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A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

Development and Synthesis of Novel Organocatalysts

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University of Glasgow

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Abstract

The unfavourable use of metal-based catalysts in organic synthesis can be overcome by using small organic molecules; organocatalysts. Herein we report the development and synthesis of a novel range of organocatalysts derived from amino acids incorporating imidazole, thiourea and phosphoramidate moieties to confer the capability to act as bifunctional organocatalysts. Our organocatalyst, a phosphoramidate derived from valine, showed initial success in the catalytic alkylation of aldimine with allyltrichlorosilane, producing 40% ee.

Oxazoline catalysts derived from 2-pyridines have been shown to be effective activators of trichlorosilane for the reduction of ketones and ketimines. The reaction however suffered from chloride promoted ring opening of the catalyst. By replacing the oxygen of the oxazoline moiety with sulphur we were able to successfully avoid this problem. Further expansion of the substrate scope was achieved, heterocyclic imines were reduced in good enantioselectivity, up to 89% ee.
Acknowledgement

I would like to start by thanking my supervisors Prof Andrei Malkov and Prof Pavel Kocovsky. I am grateful to have been given the opportunity to study in their research group and appreciate all the help and support they have given over the past few years. Prof Bob Hill’s support as my second supervisor has also been greatly appreciated.

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Abbreviations

Å  Angstrom
Aq  Aqueous
BINOL  1,1′-Binaphthol
Bn  Benzyl
Boc  tert-Butoxycarbonyl
bs  broad singlet (NMR spectroscopy)
t-Bu  Tertiary butyl
°C  Degrees centigrade
cat  Catalytic
Cl  Chemical ionisation
Cy  Cyclohexyl
d  Doublet (NMR spectroscopy)
DCC  Dicyclohexylcarbodiimide
DCM  Dichloromethane
DEAD  Diethylazodicarboxylate
DIPEA  N,N-Diisopropylethylamine
DMAP  4-Dimethylaminopyridine
DMF  N,N-Dimethylformamide
DMSO  Dimethylsulfoxide
EDAC/EDC.HCl  N-Ethyl-N’-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee  Enantiomeric excess
El  Electron impact
Eq/Equiv  Equivalents
FAB  Fast atom bombardment
GC  Gas chromatography
h  Hours
HMPA  Hexamethylphosphoramide
HOBT  1-Hydroxybenzotriazole
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>LR</td>
<td>Lawesson’s reagent</td>
</tr>
<tr>
<td>M</td>
<td>Molarity</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet (NMR spectroscopy)</td>
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<td>Polymolybdic acid</td>
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<td>4-Methoxyphenyl</td>
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</tr>
<tr>
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<td>Room temperature</td>
</tr>
<tr>
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<td>Triplet (NMR spectroscopy)</td>
</tr>
<tr>
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</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethylenediamine</td>
</tr>
<tr>
<td>Ts/Tosyl</td>
<td>4-Toluenesulfonate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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Preface

Environmentally friendly, selective and high yielding processes are integral to the development and synthesis of new therapeutic reagents and novel compounds. This, coupled with the significance of chirality in nature and, more importantly, the human body, makes the efficient, green, generation of enantiomerically enriched products a key goal in modern organic synthesis.

Generation of single enantiomers of chiral compounds can be achieved in a variety of ways: racemate resolution, chiral pool, chiral auxiliaries and asymmetric catalysis. Racemate resolution is undesirable as the maximum yield is 50% and the unwanted enantiomer must be disposed of. Molecules readily available from the chiral pool (amino acids, terpenes etc.) have limited variation in structure and so multi-step syntheses are required to reach the target molecule. Chiral auxiliaries must be covalently bound to the substrate, this increases the number of steps in a synthesis and the auxiliary must also be recovered or disposed of.

Asymmetric catalysis is advantageous, as it uses achiral starting materials and requires only a catalytic amount of the chiral molecule, which offers the possibility of being recovered at the end of the synthesis. Asymmetric catalysis is widely used in industry due to its advantages over other stoichiometric methods.

Most commonly in industry, transition metal complexes are used as asymmetric catalysts because of their high reactivity and high selectivity; for example ready-made mixtures of some catalytic systems are commercially available, eliminating the need to weigh several compounds. Transition metal catalysis has become so important that in 2001 the Nobel Prize for chemistry was awarded to Knowles, Noyori and Sharpless for their contributions to asymmetric catalysis. However, transition metal catalysis is not free from problems. The metals used are often expensive, toxic and can be difficult to recover from the reaction products. In pharmaceutical products this can prove problematic due to the toxicity, cost of the metal and its recovery. These issues can be resolved by employing organocatalysis.\(^{[1]}\)
In light of this, the field of organocatalysis has received considerable attention in recent years.\cite{2,3} Although organocatalysis has been known since the early part of the twentieth century at least\cite{4,5}, the past decade has seen a vast advancement in the field. There has been large growth in the number of papers published in this area and the number of new organocatalytic systems being discovered.\cite{2,6,7} Organocatalysts are small organic molecules. They offer a favourable alternative to metals as they are less toxic, cheaper and can often be used under an aerobic atmosphere with wet solvents. Small organic molecules also offer the possibility of being recovered and reused, unlike many transition metal catalysts.

Organocatalysts can act by coordination to the substrate to render it more reactive. This is often the case when amines are used as organocatalysts and is typified by enamine activation shown by proline.\cite{8,9} Organocatalysts can also act through weak non-covalent interactions: in this case the substrate or reagent is activated by coordination to the organocatalyst. The activation of organosilicon reagents is one such example; this chapter will focus on the reactions of silicon reagents and the organocatalysts employed in these processes.
1 Introduction

1.1 Lewis Basic Activation of Silicon

Addition of nucleophilic reagents to carbonyl compounds is an area with great importance in organic synthesis. Reactive nucleophiles such as LiAlH₄ and Grignard reagents efficiently add to carbonyl compounds, however less reactive nucleophiles such as allyltrichlorosilane and trichlorosilane do not react so readily and additional activation is required. This can be achieved by either adding a Lewis acid to trialkylsilanes or a Lewis base in the case of trichlorosilanes (Scheme 1.1).

![Scheme 1.1: Activation of silanes.](image)

Activation can occur through either Lewis acid coordination to the carbonyl oxygen or through Lewis basic activation of the nucleophilic silane compound. Typically in organocatalysis activation of silanes by Lewis bases is the preferred method. As organosilicon reagents are generally unreactive, only the coordinated silicon species will react. If the activator employed can dissociate from the silicon intermediate at a sufficient rate, it can act as a catalyst rather than a stoichiometric reagent. The use of a chiral Lewis basic catalyst would naturally allow for the preferential formation of a single enantiomer.
Coordination of a Lewis base to an organosilicon reagent, 1, can expand the coordination sphere of silicon resulting in a pentacoordinate, 2, or hexacoordinate, 3, species.\textsuperscript{[11,12]} This results in increased positive charge on silicon and increases the negative charge on the ligands (Figure 1.1).\textsuperscript{[13,14]} If the increased negative charge lies on a ligand which may act as a nucleophile the hypervalent species can be considered as activated towards nucleophilic attack on an electrophile. In the case of hexacoordinate silicon, 3, it is possible for a cationic species to be generated by ionisation of an electron-withdrawing ligand, such as a halide. This results in a significant increase in Lewis acidity at silicon and can hence facilitate the activation of an electrophile, such as a carbonyl group, by coordinating to a non-bonding lone-pair of oxygen.\textsuperscript{[15]} Organocatalytic protocols based on silane reagents have taken advantage of the tendency of Lewis bases to activate silane reagents as nucleophiles and enhance the Lewis acidic character of silicon.\textsuperscript{[16]}
1.2 Allylation Reactions at C=O

The addition of allylsilanes to aldehydes is an important carbon-carbon bond forming reaction that has come under much recent scrutiny.\cite{2,17,18} Part of the reason for the interest in this reaction has been the ability to generate homoallylic alcohols with high enantio- and diastereoselectivity and the synthetic versatility of the end product. Although the reaction is typically carried out by Lewis-acidic (metallic) activation of the carbonyl component or by employing reactive organometallic allyl reagents, the development of Lewis basic activation of allylsilanes has allowed the use of organic molecules as promoters (organocatalysts).

Lewis base promoted allylation of aldehydes with allylsilanes was pioneered by Kobayashi using dimethylformamide as a stoichiometric activator of allyltrichlorosilane, 4.\cite{19,20} Interestingly, when crotlytrichlorosilanes, 5, were used, the reaction proceeded stereospecifically suggesting the reaction operates via a closed cyclic transition state, 6 (Scheme 1.2). Since this initial discovery, a range of further Lewis basic substances that facilitate the allylation reaction have been identified. Typical Lewis basic activators include DMSO\cite{19-22} and HMPA\cite{22,23} as well as compounds with formamide\cite{24,25} and urea\cite{26} structural motifs.

\[
\begin{align*}
\text{R}^1\text{R}^2\text{SiCl}_3 + \text{R}^1\text{R}^2\text{CHO} & \xrightarrow{\text{DMF}} \text{R}^1\text{R}^2\text{OH} \\
4: \text{R}^1=\text{H}, \text{R}^2=\text{H} \\
\text{(trans)-5}: \text{R}^1=\text{Me}, \text{R}^2=\text{H} \\
\text{(cis)-5}: \text{R}^1=\text{H}, \text{R}^2=\text{Me}
\end{align*}
\]

\textbf{Scheme 1.2:} Kobayashi closed TS
1.2.1 Phosphoramide Organocatalysed Allylations

The asymmetric Lewis base promoted allylation of aldehydes was pioneered by Denmark who showed that chiral phosphoramides were able to successfully produce enantioenriched homoallylic alcohols,[22] although the phosphoramide catalyst 7 exhibited only modest enantioselectivity. It was shown that the addition of trans and cis 5 resulted in generation of the anti or syn products respectively, 9, with high diastereoselectivity (Scheme 1.3). The transfer of stereochemistry from double bond to product in the crotylation reaction strongly suggests that the reaction proceeds via a closed cyclic transition state, much like that proposed by Kobayashi.

\[
\begin{align*}
\text{R}^1\text{R}^2\text{SiCl}_3 + \text{C}6H_5\text{CHO} &\rightleftharpoons \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \\
4: \text{R}^1=\text{H}, \text{R}^2=\text{H} &\quad \text{(trans)-5: R}^1=\text{Me}, \text{R}^2=\text{H} \\
\text{cis}-5: \text{R}^1=\text{H}, \text{R}^2=\text{Me} &
\end{align*}
\]

<table>
<thead>
<tr>
<th>silane</th>
<th>cat loading (%)</th>
<th>yield (%)</th>
<th>anti/syn</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>100</td>
<td>80</td>
<td>N.A.</td>
<td>60</td>
</tr>
<tr>
<td>(trans)-5</td>
<td>100</td>
<td>68</td>
<td>98/2</td>
<td>64</td>
</tr>
<tr>
<td>(cis)-5</td>
<td>100</td>
<td>72</td>
<td>2/98</td>
<td>60</td>
</tr>
</tbody>
</table>

Scheme 1.3: Phosphoramide catalysed allylation of benzaldehyde – Denmark

To further probe the reaction mechanism and dependence of selectivity on catalyst loading, a kinetic study was carried out by Denmark.[27] A non-linear relationship between the enantiopurity of catalyst 7 and product 8 was found, suggesting that two molecules of catalyst are involved in the transition state. It was also proposed that a second, less selective one-catalyst pathway may operate at low phosphoramide levels. In order to reduce the effects of the second, less selective pathway, Denmark designed bisphosphoramide catalysts (Chart 1.1).[27,28]
Variation of the length of carbon chain linking the phosphoramidate units identified a five-methylene tether as the optimum, 10b. Increased selectivity was observed with the use of organocatalysts 11a-c, derived from (R,R)-2,2’-bispyrrolidine. Again, the optimum tether length was determined as five methylene units. Bis-phosphoramidate 11b catalysed allylation of benzaldehyde 6 (loading of 5 mol%) furnishing the allylic alcohol in 85% yield and 87% ee. Catalyst 11b was also successful in the allylation of a range of aromatic, heteroaromatic and unsaturated aldehydes.[28]

![Chart 1.1: Bis-phosphoramidate organocatalysts.](image)

In order to further understand the reaction mechanism, Denmark carried out a number of studies involving bis-phosphoramidate catalysts 10b and 11b.[29] In these studies, complexes of phosphoramides with SnCl₄ were synthesised and their properties were studied both in solution and in solid state. Complexes with Sn exhibit similar bonding to those of Si but are also more stable making them easier to study. The similarity in bonding between Si and Sn complexes allows results based on Sn to be extrapolated to the corresponding Si complexes. Based on crystallographic data and ³¹P and ¹¹⁹Sn NMR studies, Denmark proposed that trans-coordination of the silane to the Lewis basic organocatalyst enhances the nucleophilicity of the allyl group. In addition, the aldehyde should preferably coordinate trans to the electron-withdrawing chloride group to enhance its anionic character. Coordination of both Lewis basic catalyst and aldehyde to silicon in this fashion generates a chiral pocket, 12, in which enantioselective allylation can occur (Figure 1.2).
1.2.2 N-Oxide Organocatalysed Allylations

Another successful class of organocatalysts for the Lewis-base promoted allylation with allyltrichlorosilanes are N-oxides (Chart 1.2). The use of N-oxides was pioneered by Nakajima, who demonstrated that chiral $N,N'$-bisoxide 13 allowed successful transformation in high yield and selectivity (71 – 92% ee) at -78 °C with a catalyst loading of only 10 mol% (Table 1.1, entries 1-4). Similar to the phosphoramidate catalysed allylation reactions, a six-membered transition state was
proposed due to the high diastereoselectivity observed upon the addition of trans and cis croytysilanes (Figure 1.2).

Further to Nakajima’s work, a more active N,N’-bisoxide 14 was developed by Hayashi. High yields are observed with as little as 0.1 mol% catalyst loading; however enantioselectivity was highly dependent on the electronic nature of the substrate aldehyde (Table 1.1, entries 5, 6). Electron-deficient aldehydes produced homoallylic alcohols with lower enantioselectivity than that of their electron-rich counterparts. Hayashi suggested that the difference between electron-rich and electron-poor aldehydes could be attributed to π-stacking between the aldehyde and catalyst in the transition state.

\[
\begin{align*}
\text{R}_1\text{R}_2\text{SiCl}_3 + \text{ArCHO} \rightarrow \text{Ar}\text{R}_1\text{R}_2\text{OH}
\end{align*}
\]

4: \( R^1=\text{H}, R^2=\text{H} \)
(trans)-5: \( R^1=\text{Me}, R^2=\text{H} \)
(cis)-5: \( R^1=\text{H}, R^2=\text{Me} \)

<table>
<thead>
<tr>
<th>entry</th>
<th>silane</th>
<th>Ar</th>
<th>catalyst</th>
<th>yield (%)</th>
<th>anti/syn</th>
<th>ee (%)</th>
</tr>
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<tr>
<td>1</td>
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<td>Ph</td>
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<td>85</td>
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<td>88 (R)</td>
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<tr>
<td>2</td>
<td>4</td>
<td>4-MeOC_6H_4</td>
<td>13</td>
<td>91</td>
<td>NA</td>
<td>92 (R)</td>
</tr>
<tr>
<td>3</td>
<td>(trans)-5</td>
<td>Ph</td>
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<td>64</td>
<td>1/99</td>
<td>84 (R)</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>Ph</td>
<td>14</td>
<td>95</td>
<td>NA</td>
<td>84 (S)</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>4-MeOC_6H_4</td>
<td>14</td>
<td>96</td>
<td>NA</td>
<td>94 (S)</td>
</tr>
</tbody>
</table>

Table 1.1: Allylation with bis-N-oxides 13 and 14.

Malkov and Kocovsky reported the use of a series of catalysts derived from terpenes; bypyridine N-monoxides 15 – 17. N-oxide 15, PINDOX, emerged as an efficient catalyst for the allylation of aromatic and heteroaromatic aldehydes (Table 1.2, entries 1 - 5). Further studies, however, revealed that Me_2-PINDOX 16 was much more efficient than its analogues PINDOX, 15, and iso-PINDOX, 17. It was proposed that the restriction to axial rotation imposed by 3,3’-methyl groups created a favourable chiral environment upon coordination to silicon. Asymmetric
induction is controlled by the configuration of the 2,2’-bipyridyl bond as shown by using both the (+) and (-) atropisomers of Me₂-PINDOX, 16. Thus, when the (+) atropisomer (10 mol%) was used, the homoallylic alcohol (S)-8 was isolated in 72% yield and 98% ee (Table 1.2, entry 6); while (-)-16 results in the formation of the (R)-8 in 82% ee and 67% yield (Table 1.2, entry 7). To account for the observed results, a bidentate coordination of silicon through both O and N resulting in a hexacoordinate silicon species was proposed.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>Ar</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
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<td>15</td>
<td>Ph</td>
<td>78</td>
<td>90 (S)</td>
</tr>
<tr>
<td>2</td>
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<td>68</td>
<td>87 (S)</td>
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<td>15</td>
<td>4-NO₂C₆H₄</td>
<td>58</td>
<td>65 (S)</td>
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<td>4</td>
<td>15</td>
<td>PhCH=CH₂</td>
<td>52</td>
<td>83 (S)</td>
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<tr>
<td>5</td>
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<td>7</td>
<td>(-)-16</td>
<td>Ph</td>
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<td>4-MeOC₆H₄</td>
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<td>10</td>
<td>17</td>
<td>PhCH=CH₂</td>
<td>25</td>
<td>96 (S)</td>
</tr>
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</table>

Table 1.2: Allylation of aldehydes with PINDOX and its derivatives.

It was discovered that METHOX, 18, lacking the second pyridine ring was much more active and achieved the same levels of enantioselectivity as PINDOX analogues, 15 - 17.³⁴,³⁵ In light of this Malkov and Kocovsky proposed that aromatic interactions between the catalyst and substrate may play a crucial role in determining the configuration of the transition state, rather than a second coordination point for Si. In addition it was found that METHOX, 18, remained highly active even at low loadings (1 mol%) and is tolerant of aldehyde electronics (Table 1.3, entries 1-5).

While METHOX exhibited good selectivity regardless of aldehyde electronics, related N-oxide catalyst, 19, QUINOX displays high dependence on the electronics of the substrate aldehyde.³⁶ Employing QUINOX, 19, it was found that the reaction of electron-poor aldehydes proceeded with higher rate and selectivity than the
equivalent electron-rich aldehydes (Table 1.3, entries 6–9). More recent investigations involving computational and kinetic studies by Malkov and co-workers have indicated that the reaction is likely to proceed via an associative reaction mechanism involving one molecule of organocatalyst that generates an octahedral silicon complex, 20 (Figure 1.3).[37]

<table>
<thead>
<tr>
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<th>loading (%)</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<td>MeCN</td>
<td>95</td>
<td>96 (S)</td>
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<td>Ph</td>
<td>1</td>
<td>MeCN</td>
<td>68</td>
<td>95 (S)</td>
</tr>
<tr>
<td>3</td>
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<td>4-CF₃-C₆H₄</td>
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<td>MeCN</td>
<td>86</td>
<td>93 (S)</td>
</tr>
<tr>
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<td>18</td>
<td>4-MeO-C₆H₄</td>
<td>5</td>
<td>MeCN</td>
<td>95</td>
<td>96 (S)</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>2-MeO-C₆H₄</td>
<td>5</td>
<td>MeCN</td>
<td>95</td>
<td>89 (S)</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>Ph</td>
<td>5</td>
<td>CH₂Cl₂</td>
<td>60</td>
<td>87 (R)</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>4-MeO-C₆H₄</td>
<td>5</td>
<td>CH₂Cl₂</td>
<td>70</td>
<td>12 (R)</td>
</tr>
<tr>
<td>8ᵇ</td>
<td>19</td>
<td>4-NO₂-C₆H₄</td>
<td>5</td>
<td>CH₂Cl₂</td>
<td>73</td>
<td>89 (R)</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>4-CF₃-C₆H₄</td>
<td>5</td>
<td>CH₂Cl₂</td>
<td>85</td>
<td>96 (R)</td>
</tr>
</tbody>
</table>

[a] All reactions carried out at -40 °C. [b] Reaction complete after 12h

Table 1.3: Allylation of aldehydes with 18 and 19.

Figure 1.3: Proposed TS for allylation of aldehydes with QUINOX 19.

Crotylation of aldehydes catalysed by PINDOX and its derivatives, 15 - 17, resulted in the highly diastereoselective formation of homo-allylic alcohols 9. The transfer of stereochemistry from double bond to alcohol was consistent with the presence of a closed cyclic transition state, i.e. the trans alkene produces the anti product and cis gives the syn products. METHOX reacts well with trans-5, generating anti-9 with very high diastereoselectivity (>99:1) and high ee (95%). The reaction with cis-5 however is slow and not as diastereoselective (6:1).
Crotylation with QUINOX, 19, as the organocatalyst has been shown to exhibit high diastereoselective control\textsuperscript{[36,37]}.

Reaction with trans and cis-5 formed the corresponding allylic alcohols with high diastereoselectivity, 95:5 and 1:99 respectively (Table 1.4). It was again observed that electron-rich aldehydes did not react as well as their electron-poor counterparts. The results indicate that crotylation with QUINOX, 19, proceeds via a closed chair-like transition state, similar to that proposed by Denmark (Figure 1.4). Computational studies also suggested that aromatic interactions between catalyst and substrate may play a contributory role in the enantiodifferentiation process.

\begin{center}
\begin{tabular}{c c c c}
\hline
\textbf{R} & \textbf{Silane} & \textbf{Yield} & \textbf{anti:syn} \\
\hline
CF\textsubscript{3} & trans & 75 & 96:4 \\
H & trans & 65 & 95:5 \\
MeO & trans & 40 & 83:17 \\
CF\textsubscript{3} & cis & 85 & 1:99 \\
H & cis & 78 & 1:99 \\
MeO & cis & 50 & 4:96 \\
\hline
\end{tabular}
\end{center}

\textbf{Table 1.4:} Crotylation of aldehydes with QUINOX

\begin{center}
\begin{enumerate}
\item \textbf{(trans)-5:} R\textsubscript{1}=Me, R\textsubscript{2}=H \\
\item \textbf{(cis)-5:} R\textsubscript{1}=H, R\textsubscript{2}=Me \\
\item \textbf{(anti)-9:} R\textsubscript{1}=Me, R\textsubscript{2}=H \\
\item \textbf{(syn)-9:} R\textsubscript{1}=H, R\textsubscript{2}=Me
\end{enumerate}
\end{center}

\textbf{Figure 1.4:} Allylation transition state, LB\textsuperscript{*} = chiral Lewis Base (organocatalyst)
The application of tri-N-oxides as Lewis basic activators for this reaction has also been reported by Kwong.\cite{38} Terpene derived pyridine-N-oxides 21 – 22 were shown to be effective with loadings of 10 mol% (Chart 1.3, Table 1.5). Enantiomeric excess of up to 86% ee was reported however the selectivity proved to be dependent on the electronics of the aldehyde; again; electron-poor aldehydes gave the highest selectivity.

