Amino Acid Substituted Guanidines as Organocatalysts

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Amino Acid Substituted Guanidines as Organocatalysts

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In the

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By

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Presentations and awards

The following presentations were based on work described in this thesis:

1. Advances in Organocatalysis and Spotlight on Photoredox Catalysis and Photochemistry at SCI, London, UK on 25th February 2019, and contributed to the conference by presenting a poster.

2. Scientific Diversity in Inorganic/Organic of the ACS Publications Chemistry in Europe at University of Heidelberg, on 1-11, October, 2018 and contributed to the conference by presenting a poster.

3. The 33rd Young Scientist Symposium hosted by The Royal Society of Chemistry, at Bangor University on 22nd June 2018, presentation of a poster and talk with poster prize as the best poster.


5. Symposium on Advances in Heterocyclic Organic Chemistry, at University of Sheffield, UK on 1st-2nd September 2016.
Abstract

A series of amino acid substituted guanidines of general structure I and II (AA = L-Proline, L-alanine and L-phenylalanine derivatives; (R, R¹, R² = H, Me, Alkyl, Aryl, Boc, Cbz) were prepared and their applications in asymmetric Michael reactions investigated. Initially, the project focused on the synthesis a range of N-alkylated-L-proline amides of several guandines. The catalysts prepared were applied to the Michael reaction between 2-nitrostyrene III and quinone IV leading to the conjugate product V in 17-99% yield and up to 56% enantiomeric excess. Hydrazine and several heterocyclic derivatives were also prepared which proved less effective. A series of N,N-dimethyl-L-alanine and N,N-dimethyl-L-phenylalanine derivatives were similarly prepared and these gave enantioselectivities of up to 31% ee in this reaction. The influence of racemisation of these catalysts during CDI coupling was also studied. Finally, N-protected-L-proline, L-alanine and L-phenylalanine derivatives were prepared to counter the observed racemisation and these gave enantioselectivities of up to 26% ee.

X-ray crystallographic structures were determined for several of these compounds and the hydrogen bonding patterns observed were used to speculate on the mechanism of the reaction and the magnitude of the asymmetric induction observed. The X-ray crystallographic results proved that partial racemisation was occurring during the formation of the catalysts in a CDI mediated coupling reaction.
Abbreviations

General

[α] Specific rotation
br. Broad
d Day(s)
DEPTQ Distortionless Enhancement by Polarization Transfer.
Equiv. molar equivalents
h Hour(s)
HBD Hydrogen-Bond Donor
HMBC Heteronuclear Multiple Bond Correlation
HPESW Hajos–Parrish–Eder–Sauer–Wiechert reaction
HPLC High-performance liquid chromatography
HSQC heteronuclear single quantum correlation
IR Infrared spectroscopy
L Cell path length (in dm)
min Minute(s)
MS Mass spectrometry
NA Not applicable
ND Not determined
NMR Nuclear magnetic resonance
Rf retention factor
rt Room temperature
T Temperature (degree centigrade)
TLC Thin layer chromatography
TM target molecule
Cons. Conditions

Reagents

BA Benzoin acid
CbzCl Benzyl chloroformate
CDI Carboxyldiimidazole
SOCl₂ Thionyl chloride
CAN Ceric ammonium nitrate
(-)-CSA    Camphorsulfonic acid
(CH₂O)ₙ    Paraformaldehyde
EDCI     3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine
Et₃N     triethylamine
DEPC   diethylphosphorocyanidate
DCC      N,N'-Dicyclohexylcarbodiimide
DIAD    diisopropyl azodicarboxylate
DMAP    4-Dimethylaminopyridine
HOBT    Hydroxybenzotriazole
HBTU    (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
NHS     N-Hydroxysuccinimide
iPrNEt   N,N-Diisopropylethylamine
PTSA    p-Toluenesulfonic acid
NaH      sodium hydride
TBME     tert-butyl methyl ether
TFA      trifluoroacetic acid
TfOH    Triflic acid
Yb(OTf)₃  Lanthanide trifluoromethanesulfonates

**Functional groups**

Ac    Acetyl
Bn    Benzyl
Boc   i-Butyloxy carbonyl
Cbz   Carbobenzyloxy
Cy    Cyclohexyl
Et    Ethyl
iPr   i-Propyl
Me    Methyl
Ph    Phenyl
PBB   p-bromobenzyl
PMP   paramethoxphenyl
TBS   tert-Butyldimethylsilyl ethers
### Solvents

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<tbody>
<tr>
<td>tBuOH</td>
<td>t-Butyl alcohol</td>
</tr>
<tr>
<td>CF</td>
<td>Chloroform</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DE</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>EA</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Hex</td>
<td>Hexane</td>
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<td>IPA</td>
<td>Isopropyl alcohol</td>
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</tr>
<tr>
<td>PhH</td>
<td>Benzene</td>
</tr>
<tr>
<td>PhMe</td>
<td>Toluene</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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Chapter one: Introduction

1.1 Asymmetric Organocatalysis

The use of metal based catalysts in fields such as materials science, medicinal chemistry and natural products chemistry over the last 50 years has been considerable. However, the use of metals, particularly transition metals can be problematic due to the negative impacts of these transition metals in the environment and their effect on human and animal health. Additional problems can be the poor stability of metal catalysts toward air and moisture and the toxicity, expensive and technical difficulties encountered when using transition metals can preclude their use on a large scale. These aspects are also opposed to the principles of green chemistry.

Over the last two decades, a new approach has been developed which has been termed “organocatalysis”. This methodology has the potential to be more environmentally benign and use mild conditions to effect organic transformations. Asymmetric organocatalysis has been extensively studied and has shown potential for the preparation enantiomerically pure natural products, drugs, building-blocks and important molecules for materials chemistry. Several definitions of organocatalysis have been put forward as follows:

“Organocatalysis is the field wherein small organic molecules efficiently and selectively catalyse organic transformations.” David W. C. MacMillan

“Organocatalysis is the catalysis of a reaction with an organic small molecule. By accepted convention, organic small molecule means a molecule without a metal, and not a macromolecule like protein, nucleic acid, or polymer.” K. N. Houk

“Organocatalysis is catalytic reactions mediated by small organic molecule in absence of metals or metal ions.” Carlos F. Barbas, III
An organocatalyst is defined as “a material that facilitates a synthetic conversion, without being incorporated into the final product, and can perform many such transformations (turnover)”\(^5\). A measure of the importance of organocatalytic processes can be gained from the SciFinder\textsuperscript{®} search of the term “Organocatalysis” over the period 2000-2019, which has demonstrated a steady growth in the publication of papers on this topic. (Figure 1)

![Figure 1: Annual publications containing the keyword “Organocatalysis”](image)

Many organocatalysts are derived from naturally occurring homochiral compounds (enantiomerically pure), particularly alkaloids as these contain a basic amine functional group and have a diverse structural nature. Several reaction types have been reported and these include hydrogen-bonding catalysis,\(^6\) iminium catalysis,\(^7\) counterion catalysis\(^8\) and enamine catalysis.\(^9\) These processes are discussed in more detail later.
1.2 Enamine catalysis

1.2.1 Aldol reactions and Mannich reactions

In 1971, there were two independent reports, by Zoltan Hajos and David Parrish and by Rudolf Weichert, Gerhard Sauer and Ulrich Eder of an enantioselective intramolecular aldol reaction catalysed by L-proline for the synthesis of the Wieland–Miescher ketone 4. For example, Wiechert reported that 4 was formed in 83% yield and in 71% ee on treatment with natural amino acid L-proline 2 in the presence of perchloric acid. Subsequently Hajos and Parrish reported that the preparation of the intermediate 3 was possible in 99% yield in a 93% ee, by using a different solvent, temperature and omitting the perchloric acid. (Scheme 1)

Scheme 1: (a) CH$_3$CN, rt, 80 °C, 24 h, proline (0.47 equiv.), HClO$_4$ (1 M).
(b) DMF, rt, (L)-Proline (0.03 equiv.)

An enamine catalysis mechanism was initially proposed (Figure 2) involving iminium ion (5 and 7), and enamine (6) intermediates. This mechanism is essentially identical to the accepted mechanism of class I aldolases. The carboxylic acid group was proposed to act as a general Brønsted co-catalyst, replacing the several acid/base functional groups involved in the aldolase mechanism. In the transition state of the carbon-carbon bond formation (6), protonation of the acceptor carbonyl group occurs by the carboxylic acid, which is anti with respect to the (E)-enamine double bond. In this context, proline not only acts as an enamine catalyst but also brings along its own Brønsted acid co-catalyst and therefore can be viewed as a “bifunctional catalyst”.
Figure 2: Proposed mechanistic cycle of the L-proline catalysed intermolecular aldol reaction.

This extraordinary result was very well received by the scientific community, however the underlying activation mode was not exploited for other reactions until more than 30 years later. In 2000, with the ingenious work of Barbas, Lerner and List who used enamine catalysis to functionalize carbonyl-containing compounds at the α-carbon that the broad applicability of this mode of activation became evident. The authors reported the first direct intermolecular aldol reaction between acetone 8 and benzaldehyde 9 promoted by L-proline 2 and the L-proline derived 2a and 2b to give 10 in good yields and ee’s.12b

Scheme 2: catalyst 2 (0.3 equiv.), DMSO/acetone (4:1), 4 h, rt.

The authors12b assumed that the asymmetric aldol reaction occurs via an enamine mechanism as shown in figure 3. They also assumed that the L-proline might function as a
“micro-aldolase” providing both a nucleophilic amino group and an acid/base co-catalyst in the form of the carboxylic acid/carboxylate anion. Thus L-proline might facilitate each individual step of the mechanism including the two steps leading to the formation of the iminium ion 11 (nucleophilic attack of the amino group and subsequent dehydration of the intermediate carbonyl amine) and the deprotonation of the iminium species leading to the enamine 12. The formation of the intermediate transition state 13 is assisted by the hydrogen bonding to the carboxylic acid and both steps of the hydrolysis of the iminium-aldol intermediate 14 via 15 is mediated by the carboxylic acid as well. The enantioselectivity can be explained using a metal free version of a Zimmerman/Traxler type transition state with the enantioselectivity directed by the hydrogen bonding to the carboxylic acid.

\[ \text{Figure 3: Proposed enamine mechanism of the proline-catalysed asymmetric aldol reaction.} \]

Several features make this reaction very appealing, firstly, proline is non-toxic, inexpensive, and readily available in both enantiomeric forms.\(^{13}\) Secondly, the reactions do not require inert conditions and are performed at ambient temperature. Proline itself needs no prior modification and the catalyst is water-soluble and can be easily removed by aqueous extraction. In addition, the reaction has the potential to be applied on an industrial scale. These reactions represent the first example of a nonmetallic small-molecule catalyst for direct intermolecular asymmetric aldol reactions and the proline most likely functions as a micro-aldolase with enamine formation as in the aldolase catalytic antibodies and natural class I aldolases.\(^{12}\)

Since this report, a significant amount of research has been directed towards identifying new types of chiral enamine catalysts. Mechanistically, enamine catalysis can be better described as bifunctional catalysis, as proline typically interacts with a ketone substrate to form an intermediate enamine intermediate but simultaneously engages with an electrophilic
reaction partner through either hydrogen bonding or via an electrostatic interaction attraction. This mode of activation has been used in a wide range of enantioselective processes.\textsuperscript{14}

The closely related Mannich reaction can also be catalysed by L-proline 2 to form syn-β-amino aldehydes and ketones that can be converted to a range of amino acid and alcohol products.\textsuperscript{15, 16} A one-pot imine formation/Mannich reaction is also possible, although, in some cases, the enantiomeric excess is moderate.\textsuperscript{17} Notz \textit{et al.} 2004, and Cordova \textit{et al.} 2002, have described the unprecedented use of unmodified aldehydes as donors in a catalytic asymmetric Mannich-type reaction. The L-proline 2 catalysed reaction of N-PMP-protected α-imino ethyl glyoxylate 17 with unmodified aliphatic aldehydes 16 provided a general and very mild entry to either enantiomer of β-amino and α-amino acids and derivatives 18 in high yield and stereoselectivity. Six of the seven aldehydes 16 studied yielded products 18 with ee values of 99\% or greater (Scheme 3). The diastereoselectivity of the reaction increased with the bulkiness of the substituents of the aldehyde donor in the order $R = \text{Me < Et < } i\text{-Pr < } n\text{-Pent}$. In five of the cases studied, excellent syn-stereoselectivities were achieved.\textsuperscript{15, 16}

\begin{center}
\textbf{Scheme 3:} (a) Catalyst 2 (0.05 equiv.) dioxane, 2-24 h, rt, $R = \text{Me, Et, } i\text{Pr, } n\text{-pentyl.}$
\end{center}

A powerful application of the L-proline catalysed aldol reaction, is the use of α-hydroxyl ketones as enamine precursors in reaction with aldehydes, a process that affords anti-diols and offers a complementary approach to the Sharpless dihydroxylation protocol. Notz and List found\textsuperscript{18} that L-proline 2 catalyses the aldol reaction between the aldehydes 20 and hydroxyacetone 19 to furnish anti-diols 21 in moderate to good yield and stereoselectivity. (Scheme 4)

\begin{center}
\textbf{Scheme 4:} (a) Catalyst 2 (0.2-0.3 equiv.) DMSO, rt, 24-72 h; $R = \text{Cy, 3,3-dimethyl butyl, 2-chlorobenzyl, } \alpha\text{-oxygenated } D\text{-isopropylidene-glyceryl.}$
\end{center}
MacMillan and co-workers, who describe a crossed aldehyde aldol coupling, have reported an impressive development of this process. (Scheme 5)\textsuperscript{19} A requirement of this reaction is that a given aldehyde can be defined clearly as donor and acceptor. This means that only one aldehyde should be able to form an enamine (donor) and the other can act as the acceptor. Thus, chemo selective coupling leads to excellent yields, and diastereo- and enantioselectivities of anti-aldol products.\textsuperscript{20}

\[
\begin{align*}
\text{H} & \quad \text{R}^1 \quad \text{H} \quad \text{R}^2 \\
\text{22} & + \quad \text{23} \quad \text{2} \quad \text{OH} \\
\text{(a)} & \quad 80\% \text{ (99\% ee)} \\
\text{24} & \\
\end{align*}
\]

Scheme 5: (a) Catalyst 2 (0.1-0.2 equiv.), DMF, 4 °C, 11 h, \( \text{R}^1 = \text{Me}, \text{n-Bu}, \text{Bn}, \text{R}^2 = \text{Et}, \text{i-Bu}, \text{C}_6\text{H}_{11}, \text{Ph}, \text{i-Pr} \).

1.2.2 Michael reactions

Other reactions that are of considerable interest in the area of asymmetric catalysis are conjugate addition-type reactions. Although early reports of the addition of aldehydes 25 to nitro olefins 26 via enamines afforded only modest ee’s using L-proline and related catalysts,\textsuperscript{21} this research accelerated the search for proline alternatives.\textsuperscript{22,23} The best reported example of this type of reaction is the use of the prolinol catalyst 27 that provides excellent yields and ee’s for the formation of the Michael adduct 28. (Scheme 6)\textsuperscript{24} It is worth noting that the stereochemical control in this reaction seems to be due to the steric properties of the catalyst and does not rely on H-bonding.

\[
\begin{align*}
\text{H} & \quad \text{R}^1 \quad \text{NO}_2 \\
\text{25} & + \quad \text{26} \quad \text{27} \quad \text{Ph} \quad \text{Ph} \\
\text{(a)} & \quad 52-83 \% \text{ (68-99\% ee)} \\
\text{28} & \\
\end{align*}
\]

Scheme 6: (a) Catalyst 27 (0.1-0.2 equiv.), MeCN, (0-23) °C, 1-96 h; \( \text{R}^1 = \text{Me}, \text{i-Pr}, \text{n-Pr}, \text{R}^2 = \text{Ph}, \text{Ar}, \text{Het}, \text{Cy} \).
Although the addition of enamines to enones has proved to be a troublesome reaction, Gellman et al. recently showed the prolinol catalyst 27 also readily catalysed the Michael addition of aldehydes 29 to simple enones 30 in excellent ee (Scheme 7).25,26

\[
\text{HCO}_2 + \text{C}_2\text{H}_5\text{C} = \text{CH}_2 \xrightarrow{\text{27}} \text{HCO}_2\text{CH}_2\text{C} = \text{CH}_2
\]

**Scheme 7:** (a) Catalyst 27 (0.05 equiv.), no solvent 4 °C, 25-48 h; R\(^1\), R\(^2\) = Alkyl, Bn.

The proline-derived azide 34 has been shown to be a good organocatalyst for the asymmetric Michael addition reaction between isobutylaldehyde 32 and a range of aryl-substituted β-nitrostyrenes 33 to give the Michael adduct 35 in high ee and in very good to excellent yields. (Scheme 8)27

\[
\text{HCO}_2 + \text{O}_2\text{NCH} = \text{C}_6\text{H}_5\text{CH}_2 \xrightarrow{\text{34}} \text{HCO}_2\text{CHCH} = \text{C}_6\text{H}_5\text{CH}_2
\]

**Scheme 8:** (a) Catalyst 34 (0.2 equiv.), 10 °C -rt, 3-12 d, IPA-H\(_2\)O (3:1);
R = H, CH\(_3\), CH\(_3\)O, Br, Cl, F, NO\(_2\)

### 1.3 Iminium catalysis

The iminium based catalysis strategy was the first organocatalytic activation mode to be designed (rather than discovered) and introduced as a general strategy for asymmetric organic synthesis.28 It is based upon the capacity of chiral amines to function as enantioselective catalysts for several transformations that traditionally use Lewis acid catalysis. The concept was founded on the mechanistic hypothesis that the reversible formation of iminium ions from α,β-unsaturated aldehydes and chiral amines might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis (that is, lowest-unoccupied molecular orbital (LUMO)-lowering activation). The use of chiral secondary amines as catalysts to activate enals via the iminium ion was reported during the late 1990s by MacMillan and co-workers. The almost simultaneous reporting of the proline aldol research12
and MacMillan’s iminium ion catalysis set the scene for an explosion of organocatalytic research.

MacMillan et al. designed a new strategy for organocatalysis that has enabled the development of the first highly enantioselective amine-catalysed Diels-Alder reaction. They were first evaluated using substituted dienes with enals and the chiral secondary amine HCl salt as the catalyst. This LUMO-lowering strategy was successful using only catalytic quantities of providing the Diels-Alder adduct in excellent yield and stereo-selectivity. (Scheme 9)

\[ \text{Scheme 9: (a) Catalyst 38 (0.2 equiv.), MeOH-H}_2\text{O, 23 °C, 14-42 h; } \]
\[ R_1 = \text{Me, H; } R_2 = \text{Me, Ph, OAc.} \]

The mechanism of this reaction involves the formation of the intermediate iminium species (Figure 4) in which the LUMO orbital of the iminium species is lowered in energy such that it can now interact with suitable coupling partner’s either through pericyclic reactions or by conjugate addition. The operational simplicity of these processes makes them attractive alternatives to Lewis acid catalysis.

\[ \text{Ph group blocks top face} \]
\[ \text{Preferred geometry to minimise steric interactions} \]
\[ \text{Reaction from lower face} \]

**Figure 4:** Stereocontrol elements in the iminium ion
In addition, they demonstrated that this catalytic strategy is also amenable to [3+2] cycloadditions between nitrones and α,β-unsaturated aldehyde. For example, nitrones 42 and the α,β-unsaturated aldehyde 41 gave the isoxazolidine 43 in high yield and ee. (Scheme 10) These compounds are useful intermediates for the construction of biologically important amino acids, β-lactams, amino carbohydrates, and alkaloids. Moreover, this study further documents that chiral amines can be employed as asymmetric catalysts for a range of transformations that traditionally utilise metal salts.

![Scheme 10](attachment:image.png)

**Scheme 10:** (a) Catalyst 38 (0.2 equiv.), MeNO₂-H₂O (1:10), 40 °C, 72 h.

Activation via iminium ion formation also renders facile conjugate addition processes with soft nucleophiles. A range of aromatic and hetero-aromatic nucleophiles, such as the indole 45, can be added to enals such as 44 in high yields and enantiomeric excesses. For example, catalyst 46 gave 47 in high yields and ee’s. (Scheme 11).

![Scheme 11](attachment:image.png)

**Scheme 11:** (a) Catalyst 46 (0.2 equiv.), CH₂Cl₂-IPA, - 83 to - 55 °C, 6-45 h, R = Me, Pr, iPr, CH₂OBz, Ph, CO₂Me.

A similar reaction was reported for the reaction of anilines 48 to give 49 which can be modified to synthetically useful compounds. (Scheme 12)
Scheme 12: (a) Catalyst 46 (0.1 equiv.) CH$_3$Cl, -20 °C-rt, 0.1-80 h; R = Me, CH$_2$OBz, CO$_2$Me, Ph; R$_1$ = OMe, Me, Cl; NR$_2$ = NMe$_2$, NBn$_2$, 1-pyrrolidinyl.

1.4 Hydrogen-bonding catalysis

In the early 1980’s researchers uncovered several catalytic asymmetric processes that suggested that the activation of a substrate and the organization of the transition state could occur through well-defined hydrogen-bonding interactions.$^{34,35,36}$ These reports were widely appreciated, however they were considered to be exceptions to the generally held idea that hydrogen bonding was insufficiently activating or directional for use in asymmetric catalysis. This proposition was disproved by reports published in 1998 and 1999, when Jacobsen$^{37}$ and Corey$^{38}$ independently reported an asymmetric variant of the Strecker reaction that used well-defined hydrogen-bonding donation (HBD) organocatalysts that activate imine electrophiles. For example, Corey reported that the imine 50 was converted to the Strecker product 53 in high ee using the bicyclic guanidine catalyst 52 and HCN 51.

Scheme 13: (a) Catalyst 52 (0.1 equiv.), HCN 51, toluene, -40 °C, 20 h.

The mechanism of this reaction involves the protonation of the catalyst 52 with HCN 51 leading to the guanidinium cyanide complex 54, which can serve as a hydrogen bond donor to the aldimine 50 forming the pre-transition-state intermolecular assembly 55. Finally, attack by cyanide ion within the ion pair on the hydrogen-bond-activated aldimine affords the Strecker product 53. It is likely that the last step in the process is the rate limiting since hydrogen bond making and breaking are considered to be relatively fast processes.
Along similar lines, Miller et al. reported the design and synthesis of new functional peptides 57 that catalyse the kinetic resolution of secondary alcohols. The design of the catalyst mimics structural features found in enzymes and the N-alkyl-imidazole fragment of the catalyst was found to be key for the activity. The presumed hydrogen bond shown in structure 57 was proposed to add rigidity to the catalyst. It was found that the best substrates for the catalyst were the $\alpha$-N-acetyl alcohols 56, which were acetylated in 84% ee and in high yield. This is probably due to the existence of a favourable transition state hydrogen bond between the amide of 56 and the peptide backbone of 57.

Several early examples of hydrogen bonding catalysis were reported, for example in 1981, Wynberg reported the Michael-addition of aromatic thiols, such as 59 to conjugated...
cycloalkenone 60, was catalysed by alkaloids such as cinchonidine 61 to give 62 in quantitative yield and 75% ee. (Scheme 15) Wynberg proposed that the reaction proceeded via the formation of a thiolate-alkyl ammonium tight ion pair 63 and activation of the enone electrophile occurs by the formation of a hydrogen bond from the hydroxyl group on the catalyst. It is however more likely that the H-bonding interaction is between the ammonium N-H and the enone, whilst the thiolate is H-bonded to the hydroxyl group as shown in 64. (Figure 6).40

![Scheme 15: (a) Catalyst 61 (0.01 equiv.), PhH, rt.](image)

Similarly Wang et al. reported the Michael-addition of benzotriazole 65 to a variety of nitroolefins 66 catalysed by the alkaloid 67 in high ee and yield. (Scheme 16) The mechanism of this reaction probably proceeds via the deprotonation of the benzotriazole to give an anion, which then attacks the double bond of the H-bonded nitro-olefin.41 (Figure 7)
Possibly the most significant discovery in this area was made by Jacobsen in 2002.\textsuperscript{42} He showed that thioureas such as 72 were versatile enantioselective hydrogen-bonding catalysts. For example, the N-Boc imines 70 on reaction with the of silyl ketene acetal 71 in the presence of 72 gave rise to the desired Mannich product 73 in high yield and with high levels of enantioselectivity.

