \text{Na}$. $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}$ Requires: 285.1103)

HPLC Data for recovered ester **233a**:

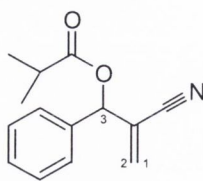
Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 90/10, 1.0 mL min^{-1} , RT, UV detection at 220 nm, retention times: 6.0 min (*S*) minor and 6.7 min (*R*) major.

HPLC Data for recovered alcohol **232a**:

Chiralcel AS-H (4.6 x 250 mm), hexane/*i*PrOH, 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 comparison of optical rotation²¹⁴ and CSP-HPLC data with that in the literature.²¹⁵

5.3.3.2.2 2-(*Iso*-butyryloxy-phenyl-methyl)-acrylonitrile (**233b**)



Procedure S was followed using **221** (1.6 mg, 2.34 μmol) and **232b** (37.3 mg, 0.234 mmol), at $-78\text{ }^{\circ}\text{C}$. The alcohol, its ester and the catalyst were separated and isolated by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel to give **233b** (24.8 mg, 46%) as a colourless oil. $[\alpha]_{\text{D}}^{20} = -14.2$ (c 0.29, CHCl_3) and **232b** (16.9 mg, 45%)

^1H NMR of **233b**

δ_{H} (400 MHz, CDCl_3): 1.22-1.28 (m, 6H, CH_3), 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).

^{13}C NMR of **233b**:

δ_{C} (100 MHz, CDCl_3): 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).

ν_{max} (film)/ cm^{-1} : 2976, 2228, 1739, 1496, 1243.

HRMS (m/z - ES): Found 252.1009 ($\text{M}^+ + \text{Na}$. $\text{C}_{14}\text{H}_{15}\text{NO}_2\text{Na}$ Requires: 252.1000)

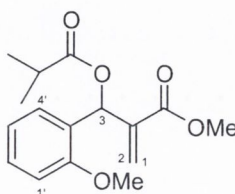
HPLC Data for recovered ester **233b**:

Could not be resolved by CSP-HPLC using Chiralcel OD-H, Chiralpak AS-H or Chiralpak AD-H columns.

HPLC Data for recovered alcohol **232b**:

Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 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*-butyryloxy-(2-methoxy-phenyl)-methyl]-acrylic acid methyl ester (233c)



Procedure S was followed using **221** (1.6 mg, 2.34 μ mol) 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. $[\alpha]_D^{20} = -62$ (c 0.1, CHCl₃) and **232c** (20.9 mg, 40%)

¹H NMR of **233c**

δ_H (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**:

δ_C (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).

$\nu_{\max}$ (film)/cm⁻¹: 2973, 2840, 1725, 1492, 1246.

HRMS (*m/z* - ES): Found 315.1216 (M⁺ + Na. C₁₆H₂₀O₅Na Requires: 315.1208)

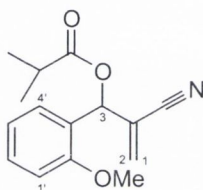
HPLC Data for recovered ester **233c**:

Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 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/*i*PrOH, 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-[*Iso*-butyryloxy-(2-methoxy-phenyl)-methyl]-acrylonitrile (**233d**)



Procedure S was followed using **221** (1.6 mg, 2.34 μ mol) 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. $[\alpha]_D^{20} = -11.9$ (c 0.26, CHCl₃) and **232d** (7.5 mg, 17%)

¹H NMR of **233d**

δ_H (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**:

δ_{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).

ν_{max} (film)/ cm^{-1} : 2975, 2841, 2228, 1740, 1492, 1247, 1142.

HRMS (m/z - ES): Found 282.1118 ($\text{M}^+ + \text{Na}$. $\text{C}_{15}\text{H}_{17}\text{NO}_3\text{Na}$ Requires: 282.1106)

HPLC Data for recovered ester **233d**:

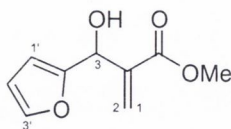
Could not be resolved by CSP-HPLC using Chiralcel OD-H, Chiralpak AS-H or Chiralpak AD-H columns.