![Chart 1.3: Terpene derived N-oxide organocatalysts](chart)

Table 1.5: Allylation catalysed by tri-N-oxides 21 – 22.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>Ph</td>
<td>85</td>
<td>34 (R)</td>
</tr>
<tr>
<td>2</td>
<td>22a</td>
<td>Ph</td>
<td>87</td>
<td>67 (R)</td>
</tr>
<tr>
<td>3</td>
<td>22b</td>
<td>Ph</td>
<td>89</td>
<td>74 (R)</td>
</tr>
<tr>
<td>4</td>
<td>22b</td>
<td>4-MeO-C₆H₄</td>
<td>94</td>
<td>65 (S)</td>
</tr>
<tr>
<td>5</td>
<td>22b</td>
<td>4-CF₃-C₆H₄</td>
<td>91</td>
<td>86 (R)</td>
</tr>
</tbody>
</table>
1.2.3 Formamide Organocatalysed Allylations

Chiral formamides have also been employed as organocatalysts for the allylation of aldehydes based upon the work of Kobayashi.\textsuperscript{[19]} Chiral DMF analogues were developed by Iseki and employed in the allylation reaction.\textsuperscript{[24,25]} Formamide 23 was found to be an activator for the reaction however long reaction times at low temperature (7 days at -78 °C) were required to produce the allylic alcohol 24 in 81% yield and 68% ee (Scheme 1.4). It was found that the addition of 1.0 equivalents of HMPA was beneficial to the reaction. The product was formed in 80% yield and 98% ee under optimum conditions, 1.0 eq HMPA as an additive, -78 °C, 14 days. Although 23 operates as a highly selective catalyst, the reaction rate is too sluggish to be considered synthetically useful. It is worth noting, however, that 23 exhibits high selectivity for aliphatic aldehydes (≥ 98% ee) but not with aromatic aldehydes.

\[
\text{Me} \quad \text{Me} \\
\text{O} \\
\text{H} \\
\text{SiCl}_3 \\
\text{OH} \\
\text{H} \\
\text{Cl} \\
\text{Cl} \\
\text{CH}_2 \\
\text{Cl} \\
\text{Cl} \\
\text{Me} \\
\text{Me} \\
\text{N}
\]

\[
\text{Me} \quad \text{Me} \\
\text{O} \\
\text{H} \\
\text{SiCl}_3 \\
\text{OH} \\
\text{H} \\
\text{Cl} \\
\text{Cl} \\
\text{CH}_2 \\
\text{Cl} \\
\text{Cl} \\
\text{Me} \\
\text{Me} \\
\text{N}
\]

Scheme 1.4: Allylation reaction promoted by (S,S)-23.

More recently, Kobayashi described the use of a polymer supported formamide, 25, which can act as a recyclable promoter for the allylation of aldehydes with silanes (Scheme 1.5).\textsuperscript{[39]} Allylic alcohol 26 was formed in 91% yield using one equivalent of polymer supported catalyst 25. It was also found that 25 maintained its activity through several uses.
1.2.4 Pyridine-oxazoline Organocatalysed Allylations

The use of pyridine-oxazoline derivatives as activators for crotylation of aromatic aldehydes was reported by Barrett.\footnote{40} Organic activator 27 derived from leucinol showed the best results for this transformation, giving excellent diastereoselectivity, >99% and moderate-to-good enantioselectivity, 36 – 74% ee (Scheme 1.6). Formation of the anti-allylic alcohol only, indicates the involvement of a hyper-valent silicon species in a closed transition state.

\[
\begin{align*}
\text{R} & \quad \text{Yield} (\%) \quad \text{ee} (\%) \\
1 & \quad \text{Ph} & 72 & 74 \\
2 & \quad 4-\text{MeO-}C_6H_4 & 79 & 46 \\
3 & \quad 4-\text{F-}C_6H_4 & 61 & 74 \\
4 & \quad 4-\text{O}_2N-C_6H_4 & 66 & 36 \\
\end{align*}
\]

Scheme 1.6: Crotylation of aldehydes catalysed by pyridine-oxazolines.
1.3 Reduction of Ketones With Silanes

Silanes are widely accepted as efficient reagents for the reduction of carbonyl functionality. In the case of alkyl silanes, transition metal catalysts are required to activate the reagent; in the case of more Lewis acidic trichloro- and trialkoxysilanes, a metal-free variation can be attained by employing an organic activator (Scheme 1.7).

\[
\begin{align*}
\text{OR}^1 & \text{R}^2 & + & X_3\text{SiH} & \rightarrow & \text{OH} \\
\text{Activator} & & & & & \text{R}^1 & \cdot \text{R}^2
\end{align*}
\]

**Scheme 1.7:** Reduction of ketones with silanes

1.3.1 Anion Promoted Reduction

Trialkoxysilanes were reported as reducing agents for carbonyl compounds by Corriu. Although generally unreactive towards carbonyl functionality, triethoxysilane turned into a reactive hypervalent silicon species upon coordination of fluoride anions. A range of carbonyl compounds were reduced by silanes catalysed by alkali metal fluorides.

More recently, Lawrence has reported the use of chiral quinidine fluoride salts as phase-transfer catalysts for an asymmetric variant of this reaction. Activation of trimethoxysilane is again achieved by forming a hypervalent silicon species with fluoride anions. The use of chiral cinchona derived catalyst 28 led to the formation of sec-alcohols in up to 78% ee (Scheme 1.8). It was also found that aromatic sec-alcohols were formed with higher levels of enantiodiscrimination than their aliphatic counterparts.
Scheme 1.8: Reduction of ketones with cinchona derivative 28

Alkoxides also turned into effective activators of silicon for the reduction of ketones to alcohols with silanes as shown by Hosomi (Chart 1.4). Lithium alkoxide 31 generated a hypervalent silicon species which converted a range of ketones to the corresponding alcohols in good yield. Hosomi then developed chiral alkoxides as activators of silicon, resulting in an asymmetric transformation. Alkoxide 32 successfully reduced acetophenone, 29, in 78% yield and 44% ee with a loading of 40 mol%.

Additionally, lithium salts of L-Histidine and BINOL have been developed as activators of trialkoxysilanes by Brook and Kagan respectively. The lithium salt of L-Histidine, 33, formed (S)-phenylethanol, 30, in 70% yield and only 26% ee; the monolithium salt of BINOL, 34, formed (S)-phenylethanol, 30, in 92% yield and 70% ee; 34 was also shown to be highly effective for a range of ketones forming the sec-alcohol products in good selectivity (up to 93% ee). In both cases the addition of TMEDA was found to be beneficial to the activity of the catalytic system, presumably as it prevents the organolithio compounds from aggregating.
1.3.2 Formamide Promoted Reduction

Kobayashi described the reduction of ketones to sec-alcohols with the use of a dimethylformamide-trichlorosilane complex.\textsuperscript{[50]} The hypervalent silicon complex thus generated was shown to be an effective reducing agent for ketones, aldehydes and imines. Trichlorosilane proved to be a more desirable reducing agent than trialkoxysilanes as it is less toxic, cheap and easy to handle. Perhaps unsurprisingly, this led to the development of chiral formamide derivatives as activators of trichlorosilane for the reduction of the carbonyl functionality.

Matsumura showed that N-formylpyrrolidine derivatives were able to effectively activate trichlorosilane towards reduction in only catalytic quantities (Chart 1.5).\textsuperscript{[51]} The initial non-enantioselective reduction was carried out with 10 mol\% of formamide 35, resulting in formation of phenylethanol in 92\% yield. By employing chiral formamide 36 derived from proline some enantiodiscrimination was observed. Enantioselectivity was increased when formamide 37 was employed, giving the product in 43\% ee. Matsumura proposed steric repulsion
between the aryl groups of the catalyst and ketone as a rationale for enantioinduction (Figure 1.5).

![Figure 1.5: Matsumura’s proposed transition state.](image)

More recently, Matsumura reported the related formamide 38 (Chart 1.5) as an efficient activator of silanes towards reduction of ketones.\textsuperscript{[52]} Formamide 38 reduced aromatic ketones containing both electron-donating and electron-withdrawing substituents in high selectivity, up to 97% ee (Table 1.6). Acetyl ferrocene was also successfully reduced by 38 at \(-60^\circ\text{C}\) in 97% yield and 99.7% ee. It was found that the carboxyl group and 2,4,6-triethylphenyl group at the \(\alpha\) and \(\alpha'\) positions were required for high selectivity and reactivity. This may suggest hydrogen bonding interactions between the catalyst and either ketone or silane. Aromatic interactions between catalyst and substrate may also be suggested as a rationale for selectivity.

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>90</td>
<td>95 (R)</td>
</tr>
<tr>
<td>2</td>
<td>4-NO\textsubscript{2}-C\textsubscript{6}H\textsubscript{4}</td>
<td>93</td>
<td>97 (R)</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>93</td>
<td>97 (R)</td>
</tr>
<tr>
<td>4</td>
<td>4-F-C\textsubscript{6}H\textsubscript{4}</td>
<td>91</td>
<td>94 (R)</td>
</tr>
</tbody>
</table>

Table 1.6: Reduction of ketones with formamide 38.
Pipecolinic derived formamides, 39 – 43 (Chart 1.6), were found to be effective for the reduction of ketones with trichlorosilane by Sun and co-workers.\textsuperscript{[53]} Formamide derivative 43 was found to be the most efficient promoter of the reduction reaction; aromatic ketones were reduced in high yield and enantioselectivity (Table 1.7, entries 1 – 3). Interestingly, aliphatic ketones were effortlessly reduced in moderate to high selectivity (Table 1.7, entries 4 and 5).

![Chart 1.6: Pipecolinic derived formamide organocatalysts.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CF\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}</td>
<td>92</td>
<td>92 (R)</td>
</tr>
<tr>
<td>2</td>
<td>4-NO\textsubscript{2}-C\textsubscript{6}H\textsubscript{4}</td>
<td>92</td>
<td>91 (R)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>94</td>
<td>81 (R)</td>
</tr>
<tr>
<td>4</td>
<td>c-C\textsubscript{6}H\textsubscript{11}</td>
<td>90</td>
<td>88 (R)</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>81</td>
<td>53 (R)</td>
</tr>
</tbody>
</table>

Table 1.7: Reduction of ketones with formamide 43.

The methoxy substituent at the 2’ position was found to be crucial to enantiodifferentiation as replacement of this group results in lower selectivity. Furthermore it was found that reversal of the stereochemistry at C-2’ or removal of
the alkoxy group had a detrimental effect on both selectivity and reactivity. Based on their observed results, Sun et al proposed a transition state based on tricoordinate activation of silane by the organocatalyst to generate a heptacoordinate silicon species, 44, as the active reducing agent (Figure 1.6).

![Figure 1.6: Sun proposed transition state for reduction of ketones.](image)

### 1.3.3 Oxazoline Promoted Reduction

![Chart 1.7: Pyridine oxazoline activators of silanes](image)

More recently Malkov and Kocovsky described the use of pyridine oxazolines as highly effective organocatalysts for the reduction of ketones with trichlorosilane (Chart 1.7). When phenylglycine derived pyridine oxazoline 45 was effectively employed for the hydrosilylation of acetophenone, 29, the resulting alcohol, 30, was obtained in low yield and moderate enantioselectivity (Table 1.8, entry 1). In contrast, the isomeric pyridine oxazoline 46, obtained from mandelic acid, reduced acetophenone, 29, in 85% yield and 78% ee (Table 1.8, entry 2). Steric interactions between the chiral aryl group and the silane ligands, resulting in poor coordination of the silane to 45, were proposed to account for the difference in selectivity between 45 and 46. A range of ketones were examined in the
reduction reaction catalysed by 46, high enantioselectivity was observed only in aromatic ketones (>80% ee), while aliphatic ketones performed rather poorly.

In order to increase activity and selectivity, catalyst 47 derived from 1-isoquinoline and mandelic acid was developed. Catalyst 47 was shown to be much more active over a range of substrates and allowed the catalyst loading to be dropped to 10 mol%. Aromatic ketones were reduced in good yield with high enantioselectivity, >94% (Table 1.8, entries 3 – 7). Malkov and Kocovsky proposed a transition state accounting for the high selectivity in which the oxazoline catalyst coordinates to trichlorosilane to form a hypervalent silicon species. The ketone, coordinated to a second molecule of trichlorosilane, then approaches from the less hindered face; it was also suggested that aromatic interactions between ketone and catalyst may play a role in stabilising the transition state, 48 (Figure 1.7).

\[
\text{Organocatalyst} + \text{Cl}_3\text{SiH} \rightarrow \text{OH} \]

\[\begin{align*}
\text{Entry} & \quad \text{Catalyst (mol%)} & \quad \text{R}^1, \text{R}^2 & \quad \text{Yield} (%) & \quad \text{ee} (%) \\
1 & 45 (20) & \text{Ph, Me} & 29 & 66 \\
2 & 46 (20) & \text{Ph, Me} & 85 & 78 \\
3 & 47 (10) & \text{Ph, Me} & 85 & 84 \\
4 & 47 (10) & \text{Ph, Et} & 55 & 86 \\
5 & 47 (10) & 2-\text{MeO-C}_6\text{H}_4 & 50 & 87 \\
6 & 47 (10) & 2-\text{F-C}_6\text{H}_4, \text{Me} & 35 & 70 \\
7 & 47 (10) & \text{2-naphth, Me} & 93 & 94 \\
\end{align*}\]

Table 1.8: Organocatalytic reduction of ketones with oxazoline derivatives

\[\begin{align*}
\text{Figure 1.7:} & \quad \text{Proposed transition state for catalyst 46.}
\end{align*}\]
1.4 Reduction of Imines with Silanes

1.4.1 Anion Promoted Reduction

As an outcome to the activation of trialkoxysilanes for the hydrosilylation of ketones, Hosomi reported the use of lithium methoxide as a catalyst for the reduction of \(N\)-tosyl imines with trimethoxysilane.\(^{[35]}\)

Attempts to render the reaction enantioselective by using lithium salts of various amino alcohols were unsuccessful however.\(^{[56]}\) An improvement in selectivity was observed using the dilithium salt of BINOL, 34. The reduction of 49 to 50 was carried out successfully in 65% enantioselectivity.

![Scheme 1.9: Reduction of \(N\)-tosyl imines](image)

1.4.2 Formamide Promoted Reduction

Analogous to the reduction of ketones, Kobayashi described the generation of a hypervalent dimethylformamide-trichlorosilane complex and its effectiveness as a mild reducing agent for ketimines (Scheme 1.10).\(^{[50]}\)

![Scheme 1.10: Reduction of ketimines with DMF-trichlorosilane.](image)
In a similar manner, Matsumura investigated the potential of pyrrolidine derived formamides as catalytic Lewis basic activators for the reduction of prochiral ketimines with trichlorosilane.\[^{57}\] Formamide 35 was shown to be much more effective than DMF for the achiral reaction, generating amine 52 in 79% yield. By employing enantiomerically pure formamides 36 and 37, a small range of ketimines were reduced to the corresponding chiral amines in moderate enantioselectivity (Table 1.9).

![Reduction of ketimines with pyrrolidine derived formamides.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ar</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>Ph</td>
<td>Ph</td>
<td>79</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
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<td>Ph</td>
<td>91</td>
<td>55 (R)</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>Ph</td>
<td>Ph</td>
<td>52</td>
<td>66 (R)</td>
</tr>
</tbody>
</table>

*Table 1.9: Reduction of ketimines with pyrrolidine derived formamides.*

In a modification of the chiral scaffold developed by Matsumura, Malkov and Kocovsky reported valine derived formamides as highly selective organocatalysts for the reduction of ketimines with trichlorosilane (Chart 1.8).\[^{58}\] Replacing the rigid cyclic core of the pyrrolidine formamides with a more flexible skeleton resulted in much higher levels of enantiodiscrimination; presumably as the more flexible system allows the catalyst to adopt a more favourable geometry in the transition state. Although both 37 and valine derived formamide 54 have the same absolute configuration, the latter results in formation of the opposite enantiomer.
A range of prochiral ketimines were reduced with 53 and 54 as a catalyst (Table 1.10, entries 1 - 5); tuning the steric properties of the aromatic ring of the catalyst, as in 54, improved the reactivity. It was found that selectivity was only observed with N-aryl imines. In addition, non-polar solvents proved to be superior in terms of reactivity and enantioselectivity, with chloroform and toluene as the optimum. Variation of the amino acid side-chain showed that bulkier groups such as cyclohexyl and t-butyl groups, 55 and 56, exhibited marginally reduced selectivity (Table 1.10, entries 6 and 7), while catalysts derived from alanine, phenylalanine and phenylglycine, 57, 58 and 59, were considerably less selective (Table 1.10, entries 8 – 10).

It was proposed that activation of trichlorosilane occurs through coordination to the formamide moiety in 54, it was also conjectured that the amide oxygen may play a role in coordinating silicon. Arene-arene interactions between the catalyst and the N-aryl moiety of the imine were suggested as contributing to the enantiodifferentiating process. The chirality of the amino acid side-chain is thought to be transmitted through the N-Me moiety of the catalyst.
A range of formamide derived organocatalysts were developed by Sun, 60 – 63, and shown to be effective for the reduction of ketimines with trichlorosilane (Chart 1.9). The most successful was shown to be 63, a formamide derivative of L-pipecolinic acid. Similar to the reactivity of ketones (Table 1.7), formamide 63 effectively reduced not only aromatic ketimines, but aliphatic ketimines as well, in high yield and selectivity (Table 1.11). Sun suggested that the reaction could not proceed through the analogous transition state as for ketone reduction (Figure 1.6) due to steric repulsion between the $N$-aryl moiety and catalyst methoxy group. Instead it was suggested that the reduction of ketimines proceeds via a hexacoordinate silicon species (Figure 1.8).

### Table 1.10: Reduction of ketimines with amino acid derived formamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ar</th>
<th>R</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Ph</td>
<td>Ph</td>
<td>CHCl$_3$</td>
<td>49</td>
<td>92 (S)</td>
</tr>
<tr>
<td>2$^a$</td>
<td>54</td>
<td>Ph</td>
<td>Ph</td>
<td>CHCl$_3$</td>
<td>94</td>
<td>92 (S)</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>Ph</td>
<td>Ph</td>
<td>Toluene</td>
<td>81</td>
<td>92 (S)</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>Ph</td>
<td>PMP</td>
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<td>48</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>Ph</td>
<td>PMP</td>
<td>Toluene</td>
<td>95</td>
<td>82 (R)</td>
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<td>7</td>
<td>56</td>
<td>Ph</td>
<td>PMP</td>
<td>Toluene</td>
<td>95</td>
<td>83 (S)</td>
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<td>57</td>
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<td>92</td>
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<tr>
<td>9</td>
<td>58</td>
<td>Ph</td>
<td>PMP</td>
<td>Toluene</td>
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<td>49 (S)</td>
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<tr>
<td>10</td>
<td>59</td>
<td>Ph</td>
<td>PMP</td>
<td>Toluene</td>
<td>76</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Reaction carried out at -20 °C
Chart 1.9: Organocatalysts developed by Sun.

Figure 1.8: Proposed transition state for reduction of ketimines with 63.

Table 1.11: Reduction of ketimines with formamide 63.
1.4.3 Oxazoline Promoted Reduction

In conjunction with their studies of pyridine-oxazoline promoted reduction of ketones, Malkov and Kocovsky described the reduction of ketimines with catalyst 47. A small range of aromatic ketimines were converted to their corresponding amines in high enantioselectivity (≤87%, Table 1.12). A similar mechanism to the reduction of ketones was proposed, with the N-aryl moiety replacing Cl₃SiH coordinated to oxygen in the transition state (Figure 1.9).

![Reduction of ketimines with pyridine-oxazoline 47.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>65</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>PMP</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>2-naphth</td>
<td>PMP</td>
<td>67</td>
<td>86</td>
</tr>
</tbody>
</table>

**Table 1.12:** Reduction of ketimines with pyridine-oxazoline 47.

![Proposed transition state for reduction of ketimines with 47.](image)

**Figure 1.9:** Proposed transition state for reduction of ketimines with 47.
1.5 Conclusions

The past decade has seen considerable advancement in the field of organocatalysis. A vast number of small organic molecules have been reported as catalytic activators of asymmetric organic reactions. A number of these organocatalysts may offer a viable alternative to traditional metal based catalysis due to the reported high yields and high enantioselectivity. Although some organocatalysts may have some foreseeable industrial or commercial applications the field still suffers from several drawbacks.

Many organocatalysts are reaction specific and subtle changes in the catalytic structure can often render the organocatalyst completely inactive. Although general structural motifs can be identified and used as building blocks for new organocatalysts there are few examples of general organocatalysts. Only proline seems to have any great ability to be active for a number of different reactions, however even proline is limited to reactions involving an enamine as the reactive species.

Substrate specificity is another drawback of contemporary organocatalytic reactions. With the exception of formamides \(23\) and \(43\); the organocatalysts reviewed within are dependant on aromatic substrates to obtain good selectivity. In addition high catalytic loadings are often required compared to those used by metal catalysts.

These drawbacks can be capitalised on to improve the field of organocatalysis. By endeavouring to develop more active organocatalysts it may be possible to lower catalyst loadings, improve substrate tolerance and increase crossover between different reactions. In this way it should be possible to make organocatalysis a practicable alternative to metal based catalysis.
2 Bifunctional Organocatalysts

2.1 Introduction

Organocatalysts can act by coordination/activation of substrate or reagent as discussed above. However another class of organocatalysts exists, which may activate both reagent and substrate at the same time. These bifunctional organocatalysts allow the substrate and the reagent to be brought close together and held in a specific geometry, mimicking the closed transition states of intramolecular reactions. In this way, the use of bifunctional organocatalysts often exhibits a greater stereocontrol and an improved reactivity compared to monodentate organocatalysts.