Ureas and thioureas are small organic molecules capable of reliable catalysis of a variety of reactions through dual hydrogen bonding interactions.\textsuperscript{43,44,45,46} The success of these compounds as catalysts is due to their ability to recognize and activate selective functional groups through hydrogen bonds.\textsuperscript{47,48,49} The interest in Hydrogen-Bond Donor catalysts (HBD), led to the study and design of structural elements of the urea and thiourea catalyst scaffold to enhance catalyst performance in terms of both activity and selectivity. The use of 3,5-bis-(trifluoromethyl) phenyl motifs in these catalysts is a good example of this. The iterative development of highly active urea and thiourea catalysts this motif stemmed from a report by
Etter who observed that 1,3-bis(m-nitrophenyl) urea 74 is an excellent hydrogen-bond donor in the solid state.\textsuperscript{47,48,49} Subsequently Wilcox and Curran reported significant substituent effects in the hydrogen bonding abilities of aryl urea 75\textsuperscript{50,51} whilst Shreiner reported that the 3,5-bis(trifluoromethyl)phenyl containing catalyst 76 afforded large rate enhancement (up to 8.2 times) of Diels–Alder reactions when compared to other ureas examined.\textsuperscript{52,53}

![Figure 8: Evolution of the 3,5-bis(trifluoromethyl)phenyl functionality in urea catalysts.](image)

Takemoto and co-workers reported that the 3,5-bis(trifluoromethyl) phenyl group improved yield and stereoselectivity in the series of thiourea catalysts 79-81, when applied to the enantioselective addition of diethyl malonate 78 to \textit{trans}-\textbeta-nitrostyrene 77.\textsuperscript{54,55} They reported that the yield and stereoselectivity improved as the acidity of the thiourea NH protons increased from 79 through to 81. (Scheme 18)

![Scheme 18: (a) catalyst 79-81 (0.1 equiv.), toluene, rt, 48 h.](image)

Ellman and co-workers reported the synthesis of a class of ureas and thioureas containing chiral \textit{N}-sulfinyl substituents as auxiliaries.\textsuperscript{56} They prepared a range of organocatalysts in which the electron-withdrawing nature of the \textit{N}-sulfinyl group provides the necessary acidification, while concurrently installing a stereogenic center adjacent to the active
site of the catalyst. A comparison of the pKa values of these compounds indicated a $10^2$–$10^3$ fold increases in the acidity of $N$-sulfinylthioureas 85 and 86 when compared with the corresponding 3,5-bis(trifluoromethyl)phenyl substituted analogues 83 and 84. (Figure 9)

![Diagram of compounds](image)

**Figure 9:** $N$-Sulfinyl substituents as chiral acidifying groups

They reported that the $N$-sulfinylurea catalysts 89 and 90 were used in the stereoselective aza-Henry reaction between the aromatic $N$-Boc imine 87 and nitroethane 88 to give 91. It was reported, that the urea 89 was the best catalyst leading to 91 in 95% ee with a 95% conversion over 32 hours.\(^{56}\)

![Scheme of reaction](image)

**Scheme 19:** (a) Catalyst 89 or 90 (0.1 equiv.), tPrNEt (0.5 equiv.), MeCN, -40 °C, 32 h.

Smith and co-workers studied the effects of structural alteration on their urea-activated thiourea in an HBD catalyses Mukaiyama–Mannich reaction between ketene 92 and both aliphatic and aromatic imines 93, leading to 95 and found that a 1,2-\textit{trans-}diaminopyrrolyl substituent was most the effective substituent.\(^{57}\) (Scheme 20).
In a more recent example, Jin et al. reported the use of L-proline-urea bifunctional organocatalysts, which were applied to the Michael addition of dithiomalonates 97 to trans-$\beta$-nitroolefins 96. Using catalyst 98, the reaction gave high yields of 99 (88-99%) with high ee’s (86-97% ee) over 12 examples. (Scheme 21).

A catalytic diastereoselective Mannich reaction promoted by chiral bifunctional urea-type organocatalysts has also been reported. Treatment of $N$-Boc-3-ketoproline 100 with $N$-Boc-aldimines 101 using catalyst 102a,b gave the proline derivatives 104a and 104b with a selectivity of up to 73% ee in 68% yield. (Scheme 22) The transition state shown in (Figure 10) was proposed in which the catalyst deprotonates the $\beta$-ketoester as well as forming a hydrogen-bonded intermediate with both reactants.
Scheme 22: (a) catalyst 102a,b (0.2 equiv.), DCM/THF/ACN/Toluene, 20 °C, 36 h; 
R₁ = Ph, 4-NO₂-C₆H₄, 4-CF₃-C₆H₄, 4-Cl-C₆H₄, 4-F-C₆H₄, 2-furyl, 2-benzofuryl.

1.5 Counterion catalysis.

Jacobsen recently developed a conceptually novel form of organocatalytic activation that directs highly enantioselective additions into transiently generated N-acyl-iminium ions and oxocarbenium ions. In this system, chiral thiourea catalysts, which are known to form strong complexes with halide ions, electrostatically bind to, and ionise weak ions to generate transient ion pairs. The resultant anionic catalyst–chloride complex functions as a chiral counter-ion, biasing the approach of nucleophiles to a single face of the intermediate cationic species. These results are remarkable in that forces acting through space, rather than through bonds, are sufficient to transfer stereochemical information from the catalyst to the substrate. Jacobsen reported that the thiourea 107 catalysed the enantioselective substitution of silyl ketene acetal 106 onto 1-chloroisochromans 105 to give 109 in good yields and ee’s. The mechanism of this reaction involves anion binding by the chiral catalyst to generate a reactive oxocarbenium ion 108. Catalysts bearing tertiary benzylic amide groups afforded highest enantioselectivities with the optimal structure derived from enantioenriched 2-arylprrrolidine derivatives (Scheme 23)
Scheme 23: (a) i) BCl$_3$, DCM, 0 °C to rt, 6-22 h; ii) Catalyst 107 (0.01 equiv.), - 78 °C, TBME ; R = H, 5-Me, 6-Me, 7-Me, 6-F, 6-OMe. Ar = 2-methyl-5-phenyl-pyrrole

1.6 Organocatalysts containing the guanidine functional group.

1.6.1 Guanidine

The guanidine functional group and the protonated guanidinium ion is a common motif found in many naturally occurring compounds, with the most obvious example being the amino acid arginine 110, which is ubiquitous in protein structures. The motif is common to many heterocyclic natural products, for example in nucleic acids as the base guanine 111 and also in terrestrial and marine natural products, such as mirabilin 112. The guanidine and guanidinium functional groups hold a key role in many biological processes. This is due to their capability to take part in strong hydrogen bonding interactions with both carboxylate and phosphate ions, as well as with the complementary base cytosine in the case of guanine and with other oxygen and nitrogen containing functional groups. (Figure 12).

Figure 12: Some natural products containing the guanidine functionality.
Guanidine 113 consists of a central carbon bound to three nitrogen atoms and forms a Y-shaped functional group, which on protonation gives the delocalised cationic guanidinium ion 114-116. This delocalisation of the positive charge to each of the nitrogen atoms stabilizes the positive charge (Figure 13).\(^65\)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH} \quad \text{H}_2\text{N} \\
\begin{array}{c}
\begin{array}{c}
\text{113} \\
\text{114} \\
\text{115} \\
\text{116}
\end{array}
\end{array}
\end{align*}
\]

**Figure 13:** Guanidine and the guanidinium cation.

Due to the high stability of the conjugated acid of guanidine 113, the pK\(_a\) value of guanidine is uncommonly high, and has been determined as 12.5 in water, (20.6 in acetonitrile), which is considerably more basic that common amines.\(^66\) Several synthetic guanidine bases have pK\(_a\) values as high as 19-26, and are referred to as organic superbases; these bases remain protonated over a wide pH range. (Figure 14)\(^65,67,68\) There are several definitions of the term “superbase”, one of the oldest of which was introduced by Caubere, who proposed that this term would be kept for describing a base that consists of the sum of two or more bases which form a new basic species with inherent characteristics not found in its parts.\(^69\) A more recent definition by Ishikawa defines a superbase a non-ionic robust amine derivative with equivalent to or a higher to that of the proton sponge (1,8-bis(dimethylamino)naphthalene; DMAN) 121 (Figure 14).\(^70\)

\[
\begin{align*}
\text{117} & \quad \text{118} & \quad \text{119} & \quad \text{120} & \quad \text{121} \\
\text{DBN} & \quad \text{TMG} & \quad \text{TBD} & \quad \text{MTBD} & \quad \text{DMAN} \\
pK_a 23.4 & \quad pK_a 23.37 & \quad pK_a 26.03 & \quad pK_a 25.49 & \quad pK_a 18.62
\end{align*}
\]

**Figure 14:** pK\(_a\) values (in acetonitrile) of (DMAN) and guanidine superbases.
1.6.2 Guanidines and the guanidine motif in organocatalysts.

The basicity of guanidine and the ability of the guanidinium ion to undergo hydrogen-bonding interactions has resulted in the use of guanidines as both basic catalysts but also as motifs for hydrogen bonding interactions with anions in organocatalysis.

An early use of chiral guanidines in asymmetric catalysts was the report by Najera et al. of the asymmetric nitro-aldo (Henry) reaction.\textsuperscript{71} They reported the nitro-aldo reaction took place with good chemical yields especially using the chiral guanidine \textit{123}, providing enantiomeric excess up to 54%. A bifunctional catalytic model was suggested to rationalize the observed enantioselection in which the guanidine deprotonates an active hydrogen from the nitroalkane to form a guanidinium cation. It would then bind the nucleophile in a dual hydrogen-bonding manner \textit{124}.

\begin{center}
\textbf{Scheme 24:} (a) Catalyst \textit{123} (0.1 equiv.), -65 °C to rt, 9-72 h; THF, R = Bu, Ph.
\end{center}

Following this work, in 2005 Nawasaga et al. designed the novel bifunctional catalyst \textit{127} bearing guanidine and thiourea moieties within the same molecule.\textsuperscript{72,73,74} This was found to catalyze the reaction of nitromethane \textit{88} with \(\alpha\)-branched aldehydes \textit{126} giving the product \textit{128} in up to 88% ee.

\begin{center}
\textbf{Scheme 25:} (a) Catalyst \textit{127} (0.1 equiv.), PhMe/H\(_2\)O (1:1), KOH, KI, 0 °C, 5-45 h. R = cyclopentyl, 2,2-dimethylpropanyl, isopentenyl, 2-ethyl-2-methylbutan-yl, ethylbenzene.
\end{center}
Following on from this work, both Nájera et al.\textsuperscript{75} and Park et al.\textsuperscript{76} independently reported the use of bifunctional 2-aminobenzimidazole-derived as HBD scaffolds in 2009 as efficient catalysts for the conjugate addition of malonates to nitroolefins. Following this Nájera reported the trans-cyclohexane-1,2-diamine-derived benzimidazole scaffold 130 gave high levels of enantiocontrol in Michael addition of dimethylmalonate 129 to the nitrostyrene 77, whilst Park 131 obtained slightly better yields and enantioselectivity. (Scheme 26)

\begin{align*}
\text{Ph} & \xrightarrow{\text{MeO}_2\text{C} & \text{CO}_2\text{Me}} \text{NO}_2 \\
\text{129} & \quad \text{(a) or (b)} \\
\text{132} & \quad 89\% \ (95\% \ ee) \\
\text{133} & \quad 99\% \ (97\% \ ee)
\end{align*}

**Scheme 26:** (a) Catalyst 130 (0.1 equiv.), CF\textsubscript{3}CO\textsubscript{2}H (0.1 equiv), toluene, 23 °C, 48 h.  
(b) Catalyst 131 (0.02 equiv.), DCM, -20 °C, 40 h.

Takemoto and co-workers have capitalised on covalent intramolecular activation of HBDs in their design of catalyst scaffolds containing electron-withdrawing group bridges that link the HBD functionalities to their parent aryl substituents.\textsuperscript{77} They reported the two HBD catalyst scaffolds that displayed enhanced activity, firstly the quinazolines 136a-e, with a carbonyl linker which when compared with thiourea 137 or urea 138, provided better or comparable yields and much higher enantioselectivity in the α-hydrazination of α-keto ester 139. (Scheme 27)\textsuperscript{77}
Scheme 27: (a) Catalyst (0.1 equiv.), toluene, 23 °C, 5 h,  
136a-e: R = H, 8-F, 7-F, 6-F, 5-F.

Takemoto also reported that the benzothiadiazine 141a, with a sulfonyl linker a dynamic kinetic resolution process that gave (S)-allenoate 142 from racemic alkynoate 140. (Scheme 28)\(^7\) This reversible probably occurs via a catalyst-facilitated, facial-selective protonation of a (Z)-enol formed in situ. When quinazoline 136a was employed, it was found to be inferior the “unlinked” bifunctional thiourea 137, however benzothiadiazine 141a was the optimal catalyst leading to 142 in high yield (91%) and in 96% ee.

Scheme 28: (a) Catalyst (0.1 equiv.), 60 °C, DCM, 168 h.

Takemoto further reported an asymmetric intramolecular oxa-Michael reaction of substrate 143 catalysed by benzothiadiazines 141a and 141b giving excellent yields and enantioselectivity 144. (Scheme 29)\(^79,80\)
Shubina later reported that the guanidine derived chiral thiourea 146 catalysed the asymmetric nitro-Michael addition of dialkyl malonate 145 to trans-$\beta$-nitrostyrene 77, giving high yields (up to 96%) of adduct 147 but with quite low enantioselectivities. (Scheme 30) The authors reported computational studies, which indicated that the poor enantioselectivity was due to high catalytic activity twinned with high conformational flexibility of the catalyst, which led to thermodynamic control in the formation of the reaction products. Similar applications of 146 in asymmetric Henry reactions gave good yields but no appreciable enantioselectivity. 

In 2012, Tang et al. prepared a range of novel aminoimidazole derived L-proline derived organocatalysts 149-154 and applied them to aldol reactions. Of these compounds the catalyst 152 was the most successful which was catalytic in the presence of an appropriate acid (succinic acid, AcOH, CF$_3$COOH, CF$_3$SO$_2$OH or HCl) which serves to control and activate the acceptor carbonyl group 9. Under optimized reaction conditions using catalyst 152 (0.1 equiv)/TFA (0.1 mol of TFA)/H$_2$O/EtOAc) a high yield (86%) and an ee of 98% was achieved for the product 156. The reaction is thought to proceed via the intermediate enamine

Scheme 29: (a) Catalyst 141a or 141b (0.1 equiv.), 23 °C, DCM, 24 h.

Scheme 30: (a) Catalyst 146 (0.2 equiv.), toluene, rt; R = Me, 120 h; R = OEt, 2 h.
in which the protonated guanidine, hydrogen bonds with the incoming aldehyde and directs
the reaction of the enamine in the transition state. (Scheme 31)

\[
\begin{align*}
\text{O} & + \text{CHO} \\
\text{148} & \rightarrow \text{CHO} \\
\text{9} & \rightarrow \text{O}_2 \text{N} \text{HO} \text{O} \\
156 &
\end{align*}
\]

Scheme 31: (a) Catalyst (0.01-0.1 equiv.), acid catalyst (0.01-0.05 equiv.), Solvent (DMSO, EtOAc, MeOH, DCM, THF or H\textsubscript{2}O), rt, 18-72 h.

J. Lin et.al reported the synthesis of a four similar L-proline derived pyrrolidine-aminobenzimidazoles 152-(157-159)\textsuperscript{83} and applied these to the Michael reactions of cyclohexanone 148 with several nitroolefins 77 in brine. High enantioselectivities (89-99% ee), yields (80-93%) and diastereoselectivities (to 88-99/1) were observed for catalyst 157. (Scheme 32)

\[
\begin{align*}
\text{O} & \rightarrow \text{Ar} \text{NO}_2 \\
\text{148} & \rightarrow \text{160} \\
\text{Ar} & \text{NO}_2
\end{align*}
\]

Scheme 32: Conditions (a) Catalyst 152-(157-159) (10 mol %), p-methoxybenzoic acid (10 mol %), brine, rt (25 °C) and 7-10 h.
1.7 Conclusion

As can be seen there are a significant number of reports of the use of guanidine and guanidinium containing compounds in organocatalysis and some other related examples not reported here are known.\textsuperscript{84} These have shown some success, however excessive complexity in their structures has led to limited applicability in general catalysis. The Murphy research group has studied some aspects of the use of guanidines in catalysis and a summary of this work will form the basis of the next chapter.
1.8 Previous work with guanidine catalysts in the Murphy research group.

Early work within the group focused on the synthesis and use of \( \text{C}_2 \)-symmetric guanidinium salts such as 162. These catalysts were studied in a variety of reactions with mixed success. Initial studies focused on the asymmetric Henry reaction between nitromethane 88 and isovaleraldehyde 161, which gave \((R\)-163 in 52% yield and in 20% ee. (Scheme 33)\(^{85}\)

\[
\begin{align*}
\text{HO} & \quad \text{O}_2\text{NCH}_3 \\
161 & \quad 88 \\
\text{Catalyst 162 (0.1 equiv.), NaOMe (0.09 equiv.), MeOH, 30 min then remove solvent; ii) CCl₄, rt, 88, 161, 16 h.}
\end{align*}
\]

Scheme 33: (a) i) Catalyst 162 (0.1 equiv.), NaOMe (0.09 equiv.), MeOH, 30 min then remove solvent; ii) CCl₄, rt, 88, 161, 16 h.

Following this, success was achieved in the phase transfer epoxidation of chalcones 164 using alkali metal hypochlorites, which gave epoxides 165 in 85-94% ee. (Scheme 34)\(^{86}\)

\[
\begin{align*}
\text{R}^1\text{C=O} & \quad \text{R}^2 \\
164 & \quad 162 \\
\text{Catalyst 162 (0.1-0.025 equiv.), MOCl (aq), toluene, 16-72 h, 0 °C-rt; M = Li, Na, K; R^1, R^2 = Ph, C_6H_{13}, 4-(Cl)-Ph}
\end{align*}
\]

Scheme 34: (a) Catalyst 162 (0.1-0.025 equiv.), MOCl (aq), toluene, 16-72 h, 0 °C-rt; M = Li, Na, K; \( R^1, R^2 = \text{Ph}, C_6H_{13}, 4-(\text{Cl})-\text{Ph} \)

Similarly, phase transfer benzylaion of the glycinate Schiff’s base 166 with benzyl bromide in dichloromethane with gave 167, which was obtained as the \( R \)-enantiomer in 86% ee. \(^{86}\)
Scheme 35: (a) Catalyst 162 (0.1 equiv.), NaOH (2 M), BnBr (2 equiv.), DCM, 16 h, 0 °C-rt.

Guanidinium salt 162 (as its BPh$_4^-$ salt) was also investigated as a catalyst for the Michael addition reaction of 2-hydroxy-1,4-naphthoquinone 168 with trans-$\beta$-nitrostyrene 77 and was found to be an effective catalysts especially in the presence of L-proline 2. It was observed that the two substrate molecules 168 and 77 which were unreactive on combination in THF were slowly converted to the product 170 in the presence of catalyst 162 with a T$_{1/2}$ of 465 h. The reaction was also catalysed by L-proline with a T$_{1/2}$ of 579 h in THF, which was slightly slower than 162. However if the two catalysts 162 and L-proline 2 were used in combination the reaction proceeded with a T$_{1/2}$ of 80 h. Unfortunately no appreciable enantioselectivity was observed in any of the catalysed reactions which again, might be attributed to the site of reaction being too far removed from the point of asymmetric induction within the proposed intermediate 169. (Scheme 36, Figure 17)$^{86}$

Scheme 36: Catalysed Michael additions;
Conditions (a) Catalysts (0.05 equiv.), THF.
1.9 Guanidine-Proline catalysts

Following this work, we put forward a proposal to incorporate a guanidine, a basic group and a chiral amino acid into a single molecule. We felt that incorporating an N-alkylated-L-proline as the base and chiral group together with a substituted guanidine into the same catalyst would offer several desirable features (generalised structure 171). These catalysts could be “tuned” by the nature of the R1 groups on the non-amide nitrogens, leading to some measure of electronic and hydrogen bonding control which might occur for example with a nitroalkene (structure 174). Protonation of the catalysts, either during deprotonation or by the addition of acid, might result in a range of possible structures in which one might imagine protonation at the proline nitrogen 172 or at the guanidine 173. This could lead to a range of intramolecular hydrogen bonding patterns and offer more flexibility of reactions. It was hoped that these catalysts would lead to the formation of rigid intermediate H-bonded adducts and thus enable stereospecific reactions to be achieved. The catalysts were modelled on a L-proline scaffold as this appears to be one that has been successfully applied to a range of other successful catalytic processes. Furthermore, modification at the nitrogen of the L-proline R-group could offer control over steric factors encountered in any potential reactions.

![Proposed catalyst 171](image)

**Figure 18:** Proposed catalyst 171.

Thus a range of L-proline derived guanidines 176-179 (Figure 19) were prepared and investigated in a nitrostyrene Michael reaction.97 These compounds were from the corresponding N-alkylated-L-proline 175a-d and the corresponding guanidines, which were coupled using CDI in DMF. (Scheme 37)
Scheme 37: Preparation of catalysts 176-179: Conditions: (a) i) 175a-d, CDI, DMF, 0 °C; ii) guanidine species, rt. R = (a) Me, (b) Bn, (c) iPr (d) Cy.

The best catalysts for the Michael addition of hydroxyquinone 168 to 2-nitrostyrene 77 were 176a, 178a and 179a (all R = Me) with ee’s in the range of 7-44% ee. (Figure 20) The best solvents for these processes was dichloromethane or toluene, which gave 21-44% ee, whilst reaction time was typically slow (39-100 h) apart from one example (178a, R = Me in dichloromethane), which proceeded in 4 h. The reactions all gave moderate to high yield (50-99%). Interestingly catalysts with the more bulky benzyl group (PhCH₂-), isopropyl ((CH₃)₂CH-) or cyclohexyl (Cy-) gave appreciably lower selectivity leading to the conclusion that increasing steric bulk at the N-substituent was detrimental to catalyst efficiency.

Figure 20: Michael reaction catalysed by 176a, 178a and 179a.

Conditions, - 20 °C - rt, 4-100 h
1.10 Conclusion.

As described in the examples reviewed above, the research area of asymmetric catalysis using a variety of organocatalysts has been growing rapidly since the beginning of the 20th century. The main feature of these compounds is their ability to effect transformations in the absence of transition metals. Organocatalysis has several advantages over traditional transition metal based chemistry, for example, the high efficiency in the C-C bond forming reactions, especially those forming enantiomerically enriched molecules. Additionally, these molecules offer simplicity in handling and catalyst recovering, with the potential for easy of catalyst design to tailor them to specific substrates. From our perspective, the guanidine motif is interesting in so much as it can act as both a base to remove a proton and then once deprotonated as an acid site for coordination of the anionic species formed. In addition, the basicity of the guanidine can be lowered by the addition of acyl containing substituents, which will lead to a similar behaviour (acidic) to that observed in thioureas or ureas. Within this project, we hope to prepare a range of homochiral-substituted guanidine, which are simplistic in nature and are easily prepared, and to investigate their application to enantioselective transformations.

1.11 Aims of this study.

The group previous work in catalytic reactions involving guanidines and guanidinium salts has met with mixed results in that the reactions of the $C_2$-symmetric guanidinium salt work well in phase transfer reactions, however their use in other base mediated reactions was shown to be limited. The reasons behind this are unclear but it is likely that the site of reaction at which enantioselectivity is determined might be too distant from the chirality present in the bases. Additionally, the catalysts are complex in nature and require several non-trivial synthetic steps to prepare.

We wished to develop homochiral catalysts and the previous work\textsuperscript{85,86} on the catalysts 162 has given some initial success but ee’s obtained are low as are rates of reaction in some cases. In this work we strived to have a simplistic approach to catalyst design focusing on easily available L-proline derivatives and tried to adapt simplistic structural elements into these catalysts to minimise the potential for “over engineering” to minimise cost and maximise applicability if successful. With the original work in mind we initially wanted to embark on the preparation of a second generation of $C_2$- (really pseudo-$C_2$) catalysts with the general structure 180. (Figure 21)
The nature of the structure 180 might offer a simple method for the control of the steric nature of the active part of the catalyst via the R-groups and some control over the electronic nature of the reaction by modifying the nature of the R$^1$-groups to increase or decrease the acidity of the central guanidine functional group. Initial work will focus on the preparation of some sterically varied compounds 182-185 and their application to the previously studied nitro-Michael reaction to give 170.

Scheme 38: Proposed second-generation catalysts 182-185. (a) Catalyst 182-185, Solvent.

The possibility of a third-generation of catalysts exists in which the catalyst is tetra-substituted to give the guandine 186. These catalysts will require protonation to become active in a bidentate co-ordination mode, which might possibly be the structure 187 or more
Interestingly structure 188, in which the proton on the L-proline is associated with the guanidine and might suggest a more ordered intermediate.

![Chemical structure](image)

**Figure 22:** Third generation catalysts 187 and 188.

Whilst the preparation of the second- and third-generation catalysts was the main goal of the initial work, during the course of this project we also investigated the synthesis of several related L-proline derived catalysts, as well as various heterocyclic substituted catalysts. We also performed various mechanistic studies related to the catalysts prepared by previous workers. The remainder of the thesis will discuss the preparation of these catalysts and their use and will not be in chronological order, but will follow the general order:

i) Preparation of catalysts studies.

ii) Discussion of enantioselective reactions attempted.

iii) Mechanistic and X-ray crystallographic studies.

iv) Conclusions and further work.
Chapter 2: Results and Discussion.

As stated previously, the initial aim of this project was to prepare a range of $C_2$-symmetrical catalysts and to study their application to asymmetric transformations. It was intended to study the Michael reaction between $\beta$-nitrostyrene 77 with 2-hydroxy-1,4-naphthoquinone 168 which in the presence of a catalyst should lead to the formation of the adduct 170. (Scheme 39) The preparation of these and other catalysts is discussed in this chapter, which also details the successes and the problems encountered in this investigation.