HPLC Data for recovered alcohol **232d**:

Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 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*) $[\alpha]_{\text{D}}^{20} = +31.8$ (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**)

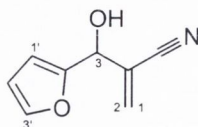


Procedure R was followed using **234a** (500 mg, 5.20 mmol), **235a** (703 μL , 7.81 mmol), PEG (1 mL) and DABCO (116.7 mg, 1.04 mmol). Purification by column chromatography (CH_2Cl_2 , $R_f = 0.1$), gave **236a** (530 mg, 56%) as a colourless oil.

¹H NMR of **236a**

δ_{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**)

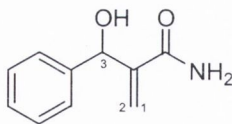


Procedure R was followed using **234b** (500 mg, 5.20 mmol), **235b** (514 μL , 7.81 mmol), PEG (1 mL) and DABCO (116.7 mg, 1.04 mmol). Purification by column chromatography (CH_2Cl_2 , $R_f = 0.2$), gave **236b** (489 mg, 63%) as a colourless oil.

¹H NMR of **236b**

δ_{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**)

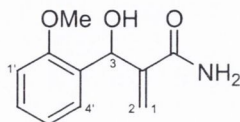


Procedure R was followed using **234c** (500 mg, 4.71 mmol), **235c** (502 mg, 7.06 mmol), PEG (1 mL) and DABCO (115.1 mg, 0.94 mmol). Purification by column chromatography (CH_2Cl_2 , $R_f = 0.1$), gave **236c** (376 mg, 45%) as a white solid. M.p. 98-100 $^{\circ}\text{C}$ (lit.²¹⁷ 97-99 $^{\circ}\text{C}$).

¹H NMR of **236c**

δ_{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 Synthesis of 2-[hydroxyl-(2-methoxyphenyl)methyl]acrylamide (**236d**)

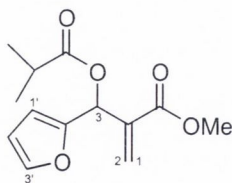


Procedure R was followed using **234d** (500 mg, 3.67 mmol), **235d** (167 mg, 5.51 mmol), PEG (1 mL) and DABCO (89.7 mg, 0.73 mmol). Purification by column chromatography (CH₂Cl₂, R_f = 0.1), gave **236d** (273.8 mg, 36%) as a white solid. M.p. 164-166 °C (lit.²¹⁷ 164-166 °C).

¹H NMR of **236c**

δ_{H} (400 MHz, DMSO-*d*₆): 3.75 (s, 3H, OCH₃), 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**)



Procedure S was followed using **169** (1.0 mg, 2.34 μmol) 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 (CH₂Cl₂) through a pad of silica gel.

¹H NMR of **237a**

δ_{H} (400 MHz, CDCl_3): 1.18 (d, 3H, J 7.0, CH_3), 1.20 (d, 3H, J 7.0, CH_3), 2.55 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 3.77 (s, 3H, OCH_3), 6.00 (s, 1H, H-2), 6.36 (m, 2H, H-1', H-2'), 6.49 (s, 1H, H-3), 6.76 (s, 1H, H-1), 7.41 (d, 1H, J 5.5, H-3').

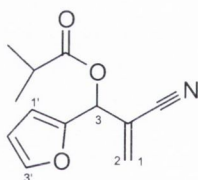
HPLC Data for recovered ester **237a**:

Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 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/*i*PrOH, 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. *Iso*-butyric acid 2-cyano-1-furan-2-yl-allyl ester (**237b**)



Procedure S was followed using **169** (1.0 mg, 2.34 μmol) and **236b** (34.9 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_2Cl_2) through a pad of silica gel.