The simple amino acid proline has emerged in recent years as one of the most effective organocatalysts for a wide number of bond forming reactions, in particular at the position α to the carbonyl group in aldehydes and ketones.\[9,18,62\] It is now widely accepted that proline acts as a bifunctional organocatalyst involving both amine and carboxyl groups in the reaction pathway.\[63\] The amine group is involved in generation of a nucleophilic enamine intermediate after undergoing condensation with the carbonyl group of the substrate. The electrophile is then activated towards the nucleophilic attack by the enamine by H-bonding to the carboxylic acid group (Scheme 2.1). In this way, dual activation of both the nucleophile and electrophile by the same molecule has led to the impressive generality of proline catalysis.
A similar strategy has also been used in the stereoselective silylation of diols by exploiting the ability of silicon to form hypervalent species.$^{12,64}$ Hoyveda and Snapper et al. developed a simple amino acid based bifunctional catalyst for selective silylation of diols.$^{65,66}$ Lewis basic sites incorporated in the catalyst structure, a secondary amine and amide oxygen, allow the substrate diol to coordinate to the catalyst backbone. Generation of the activated hypervalent silicon species is mediated by the N-methylimidazole group integrated into the catalyst framework (Figure 2.1). This facilitates quasi-intramolecular transfer of the electrophilic silicon moiety to the hydroxyl group.$^{66}$
Inspired by this we sought to develop a range of novel bifunctional organocatalysts.
2.2 Target Compounds

Amino acids are among the simplest chiral frameworks and as such were chosen as the foundation for the new organocatalysts. The naturally occurring α-amino acids are widely available and are relatively cheap. In addition both enantiomers are easily obtainable and many unnatural analogues are also available. Amino acids lend themselves to synthesis of bifunctional catalysts as they bear both an amino group and a carboxyl group making them easy to derivatise. The chiral core would accommodate a formamide group for coordination of silane reagents. Substrate coordination would be achieved by incorporation of a group capable of hydrogen bonding to oxygen or nitrogen; in our case a thiourea or amide moiety. As we intend to carry out reactions on aromatic ketones or imines, an aromatic group would also be present to aid organisation of the organocatalyst and substrate through possible π-π interactions (Scheme 2.2).

\[
\begin{align*}
\text{R}^1 &= \text{Me, iPr, Ph; R}^2 = \text{H, Me;} \\
\text{R}^3 &= \text{Aromatic; R}^4 = \text{H, Me;} \\
\text{X} &= \text{O, NAr; Y} = \text{H, allyl, crotyl etc.}
\end{align*}
\]

Scheme 2.2: Planned mechanism of action for bifunctional organocatalysts.
2.3 Synthesis

The initial targets were identified as compounds 64 to 66 (Chart 2.1). The \( N-\alpha \)-methyl group on target 64 is required to transmit the chirality of the amino acid scaffold closer to the reaction centre.\(^{67}\) In target 65 this methyl group is not required as the formamide moiety is not adjacent to the chiral group. Imidazole is a known activator of silanes\(^{11}\) and as such, histidine based catalyst 66 offers an additional coordination point for a silicon reagent. Methylation of the imidazole ring proved to be necessary as previous tests demonstrated that \( N-\alpha \)-Boc-histidine formed an insoluble complex with trichlorosilane.

![Chart 2.1: Target organocatalysts.](image)

It is known that direct ring alkylation of histidine usually results in a mixture of \( \tau (N-1) \) and \( \pi (N-3) \) alkylated products.\(^{68}\) Generally alkylation at the \( \tau (N-1) \) position is carried out by first protecting the \( \pi (N-3) \) position, as exemplified by Beyerman.\(^{69}\) A recent report, however, showed that at low temperature \( N-\alpha \)-Boc-histidine underwent selective deprotonation at the \( \tau -(N-1) \) position using NaH in DMF,\(^{70}\) which upon reaction with alkyl halides produced exclusively \( \tau \)-alkylated products. Following this protocol, \( N-\alpha \)-Boc-\( \tau \)-methyl-histidine was obtained by deprotonation of \( N-\alpha \)-Boc-histidine, 67, with NaH in acetonitrile at \(-15 \, ^\circ \text{C} \) followed by reaction with methyl iodide. The desired \( N-\alpha \)-Boc-\( \tau \)-methyl-histidine, 68, was isolated as pale yellow crystals in 66% yield (Scheme 2.3).

Various coupling methods were tried to convert 68 to amide 69. Coupling using the mixed anhydride method was unsuccessful. Coupling using DCC under standard conditions resulted in formation of the desired amide, 69; however 69
was found to be inseparable from the reaction by-product, DCU. To facilitate separation of the product from the coupling by-products, it was decided to switch to related carbodiimide EDC.HCl. The resulting urea is water soluble and therefore ought to be easily separated from the amide product by extraction. Carrying out the coupling step using EDC.HCl, HOBT and NMM resulted in formation of the desired amide, 69. Purification was easily accomplished by aqueous extraction of the reaction by-products followed by column chromatography to furnish 69 in 65% yield.

Further investigation showed that EDAC.HCl could be utilized without employing other reagents, such as HOBT and NMM, thus simplifying the reaction procedure. The N-Boc group was then removed with TFA in CH$_2$Cl$_2$ and converted to the formamide, 66, using a mixture of acetic anhydride and formic acid. The target catalyst, 66, was obtained in 59% yield.

![Scheme 2.3: Synthesis of N-α-formyl histidine derivative.](image)

Synthesis of thiourea derived catalyst 75 began with reduction of Boc-valine to afford 71, followed by N-Boc protection to generate N-Methyl-N-Boc valinol, 72,
in good yield (87%). Conversion of the alcohol to an amine was achieved by introduction of a phthalimide group via the Mitsunobu reaction. This was then easily removed with hydrazine hydrate in ethanol to give the required amine, 73, in 99% yield over two steps. Treatment of the free amine 73, with phenylisothiocyanate afforded thiourea 74 in good yield, 88%. Deprotection of the amine was achieved under standard TFA conditions. Formylation with acetic anhydride and formic acid unexpectedly yielded either trifluoroacetamide 75, or acetamide 76 (Scheme 2.4). Since the deprotected amine was isolated as the TFA salt it was thought that this was interfering in the formylation reaction. Washing the crude deprotection mixture with a basic solution would remove any TFA and allow formation of the formamide, however when this was attempted only the amine 77 was isolated after 24h (Scheme 2.5). Attempts to generate the desired compound by treatment with acetic formic anhydride were also unsuccessful.

Scheme 2.4: Synthesis of valine-thiourea derivative.
Scheme 2.5: Attempted formylation of 74.

It was thought that formylation of N-methyl valinol instead of Boc protection would circumvent the problems with formylation later in the synthesis (Scheme 2.6). Formylation of N-methyl valinol, 71, by refluxing overnight in ethyl formate afforded the desired product, 78, in excellent yield (99%). The phthalimide group was then introduced using the Mitsunobu protocol however it was discovered that 79 was inseparable from the reaction by-products. It was found that to successfully synthesise and isolate the target catalyst 64; the deprotection/formylation step had to occur between the Mitsunobu and phthalimide removal steps. N-Me-N-Boc valinol was converted to phthalimide derivative 80 under Mitsunobu conditions. Deprotection of the Boc group and formylation was carried out under standard conditions to afford 81. Removal of the phthalimide group to reveal the amine 82 was effected with hydrazine in ethanol. Treatment of N-Me-N-formyl valamine 82 with phenylisothiocyanate yielded the desired compound 64 in 56% yield (Scheme 2.7).

Scheme 2.6: Alternative formylation protocol.
Scheme 2.7: Synthesis of thiourea derivative 64.

The synthesis of thiourea derivative 65 commenced with reduction of L-valine, 83, with LiAlH₄ (Scheme 2.7), which afforded L-valinol, 84, in 66% yield. Protection of the amine was carried out with di-tert-butyl dicarbonate in the presence of triethylamine, to afford the protected amino alcohol, 85, in 84% yield, which was then converted to the phthalimide derivative, 86, by Mitsunobu reaction in 48% yield. Phthalimide deprotection by hydrazine hydrate in ethanol yielded the mono protected diamine 87. The formamide derivative, 88, was obtained by refluxing the mono protected diamine in ethyl formate. The Boc group was then removed with a TFA/DCM mixture (1:2) and the amino formamide treated with phenylisothiocyanate to afford catalyst 65 in 12% yield from 88.
Scheme 2.8: Synthesis of thiourea derivative 65.
2.4 Application in Model Catalytic Reactions

Allylation of aldehydes and reduction of ketones and imines are reactions that can be carried out using silane reagents.\textsuperscript{[18]} The synthetic versatility of the chiral end-products of these reactions has prompted investigation into an organocatalytic protocol. With this in mind it was proposed that the prospective catalysts would be tested in the reduction of ketones and ketimines with trichlorosilane, and allylation of aldehydes with allyltrichlorosilane respectively (Scheme 2.9).

\begin{center}
\begin{tabular}{c c}
\hline
\textbf{Catalyst} & \textbf{Catalyst} \\
\hline
30 & 89 \\
X = O & X = NAr \\
\end{tabular}
\end{center}

\textbf{Scheme 2.9:} Model catalytic reactions.

Reduction of acetophenone 29 and a simple ketimine with thiourea catalyst 64 (20% catalyst loading) in both cases gave the product in 40% yield, however no enantioselectivity was observed. Catalyst 65 proved to be less reactive in the reduction reactions, the observed yields were 20%, however some selectivity was observed for the reduction of acetophenone, 10% ee, highlighting the importance of having the thiourea moiety next to the stereogenic centre. Reduction using histidine catalyst 66 did not proceed and only starting material was isolated. Disappointingly, none of the catalysts exhibited activity in the allylation of benzaldehyde; only 5% product was isolated for catalysts 64 and 66.
Although the thiourea catalysts were equally active for reduction of both ketones and ketimines the conversion was too low to be considered active enough to carry on. It was thought that replacement of the thiourea-phenyl group with a 3,5-trifluoromethylphenyl group would improve reactivity and selectivity through stabilisation of the thiourea conformation. It has been shown that when the ortho hydrogen atoms are more positively polarized due to meta electron withdrawing groups they form hydrogen bonds to the sulfur atom hindering the rotation of the phenyl group (Scheme 2.10). This increases the rigidity of the structure and has been shown to increase the binding ability of the thiourea fragment. Attempts to introduce the 3,5-bistrifluoromethylphenyl group to the catalyst, as in 90, did not yield enough material to be used. Histidine derived catalyst 66 was not considered promising enough to be carried on, thus alternative structural motifs were sought.

Table 2.1: Reduction test reaction results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>64</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>N-PMP</td>
<td>64</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>65</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>N-PMP</td>
<td>65</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>N-PMP</td>
<td>66</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.2: Allylation test reaction results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>
Scheme 2.10: Attractive S-H interaction
2.5 Phosphoramidine Targets

Phosphoramidine groups can be used as a coordinating group alternative to formamides for activation of silicon reagents. Our new catalyst design included this as well as an aromatic amide group to promote hydrogen bonding and possibly aromatic interactions between the catalyst and substrate. A selection of intended catalyst structures is shown in Chart 2.2.

![Chart 2.2: Phosphoramidine based catalysts.](image)

Initial catalytic tests were carried out using catalyst 91 which was assessed in the reduction of 29 and 89 and the allylation of benzaldehyde 6. Additionally 91 was also tested in the allylation of 2-hydroxyphenyl imine 97 following the publications by Kobayashi\cite{73} and Tsoegova\cite{74} (Scheme 2.11).
**Scheme 2.11**: Test reactions for proposed phosphoramidate organocatalysts.
2.6 Synthesis

The synthesis of valine-derived organocatalysts 91 and 92 began with coupling of \( N\)-Boc valine, 70, to 3,5-dimethylaniline, 99, employing the mixed anhydride method to afford amide 100 (Scheme 2.12). The resulting amide was then treated with TFA in DCM to remove the Boc protecting group. Treatment of the deprotected material with diphenylphosphinic acid chloride and dimethylphosphinic acid chloride yielded 91 and 92 respectively. Ligand 93 was synthesised in an analogous manner with benzhydrylamine, both 92 and 93 were available in our lab. Treatment of 2,2’-dihydroxy biphenyl with trichlorophosphine afforded 101. Ligand 94 was obtained by treating amide 100 with 101 after Boc deprotection (Scheme 2.12).

Catalyst 95 was obtained in 67% yield by treating valinol, 84, with diphenylphosphinyl chloride (Scheme 2.13). The synthesis of catalyst 96 commenced with conversion of racemic binol to the corresponding phosphoryl chloride 102. Treatment of 102 with (S)-methylbenzylamine, 103, generated the phosphoramidate 96 in 70% overall yield. Resolution of the diastereomers was carried out by recrystallisation from ethanol. Finally, ligand 105 was synthesised from enantiopure diamine 104 and diphenylphosphinylchloride; recrystallisation from toluene afforded the pure phosphoramidate in 72% yield (Scheme 2.13).
Scheme 2.12: Synthesis of Phosphorous containing ligands.
Scheme 2.13: Synthesis of diastereomeric phosphorous ligands.
2.7 Allylation at C=N

Allylation of imines is an important C-C bond forming reaction as it leads to the generation of chiral amines which represent synthetically useful intermediates for many applications.\cite{75,76} However, it is one of the few reactions that has remained solely in the realm of transition metal catalysis and to date there has been no publication of a true organocatalytic reaction for the allylation of aldimes.\cite{2,18} Recent advances are pushing closer to development of an organocatalytic protocol for this elusive reaction.\cite{39,74} Although not purely catalytic, some organic molecules have emerged as good activators of allylsilanes when employed in stoichiometric quantities.\cite{2,18,39,74}

Work carried out by Kobayashi showed that allylation of acylhydrazones derived from aldehydes with allyltrichlorosilane could be achieved in the presence of neutral coordinate organocatalysts (NCOs). It was shown that NCOs such as DMF and HMPA were able to efficiently promote the racemic reaction when used as solvent.\cite{39} Further development identified sulfoxides as another NCO capable of promoting the reaction; in particular the use of a chiral sulfoxide resulted in an asymmetric reaction taking place.\cite{73} By using chiral sulfoxide 107 at a loading of 300 mol%, chiral amine derivative 108 was obtained in 73% yield and 93% ee (Scheme 2.14). While N-acylhydrazones showed good reactivity in the allylation reaction, simple aldimes remained unreactive towards allyltrichlorosilanes.

\[
\begin{align*}
\text{Ph} & \quad \text{NHBz} \\
106 & \\
\text{Cl}_3\text{Si} & \quad \text{CH}_2\text{Cl}_2 \\
-78 \degree\text{C}, 1 \text{h} & \\
\text{Ph} & \quad \text{NHBz} \\
108 & \quad 73\%, \quad 93\% \text{ ee}
\end{align*}
\]

Scheme 2.14: Asymmetric addition of allylsilanes to acylhydrazones with NCO’s.
More recently a chiral bisformamide 109, (Chart 2.3) has emerged as a stoichiometric activator for the allylation of simple aldimines.\textsuperscript{[74]} Tsogoeva \textit{et al} showed that aldimines derived from benzaldehyde and 2-aminophenol could be successfully converted to allylic amines by using allyltrimchlorosilane in the presence of bisformamide 109 in conjunction with L-proline. Homoallylic amines were formed in good yield (>89\%) and high selectivity (≤85\%), however 2 equivalents each of bisformamide 109 and L-proline are required (Table 2.3, entries 1 – 4). It was suggested that proline forms a chiral silane reagent in situ, 113. This silane complex is then able to coordinate both the imine through the aromatic hydroxyl group and bisformamide 109 to generate the chiral transition state (Figure 2.2). In the absence of the 2-hydroxyl group no reaction occurs, supporting the interaction with silicon. Further studies with monoformamides 110 (Chart 2.3) showed that the second formamide group is integral to the selectivity observed with 109\textsuperscript{[77]}.

Based on these results, Tsogoeva proposed a transition state involving a hexacoordinate silicon species. It was suggested that the imine was activated by forming a bond with silicon through the \textit{ortho}-hydroxy group; coordination of a formamide moiety to silicon results in a hypervalent silicon species with enhanced nucleophilicity (Figure 2.2).

\begin{center}
\includegraphics[width=\textwidth]{chart23.png}
\end{center}

\textbf{Chart 2.3:} Formamide catalysts developed by Tsogoeva.
Table 2.3: Allylation of imines with allyltrichlorosilane and bis-formamide activator.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO₂</td>
<td>94</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>CF₃</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>94</td>
<td>68</td>
</tr>
</tbody>
</table>

Figure 2.2: Transition state proposed by Tsogoeva
2.8 Applications in Model Catalytic Reactions

Phosphoramidate 91 showed some promise in the allylation of aldimine 111 with allyltrichlorosilane, forming the chiral amine in 51% yield and 40% ee with catalyst loading 20 mol% (Scheme 2.15). Unfortunately, the catalyst 91 turned out to be inactive in the allylation of aldehydes or reduction of ketones and ketimines.

![Scheme 2.15: Organocatalytic allylation reactions with 91 as organocatalyst.](image)

Variation in the temperature of the reaction identified room temperature as the optimum (Table 2.4). Surprisingly, when the reaction mixture was cooled, selectivity also dropped. It may be that at lower temperatures an uncatalysed reaction mechanism may be favoured over the more selective pathway. The additive was found to be required for enantiodiscrimination (Table 2.5, entry 1). A range of additives other than (L)-proline were also examined (Table 2.5). In the presence of N-methyl imidazole, iso-propanol and dimethylaminopyridine the desired sec-amine was formed in moderate yields however the enantioselectivity was much lower than that observed for proline (Table 2.5, entries 2-4). In the case of (D)-proline (Table 2.5, entry 5), the opposite enantiomer of sec-amine 112 was formed in good yield (61%) and similar selectivity (38%), indicating that proline is involved in the enantiodifferentiation process in the transition state. Additionally the allylation of 111 did not proceed in the absence of di-isopropylethylamine.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-20</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>44</td>
<td>20 (S)</td>
</tr>
<tr>
<td>3</td>
<td>rt</td>
<td>51</td>
<td>40 (S)</td>
</tr>
</tbody>
</table>

Table 2.4: Effects of temperature on catalytic allylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>activator</th>
<th>yield (%)</th>
<th>ee (%)</th>
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</thead>
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<tr>
<td>1</td>
<td>91</td>
<td>none</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>91</td>
<td>NMI</td>
<td>58</td>
<td>13 (S)</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>iPrOH</td>
<td>59</td>
<td>11 (S)</td>
</tr>
<tr>
<td>4</td>
<td>91</td>
<td>(D)-proline</td>
<td>61</td>
<td>38 (R)</td>
</tr>
<tr>
<td>5</td>
<td>91</td>
<td>DMAP</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2.5: Activators for allylation reaction.

After identifying a set of optimum conditions a range of other chiral nitrogen-phosphorous ligands were tested in the allylation of aldimine 111 (Table 2.6).

A number of structural changes were made to the parent catalyst 91 (Chart 2.2). Posphinamide 92 where Ph₂P moiety was replaced with Me₂P resulted in a significant decrease in selectivity. Likewise, phosphate derivative 93 was active, however not as selective as 91. The important role of the aromatic amide moiety present in 91 was demonstrated by the reduced selectivity observed with catalyst 95, which produced only racemic product. Attempts to tune selectivity by replacing the phenyl group with a larger aromatic moiety 93 were unsuccessful, resulting in a marginal drop in enantiodifferentiation. Diastereomeric phosphoramides 96, derived from BINOL and 105, did not succeed in the formation of 112, identifying 91 as the superlative phosphoramide organocatalyst tested.
Table 2.6: Effects of catalyst structure variation on catalytic allylation reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>91</td>
<td>51</td>
<td>40 (S)</td>
</tr>
<tr>
<td>2</td>
<td>92</td>
<td>70</td>
<td>7 (S)</td>
</tr>
<tr>
<td>3</td>
<td>93</td>
<td>54</td>
<td>30 (S)</td>
</tr>
<tr>
<td>4</td>
<td>94</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>105</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
2.9 Summary

Design and synthesis of a number of potential bifunctional organocatalysts incorporating imidazole, thiourea and phosphoramid moieties was successfully achieved. The organocatalysts were tested in the allylation and reduction reactions of carbonyl compounds and imines.

The greatest success was achieved by valine derived phosphoramide 91 which catalysed the allylation of imine 111 to homoallylic amine 112 in 40% ee with a loading of 20 mol%, the reaction hitherto reported only with the use of stoichiometric activators. Our other bifunctional ligands did not show much promise in the model test reactions, however they may still find use in other catalytic processes, so further testing to reveal potential applications is required.
3 Quinoline Derived Organocatalysts

3.1 Introduction and Target Compounds

Reduction of prochiral ketones and imines is most commonly carried out in industry via asymmetric hydrogenation. However, this method is not free from problems, namely those associated with metal leaching, high pressure, and the cost of the catalyst and its regeneration. The alternative metal-free protocols are rare, however high selectivity has been attained with the use of formamide derivatives and trichlorosilane.\textsuperscript{[58]}

As part of our group’s focus into Lewis-basic activators for silanes, (2-pyridyl) oxazolines were identified as an efficient class of catalysts for the reduction of ketones with trichlorosilane. A range of ketones were successfully converted to the corresponding secondary alcohols with high selectivity.\textsuperscript{[54]} The initial results also showed the catalysts 45 and 46 were effective for the reduction of a small range of aromatic ketimines (Scheme 3.1).

\begin{equation}
\text{Catalyst} \quad \text{OH} \\
\end{equation}

\begin{equation}
\text{X} \quad \text{Ph} \quad \text{O} \\
\end{equation}

\textbf{Scheme 3.1:} Reduction of ketones with 2-pyridyl oxazolines.

Although catalyst 46 successfully reduced aromatic ketones and ketimines with high selectivity, in some cases it suffered from low conversion. Subsequent studies showed that the catalyst decomposed under the reaction conditions.
Bidentate coordination of the catalyst to trichlorosilane generates a hexacoordinate silicon species, 113; a chloride can then dissociate to form a stable pentacoordinate silicon species, 114. In this species, the Lewis acidic silicon activates the oxazoline towards nucleophilic attack. The dissociated chloride is able to attack at the benzylic position and leads to opening of the oxazoline ring, 115 (Scheme 3.2).

Scheme 3.2: Decomposition of oxazoline derived catalyst.

Amide 116 was isolated from the reaction mixture and its structure was confirmed by spectroscopic data. The susceptibility of the oxazoline 5-position to nucleophilic attack is due in part to the electronegativity of oxygen. It was proposed that replacing the oxazoline moiety with thiazoline would prevent chloride promoted ring-opening as the decreased electronegativity of sulfur should reduce the propensity for nucleophilic attack at the benzylic position. Further, it was considered that replacement of oxygen with either an N-methyl group or a CH$_2$ group could also prevent ring-opening.
To this end, we identified structures 117 to 122 as alternatives to 46 that would not be as susceptible to ring opening (Chart 3.1). Pyridine imidazoline 117 was synthesized in our group and shown to be inferior to 46 as a promoter for the reduction of ketones. Reduction of acetophenone 29 with 117 afforded alcohol 30 in 17% conversion and 34% ee, compared with 40% conversion, 64% ee for the corresponding oxazoline under the same conditions.
3.2 Synthesis

The synthesis of (2-pyridyl) thiazoline derivatives 119 to 122 was based on generation of the general thioamide 124 through coupling with mandelic acid derivative 123 followed by cyclisation with mesyl chloride (Scheme 3.3).