![Scheme 39: Michael reaction between $\beta$-nitrostyrene 77 and 2-hydroxy-1,4-naphthoquinone 168.](image)

2.1 Preparation of $N$-substituted amino acids.

The first requirement was to prepare $N$-methyl-L-proline 175a, which is a key compound in these investigations and was achieved using a literature method.\(^8\) Thus L-proline 2 was dissolved in methanol with aqueous 40% formaldehyde under hydrogenation conditions using 10 % Pd/C. After 24 h, filtration of the reaction through a Celite© pad gave on evaporation the desired compound 175a as a white crystalline solid in 99% yield. Analysis of the proton NMR spectrum of the product illustrated the presence of a diagnostic singlet at $\delta_H$ 2.75 (3H, s, Me) ppm which indicated the incorporation of the methyl group. The compound had the desired melting point (142-144 °C, 143-144 °C lit.) and specific rotation ($-74.7$ (c = 2.00, MeOH); Lit. –78.0 (c = 2.0, MeOH)).\(^8\) (Scheme 40)

![Scheme 40: (a) CH$_2$O (40%, aq), H$_2$, 10% Pd/C, MeOH, 24 h.](image)

The next precursor $N$-benzyl-L-proline 175b was prepared in a different manner, by the dropwise addition of BnCl 189 to a solution of 2 and KOH in iPrOH at 40 °C over 3 h. After
stirring for a further 6 h the reaction was then neutralised with HCl to pH 5-6 then stirred overnight. The product was removed by filtration and washed with chloroform to give 175b in 46% yield. This compound had spectroscopic and specific rotation data in agreement with the literature.89 (Scheme 41)

Scheme 41: (a) 189, KOH, iPrOH, HCl, 40 °C, 20 h.

N-Isopropyl-L-proline 175c was prepared by the hydrogenation of L-proline 2 in the presence of acetone over Pd/C. After stirring for two days, work up gave 175c as a crystalline yellow solid in 95% yield, which had spectroscopic and specific rotation data in agreement with the literature.(Scheme 42)90

Scheme 42: (a) acetone, H2, 10% Pd/C, rt, MeOH, 24 h.

We next prepared N-cyclohexyl-L-proline 175d, using cyclohexanone 148 under the same conditions used to prepare 175a.91 In our hands, this reaction proceeded in 96% yield to give the desired compound 175d as a yellow crystalline solid. Analysis by proton NMR gave a signal at δH 3.74-3.69 (1H, m, CH) ppm corresponding to the methine of the cyclohexane adjacent to the proline nitrogen. The compound had a melting point of 178 °C and an specific rotation of -36.5 (c = 2.8, MeOH) but unfortunately no literature data is reported. (Scheme 43).

Scheme 43: (a) 148, H2, MeOH, 10% Pd/C, 24 h.
$N,N$-dimethyl-L-alanine 191 was similarly prepared by the hydrogenation of L-alanine 190 in the presence of an aqueous 40% formaldehyde over 10% Pd/C. This reaction proceeded in 69% yield to give the desired compound 191 as a white crystalline solid. Analysis by proton NMR gave a signal at $\delta_H$ 2.84 (6H, s, 2 $\times$ Me) ppm corresponding to the dimethylamine group. The compound had a melting point of 185 °C and an specific rotation of $[\alpha]_D^{23}$ +8.3 (c = 8; H$_2$O), which was in agreement with literature data. (Scheme 44)

Scheme 44: (a) CH$_2$O (40%, aq), H$_2$, 10% Pd/C, MeOH, 24 h.

$N,N$-dimethyl-L-phenylalanine 193 was similarly prepared by the hydrogenation of L-phenylalanine 192 in the presence of an aqueous 40% formaldehyde over 10% Pd/C. After work up, the crude product was recrystallized from EtOH to give the desired compound 193 as a white crystalline solid in 85% yield. Analysis by proton NMR gave a signal at $\delta_H$ 2.83 (6H, s, 2 $\times$ Me) ppm corresponding to the dimethylamino group, whilst the melting point (214-216 °C) and specific rotation data ($[\alpha]_D^{23}$ +76.8 (c = 1.98; H$_2$O)) were in good agreement with the literature values. (Scheme 45)

Scheme 45: (a) CH$_2$O (40%, aq), H$_2$, Pd/C, MeOH, 24 h.

$N,N$-dimethyl-L-valine 195 was also prepared in a similar manner to give 195 in 98% yield. Analysis by proton NMR gave a signal at $\delta_H$ 2.83 (6H, s, 2 $\times$ Me) ppm corresponding to the dimethylamino group, whilst the melting point (148-150 °C) and specific rotation data (34.9, c = 1; MeOH) are in good agreement with the literature values. (Scheme 46)

Scheme 46: (a) CH$_2$O (40%, aq), H$_2$, 10% Pd/C, MeOH, 24 h.
We also prepared \( N,N \)-dibenzylglycine \( \textbf{197} \) by conversion of glycine \( \textbf{196} \) to its Schiff’s base with benzaldehyde under basic condition and in situ reduction of the imine formed with NaBH\(_4\). The step was repeated with the addition of excess benzaldehyde and NaBH\(_4\) reduction again. Isolation of the product was achieved by neutralisation to pH 6.5, which on standing gave \( \textbf{197} \) in 59\% yield as a white precipitate with a melting point of 192-194 °C (lit.\(^{96} \) 200 °C). \(^1\)H NMR data for \( \textbf{197} \) gave diagnostic signals at \( \delta_H \) 7.42 (10H, s, CH), 3.90 (4H, s, CH\(_2\)) and 3.14 (2H, s, CH\(_2\)) ppm.\(^{96}\)

![Diagram of reaction](image)

**Scheme 47:** (a) i) PhCHO, NaOH (10 M), 30 min; ii) 0 °C, NaBH\(_4\), 3h; iii) pH 6.5

2.2 Preparation of catalysts.

With the required amino acids available, we proceeded onto the coupling of these compounds with the desired substituted guanidines. In previous cases\(^{97}\) carbonyldiimidazole (CDI) \( \textbf{199} \) was used as the amino acid activating agent as this has been shown to be an effective peptide-coupling reagent. It was intended that by varying the stoichiometry of the reaction the preparation of either singularly \( \textbf{201} \) or doubly \( (C_2) \) \( \textbf{202} \) derived guanidines. Would be achieved (Scheme 48)

![Diagram of catalyst synthesis](image)

**Scheme 48:** Schematic plan for catalysts synthesis. Conditions
(a) \( \textbf{199} \), DMF; (b) substituted guanidine; (c) guanidine. \( R = \text{H, alkyl, aryl, acyl} \).
2.2.1 Preparation of the C₂-symmetric L-proline catalysts.

With the amino acid derivatives available, we embarked upon the synthesis of the disubstituted C₂-symmetric catalysts. We initially reacted N-benzyl-L-proline 175b with CDI 199 in DMF for 16 h, whilst in a separate flask, NaH was suspended in dry DMF and half an equivalent of guanidinium chloride was added. After stirring for 1 h the activated proline solution was transferred into this flask via cannula and the mixture stirred for 48 h. After aqueous work up and silica gel chromatography the catalyst 183 was obtained in 79% yield as a white solid. (Scheme 49)

![Scheme 49](image_url)

Scheme 49: (a) i) CDI, DMF, 24 h; ii) guanidine.HCl (0.5 equiv.); NaH, 1 h; iii) combine.

The analytical data obtained for 183 confirmed its structure. The compound gave a negative specific rotation value of [α]D²⁰ -83.3 whilst the proton NMR spectrum gave a signal at δH 8.17-11.43 (3H, br s, 3 × NH) ppm for the guanidine NH protons and a complex multiplet at δH 7.19-7.39 (10H, m, 2 × Ph) ppm for the aromatic protons. The benzyl methylene was observed as two signals at δH 3.86 (2H, d, J 12.8 Hz, 2 × CH) and 3.61 (2H, d, J 12.8 Hz, 2 × CH) ppm, whilst a signal at δH 3.22 (2H, dd, J 9.7, 5.9 Hz, 2 × CH) ppm was obtained for the two proline ring methine protons. Other signals belonging to the proline ring were observed at δH 3.11-3.15 (2H, m, 2 × CH), 2.38-2.44 (2H, m, 2 × CH), 2.17-2.28 (2H, m, 2 × CH), 1.91-2.02 (2H, m, 2 × CH), and 1.76-1.90 (4H, m, 2 × CH₂) ppm. The ¹³C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon in the proline ring appearing at δC 68.9 ppm. Analysis by high resolution mass spectrometry gave a mass of 434.2540 Daltons, which is in close agreement with the theoretical mass of 434.2551 Daltons, required for [C₂₅H₃₂N₅O₂]⁺ corresponding to [M+H]⁺. An X-ray structure was also obtained for 183 (vide infra).

Similarly the isopropyl catalyst 184 was prepared by reacting N-isopropyl-L-proline 175c with CDI in dry DMF over 24 h at rt. Separately NaH was suspended in dry DMF and half an equivalent of guanidinium chloride was added and after stirring for 1 h the activated proline solution was transferred into this flask via cannula and the mixture stirred for 48 h.
After aqueous work up and silica gel chromatography the catalyst 184 was obtained in 93% yield as an off-white solid. (Scheme 50)

![Scheme 50](image)

**Scheme 50:** (a) i) CDI, DMF, 24 h; ii) Guanidine.HCl (0.5 equiv.), NaH, 1 h; iii) combine.

Analysis of the proton NMR spectrum of 184 in CDCl₃ gave a broad signal at δH 10.22-12.70 (1H, br s, NH) and 8.05-10.22 (2H, br s, 2 × NH) ppm for the guanidine NH protons. Signals at δH 3.25-3.28 (2H, m, 2 × CH) and 2.70-2.80 (2H, m, 2 × CH) ppm corresponded to the methine protons of the proline ring and the isopropyl groups, respectively. The remaining signals for the proline ring were at δH 3.04-3.16 (2H, m, 2 × CH), 2.46-2.52 (2H, m, 2 × CH), 2.00-2.10 (2H, m, 2 × CH), 1.83-1.94 (2H, m, 2 × CH), and 1.64-1.77 (4H, m, 2 × CH₂) ppm whilst the dimethyl signal was observed as a doublet at δH 1.01 (12H, d, J 6.4 Hz, 4 × Me). The ¹³C NMR spectrum gave the required 10 non-equivalent signals with the methyl carbons in the isopropyl group appearing as two signals at δC 21.2 and 19.9 ppm, whilst the two methine carbons of the proline and isopropyl groups appeared at δC 64.9 and 53.0 ppm respectively. Analysis by mass spectrometry gave an ion 338.3 (M+H⁺) which gave an accurate mass of 338.2553 Daltons which corresponded closely to the required mass of 338.2551 Daltons required for [C₁₇H₃₂N₅O₂⁺]⁺ ([M+H⁺⁺]).

We applied the same synthetic method to the preparation of the cyclohexyl containing catalyst 185 from N-cyclohexyl-L-proline 175d. Following the standard procedure led to a good chemical yield of the impure compound after work-up, however attempted purification by column chromatography was problematic, as there appeared to be a minor contaminant in the majority of the fractions obtained. Despite this, we obtained a 16 % yield of pure 185 and a 46 % yield of 95 % impure material, which we attempted to purify by recrystallization without success. (Scheme 51)
Scheme 51: (a) i) CDI, DMF, 24 h; ii) Guanidine. HCl (0.5 equiv.), NaH, 1 h; iii) combine.

Analysis of the proton NMR spectrum of the product illustrated the presence of a broad singlet signals at $\delta_H$ 10.44-12.71 and 8.26-10.44 ppm corresponding to NH of the guanidine. A signal as double of doublets was observed at $\delta_H$ 3.37 (2H, dd, $J$ 10.3, 3.2 Hz, 2 × CH) ppm corresponding to the methine protons of the proline rings together with a signals at $\delta_H$ 3.15-3.25 (2H, m, 2 × CH) ppm for the cyclohexyl methine proton. Other signals belonging to proline and cyclohexyl rings were observed at $\delta_H$ 2.52-2.62 (2H, m, 2 × CH), 2.32-2.45 (2H, m, 2 × CH), 2.04-2.17 (2H, m, 2 × CH), 1.87-1.98 (4H, m, 4 × CH), 1.69-1.85 (10H, m, 10 × CH), 1.61 (2H, br d, $J$ 12.1 Hz, 2 × CH), and 1.03-1.31 (10H, m, 10 × CH) ppm. The $^{13}$C NMR spectrum gave 12 non-equivalent signals with the methine carbon in the proline ring at $\delta_C$ 65.3 ppm. Analysis by high resolution mass spectrometry gave a mass of 418.3168 Daltons which is in close agreement with the theoretical mass of 418.3177 Daltons required for [C$_{23}$H$_{40}$N$_5$O$_2$]$^{+}$ corresponding to M+H$^+$. An X-ray structure was also obtained for 185 (vide infra).

With the successful preparation of these three catalysts, we envisaged the preparation of the corresponding N-methyl substituted catalyst 182 to be relatively straightforward. We thus repeated the reaction as detailed above but were disappointed to observe only a low mass yield of material from the reaction. Analysis of this by NMR and TLC indicated that the composition of this material was mostly imidazole, which is a by-product of the coupling reaction and if any product was present it was in very low yield. We attempted to re-extract the aqueous layer of the reaction after saturating with salt in an attempt to recover any material but this was unsuccessful. It was possible that this reaction failed because of experimental error or possibly because of the higher polarity of the product leading to high water solubility. The reaction was therefore repeated under identical conditions, however the aqueous extraction was omitted and the reaction was freeze-dried instead. The crude product indicated a successful coupling (NMR) and purification was by column chromatography, however the product which was highly polar (Rf = 0.18 in 20% ME/CF) appeared to decompose on column chromatography as only a very low yield of impure material was obtained which was contaminated with the starting material 175a and imidazole 199. These results led to the
conclusion that an aqueous work up and chromatography are deleterious to purification of the catalyst 182 and in our hands this process was not successful.

![Chemical structures](image)

**Scheme 52**: (a) i) CDI, DMF, 24 h; ii) Guanidine. HCl (0.5 equiv.) NaH, 1 h; iii) combine.

As we intended to investigate the substitution pattern of the guanidine in these catalysts, we wished to prepare the N-substituted guanidine catalyst 204a from phenyl guanidinium nitrate 203. We thus reacted N-methyl-L-proline 175a under our standard conditions by activating it using CDI, followed by the addition of this activated ester to a solution of phenyl guanidine generated from its nitrate salt by treatment with sodium hydride. After hydrolysis and extractive work up and purification by column chromatography, it unfortunately gave only the previously prepared mono-substituted catalyst 178a in 27% yield as a pale yellow solid.

![Chemical structures](image)

**Scheme 56**: (a) (i) 175a, CDI, DMF, 4 h (ii) Add to 203 (0.5 equiv.) treated with NaH for 3 h, then rt, 2 d.

Repeating this reaction with excess NaH did not lead to the formation of the desired catalyst 204a a possibly indicating that the deprotonated guanidine 203 has low nucleophilicity or that the system is too sterically hindered or unreactive towards reaction with a second CDI activated amino acid. With the problems experienced with N-methyl-L-proline 175a, the preparation of the N-benzyl 175b, N-cyclohexyl 175c and the N-isopropyl-L-proline 175d derivatives were attempted as these had been successful with guanidine. Thus the required N-substituted-L-proline 175b-d, was activated using with CDI in dry DMF over 2-12 h. This
solution was added via cannula to a solution of phenyl guanidine (generated by reacting the nitrate salt of 203 with a slight excess of NaH in DMF for 1 h and the mixture stirred for 4-6 days. After work-up, purification by column chromatography again led only to the formation of previously prepared mono-substituted catalysts 178b-d.

![Scheme 54: Attempted preparation of 204b-d.](image)

(i) CDI, DMF, 24-72 h,
(ii) Add to 203 (0.5 equiv.) treated with NaH for 3 h, then rt, 2 d.

It was apparent that whilst phenyl guanidine is able to reaction with a single activated N-alkyl L-proline, the second substitution appears to be difficult. This might be due to steric hindrance or might be due to a lower nucleophilicity as the phenyl group is electron-withdrawing in nature and this combined with the acyl group might be sufficiently deactivating.

### 2.2.2 Preparation of L-proline derived catalysts

The preparation of a series of mono-substituted acyl derived guanidine similar in structure to those prepared previously was attempted. As the Cbz-substituted guanidine catalyst 176a was found to be the most successful from the previous study we wished to prepare the corresponding Boc-substituted catalyst 208. The required precursor 207 was prepared by the addition of a solution di-tert-butyl dicarbonate 205 in dioxane to a cooled solution of guanidine hydrochloride 206 and NaOH in water over 8 h. After stirring for 20 h, an extractive work up and recrystallization gave Boc-protected guanidine 207 as a white solid in 98% yield, which had spectroscopic data in agreement with the literature.101 (Scheme 55)

![Scheme 55: Preparation of N-Boc-guanidine 207: (a) NaOH, Dioxane, water, 28 h](image)
The Boc-protected guanidine 207 was coupled with N-methyl-L-proline 175a by activating with CDI coupling agent in dry DMF for 24 h, followed by the addition of guanidine 207. After 24 h, extractive work up and column chromatography gave 208 in 38% yield as a white solid. (Scheme 56)

Scheme 56: Preparation of 208: (a) (i) CDI, DMF, rt, 24 h; ii) 207, 2 d.

The analytical data obtained for 208 confirmed its structure. The compound gave a negative specific rotation value of [α]D 20 -46 whilst the proton NMR spectrum gave a signal at δH 8.21-10.03 (3H, br s, NH, NH2) ppm for the guanidine NH protons. The methine proton of the proline was observed as double doublet at δH 2.95 (1H, dd, J 10.5, 4.8 Hz, CH) ppm, whilst the N-methyl signal was observed at δH 2.31 (3H, s, Me) ppm, with the tert-butyl appearing at δH 1.46 (9H, s, 3 × Me) ppm. Other signals for the methylenes of the proline ring were observed at δH 3.00-3.07 (1H, m, CH), 2.30-2.38 (1H, m, CH), 2.15-2.26 (1H, m, CH), 1.79-1.89 (1H, m, CH) and 1.64-1.97 (2H, m, 2 × CH) ppm. The 13C NMR spectrum gave the required 10 non-equivalent signals with the methine carbon in the proline ring resonating at δC 69.0 ppm. Finally, analysis by mass spectrometry gave an ion 271.2 (100%) for [M+H]+, which on accurate mass measurement gave a mass of 271.1765 Daltons which was in exact agreement with the required mass of 271.1765 Daltons for C12H23N4O3+ ([M+H]+). An X-ray structure was also obtained for 208 (vide infra).

It was intended to study more highly substituted guanidines in these catalysts and in order to prepare the required substituted guanidines we prepared N-Boc-1H-pyrazole-1-carboxamide 210 by the reaction of 1H-pyrazole-1-carboxamidine hydrochloride 209 and di-tert-butyl dicarbonate 205 in present of N,N-diisopropylethylamine in THF. After stirring for 24 h, an extractive work up and recrystallization gave 210 as a white solid in 75% yield, which had spectroscopic data in agreement with the literature.98 (Scheme 57)
We next prepared \(N\)-methyl-\(N'\)-Boc guanidine \(211\) by reacting \(210\) with two equivalent of aqueous methylamine in THF. The reaction was monitored by TLC, which showed after 4 h there was starting material remaining, so a further equivalent of methylamine was added. After stirring for a further 24 h, TLC indicated that there was no starting material remaining and an extractive work up followed by recrystallization gave \(211\) as an off-white solid in an 82% yield. (Scheme 58)

Literature data were not available for \(211\)99 however the proton NMR spectrum gave a broad signal at \(\delta_H 5.93\) (3H, br s, 3 × NH) ppm for the guanidine NH protons, whilst the proline \(N\)-methyl signal was observed at \(\delta_H 2.85\) (3H, s, Me) ppm and the t-butyl signal was at \(\delta_H 1.47\) (9H, s, 3 × Me) ppm. The \(^{13}\)C NMR spectrum gave the required 4 non-equivalent signals with the methyl carbon in the guanidine appearing at \(\delta_C 27.7\) ppm. Finally, analysis by mass spectrometry gave an ion 174.1 (100%) for \([M+H]^+\), which on accurate mass measurement gave a mass of 174.1237 Daltons which in in very close agreement with the required mass of 174.1237 Daltons for \(C_7H_{16}N_3O_2^+\) (\([M+H]^+\)).

With \(211\) in hand, the catalyst \(212\) was prepared by treating \(N\)-methyl-L-proline \(175a\) with CDI in DMF for 24 h, followed the addition of \(211\), followed by stirring for 5 days. After an aqueous work up, trituration with diethyl ether gave the target product \(212\) in 94% yield as an off-white solid. (Scheme 59)
Scheme 59: Preparation of 212. (a) i) CDI, DMF, rt, 24 h; ii) 211, rt, 5 d.

The analytical data obtained for 212 confirmed its structure. The compound gave a negative specific rotation value of $\left[\alpha\right]_D^{18} -36.4$ whilst the proton NMR spectrum gave signals at $\delta_H 12.80$ (1H, s, NH), and $8.81$ (1H, s, NH) ppm for the guanidine NH protons. The methine proton of the proline was observed as a double doublet at $\delta_H 2.99$ (1H, dd, $J 4.6, 9.9$ Hz, CH) ppm. The $N$-methyl guanidine signal appeared as a doublet at $\delta_H 2.95$ (3H, d, $J 4.9$ Hz, CH$_3$) ppm, whilst the proline $N$-methyl and the t-Butyl groups were observed as singlets at $\delta_H 2.41$ (3H, s, Me) and $1.51$ (9H, s, $3 \times$ Me) ppm. Other signals for the proline appeared at $\delta_H 3.21$-3.28 (1H, m, CH), 2.36-2.44 (1H, m, CH), 2.16-2.29 (1H, m, CH), and 1.75-1.93 (3H, m, $3 \times$ CH) ppm. The $^{13}$C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon in the proline ring appearing at $\delta_C 69.5$ ppm. Finally, analysis by mass spectrometry gave an ion 285.2 (100%) for M+H$^+$, which on accurate mass measurement gave a mass of 285.1919 Daltons which in in very close agreement with the required mass of 285.1921 Daltons for C$_{13}$H$_{25}$N$_4$O$_3$+ ([M+H$^+$]). An X-ray structure was also obtained for 212 (vide infra).

We next investigated the synthesis of a $N,N$-dimethylguanidine catalyst 214 and prepared $N,N$-dimethyl-Boc-guanidine 213 by treatment of $N$-Boc-$H$-pyrazole-carboxamide 210 with excess (4 equivalent) aqueous dimethylamine in THF. The reaction was monitored by TLC and after 24 h there was some starting material remaining and so a further one equivalent of dimethyl amine was added. Again after a further 24 h, TLC indicated a trace amount of starting material remaining and a further one equivalent of dimethylamine was added. After another 24 hours, an extractive work up followed by column chromatography gave guanidine 213 as a white solid in 98% yield. (Scheme 60)

Scheme 60: Preparation of 213: (a) Me$_2$HN (aq., 6 equiv.), THF, 3d.
The formation of 213 was confirmed by NMR and incorporation of the dimethyl group was evident by a six hydrogen singlet at $\delta_H$ 3.01 (6H, s, 2 × Me) ppm and a nine hydrogen singlet at $\delta_H$ 1.49 (9H, s, 3 × Me) ppm corresponded to the Boc-protecting group. The $^{13}$C NMR spectrum displayed the expected 5 signals and the structure was confirmed by high resolution mass spectrometry which gave a mass of 188.1394 Daltons corresponding very closely to the calculated mass of 188.1393 Daltons for C$_8$H$_{18}$N$_3$O$_2$+ ([M+H]$^+$).

With 213 in hand, synthesis of the catalyst 214 was attempted. Thus, $N$-methyl-L-proline 175a was activated using CDI in dry DMF over 24 h following which 213 was added and the mixture stirred. The reaction was monitored by TLC, which indicated that no new product was evident after 3 days, a sample of the reaction was removed and subjected to an aqueous work up. Analysis by proton NMR indicted that coupling was not apparent and the remaining reaction mixture was heated to 40 °C for 2 days and on aqueous work up using K$_2$CO$_3$ (aq. 10%) gave a product which on analysis was composed of mainly the starting material 213. It was felt that the reason for the failure of this reaction was possibly due to the low nucleophilicity or steric factors associated with the dimethyl group in 213. Thus, the reaction was repeated in the presence of NaH, which it was thought might help deprotonate the guanidine and increase its reactivity. Unfortunately, this was also not successful and only recovered 213 was obtained on work-up. (Scheme 61)

![Scheme 61: Attempted preparation of 214. (a) (i) CDI, DMF, 24 h; ii) 213, rt, 3 d, 40 °C, 2 d. (b) i) CDI, DMF, 24 h. ii) NaH, DMF, rt, 4 d.](image)

Whilst low nucleophilicity 213 or steric factors associated with the dimethyl group might be a problem in this reaction two other factors are also possible. Firstly, the increased basicity of the guanidine caused by the inclusion of the dimethyl group might make this compound more likely to form a hydrate in water and lead to an increased solubility. The other possibility is that this guanidine is a very good leaving group (possibly aided by protonation in water) and is easily hydrolysed on work up. Support for this proposition can be drawn from a previous study in this group, which indicated that the catalysts 216a-d could not be prepared under similar conditions. (Scheme 62)
Previous attempts at preparing catalysts 216a-d. Conditions (a) i) CDI, DMF, 24-72 h; ii) Add to 215 treated with NaH for 3 h, then rt, 2 d; R = Me, Bn, Cy, iPr.