¹H NMR of **237b**

δ_{H} (400 MHz, CDCl_3): 1.19 (d, 3H, J 7.0, CH_3), 1.21 (d, 3H, J 7.0, CH_3), 2.52 (app. hept, 1H, $\text{CH}(\text{CH}_3)_2$), 6.10 (s, 1H, H-2), 6.18 (d, 1H, J 3.5, H-1'), 6.42 (m, 2H, H-2', H-3), 6.52 (s, 1H, H-1), 7.47 (m, 1H, H-3').

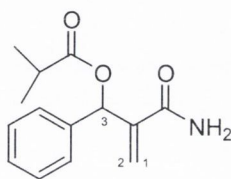
HPLC Data for recovered ester **237b**:

Could not be resolved by CSP-HPLC using Chiralcel OD-H, Chiralcel AS-H or Chiralpak AD-H columns.

HPLC Data for recovered alcohol **236b**:

Chiralcel OD-H (4.6 x 250 mm), hexane/*i*PrOH, 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**)



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**

δ_H(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/*i*PrOH, 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/*i*PrOH, 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).

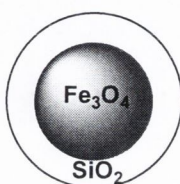
5.3.4.2 One pot synthesis and resolution of **232c**

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_2Cl_2) to give (*S*)-**232c** (6.9 mg, 25%, 89% *ee*) as a colorless oil $[\alpha]_{\text{D}}^{20} = +83$ (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**.

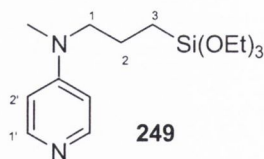
5.4.1 Experimental data for Section 4.1

5.4.1.1 Nanoparticle synthesis and subsequent silica coating



Stock solutions of 25 mL of each of 1 M $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (6.56 g, 0.024 mol), 0.5 M $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (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 (5×20 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 (CHCl₂-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.

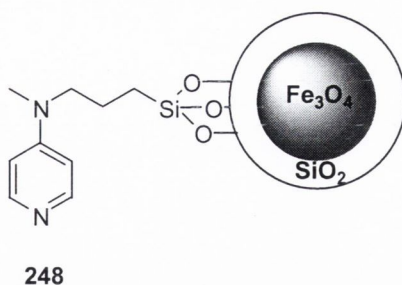
¹H NMR of **249**

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 ¹H 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 ¹H NMR analysis (t = 24 h)). The remaining magnetite was washed repeatedly with THF and dried under vacuum. Catalyst loading was then determined by ¹H NMR spectral analysis. A comparison of the integrals for the ¹H resonances of the pyridine ring in **249** relative to the ¹H 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



Procedure T was followed using **249** (55 mg, 0.177 μmol) and (*E*)-stilbene (0.177 mmol) in THF.

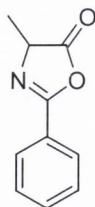
Capping of any unreacted silanol moieties was subsequently carried out. The vessel containing the nanoparticles was placed under an atmosphere of Ar (balloon). To this was added a solution of *N*-propyltriethoxysilane (990 μL , 4.3 mmol) in toluene (2 mL) and heated at 50 $^{\circ}\text{C}$ for 2 h. 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 NEt_3 (68 μL , 0.491 mmol) in CH_2Cl_2 (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 (CH_2Cl_2).

5.4.2.2 Synthesis of 2-phenyl-4-methyloxazolone (256).

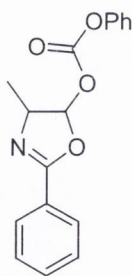


A round bottom flask charged with 2-benzoylamino-propionic acid (1.0g, 5.18 mmol), prepared according to literature precedent²¹⁸ from alanine methyl ester hydrochloride, was placed under an atmosphere of Ar (balloon). To this was added acetic anhydride (3.1 mL, 32.8 mmol) and heated to 65 °C for 3 h. 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-CHCl₂, 1:1, R_f = 0.3) to give 2-phenyl-4-methyloxazolone as white solid (650 mg, 72%). M.p. 39.5-40.5 °C (lit.,²¹⁹ 38-39 °C).