Scheme 3.3: General method for formation of thiazoline via cyclisation.

Amino alcohol 123 was generated from mandelic acid in a two-step process, according to the protocol developed by Brunner.\(^{[78]}\) First, mandelic acid, 126, was converted to mandelamide 127 in 90% yield. The resulting amide 127 was then reduced with lithium aluminium hydride in refluxing tetrahydrofuran to produce amino alcohol 123 in 84% yield (Scheme 3.4).

Scheme 3.4: Synthesis of mandelic acid derived amino alcohol.

Synthesis of pyridyl-thiazoline derivative 119 began with generation of thioester 129 from 2-chloromethylpyridine, 128, sulfur and methyl iodide in 51% yield. The resulting thioester was then coupled with amino alcohol 123 in THF in the presence of triethylamine. Thioamide 130 was isolated in 78% yield. Cyclisation was then achieved by treating thioamide 130 with mesyl chloride, furnishing pyridine-thiazoline 119 in 82% yield as a white crystalline solid (Scheme 3.5).
Scheme 3.5: Synthesis of 2-pyridyl thiazoline

Synthesis of (2-quinolyl) thiazoline 122 was carried out in analogous manner to 119, beginning with generation of thioester 132 from 2-chloromethyl quinoline, 131 (99%). Thioester 132 was then coupled with amino alcohol 123 to yield thioamide 133 in 78% yield. Cyclisation was again achieved by treating thioamide 133 with mesyl chloride, furnishing 2-quinoline-thiazoline 122 as a black oil which yielded black crystals on recrystallisation from ethanol (77%, Scheme 3.6).

Scheme 3.6: Synthesis of 2-quinolinyl thiazoline
Taking into account that 1-chloromethylisoquinoline is not readily available; 1-isoquinoline carboxylic acid, 135, was identified as an alternative starting material. It was thought that coupling of the acid with amino alcohol 123 followed by thionation would result in the desired thioamide 136. Lawesson’s reagent, 134, was chosen because it was shown to be superior to P2S5 for conversion of carbonyl groups to thiocarbonyl groups (Scheme 3.7).\cite{79,80} Lawesson also showed that HMPA could act as a non-covalent protecting group to prevent thionation of alcohols, thus preventing an additional two steps being carried out to prevent undesired thionation of the hydroxyl group.

**Scheme 3.7**: Mechanism of action of Lawesson’s reagent

Coupling of 1-isoquinoline carboxylic acid, 135, with amino alcohol 123 was carried out using the mixed anhydride method and produced the amide 136 in 89% yield (Scheme 3.8). Thionation of the amide with Lawesson’s reagent was carried out in HMPA; however conversion to the desired thioamide 137 was very low, furthermore it could not be isolated from the crude reaction mixture. It is known that thionation with Lawesson’s reagent is very sensitive to solvent and depends on the substrate therefore it was decided to investigate influence of different solvents.

Toluene is known to be an efficient solvent for thionation using Lawesson’s reagent and so was chosen as a starting point for solvent investigations. As HMPA would not be employed, the hydroxyl was protected with a TBS ether to afford 138
(63%). The silylated compound was then subjected to Lawesson’s reagent in refluxing toluene overnight after which successful thionation was observed. Treatment of the crude reaction mixture with acid followed by column chromatography led to the isolation of desired catalyst 120 in 74% yield (Scheme 3.8).

**Scheme 3.8: Synthesis of 1-isoquinoline thiazoline**

Synthesis of catalyst 121 was first attempted employing the same method used for 1-isoquinoline derivative 120. Coupling of 3-isoquinoline carboxylic acid 139 to mandelamine 123 was achieved using the mixed anhydride method and the target molecule, 140, was isolated in 43% yield. Protection of the hydroxyl group was then carried out with TBDMSI furnishing the protected compound 141 in 59% yield. On treatment with Lawesson’s reagent in refluxing toluene however, the only material recovered was amide 140 (Scheme 3.9).
Scheme 3.9: Synthesis of 3-isoquinoline thiazoline, strategy 1.

An alternative strategy beginning with 3-methyl isoquinoline 142 as a precursor was employed (Scheme 3.10). Conversion of 3-methyl isoquinoline, 142, to thioester 144 was achieved by chlorination with trichlorisocyanuric acid in refluxing chloroform followed by treatment with sulphur and methyl iodide. Thioester 144 was then coupled to mandelamine 123 to produce thioamide 145 in 50% yield. Thioamide 145 was then treated with mesyl chloride in the presence of triethylamine to affect cyclisation. The cyclisation did not proceed as well as anticipated, however enough of the target thiazoline 121 (5%) was isolated to allow catalytic screening (Scheme 3.10).
Scheme 3.10: Synthesis of 3-isoquinoline thiazoline, strategy 2.

To allow comparison with thiazoline catalyst, an oxazoline analogue 148 was prepared. Synthesis of 1-isoquinoline oxazoline, 148, commenced with coupling of 1-isoquinoline carboxylic acid 146 to mandelamine 123 using the mixed anhydride method. The resulting amide 147 was formed in 89% yield and isolated as a white crystalline solid. Amide 147 was then treated with mesyl chloride in the presence of triethylamine to affect cyclisation. The desired 1-isoquinoline oxazoline 148 was recrystallised from ethanol and isolated as a white solid in 95% yield (Scheme 3.11).
Finally, synthesis of pyrroline catalyst 118 was attempted. It was proposed that intramolecular condensation of 1,4-amino-ketone 149 would yield the desired pyrroline 118. Aldol condensation of 2-acetyl pyridine, 152, and benzaldehyde, 6, to generate 151, followed by Michael addition of nitromethane, would form a suitable starting material for formation of 1,4-amino-ketone 149 (Scheme 3.12).

Scheme 3.12: Retrosynthetic analysis of 2-pyridine pyrroline.
Synthesis of 2-pyridine pyrroline 118 commenced with aldol condensation of acetyl pyridine, 152, and benzaldehyde, 6, in aqueous sodium hydroxide to afford 151 in 35% yield (Scheme 3.13). Michael addition of nitromethane to 151 in methanol resulted in the nitro compound 150 (41%). Reduction of the nitro group had to be carried out selectively to prevent unwanted reduction of the ketone group. Initial reduction of the nitro group with SnCl₂ did not result in formation of 149 and only starting material was isolated. Attempts to reduce 150 with NaBH₄ or by hydrogenation were equally unsuccessful. Further attempts at reduction with the more reactive species NiCl₂/NaBH₄ resulted in over-reduction to amino alcohol 153. Although 153 was formed in 98% yield, re-oxidation to the ketone was unsuccessful.

Scheme 3.13: Synthesis of 2-pyridine pyrroline

It was believed that protection of the ketone before treatment with NaBH₄/NiCl₂ would prevent over-reduction; however attempts to form the protected ketone 154 were unsuccessful (Scheme 3.14). We then attempted to re-oxidise the fully reduced amino alcohol 153, first protecting the amino group. Attempts to protect the amino functionality with a Boc group, 156, in order to allow
oxidation of the alcohol to ketone however, did not produce the desired products (Scheme 3.14). At this point the synthesis of 118 was discontinued.

Scheme 3.14: Protection of ketone and amino groups.
3.3 Applications in Organocatalytic Reduction Reactions

Prospective thiazoline activators 119 to 122 were tested in the organocatalytic reduction of acetophenone 29 and simple ketimine 89 (Scheme 3.15). After completion the reaction mixtures were analysed by chiral GC and NMR to evaluate enantioselectivity and catalyst degradation.

![Scheme 3.15: Model catalytic reactions.](image)

Pyridine derived thiazoline 119 showed promising initial results; phenylethanol, 30, was obtained in 25% yield and 64% ee. Chiral amine 89 was also isolated in reasonable yield, 29%, and selectivity of 28% ee (Table 3.1, entries 1 and 2). Analysis of the reaction mixture after work up by $^1$H NMR showed that the thiazoline catalyst 119 had remained intact and was not degraded. However, the reactivity of the thiazoline catalyst was considerably reduced compared to the related oxazoline, 46.

The addition of further steric constraints from the quinoline and isoquinoline fragments reduced the activity of the thiazoline derived organocatalysts even further. Thiazolines 120 and 122 derived from 1-isoquinoline and 2-quinoline were unsuccessful in the reduction of both ketones and ketimines. Thiazoline 121 obtained from 3-isoquinoline showed some activity in the reduction of acetophenone (~5% conversion), however was inactive in the reduction of ketimines (Table 3.1). Oxazoline catalyst 148 however performed well in the reduction of both acetophenone 29 and ketimines (Table 3.1, entries 9 and 10) although some degradation product was observed. It may be that 120 does not allow efficient coordination of the silane due to the extra aromatic steric constraints while the increased size of sulfur compared to oxygen, forced the rings out of plane.
in the case of 122. Thiazoline 121 may allow weak coordination to the silane however apparently it remains insufficient to successfully activate trichlorosilane towards reduction.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>X</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>119</td>
<td>O</td>
<td>25</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>119</td>
<td>N-PMP</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>O</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>N-PMP</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>5</td>
<td>121</td>
<td>O</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>6</td>
<td>121</td>
<td>N-PMP</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>7</td>
<td>122</td>
<td>O</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>8</td>
<td>122</td>
<td>N-PMP</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>9</td>
<td>148</td>
<td>O</td>
<td>96&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>148</td>
<td>N-PMP</td>
<td>60</td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conversion determined by GC after standard reaction work-up; <sup>b</sup> previously reported results<sup>[54]</sup>

**Table 3.1:** Reduction with ligands 119 – 122, 148.

Based on these results it is believed that catalysts 120 and 122 do not permit favourable coordination of the silane whereas 3-isoquinoline derived catalyst 121 was not sufficiently active to promote reduction of ketones and ketimines. Pyridine thiazoline 119, although successful, proved to be too sluggish to be further investigated. The initial results, however, show that 1-isoquinoline oxazoline 148 is a superior organocatalyst for the reduction of ketones and ketimines. It was decided to carry out further studies with organocatalyst 148 in order to expand the substrate range and investigate the scope of the reaction.

A range of α-chloro and heterocyclic ketones and ketimines were subjected to reduction with trichlorosilane in the presence of oxazoline 148 (Table 3.2).
Ketones and imines derived from α-chloro acetophenone after reduction to the corresponding alcohols and amines can be cyclised into the corresponding epoxides and aziridines. Reduction of heterocyclic ketones or imines allows easy generation of chiral alcohols and amines finding application as chiral building blocks and synthetic intermediates in target synthesis.

Reduction of a range of ketones was carried out with 20 mol% of oxazoline catalyst \textit{148} in CHCl$_3$ using HSiCl$_3$ as the reducing agent. Only 2-acetylthiophene and 2-methyl-5-acetylfuran exhibited reasonable reactivity, although the resulting alcohols were found to be racemic (Table 3.2, entries 1 and 2). Unfortunately, no product was formed with other ketones tried (Table 3.2, entries 3 – 8). It is possible that the Lewis basic heteroatom in the tested heterocyclic ketones coordinates to silane interfering with the catalytic process and preventing reduction from occurring.

\begin{table}[h]
\centering
\begin{tabular}{lllll}
\hline
\textbf{Entry} & \textbf{R} & \textbf{X} & \textbf{Conversion (\%)} & \textbf{ee (\%)} \\
\hline
1 & 2-thiophene & H & 70 & 0 \\
2 & 2-methyl-5-furan & H & 50 & 0 \\
3 & Ph & Cl & - & - \\
4 & 2-pyridine & H & - & - \\
5 & 4-pyridine & H & - & - \\
6 & 2-thiazole & H & - & - \\
7 & 2,5-dimethyl-3-furan & H & - & - \\
8 & 1-(benzofuran-2-yl) & H & - & - \\
9$^a$ & 2-MeO-C$_6$H$_4$ & H & 50 & 87 \\
10$^a$ & 2-F-C$_6$H$_4$ & H & 35 & 70 \\
11$^a$ & Ph & H & 85 & 84 \\
\hline

$^a$Previously reported results$^{[54]}$
\end{tabular}
\caption{Reduction of prochiral ketones with thiazoline \textit{148}.}
\end{table}
Reduction of prochiral imines was more successful. It was carried out in CHCl₃ with 20 mol% of oxazoline catalyst 148 using HSiCl₃ as the reducing agent. Propiophenone was reduced in 90% yield and 79% ee (Table 3.3, entry 1). Chiral α-chloro amines were obtained in 88 to 89% ee and good yield; 47% to 90% (Table 3.3, entries 2-4). Furan and thiophene derived imines were successfully reduced in 73% yield, 55% ee and 77% yield, 60% ee respectively (Table 3.3, entries 5 and 6). Even imine derived from pyridine was successfully transformed to its corresponding amine in 41% yield and 82% ee (Table 3.3, entry 7). The results obtained are consistent with our current theory of enantiocifferentiation (Figure 3.2).[54]
**Table 3.3:** Reduction of prochiral ketimines with oxazoline 148.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>phenyl</td>
<td>Et</td>
<td>90</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>phenyl</td>
<td>CH₂Cl</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>1-chloro-4-benzene</td>
<td>CH₂Cl</td>
<td>47</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>1-fluoro-4-benzene</td>
<td>CH₂Cl</td>
<td>70</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>2-furan</td>
<td>Me</td>
<td>73</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>2-thiophene</td>
<td>Me</td>
<td>77</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>4-pyridine</td>
<td>Me</td>
<td>41</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>2-pyridine</td>
<td>Me</td>
<td>88</td>
<td>75</td>
</tr>
</tbody>
</table>
3.4 Summary

Thiazoline catalysts derived from 2-pyridines have been shown to be effective activators of trichlorosilane for the reduction of ketones and ketimines. The problem of chloride promoted ring opening of the catalyst can be successfully avoided however at the cost of catalyst activity and selectivity.

Due to the lower reactivity of the thiazoline catalysts, further investigation was carried out with oxazoline catalyst 148. Catalyst 148 was shown to be an efficient organocatalyst for the reduction of a range of ketimines with a large substrate scope. The reactivity observed was in line with our previous mechanistic proposals.
4 Experimental

General Methods

All reactions were carried out under an inert atmosphere in oven-dried glassware unless otherwise stated. Room temperature refers to ambient room temperature (20-22 °C); 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by Thin Layer Chromatography using aluminium backed silica gel 60 (F254) plates, visualised using UV254/286 nm and PMA, Dragendorf, Platinum and Ninhydrin dips as appropriate. Flash chromatography was carried out using 60 Å silica gel as the stationary phase.

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in CHCl₃ at 25 °C unless otherwise indicated, with an error of ±0.1. The [α]D values are given in 10⁻¹ deg cm³ g⁻¹. The NMR spectra were recorded in CDCl₃, ¹H at 400 MHz and ¹³C at 100.6 MHz on a Bruker Spectrospin 400 (400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million with chloroform-d₁ (δ 7.26, ¹H; δ 77.0, ¹³C) as internal standard unless otherwise indicated. Coupling constants (J) are measured in Hz and are unadjusted; therefore due to limits in resolution, in some cases there are small differences (<1 Hz) in the measured J value of some coupling constants. The IR spectra were recorded on a JASCO FT-IR spectrophotometer for a thin film between NaCl plates. The mass spectra (EI, CI and/or FAB) were measured on a Joel JMS700 spectrometer.

Enantiomeric excess was determined by chiral GC analysis (using a Hewlett Packard 6890 Series GC system, Hewlett Packard 3395 integrator and Supelco α-Dex™ or Supelco β-Dex™ column) or by chiral HPLC analysis (using a Hewlett Packard Agilent 1100 Series quarternary pump, vacuum degasser, diode array detector, manual injector and Hewlett Packard ChemStation). The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures.
Imines used for catalytic reduction reactions were available in the laboratory and were synthesised using known methods.

**Bifunctional Organocatalysts**

![Image of bifunctional organocatalyst](image)

**(S)-(-)-N-Methyl-N-[2-methyl-1-[[3-phenyl-thioureido]-methyl]-propyl]-formamide (64):** To a solution of \(N\)-(1-Aminomethyl-2-methyl-propyl)-\(N\)-methyl-formamide (524 mg, 1.88 mmol) in \(\text{CH}_2\text{Cl}_2\) was slowly added phenylisothiocyanate (0.26 mL, 2.0 mmol). The reaction mixture was allowed to stir at room temperature overnight. The solvent was then removed in vacuo. The crude mixture was then purified on a column of silica gel with a \(\text{CH}_2\text{Cl}_2\)-MeOH mixture (5:1) to afford **64** as a colourless oil (56%): \([\alpha]_D\) -65.20 (c = 0.75, CHCl_3/MeOH, 3:1); \(^1\text{H NMR}\) (400MHz, CDCl_3) \(\delta \) 0.78 (3H, d, \(J_{3,4,4,5} = 6.4 \text{ Hz}, 4\)-H), 0.93 (3H, d, \(J_{3,4,4,5} = 6.2 \text{ Hz}, 5\)-H), 1.65 – 1.74 (1H, m, 3-H), 2.61 (3H, s, 7-H), 3.63 - 3.70 (2H, m, 1-H), 4.10 – 4.17 (1H, m, 2-H), 7.08 – 7.14 (2H, m), 7.29 – 7.45 (2H, m), 7.54 (1H, bs); \(^{13}\text{C NMR}\) (100MHz, CDCl_3) \(\delta\) C 16.7 (CH_3, 4-C), 19.0 (CH_3, 5-C), 27.7 (CH, 3-C), 32.5 (CH_3, 7-C), 42.7 (CH_2, 1-C), 64.9 (2-C), 124.8 (CH), 126.6 (CH), 129.4 (CH), 137.2 (C, 9-C), 175.9 (CH, 6-C), 182.2 (C, 8-C); **MS CI** \(m/z\) (%) 280.3 (100, M+H), 246.3 (44), 218.3 (18), 163.1 (38), 145.2 (30); **HRMS** (Cl) 280.1484 (C_{14}H_{22}N_{3}OS requires 280.1483.
(S)-(−)-N-[3-Methyl-2-(3-phenyl-thioureido)-butyl] formamide (S)-(−)-65: (S)-88 (736 mg, 3.2 mmol) was dissolved in a CH₂Cl₂-TFA (2:1) mixture (15 mL) and stirred at room temperature for 1 h. The reaction mixture was then poured into saturated NaHCO₃ solution (25 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The aqueous layer was then evaporated to dryness and the resulting solid extracted three times with CH₂Cl₂. The organic layer was concentrated in vacuo and the residue dissolved in dry CH₂Cl₂ to which was added phenyl isothiocyanate (0.4 mL, 3.3 mmol) and the reaction was allowed to stir at room temperature overnight. The solvent was then removed in vacuo and the crude residue purified on a column of silica gel with a Petrol – EtOAc mixture (3:2). The product was then recrystallised from hexane/EtOAc to afford (S)-(−)-65 as an off white solid (100 mg, 12%): [α]₀ -96.6 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δₗH 0.81 (d, J₄-H,₃-H = 7.1 Hz, 3H, 4-H), 0.88 (d, J₅-H,₃-H = 6.8 Hz, 3H, 5-H), 1.75 – 1.81 (m, 1H, 3-H), 3.18 – 3.23 (m, 1H, 1α-H), 3.45 – 3.49 (m, 1H, 1β-H), 4.06 – 4.22 (m, 1H, 2-H), 5.99 (d, J = 9.1 Hz, 1H, 2-NH), 6.52 (bs, 1H, 1-NH), 7.16 (d, J = 8.3 Hz, 2H), 7.24 – 7.35 (m, 1H), 7.37 – 7.42 (m, 1H), 8.12 (s, 1H, 6-H); ¹³C NMR (100MHz, CDCl₃) δ₁₃C 18.3 (CH₃, 4-C), 19.3 (CH₃, 5-C), 30.8 (CH, 3-C), 41.5 (CH₂, 1-C), 59.5 (CH, 2-C), 125.7 (CH), 127.9 (CH), 130.3 (8-C), 130.4 (CH), 161.9 (6-C), 181.69 (7-C).
(S)-N-(3,5-Dimethyl-phenyl)-2-formylamino-3-(τ-methyl-1H-imidazol-4-yl)-propionamide (S)-66: A solution of (S)-69 and trifluoroacetic acid (5 mL) in dichloromethane (5 mL) was stirred at room temperature for 1 h. The solvent was evaporated in vacuo and the crude TFA salt was dissolved in formic acid (5 mL). Acetic anhydride (2.5 mL) was added and the solution was allowed to stir at room temperature for 72 h. The mixture was then evaporated to dryness and the crude product was purified by chromatography on a column of silica gel (60g) with a CH₂Cl₂–MeOH mixture (5:1) to afford (S)-66 (100 mg, 59%) as an orange solid: [α]₀ 0.0 (c 1.0, CHCl₃) [81]; ¹H NMR (400 MHz, CDCl₃) δ H 2.21 (6H, s, 15-H), 2.94 (1H, dd, J₃α-H, 3β-H = 15.2 Hz, J₃α-H, 2-H = 7.2 Hz, 3α-H), 3.11 (1H, dd, J₃α-H, 3β-H = 15.2 Hz, J₃β-H, 2-H = 4.0 Hz, 2-H), 3.59, (3H, s, 10-H), 4.77 (1H, bd, J₃β-H, 2-H = 4.0 Hz, 2-H), 6.66 (1H, s, 5-H), 6.73 (1H, s, 7-H), 7.10 (2H, s, 12-H), 7.39 (1H, s, 14-H), 7.64 (1H, bs, 2-NH), 8.24 (1H, s, 1-NH), 9.83 (1H, bs, 9-H); ¹³C NMR (100 MHz, CDCl₃) δ C 21.4 (CH₃, 15-C), 29.7 (CH₂, 3-C), 33.7 (CH₃, 10-C), 52.5 (CH, 2-C), 117.6 (CH, 5-C), 118.3 (CH, 7-C), 126.0 (CH), 138.6 (C), 161.4 (CH), 168.82 (9-C); IR (NaCl) v 3019, 2399, 1215 cm⁻¹; MS (Cl) m/z (%) 318.29 (100, M + NH₄).
(S)-(+-)N-τ-Me-N-α-Boc-Histidine (S)-(+-)68: Sodium hydride (705 mg, 29.4 mmol) was placed in a two-neck flask, flushed with Ar, washed 3× with petroleum ether, and dried under vacuum. The dry NaH was then added slowly to a suspension of N-α-Boc-histidine 67 (2.5 g, 9.8 mmol) in CH₃CN at –15 °C and stirred for 30 min. Methyl iodide (1.53 g, 10.7 mmol) was added and the reaction mixture was then heated to –5 °C and allowed to stir overnight at this temperature. The reaction was quenched with excess MeOH and the solvent was removed on a rotary evaporator. The resulting solid was then extracted with CHCl₃ (3 × 50 mL), the solvent was evaporated and the resulting solid was purified by chromatography on a column of silica gel (50g), with a CH₂Cl₂–MeOH mixture (5:1), to give N-τ-Me-N-α-Boc-Histidine (S)-(+-)68 as a pale yellow solid (1.64 g, 66%): mp (decomposition) 166-168 °C; [α]D²⁵ +29.5 (c 1.0, CHCl₃); ¹H NMR (400 MHz, DMSO-d₆) δ H 1.36 (9H, s, 11-H) 2.82 (2H, d, J = 4.8 Hz, 3-H) 3.56 (3H, s, 12-H) 3.91 (1H, bs, 2-H) 6.17 (1H, d, J = 5.6 Hz, 5-H), 6.77 (1H, s, 7-H) 7.49 (1H, s, NH) in accordance with literature.⁷⁰

(S)-(+-)-[1-(3,5-Dimethyl-phenylcarbamoyl)-2-(1-methyl-1H-imidazol-4-yl)-ethyl]-carbamic acid tert-butyl ester (S)-(+-)69:
Mixed anhydride method:

*N-τ*-Me-*N*-α-Boc-Histidine *(S)-(+)\textsuperscript{-}68* (600 mg, 2.3 mmol) and triethylamine (0.38 mL, 2.8 mmol) were dissolved in THF and cooled to 0°C. Methylchloroformate (0.27 mL, 2.8 mmol) was then added drop wise and the reaction allowed to stir for 1 hour. The precipitate was then filtered off. Triethylamine (0.38 ml, 2.8 mmol) and 3,5-dimethylaniline (0.35 ml, 2.8 mmol) were added and the reaction mixture left to stir overnight. No product was observed.