The preparation of analogous Cbz-protected N-alkylated guanidine catalysts was also investigated. We intended to study the simple N-methyl-Cbz guanidine catalyst 219, which should be easily prepared in two steps from N-methyl-L-proline. We initially prepared N-Cbz-1H-pyrazole-1-carboxamide 217 by the reaction of 1H-pyrazole-1-carboxamidine hydrochloride 209 with benzyl chloroformate in the present of N,N-diisopropylethylamine in THF. After 24 h, an extractive work up followed by recrystallization gave 217 as a white solid in 80% yield, which had spectroscopic data in agreement with the literature. (Scheme 63)

This guanidine 217 was stirred with two equivalent of solid methylamine hydrochloride and triethylamine in THF under anhydrous conditions. After stirring for 17 h, starting material was still present and a further three equivalents of methylamine hydrochloride and triethylamine were added. Again, after a further 36 h, TLC indicated an incomplete reaction and this attempt was abandoned. The reaction was repeated using two equivalents of aqueous methylamine and guanidine 217 in THF. After 90 min TLC indicated the complete consumption of 217 and an extractive work up and recrystallization gave guanidine 218 as a white solid in 82% yield. (Scheme 64)
Incorporation of the new methyl group was evident by the appearance of a singlet at $\delta_H$ 2.73 (3H, s, Me) ppm in the $^1$H NMR as well as a signal at 27.4 ppm in the $^{13}$C NMR. The $^{13}$C NMR spectrum displayed signals representative of 8 different carbon environments as expected for guanidine 218. The success of the reaction was confirmed by high resolution mass spectrometry which gave a mass of 208.1091 Daltons which corresponds closely to the calculated mass of 208.1086 Daltons required for $C_{10}H_{14}N_3O_2^+$ ($[M+H]^+$).

With the guanidine 218 in hand, the catalyst 219 was prepared by reacting 218 with $N$-methyl-$L$-proline 175a after activation with CDI in dry DMF over 24 h. After 4 d, an extractive work up followed by trituration of the resulting solid with diethyl ether gave the desired product 219 as a white solid in 89% yield. (Scheme 65)

Scheme 65: Preparation of catalyst 219. (a) i) CDI, DMF, 24 h, rt, ii) 218, rt, 4 d.

Catalyst 219 gave a negative specific rotation value of $[\alpha]_D^{20}$ -54.0 whilst the proton NMR spectrum gave two signals at $\delta_H$ 12.81 (1H, s, NH), and 8.99 (1H, s, NH) ppm for the guanidine NH protons. Signals at $\delta_H$ 7.42 (2H, d, J 7.0 Hz, 2 × CH), and 7.28-7.37 (3H, m, 3 × CH) ppm corresponded to the phenyl ring whilst the benzyl methylene was observed as a singlet at $\delta_H$ 5.16 ppm. Signals for the proline methylenes were observed at $\delta_H$ 3.25-3.32 (1H, m, CH), 2.37-2.43 (1H, m, CH), 2.20-2.32 (1H, m, CH), and 1.77-1.94 (3H, m, 3 × CH) ppm. The methine proton for the proline was observed as a double doublet at $\delta_H$ 3.00 (1H, dd, J 4.7, 10.0 Hz, CH) ppm. Interestingly the $N$-methyl of the guanidine was observed as a doublet at $\delta_H$ 2.97 (3H, d, J 4.9 Hz, Me) ppm indicating a coupling to the adjacent N-H proton, whilst the $N$-methyl of the proline was a singlet at 2.43 (3H, s, Me) ppm. The $^{13}$C NMR spectrum gave the required 14 non-equivalent signals with the methine carbon in the proline ring at $\delta_C$ 69.6 ppm. Finally analysis by mass spectrometry gave an ion 319.2 (100%) for $[M+H]^+$, which on accurate mass measurement gave a mass of 319.1767 Daltons which corresponded well to the required mass of 319.1765 Daltons for $C_{16}H_{23}N_4O_3^+$ ($[M+H]^+$). An X-ray structure was also obtained for 219 (vide infra).

The corresponding $N,N$-dimethyl-Cbz-guanidine 220 was also prepared by reacting $N$-
Cbz-\(H\)-pyrazolecarboxamide 209 with 3 equivalents of aqueous dimethylamine in THF. After 24 h TLC indicated a trace of starting material present and so a further equivalents of dimethyl amine was added. After a further 24 h, an extractive work-up followed by column chromatography gave guanidine 220 as a white solid in 97% yield. (Scheme 66)

**Scheme 66:** Preparation of 220: (a) \(\text{Me}_2\text{NH (aq., 4 equiv.)}, \text{THF}, 24 \text{ h}\).  

Incorporation of the dimethyl group was evident by the appearance of a singlet at \(\delta_H 3.04 (6\text{H}, s, 2 \times \text{Me}) \text{ ppm} \) in the \(^1\text{H NMR}\) as well as a corresponding signal at \(\delta_C 36.9 \text{ ppm} \) in the \(^{13}\text{C NMR}\). The \(^{13}\text{C NMR}\) spectrum displayed signals representative of 8 different carbon chemical environments as expected for guanidine 220. The success of the reaction was confirmed by high resolution mass spectrometry which gave a mass of 222.1237 Daltons which is in exact agreement with the calculated mass of 222.1237 Daltons required for the formula \(\text{C}_{11}\text{H}_{16}\text{N}_3\text{O}_2+([\text{M+H}^+])\).

The coupling of the guanidine 220 with \(N\)-methyl-L-proline 175a was attempted under the conditions previously employed. After activation using CDI in dry DMF over 24 h, the guanidine 220 was added and the reaction monitored by TLC. No reaction was apparent over 6 days and after work-up, column chromatography of the product gave only recovered 220 as the only identifiable product. (Scheme 67)

**Scheme 67:** Attempted preparation of 221. (a) i) CDI, DMF, rt, 24 h. ii) 220, rt, 6 d.

The failure of this reaction was attributed to either, the poor nucleophilicity of 220, the steric hindrance found in 220, the possibility of hydrolysis of the product during work up or a combination of these factors.

To investigate the steric effects present at the carbamate substituents on guanidine, the preparation of a methylcarbamate containing catalyst was attempted. The preparation of the
required carbomethoxyguanidine 222 was thus attempted using a literature procedure. This required the simultaneous addition of a solution of methyl chloroformate in dioxane and a aqueous solution of NaOH (10 M) to a cooled solution of guanidine hydrochloride 206 and NaOH. After stirring for 2 h, extraction of the reaction with chloroform followed by recrystallization gave a white crystalline product. Unfortunately analysis of the proton NMR seemed to indicate the formation of \( N,N' \)-dicarbomethoxyguanidine 223 as the methyl signal at \( \delta_H 3.61 \) (6H, s, 2 × Me) ppm integrated to 6 hydrogens when compared to the NH signals at 10.81 (1H, br s, NH), and at 8.66 (2H, br.s, NH₂) ppm which integrate to 3 hydrogens. The \(^{13}\)C NMR spectrum displayed signals representative of 3 different carbon atom chemical environments as expected for either guanidine 222 or 223. Confirmation of the structure was obtained by mass spectrometry, which gave a mass ion at 176.1 (100%, [M+H⁺]) Daltons, which corresponds to compound 223 and not 222, which has a predicted protonated mass of 118.1 Daltons. This reaction was repeated again with using an excess (5 equiv.) of guanidinium hydrochloride 206 and the slow addition of methyl chloroformate over 15 h. After stirring for 24 h, the crude mixture was extracted with chloroform, but again no appreciable amount of either product was formed, even on saturation of the aqueous layer with brine and re-extraction. (Scheme 68)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH} \quad \text{NH}_2\text{HCl} \quad \text{(a)} \quad \text{MeO}_2\text{C} & \quad \text{NH} \quad \text{NHCO}_2\text{Me} \\
\text{206} & \quad \text{not} \quad \text{H}_2\text{N} & \quad \text{NH} \quad \text{NHCO}_2\text{Me} \\
\text{223} & \quad \text{222}
\end{align*}
\]

**Scheme 68:** Attempted preparation of 222: (a) methyl chloroformate, NaOH, Dioxane, water, 2 h

It is difficult to rationalize the failure of this reaction however there is sometimes difficulty in controlling reaction with free guanidine as it is a good nucleophile and readily undergoes multiple nucleophilic reactions. One additional reason for the failure to isolate 222 might be its increased water solubility.

We wished to investigate the deprotection of the previously prepared catalyst 176a\(^97\) as the free guanidine might be of interest as a catalyst. The required \( N \)-/Cbz-guanidine 224, was prepared by the addition of a solution of benzyl chloroformate dissolved in dioxane to a solution of guanidine hydrochloride 206 and NaOH were dissolved in water. After stirring for
15 h, an extractive work up followed by recrystallization gave guanidine 224 as a white solid in 82% yield. Spectroscopic data was in agreement with the literature.101 (Scheme 69)

Scheme 69: Preparation 224: (a) CbzCl, NaOH, Dioxane, water, 22 h.

Activation of N-methyl-L-proline 175a with CDI in dry DMF over 4 h, was followed by the addition of Cbz-guanidine 224 at 0 °C and after stirring for five days, the reaction was diluted with water. Extraction with ethyl acetate and chromatography gave catalyst 176a as a white solid in 47% yield. Spectroscopic data was in agreement with the literature.97 (Scheme 70)

Scheme 70: Preparation of 176a. (a) i) CDI, DMF, 0 °C, 4 h. (ii) 224, rt, 5 d

With 176a in hand, hydrogenation was attempted by dissolving the catalyst in dry methanol together with 10% Pd/C. This mixture was stirred at rt for 2 h under a hydrogen atmosphere then filtered through Celite© and the filtrate concentrated in vacuum to give the product as a white solid. Purification by silica gel chromatography, gave the product as a yellow gum. Analysis of the proton NMR unusually indicated the presence of two methyl signals, the first as a singlet at δH 3.86 (3H, s, Me) ppm whilst the second which was assumed to be the N-methyl of the proline was observed as a singlet at δH 3.02 (3H, s, Me) ppm. This indicated that a methoxy-group has become incorporated into the molecule and this was confirmed by mass spectrometry which gave a mass ion at 166.1 (100%, [M+Na]+) Daltons which on accurate mass measurement gave a mass of 166.0835 Daltons which corresponded well to the required mass of 166.0844 Daltons for C7H13NONa+ ([M+Na]+). This evidence seems to suggest the formation of methyl N-methyl-L-proline 226, a conclusion supported by the NMR data. The compound gave a negative specific rotation value of [α]D 40 -72.2 (c = 3.3, CF) which corresponds very closely to the reported value of [α]D 22 -70.8 (c = 3.3, CF).102 (Scheme 71)
We wished to continue the studies on the N-methyl-L-proline-2-aminobenzimidazole catalyst 179a, previously prepared in the group.\textsuperscript{97} We repeated the preparation by activating 175a with CDI in dry DMF over 24 h at rt, followed by the addition of commercially available 2-aminobenzimidazole 227. After stirring for 72 h, an aqueous work up followed by extraction with ethyl acetate and chromatography gave 179a in 93% yield as a white solid which had spectroscopic data in agreement with the literature.\textsuperscript{97} (Scheme 72)

The amide 179a was subsequently reduced in dry diethyl ether using LiAlH\textsubscript{4}. After 24 h stirring at rt followed by 5 h under reflux, hydrolysis with a 9:1 mixture of methanol and water and evaporation gave a crude product which was purified by column chromatography to give 228 as a pale yellow gum in 81% yield. (Scheme 73)

The analytical data obtained for 228 confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{16}$ -75.4, whilst the proton NMR spectrum gave signals
at $\delta_H$ 7.13-7.23 (2H, m, 2 $\times$ CH), and 6.94-7.00 (2H, m, 2 $\times$ CH) ppm for the aromatic ring protons. Two double doublets at $\delta_H$ 3.59 (1H, dd, $J$ 13.6, 4.5 Hz, CH) and 3.41 (1H, dd, $J$ 13.6, 5.6 Hz, CH) ppm were observed for the methylene CH$_2$ protons. The methine proton of the pyrrolidine ring was observed as a multiplet at $\delta_H$ 2.67-2.76 (1H, m, CH) ppm, whilst the N-methyl signal was observed as a singlet at $\delta_H$ 2.53 (3H, s, CH$_3$) ppm. The remaining signals for the pyrrolidine ring were at $\delta_H$ 3.12-3.20 (1H, m, CH), 2.38-2.47 (1H, m, CH), 2.00-2.11 (1H, m, CH), and 1.69-1.87 (3H, m, CH, CH$_2$) ppm. The $^{13}$C NMR spectrum gave the required 10 non-equivalent signals with the methylene carbon of the pyrrolidine appearing at $\delta_C$ 45.7 ppm and the methine carbon of the pyrrolidine ring at $\delta_C$ 67.0 ppm. Moreover, inspection of the IR spectrum of the purified material showed the absence of a carbonyl stretch. Finally, analysis by mass spectrometry gave an ion 231.2 for [M+H]$^+$, which on accurate mass measurement gave 231.1604 Daltons which matched exactly the required mass of 231.1604 Daltons for C$_{13}$H$_{19}$N$_4$+$^+$ ([M+H]$^+$]).

We also wished to prepare analogues of 227 in which the amine positions on the guanidine are selectively methylated. In order to prepare these catalysts a preparation of 1-methyl-1H-benzo[d]imidazol-2-amine 229 was required. This was prepared by a literature method$^{103}$ in which powdered KOH was added to a stirring solution of 2-aminobenzimidazole in acetone. After 10 min, a thick colourless precipitate was observed, whereupon CH$_3$I was then added. After 30 min stirring, an aqueous work up followed by recrystallization from toluene/CHCl$_3$ gave crude 229 as an amorphous solid. This solid was dissolved in HCl (aq. 1 M, pH = 2) and extracted with CHCl$_3$, then the aqueous layer was basified (10% NaOH) and further extracted with DCM, dried and evaporated to give the pure product as a pale brown solid in 25% yield. (Scheme 74)

![Scheme 74: Preparation of 229. (a) CH$_3$I, KOH, 30 min](image)

Data was not given in the literature,$^{103}$ however incorporation of the methyl group was evident by the appearance of a singlet at $\delta_H$ 3.35 (3H, s, Me) ppm in the $^1$H NMR, together with a corresponding signal at $\delta_C$ 28.7 ppm in the $^{13}$C NMR. The $^{13}$C NMR spectrum also...
displayed signals representative of 8 different carbon chemical environments as expected for guanidine 229. The success of the reaction was confirmed by high resolution mass spectrometry which gave a mass of 148.0872 Daltons which is in close agreement with the calculated mass of 148.0875 Daltons required for the formula C₈H₁₀N₃⁺([M+H⁺]).

We next attempted the coupling of 229 with one equivalent of N-methyl-L-proline 175a which was activated with CDI in dry DMF for 2 h at rt followed by the addition of 229. After 5 days, an aqueous workup extracting with ethyl acetate followed by column chromatography gave the catalyst 230 in very low crude yield, which was contaminated with considerable amounts of the starting amine 229. Because of this low yield, the reaction was repeated using DCC as the coupling agent. Thus 175a and 229 were suspended in dry THF and stirred for 3 h whereupon the mixture was cooled (0 °C) and DCC and DMAP were then added with stirring for 45 min at same temperature. By this time, the yellow suspension disappeared and a white precipitate was visible. After stirring at rt for 24 h, TLC showed an incomplete reaction and a further 0.2 equivalent of DCC were added. After 6 days TLC indicated a near complete conversion of the reaction, however ¹H NMR showed the success of the coupling however several by-products were present, which proved difficult to separate from 230 which was very polar (Rf 0.24 in 50% CHCl₃ in MeOH). A similar coupling was attempted using HBTU as the coupling agent. Thus N-methyl-L-proline 175a and HBTU were dissolved in dry THF/DMF (1:1), stirred for 1 h whereupon triethylamine was added. After 2 h, 1-methyl-1H-benzo[d]imidazol-2-amine 229 was added and the mixture stirred for 3 days. After an aqueous work up with extraction with ethyl acetate a low crude yield of material was obtained. which again proved difficult to purify by column chromatography. We rationalized that the initial reaction using CDI was probably the most successful and it was repeated this using a different purification method. Thus on repeating the reaction, the DMF was removed under high vacuum (freeze dryer) and the crude product triturated sequentially with hexane, diethyl ether and dichloromethane. The diethyl ether and dichloromethane triturations contained 230, contaminated with the starting material 229 which were inseparable by chromatography. We next repeated the reaction with the addition of two equivalents of triethylamine. This gave a higher yield but the inseparable starting material 229 was still present in the crude product. Finally, the reaction was repeated with an excess of N-methyl-L-proline 175a (1.5 equivalent) activated with excess (2.5 equivalent) CDI, and one equivalent of amine 229 was added. After 10 days stirring, an aqueous workup extracting with ethyl acetate followed by column chromatography of the residue gave 230 in a 41% yield. (Scheme 75)
Scheme 75: Preparation of 230. (a) i) CDI, DMF, 2 h. (ii) 229, rt, 5 d. (b) i) DCC, DMAP, THF, 3 h. (ii) 229, rt, 7 d. (c) (i) HBTU, Et$_3$N, THF, 3 h. (ii) 229, rt, 3 d.

The analytical data obtained for 230 confirmed its structure. The compound gave a negative specific rotation value of [α]$_D$ -32.2 whilst the proton NMR spectrum gave a broad signal at δ$_H$ 9.40-11.24 (1H, br s, NH) ppm for the guanidine NH protons and two signal at δ$_H$ 7.53 (1H, br d, J 6.0 Hz, CH), and 7.22-7.30 (3H, m, 3 × CH) ppm for the aromatic ring protons. The methine proton of the proline ring was observed as a complex multiplet at δ$_H$ 3.10-3.18 (1H, m, CH) ppm, whilst the N-methyl signals of benzimidazole and proline were observed as singlets at δ$_H$ 3.69 (3H, s, CH$_3$) and 2.54 (3H, s, CH$_3$), respectively. The remaining signals for the proline ring were at δ$_H$ 3.26 (1H, br t, J 7.5 Hz, CH), 2.40-2.51 (1H, m, CH), 2.25-2.36 (1H, m, CH), 2.02-2.12 (1H, m, CH), and 1.81-2.00 (2H, m, 2 × CH) ppm. The $^{13}$C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon in the proline ring at δ$_C$ 70.2 ppm. Finally analysis by mass spectrometry gave an ion 259.2 for [M+H]$^+$, which on accurate mass measurement gave a mass of 259.1555 Daltons which corresponded well to the required mass of 259.1553 Daltons for C$_{14}$H$_{19}$N$_4$O$^+$ ([M+H$^+$]).

We similarly wanted to prepare the N-methyl-1H-benzo[d]imidazol-2-amine 232 and again a literature preparation was reported from 2-aminobenzimidazole 227. Thus 227, p-thiocresol and aqueous formaldehyde were refluxed for 7 h in absolute ethanol and on cooling the product 231 precipitates. This was then collected by filtration, washed with chloroform and recrystallized from ethanol, then reduced using sodium borohydride in absolute ethanol at reflux for 1h. After cooling to rt, the product was purified via an acid base extraction protocol to give the N-methyl-1H-benzo[d]imidazol-2-amine 232 as a white solid in 69% yield which had spectroscopic data in agreement with the literature.$^{104}$ (Scheme 76)
Scheme 76: Preparation of 232. (a) \( p \)-thiocresol, \( \text{CH}_2\text{O} \) (39%, aq), ethanol, reflux 7 h, (b) \( \text{NaBH}_4 \), reflux 1 h, absolute ethanol.

With 232 in hand we next attempted the preparation of catalyst 233. Thus \( N \)-methyl-\( L \)-proline 175a was activated with CDI in DMF over 24 h and transferred by cannula to a solution of 232 (1.0 equiv.) and triethylamine (2.0 equiv.) in DMF. After stirring for 3 days, an aqueous workup extracting with ethyl acetate was followed by column chromatography to give 233 in very low yield as an off-white solid. As the crude yield of the catalyst 233 was higher than the chromatography yield, it was proposed that the product might be unstable to column chromatography. Thus, the reaction was repeated without purification by column chromatography and under the same conditions as previously and after stirring for 4 days an aqueous workup extracting with ethyl acetate was followed by recrystallization from ether/petroleum ether which gave 233 in 44% yield with an 85% purity as estimated by NMR. The contaminant was unreacted amine 232 and it was felt that in a similar manner to the previous catalyst 230, low nucleophilicity or steric hindrance might be a reason for the low yield. We thus repeated the reaction again using an excess of activated methyl proline 175a (2.5 equiv.) which gave 233 in 45% yield with a 98% purity as an off-white solid after recrystallization. (Scheme 77)

\[
\begin{align*}
\text{Scheme 77: Preparation of 233. (a) i) CDI, DMF, 8 h; ii) 232, rt, 72 h.}
\end{align*}
\]

The analytical data obtained for 233 confirmed its structure. The compound gave a negative specific rotation value of [\( \alpha \)]_{D}^{18} -84.4, whilst the \(^1\text{H} \) NMR spectrum gave a broad signal at \( \delta_{\text{H}} \) 11.60 (1H, s, NH) ppm for the guanidine NH proton. Signals at \( \delta_{\text{H}} \) 7.64 (1H, d, \( J \) 5.8 Hz, CH), 7.39 (1H, d, \( J \) 5.8 Hz, CH), and 7.16-7.25 (2H, m, 2 \times \text{CH}) ppm correspond to the aromatic ring protons. The methine proton of the proline ring was observed as a multiplet at \( \delta_{\text{H}} \) 3.22-3.29 (1H, m, CH) ppm, whilst the \( N \)-methyl signals on the benzimidazole and proline
were observed as a singlet at $\delta$H 3.78 (3H, s, Me), and at $\delta$H 2.44 (3H, s, Me) respectively. The remaining signals for the proline ring were at $\delta$H 3.39 (1H, dd, J 8.6, 7.2 Hz, CH), 2.25-2.47 (2H, m, 2 $\times$ CH), and 1.82-2.08 (3H, m, 3 $\times$ CH) ppm. The $^{13}$C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon in the proline ring at $\delta$C 68.0 ppm. Finally analysis by mass spectrometry gave an ion 259.2 for [M+H]$^+$, which on accurate mass measurement gave a mass of 259.1555 Daltons which corresponded well to the required mass of 259.1553 Daltons for C$_{14}$H$_{19}$N$_4$O$^+$ ([M+H$^+$]).

2.2.3 Hydrazine catalysts

Following a report by Bhowmick et al. who reported that the L-proline hydrazide 236 was the smallest and, most importantly, one of the best organocatalysts reported thus far in the literature. The existence of a suitable hydrogen-bonding pocket (two hydrogen bonds within a short space) in the catalyst structure was the reason for the impressive result for this catalyst. Generally, good yields (up to 99%) were achieved in aqueous aldol reactions, with high anti/syn diastereoselectivities (up to 95:5) and enantioselectivities (up to 99.9%). (Scheme 78)

![Scheme 78. Direct Asymmetric Aldol organocatalyst reaction for L-proline hydrazide 236.](image)

(a) 236 (0.1 equiv.), PTSA, (0.05 equiv.) in H$_2$O; R = alkyl, R$^1$ = H, alkyl, R$^2$ = Aryl.

We felt that similar catalysts might be of use in our work and sought to prepare a series of N-alkylated L-proline hydrazine catalysts with minimum bulk (steric environment) as well as the potential for tight hydrogen-bonding interactions.

The first catalyst was prepared by initially converting N-methyl-L-proline 175a into its methyl ester 226 using acetyl chloride and methanol under reflux for 12 h, then reacting this compound with an excess of hydrazine monohydrate in methanol. Work up gave the desired catalyst 238 as a pale yellow liquid in 73% yield. (Scheme 79)
Scheme 79: (a) AcCl, MeOH, reflux, 12 h. (b) NH₂NH₂.H₂O, reflux 3 h, then 24 h at rt.

The analytical data obtained for 238 confirmed its structure. The compound gave a negative specific rotation value of [α]D²⁰ -121.6 whilst the proton NMR spectrum gave a broad signal at δH 8.25 (1H, br s, NH) and 3.74 (2H, br s, NH₂) ppm for the hydrazine NH protons. The methine proton of the proline ring was observed as a doublet of doublets at δH 2.93 (1H, dd, J 10.3, 5.1 Hz, CH) ppm, whilst the N-methyl signal was observed as a singlet at δH 2.32 (3H, s, Me). The remaining signals for the proline ring were at δH 3.04 (1H, ddd, J 8.5, 6.5, 2.2 Hz, CH), 2.25-2.32 (1H, m, CH), 2.12-2.22 (1H, m, CH), and 1.66-1.84 (3H, m, CH, CH₂) ppm. The ¹³C NMR spectrum gave the desired 6 non-equivalent signals with the methine carbon in the proline ring at δC 68.1 ppm. Finally analysis by mass spectrometry gave an ion at 114.1 for [M+H]+, which on accurate mass measurement gave a mass of 144.1128 Daltons which corresponded well to the required mass of 144.1131 Daltons for C₆H₁₄N₃O⁺ ([M+H⁺]).