¹H NMR of **256**

δ_H (400 MHz, CDCl₃): 1.45 (d, 3H, J 7.5, CH₃), 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-phenoxy-carbonyl-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 NEt₃ (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 H₂O (5 mL) and extracted with Et₂O (2 x 10 mL). The combined organic extracts were washed with 1M HCl (2 x 20 mL), sat. NaHCO₃ (2 x 20

mL), brine (2 x 20 mL) and dried over MgSO₄. The residue was purified by flash chromatography (Hex-DCM, 1:1, R_f = 0.2) to yield **255** as a white solid (915 mg, 90.3%).

¹H NMR of **255**

δ_H (400 MHz, CDCl₃): 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').

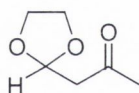
¹³C NMR of **255**

δ_C (100 MHz, CDCl₃): 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.

ν_{max} (film)/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**)

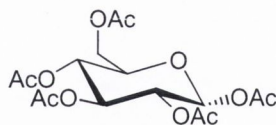


A 5 mL round bottom flask charged with **248** (82 mg, 0.0164 mmol) was placed under an atmosphere of Ar (balloon). Ethylene glycol (454 μL, 3.6 M) was added *via* syringe and the reaction cooled to 0 °C. **252** (127 μL, 1.64 mmol) Was subsequently added and the reaction raised to rt. After 16 h crude 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]

¹H NMR of **257**

δ_H (400 MHz, CDCl₃): 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).

5.4.2.4.1 Synthesis of acetic acid 4,5,6-triacetoxy-2-acetoxymethyl-tetrahydropyran-3-yl ester (**258**)

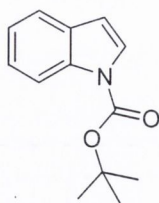


A 5 mL round bottom flask charged with **248** (82 mg, 0.0164 mmol) and D-glucose (29.5 mg, 0.164 mmol) was placed under an atmosphere of Ar. To this was added a solution of NEt₃ (204 μ L, 1.47 mmol) in CH₂Cl₂ (0.5 mL). The resulting suspension was shaken (mechanical agitation) for 5 min. Acetic anhydride (108 μ L 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.²²¹

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, J 8.0, β -anomer, 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**)



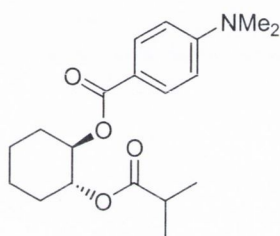
A 5 mL round bottom flask charged with **248** (82 mg, 0.0164 mmol) and **254** (19 mg, 0.164 mmol) was placed under an atmosphere of Ar (balloon). To this was added a solution of (BOC)₂O (71.4 mg, 0.327 mmol) in THF (0.5 mL). The resulting suspension was shaken (mechanical agitation). After 16 h crude 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_2Cl_2) gave **259** as colourless oil. **259** Exhibited spectral characteristics consistent with those in the literature.^[222]

¹H NMR of **259**

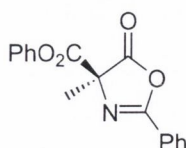
δ_{H} (400 MHz, CDCl_3): 1.69 (s, 9H, CH_3), 6.58 (d, 1H, J 4.0, H-2), 7.22-7.32 (m, 2H, H-5, H-6), 7.57-7.61 (m, 2H, H-1, H-7), 8.12-8.15 (m, 1H, H-4).

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 μL , 0.491 mmol) in THF (0.5 mL). The resulting suspension was shaken (mechanical agitation) for 5 min. *Iso*-butyric anhydride (108 μL , 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_2Cl_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**

δ_{H} (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').

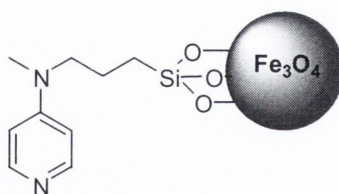
¹³C NMR of **260**

δ_{C} (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.

ν_{max} (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**



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 μ L, 4.3 mmol) in toluene (2 mL) and heated at 50 $^{\circ}$ 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

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