DCC Coupling Method:

*N-τ*-Me-*N*-α-Boc-Histidine *(S)-(+)\textsuperscript{-}68* (200 mg, 0.76 mmol) was dissolved in *CH\textsubscript{2}Cl\textsubscript{2} and a solution of DCC (190 mg, 0.92 mmol) in *CH\textsubscript{2}Cl\textsubscript{2} (2 mL) was added. 3,5-dimethylaniline (130 mg, 1.07 mmol) was slowly added and the reaction mixture was left to stir overnight. Although formation of the desired product was observed, it was found to be inseparable from DCU, the reaction by-product.

EDC.HCL Coupling Method:

Prepared by modification of the procedure developed by Rosenberg.\textsuperscript{[82]} 3,5-dimethylaniline (95 mg, 0.79 mmol) was dissolved in DMF (5 mL). *N-τ*-Me-*N*-α-Boc-Histidine *(S)-(+)\textsuperscript{-}68* (200 mg, 0.76 mmol), 1-hydroxybenzotriazole hydrate (233 mg, 1.7 mmol) and 4-methylmorpholine (96 mg, 0.91 mmol) were added sequentially. The reaction mixture was then cooled to –23 °C, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (226 mg, 1.14 mmol) added and the reaction allowed to stir for two hours. The reaction was then heated to room temperature and left to stir overnight. The reaction mixture was then poured into saturated NaHCO\textsubscript{3} solution and extracted 3x with EtOAc. The organic layer was then washed with water and brine and dried over MgSO\textsubscript{4}. The solvent was removed and the crude mixture purified by column chromatography (PE:EtOAc 5:1). The product *(S)-(+)\textsuperscript{-}69* was obtained as yellow crystals in 65% yield.
EDAC Coupling Method:
3,5-Dimethylaniline, (472 mg, 3.9 mmol) was added to a solution of N-τ-Me-N-α-
Boc-Histidine (S)-(+)−68 (1.0 g, 3.9 mmol), in dry MeCN. The solution was cooled to
0 °C and EDAC.HCl (910 mg, 4.7 mmol) was added and the reaction mixture was
allowed to stir at room temperature for 48 h. The mixture was then poured into
saturated NaHCO₃ solution and extracted 3× with EtOAc. The organic layer was
washed with water and brine and dried over MgSO₄. The solvent was evaporated in
vacuo and the crude product was purified by chromatography on a column of silica
gel (75g) with a CH₂Cl₂–MeOH mixture (5:1) to afford (S)-(+)−69 as a pale orange
solid (896mg, 60%): [α]D +53 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ H 1.38 (9H, s,
11-H), 2.20 (6H, s, 17-H), 2.91 (1H, dd, J₃α-H, 3β-H = 15.6 Hz, J₃α-H, 2-H = 6.4 Hz, 3α-H),
3.05 (d, J₃α-H, 3β-H = 15.6 Hz, J₃β-H, 2-H = 2H), 3.64 (3H, s, 12-H), 4.46 (1H, s, 2-H), 6.23
(1H, s.), 6.65 (1H, s, 5-H), 6.67 (1H, s, 7-H), 7.19 (2H, s, 14-H), 7.37 (1H, s, 16-H); ¹³C
NMR (100 MHz, CDCl₃) δ C 21.4 (CH₃, 17-C), 28.3 (CH₃, 11-C), 30.7 (CH₂, 3-C), 33.4
(CH₃, 12-C), 50.4 (CH, 2-C), 80.0 (10-C), 117.6 (CH, 5-C), 118.6 (CH, 7-C), 125.9 (CH,
16-C), 137.2 (CH, 14-C), 138.5 (15-C), 155.1 (9-C), 170.2 (1-C).

(S)-N-methyl valinol (S)-71: To a suspension of LiAlH₄ (3.8 g, 0.1 mol) in THF (60 mL)
at 0 °C was slowly added N-Boc valine (5.0 g, 23.0 mmol). The reaction was allowed
to stir at this temperature for 2h and was then heated overnight at 70 °C. The
mixture was then cooled to 0 °C, NaSO₄.10H₂O was added to remove excess LiAlH₄
and the mixture was then filtered through Celite. The solvent was then removed in
vacuo to afford N-methyl valinol as a colourless oil (2.36 g, 87%): ¹H NMR (400 MHz,
CDCl₃) δ H 0.82 (3H, d, J₄-H,5-H = 6.8 Hz, 4-H), 0.89 (3H, d, J₄-H,5-H = 6.8 Hz, 5-H), 2.35
(3H, s, 6-H), 3.26 (1H, dd, J = 7.2 Hz, J₁α-H,1β-H = 10.8 Hz, 1α-H), 3.55 (1H, dd, J = 4.4
Hz, $J_{1\alpha-H,1\beta-H} = 10.8$ Hz, $1\beta-H$), 3.69 (1H, t, $J = 6.8$ Hz, 2-H) in agreement with literature.\[^{[83]}\]

(5S)-(−)-N-methyl-N-tert-butoxycarbonyl valinol (5S)-72: To a solution of di-tert-butyl-dicarbonate in CH$_2$Cl$_2$ (25 mL) at 0°C was added N-methyl valinol (2.36 g, 20.1 mmol) and triethylamine (6.2 mL, 44.22 mmol). The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction mixture was then acidified to pH 5 with 1M citric acid and extracted with CH$_2$Cl$_2$ (3 x 25 mL). The organic phase was then dried over MgSO$_4$ and evaporated to dryness. The crude mixture was then purified on a column of silica gel with a Pet Ether-EtOAc mixture (2:1) to afford (5S)-N-methyl-N-tert-butoxycarbonyl valinol as a colourless oil (3.8 g, 87%): $[\alpha]_D^{-25.00}$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.81 (3H, d, $J_{4-H,5-H} = 6.8$ Hz, 4-H), 0.90 (3H, d, $J_{4-H,5-H} = 6.8$ Hz, 5-H), 1.47 (9H, s, 9-H), 1.8 (1H, m, 3-H), 2.69 (3H, s, 6-H), 3.40 – 3.48 (1H, m), 3.60 – 3.69 (1H, m), 3.91 – 4.23 (1H, m); CI MS m/z (%) 218.2 (20, M+H), 162.1 (100), 118.2 (18); HRMS (Cl+) 218.1756 (C$_{11}$H$_{24}$O$_3$N requires 218.1758).
(S)-(1-Aminomethyl-2-methyl-propyl)-methyl-carbamic acid tert-butyl ester (S)-73: To a dry round bottomed flask was added phthalimide (2.04 g, 13.88 mmol), THF (25 mL), triphenylphosphine (7.28 g, 27.75 mmol) and N-methyl-N-tert-butoxycarbonyl valinol (2.0 g, 9.25 mmol) in that order. The mixture was cooled to 0°C and diethylazodicarboxylate (4.02 g, 23.12 mmol) added. The reaction mixture was warmed to rt and allowed to stir overnight. The solvent was then removed in vacuo and the residue passed through a column of silica gel with a Pet Ether-EtOAc mixture (5:1). $^1$H NMR (400 MHz, CDCl$_3$) δ $^1$H 0.78 – 1.19 (m, 15H), 1.72 (bs, 1H), 2.55 (s, 3H), 3.61 – 3.72 (m, 2H), 3.95 (m, 1H), 7.52 – 7.61 (m, 2H), 7.70 – 7.80 (m, 2H).

To a solution of the crude material in EtOH (5 mL) was added hydrazine hydrate (1.44 g, 45.0 mmol). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then filtered and washed with Et$_2$O, the solvent was removed in vacuo to afford (1-Aminomethyl-2-methyl-propyl)-methyl-carbamic acid tert-butyl ester as an off white solid (99%). $^1$H NMR (400 MHz, CDCl$_3$) δ $^1$H 0.85 (3H, dd, $J$ = 2.0 Hz, $J$ = 6.4 Hz, 4-H), 0.99 (3H, dd, $J$ = 6.0 Hz, $J$ = 6.8 Hz, 5-H), 1.49 (9H, s, 9-H), 1.65 (1H, m, 3-H), 2.73, 2.80 (2 x s, 2 x 3H), 2.93 (1H, dd, $J$ = 4.4 Hz, $J$ = 12.4 Hz, 1α-H), 2.98 (1H, dd, $J$ = 3.6 Hz, $J$ = 13.6 Hz, 1β-H), 3.78 (1H, m, 2-H).

(S)-(-)-Methyl-[2-methyl-1-[[3-phenyl-thioureido]-methyl]-propyl]-carbamic acid tert-butyl ester (S)-74: To a solution of (1-Aminomethyl-2-methyl-propyl)-methyl-
carbamic acid tert-butyl ester \((S)-73\) (1.61 g, 4.60 mmol) in \(\text{Et}_2\text{O}\) was slowly added phenylisothiocyanate (676 mg, 5.0 mmol). The reaction mixture was allowed to stir at room temperature overnight. The solvent was then removed in vacuo and the crude product purified purified on a column of silica gel with a Pet Ether-EtOAc mixture (2:1) to afford \((S)-74\) (1.43 g, 88%) as a white solid: \([\alpha]_D -29.9\) (c = 1.0, \(\text{CHCl}_3\)); \(^1\text{H NMR}\) (400 MHz, \(\text{CDCl}_3\)) \(\delta\)H 0.75 (3H, d, \(J_{4-H, 3-H} = 6.8\) Hz, 4-H), 0.95 (3H, d, \(J_{5-H, 3-H} = 6.8\) Hz, 5-H), 1.27 (9H, s, 9-H), 1.70 (1H, m, 3-H), 2.62 (3H, s, 6-H), 3.72 (2H, m, 1-H), 4.02 (1H, m, 2-H), 7.08 – 7.12 (2H, m, 12-H), 7.20 - 7.33 (3H, m, 13-H, 14-H); CI MS \(m/z\) (%) 352.3 (82, M+H), 218.3 (100); HRMS (Cl) 352.2059 (C\(_{18}\)H\(_{30}\)N\(_3\)O\(_2\)S requires 352.2061).

\((S)-2,2,2\)-Trifluoro-\(N\)-methyl-\(N\)-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-acetamide \((S)-75\): Methyl-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-carbamic acid tert-butyl ester \((S)-74\) (98 mg, 0.28 mmol) was dissolved in a CH\(_2\)Cl\(_2\)-TFA (2:1) mixture (5 mL) and stirred at room temperature for 1 hour. The solvent was then removed in vacuo. The crude TFA salt was dissolved in formic acid (1 mL) and acetic anhydride (224 mg, 2.2 mmol) added and the reaction mixture was allowed to stir for 16h. The solvent was then removed in vacuo and the crude residue purified on a column of silica gel with a Pet Ether – EtOAc mixture (2:1) to afford \((S)-75\) as a white solid (62 mg, 64%): \(^1\text{H NMR}\) (400 MHz, \(\text{CDCl}_3\)) \(\delta\)H 0.96 (3H, d, \(J_{4-H, 3-H} = 6.8\) Hz, 4-H), 1.05 (3H, d, \(J_{5-H, 3-H} = 6.8\) Hz), 2.05 (1H, m, 3-H), 2.56 (3H, s, 6-H), 3.41 (1H, m, 1α-H), 3.51 (1H, m, 1β-H), 4.10 (1H, m, 2-H), 7.07 – 7.26 (5H, m), 7.79 (1H, bs, 9-NH), 8.63 (1H, bs, 11-NH); \(^{13}\text{C NMR}\) (100 MHz, \(\text{CDCl}_3\)) \(\delta\)C 16.8 (CH\(_3\), 4-C), 19.1 (CH\(_3\), 5-C), 27.7 (CH, 3-C), 32.4 (CH\(_3\), 6-C), 42.6 (CH\(_2\), 1-C), 64.9 (CH, 2-C), 124.8 (CH), 126.5 (CH), 129.3 (CH), 137.3 (C), 162.5 (C, 7-C), 182.2 (C, 10-C).
(S)-N-Methyl-N-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-acetamide (S)-76: Methyl-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-carbamic acid tert-butyl ester (S)-74 (1.43 g, 4.07 mmol) was dissolved in a CH$_2$Cl$_2$-TFA (2:1) mixture (10 mL) and stirred at room temperature for 1 hour. The solvent was then removed in vacuo. The crude TFA salt was dissolved in formic acid (10 mL) and acetic anhydride (3.32 g, 32.6 mmol) added and the reaction mixture was allowed to stir for 16h. The solvent was then removed in vacuo and the crude residue purified on a column of silica gel with a Pet Ether – EtOAc mixture (5:1) to afford N-Methyl-N-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-acetamide as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 1.05 (3H, d, $J_{4-H, 3-H}$ = 6.8 Hz, 4-H), 1.12 (3H, d, $J_{5-H, 3-H}$ = 6.8 Hz, 5-H), 1.99 (3H, s, 8-H), 2.11 (1H, m, 3-H), 2.18 (3H, s, 6-H), 3.44 (1H, bs, 1α-H), 3.62 (2H, m, 1β-H, 2-H), 7.17 – 7.41 (m, 5H), 8.29 (1H, bs, 9-NH), 8.61 (1H, bs, 11-NH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ$_C$ 16.7 (CH$_3$, 4-C), 18.9 (CH$_3$, 5-C), 20.8 (CH$_3$, 8-C), 27.7 (CH, 3-C), 32.5 (CH$_3$, 6-C), 42.7 (CH$_2$, 1-C), 64.9 (CH, 2-C), 124.8 (CH), 126.6 (CH), 129.4 (CH), 137.2 (C, 12-C), 175.9 (C, 7-C), 182.2 (C, 10-C); CI MS m/z (%) 280.3 (100, M+H), 246.3 (43), 218.3 (28), 163.1 (38), 145.2 (30); HRMS (EI) 279.1405 (C$_{14}$H$_{21}$ON$_3$S requires 279.1404).
(S)-(-)-N-Methyl-N-formyl valinol (S)-(-)-78: N-Methyl valinol (1.64 g, 13.9 mmol) was dissolved in ethyl formate (10 mL) and allowed to reflux for 16h. The solvent was then removed in vacuo to afford N-Methyl-N-formyl valinol as a yellow oil (99%), which was carried on without purification: $[\alpha]_D$ -16.80 (c = 1.0, CHCl$_3$); $^1$H NMR (400MHz, CDCl$_3$) $\delta_H$ 0.88 (3H, d, $J_{3-H,4-H}$ = 6.4 Hz, 4-H), 1.00 (3H, d, $J_{3-H,5-H}$ = 6.4 Hz, 5-H), 1.83 – 1.87 (1H, m, 3-H), 2.79 (3H, s, 7- H), 3.02 – 3.07 (1H, m, 2-H), 3.78 – 3.82 (2H, m, 1-H), 8.03 (1H, s, 6-H).

(S)-N-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-N-methyl-formamide (S)-79:

Method A: To a dry round bottomed flask were added phthalimide (3.07 g, 41.7 mmol), THF (25 mL), triphenylphosphine (10.94 g, 20.85 mmol) and N-Methyl-N-formyl valinol (3.81 g, 13.9 mmol) in that order. The mixture was cooled to 0°C and diethylazodicarboxylate (6.05 g, 34.75 mmol) added. The reaction mixture was warmed to rt and allowed to stir overnight. The reaction mixture could not be purified.
Method B: [1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-methyl-carbamic acid tert-butyl ester (2.16 g, 6.26 mmol) was dissolved in a mixture of CH₂Cl₂-TFA (2:1, 10 mL) and stirred at room temperature for 1h. The solvent was then removed in vacuo and the residue dissolved in CH₂Cl₂ (20 mL) and washed with sat. NaHCO₃ (2 x 10 mL). The organic phase was dried over MgSO₄ and concentrated in vacuo. The resulting solid was then dissolved in formic acid (10 mL) and acetic anhydride (5 mL, 50 mmol) added. The reaction mixture was allowed to stir at room temperature overnight. The solvent was then removed in vacuo and the residue purified on a column of silica gel with a Pet Ether-EtOAc mixture (2:1) to afford N-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-N-methyl-formamide (S)-79 as a white solid (1.03 g, 60%): ¹H NMR (400MHz, CDCl₃) δ 0.94 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.4 Hz, 3H), 1.97 (m, 1H), 2.71, 2.93 (2 x s, 2 x 3H), 3.54 (dt, J = 3.6 and 10.8 Hz, 1H), 3.7 – 3.9 (m, 2H), 7.58 – 7.82 (m, 5H).

(S)-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-methyl-carbamic acid tert-butyl ester (S)-80: To a dry round bottomed flask was added phthalimide (2.04 g, 13.88 mmol), THF (25 mL), triphenylphosphine (7.28 g, 27.75 mmol) and N-methyl-N-tert-butoxycarbonyl valinol (2.0 g, 9.25 mmol) in that order. The mixture was cooled to 0°C and diethylazodicarboxylate (4.02 g, 23.12 mmol) added. The reaction mixture was warmed to rt and allowed to stir overnight. The solvent was then removed in vacuo and the residue purified on a column of silica.
gel with a Pet Ether-EtOAc mixture (5:1). After column chromatography the product was not pure however further attempts at purification were not successful.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.78 – 1.19 (15H, m, 4-H, 5-H, 9-H), 1.72 (1H, bs, 3-H), 2.55 (3H, s, 6-H), 3.61 – 3.72 (2H, m, 1-H), 3.95 (1H, m, 2-H), 7.52 – 7.61 (2H, m, 13-H), 7.70 – 7.80 (2H, m, 12-H).

(S)-N-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-N-methylformamide (S)-81: (S)-80 (2.16 g, 6.26 mmol) was dissolved in a mixture of CH$_2$Cl$_2$-TFA (2:1, 10 mL) and stirred at room temperature for 1h. The solvent was then removed in vacuo and the residue dissolved in CH$_2$Cl$_2$ (20 mL) and washed with sat. NaHCO$_3$ (2 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated in vacuo. The resulting solid was then dissolved in formic acid (10 mL) and acetic anhydride (5 mL, 50 mmol) added. The reaction mixture was allowed to stir at room temperature overnight. The solvent was then removed in vacuo and the residue purified on a column of silica gel with a Pet Ether-EtOAc mixture (2:1) to afford $N$-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-$N$-methylformamide (S)-81 as a white solid (1.03 g, 60%): $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 0.94 (3H, d, $J$ = 6.8 Hz, 4-H), 1.19 (3H, d, $J$ = 6.4 Hz, 5-H) 1.95 – 1.98 (1H, m, 3-H), 2.71, 2.93 (2 x 3H, 2 x s, 6-H), 3.54 (1H, dt, $J$ = 3.6 and 10.8 Hz, 2-H), 3.7 – 3.9 (2H, m, 1-H), 7.58 – 7.82 (4H, m, 10-H, 11-H).
(S)-N-(1-Aminomethyl-2-methyl-propyl)-N-methyl-formamide (S)-82: (S)-81 (516 mg, 1.88 mmol) was dissolved in EtOH and hydrazine hydrate (302 mg, 9.45 mmol) added. The reaction mixture was allowed to stir at room temperature overnight. The mixture was then filtered and the precipitate washed with Et₂O. The solvent was removed and the crude mixture carried on without purification.

(5)-Valinol (S)-84: To a suspension of valine 83 (10.04 g, 85.7 mmol) in THF (100 mL) at 0 °C was slowly added LiAlH₄ (6.7g, 0.18 mol). The reaction was allowed to stir at this temperature or 2h and was then heated overnight at 70 °C. The mixture was then cooled to 0 °C, NaSO₄.10H₂O was added to remove excess LiAlH₄ and the mixture was then filtered through Celite. The solvent was then removed in vacuo to afford (S)-valinol (5.81 g, 66%) as a pale yellow oil: 

\[ \text{¹H NMR (400MHz, CDCl}_3\text{)} \delta_H 0.98 (3H, d, J_{4-H,5-H} = 4.1 \text{ Hz, 4-H}), 1.01 (3H, d, J_{4-H,5-H} = 6.5 \text{ Hz, 5-H}), 1.59 – 1.61 (1H, m,), 1.86 (3H, br s,), 2.54 – 2.57 (1H, m,), 3.32 (1H, m,), 3.66 (1H, dd, J = 3.95, 10.44 Hz,) \] in accordance with literature.\[84\]
(S)-(-)-N-tert-butoxycarbonyl valinol (S)-(-)-85: To a solution of valinol (S)-84 (5.0 g, 48.5 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added di-tert-butyl dicarbonate (12.7 g, 58.15 mmol) and triethylamine (13.5 mL, 96.9 mmol) and the reaction mixture allowed to stir at room temperature for 16 h. The reaction mixture was then acidified to pH 5 with 2 M HCl and extracted with CH₂Cl₂ (3 x 25 mL). The organic layer was then dried over MgSO₄, filtered and concentrated in vacuo to afford N-tert-butoxycarbonyl valinol (S)-(-)-85 (8.32 g, 84%) as a yellow oil; [α]D -15.0 (c = 2.0, CHCl₃); ¹H NMR (400MHz, CDCl₃) δ H 0.84 (3H, d, J₃-H,4-H = 7.6 Hz, 4-H), 0.90 (3H, d, J₃-H,5-H = 7.1 Hz, 5-H), 1.38 (9H, s, 8-H), 1.77 (1H, m, 3-H), 3.35 (1H, m, 2-H), 3.55 (1H, m, 1α-H), 3.63 (1H, m, 1β-H), 4.58 (1H, bs, NH); ¹³C NMR (100 MHz, CDCl₃) δ C 18.6 (CH₃, 4-H), 19.5 (CH₃, 5-H), 28.4 (CH₃, 8-C), 29.4 (CH₃, 3-C), 46.2 (CH₂, 1-C), 58.1 (CH, 2-C), 85.2 (C, 7-C), 156.9 (C, 6-C) in agreement with literature values.[85]

(S)-[1-(1,3-Dioxo-1,3-dihydro-isooindol-2-ylmethyl)-2-methyl-propyl]carbamic acid tert-butyl ester (S)-86: To a dry round bottomed flask was added phthalimide (4.51 g, 30.68 mmol), THF (100 mL), triphenylphosphine (16.08 g, 61.3 mmol) and N-tert-butoxycarbonyl valinol (S)-85 (4.15 g, 20.45 mmol) in that order. The mixture was cooled to 0 °C and diethylazodicarboxylate (8.04 mL, 51.0 mmol) added. The
reaction mixture was warmed to room temperature and allowed to stir overnight. The solvent was then removed *in vacuo* and the residue purified on a column of silica gel with a Petrol-EtOAc mixture (5:1). After column chromatography \((S)\)-86 was isolated (48%) but was not pure and further attempts at purification were not successful. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_H \) 0.93 (3H, d, \(J_{3-H,4-H} = 6.8, 4-H\)), 0.95 (3H, d, \(J_{3-H,5-H} = 6.8, 5-H\)) 1.10 (9H, s, 8-H), 1.81 – 1.89 (1H, m, 3-H), 3.67 -3.74 (1H, m, 2-H), 3.85 – 3.93 (2H, m, 1-H), 4.70 (1H, d, \(J = 9.8 \text{ Hz, NH}\)), 7.67 – 7.77 (2H, m), 7.78 – 7.91 (2H, m); MS CI \(m/z\) (\%) 333.3 (M+H, 27), 277.2 (100), 233.2 (55), 172.3 (31).