We next prepared the Boc-substituted hydrazine 240 under our standard conditions by activating N-methyl-L-proline 175a with CDI and treating this with commercially available Boc-hydrazine 239 in DMF over 72 h at rt. After an aqueous work and recrystallization from chloroform/methanol the compound 240 was obtained in 60% yield as a white solid. (Scheme 80)

Scheme 80: Preparation of 240. (a) i) CDI, DMF, 8 h; ii) 239, rt, 72 h.

The analytical data obtained for 240 confirmed its structure. The compound gave a negative specific rotation value of [α]D²⁰ -73.3 whilst the proton NMR spectrum gave a signals at δH 8.74 (1H, br s, NH), and 6.47 (1H, br s, NH) ppm for the hydrazine NH protons. The methine proton for the proline was observed as double doublet at δH 3.00 (1H, dd, J 10.2, 4.4 Hz, CH) ppm whilst the methyl signal was observed at δH 2.42 (3H, s, Me) ppm and the tert-
butyl at δH 1.47 (9H, s, 3 × Me) ppm. The proline methylene was observed at δH 3.05-3.13 (1H, m, CH), 2.28-2.37 (1H, m, CH), 2.16-2.27 (1H, m, CH), and 1.73-1.97 (3H, m, CH, CH₂) ppm. The 13C NMR spectrum gave the required 9 non-equivalent signals with the methine carbon in the proline ring at δC 68.3 ppm. Finally, analysis by mass spectrometry gave an ion 244.2 (100%) for M+H⁺, which on accurate mass measurement gave a mass of 244.1663 Daltons which corresponded well to the required mass of 244.1661 Daltons for C₁₁H₂₂N₃O₃⁺ ([M+H⁺]). An X-ray structure was also obtained for 240 (vide infra).

Similarly, the Cbz-hydrazine catalyst 242 was prepared under identical conditions and purified by triturating with diethyl ether. The residue was dried under high vacuum to give 242 in 90% yield as a pale yellow viscous liquid. (Scheme 81)

![Scheme 81: Preparation of 242](image)

The analytical data obtained for 242 confirmed its structure. The compound gave a negative specific rotation value of [α]D²¹ -61.3 whilst the proton NMR spectrum gave signals at δH 8.82 (1H, s, NH), and 6.75 (1H, s, NH) ppm for the two NH protons and signals at δH 7.41-7.29 (5H, m, CH) ppm for the aromatic ring. The benzyl methylene was observed at δH 5.16 (2H, s, CH₂) ppm, whilst the methine proton for the proline was observed as a multipet at δH 3.05-2.95 (1H, m, CH) ppm. The methyl signal was observed at δH 2.42 (3H, s, Me) ppm, whilst the other proline protons were observed at δH 3.15-3.06 (1H, m, CH₅), 2.34 (1H, m, CH), 2.27-2.13 (1H, m, CH), 2.00-1.87 (1H, m, CH), and 1.83-1.67 (2H, m, CH₂) ppm. The 13C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon of the proline appearing at δC 68.0 ppm. Finally analysis by mass spectrometry gave an ion 278.2 (100%) for [M+H]⁺, which on accurate mass measurement gave a mass of 278.1505 Daltons which was in close agreement with the required mass of 278.1499 Daltons for C₁₄H₂₀N₃O₃⁺ ([M+H⁺]).

We next prepared the phenyl substituted hydrazine catalyst 244 by activation of 175a with CDI followed by the addition of phenyl hydrazine 243. After stirring for two days, an
aqueous work up followed by column chromatography gave 244 as a yellow solid in 50% yield. (Scheme 82)

Scheme 82: Preparation of 244. (a) i) CDI, DMF, 24 h; ii) PhNHNH$_2$ 243, rt, 48 h.

The analytical data obtained for 244 confirmed its structure. Compound 244 gave a negative specific rotation value of $[\alpha]_D^{20}$ -64.6, whilst the proton NMR spectrum gave signals at $\delta$H 8.90 (1H, s, NH) and 6.15 (1H, s, NH) ppm for the NH protons. Signals at $\delta$H 7.21 (2H, d, $J$ 7.6 Hz, CH), 6.89 (1H, t, $J$ 7.3 Hz, CH), and 6.81 (2H, d, $J$ 8.0 Hz, CH) ppm corresponded to the aromatic protons whilst the methine proton of the proline was observed as a double doublet at $\delta$H 3.07 (1H, dd, $J$ 10.2, 4.8 Hz, CH) ppm. The N-methyl signal was observed at $\delta$H 2.47 (3H, s, CH$_3$) ppm, whilst the remaining signals for the proline ring were at $\delta$H 3.14 (1H, m, CH), 2.38 (1H, m, CH), 2.33-2.19 (1H, m, CH), and 1.98-1.76 (3H, m, CH + CH$_2$) ppm. The $^{13}$C NMR spectrum gave the required 10 non-equivalent signals with the methine carbon of the proline ring appearing at $\delta$C 56.8 ppm. Finally analysis by mass spectrometry gave an ion 220.2 for [M+H]$^+$, which on accurate mass measurement gave a mass of 220.1454 Daltons which corresponded well to the required mass of 220.1450 Daltons for C$_{12}$H$_{18}$N$_3$O$^+$ ([M+H$^+$]). An X-ray structure was also obtained for 244 (vide infra).

2.2.4 L-Alanine, L-phenylalanine and L-valine catalysts

We also prepared several catalysts from N,N-dialkylated-L-alanine 191 and N,N-di alkylated-L-phenylalanine 193, as well as the attempted preparation of a series of N,N-dialkylated-L-valine 195 catalysts which was attempted by a co-worker. These compounds were prepared to move away from the L-proline catalysts, which it was thought might possibly be too conformationally restricted and on protonation might lead to diastereomeric mixtures.

2.2.4.1 N,N-Dimethyl- L-Alanine catalysts

We initially investigated catalysts derived from N,N-dimethyl-L-alanine 191, which was discussed the preparation previously. The first investigation was the preparation of the
Cbz-guanidine substituted catalyst 245. Activation of N,N-dimethyl-L-alanine 191 with CDI in dry DMF over 24 h was followed by the addition of N-Cbz-guanidine 224. After stirring for 4 days at rt an aqueous extraction and purification by column chromatography gave the catalyst 245 in 99% yield as a white solid. (Scheme 83)

Scheme 83: Preparation of 245. (a) i) CDI, DMF, rt, 24 h; ii) 224, 4 d.

The analytical data obtained for 245 confirmed its structure. The compound gave a positive specific rotation value of $[\alpha]_D^{23} +31.3$ whilst the proton NMR spectrum gave a signal at δH 8.45-10.94 (3H, br s, 3 × NH) ppm for the guanidine NH protons. A multiplet signal at δH 7.23-7.41 (5H, m, CH) ppm corresponded to the aromatic ring, whilst the benzyl methylene was observed as a singlet at δH 5.11 (2H, s, CH2) ppm. The methine proton of the alanine was observed as a quartet at δH 3.13 (1H, q, J 7.0 Hz, CH) ppm, the N,N-dimethyl amine was observed as singlet at δH 2.21 (6H, s, 2 × CH3) ppm and the methyl signal appeared as a doublet at δH 1.19 (3H, d, J 7.0 Hz, CH3) ppm. The 13C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon appearing at δC 64.6 ppm. Finally analysis by mass spectrometry gave an ion 293.2 (100%) for [M+H]+, which on accurate mass measurement gave a mass of 293.1614 Daltons which is in exact agreement with the required mass of 293.1614 Daltons for C14H21N4O3+ ([M+H]+). An X-ray structure was also obtained for 245 (vide infra).

The corresponding N,N-dimethyl-Boc protected catalyst 246 was prepared in a similar manner, by reaction N,N-dimethyl alanine 191 with CDI in dry DMF for 6 h at rt followed by the addition of N-Boc-guanidine 207. After stirring for 4 days, aqueous work up and column chromatography gave 246 in 40% yield as as a white solid. (Scheme 84)
Scheme 84: Preparation of 246. (a) i) CDI, DMF, rt, 6 h, ii) 207, rt, 4 d.

The analytical data obtained for 246 confirmed its structure. The compound gave a positive specific rotation value of $[\alpha]_{D}^{18} +27.8$ whilst the proton NMR spectrum gave one signal at $\delta_H 8.96$ (3H, br s, 3 × NH) ppm for the guanidine NH protons. The methine proton of the alanine was observed as a quartet at $\delta_H 3.12$ (1H, q, $J$ 6.9 Hz, CH) ppm with the dimethyl groups appearing at $\delta_H 2.22$ (6H, s, 2 × Me) ppm. The t-butyl singlet appeared at $\delta_H 1.49$ (3H, s, 3 × Me) ppm whilst the methyl of the alanine residue was a doublet at $\delta_H 1.20$ (3H, d, $J$ 7.0 Hz, Me) ppm. The $^{13}$C NMR spectrum gave the required 7 non-equivalent signals with the methine carbon of the appearing at $\delta_C 64.9$ ppm. Finally analysis by mass spectrometry gave ions at 275.2 (100%, $[\text{M+H}_2\text{O-H}]$) and 259.2 (43%, $[\text{M+H}]^{+}$), which on accurate mass measurement gave a mass of 259.1768 Daltons which corresponded closely to the required mass of 259.1765 Daltons for C$_{11}$H$_{23}$N$_4$O$_3$ ([M+H$^+$]).

The corresponding 2-aminobenzimidazole catalyst 247 was prepared in a similar manner, by reaction $N,N$-dimethyl-L-alanine 191 with CDI in dry DMF for 24 h at rt, followed by the addition of commercially available 2-aminobenzimidazole 227. After stirring for 24 h, an aqueous work up, followed by column chromatography gave 247 in 92% yield as a white solid. (Scheme 85)

Scheme 85: Preparation of 247. (a) i) CDI, DMF, rt, 24 h; ii) 227, rt, 24 h.

The analytical data obtained for 247 confirmed its structure. The compound gave a positive specific rotation value of $[\alpha]_{D}^{20} +24.3$ whilst the proton NMR spectrum gave a two signals at $\delta_H 12.08$ (1H, br s, NH), and 11.20 (1H, br s, NH) ppm for the guanidine NH protons.
Signals for the aromatic ring were observed at $\delta_H 7.37$-$7.50$ (2H, m, 2 $\times$ CH), and $7.07$-$7.09$ (2H, m, 2 $\times$ CH) ppm, whilst the methine proton for alanine was observed as a quartet at $\delta_H 3.32$ (1H, q, $J$ 6.8 Hz, CH) ppm. The dimethyl group was observed at $\delta_H 2.28$ (6H, s, 2 $\times$ CH$_3$) ppm whilst that of the other methyl group was a doublet at $\delta_H 1.20$ (3H, d, $J$ 6.8 Hz, CH$_3$) ppm. The $^{13}$C NMR spectrum gave the required 8 non-equivalent signals with the methine carbon at $\delta_C 62.2$ ppm. Finally analysis by mass spectrometry gave an ion 233.1 (100%) for [$\text{M+H}^+$], which on accurate mass measurement gave a mass of 233.1404 Daltons which corresponded closely to the required mass of 233.1402 Daltons for $\text{C}_{12}\text{H}_{17}\text{N}_4\text{O}^+$ [$\text{M+H}^+$]).

We next attempted the preparation of the corresponding phenyl substituted catalyst 250. Thus, phenylguanidinium nitrate 203$^{106}$ was added to a suspension of petroleum ether washed NaH in dry DMF and the mixture stirred for 1 h. At this point activated $N,N$-dimethyl-$L$-alanine 191 in DMF solution was transferred into this flask via cannula and the mixture stirred for 4 days. After aqueous work up and silica gel chromatography, the catalyst 250 was obtained in reasonable yield (ca. 55% yield) as a pale yellow solid which was heavily contaminated with phenylguanidine 203. Repeated chromatography failed to give a pure sample of 250 and the reaction was repeated using commercially available phenyl guanidinium carbonate 248. This was added to a suspension of NaH in dry DMF and stirred for 6 h, then treated with activated $N,N$-dimethyl-$L$-alanine 191. Again, after an aqueous work-up a good material yield was obtained (ca. 88%) but attempted silica gel chromatography was problematic and the catalyst 250 was difficult to separate from various impurities. We felt the problems might be associated with the poor solubility of phenyl guanidinium carbonate 248 in DMF and thus it was converted into phenyl guanidinium hydrochloride 249 by dissolving it in a minimum amount of methanol followed by the drop-wise addition of a slight excess of concentrated hydrochloric acid. After evaporation and rigorous drying (P$_2$O$_5$), this was treated with NaH in DMF for 24 h, followed by the addition of activated $N,N$-dimethyl-$L$-alanine 191. Again an aqueous work up followed by silica gel chromatography was highly problematic and only impure samples of 250 were obtained. The attempted preparation of 250 was discontinued at this point. (Scheme 86)
We next attempted to prepare L-alanine derived $C_2$-symmetric catalyst $251$. We thus suspended hexane washed NaH in dry DMF and added half an equivalent of guanidinium chloride $206$. After 24 h this solution was added to a DMF solution of 2 equivalents of CDI activated $N,N$-dimethyl-L-alanine $191$. After 72 h an aqueous work-up extracting with ethyl acetate gave a very low material yield which on proton NMR analysis gave no indication of the formation of $251$. It was theorized that perhaps the product was highly water soluble and a small sample of the aqueous phase was evaporated and purified by silica gel chromatography which gave the catalyst $251$ which was inseparable from imidazole in very low material yield. In order to eliminate the problems with imidazole we repeated the coupling by activating $N,N$-dimethyl-L-alanine $191$ with EDCI and HOBT in dry DMF. This mixture was added to a solution of guanidine in DMF generated in the same manner as in the previous reaction. After stirring for 7 days an aqueous work up gave a higher material yield but silica gel chromatography gave the catalyst $251$, which again was contaminated with impurities from the coupling reagents. The product was only mobile on chromatography in high polarity solvents, which seems to be a trend with the L-alanine derived catalysts. (Scheme 87)

Scheme 87: Attempted preparation of $251$ (a) CDI, DMF, rt, 24 h. (b) i) Guanidine hydrochloride $206$ (0.5 equiv.), NaH, DMF, 24 h. ii) combine, stir 3 d. (c) HOBT, EDCI, DMF, rt, 7 h
2.2.4.2 \textit{N,N-Dimethyl-L-Phenylalanine catalysts}

The poor separations observed in the last two synthetic schemes together with the supposed water solubility problems, led us to investigate the possibility of using \textit{N,N-dimethyl-L-phenylalanine} 193 as a precursor for these catalysts, as this should have a higher solubility in organic solvents.

We initially prepared the Cbz-guanidine substituted catalysts 252. Thus \textit{N,N-dimethyl-L-phenylalanine} 193 was dissolved in dry DMF and activated using CDI over 24 h, following which Cbz-guanidine 224 was added. After stirring for six days the reaction was diluted with water, extracted with ethyl acetate and after chromatography, catalyst 252 was obtained in 79\% yield as a white solid. (Scheme 88)

\textbf{Scheme 88:} Preparation of 252. (a) i) CDI, DMF, rt, 24 h; ii) 224, rt, 6 d.

The analytical data obtained for 252 confirmed its structure. The compound gave a positive specific rotation value of \[\alpha\]$_{D}^{23}$ +30 whilst the proton NMR spectrum gave a broad signal at \[\delta_{H} 7.99-10.49\] (3H, br s, 3 × NH) ppm for the guanidine NH protons and a complex multiplet at \[\delta_{H} 7.11-7.32\] (10H, m, 2 × Ph) ppm for the aromatic protons. The benzyl methylene for the Cbz group was observed as singlet at \[\delta_{H} 5.05\] (2H, s, CH$_2$) ppm whilst the benzyl methylene of alanine was observed as of two double doublets at \[\delta_{H} 3.04\] (1H, dd, \(J 14.0, 7.4\) Hz, CH), and \[\delta_{H} 2.85\] (1H, dd, \(J 14.0, 5.8\) Hz, CH) ppm. The distinctive methine proton for the phenyl alanine was observed as a double doublet at \[\delta_{H} 3.36\] (1H, dd, \(J 7.4, 5.8\) Hz, CH) ppm, whilst the \textit{N,N-dimethyl} signals were at \[\delta_{H} 2.32\] (6H, s, 2 × Me) ppm. The $^{13}$C NMR spectrum gave the required 15 non-equivalent signals with the methine carbon in the proline ring appearing at \[\delta_{C} 71.3\] ppm. Finally analysis by mass spectrometry gave an ion at 369.2 Daltons for [M+H]$^+$, which on accurate mass measurement gave a mass of 369.1926 Daltons which corresponded closely to the required mass of 369.1921 Daltons for C$_{20}$H$_{25}$N$_4$O$_3$ ([M+H$^+$]). An X-ray structure was also obtained for 252 \textit{(vide infra)}. 

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Similarly the Boc-protected catalyst was prepared by activating the \textit{N,N}-dimethyl-L-phenylalanine 193 with CDI in dry DMF over 24 h followed by the addition of \textit{N}-Boc-guanidine 207. After 13 days, an extractive work-up and column chromatography gave 253 in 87\% yield as a white solid. (Scheme 89)

![Scheme 89: Preparation of 253. (a) i) CDI, DMF, rt, 24 h; ii) 207, rt, 13 d.](image)

The analytical data obtained for 253 confirmed its structure. The compound gave a positive specific rotation value of $[\alpha]_{D}^{18} +37.0$ whilst the proton NMR spectrum gave one signal at $\delta_{H} \text{8.95 (3H, br s, 3 \times NH) ppm for the guanidine NH protons and a signals at } \delta_{H} \text{7.30-7.15 (5H, m, CH) ppm for aromatic protons. The methine proton for the phenylalanine was observed as a multiplet at } \delta_{H} \text{3.42-3.35 (1H, m, CH) ppm whilst the benzyl methylene of phenylalanine was observed as two double doublets signals at } \delta_{H} \text{3.08 (1H, dd, } J \text{14.0, } 7.4 \text{ Hz, CH), and 2.88 (1H, dd, } J \text{14.1, 5.9 Hz, CH}_2 \text{) ppm. The } \text{N,N}-\text{dimethyl was observed at } \delta_{H} \text{2.27 (6H, s, 2 \times CH}_3 \text{) ppm whilst the tert-butyl was a singlet at } \delta_{H} \text{1.47 (3H, s, 9H) ppm. The } ^{13}\text{C NMR spectrum gave the required 12 non-equivalent signals with the methine carbon observed at } \delta_{C} \text{71.4 ppm. Finally analysis by mass spectrometry gave an ion 335.2 (100\%, [M+H]^+), which on accurate mass measurement gave a mass of 335.2082 Daltons which was in good agreement with the required mass of 335.2078 Daltons required C_{17}H_{27}NaO_3^+ ([M+H^+]).}

The 2-aminobenzimidazole catalyst, 254 was similarly prepared by activating \textit{N,N}-dimethyl-L-phenylalanine 193 with CDI in dry DMF over 24 h at rt, followed by the addition of commercially available 2-aminobenzimidazole 227. After stirring for 7 days, an aqueous work up followed by chromatography gave 254 in 42\% yield as a white solid. (Scheme 90)
The analytical data for 254 confirmed its structure. The compound gave a positive specific rotation value of $[\alpha]_D^{20} +33.5$ whilst the proton NMR spectrum gave a broad singlet at $\delta_H 10.32$ (2H, br s, 2 $\times$ NH) ppm for the guanidine NH protons. Signals at $\delta_H 7.44-7.46$ (2H, m, 2 $\times$ CH), and 7.13-7.25 (7H, m, Ph, 2 $\times$ CH) ppm corresponded to the aromatic protons, whilst the methine proton for the phenylalanine was observed as a double doublets at $\delta_H 3.57$ (1H, dd, J 7.8, 5.7 Hz, CH) ppm. The protons of the benzyl methylene were observed as a double doublet at $\delta_H 3.21$ (1H, dd, J 13.9, 7.8 Hz, CH), and 2.97 (1H, dd, J 13.9, 5.7 Hz, CH) ppm whilst the N,N-dimethyl signal was observed as a singlet at $\delta_H 2.35$ (6H, s, 2 $\times$ CH$_3$) ppm. The $^{13}$C NMR spectrum gave the 11 non-equivalent signals with the methine in the proline ring at $\delta_C 70.6$ ppm. Finally analysis by mass spectrometry gave an ion 309.2 for [M+H]$^+$, which on accurate mass measurement gave a mass of 309.1712 Daltons which corresponded closely to the required mass of 309.1710 Daltons required for C$_{18}$H$_{21}$N$_4$O$^+$ ([M+H$^+$]).

We next attempted the preparation of the phenyl substituted catalyst 255 and firstly added phenylguanidinium carbonate 248 to hexane washed NaH suspended in dry DMF. After stirring for 24 h a solution of CDI activated N,N-dimethyl-L-phenylalanine 193 in DMF was added via cannula and the mixture stirred for 4 days. After an aqueous work up, chromatography gave the catalyst 255 in 46% yield as a pale yellow solid. (Scheme 91)
The analytical data obtained for 255 confirmed its structure. The compound gave a positive specific rotation value of \([\alpha]_D^{19} + 49.7\), whilst the \(^1\)H NMR spectrum gave a broad multiplet at \(\delta_H 7.09-7.51\) (11H, m, NH, NH\(_2\), Ph, 3 \(\times\) CH) ppm for both the guanidine NH protons with the other aromatic protons at \(\delta_H 7.02\) (2H, br d, J 8.0 Hz, 2 \(\times\) CH) ppm. The aliphatic methine proton was observed as a double doublet at \(\delta_H 3.50\) (1H, dd, J 7.1, 6.2 Hz, CH) ppm. The methylene protons of the benzyl were observed as a pair of double doublets at \(\delta_H 3.22\) (1H, dd, J 14.2, 7.1 Hz, CH), and 2.95 (1H, dd, J 14.1, 6.2 Hz, CH) ppm whilst the N, N-dimethyl signal was observed as a singlet at \(\delta_H 2.38\) (6H, s, 2 \(\times\) CH\(_3\)) ppm. The \(^{13}\)C NMR spectrum gave the required 13 non-equivalent signals with the aliphatic methine carbon appearing at \(\delta_C 71.5\) ppm. Finally mass spectrometry gave an ion at 309.2 for \([M-H]^-\) (negative ion mode), which on accurate mass measurement gave a mass of 309.1720 Daltons which corresponded closely to the calculated mass of 309.1721 Daltons for \(C_{18}H_{21}N_4O^-\) ([M-H\(^-\)]). An X-ray structure was also obtained for 255 (\textit{vide infra}).

We next attempted to prepare the L-phenylalanine derived \(C_2\)-symmetric catalyst 256 and thus suspended hexane washed NaH in dry DMF and added half an equivalent of guanidinium chloride. After 24 h this solution was added to a DMF solution of 2 equivalents of CDI activated \(N,N\)-dimethyl-L-phenylalanine 193. After stirring for 7 days and an aqueous work up, silica gel chromatography gave the catalyst 256 in 77% yield as an off-white waxy solid. (Scheme 92)

**Scheme 92:** Preparation of 256. (a) i) CDI, DMF, rt, 24 h; ii) Guanidine hydrochloride 206 (0.5 equiv.), NaH, DMF, 24 h; iii) combine, stir, 7 d.

The analytical data obtained for 256 confirmed its structure. The compound gave a negative specific rotation value of \([\alpha]_D^{16} + 61.9\) whilst the proton NMR spectrum gave signals at \(\delta_H 8.06-10.70\) (3H, br s, 3 \(\times\) NH) ppm for the guanidine NH protons and signals at \(\delta_H 7.20-7.24\) (10H, m, 2 \(\times\) Ph) ppm for the aromatic protons. The aliphatic methine proton was observed at \(\delta_H 3.39\) (2H, dd, J 8.5, 5.3 Hz, 2 \(\times\) CH) ppm, whilst benzyl methylene appeared as two double doublets at \(\delta_H 3.12\) (2H, dd, J 13.6, 8.6 Hz, 2 \(\times\) CH), 2.98 (2H, dd, J 13.6, 5.3 Hz, 2 \(\times\) CH)
ppm. The dimethyl phenylalanine groups appear as a singlet at δ 2.41 (6H, s, 2 × Me). The $^{13}$C NMR spectrum gave the required 9 non-equivalent signals with the methine carbon appearing at δC 73.1 ppm. Finally, analysis by high resolution mass spectrometry gave a mass at 410.3 Daltons for [M+H]$^+$ which on high resolution mass spectrometry gave a mass of 410.2543 Daltons which is in good agreement with the theoretical mass of 410.2551 Daltons required for [C$_{23}$H$_{32}$N$_5$O$_2$]$^+$ ([M+H]$^+$).  

2.2.4.3 N,N-Dimethyl-L-valine catalysts.

In concert with this research, work was performed by an Erasmus visitor to investigate the preparation of the corresponding catalysts from N,N–dimethyl-L-valine 193. Initial attempts utilising the standard coupling methodology with CDI activation in DMF followed by reaction with N-Cbz-guanidine 224. This however did not produce the desired compound and instead the imidazole intermediate 257 was isolated. Similar coupling using N-hydroxysuccinimide and HBTU in DMF again did not give the catalyst 258 and again the intermediate ester 259 was isolated after column chromatography. A mixed anhydride method, using methyl chloroformate was also attempted, however this met with failure and only 260 was isolated from the reaction mixture. The intermediates 257 and 259 were isolated and treated separately with a range of guanidines (207, 224 or 227) which again led to no reaction even on heating in THF at reflux. (Scheme 93)

Scheme 93: Attempted preparation of 258. (a) CDI, DMF, 24 h. (b) 224, 48 h. (c) NHS, HBTU, DMF, 0 °C . 30 min. (d) Methyl chloroformate, THF, Et$_3$N, 0 °C, 2 h. (e) 207, 224 or 227, THF, reflux 48 h.
The reason for the failure of these coupling is probably two-fold. Firstly, the guanidines employed are relatively poor nucleophiles as they are bulky and contain electron-withdrawing groups. Secondly the \(N,N\)-dimethyl-\(L\)-valine itself is a very hindered electrophile and the combination of these two factors led to a difficult coupling.