\((S)-1\)-amino-2-\textit{tert}-butyl carbamate-3-methyl butane \((S)-87\): To a solution of crude \((S)-86\) in EtOH (10 mL) was added hydrazine hydrate (2.88 g, 90.0 mmol). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then filtered and washed with Et\(_2\)O, the solvent was removed *in vacuo* to afford \((S)\)-87 as an off white solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_H \) 0.83 (3H, d, \(J_{3-H,4-H} = 6.8 \text{ Hz, 4-H}\)), 0.86 (3H, d, \(J_{3-H,5-H} = 6.8 \text{ Hz, 5-H}\)), 1.38 (9H, s, 8-H), 1.67 (1H, m, 3-H), 2.54 (1H, dd, \(J_{1\alpha-H,1\beta-H} = 13.1 \text{ Hz, 1\alpha-H}\), \(J_{1\alpha-H,2-H} = 7.8 \text{ Hz, 1\beta-H}\)), 2.73 (1H, dd, \(J_{1\alpha-H,1\beta-H} = 13.1 \text{ Hz, 1\beta-H}\), \(J_{1\beta-H,2-H} = 4.0 \text{ Hz, 1\beta-H}\)), 3.30 – 3.35 (1H, m, 2-H), 4.50 (1H, d, \(J = 10.1 \text{ Hz, NH}\)); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta_C \) 17.5 (CH\(_3\), 4-C), 18.5 (CH\(_3\), 5-C), 28.3 (CH\(_3\), 8-C), 30.3 (CH, 3-C), 43.8 (CH\(_2\), 1-C), 79.0 (C, 7-C), 156.5 (C, 6-C).
(S)-1-formylamino-2-tert-butyl carbamate-3-methyl butane (S)-88: Crude (S)-87 was dissolved in ethyl formate (50 mL) and stirred at reflux for 24 h after which the solvent was removed to afford (S)-88 as an off white solid: $^1$H NMR (400 MHz, CDCl$_3$) δH 0.88 (3H, d, J$_{3-H,4-H}$ = 7.6 Hz, 4-H), 0.89 (3H, d, J$_{3-H,5-H}$ = 7.1 Hz, 5-H), 1.37 (9H, s, 8-H), 1.71 (1H, m, 3-H), 3.29 (2H, m, 1-H), 3.48 (1H, m, 2-H), 4.57 (1H, d, J = 8.6 Hz, NH), 8.11 (1H, s, 9-H).

(S)-N-[2-[3-(3,5-Bis-trifluoromethyl-phenyl)-thioureido]-3-methyl-butyl]-formamide (S)-90: Reaction performed on 3.2 mmol scale utilising the same procedure for the preparation of (S)-65. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.5 mL, 3.3 mmol) was substituted for phenyl isothiocyanate. (S)-90 was purified on a column of silica gel using a Petrol – EtOAc mixture (1:2). The product was then recrystallised from EtOAc/Hexane but was still impure; $^1$H NMR (400 MHz, CDCl$_3$) δH 0.96 (6H, m, 4-H, 5-H), 1.67 (1H, m, 3-H), 3.15 (1H, m), 3.34 – 3.59 (2H, m), 4.72 (1H, bs, NH), 6.27 (1H, bs, NH), 6.61 (1H, bs, NH), 7.56 (2H, s, 9-H and 13-H), 8.05 (1H, s, 11-H), 8.16 (1H, s, 6-H).
(S)-(−)-1-(3,5-dimethylphenylcarbamoyl)-2-methylpropyldiphenyl phosphoramide  
(S)-(−)-91:  
(S)-tert-butyl-1-(3,5-dimethylphenylcarbamoyl)-2-methylpropylcarbamate (S)-100 (1.21 g, 3.7 mmol) was dissolved in a TFA/DCM (1:2) mixture and stirred at room temperature for 1h. To the mixture was added saturated NaHCO$_3$ until pH = 7 and the resulting mixture was then extracted with CH$_2$Cl$_2$ (3 x 25 mL). The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (25 mL) and diphenylphosphinic acid chloride (0.73 mL, 3.8 mmol) and triethylamine (1.03 mL, 7.4 mmol) were added. The mixture was allowed to stir at room temperature overnight after which the solvent was removed. The residue was then dissolved in EtOAc (10 mL) and washed with sat. NaHCO$_3$ solution (10 mL), 1M HCl (10 mL) and brine (10 mL). The organic phase was dried over MgSO$_4$ and the solvent removed under reduced pressure. The residue was then recrystallised from ethanol to afford (S)-(−)-91 as an off white solid 80%; mp 184 – 187°C $[\alpha]_D$ = -158.4 ($c = 1.0$, CHCl$_3$); $^1$H NMR (400MHz, CDCl$_3$) $\delta$H 0.80 (3H, d, $J_{3-H,4-H} = 6.4$ Hz, 4-H), 0.98 (3H, d, $J_{3-H,5-H} = 6.4$ Hz, 5-H), 2.11 (1H, m, 3-H), 2.14 (6H, s, 18-H), 3.98 (2H, m, 2-H), 6.65 (1H, s, 1-NH), 6.93 – 7.36 (8H, m), 7.47 (2H, m), 8.89 (1H, s, 2-NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 17.9 (CH$_3$, 4-C), 18.5 (CH$_3$, 5-C), 21.4 (CH$_3$, 18-C), 29.7 (CH, 3-C), 61.9 (CH, 2-C), 117.7 (CH), 121.6 (CH), 121.8 (CH), 126.0 (CH), 126.4 (CH), 128.4 (C), 129.7 (CH), 129.9 (CH), 130.1 (CH), 130.2 (CH), 137.8 (C), 138.5 (C), 147.7 (C), 170.3 (1-C); EI MS m/z (%) HRMS 450.1708 (C$_{25}$H$_{27}$O$_4$N$_2$P requires 450.1708); Anal. Calcd. for C$_{25}$H$_{29}$N$_2$O$_2$P: C 71.87 H 7.19 N 6.45. Found C 71.61 H 6.86 N 6.43.
**Reaction carried out on 3.92 mmol scale utilising the same procedure as for (S)-91.** (S)-94 was isolated by crystallisation form EtOH in 33% yield: \( \text{mp} \ 218 - 221 ^\circ C \); \(^1\text{H NMR}\ (400MHz, CDCl}_3\) \( \delta_{H} \ 0.80\ (3H, d, J_{3-H,4-H} = 6.4\ Hz, 4-H), 0.98\ (3H, d, J_{3-H,5-H} = 6.4\ Hz, 5-H), 2.06\ (1H, m, 3-H), 2.14\ (6H, s, 16-H), 4.01\ (1H, m, 2-H), 6.65\ (1H, s, 1-NH), 7.13\ (2H, s, Ar-H), 7.35\ (4H, m, Ar-H), 7.48\ (2H, m, Ar-H), 8.89\ (1H, s, 2-NH); \(^{13}\text{C NMR}\ (100 MHz, CDCl}_3\) \( \delta_{C} \ 17.9\ (CH, 4-C), 18.5\ (CH, 5-C), 21.4\ (CH, 16-C), 29.7\ (CH, 3-C), 61.9\ (CH, 2-C), 117.7\ (CH), 121.6\ (CH), 121.8\ (CH), 126.0\ (CH), 126.4\ (CH), 128.4\ (C), 129.7\ (CH), 129.9\ (CH), 130.1\ (CH), 130.2\ (CH), 137.8\ (C), 138.5\ (C), 147.7\ (C), 170.3\ (C, 1-C); \text{MS} \text{ EI \ m/z} (\%)\ 450.1\ (19, M), 302.1\ (100); \text{HRMS} \text{ (EI)}\ 450.1708\ \text{(C}_{25}\text{H}_{27}\text{N}_{2}\text{O}_{4}\text{P requires} \ 450.1705).}

**(S)-N-(diphenylphosphine oxide)-valinol (S)-95:** To a solution of valinol (1.0 g, 9.69 mmol) in CH\(_2\)Cl\(_2\) (20 mL) at 0 °C was added triethylamine (3.23 mL, 23.2 mmol) and diphenylphosphinonic acid chloride (2.22 mL, 11.69 mmol). The mixture was then allowed to reach room temperature and stirred for 16 h. The reaction mixture was then diluted with 1M HCl until neutral and extracted with CH\(_2\)Cl\(_2\) (3 x 25 mL). The organic layer was dried over MgSO\(_4\), filtered and the solvent removed under
reduced pressure. The residue was purified on a column of silica gel with a Pet Ether-EtOAc mixture (4:1) and then recrystallised from hexane/ethyl acetate to afford a white solid (67%) which was identified as a mixture of cis/trans isomers of (S)-95; mp 84 – 86 °C and 95 – 101 °C; \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 0.62 (d, \(J = 6.8\) Hz, 4-H), 0.81 (d, \(J = 6.8\) Hz, 5-H), 0.87 (d, \(J = 6.8\) Hz, 4-H), 0.95 (d, \(J = 6.8\) Hz, 5-H), 1.45 (m, ), 1.91 (m, ), 2.40 (m, ), 2.99 (m, ), 7.42 (6H, m), 7.87 (4H, m).

(R,S)-(+)1,1′-Binaphthyl-2,2′diyl-N-(\(\alpha\)-(S)-methylbenzyl) phosphoramidate (R,S)-(+)96: Prepared by modification of the protocol developed by Hu\(^{[86]}\). The crude phosphoric acid chloride 101 was dissolved in CH\(_2\)Cl\(_2\) (10 mL) and cooled in a salt-ice bath. A solution of (S)-methylbenzylamine (1.4 mL, 10.5 mmol) and triethylamine (1.67 mL, 12.08 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added. The mixture was left to stir for 30 minutes then allowed to reach room temperature and left to stir for 36 hours. The solution was then washed with 0.5M HCl (20 mL) and brine (25 mL), dried over MgSO\(_4\) and the solvent removed under reduced pressure. The crude mixture (70%) of diastereomers was dissolved in refluxing ethanol (50 mL) and left to recrystallise over 48 hours to afford (R,S)-(+)96 as yellow crystals; \([\alpha]_D = +316^\circ\); \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 1.48 (3H, \(J = 6.8\) Hz, ), 3.31 (1H, t, \(J = 10.4\) Hz, NH), 4.42 (1H, m, ), 6.69 – 7.50 (12H, m), 7.53 (1H, d, \(J = 4.8\) Hz), 7.77 (1H, d, \(J = 9.2\) Hz), 7.85 (2H, dd, \(J = 2.8\) Hz, \(J = 8.4\) Hz), 7.93 (1H, d, \(J = 8.8\) Hz); \(^{31}\)P NMR (160 MHz, CDCl\(_3\)) \(\delta\) 12.30 in agreement with the literature.\(^{[86]}\)
(S)-(-)-tert-butyl-1-(3,5-dimethylphenylcarbamoyl)-2-methylpropylcarbamate (S)-(-)-100: Methyl chloroformate (0.55 mL, 7.15 mmol) was added dropwise to a stirred solution of (S)-70 (1.40 g, 6.05 mmol) and triethylamine (1.0 mL, 7.15 mmol) in anhydrous THF (30 mL) at 0 °C under an argon atmosphere and the mixture was stirred at that temperature for 2 h. The precipitate was removed by suction filtration and the filtrate was added dropwise to a solution of the corresponding amine (8.5 mmol) and triethylamine (1.0 mL, 7.15 mmol) in anhydrous THF (30 mL) at 0 °C. The mixture was allowed to stir at room temperature overnight under an argon atmosphere and the solvent was then removed under reduced pressure. The residue was purified using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (4:1) to afford (S)-(-)-tert-butyl-1-(3,5-dimethylphenylcarbamoyl)-2-methylpropylcarbamate (S)-(-)-100 as a white solid; mp 137 – 140 °C; [α]D -12.0 (c = 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δH 0.75 (6H, d, J = 6.8 Hz, 4-H, 5-H), 1.37 (9H, s, 8-H), 2.20 (6H, s, 15-H), 2.24 (1H, m, 3-H), 4.04 (2H, m, 2-H), 5.36 (1H, d, J = 8.4 Hz, 2-NH), 6.59 (1H, s, 12-H), 7.18 (2H, s, 10-H, 14-H), 8.46 (1H, bs, 1-NH); ¹³C NMR (100 MHz, CDCl₃) δC 17.6 (CH₃, 4-C), 18.3 (CH₃, 5-C), 20.2 (CH₃, 13-C), 27.3 (CH₃, 8-C), 30.2 (CH, 3-C), 59.9 (CH, 2-C), 78.9 (C, 7-C), 116.7 (CH, 10-C), 124.7 (CH, 12-C), 136.6 (C, 9-C), 137.3 (C, 11-C), 155.5 (C, 6-C), 169.9 (C, 1-C); MS El m/z (%) 320.1 (100, M), 121.1 (100), 72.1 (88), 57.1 (73); HRMS (El) 320.2100 (C₁₉H₂₈N₂O₃ requires 320.2099); Anal. Calcd. for C₁₉H₂₈N₂O₃: C 66.79 H 7.56 N 10.16. Found C 66.49 H 8.78 N 9.03.
Biphenyl-2,2'-chlorophosphate 101: 2,2'-biphenol (2.00 g, 10.7 mmol) was dissolved in toluene (25 mL) and cooled to 0 °C. To the reaction mixture, a solution of POCl₃ (2.40 mL, 16.0 mmol) and Et₃N (4.5 mL, 32.0 mmol) was added slowly. The reaction mixture was then allowed to warm to room temperature and stirred for 36 h after which the solid residue was removed via vacuum filtration and the solution concentrated *in vacuo* to afford 101 as a yellow oil 95%: ¹H NMR (400MHz, CDCl₃) δH

¹³C NMR (100 MHz, CDCl₃) δC 120.7 (CH), 126.7 (CH), 127.3 (6-C), 129.4 (CH), 129.7 (CH), 146.7 (1-C); ³¹P NMR (160 MHz, CDCl₃) δP 10.17; EI MS m/z (%) 266.0 (100, M), 168.1 (76), 139.1 (24), 82.9 (48); HRMS (EI) 265.9900 (C₁₂H₈O₃ClP requires 265.9902) in agreement with literature.[⁸⁷]

Phosphoric acid chloride 102: Prepared following the protocol developed by Hu[⁸⁶]. Racemic Binol (3 g, 10.5 mmol) was slurried in CH₂Cl₂ (100 mL) and POCl₃ (2.25 g, 14.7 mmol) was added followed by slow addition with stirring of triethylamine (2.6 g, 25.5 mmol) so as to maintain gentle reflux. After 1h the reaction mixture was washed with water (25 mL) and evaporated to afford the crude acid chloride 102 which was carried on without purification.
(R),(R)-105: Diamine (-)-104 (50 mg, 0.24 mmol) was dissolved in CH₂Cl₂ (2 mL) and diphenylphosphinic acid chloride (110 mg, 0.50 mmol) and triethylamine (0.14 mL, 0.60 mmol) were added. The mixture was allowed to stir at room temperature overnight after which the solvent was removed. The residue was then dissolved in EtOAc (10 mL) and washed with sat. NaHCO₃ solution (10 mL), 1M HCl (10 mL) and brine (10 mL). The organic phase was dried over MgSO₄ and the solvent removed under reduced pressure. The residue was then recrystallised from toluene to afford (R),(R)-105 as an off white solid (72%): 

1H NMR (400MHz, CDCl₃) δ H 4.19 (2H, m, 1-H), 5.81 (2H, m, NH), 6.77 (4H, m, Ar-H), 7.04 (6H, m, Ar-H), 7.15 (6H, m, Ar-H), 7.32 (8H, m, Ar-H), 7.43 (2H, m, Ar-H), 7.58 (4H, m, Ar-H), 7.71 (4H, m, Ar-H); 13C NMR (100 MHz, CDCl₃) δ C 61.7 (CH), 126.9 (CH), 127.4 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 131.0 (C), 131.5 (CH), 131.6 (CH), 131.6 (CH), 131.8 (C), 131.9 (C), 131.9 (CH), 133.0 (CH), 141.9 (C), 142.0 (C); MS FAB m/z (%) 613.1 (77, M+H), 396.1 (48), 306.1 (86), 201.5 (100), 107.7 (41); HRMS (FAB) 613.2174 (C₃₈H₃₅N₂O₂P₂ requires 613.2179).
**(S)-(-)-N-Formyl-valinol:** Valinol (4.64 g, 44.9 mmol) was dissolved in ethyl formate (20 mL) and allowed to reflux for 16h. The solvent was removed in vacuo to afford *N*-Formyl-valinol as a yellow oil which was carried on without purification; \([\alpha]_D\) -32.9 (c = 1.0, CHCl₃); \(^1\)H NMR (400MHz, CDCl₃) δH 0.90 (3H, d, \(J_{4\alpha-H,3-H} = 6.8\) Hz, 4-H), 0.98 (3H, d, \(J_{5\alpha-H,3-H} = 6.8\) Hz, 5-H), 1.85 (1H, m, 3-H) 2.29 (1H, m, 2-H), 3.34 (1H, dd, \(J_{1\alpha-H,1\beta-H}, J_{1\alpha-H,2-H} = 10.4\) Hz, 1α-H), 3.64 (1H, dd, \(J_{1\alpha-H,1\beta-H} = 6.4\) Hz, \(J_{1\beta-H,2-H} = 4.0\) Hz, 1β-H), 8.19 (1H, s, 6-H); \(^{13}\)C NMR (100 MHz, CDCl₃) δC 18.6 (CH, 4-C), 19.3 (CH, 5-C), 29.3 (CH, 3-C), 55.9 (CH, 2-C), 63.3 (CH₂, 1-C), 165.7 (C, 6-C); CI MS \(m/z\) (%) 132.2 (100, M+H), 114.2 (45), 104.2 (22); HRMS (Cl) 132.1025 (C₆H₁₄NO₂ requires 132.1022); Anal. Calcd. for C₇H₁₅NO₂: C 57.90 H 10.41N 9.65. Found: C 57.87 H 10.36 N 9.47 in agreement with literature values.\(^{[88]}\)
**Quinoline Derived Organocatalysts**

**(S)-(−)-2-(5-Phenyl-4,5-dihydro-thiazol-2-yl)-pyridine (S)-(−)-119:** To a solution of **(S)-130** (1.29 g, 4.99 mmol) in THF (15 mL) at 0°C was added mesyl chloride (0.57 mL, 7.01 mmol) and triethylamine (2.15 mL, 14.3 mmol). The reaction was then allowed to stir at room temperature for 48 h. Water (10 mL) was then added and the mixture extracted with DCM (3 x 20 mL). The organic layer was dried over MgSO₄ and the solvent removed in vacuo. The crude solid was then purified on a column of silica gel (20 g) with a Pet Ether-EtOAc mixture (1:1) to afford an off white solid which was recrystallised from EtOH to afford 2-(5-Phenyl-4,5-dihydro-thiazol-2-yl)-pyridine **(S)-(−)-119** as a white crystalline solid (0.98 g, 82%); **mp** 105 – 106 °C; [α]₀ −77.50 (c 1.0, CHCl₃); **¹H NMR** (400 MHz, CDCl₃) δ H 4.60 (1H, dd, J₈α-H,₈β-H = 16.4 Hz, J₉-H,₈α-H = 5.8 Hz, 8α-H), 4.82 (1H, dd, J₈α-H,₈β-H = 16.4 Hz, J₉-H,₈β-H = 9.1 Hz, 8β-H), 4.99 (1H, dd, J₉-H,₈α-H = 5.8 Hz, J₉-H,β-H = 9.1 Hz, 9-H), 7.17 – 7.33 (6H, m), 7.73 (1H, dt, J = 7.8 Hz, J = 1.8 Hz), 8.05 (1H, dt, J = 7.8 Hz, J = 1.0 Hz), 8.60 (1H, dd, J = 4.8 Hz, J = 1.0 Hz, J = 0.8 Hz); **¹³C NMR** (100 MHz, CDCl₃) δ C 53.5 (CH, 9-C), 73.9 (CH₂, 8-C), 121.6 (CH), 125.5 (CH), 127.2 (CH), 127.7 (CH), 128.9 (CH), 136.6 (CH), 142.2 (C, 2-C), 149.4 (CH), 151.2 (C, 9-C), 170.2 (C, 7-C); **MS EI+ m/z (%)** 240.1 (M+, 100), 118.0 (49), 78.0 (74), 51.0 (20); **HRMS (EI)** 240.0721 (C₁₄H₁₂N₂S requires 240.0718).
(S)-(−)-1-(5-Phenyl-4,5-dihydro-thiazol-2-yl) isoquinoline (S)-(−)-120:

Method A: (R)-(−)-N-(2-hydroxy-2-phenylethyl)isoquinoline-1-carboxamide (R)-136 (100 mg, 0.34 mmol) and Lawesson’s reagent (165 mg, 0.41 mmol) were dissolved in HMPA (2.0 mL) and heated at 120 °C overnight. The reaction mixture was then allowed to cool down and acidified to pH = 3 with 2M HCl and the precipitate filtered off. The filtrate was then extracted with CH$_2$Cl$_2$ (3 x 30 mL) and the organic layer washed with water (3 x 15 ml). The organic layer was dried over MgSO$_4$, filtered and the solvent removed. The crude residue was then purified on a column of silica gel with a Petrol – EtOAc mixture (5:1) to afford (S)-(−)-120 as a brown oil (7 mg, 7%).