2.2.5 Other heterocyclic catalysts.

We also prepared the benzothiazole catalyst 262 from the addition of 2-aminobenzothiazole 261 to a CDI activated solution of \(N\)-methyl-\(L\)-proline 175a. After stirring for 7 days at rt an aqueous extraction and purification by column chromatography gave 262 in 74% yield as a pale yellow solid. (Scheme 94)

![Scheme 94: Preparation of 262. (a) i) CDI, DMF, 24 h; ii) 261, rt, 7 d.](image)

The analytical data obtained for 262 confirmed its structure. The compound gave a negative specific rotation value of \([\alpha]_D^{19}\) -38.0 whilst the proton NMR spectrum gave a broad singlet at \(\delta_H 9.82-11.72\) (1H, br s, NH) ppm for the NH proton. The aromatic protons appeared at \(\delta_H 7.82\) (1H, d, \(J 7.9 \text{ Hz, CH}\)), \(7.78\) (1H, d, \(J 8.1 \text{ Hz, CH}\)), \(7.44\) (1H, dd, \(J 8.1, 7.5 \text{ Hz, CH}\)), and \(7.31\) (1H, dd, \(J 7.9, 7.5 \text{ Hz, CH}\)), whilst the methine proton of the proline was observed as a multiplet at \(\delta_H 3.17-3.30\) (2H, m, \(2 \times \text{ CH}\)) ppm. The \(N\)-methyl group was observed at \(\delta_H 2.49\) (3H, s, \(\text{CH}_3\)) ppm, whilst the methylene protons appeared at \(\delta_H 2.44-2.55\) (1H, m, CH), 2.26-2.40 (1H, m, CH), 1.97-2.07 (1H, m, CH), and 1.76-1.92 (2H, m, \(\text{CH}_2\)) ppm. The \(^{13}\text{C}\) NMR spectrum gave the required 13 non-equivalent signals with the methine carbon in the proline ring at \(\delta_C 68.5 \text{ ppm}\). Finally analysis by mass spectrometry gave an ion 262.1 (98%, \([\text{M+H}]^+\)), which on accurate mass measurement gave a mass of 262.1011 Daltons which corresponded well to the required mass of 262.1009 Daltons for \(C_{13}\text{H}_{16}\text{N}_3\text{OS}^+ ([\text{M+H}]^+)\).

We also attempted to prepare the analogous benzoxazole catalyst 264 under identical conditions, however treatment of a CDI activated solution of \(N\)-methyl-\(L\)-proline 175a with 2-aminobenzoxazole 263 did not lead to the formation of the desired product. Repeating the reaction under longer coupling conditions (CDI, rt, 7 d) or higher temperatures (CDI, 45-55 °C, 3 d) did not lead to the formation of 264. The reason for this is not apparent but it may be
due to the low nucleophilicity of 2-aminobenzoxazole 263 or perhaps the amide once formed is easily hydrolised (although no evidence for its formation was found using TLC). (Scheme 95)

Scheme 95: Preparation of 264. (a) i) CDI, DMF, 24 h; ii) 263, rt, 7 d.

The preparation of a range of N-heterocyclic catalysts 268a-c was also attempted by reaction of the CDI activated N-methyl-L-proline 175a with 2-aminopyridine 265, 2-aminopyrimidine 266 or 2-aminopyrazine 267. These heterocycles proved to be difficult to couple and the only one that went with any success was in the formation of catalyst 268a in 18% yield as a yellow solid. Various conditions were employed including longer reaction times and higher coupling temperatures to no effect. Again the reason behind this failure is not apparent but it may be due to the low nucleophilicity of the amines employed or perhaps the amide once formed is easily hydrolised (although again no evidence for their formation was observed using TLC). (Scheme 96)

Scheme 96: Preparation of 268a-c. (a) i) CDI, DMF, 24 h; ii) 265, 266 or 267, rt, 7 d.

The analytical data obtained for 268a confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{20} -78.9$ whilst the proton NMR spectrum gave singlet at $\delta_H 9.85$ (1H, br s, NH) ppm for the NH proton. The aromatic ring protons signals were observed
at $\delta$H 8.29 (1H, br d, $J$ 4.7 Hz, CH), 8.26 (1H, br d, $J$ 8.4 Hz, CH), 7.69 (1H, ddd, $J$ 8.4, 7.2, 1.6 Hz, CH) and 7.02 (1H, t, $J$ 7.2, 4.7 Hz, CH) ppm. The methine proton of the proline was observed as a broad multiplet at $\delta$H 2.99-3.10 (1H, m, CH) ppm, whilst the N-methyl signal was at $\delta$H 2.46 (3H, s, Me) ppm. The remaining signals for the proline ring were observed at $\delta$H 3.17-3.22 (1H, m, CH) ppm, 2.39-2.46 (1H, m, CH), 2.24-2.35 (1H, m, CH), 1.92-2.02 (1H, m, CH$_2$) and 1.77-1.88 (2H, m, CH$_2$). The $^{13}$C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon in the proline ring at $\delta$C 69.5 ppm. Finally analysis by mass spectrometry gave an ion at 206.1 (20%, [M+H]$^+$) Daltons, which on accurate mass measurement gave a mass of 206.1289 Daltons which corresponded well to the required mass of 206.1288 Daltons for C$_{11}$H$_{16}$N$_3$O$^+$ ([M+H]$^+$).

As some success had been achieved with benzamidazole derived catalysts, it was decided to attempt to couple 2-aminoimidazole 269 with the N-alkyl-L-prolines 175a-b. Thus N-methyl-L-proline 175a was activated with CDI in DMF for 24 h and separately triethylamine was added to 2-aminoimidazole hemisulphate salt 269 in DMF for 2 h. The activated proline mixture was then transfered to imidazole via cannula and the mixture stirred for 24 h. After an aqueous work up and column chromatography, 270 was formed in a 97% yield as a white solid. (Scheme 97)

**Scheme 97:** Preparation of 270. (a) i) CDI, DMF, 24 h; ii) 269, NEt$_3$, rt, 2 h, (iii) rt, 24 h

The analytical data obtained for 270 confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{20}$ -73.3 whilst the proton NMR spectrum gave a broad singlet at $\delta$H 9.55-11.41 (2H, br s, 2 × NH) ppm for the NH protons. The CH protons of the imidazole appeared as a singlet at $\delta$H 6.82 (2H, s, 2 × CH) ppm, whilst the methine proton for the proline was observed as double of doublets at $\delta$H 3.08 (1H, dd, $J$ 10.5, 4.6 Hz, CH) ppm. The N-methyl signal appeared as a singlet at 2.44 (3H, s, Me) ppm, whilst the methylene signal of the proline were at $\delta$H 3.15-3.19 (1H, m, CH) ppm, 2.40-2.47 (1H, m, CH), 2.23-2.33 (1H, m, CH), 1.91-1.98 (1H, m, CH), and 1.74-1.86 (2H, m, CH$_2$) ppm. The $^{13}$C NMR spectrum gave only 7 non-equivalent signals as the two CH signals for the imidazole were not detected
even on long acquisition time or in the HSQC or HMBC spectrum. This was a common problem for other compounds in this series. The methine carbon of the proline ring was observed at $\delta_C 68.5$ ppm and finally analysis by mass spectrometry gave an ion 195.1 (100%, [M+H]$^+$), which on accurate mass measurement gave a mass of 195.1240 Daltons which corresponded closely to the required mass of 195.1241 Daltons for $\text{C}_9\text{H}_{15}\text{N}_4\text{O}^+$ ([M+H$^+$]).

Similarly the catalyst $271$ was prepared activating $N$-benzyl-L-proline $175b$ with CDI in DMF for 24 h, followed the addition of $269$, followed by stirring for 2 days. After an aqueous work up, trituration with diethyl ether gave the target product $271$ in 68% yield as an off-white solid. (Scheme 98)

![Scheme 98: Preparation of 271.](image)

The analytical data obtained for $271$ confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{20} -198$ whilst the proton NMR spectrum gave a broad multiplet at $\delta_H 9.38-11.51$ (2H, br m, 2 $\times$ NH) ppm for the imidazole NH protons. The aromatic ring protons for the benzyl groups were observed at $\delta_H 7.15-7.31$ (5H, m, Ph) ppm, whilst the imidazole CH protons were a singlet at $\delta_H 6.76$ (2H, s, 2 $\times$ CH). Signals at $\delta_H 3.82$ (1H, d, $J$ 12.7 Hz, CH), and 3.57 (1H, d, $J$ 12.7 Hz, CH) ppm correspond to the methylene of the benzyl group whilst the methine proton for the proline was observed as double doublet at $\delta_H 3.31$ (1H, dd, $J$ 10.4, 4.2 Hz, CH) ppm. The remaining signals of the proline ring were at $\delta_H 3.00-3.07$ (1H, m, CH), 2.37-2.46 (1H, m, CH), 2.16-2.27 (1H, m, CH), 1.87-1.97 (1H, m, CH), and 1.66-1.82 (2H, m, 2 $\times$ CH) ppm. The $^{13}$C NMR spectrum again only gave 12 non-equivalent signals with two CH Imidazole not detected as previously observed for compound $270$. The methine carbon in the proline ring was at $\delta_C 66.7$ ppm and finally analysis by mass spectrometry gave an ion 293.1 (55%, [M+Na]$^+$), which on accurate mass measurement gave a mass of 293.1376 Daltons which corresponded well to the required mass of 293.1373 Daltons for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{ONa}^+$ ([M+Na]$^+$). An X-ray structure was also obtained for $271$ (vide infra).
2.3 Conclusion.

In conclusion, from the work in this chapter we were able to prepare a range of catalysts which are L-proline (Figure 23(i)) or L-alanine/phenylalanine (Figure 23(ii)) derived. In both these cases, the \( N \)-substituent is intended to act as the base in any catalytic reactions whilst the guanidine, amidine or hydrazine moiety is intended to act as a hydrogen bonding site. The next chapter of the thesis will discuss the applications of these catalysts to the Michael reaction.

![Catalysts prepared in this chapter](image)

**Figure 23:** Catalysts prepared in this chapter
2.4 The Michael addition reaction of 2-hydroxy-1,4-naphthoquinone to β-nitrostyrene

As previously stated, the initial aim of this project was to prepare a range of C₂-symmetrical catalysts to study their application to asymmetric transformations. To this end, the Michael reaction between β-nitrostyrene 77 with 2-hydroxy-1,4-naphthoquinone 168 was found to be a robust reaction in our hands. This was because it did not suffer from problems associated with side reactions with the catalysts and the formation of polymeric by-products, which had been experienced in a previous study. The reaction does also not go at an appreciable rate in the absence of catalyst which makes it ideal to study this process. In general the reaction is performed by dissolving a mixture of the quinone 168 with the catalyst being studied in a given solvent and cooling this to the desired temperature, at which point the β-nitrostyrene 77 is added and the reaction monitored by sampling and ¹H NMR analysis. On completion or near completion, reaction work-up by aqueous extraction into dichloromethane followed by chromatography gave 170. The enantiomeric excess (ee) of the product was then determined using chiral HPLC. (Scheme 99) Each one of the catalyst groups prepared is discussed in turn and the results compared to previous work.

![Scheme 99: Michael reaction between β-nitrostyrene 77 and 2-hydroxy-1,4-naphthoquinone 168. (a) Catalyst, solvent, -78 °C-rt.](image)

We firstly investigated the C₂-symmetric L-proline catalysts 183-185 in this reaction and the results are given in Table 1. (Scheme 100) The catalysts 183-185, all proved to be effective catalysts leading to good conversions over (5-96) h as evidenced by ¹H NMR sampling of the reaction mixtures. However, analysis of the ee’s of the product was disappointing as the level across all solvents employed (DCM, MeCN, PhMe, THF, xylenes and benzene) were very low (1-7% ee) and essentially gave racemic mixtures even if performed at lower temperatures. The best conversions were obtained in dichloromethane and toluene, but using toluene presented some solubility problems associated with the starting material 168, which was overcome by performing the reaction at a higher dilution. We attempted the reaction in the presence of BA and this increased the rate of reaction but had no effect on the ee (Table...
The reasons for the low ee in these reactions probably stems from observations made in the previous study\(^9\) that increasing the steric hindrance at the \(N\)-substituent leads to a lowering in ee. In this respect the failure to prepare the \(N\)-methyl substituted \(C_2\)-symmetric L-proline catalyst 182 was unfortunate at this might be expected to give a higher ee.

**Scheme 100:** Formation of 170 using catalysts 183, 184 and 185:

Conditions: Catalyst (0.1 equiv.) then either (a) 0 °C, 7-8 h then rt or (b) -78 °C - -20 °C, or (c) with benzoic acid (BA); see table 1

**Table 1**: Entries and results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
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<th>PhMe</th>
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</tr>
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<td></td>
<td></td>
<td>b</td>
<td>3 (5/48)</td>
<td>----</td>
<td>----</td>
<td>4 (5/53)</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
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<td>----</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c</td>
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<td>----</td>
<td>----</td>
<td>1 (24/41)</td>
<td>1 (24/53)</td>
<td>----</td>
</tr>
</tbody>
</table>

i) Results are given as ee (time (h)/yield (%))

The next series of catalysts to be tested were analogues of the previously studied \(N\)-methyl-L-proline catalyst 176a. In these catalysts the guanidine 219 is substituted with a methyl-group in order to disrupt H-bonding possibilities and the Boc-protected analogues of these catalysts 208 and 212 were also prepared in an attempt to increase steric bulk at the guanidine. Catalyst 176a had been previously studied\(^9\) in toluene and dichloromethane, which gave the best results from this work (Table 2, entries 1a). We initially repeated the reactions using BA as an additive and whilst the reactions were successful, the yields and ee’s were generally lower indicating that BA did not improve the reaction. (Table 2, entries 1b) Despite
this, some apparent increase in the rate of reaction was observed, particularly in the case of the reaction in toluene (Table 2, entry 1b). The corresponding catalyst 219 with an N-methyl substituent on the guanidine was studied next and it was apparent that this modification had a very detrimental effect on the ee’s observed as reactions in dichloromethane and toluene did occur, however the ee’s and yields were comparatively lower in both cases (Table 2, entry 2a). (Scheme 101).

Scheme 101: Formation of 170 using catalysts 176a, 219, 208 and 212:

Conditions: Catalyst (0.1 equiv.) then either (a) 0 °C, 7-8 h then rt, or (b) with benzoic acid (BA), or (c); -78 °C - -20 °C; see table 2

Table 2: Entries and results.

<table>
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<tr>
<th>Entry</th>
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<th>Cons.</th>
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<th>Et2O</th>
<th>PhH</th>
<th>CCl4</th>
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<td>37</td>
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<td>26</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>13</td>
<td>17</td>
<td>9</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>2</td>
<td>219</td>
<td>a</td>
<td>5</td>
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<td>1</td>
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<td>----</td>
<td>----</td>
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<td></td>
<td></td>
<td>b</td>
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<td>----</td>
<td>----</td>
<td>----</td>
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<td>4</td>
<td>212</td>
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<td>7</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>3</td>
</tr>
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</table>

i) Results are given as ee (time (h)/yield (%))

The analogous Boc-substituted catalyst 208 was also studied, which gave broadly comparative results with catalyst 208 (Table 2, entry 3a-c), however in dichloromethane and toluene reactions the ee’s were lower at 19% and 22% respectively. Despite this we observed that the rate of reaction appeared to be increased and indeed in toluene the reaction was essentially complete after 2 h compared to 100 h for catalyst 176a. We thus repeated both reactions using BA as an additive (Table 2, entry 3b) and in both cases observed an improved ee (28% and
37%) over a longer time (168 h and 48 h). One experiment was performed in toluene at a lower temperature (Table 2, entry 3c) however, this gave no improvement in the ee of the product and was found to be lower yielding and slower. Finally, the guanidine N-methyl substituted catalyst 212 was studied (Table 2, entry 4a) and across the solvents used in comparison with 208 (Table 2, entry 3a), the catalyst gave lower ee’s (3-9%), was slower and gave lower yields. (Scheme 101).

The catalysts 212 and 219 in which the guanidine is N-methyl substituted might be offering some insight into the mode of the reaction and obviously three factors are at play. Firstly the steric hindrance from the methyl group, which might be considered to be minimal and secondly, the donation of electron density by the methyl group which again might be considered to be small. Probably the most important factor might be the disruption of H-bonding within the molecule as blocking this position will obviously interfere with intramolecular H-bonding. The introduction of the methyl group obviously seems to have a very detrimental effect on the reaction and a rationale of the effect of this will be discussed later.

The next group of catalysts studied were the benzimidazole, imidazole and related heterocyclic catalysts. Again, the results for catalyst 179a from the previous study97 (Table 3, entry 1a) were taken as standards to compare against. Initial reactions with the guanidine N-methyl substituted catalysts 230 (Table 3, entry 2a) and 233 (Table 3, entry 3a) gave typically good yields across most solvents, however the ee’s observed were always very low (3-14%) and reaction times slower than for 179a. This observation seems to support those made for catalysts 230 and 233 and a rationale for this effect is discussed in a later chapter. Catalyst 228 in which the amide group has been reduced to give an amine was studied in toluene and this had proven to be the best solvent for these catalysts, however the ee obtained was surprisingly low and the reaction was sluggish (Table 3, entry 4a). Interestingly the addition of BA to the reaction led to an increase in ee (Table 3, entry 4b) in toluene to 21%, a result which was similar to that in dichloromethane (21% ee). It is likely that the mechanism of this reaction will differ from the other amide catalysts and as such we did not study this process with other catalysts as the level of ee was still fairly low. Results for the imidazole catalysts 270 and 271 (Table 3, entries 5a and 6a) were similar to those for the benzimidazole example in that the catalysts worked but were sluggish, however the ee’s were low in both solvents studied. The heterocyclic catalyst 268a and 262 (Table 3, entries 7 and 8) gave very poor ee’s and variable yields and reaction times particularly in toluene, which was probably due to solubility problems. This was improved to some extent by the use of benzene as a solvent, however the ee’s obtained for the
product were still poor. These results seem to indicate that a bidentate H-bonding motif seem to be essential for these catalysts to give any ee and removing this feature from the catalysts has a detrimental effect on the process. (Table 3) (Scheme 102)

Scheme 102: Formation of 170 using catalysts 179a, 228, 230, 233, 270, 268a and 262:

Conditions: Catalyst (0.1 equiv.) then either (a) 0 °C, 7-8 h then rt, or (b) with benzoic acid (BA).

Table 3: Entries and results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Cons.</th>
<th>DCM</th>
<th>PhMe</th>
<th>Xylenes</th>
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<td>10 (22/48)</td>
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<td>7</td>
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i) Results are given as ee (time (h)/yield (%))

We next investigated the hydrazine derived N-methyl-L-proline catalysts 238, 240, 242 and 244; the results are shown in Table 4. Initially the unsubstituted hydrazine catalyst 238 was studied and the first general observation was that it was a successful catalyst in all solvents with the exception of benzene (Table 4, entry 1a). Interestingly the reaction was generally slow giving yields of 41-70% over 72-124 h, however the reaction in toluene was quite rapid giving 71% yield over 2 h. In all these reactions, the ee’s were very low (3-5%) which is essentially
r racemic. We next investigated the phenyl-substituted catalyst 244 and found that the reaction was again successful in all the solvents studied, but that the reactions in the aromatic solvents toluene, benzene and xylenes were very rapid (1-2 h) in comparison with dichloromethane (48 h) (Table 4, entry 2a). We thus repeated the reaction in toluene at a lower temperature and obtained an improved 17% ee over a longer reaction time (24 h) (Table 4, entry 2b). Studies on the Boc-substituted catalyst 240 (Table 4, entry 3a) indicated that the reaction was very slow with this catalyst taking 168 h to give yields of 10-71% with some solubility problems occurring in toluene, xylenes and diethyl ether. The ee’s observed in the products were generally low 2-13% with the highest being in toluene. On studying the Cbz-substituted catalyst 242 (Table 4, entry 4a) it was found that the yields were generally better (27-74%) and the conversion times shorter (10-96 h). However, the ee’s were low (2-10%) with the best result being observed in toluene, which unfortunately was the lowest yielding reaction. The reaction in dichloromethane was repeated (Table 4, entry 4b) at a lower temperature, however this led to no appreciable improvement in ee. (Scheme 103)

Scheme 103: Formation of 170 using catalysts 238, 240, 242 and 244: Conditions: Catalyst (0.1 equiv.) then either (a) 0 °C, 7-8 h then rt or (b) -78 °C - -20 °C, see table 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
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<td>4 (124/41)</td>
<td>NR</td>
</tr>
<tr>
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<td></td>
<td></td>
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<td>3 (1/59)</td>
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<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>3</td>
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<td>a</td>
<td>4 (168/42)</td>
<td>13 (168/19)</td>
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<td>9 (168/71)</td>
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<td>b</td>
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i) Results are given as ee (time (h)/yield (%))
Following the work on the L-proline derived catalysts we examined those derived from L-alanine and L-phenylalanine and initially we investigated the catalysts. The N-Cbz-protected guanidines 245 and 252 were initially investigated, and these were found to be effective catalysts giving good yields and reasonable reaction times in all the solvents studied (Table 5, entries 1a and 2a). Compound 245 gave an ee of 7% in dichloromethane over 4 d and 13% in toluene over 20 h, whilst 252 gave a 4% ee in dichloromethane over 28 h and 15% ee in toluene over 3 d. The latter result was repeated using benzoic acid as a co-catalyst and this led to a considerably more rapid reaction time (2 h) and an improvement in ee to 25% (Table 5, entries 2b). A further reaction was performed at -78 °C over 10 h followed by stirring overnight at -20 °C (Table 5, entries 2c) which gave an ee of 22%. Following this the N-Boc-protected guanidines 246 and 253 were investigated and again were found to be effective catalysts (Table 5, entries 3a and 4a). Compound 246 gave an ee of 10% in dichloromethane over 2 d and 11% ee in toluene over 20 h, whilst catalyst 253 gave a 9% in dichloromethane over 2 d and 18% ee in toluene over 1 h. This latter result was interesting as it was a very fast conversion when compared to the other catalyst and was repeated at -78 °C over 8 h followed by 16 h at -20 °C, which gave an improved ee of 31% (Table 5, entries 4c). The phenyl-substituted catalyst 255 (Table 5, entry 5a) gave and ee of 18% in dichloromethane over 8 h and 21% in toluene over 10 h. Finally the $C_2$-symmetric catalyst 256 (Table 5, entry 6a) gave an ee of 21% in dichloromethane over 2 h and 23% ee in toluene over 2 h. These rapid reactions were repeated at -20 °C and improved ee’s of 25% in dichloromethane over 3 d and 25% in toluene over 1 d were obtained (Table 5, entry 6c). These results seem to suggest the bulkier benzyl group found in the L-phenylalanine catalysts gives better ee’s and more rapid reaction times than that of the methyl in L-alanine. This observation is contrary to the effect noticed in the L-proline series where increased steric bulk at the nitrogen led to a nearly complete loss of stereoselectivity in most cases. A rationale for this effect will be discussed later. (Table 5, Scheme 104)
Scheme 104: Formation of 170 using catalysts 245, 252, 246, 253, 255 and 256:

Conditions: Catalyst (0.1 equiv.) then either (a) 0 °C, 7-8 h then rt, or
(b) with (BA); or (c); -78 °C - -20 °C; see table 5

<table>
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<th>Entry</th>
<th>Cat.</th>
<th>DCM</th>
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<th>Et2O</th>
<th>PhH</th>
<th>CCl4</th>
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<td></td>
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<tr>
<td>3</td>
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<td>----</td>
<td>----</td>
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<tr>
<td>4</td>
<td>253</td>
<td>a</td>
<td>9 (8/49)</td>
<td>18 (1/46)</td>
<td>20 (15/41)</td>
<td>15 (10/85)</td>
<td>11 (10/57)</td>
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<td>c</td>
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</table>

i) Results are given as ee (time (h)/yield (%))
Finally, the benzimidazole catalysts 247 and 254 were investigated (Table 6) and it was observed that the reactions were typically slower that those previously investigated for similar structures. Thus 247 gave an ee of 10% in dichloromethane over 4 d and 16% in toluene over 7 d (Table 6, entry 1), whilst 254 gave a 10% ee in dichloromethane over 5 d and 20% ee in toluene over 5 d (Table 6, entry 2). (Scheme 105)

Scheme 105: Formation of 170 using catalysts 247 and 254:

Conditions: Catalyst (0.1 equiv.) the either i) 0 °C, 7-8 h then rt, see table 6.