Method B: (R)-138 (253 mg, 0.71 mmol) and Lawesson’s reagent (344 mg, 0.85 mmol) were dissolved in toluene (20 mL) and heated at 85 °C overnight. The reaction mixture was then allowed to cool down and acidified to pH = 3 with 2M HCl and the precipitate filtered off. The filtrate was then extracted with CH$_2$Cl$_2$ (3 x 30 mL) and the organic layer washed with water (3 x 15 ml). The organic layer was then dried over MgSO$_4$, filtered and the solvent removed. The crude residue was then purified on a column of silica gel with a Pet Ether – EtOAc mixture (5:1) to afford (S)-(−)-120 as a yellow oil (74%): [α]$_D$ = -22.9$^\circ$ (c = 1.0, CHCl$_3$); $^1$H NMR (400MHz, CDCl$_3$) $\delta$H 4.78 (1H, dd, $J$ = 4.3, 15.2 Hz, 2-H), 4.83 – 4.89 (1H, m, 1α-H), 5.02 – 5.06 (1H, m, 1β-H), 7.17 (m, 1H), 7.21 – 7.25 (m, 2H), 7.33 – 7.35 (m, 2H), 7.59 – 7.66 (m, 3H), 7.89 - 7.97 (m, 1H), 8.52 (d, $J$ = 5.6 Hz, 1H), 9.42 (dd, $J$ = 1.5, 7.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 52.2 (CH, C-2), 75.2 (CH$_2$, C-1), 123.2 (CH), 126.4 (C-3), 127.0 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 128.9 (CH), 130.4 (CH), 136.9 (C-14), 141.5 (CH), 142.4 (CH), 149.2 (C-9), 168.1 (C-8), 170.9 (C-7); MS EI m/z
(% 290.1 (M+, 100), 186.0 (44), 128.0 (92), 91.0 (28); HRMS El 290.0878 (C₁₈H₁₄N₂S requires 290.0879).

(S)-(+)\text{-}2\text{-}(5\text{-}Phenyl\text{-}4,5\text{-}dihydro-thiazol\text{-}2\text{-}yl)\text{-}quinoline (S)-(+)\text{-}122: Reaction carried out on a 3.66 mmol scale utilising the same procedure as for (S)-( )\text{-}119. After recrystallisation from EtOH (S)-(+)\text{-}122 was isolated as black crystals (77%); mp 118 – 120 °C; [α]₀ +126.6 (CHCl₃, c = 0.25); \textsuperscript{1}H NMR (400MHz, CDCl₃) δ H 4.66 (1H, dd, J₁₂α\text{-}13 = 6.0 Hz, J₁₂α\text{-}12β = 16.4 Hz, 12α-H), 4.87 (1H, dd, J₁₂β\text{-}13 = 9.2 Hz, J₁₂α\text{-}12β = 16.8 Hz, 12β-H), 5.02 (1H, dd, J₁₂α\text{-}13 = 6.0 Hz, J₁₂β\text{-}13 = 9.2 Hz, 13-H), 7.20 (1H, m, Ar-H), 7.25 (2H, m, Ar-H), 7.32 (2H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.67 (1H, m, Ar-H), 7.78 (1H, m, Ar-H), 8.15 (3H, m, Ar-H); \textsuperscript{13}C NMR (100 MHz, CDCl₃) δ C 53.4 (CH, 12-C), 74.1 (CH₂, 13-C), 118.7 (CH), 127.3 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.9 (CH), 128.9 (C), 130.0 (CH), 130.1 (CH), 136.6 (CH), 142.3 (C), 147.6 (C), 151.1 (C), 171.0 (C); MS Cl m/z (%) 291.2 (100, M+H); HRMS (Cl) 291.0956 (C₁₈H₁₅N₂S requires 291.0953).

(R)-(\text{-})\text{-}2\text{-}Hydroxy\text{-}2\text{-}phenyl acetamide (R)-(\text{-})\text{-}127: Prepared according to the protocol of Brunner\textsuperscript{[78]}, acetyl chloride (4.4 mL) was added to a solution of (R)-mandelic acid (8.4 g, 54.6 mmol) in methanol (200 mL) at 0 °C. The reaction was then allowed to reach room temperature and stirred overnight. The solvent was then removed and the solid residue dissolved in a mixture of methanol (150 mL) and aqueous ammonium hydroxide (28%, 445 mL) and stored in the fridge
overnight. The solvent was then removed and the solid residue recrystallised from toluene to give pure amide (90%) as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 2.19 (1H, bs, OH), 5.11 (1H, s, 2-H), 5.59 (1H, bs, NH), 6.02 (1H, bs, NH), 7.36-7.47 (5H, m, Ar) in agreement with the literature.$^{[78]}$

(R)-(-)-2-amino-1-phenyl ethanol (R)-(-)-124: Prepared according to the protocol developed by Brunner,$^{[78]}$ to a suspension of (R)-(-)-2-Hydroxy-2-phenyl-acetamide (R)-(-)-127 (1.88 g, 12.4 mmol) in THF (100 mL) at 0 °C was slowly added LiAlH$_4$ (1.2 g, 31.03 mmol). The reaction was allowed to stir at this temperature for 2 h and was then heated overnight at 70 °C. The mixture was then cooled to 0 °C, NaSO$_4$.10H$_2$O was added to remove excess LiAlH$_4$ and the mixture was then filtered through Celite. The solvent was then removed in vacuo to afford (R)-(-)-2-amino-1-phenyl ethanol as a yellow oil (84%); $[\alpha]_D$ -26.6 (c = 0.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 1.78 (bs, 3H), 2.74 (1H, dd, $J_{2\alpha,2\beta}$ = 12.8 Hz, $J_{1,2\alpha}$ = 7.8 Hz, 2α-H), 2.93 (1H, dd, $J_{2\alpha,2\beta}$ = 12.8 Hz, $J_{1,2\beta}$ = 4.0 Hz, 1-H), 7.19-7.36 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ$_C$ 49.2 (CH$_2$, 2-C), 68.0 (CH, 1-C), 126.0 (CH), 127.7 (CH), 128.5 (CH), 142.6 (C); MS CI m/z (%) 138.2 (100, M+H), 120.2 (70); HRMS (Cl) 138.0919 (C$_8$H$_{12}$NO requires 138.0918) in accordance with the literature.$^{[78]}$
Methyl 2-pyridylthiocarboxylate 129: Prepared according to the protocol developed by Metzner et al.\textsuperscript{[89]} To a mixture of 2-picolylichloride hydrochloride (2.0 g, 12.2 mmol) in DCM (5.0 mL) and H\textsubscript{2}O (5.0 mL), was added a saturated aqueous solution of NaHCO\textsubscript{3} until neutralisation. The mixture was then extracted with DCM and the organic layer dried over MgSO\textsubscript{4}. The solvent was removed to afford the free amine. Sulfur (1.18 mg, 34.5 mmol), DMF (6.0 mL) and triethylamine (5.0 mL, 34.5 mmol) were added to the free amine and the mixture was allowed to stir for 18h. The reaction mixture was then cooled to 0 °C and methyl iodide (6.8 mL, 109 mmol) was added dropwise. The reaction mixture was then stirred at room temperature for 20 minutes after which ether was added until the mixture was homogeneous. The reaction mixture was then washed with brine (20 mL) and the red aqueous layer extracted with ether until it became yellow. The organic layer was then dried over MgSO\textsubscript{4} and the solvent removed in vacuo. The residue was then purified on a column of silica gel (25 g) with a Pet Ether-EtOAc mixture (1:1) to afford methyl 2-pyridylthiocarboxylate as deep red crystals (1.05 g, 51%); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textsuperscript{\textsuperscript{\textsuperscript{\delta}}H 2.68 (3H, s, 8-H), 7.41 (1H, ddd, J = 7.6 Hz, J = 4.8 Hz, J = 1.2 Hz), 7.72 (1H, dt, J = 7.8 Hz, J = 1.8 Hz), 8.26 (1H, dt, J = 8.1 Hz, J = 1.0 Hz), 8.56 (1H, ddd, J = 1.0 Hz, J = 4.8 Hz, J = 1.8 Hz) in agreement with literature.\textsuperscript{[89]}

N-((S)-2-hydroxy-2-phenylethyl)pyridine-2-carbothioamide (S)-130: Prepared by modification of the protocol developed by Masson\textsuperscript{[90]}. To a solution of thioester
(1.05 g, 6.4 mmol) in THF was added amino alcohol (1.20 g, 8.5 mmol) and triethylamine (1.12 mL, 8.5 mmol). The reaction mixture was allowed to stir at room temperature for 18h after which the solvent was removed in vacuo. The residue was then purified on a column of silica gel (35 g) with a Pet Ether-EtOAc mixture (1:1) to afford Pyridine-2-carbothioic acid (2-hydroxy-2-phenyl-ethyl)-amide as a colourless oil (1.289 g, 78%); $^1$H NMR (400 MHz, CDCl$_3$) δ H 3.82 (1H, ddd, J = 10.1 Hz, J = 8.8 Hz, J = 4.8 Hz, 8α-H) 4.35 (1H, ddd, J = 13.9 Hz, J = 7.1 Hz, J = 3.3 Hz, 8β-H) 5.11 (1H, dd, J = 8.8 Hz, J = 3.3 Hz, 9-H), 7.24 – 7.42 (6H, m), 7.77 (1H, dt, J = 7.8 Hz, J = 1.7 Hz), 8.42 (1H, ddd, J = 4.8 Hz, J = 1.8 Hz, J = 1.0 Hz), 8.63 (1H, dt, 8.1 Hz, J = 1.0 Hz), 10.50 (1H, bs, N-H).

Methyl 2-quinolinylldithiocarboxylate 132: Reaction carried out on a 4.67 mmol scale utilising the same procedure as for 129$^{[89]}$. The residue was purified on a column of silica gel (25 g) with a Pet Ether-EtOAc mixture (1:1) to afford 132 as a deep pink solid (1.02 g, 100%); mp 98 – 101 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ H 2.73 (3H, s, 12-H), 7.57 (1H, ddd, J = 1.3 Hz, J = 7.1 Hz, J = 8.1 Hz), 7.72 (1H, ddd, J = 1.3 Hz, J = 6.8 Hz, J = 8.3 Hz), 7.79 (1H, dd, J = 1.0 Hz, J = 8.3 Hz), 8.16 (2H, dd, J = 3.0 Hz, J = 8.6 Hz), 8.37 (1H, d, J = 8.6 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ C 20.2 (CH$_3$, 12-C), 119.5 (C, 5-C), 127.6 (CH), 128.4 (CH), 129.5 (C, 10-C), 130.4 (CH), 130.6 (CH), 136.6 (CH), 146.3 (C, 2-C), 228.7 (C, 11-C); MS FAB m/z (%) 220.3 (M+H, 100), 172.8 (69), 154.9 (40), 137.2 (46), 129.3 (38); HRMS (FAB) 220.0255 (C$_{11}$H$_{10}$NS$_2$ requires 220.0252).
(R)-Quinoline-2-carbothioic acid (2-hydroxy-2-phenyl-ethyl)-amide (R)-133:

Reaction carried out on a 4.67 mmol scale utilising the same procedure as for 130[90]. 133 was isolated as a yellow/orange oil (1.13 g, 78%); $^1$H NMR (400MHz, CDCl$_3$) $\delta$H 3.91 (1H, ddd, $J$ = 4.8 Hz, $J$ = 8.6 Hz, $J_{12\alpha-H,NH}$ = 13.6 Hz, $12\alpha$-H), 4.41 (1H, ddd, $J$ = 3.5 Hz, $J$ = 7.1 Hz, $J_{12\beta-H,NH}$ = 13.9 Hz, $12\beta$-H), 5.18 (1H, dd, $J$ = 3.5 Hz, $J$ = 8.8 Hz, 13-H), 7.27 – 7.30 (1H, m), 7.34 – 7.38 (2H, m), 7.43 – 7.48 (2H, m), 7.56 (1H, ddd, $J$ = 1.3 Hz, $J$ = 7.1 Hz, $J$ = 8.1 Hz), 7.70 (1H, ddd, $J$ = 1.3 Hz, $J$ = 6.8 Hz, $J$ = 8.3 Hz), 7.80 (1H, d, $J$ = 7.8 Hz), 8.02 (1H, d, $J$ = 8.6 Hz), 8.21 (1H, d, $J$ = 8.6 Hz), 8.77 (1H, d, $J$ = 8.6 Hz), 10.70 (1H, bs, NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 52.9 (CH$_2$, 12-C), 72.6 (CH, 13-C), 121.4 (CH), 125.9 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.8 (CH), 129.2 (C, 14-C), 129.9 (CH), 130.4 (CH), 137.0 (CH), 141.5 (C, 5-C), 145.5 (C, 10-C), 150.2 (C, 2-C), 192.1 (C, 11-C).

(R)-(-)-N-(2-hydroxy-2-phenylethyl)isoquinoline-1-carboxyamide (R)-(-)-136:

Methylchloroformate (0.68 mL, 8.79 mmol) was added dropwise to a solution of 1-isoquinoline carboxylic acid, 135 (1.17 g, 7.33 mmol) and triethylamine (1.23 mL, 8.79 mmol) in THF (30 mL) at 0 °C and stirred at that temperature for 1 h. The precipitate was removed by filtration in vacuo and the filtrate added to a solution of (R)-2-amino-1-phenyl-ethanol, 124, (1.19 g, 8.79 mmol) and triethylamine (1.23
mL, 8.79 mmol) in THF (30 mL) at 0 °C and the mixture allowed to reach room temperature and stirred overnight. The solvent was then removed and the residue purified on a column of silica gel with a Petrol – EtOAc mixture (1:1) to afford (R)-(−)-136 as a white solid (89%); \([\alpha]_D\) -78.6 (c = 0.5, CHCl₃); \(^1^H\) NMR (400 MHz, CDCl₃) \(\delta_H\) 3.48 (1H, ddd, \(J_{1\alpha,1\beta} = 13.9\) Hz, \(J_{1\alpha,2} = 8.6\) Hz, \(J_{1\alpha,NH} = 5.3\) Hz, 1α-H), 3.85 (1H, ddd, \(J_{1\alpha,1\beta} = 13.9\) Hz, \(J_{1\beta,NH} = 7.1\) Hz, \(J_{1\beta,2} = 3.3\) Hz, 1β-H), 5.08 (1H, dd, \(J_{1\alpha,2} = 8.6\) Hz, \(J_{1\beta,2} = 3.3\) Hz, 2-H), 7.15-7.26 (3H, m), 7.37 (2H, d, \(J = 7.1\) Hz), 7.49-7.57 (2H, m), 7.59 (d, \(J = 5.3\) Hz, 2H), 7.70 (1H, d, \(J = 7.6\) Hz), 8.17 (1H, d, \(J = 5.6\) Hz), 8.67 (1H, t, \(J = 5.8\) Hz, 18-H), 9.30 (1H, d, \(J = 8.6\) Hz, 12-H); \(^{13}_C\) NMR (100 MHz, CDCl₃) \(\delta_C\) 47.9 (CH, 1-C), 74.2 (CH₂, 2-C), 124.6 (CH), 125.9 (CH), 126.9 (CH), 127.1 (C, 3-C), 127.7 (CH), 127.9 (CH), 128.6 (CH), 128.8 (CH), 130.6 (CH), 137.4 (C, 11-C), 140.28 (CH), 141.9 (C, 16-C), 147.9 (C, 10-C), 167.5 (C, 9-C) CI MS m/z (%) 293 ([M+H]+, 100), 275 (15), 186 (7), 173 (5), 123 (4), 107 (5); HRMS (Cl) 293.1288 (C₁₈H₁₇N₂O₂ requires 293.1290).

(R)-(−)-N-(2-tert-butyldimethylsilanoxy-2-phenylethyl)isoquinoline-1-carboxyamide (R)-(−)-138: (R)-136 (500 mg, 1.71 mmol), tert-butyldimethyldisilyl chloride (309 mg, 2.05 mmol) and imidazole (291 mg, 4.28 mmol) were dissolved in DMF (5 mL) and allowed to stir at room temperature overnight. The mixture was then diluted with aqueous NH₄Cl and extracted with CH₂Cl₂. The organic phase was washed with brine (3 x 25 mL) dried over MgSO₄ and the solvent removed under reduced pressure to afford (R)-(−)-138 as a colourless oil (63%); \([\alpha]_D\) -23.70 (c = 1.00, CHCl₃); \(^1^H\) NMR (400 MHz, CDCl₃) \(\delta_H\) 0.01 (6H, s, 19-H, 20-H), 0.82 (9H, s, 22-H), 3.36 (1H, ddd, \(J = 13.89\) Hz, \(J = 8.4\) Hz, \(J = 4.8\) Hz, 1α-H), 3.90 (1H, ddd, \(J = 13.6\) Hz, \(J = 8.0\) Hz, \(J = 4.0\) Hz, 1β-H), 4.90 (1H, dd, \(J = 8.4\) Hz, \(J = 4.0\) Hz, 2-H), 7.31 – 7.41 (5H, m), 7.65 – 7.84 (3H, m), 8.44 (1H, d, \(J = 5.6\) Hz), 8.62 (1H, bs), 9.61 (1H, d, \(J = 5.2\) Hz);
\( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) C -4.6 (CH\(_3\), C-19), -3.6 (CH\(_3\), C-20), 18.2 (C-21), 25.7 (CH\(_3\), C-22), 47.9 (CH\(_2\), C-1), 74.0 (CH, C-2); \textbf{MS EI} \( m/z \) (%) 406.14 (M+, 5), 349.11 (42), 221.1 (100), 185.1 (35), 128.0 (54), 73.0 (60); \textbf{HRMS} 406.2077 (C\(_{24}\)H\(_{30}\)O\(_2\)N\(_2\)Si requires 406.2076); \textbf{Anal. Calcd.} for C\(_{24}\)H\(_{30}\)N\(_2\)O\(_2\)Si: C 70.90 H 7.44 N 6.89. Found C 70.81 H 7.44 N 6.69.

\( N\)-\((R)\)-2-hydroxy-2-phenylethyl\)isoquinoline-3-carboxamide \((R)\)-140: Reaction carried out on 2.89 mmol scale utilising the same procedure for \((R)\)-136. \((R)\)-140 was purified on a column of silica gel with a Petrol – EtOAc mixture (1:1) to afford the product as a white solid (43%); \textbf{mp} 104 – 105 \( ^\circ\)C; \textbf{\( ^{1}\text{H NMR} \)} (400 MHz, CDCl\(_3\)) \( \delta \) H 3.86 (1H, t, \( J = 10.6 \) Hz, 1\( \alpha \)-H), 4.21 (1H, dd, \( J_{1\beta,2} = 5.6 \) Hz, \( J_{1\alpha,1\beta} = 10.6 \) Hz, 1\( \beta \)-H), 5.05 (1H, dd, \( J_{1\beta,2} = 5.6 \) Hz, \( J_{1\alpha,2} = 10.4 \) Hz, 2-H), 7.23 – 7.38 (6H, m), 7.59 (1H, dt, \( J = 1.26 \) Hz, \( J = 6.8 \) Hz), 7.66 (1H, dt, \( J = 1.3 \) Hz, \( J = 6.8 \) Hz), 7.84 (1H, d, \( J = 8.3 \) Hz), 7.90 (1H, d, \( J = 8.3 \) Hz), 8.22 (1H, s), 9.07 (1H, s); \( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) C 55.7 (CH\(_2\), 1-C), 76.8 (CH, 2-C), 121.7 (CH), 126.4 (CH), 126.6 (CH), 127.5 (CH), 127.7 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.9 (C), 130.9 (CH), 135.9 (C), 137.7 (C), 148.4 (C), 150.8 (CH), 164.7 (9-C); \textbf{Cl+ MS} \( m/z \) (%) 293.3 (M+H, 100), 275.3 (15), 107.2 (72), 85.2 (88); \textbf{HRMS} (Cl+) 293.1290 (C\(_{18}\)H\(_{17}\)N\(_2\)O\(_2\) requires 293.1288).
**N-((R)-2-tert butyldimethylsilyloxy-2-phenylethyl)isoquinoline-3-carboxamide (R)-141:** Reaction carried out on 1.26 mmol scale utilising the same procedure for (R)-138. (R)-141 was isolated as a colourless oil (59%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_h\) 0.01 (6H, s, 19-H, 20-H), 0.84 (9H, s, 22-H), 3.84 (1H, t, \(J = 10.6\) Hz, 1α-H), 4.20 (1H, dd, \(J_{1\alpha,1\beta} = 10.8\) Hz, \(J_{1\beta,2} = 5.3\) Hz, 1β-H), 5.04 (1H, dd, \(J_{1\alpha,2} = 10.4\) Hz, \(J_{1\beta,2} = 5.6\) Hz, 2-H), 7.22 – 7.37 (6H, m), 7.58 (1H, dt, \(J = 1.26\) Hz, \(J = 6.8\) Hz), 7.65 (1H, dt, \(J = 1.3\) Hz, \(J = 6.8\) Hz), 7.83 (1H, d, \(J = 8.3\) Hz), 7.87 (1H, d, \(J = 8.3\) Hz), 8.20 (1H, s), 9.06 (1H, s); \(^1\)CI MS \(m/z\) (%) 423.3 (100, M+H), 155.2 (54); \(^1\)HRMS (CI) 423.1926 (C\(_{24}\)H\(_{31}\)N\(_2\)OSiS requires 423.1923).