Table 6: Entries and results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>DCM</th>
<th>PhMe</th>
<th>Xylenes</th>
<th>THF</th>
<th>Ether</th>
<th>PhH</th>
<th>CCl₄</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>247</td>
<td>10 (168/88)</td>
<td>16 (168/37)</td>
<td>14 (168/48)</td>
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<td>17 (120/75)</td>
<td>9 (120/81)</td>
<td>9 (72/65)</td>
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</tr>
</tbody>
</table>

i) Results are given as ee (time (h)/yield (%))
2.5 Conclusions.

The previous work in this area\textsuperscript{97} had demonstrated that $N$-methyl-$L$-proline derived catalysts give better ee’s in the reactions and that increasing the size of the $N$-substituent generally had a detrimental effect on the ee. Thus the studies on the $C_2$-symmetric catalysts \textbf{183}, \textbf{184} and \textbf{185} unsurprisingly gave very poor ee’s. Other reactions with $N$-methyl-substituted systems were more successful and the best substituent groups on the guanidine appears to be those with Cbz-, Boc-, phenyl- and benzimidazole substituents, whilst the $N$-methyl substituted variants of the Cbz-, Boc- and benzimidazole catalysts all led to diminished ee’s. Throughout this work the best solvent for this reaction appeared to be toluene (and other aromatic solvents) with dichloromethane also being effective in some cases. Acetonitrile and other solvents were not as successful. Cooling of the more rapid reactions appears to increase the ee of the product however, yields are lower and reaction times are prolonged. In the case of the $L$-alanine and $L$-phenylalanine $N,N$-dimethyl catalysts there is a general trend for and increased ee in the case of reactions using the $L$-phenylalanine derived catalysts. This might reflect that some level of steric bulk at the chiral centre is required for an increased ee.

Throughout this work several catalysts seemed to increase the rate of reaction leading to completion or near completion in 1-4 h instead of the more typical 2-7 days, particularly catalysts \textbf{208} + BA, \textbf{184} + BA, \textbf{185} + BA, \textbf{244}, \textbf{252} + BA, \textbf{253} and \textbf{256}. The exact reason for this was unclear and we thus decided to investigate the catalysts further using X-ray crystallography.
2.6 Crystallographic and racemisation studies

From the beginning of this project we have been interested in the crystallographic nature of our catalysts as it was felt that this information might lead to an insight into the efficiency (or not) of the systems employed.

We were interested in the presence of hydrogen bonds (H-bonds) which occur when a “donor” atom donates its covalently bonded hydrogen atom, OH or NH for example, to an electronegative “acceptor” atom. This might be the oxygen of a carbonyl or an OH or the nitrogen of an amine. Jeffrey categorized H-bonds strengths by considering the donor-acceptor distances, with a distance of 2.2-2.5 Å being “strong and mostly covalent”, 2.5-3.2 Å as “moderate and mostly electrostatic” and 3.2-4.0 Å as “weak and electrostatic”. Energies for these bonds are given as 167-58, 63-17 and <17 kJmol⁻¹ respectively. The hydrogen atoms in moderate H-bonds often do not lie on the straight line connecting the donor to acceptor, so donor-acceptor distance will slightly underestimate the length of the H-bond and the presence of an energetically significant hydrogen bond can be inferred when a donor and acceptor are within 3.5 Å of each other.

The initial crystallographic work performed by the previous student on this project gave some insight into the H-bonding patterns observed in the N-methyl-L-proline catalysts 176a, 177a, 178a and 179a catalysts. Three of these catalysts 176a, 177a and 179a, had a distinctive H-bonding pattern (Figure 24) which consisted of a strong intramolecular H-bond between the amide protons (NH) and the pyrrolidine nitrogen (bond a) and a complementary NH-bond between the guanidine NH and the amide carbonyl (bond b). This pattern holds the amide in a trans-configuration (E-) and in compound 176a we refer to this as E-abd (vide infra) as the carbamate has an H-bond to the guanidine NH₂. In the case of 177a and 179a where no carbamate is present there is an E-αb pattern found in both of them. We reasoned that the H-bonds found in these structures might still be present whilst they are in solution and might explain why these bases are slow to catalyse the Michael reaction. Some NMR evidence is also available which demonstrated that the ¹³C NMR spectrum data for compound 177a shows distinctive individual signals for each phenyl suggesting that interconversion between these two phenyls is not occurring on the NMR timescale. Some further evidence for this is found in the X-ray structure of the guanidine 178a (Figure 24) obtained by a previous worker. This compound differs in its H-bonding pattern in that the pyrrolidine amine (N1) is not intramolecularly H-bonded and only the carbonyl-NH bond (bond b; N3(H1)⋯O1 = 2.021 Å) is present as the amide is in the form of a N-methylene amide; this is termed a Free-b type
system. Whilst this evidence is tenuous, this difference in H-bonding might explain the increased reaction rate observed in the Michael addition reaction for compound 178a, which proceeded in a 91% yield over 4 h, and was rapid when compared to the timescale of the other catalysts. Another interesting feature is the N4-phenyl group found in catalyst 177a appears to eclipse the nitrogen N1. Catalysts 177a-d gave very poor ee’s in their reactions to form 170 and this eclipsing of the N might be a contributing factor. (Figure 24)

Figure 24: X-Ray structure of compounds 176a, 177a, 178a and 179a.97
However, the most surprising and somewhat troubling result from crystallography (which became apparent midway through this work) was found when examining the structure of 177a which was found to crystallise as a 2:1 (S:R) mixture of epimers within the unit cell. (Figure 25).

![Figure 25: The S:R epimeric mixture observed for 177a.](image)

Similar racemisation was observed in the crystal structures of compounds 240 and 245, both of which produced two types of crystals one of which was racemic and one which was the S-enantiomer. (Figure 26)

![Figure 26: X-Ray structure of compounds 240 and 245.](image)

This was a surprising observation as the L-proline used in the synthesis was of the reported specific rotation as was the N-methylproline, which was prepared using a literature
We investigated the epimerization of several of the catalysts by NMR in deuterated methanol under neutral, weakly basic (NEt₃) and acidic (PhCO₂H) conditions and whilst decomposition (hydrolysis) was observed over prolonged time-periods, no evidence of deuterium incorporation at the L-proline stereogentic centre was observed.

We concluded from this study that the epimerisation must be occurring at the CDI coupling stage and wanted to reinvestigate the most successful catalyst to date 176a. We repeated the preparation of 176a by coupling 175a with 224, which was activated using CDI in DMF over a range of times. Analysis of the products using chiral HPLC was performed and the traces compared with an independently prepared racemic sample of 176a. (Scheme 106, Table 7)

Scheme 106: (a) i) 175a, CDI, DMF, 5 min/1 h/24 h, rt; ii) 224, 24h.

Table 7: Preparation of catalyst 176a over varying activation times.

<table>
<thead>
<tr>
<th>Activation time</th>
<th>ee/% (HPLC)</th>
<th>[α]D</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
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<td>87</td>
<td>-70</td>
<td>47</td>
</tr>
<tr>
<td>60 min</td>
<td>57</td>
<td>-41</td>
<td>48</td>
</tr>
<tr>
<td>24 h</td>
<td>33</td>
<td>-24</td>
<td>53</td>
</tr>
</tbody>
</table>

i) Estimated errors of +/- 3%

From these experiments, it is apparent that the reaction, even under short activation times, gives a good yield of the coupled product. However, from the HPLC analysis and from the consistent drop in the specific rotation value, it was apparent that racemisation was occurring very rapidly even on short activation times. The only possible explanation of this was that the intermediate imidazole amide 272 was undergoing base catalysed epimerisation, via enolate 273. The likely base for this process is the N-methyl-L-proline 175a itself and in the cases where relatively strong guanidine bases are used in the coupling, their presence might exacerbate this process. (Scheme 107)
Scheme 107: Proposed mechanism for the racemisation of the catalyst 176a.

This is obviously a major blow to the use of these compounds as catalysts, as racemisation in the catalyst will obviously lead to lower enantiomeric excesses if they are in any way effective. We had unfortunately utilised long activation times in the synthesis of the majority of the catalyst we have studied and as a result of this and the obviously rapid onset of the racemisation (5 min) the ee’s are likely to have been lowered and are unreliable. We repeated the preparation of 176a, one of the more successful catalysts at the latter end of the study taking care to minimise racemisation and purify the compound and this work is detailed after the discussion of the X-ray structures.
We obtained X-ray structures on several of the catalysts and these gave some insight into the possible H-bonding patterns found in these catalysts in solution. The two \(C_2\)-symmetric catalysts 183 and 185 were initially studied, and were found to possess similar hydrogen bonding patterns. In compound 183, one amide NH was H-bonding to the proline nitrogen (bond a; N4(H14)...N5 = 2.437 Å) and this hydrogen was also H-bonding to the other amide carbonyl (bond c/b': N4(H14)...O2 = 1.989 Å). The amide carbonyl is also H-bonding to the guanidine NH\(_2\) (bond b; N3(H12)...O3 = 1.994 Å). The other proline nitrogen is free of intramolecular H-bonds so this H-bonding interaction overall is an \(E\)-abc/\(Free\)-b' arrangement. (Figure 27)

![Image of X-ray structure of 183](2016ncs0617)

Figure 27: X-ray structure of 183 (2016ncs0617)

An identical H-bonding patterns was observed for 185 in that one amide NH was H-bonding to the proline nitrogen (bond a; N4(H4)...N5 = 2.276 Å) and this hydrogen was also H-bonding to the other amide carbonyl (bond c/b': N4(H4)...O1 = 1.932 Å). The amide carbonyl is also H-bonding to the guanidine NH\(_2\) (bond b; N3(H3B)...O2 = 2.059 Å). Again the other proline nitrogen is free of intramolecular H-bonds so this H-bonding interaction overall is also an \(E\)-abc/\(Free\)-b’ arrangement. (Figure 28)
Figure 28: X-ray structure of 185 (2016ncs0616)

In both 183 and 185 it is apparent that the L-proline nitrogen (N1) is not involved in intramolecular hydrogen bonding and this might leave it free for base catalysed reactions. These observations might explain why several of the reactions of these catalysts (and catalyst 184) took relatively short times to complete (5-48 h, see Table 1, page 75). Unfortunately it is also apparent that the relatively strong intramolecular H-bonds of the guanidine NH’s and the carbonyls also seem to preclude the formation of the bidentate H-bonding pattern we had hoped for in our proposal.

We next looked at the X-ray structures of the compounds 176a, 219, 208, 212 and a comparison of the H-bonding patterns found in these molecules. Compound 176a had already been studied in the previous work. This compound gave two H-bonds between the amide carbonyls and two of the N-H’s of the guanidine (bond b; N3(H51) O1 = 1.871 Å and bond d; N3(H50)...O2 = 2.004 Å), as well as a H-bond between the proline nitrogen atoms (N1) and the amide NH (bond a; N2(H53)...N1 = 2.257 Å) is an E-abd type. (Figure 29)
Compound 219 was prepared in order to disrupt the intramolecular hydrogen bonding patterns in the catalysts. Unfortunately, its structure from X-ray gave more evidence of the proposed racemisation as the unit-cell had a 2:1 mixture of S:\(R\) enantiomers. The S-enantiomer crystals were studied and it was apparent a switching of H-bonding had occurred, however the compound still had two H-bonds between the amide carbonyls and two of the N-H’s of the guanidine (bond b; N7(H34)…O4 = 1.899 Å and bond c; N6(H33)…O5 = 1.949 Å). The H-bond between the proline nitrogen atom (N5) and the amide NH (bond a; N6(H33)...N5 = 2.440 Å) was also still present leading to an \(E\)-abc arrangement. (Figure 30)
The analogous Boc-protected compound 208 was prepared in order to study changes in steric factors near the guanidine and surprisingly it had the same H-bonding patterns (E-abc) as the methylated catalyst 219. Catalyst 208 had two H-bonds between the amide carbonyls and two of the N-H’s of the guanidine (bond b; N3(H3)...O1 = 1.942 Å and bond c; N2(H1)...O2 = 2.092 Å). The H-bond between the L-proline nitrogen atom (N1) and the amide NH (bond a; N2(H1)...N1 = 2.100 Å) was also present but was considerably shorter in this unmethylated case. (Figure 31)

![Figure 31: X-ray structure of 208 (2017ncs0423)](image)

This observation is interesting as catalyst 208 gave very rapid reaction times in toluene and if the enolate is able to form a bidentate complex 275a with the quinone 168 then this might act as the intermediate. Alternatively, a protonated version of 208 could interact with nitrostyrene 77 leading to the intermediate 275b and this could be the reactive intermediate. In both of these species the chiral centre of the proline is remote from the position of reaction which might explain the low ee’s observed in this reaction (Figure 32)
Finally, in this series, the catalyst 212 possesses a structure with identical H-bonding patterns (E-abc) to catalysts 219 and 208. Catalyst 212 had two H-bonds between the amide carbonyls and two of the N-H’s of the guanidine (bond b; N3(H3)...O1 = 1.921 Å and bond c; N2(H2)...O2 = 1.923 Å). The H-bond between the proline nitrogen atom (N1) and the amide NH (bond a; N2(H2)...N1 = 2.367 Å) was also present. This catalyst gave very slow reaction times and very low ee’s in all the solvents studied and this might add strength the supposition that substituting hydrogens on the guanidine leads to a lowering of ee, possibly because we are blocking a site for intermolecular H-bonding interactions. (Figure 33)
We were unable to obtain any X-ray data on the methyl-substituted benzimidazoles 230 and 233, however we were able to obtain a structure for the imidazole compound 271 and the pyridine catalyst 268a.

Compound 271 had a similar H-bonding pattern ($E$-ab) to the catalyst 179a, in that it possessed a H-bond between the proline nitrogen and the amide NH bond (bond a; N2(H2)...N1 = 2.356 Å) and a H-bond between the imidazole NH and the amide carbonyl (bond b; N4(H4)...O1 = 2.239 Å). The ee’s for the reaction of this catalyst were low, which might be due to the effect of the N-benzyl group, however the corresponding N-methyl catalyst 270 gave equally low ee’s, which might indicate the benzimidazole ring played a role in the reasonable ee’s achieved with catalyst 179a. (Figure 34)

![Figure 34: X-ray structure of 271 (2018ncs0156)](image)

The pyridine catalyst 268a had a single H-bond ($E$-a) between the proline nitrogen and the amide NH bond (bond a; N2(NH2)...N1 = 2.294 Å). Reaction times were reasonable for this catalyst (48 h) which might reflect the basicity of the pyridine, however no appreciable ee’s were observed in any reactions. (Figure 35).
Figure 35: X-ray structure of 268a (2017ncs0802)

An X-ray structure was also obtained for the Boc-hydrazine catalyst 240, which was found to be a 1:1 mixture of the R- and S-enantiomers of the catalyst. This indicates that either the reaction has proceeded with complete racemisation or that the 1:1 mixture has crystallised from a partially racemised mixture. Despite this on consideration of the S-enantiomer, a similar H-bond between the proline nitrogen and the amide HN bond (bond a; N2(H2)...N1 = 2.229 Å) was observed (E-a type). This was shorter than other similar catalysts, which might explain the slow reaction times for this compound compared to the other hydrazine catalyst. (Figure 36).

Figure 36: X-ray structure of 240 (2017ncs0860)

The X-ray structure of the phenyl hydrazine catalyst 244 was also found to be a 2:1 mixture of the S- and R-enantiomers of the catalyst, indicating partial racemisation, from which
the 2:1 mixture crystallised out preferentially. The H-bond pattern is reminiscent of the pattern in the majority of the guanidine catalysts in that it is an E-amide-ab’ type arrangement. As such, there is a H-bond between the nitrogen of the pyrrolidine and the amide NH bond (bond a; N2(H2)...N3 = 2.285 Å) and a H-bond between the amide carbonyl and the other NH of the hydrazine (bond b’; N1(H1)...01 = 2.672 Å). This catalyst gave a very short reaction time in the Michael reaction (1 h in toluene, xylenes or benzene) which might be explained by the presence of the hydrazine PhNH which is likely to be more basic than the examples where this NH is present as a carbamate. Low ee’s (2-3%) were observed for this catalyst, however on cooling the ee in toluene was improved to 17%. (Figure 37).

![X-ray structure of 244](2019ncs0081)

**Figure 37:** X-ray structure of 244 (2019ncs0081)

X-Ray structures were also obtained for the dimethyl-L-alanine catalyst 245 and the two dimethyl-L-phenylalanine catalysts 252 and 255. (Figure 37)

Again the dimethyl-L-alanine catalyst 245 crystallised as a racemic mixture but examination of the S-enantiomer indicated an E-abc type with H-bonds between the N-H of the amide and the dimethylamine together with a H-bond between a guanidine NH and the amide carbonyl (bond a; N3B(HN3)...N4 = 2.301 Å and bond b; N2(HN2A)...O3B = 2.049 Å). A third H-bond between the amide NH and the carbonyl of the Cbz groups was also observed (bond c; N3B(HN3)...O2 = 1.961 which was the shortest H-bond of the three. (Figure 38)
The dimethyl-L-phenylalanine catalyst 252 gave no signs of racemisation in the crystal and an *E*-abd H-bonding pattern. It was found that an H-bond between the N-H of the amide and the dimethylamine was present together with a H-bond between a guanidine NH and the amide carbonyl (bond a; N3(HN3)...N4 = 2.484 Å and bond b; N2(HN2B)...O3 = 2.030 Å). A third H-bond between was again observed but this time it was between the guanidine NH2 and the Cbz-carbonyl (bond d; N2B(HN2A)...O2 = 1.977 Å), which again was the shortest H-bond of the three. (Figure 39)
Finally, the structure of the dimethyl-L-phenylalanine-phenyl guanidine catalyst 255 was obtained, which showed no signs of racemisation. This was found to have a Free-b’ type H-bonding pattern, as it lacked the amide NH bond, as the amide was present as an N-methylene formamide structure. The only intramolecular H-bond was between the guanidine NH$_2$ and the amide carbonyl (bond b; N7(H7A)...O2 = 1.981 Å). (Figure 40)

![Figure 40: X-ray structure of 255 (2018ncs0072)](image)

Reflecting on the results from these three catalysis, the reaction with the dimethyl-L-alanine catalyst 245 gave poor ee’s (7-13%) over long reaction times (18-96 h), which might be a reflection on the degree of racemisation or possibly the level of H bonding. The dimethyl-L-phenylalanine catalyst 252 gave better ee’s (4-25%) but again relatively slow reaction times (2-120 h). In contrast, the dimethyl-L-phenylalanine phenyl guanidine catalyst 255 gave rapid reaction times (8-10 h) in all solvents and the ee’s (18-21%) were high when compared to the other two catalysts. This is possibly due to the more basic nature of the guanidine, which is substituted with only one electron withdrawing carbonyl containing group, or possibly due to the lack of hydrogen bonding to the dimethyl amine making it more basic in nature. These observations might suggest that the presence of the carbamate protecting groups is detrimental to the efficiency of the reaction and does not lead to a high ee product.
2.7 Conclusions from the X-ray structures and studies reported by Lygo and Moore

The first conclusion of note from the X-ray structures is that the presence of racemisation is likely to prevent the catalysts from being effective and if this problem cannot be overcome their utility is limited. Some unpublished work was performed by Professor Barry Lygo and Graham Moore, and was reported in a thesis in 2013,\textsuperscript{110} which related to the formation of diamine catalysts for organocatalysis of the aldol reaction. One initial observation from this work was that the coupling of the N-Methyl prolines 175a to form the corresponding amide 276 was problematic under a variety of conditions, as we have observed. Another route, which attempted to convert the ester 226 into 276 via substitution, also failed. (Scheme 108)

![Scheme 108](image)

Scheme 108: (a) i) EtO$_2$CCl or SOCl$_2$ or tBuO$_2$CCl, DCM, NEt$_3$. ii) NH$_3$ in MeOH, rt, 17 h; (b) NH$_3$ in MeOH, 60 °C, 24 h.

No reasoning was given for the poor yields, however high water solubility might be proposed as the synthesis of the corresponding N-ethyl, N-benzyl and N-isopropyl proline amides 278a-e, 279a-f were relatively easy to achieve via the direct coupling method. Lygo and Moore applied these catalysts to the aldol reaction of 277 with cyclohexanone 148 and catalysts 278a-e were successful in this with relatively good ee’s (46-67%). There was a correlation between increased steric bulk and increased ee which was opposite to that which we observed. (Scheme 109-I) Reaction of the catalysts 279a-f were less successful with anti-selectivity being observed (64-87%), but very poor conversion (0-11% yield), suggesting that increased steric bulk is detrimental to the reaction. No ee’s were reported for these reactions. (Scheme 109-II)
Scheme 109: Catalysts reported by Lygo and Moore\textsuperscript{110}

(a) Catalyst (3-30%), TfOH (3-30%), RT-60 °C, 24 h.

Other reactions were studied with little success including epoxidation of enones (0% ee), Biginelli reactions (7% ee), HPESW reaction (0% ee), Fluorination (10% ee), Michael addition to enones (20% ee), Robinson reactions (5% ee) and Baylis-Hillman reactions (11% ee). The Most successful of the reaction studied was the Michael reaction between cyclohexenone 281 and ethyl nitroacetate 282 which was effected with the catalysts 278b, 278d and 278e in the presence of (-)-camphor sulfonic acid ((-)CSA) leading to a 40-46% ee for the reaction with no syn-anti selectivity. (Scheme 110)

Scheme 110: Catalyst (10 mol %), (-)-CSA (10 mol %), xylenes, 48 h, 90-97% yield, 40-46% ee; R = Et, iPr, Cy.
No comments were made in this work relating to racemisation observed in the formation of these catalysts, possibly because they were predominantly made from coupling of Boc-protected L-proline followed by deprotection and reductive amination. This work also supports the poor yields we observed in the preparation of the N-Methyl-L-proline 182 and dimethyl-L-alanine 252 derived catalysts as comments relating to the instability of similar compounds in water were made. As noted, we attempted both within this work and within the group,111 the use of alternate coupling methods to CDI. However, these consistently gave poor yields, impure compounds and difficulties in purification.

As also noted, the H-bonding patterns of the compounds we have studied fall largely into four patterns (Figure 41):

- **E-abc** - The central amide takes part in three H-bonds.
- **E-abd** - The central amide takes part in two H-bonds + a carbamate H-bond.
- **E-ab** - The central amide takes part in two H-bonds.
- **Free-b** - Only the carbonyl of the amide is H-bonded to the guanidine.

Attempts to correlate ee or reaction time with the H-bonding pattern gave no clear pattern. This probably reflects that there are too many variables at play in the reactions and the only clear correlations we have are between the size of the N-substituents of the amino acid and decreased ee, and possibly, that a non H-bonded amine in the amino acid residue or a mono-carbonyl substituted guanidine leads to a faster reaction rate.

**Figure 41:** Observed common H-bonding types.

R = Me, Bn, Cy, iPr, alkyl; R' = Me, Bn, alkyl; R'' = Bn, t-Bu; R''' = H, Ph; R'''' = Me, Ph.
2.8 Repeated preparation of catalysts 176a and 208.

As the main conclusion of much of this work is that racemisation is occurring in the coupling step and that amino acid activation using CDI is a fairly rapid process (5-10 minutes) it was thought that it might be best to optimise the purity of the best catalysts to date and to retest these compounds. The two previously prepared catalysts 208 (Table 8, entry 1) and 176a (Table 8, entry 4) ee’s were firstly analysed by HPLC, specific rotation and melting point with the data shown in Table 8. Catalyst 208 was unfortunately not suitable for HPLC as we were unable to obtain data due to the lack of a strong chromophore for UV. With this data available, we also analysed various samples of the catalysts prepared under different conditions, then purified by a variety of methods. We then performed a comparative study of the data obtained. (Scheme 111). For catalyst 208 a repeat preparation at 0 °C and at RT over 5-10 minutes activation was performed and analysis by specific rotation gave consistently higher $[\alpha]_D$ values but a similar melting point (Table 8, entries 2, 3). A more compelling correlation was observed with catalyst 176a which was suitable for HPLC as it had a weak chromophore, although consistent data was hard to obtain at times, as even on repeated purification minor impurities and low solubility in hexane/IPA mixtures hindered HPLC analysis. (HPLC traces used in Table 8 are in appendix 4). Catalyst 176a was prepared on five further occasions using differing conditions (Table 8, entries 5-9). The preparations using a short activation time (entries 5, 6) were purified by column chromatography (entry 5) and then recrystallization (entry 6), and both gave higher ee’s for the products as determined by HPLC and by specific rotation. Additionally the melting point of these samples were higher than that reported by the previous worker suggesting a higher purity. As the activation time became longer (entries 7-9) the ee of the product seemed to diminish with time as determined by HPLC and specific rotation and the melting points became progressively lower as might be expected for mixed melting point depression. Interestingly a single fraction of the final experiment over 24 h activation gave an increased ee on HPLC and specific rotation analysis and a higher melting point suggesting that there might be some separation of enantiomers observed on column chromatography on silica gel112 (entry 10).
Scheme 111: Preparation of catalysts 176a and 208.

Conditions a) i) CDI, DMF, rt, 5-10 min; ii) 224 or 207, rt, 2 d.