**Chloromethyl-3-isoquinoline 143:** Prepared according to a literature procedure\(^{[91]}\).

Methyl-3-isoquinoline (250 mg, 1.75 mmol) and trichloroisocyanuric acid (162 mg, 0.7 mmol) were refluxed in CHCl\(_3\) (10 mL) overnight, the mixture was then cooled to room temperature and filtered. The filtrate was diluted with CH\(_2\)Cl\(_2\) (20 mL) and washed with NaOH (2M, 2 x 15 mL) and brine (2 x 15 mL). The organic phase was then dried over MgSO\(_4\), filtered and evaporated to afford 143 as a colourless oil (311 mg, 100%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_h\) 5.01 (2H, s, 11-H), 7.65 (1H, ddd, \(J = 1.3\) Hz, \(J = 7.1\) Hz, \(J = 8.1\) Hz), 7.78 (1H, m), 7.94 (1H, m), 8.19 (1H, m), 9.11 (1H, d, \(J = 6.6\) Hz) in agreement with literature values.\(^{[91]}\)
Methyl-3-isoquinolinyliothiocarboxylate 144: Prepared by modification of the protocol of Metzner et al[89] To a solution of 143 (311 mg, 1.75 mmol) in DMF (6.0 mL) was added sulfur (169 mg, 4.95 mmol) and triethylamine (0.69 mL, 4.95 mmol) were added and the mixture was allowed to stir for 18h. The reaction mixture was then cooled to 0°C and methyl iodide (0.97 mL, 15.6 mmol) was added dropwise. The reaction mixture was then stirred at room temperature for 20 minutes after which ether was added until the mixture was homogeneous. The reaction mixture was then washed with brine (20 mL) and the red aqueous layer extracted with ether until it became yellow. The organic layer was then dried over MgSO₄ and the solvent removed in vacuo. The residue was then purified on a column of silica gel (25 g) with a Pet Ether-EtOAc mixture (1:1) to afford 144 as brown solid (50%); mp 91-93 °C; ¹H NMR (400 MHz, CDCl₃) δ H 2.81 (3H, s, 12-H), 7.66 (1H, ddd, J = 1.0 Hz, J = 7.1 Hz, J = 8.1 Hz), 7.81 (1H, ddd, J = 1.3 Hz, J = 6.8 Hz, J = 8.3 Hz), 7.98 (1H, d, J = 8.3 Hz), 8.27 (1H, d, J = 8.6 Hz), 9.1 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ C 19.2 (CH₃, 12-C), 123.2 (CH), 126.3 (CH), 126.8 (CH), 127.7 (CH), 130.4 (C), 131.1 (CH), 133.3 (C), 149.2 (CH), 151.1 (C), 226.9 (C, 11-C).

(S)-(+-)1-(5-phenyl-4,5-dihydro-1,3-oxazol-2-yl)isoquinoline (S)-(+-)148. Triethylamine (2.2 mL, 15.6 mmol) was added to a solution of (R)-136 (1.65 g, 5.6
mmol) in CH$_2$Cl$_2$ (65 mL). The reaction was then cooled to 0 °C and mesyl chloride (0.65 mL, 8.25 mmol) was added dropwise over 15 min. The reaction vessel was then allowed to attain room temperature and stirred overnight. The reaction mixture was washed with water (3 × 40 mL) and the organic layer was dried over MgSO$_4$. Concentration in vacuo afforded a residue which was purified via column chromatography on silica gel (petroleum ether-ethyl acetate, 1:1) to give an oil which solidified on standing. Recrystallisation from ether gave (S)-(+) -148 (1.2 g, 78%) as a white solid: mp 78-80 °C (Et$_2$O); [α]$_D$ +83.5 (c 0.5, CHCl$_3$); IR (KBr) 700, 759, 838 (aryl), 1645 (C=N), 2866, 2931 (CH/CH$_2$), 3064 (aryl-H) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δH 4.19 (1H, dd, $J_{4\alpha-H,4\beta-H} = 15.2$ Hz, $J_{4\alpha-H,5-H} = 8.0$ Hz, $4\alpha$-H), 4.64 (1H, dd, $J_{4\alpha-H,4\beta-H} = 15.2$ Hz, $J_{4\beta-H,5-H} = 10.4$ Hz, $4\beta$-H), 5.75 (1H, dd, $J_{4\beta-H,5-H} = 10.4$ Hz, $J_{4\alpha-H,5-H} = 8.4$ Hz, 5-H), 7.27 - 7.39 (m, 5H), 7.61-7.70 (m, 2H), 7.73 (1H, d, $J = 5.2$ Hz), 7.83 (1H, d, $J = 7.2$ Hz), 8.61 (1H, d, $J = 5.6$ Hz), 9.18 (1H, d, $J = 8.4$ Hz); $^{13}$C NMR (100MHz, CDCl$_3$) δC 63.9 (CH$_2$), 80.7 (CH), 123.5 (CH), 126.1 (CH), 127.2 (CH), 127.3 (CH), 127.4 (C), 128.4 (CH), 128.6 (CH), 128.9 (CH), 130.5 (CH), 136.8 (C), 140.7 (C), 141.9 (CH), 146.3 (C), 162.7 (C); EI MS m/z (%) 274 (M$^{+*}$, 65), 168 (70), 128 (100), 101 (15), 82 (35), 77 (10), 47 (5); HRMS (EI) 274.1105 (C$_{18}$H$_{14}$N$_2$O requires 274.1106).

(±)-4-Amino-3-phenyl-1-pyridin-2-yl-butan-1-ol (±)-149:
Method A: SnCl$_2$.2H$_2$O (391 mg, 1.74 mmol) and 150 (158 mg, 0.58 mmol) were dissolved in anhydrous EtOH and heated to reflux overnight. The reaction mixture was then allowed to reach room temperature and sat. NaHCO$_3$ was added until pH = 8. The mixture was then extracted with EtOAc (3 x 20 mL), the organic phase was dried over MgSO$_4$, filtered and the solvent removed. Only starting material was isolated.
Method B: A solution of 150 (310 mg, 0.57 mmol) in EtOH (5 mL) was added to a round bottomed flask containing Pd/C (50 mg, 30%). The flask was evacuated and filled with hydrogen three times. The mixture was then stirred vigorously overnight at room temperature. The reaction mixture was then filtered, the precipitate washed thoroughly with EtOH and the solvent removed in vacuo. Only starting material was isolated.

Method C: To a solution of anhydrous nickel (II) chloride (91 mg, 0.7 mmol) in MeOH (5 mL) at 0 °C was added NaBH₄ (133 mg, 3.5 mmol). The mixture was allowed to stir for 15 min. after which 150 (190 mg, 0.7 mmol) and NaBH₄ (266 mg, 7.0 mmol) were added. The reaction mixture was then allowed to reach room temperature and allowed to stir for a further 45 min. The mixture was then acidified with 2M HCl and extracted with ethyl acetate (3 x 20 mL). The aqueous phase was then treated with ammonia solution and extracted with CH₂Cl₂ (3 x 20 mL). The CH₂Cl₂ phase was dried over MgSO₄ and the solvent removed to give 149 (98%) as a brown oil: ¹H NMR (400MHz, CDCl₃) δ 2.12 (m, 1H), 2.62 (m, 1H), 2.87 (m, 3H), 4.62 (m, 1H) 7.03 – 7.26 (m, 7H), 7.54 (m, 1H), 8.43 (m, 1H).

(±)-4-Nitro-3-phenyl-1-pyridin-2-yl-butan-1-one (±)-150: Diethylamine (0.26 mL, 2.5 mmol) and 151 (100 mg, 0.5 mmol) were dissolved in anhydrous methanol (2 mL). Nitromethane (0.14 mL, 2.5 mmol) was added and the mixture heated at reflux overnight. The mixture was then acidified with 2M HCl and extracted with DCM (3 x 20 mL). The organic phase was then dried over MgSO₄ and the solvent removed to afford 150 as a brown oil (41%): ¹H NMR (400MHz, CDCl₃) δ 3.60 (1H, dd, J₄α,4β = 18.4 Hz, J₃,4α = 7.1 Hz, 4α-H), 3.72 (dd, J₄α,4β = 18.4 Hz, J₃,4β = 7.1 Hz, 1H, 4β-H), 4.18 (m, 1H), 4.61 (1H, dd, J₂a,2β = 12.1 Hz, J₂a,3 = 8.1 Hz, 2α-H), 4.71 (1H, d,
$J_{2\alpha,2\beta} = 12.1$ Hz, $J_{2\beta,3} = 6.6$ Hz, $2\beta$-H), $7.22$ (m, 5H), $7.41$ (t, $J = 6.3$ Hz, 1H), $7.75$ (t, $J = 7.6$ Hz, 1H), $7.92$ (d, $J = 7.8$ Hz, 1H), $8.59$ (1H, d, $J = 4.3$ Hz, 15-H).

3-Phenyl-1-pyridin-2-yl-propenone 151: Adapting the method of Engberts[92] acetyl pyridine (2.06 g, 17.0 mmol) and benzaldehyde (1.85 g, 16.5 mmol) were mixed in water (100 mL) at 4 °C, 10% aqueous NaOH (10 ml) was added and the mixture stored in the fridge overnight. The mixture was then shaken and filtered and the resulting solid recrystallised from ethanol to give 3-phenyl-1-pyridin-2-yl-propenone 151 as yellow crystals (35%): $^1$H NMR (400MHz, CDCl$_3$) δ $H$ 7.31 – 7.37 (3H, m), 7.43 (1H, ddd, $J = 7.6$, 4.8, 1.3 Hz), 7.67 (2H, m), 7.81 (1H, dt, $J = 7.8$, 1.8 Hz), 7.88 (1H, d, $J_{2,3} = 16.2$ Hz, 2-H), 8.13 (1H, dt, $J = 1.0$, 8.1 Hz), 8.24 (1H, d, $J_{2,3} = 16.2$ Hz, 3-H), 8.64 – 8.67 (1H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ $C$ 120.9 (CH), 121.8 (CH), 122.9 (CH), 126.6 (CH), 126.9 (CH), 128.4 (CH), 130.6 (CH), 135.2 (C), 136.8 (CH), 137.1 (CH), 144.8 (CH), 148.8 (CH), 189.5 (C=O), 200.1 (C); IR (NaCl) ν 1700 (C=O), 1620 (C=C) cm$^{-1}$; MS EI HRMS (El+) 209.0841 (C$_{14}$H$_{11}$NO requires 209.0843) in agreement with the literature.[92]
**Organocatalytic Reactions**

**General procedure for the asymmetric allylation of aldime 111 with allyltrichlorosilane:**

Aldimine 111 (49 mg, 0.25 mmol), proline (57 mg, 0.50 mmol), DIPEA (0.11mL, 0.63 mmol) and catalyst (S)-91 (22 mg, 0.05 mmol) were dissolved in CH$_2$Cl$_2$ (2 mL). The solution was allowed to stir at room temperature for 20 minutes after which allyltrichlorosilane (54 μL, 0.37 mmol) was added. The reaction mixture was left to stir for 24 h after which saturated aqueous NaHCO$_3$ (3 mL) was added to quench the reaction. The mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic fractions were dried over MgSO$_4$. Concentration in vacuo followed by chromatography on a column of silica gel with a Petrol – EtOAc mixture (4:1) afforded 112 as a slightly yellow oil; $^1$H NMR (400MHz, CDCl$_3$) δH 2.44 – 2.59 (2H, m), 4.28 – 4.39 (1H, m), 5.05 – 5.11 (2H, m), 5.67 – 5.77 (1H, m), 6.31 (1H, dd, J = 8.0 Hz, J = 1.6 Hz), 6.48 – 6.51 (1H, m), 6.58 – 6.64 (2H, m), 7.10 – 7.19 (2H, m), 7.24 – 7.87 (4H, m).

**General procedure for the asymmetric reduction of ketones and ketimines:**

Trichlorosilane (86 μL, 0.84 mmol) was slowly added dropwise to a solution of catalyst (22 mg, 0.08 mmol) and the corresponding ketone (0.40 mmol) in CHCl$_3$ (2 mL) at -20 °C. The reaction mixture was stirred for 24 h at -20 °C, after which saturated aqueous NaHCO$_3$ (1 mL) was added to quench the reaction. The mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic fractions were dried over MgSO$_4$. Concentration in vacuo followed by flash chromatography on silica gel (3 × 15 cm) with CH$_2$Cl$_2$ afforded sec-alcohol 30.
(R)-(+) -1-Phenylethanol (R)-(+) -30: Isolated as a slightly yellow oil: $[\alpha]_D + 45.2$ (c 0.93, CHCl$_3$, 64% ee$^{[93]}$), gives $[\alpha]_D + 49.0$ (c 1.0, CHCl$_3$, 98% ee); $^1$H NMR (400MHz, CDCl$_3$) $\delta$H 1.52 (d, $J = 6.4$ Hz, 3H), 2.21 (bd, 1H), 4.92 (q, $J = 6.4$ Hz, 1H), 7.28-7.50 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 25.2 (CH$_3$), 70.4 (CH), 125.4 (CH), 127.5 (CH), 128.5 (CH), 145.9 (C); Chiral GC (Supelco β-DEX$^{\text{TM}}$), carrier gas: He (flow 2 mL/min), injection temp: 220 °C; column temp: initial temp, 80 °C for 2 min; rate, 1.5 °C/min; final temperature 160 °C ($t_R = 23.31$ min; $t_S = 24.21$ min).

(+)-N-(1-(benzofuran-2-yl)ethyl)-4-methoxybenzenamine: 77% yield, purified on a column of silica gel with a Petrol – EtOAc mixture (95:5) to give a colourless oil, Chiral HPLC (Chiracel OJ-H) Hexane:iPrOH 80:20 0.75 mL min$^{-1}$ ($t_{\text{major}} = 21.27$ min, $t_{\text{minor}} = 24.56$ min) showed 75% ee; $[\alpha]_D + 181$ (c = 0.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 1.56 (3H, d, $J_{11-H,10-H} = 6.8$ Hz, 11-H), 3.65 (3H, s, 16-H), 4.58 (1H, q, $J_{11-H,10-H} = 6.8$ Hz, 10-H), 6.45 (1H, s, 3-H), 6.55 (2H, m, 14-H), 6.67 (2H, m, 13-H), 7.12 (2H, m), 7.40 (2H, m); EI MS m/z (%) 267 (M$^+$, 65), 145 (100), 123 (44), 115 (42); HRMS (EI) 267.1259 (C$_{17}$H$_{17}$N$_2$O requires 267.1261).
(+)-4-methoxy-N-(1-(thiophen-2-yl)ethyl)benzenamine: 77%, yield purified on a column of silica gel with a Petrol – EtOAc mixture (95:5) to give a yellow oil, Chiral HPLC (Chiracel OJ-H) Hexane: [α]D +5.5 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δH 1.52 (3H, d, J₇-H,6-H = 6.8 Hz, 7-H), 3.65 (3H, s, 12-H), 4.66 (1H, q, J₇-H,6-H = 6.8 Hz, 6-H) 6.52 (2H, m, 8-H), 6.67 (2H, m, 9-H), 6.88 (2H, m, 3-H, 4-H), 7.17 (1H, m, 5-H); ¹³C NMR (CDCl₃, 100 MHz) δC 20.5 (CH₃, 7-C), 50.6 (CH, 6-C), 55.7 (CH₃, 12-C), 114.8 (CH), 115.2 (CH), 122.9 (CH), 123.7 (CH), 128.7 (CH), 141.0 (C, 8-C), 150.5 (C, 2-C), 152.5 (C, 11-C); EI MS m/z (%) 233 (M⁺, 39), 216 (54), 123 (37), 111 (92), 83 (100); HRMS (EI) 233.0874 (C₁₃H₁₅NOS requires 233.0873).

(-)-4-methoxy-N-(1-(pyridin-4-yl)ethyl)benzenamine: 70% yield, purified on a column of silica gel with a Petrol – EtOAc mixture (7:3) to give an off-white solid, Chiral HPLC (Chiracel OJ-H) Hexane: [α]D -19.0 (c = 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δH 1.43 (3H, d, J₆-H,5-H = 6.8 Hz, 6-H), 3.63 (3H, s, 11-H), 4.31 (1H, q, J₆-H,5-H = 6.8 Hz, 5-H), 6.33 (2H, d, J₈-H, 9-H = 3.6 Hz, 9-H), 6.61 (2H, d, J₈-H, 9-H = 3.6 Hz, 8-H), 7.22 (2H, d, J₂-H, 3-H = 2.4 Hz, 3-H), 8.46 (2H, d, J₂-H, 3-H = 2.8 Hz, 2-H); ¹³C NMR (CDCl₃, 100 MHz) δC 24.6 (CH₃, 6-C), 53.5 (CH, 5-H), 55.7 (CH₃, 11-H), 114.5 (CH), 114.8 (CH), 121.3 (CH), 140.8 (C, 7-C), 149.9 (CH), 152.3 (C, 10-C), 154.9 (C, 4-C); CI MS m/z (%)
229 (M+ 100), 213 (8), 123 (15), 108 (12), 71 (15); **HRMS** (Cl) 229.1341 (C14H17N2O requires 229.1342).

(-)-4-methoxy-N-(1-(pyridin-2-yl)ethyl)benzenamine: purified on a column of silica gel with a Petrol – EtOAc mixture (7:3) to give an off-white solid, Chiral HPLC (Chiracel OJ-H) Hexane:PrOH 80:20 0.75 mL min⁻¹ (tminor = 27.89 min, tmajor = 38.29 min) showed 79% ee; [α]D -15.0 (c = 0.1, CHCl₃); **1H NMR** (400 MHz, CDCl₃) δ 1.45 (3H, d, J = 6.8 Hz, 8-H), 3.62 (3H, s, 13-H), 4.47 (1H, q, J = 6.8 Hz, 7-H), 6.45 (2H, d, J = 8.0 Hz, 3-H), 7.27 (1H, d, J = 8.0 Hz, 6-H), 7.53 (1H, dt, J = 1.6 Hz, J = 7.6 Hz, 4-H), 8.50 (d, J = 4.98 Hz, 6-H); **EI MS** m/z (%) 228 (M⁺, 100), 213 (98), 169 (37), 150 (97), 122 (90), 106 (97); **HRMS** (EI) 228.1263 (C14H16N2O requires 228.1265) in agreement with literature values.[94]

N-(1-(furan-2-yl)ethyl)-4-methoxybenzenamine: 70% yield, purified on a column of silica gel with a Petrol – EtOAc mixture 94:6, Chiral HPLC (Chiracel OJ-H) Hexane:PrOH 80:20 0.75 mL min⁻¹ (tminor = 41.51 min, tmajor = 49.19 min) showed 55% ee; **1H NMR** (400 MHz, CDCl₃) δ 1.46 (3H, d, J = 6.8 Hz, 7-H), 3.66 (3H, s, 12-H), 4.47 (1H, q, J = 6.8 Hz, 6-H), 6.06 (1H, d, J = 7.2 Hz, J = 5.2 Hz, 5-H), 7.36 (1H, d, J = 8.0 Hz, 3-H), 7.53 (1H, dt, J = 1.6 Hz, J = 7.6 Hz, 4-H), 8.50 (d, J = 4.98 Hz, 6-H); **EI MS** m/z (%) 228 (M⁺, 100), 213 (98), 169 (37), 150 (97), 122 (90), 106 (97); **HRMS** (EI) 228.1263 (C14H16N2O requires 228.1265) in agreement with literature values.[94]
4-methoxy-N-(1-phenylethyl)benzenamine: Isolated as a slightly yellow oil, Chiral HPLC (Chiracel OJ-H) Hexane:iPrOH 99:1 0.75 mL min⁻¹ (t_major = 13.12 min, t_minor = 14.36 min) showed 79% ee; ¹H NMR (400 MHz, CDCl₃) δ_H 0.87 (3H, t, J_7-H,6-H = 7.8 Hz, 7-H), 1.73 (2H, m, 6-H), 3.56 (3H, s, 12-H), 4.08 (1H, t, J_6-H,5-H = 6.8 Hz, 5-H), 6.40 (2H, d, 9-H), 6.59 (2H, d, 10-H), 7.22 (5H, m, 1-H, 2-H, 3-H); ¹³C NMR (CDCl₃, 100 MHz) δ_C 10.9 (CH₃, 7-C), 31.7 (CH₂, 6-C), 55.8 (CH, 5-C), 60.6 (CH₃, 12-C), 114.5 (CH), 114.8 (CH), 126.6 (CH), 126.9 (CH), 128.5 (CH), 141.9 (C, 8-C), 144.2 (C, 4-C), 151.9 (C, 11-C); EI MS m/z (%) 241 (M⁺, 57), 212 (100), 91 (67); HRMS (EI) 241.1467 (C₁₆H₁₉NO requires 241.1469) in agreement with literature.²

(+)-4-methoxy-N-(1-(5-(trimethylsilyl)furan-2-yl)ethyl)benzenamine: Isolated as a colourless oil, [α]₀ +13.4 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 0.05 (9H, s, 13-H), 1.35 (3H, d, J₇-H,6-H = 6.8 Hz, 7-H), 3.55 (3H, s, 12-H), 4.38 (1H, q, J₆-H,5-H = 6.8 Hz, 6-H), 5.96 (1H, d, J₃-H,4-H = 4.6 Hz, 3-H), 6.31 (1H, d, J₃-H,4-H = 4.8 Hz, 4-H), 6.43
(2H, d, 9-H), 6.57 (2H, d, 10-H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ$_C$ 0.00 (CH$_3$, 13-C), 22.5 (CH$_3$, 7-C), 50.2 (CH, 6-C), 57.3 (CH$_3$, 12-C), 106.5 (CH, 3-C), 116.3 (CH, 4-C), 116.8 (CH, 9-C), 121.7 (CH, 10-C), 142.9 (C, 8-C), 153.9 (C, 11-C), 160.7 (C, 2-C), 163.5 (C, 5-C); EI MS m/z (%) 289 (M$^+$, 20), 167 (70), 123 (15), 83 (99), 75 (30), 49 (100); HRMS (EI) 289.1498 (C$_{16}$H$_{23}$NO$_2$Si requires 289.1495).

1-(2,5-dimethylfuran-3-yl)ethanol: Isolated as a colourless oil, $^1$H NMR (400MHz, CDCl$_3$) δ$_H$ 1.35 (3H, d, J = 6.3 Hz, 7-H), 2.16 (3H, s, 8-H), 2.17 (3H, s, 9-H), 4.71 (1H, q, J = 6.3 Hz), 5.93 (1H, s, 4-H); Chiral GC (Supelco β-DEX™), carrier gas: He (flow 2 mL/min), injection temp: 220 °C; column temp: initial temp, 80 °C for 7 min; rate, 3.0 °C/min; final temperature 200 °C ($t_1$ = 29.90 min; $t_2$ = 30.08 min).

1-(5-methylfuran-2-yl)ethanol: $^1$H NMR (400MHz, CDCl$_3$) δ$_H$ 1.55 (3H, d, J$_{7-H,8-H}$ = 6.6 Hz, 8-H), 2.31 (3H, s, 6-H), 4.85 (1H, dq, J = 1.5 Hz, J$_{7-h,8-H}$ = 6.6 Hz, 7-H), 5.93 (1H, dq, J$_{3-H,4-H}$ = 3.0 Hz, J = 1.0 Hz), 6.13 (1H, d, J = 3.0 Hz); Chiral GC (Supelco β-DEX™), carrier gas: He (flow 2 mL/min), injection temp: 220 °C; column temp: initial temp, 80 °C for 5 min; rate, 2.0 °C/min; final temperature 200 °C ($t_1$ = 12.32 min; $t_2$ = 12.65 min).
5 References


(81) Although no optical rotation was observed the product is taken to be enantiomerically pure as the synthesis was started from a single enantiomer.