PG = Cbz, Boc

Table 8: Entries and results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Activation T/°C</th>
<th>Purification method</th>
<th>ee/%</th>
<th>[(\alpha)]D</th>
<th>ee/%</th>
<th>Mp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>208</td>
<td>24 h/0 °C</td>
<td>Column</td>
<td>---</td>
<td>-46</td>
<td>61</td>
<td>130</td>
</tr>
<tr>
<td>2</td>
<td>208</td>
<td>5-10 min/0 °C</td>
<td>Column; recrystallize (DE)</td>
<td>---</td>
<td>-76</td>
<td>100</td>
<td>128-30</td>
</tr>
<tr>
<td>3</td>
<td>208</td>
<td>5-10 min/RT</td>
<td>Column; recrystallize (DE)</td>
<td>---</td>
<td>-75</td>
<td>98</td>
<td>128-30</td>
</tr>
<tr>
<td>4</td>
<td>176a\textsuperscript{iii}</td>
<td>3 h/0 °C</td>
<td>Column</td>
<td>ND</td>
<td>-65</td>
<td>87</td>
<td>67-70</td>
</tr>
<tr>
<td>5</td>
<td>176a</td>
<td>5 min/0 °C</td>
<td>Column</td>
<td>92</td>
<td>-70</td>
<td>93</td>
<td>117</td>
</tr>
<tr>
<td>6</td>
<td>176a</td>
<td>5 min/0 °C</td>
<td>Column; recrystallize</td>
<td>ND</td>
<td>-75</td>
<td>100</td>
<td>117</td>
</tr>
<tr>
<td>7</td>
<td>176a</td>
<td>1 h/RT</td>
<td>Column</td>
<td>57</td>
<td>-41</td>
<td>55</td>
<td>116-17</td>
</tr>
<tr>
<td>8</td>
<td>176a\textsuperscript{iii}</td>
<td>20 h/RT</td>
<td>Column</td>
<td>ND</td>
<td>-45</td>
<td>60</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>176a</td>
<td>24 h/RT</td>
<td>Column (all fractions)</td>
<td>33</td>
<td>-24</td>
<td>32</td>
<td>100-3</td>
</tr>
<tr>
<td>10</td>
<td>176a</td>
<td>24 h/RT</td>
<td>Column (single fraction)</td>
<td>63</td>
<td>-46</td>
<td>61</td>
<td>114-7</td>
</tr>
</tbody>
</table>

i) Estimated errors of +/- 3%  
ii) Estimated errors of +/- 3%  
iii) From compounds prepared by previous workers

The recrystallized catalysts were used in the catalytic Michael reaction of 77 with 168 and the results compared to those obtained previously. (Scheme 112, Table 9) The results for the reaction catalysed by 176a (Table 9, entry 1), were somewhat confusing as the reaction performed in dichloromethane was found to give a lower ee (12%) in comparison with the previously reported result of 37% ee. However, the ee reported for the reaction in toluene was the highest reported ee (56% ee) for this catalyst, or indeed any of the catalysts we have studied so far. For the Boc-substituted catalyst 208 (Table 9, entries 2 and 4) the reactions gave similar but consistently lower ee’s when performed in dichloromethane and the addition of benzoic acid (Table 9, BA, entries 3 and 5) gave a slightly increase in ee but not of any significance. For the Boc-substituted catalyst 208 (Table 9, entries 2 and 4) in toluene, the reactions gave similar but consistently higher ee’s and the addition of benzoic acid (Table 9, BA, entries 3 and 5) again...
gave a slightly increase in ee but not of any significance. There is a considerable variance of reaction yield and reaction time with the toluene results but this might be due to solubility problems encountered in these reactions in toluene.

Scheme 112: Formation of 170 using catalysts 176a and 208:
Conditions: Catalyst (0.1 equiv.) at -78 °C for 5 h then -20 °C;
See table 9

Table 9: Entries and results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Additive</th>
<th>DCM</th>
<th>Previous DCM</th>
<th>PhMe</th>
<th>Previous PhMe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>176a</td>
<td>---</td>
<td>12</td>
<td>(24/92)</td>
<td>37</td>
<td>(99/88)</td>
</tr>
<tr>
<td>2</td>
<td>208ii</td>
<td>---</td>
<td>22</td>
<td>(10/97)</td>
<td>19</td>
<td>(28/75)</td>
</tr>
<tr>
<td>3</td>
<td>208ii</td>
<td>BA</td>
<td>23</td>
<td>(10/98)</td>
<td>28</td>
<td>(186/63)</td>
</tr>
<tr>
<td>4</td>
<td>208</td>
<td>---</td>
<td>15</td>
<td>(10/71)</td>
<td>19</td>
<td>(28/75)</td>
</tr>
<tr>
<td>5</td>
<td>208</td>
<td>BA</td>
<td>19</td>
<td>(10/76)</td>
<td>28</td>
<td>(186/63)</td>
</tr>
</tbody>
</table>

i) Results are given as ee (time (h)/yield (%))
ii) Catalyst prepared by coupling at RT.

These repeated reactions did appear to lead to an improvement in ee in most cases and seem to support the observation that the poor ee’s might be due to the problems encountered with racemisation of the catalysts during their preparation.

2.9 The catalysts reconsidered.

The previous sections have highlighted significant problems with the catalysts and their methods of preparation. Even when care is taken to prevent racemisation of the catalysts there is some evident and the confidence level in the enantiomeric purity of the catalysts is low. The reason for this is two-fold, either the presence of an internal base (the N-methyl or N,N’-dimethyl groups) or the addition of a stronger base such as alkyl- or aryl-substituted guanidines. The N-Cbz and N-Boc are unlikely to have had an effect on these racemisations as the presence
of the electron withdrawing groups lowers the basicity of the guanidine. However, this lower basicity might lead to lower nucleophilicity and slower reaction time leading to a higher chance of racemisation.

We proposed alternate catalysts and the most obvious way to prevent this would be to remove the internal base and to move to a series of structures 284-289 in which the guanidine was acting as a H-bonding site and a base. In these structures, the problems with racemisation should be minimised as the amino acid does not contain a basic group and the guanidines in 284 and 286 are relatively weak bases. Compounds 285 and 287 might pose a problem as guanidine itself is basic but inspection of the NMR data for these compound might show the presence of a meso-compound if racemisation is occurring, as might X-ray analysis. Compounds 288 and 289 are of interest as these contain a chiral group at the guanidine which might help to increase ee; compound 289 also removes the racemisation problem as this does not contain an epimerisable centre. (Figure 42)

![Proposed catalysts](image)

**Figure 42:** Proposed catalysts; PG = Boc, Cbz; R = Me, Bn.
2.9.1 N-Cbz-L-proline and N-Boc-L-proline catalysts.

We initially prepared catalysts in which the L-proline was \( N \)-protected with a Cbz- or Boc group. Thus, \( N \)-Cbz-L-proline \( 290 \) was prepared by the addition of solutions of sodium hydroxide (aq. 4 M) and benzyl chloroformate in dioxane simultaneously into a cold mixture of L-proline \( 2 \) and 0.2 M sodium hydroxide. After an aqueous work up, recrystallization gave \( 290 \) in 78 % yield. Data for \( 290 \) was in agreement with the literature, in which the \(^{13}\text{C}\) spectrum gives two signals for most of the carbons, indicating the existence of restricted rotation about the carbamate bond (atropisomerism).\(^{113,114}\) A similar observation was seen with the commercial sample of \( N \)-Boc-L-proline \( 291 \) whose \(^{13}\text{C}\) NMR spectrum also displays doubling up of signals.\(^{115}\) (Scheme 113, Figure 43)

![Scheme 113: Preparation of 290. (a) i) 2, 0.2 M NaOH, 0 °C; ii) 4 M NaOH, CbzCl, Dioxane; iii) rt, 1.5 h, (pH~2).](image)

With \( N \)-Cbz-L-proline \( 290 \) in hand, catalyst \( 292 \) was prepared by reaction of Cbz-guanidine \( 224 \) at 0 °C with \( 290 \) which had been activated with CDI in dry DMF over 24 h. After an aqueous work up, chromatography gave catalyst \( 292 \) as a white solid in 67% yield. (Scheme 114)

![Scheme 114: Preparation of 292. (a) i) 290, CDI, DMF, rt, 24 h; ii) 224, rt, 48 h.](image)

The analytical data obtained for \( 292 \) confirmed its structure. The compound gave a negative specific rotation value of \([\alpha]_D^{20} \) -60.1, whilst results from NMR studies indicated the presence of rotamers which led to complex spectra where several of the signals were “doubled
The proton NMR spectrum gave a broad signal at $\delta_H 7.82-9.96$ (3H, br s, 3 $\times$ NH) ppm for the guanidine NH protons and a multiplet signal at $\delta_H 7.16-7.45$ (10H, m, 2 $\times$ Ph) ppm for the aromatic ring protons. The four doublets at $\delta_H 5.19$ (1H, br d, $J 11.7$ Hz, CH), 5.14 (1H, d, $J 12.5$ Hz, CH), 5.10 (1H, d, $J 12.4$ Hz, CH) and 5.02 (1H, br d, $J 11.7$ Hz, CH) ppm, represent the methylene protons of the benzyl groups, whilst the methine proton of the L-proline was observed as multiplet at $\delta_H 4.24-4.47$ (1H, m, CH) ppm. Other signals were observed corresponding to the remaining signals of the proline ring at $\delta_H 3.37-3.65$ (2H, m, CH$_2$), 1.98-2.32 (2H, m, CH$_2$) and 1.81-1.97 (2H, m, CH$_2$) ppm.

The $^{13}$C NMR spectrum gave the required 13 non-equivalent signals with the methine carbon in the proline ring at $\delta_C (61.8/61.7)$ ppm. Finally, analysis by mass spectrometry gave an ion 425.2 for [M+H]$^+$, which on accurate mass measurement gave a mass of 425.1814 Daltons which corresponded closely to the required mass of 425.1819 Daltons for C$_{22}$H$_{25}$N$_4$O$_5$ ([M+H$^+$]). The presence of rotamers was observed in all of the compounds in this series.

The analogous catalyst 293 was prepared by adding guanidine 224 to a solution of CDI activated N-Boc-L-proline 291. After stirring for 48 h, an aqueous work and chromatography gave 293 as a white solid in 40% yield. (Scheme 115)

![Scheme 115: Preparation of 293.](image)

The analytical data obtained for 293 confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{20} -53.8$. Analysis of the product by proton NMR again showed the presence of rotamers and gave a signal at $\delta_H 7.63-10.22$ (3H, br s, 3 $\times$ NH) ppm for the guanidine NH protons, whilst the protons of aromatic ring were observed at $\delta_H 7.27-7.38$ (5H, m, Ph). The methylene of the benzyl group appeared as singlet at $\delta_H 5.11$ (2H, s, CH$_2$) ppm whilst the signals for the proline ring were observed at $\delta_H 4.11-4.46$ (1H, m, CH), 3.28-3.62 (2H, m, CH$_2$), 1.94-2.30 (2H, m, CH$_2$) and 1.76-1.94 (2H, m, CH$_2$) ppm. The tert-butyl signal was observed as two singlets at $\delta_H 1.44/1.40$ (9H, 2 $\times$ m, 3 $\times$ CH$_3$) ppm. The $^{13}$C NMR spectrum gave the required 13 non-equivalent signals with two quaternary carbons not detected. The methine carbon in the proline ring appeared at $\delta_C (62.0/61.5)$ ppm. Finally, analysis by mass spectrometry gave an ion 391.2 (100%) for [M+H]$^+$, which on accurate mass measurement gave a mass of 391.1814 Daltons which corresponded closely to the required mass of 391.1819 Daltons for C$_{22}$H$_{25}$N$_4$O$_5$ ([M+H$^+$]).
measurement gave a mass of 391.1980 Daltons which was in close agreement with the required mass of 391.1976 Daltons for $C_{19}H_{27}N_4O_5^+$.

We also investigated the preparation of a $C_2$-symmetric catalyst 294 from $N$-Boc-L-proline 291. Thus, two equivalent of $N$-Boc-L-proline 291 were activated with CDI in DMF for 24 h, then added via cannula to a DMF solution of guanidine, generated from guanidinium chloride 206 and sodium hydride. After 48 h, an aqueous work up followed by column chromatography gave 294 as a white solid in 25% yield. (Scheme 116)

![Scheme 116: Preparation of 294. (a) i) 291, CDI, DMF, rt, 24 h; ii) 206, NaH, DMF, rt, 36 h; iii) Combine and stir, 48 h, rt.](image)

The analytical data for 294 confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{20}$ -77.1 and again the NMR showed doubling up of signals suggesting the presence of rotamers or possibly some non-equivalence of the two $L$-proline rings. The proton NMR spectrum gave a broad singlet at $\delta_H$ 6.93-11.12 (3H, br s, 3 x NH) ppm for the guanidine NH protons whilst the broad signal at $\delta_H$ 4.13-4.48 (2H, m, 2 x CH) ppm corresponded to the methine proton of the prolines. The methylene protons of the proline were observed at $\delta_H$ 3.29-3.69 (4H, m, 2 x CH$_2$) and 1.70-2.35 (8H, m, 4 x CH$_2$) ppm. Finally the tert-butyl signals were observed as two singlets at $\delta_H$ 1.45 (9H, s, 3 x Me) and 1.39 (9H, s, 3 x Me) ppm. The $^{13}$C NMR spectrum gave 9 non-equivalent signals with the methine of proline ring at $\delta_C$ 62.9/62.0 ppm. Finally analysis by mass spectrometry gave an ion at 454.3 (100%, [M+H]$^+$), which on accurate mass measurement gave a mass of 454.2654 Daltons which corresponds closely to the required mass of 454.2660 Daltons required for $C_{21}H_{36}N_4O^+_5$ ([M+H$^+$]).

2.9.2 Boc- and Cbz-$L$-alanine catalysts.

Similar catalysts were prepared from Boc-$L$-alanine 295 and Cbz-$L$-alanine 298. Initially the catalyst 296 was prepared from $N$-Boc-alanine 295 was activated with CDI in DMF for 30 min, followed by the addition a solution of $N$-Boc-guanidine 207 in DMF. After 72 h at
rt no reaction was observed so the mixture was heated at 40 °C for 48 h. At this point an aqueous work up followed by chromatography gave 296 as a white solid in 63% yield. (Scheme 117)

Scheme 117: (a) i) 295, CDI, DMF, rt, 30 min, ii) 207, DMF, 72 h, rt, then 48 h at 40 °C

The analytical data obtained for 296 confirmed its structure. The compound gave a negative specific rotation value of [α]D25 -24 whilst the proton NMR spectrum a broad singlets at δH 7.77-9.70 (3H, br s, 3 × NH) ppm for the guanidine NH protons and a broad singlet at δH 5.21 (1H, br s, NH) ppm for the amide NH protons. The methine proton of the alanine residue was observed as a broad multiplet at δH 3.90-4.31 (1H, m, CH) ppm, whilst the t-butyl signals were at δH 1.49 (9H, s, 3 × Me), and 1.44 (9H, s, 3 × Me) ppm. Finally, the methyl signal was observed as doublet at δH 1.38 (3H, d, J 7.1 Hz, Me) ppm. The 13C NMR spectrum gave the required 7 non-equivalent signals, with three of the quaternary carbons not being detected, whilst the methine carbon of the L-alanine residue was observed at δC 52.6 ppm. Finally, analysis by mass spectrometry gave an ion at 331.2 ([M+H]+) Daltons, which on accurate mass measurement gave a mass of 331.1973 Daltons which corresponded closely to the required mass of 331.1976 Daltons for C14H27N4O5+ ([M+H]+). No rotamers were detected for this compound by NMR.

Catalyst 297 was similarly prepared by activating 295 using DCI in DMF for 30 min at 0 °C, before the addition of N-Cbz-guanidine 224. After three days, an aqueous work-up followed by recrystallization from ethanol gave 297 in 71% yield. (Scheme 118)

Scheme 118: Preparation of 297. (a) i) 295, CDI, DMF, rt, 30 min, ii) 224, DMF, rt, 72 h.

The analytical data obtained for 297 confirmed its structure. The compound gave a negative specific rotation value of [α]D25 -18.8, whilst the proton NMR spectrum gave two signals at δH 7.93-10.03 (3H, br. s, 3 × NH) ppm for the guanidine NH protons and at δH 5.10
(1H, br s, NH) ppm for the carbamate NH protons. The aromatic protons appeared as a multiplet at δH 7.29-7.42 (5H, m, Ph) ppm, whilst the methylene of the Cbz group was a singlet at δH 5.15 (2H, s, CH₂) ppm. The distinctive methine of the L-alanine residue was found as broad multiplets at δH 4.17-4.40/3.85-4.08 (1H, br m, CH) ppm and as this effect was present in several of these compound this might again suggest the presence of rotamers. The methyl signal was present as a broad multiplet at δH 1.33-1.46 (3H, m, CH₃) ppm and the t-butyl of the Boc-group was seen at δH 1.46 (9H, s, 3 × Me) ppm.

The 13C spectrum gave the required 12 non-equivalent signals with one quaternary carbon not detected. The methine carbon of the alanine appeared at δC 51.8 ppm. Finally, analysis by mass spectrometry gave an ion at 365.2 (100%, [M+H]⁺), which on accurate mass measurement gave a mass of 365.1819 Daltons which corresponded exactly to the required mass of 365.1819 Daltons for C₁₇H₂₅N₄O₅⁺ ([M+H]⁺).

N-Cbz-L-alanine 298 was similarly used to prepare the catalyst 299. Thus 298 was activated with CDI in DMF over 90 min, followed the addition of N-Boc-guanidine 207. The mixture was stirred for 24 h after which an aqueous work up followed by chromatography gave 299 as a white solid in 49% yield. (Scheme 119)

\[
\text{Scheme 119: Preparation of 299. (a) i) 298, CDI, DMF, rt, 30 min; ii) 207, DMF, rt, 24 h.}
\]

The analytical data obtained for 299 confirmed its structure. The compound gave a negative specific rotation value of [α]D²⁸ -21.2, whilst the proton NMR spectrum a broad singlets at δH 8.16-10.21 (3H, br s, NH, NH₂) ppm for the guanidine NH protons and at δH 5.69-5.99 (1H, m, NH) ppm for the amide NH protons. The aromatic protons appeared as a multiplet at δH 7.24-7.39 (5H, m, Ph) ppm, whilst the methylene of the Cbz group was two doublets at δH 5.11 (1H, d, J 12.6 Hz, CH) and 5.07 (1H, d, J 12.6 Hz, CH) ppm. The methine proton of the alanine residue was observed as a broad multiplet at δH 4.10-4.33 (1H, m, CH) ppm, whilst the t-butyl signal was at δH 1.45 (9H, s, 3 × Me) ppm and finally the methyl signal was found at δH 1.38 (3H, d, J 7.0 Hz, Me) ppm. The 13C NMR spectrum gave the required 11 non-equivalent signals with two quaternary carbons not detected, with the methine carbon of the alanine residue at δC 53.1 ppm. Finally, analysis by mass spectrometry gave an ion at 365.2
([M+H]+) Daltons, which on accurate mass measurement gave a mass of 365.1819 Daltons, which corresponded exactly to the required mass of 365.1819 Daltons for C_{17}H_{25}N_{4}O_{5}^+ ([M+H]+).

The catalyst 300 was similarly prepared from N-Cbz-alanine 298, which was activated with CDI in DMF for 30 min, followed by the addition a solution of N-Cbz-guanidine 224 in DMF. An aqueous work up followed by chromatography gave 300 as a white solid in 75% yield. (Scheme 120)

![Scheme 120: Preparation of 300. (a) i) 298, CDI, DMF, rt, 30 min, ii) 224, DMF, rt, 72 h.](image)

The analytical data obtained for 300 confirmed its structure. The compound gave a negative specific rotation value of [α]D^-17.5, whilst the proton NMR spectrum again showed the presence of rotamers. A broad singlet was observed at δ_H 8.06-10.38 (3H, br s, NH, NH2) ppm for the guanidine NH protons and complex signal at δ_H 6.79-6.95/5.55 (1H, m and br d, J 6.3 Hz, NH) ppm represented the amide NH proton. The aromatic protons appeared as a multiplet at δ_H 7.27-7.40 (10H, m, 2 × Ph) ppm, whilst the methylene of the Cbz-groups were a singlet at 5.12 and a pair of doublet signals at δ_H 5.12 (1H, d, J 12.3 Hz, CH) and 5.07 (1H, d, J 12.3 Hz, CH) ppm. The methine proton of the alanine residue was observed as broad multiplets at 4.24-4.40/4.02-4.16 (1H, 2 × m, CH) ppm, whilst the methyl signal was observed at δ_H 1.37/1.23-1.30 (3H, d, J 6.8 Hz and m, Me) ppm. The 13C NMR spectrum gave the required 12 non-equivalent signals with two quaternary signals not detected and the methine carbon of the alanine residue was observed at δ_C 52.3 ppm. Finally, analysis by mass spectrometry gave an ion at 399.2 ([M+H]+) Daltons, which on accurate mass measurement gave a mass of 399.1664 Daltons which corresponded closely to the required mass of 399.1663 Daltons for C_{20}H_{23}N_{4}O_{5}^+ ([M+H]+).

2.9.3 Boc- and Cbz-L-phenylalanine catalysts.

Similarly, catalysts were prepared from N-Cbz- and N-Boc-L-phenylalanine. Thus N-Boc-L-phenylalanine 301 was activated with CDI in DMF over 90 mins and N-Boc-guanidine
207 was added. The reaction stir for 2 days and then purified by chromatography to give 302 in 44% yield. (Scheme 121)

![Chemical structure of 301 and 302](image)

**Scheme 121:** (a) i) 301, CDI, DMF, rt, 90 min; ii) 207, DMF, rt, 48 h.

The analytical data obtained for 302 confirmed its structure and again the compound appeared to be present as a mixture of rotamers. The compound gave a negative specific rotation value of $[\alpha]_D^{21} -21.2$ whilst the proton NMR spectrum gave two signals at $\delta_H 8.60$ (1H, br s, NH) and $\delta_H 7.57-10-34$ (2H, br s, 2 × NH) ppm for the guanidine NH protons with the carbamate NH proton appearing at $\delta_H 5.09$ (1H, br s, NH) ppm. The aromatic protons appeared as a multiplet at $\delta_H 6.99-7.24$ (5H, m, Ph) ppm, whilst the benzyl methylene of the phenylalanine was observed as complex signals at $\delta_H 3.15/3.00/2.72-2.91$ (2H, dd $J 13.6$, 5.0 Hz/dd $J 13.6$, 5.6 Hz/br m, CH$_2$) ppm. The distinctive methine proton for the phenylalanine residue was observed as a complex set of signals at $\delta_H 4.42/4.14-4.27$ (1H, dd, $J 5.0$, 5.5 Hz/br m, CH) ppm and the $t$-butyls were observed as singlets at $\delta_H 1.42$ (9H, s, 3 × Me) and 1.34 (9H, s, 3 × Me) ppm. The $^{13}$C NMR spectrum gave the required 12 non-equivalent signals with two quaternary carbons not detected, with the methine carbon of the L-phenylalanine appearing at $\delta_C 57.6$ ppm. Finally, analysis by mass spectrometry gave an ion at 407.2 (100%, [M+H]$^+$) which on accurate mass measurement gave a mass of 407.2291 Daltons which corresponds closest to the required value of 407.2289 Daltons for C$_{20}$H$_{31}$N$_4$O$_5$ ([M+H]$^+$).

Similarly $N$-Boc-phenylalanine 301 was activated with CDI in DMF over 30 min following which $N$-Cbz-guanidine 224 was added. After 72 h at rt, no reaction was observed and the mixture was then heated at 40 °C for 48 h. At this point, an aqueous work up, chromatography and recrystallization gave 303 in 72% yield as a white solid. (Scheme 122)

![Chemical structure of 301 and 303](image)

**Scheme 122:** (a) i) 301, CDI, DMF, rt, 30 min. ii) 224, DMF, rt, 72 h then 40 °C, 48 h.
The analytical data obtained for 303 confirmed its structure. The compound gave a negative specific rotation value of \([\alpha]D^25\) -20.8 whilst the proton NMR spectrum gave two signals at \(\delta_H 8.28-9.38\) (3H, br s, 3 \(\times\) NH) ppm for the guanidine NH protons and at \(\delta_H 4.90\) (1H, br s, NH) ppm for the carbamate NH proton. The aromatic protons appeared as a multiplet at \(\delta_H 7.20-7.41\) (8H, m, 8 \(\times\) CH) and as a doublet at \(\delta_H 7.13\) (2H, d, \(J 7.1\) Hz, 2 \(\times\) CH) ppm. The benzyl methylene for the Cbz group was observed as a singlet at \(\delta_H 5.14\) (2H, s, CH\(_2\)) ppm, whilst that of the phenylalanine residue was observed at \(\delta_H 3.20\) (1H, dd, \(J 14.2, 4.7\) Hz, CH), 2.79-3.13 (1H, br s, CH) ppm. The distinctive methine proton for the phenylalanine residue was observed as a broad multiplet at \(\delta_H 4.39-4.56\) (1H, m, CH) ppm, whilst the \(t\)-butyl signal was observed as a singlet at \(\delta_H 1.38\) (9H, s, 3 \(\times\) Me) ppm. The \(^{13}\)C NMR spectrum gave the required 15 non-equivalent signals with one quaternary carbon not detected, whilst the methine carbon of the L-phenylalanine was at \(\delta_C 56.9\) ppm. Finally, analysis by mass spectrometry gave an ion at 441.2 (100\%, \([\text{M+H}]^+\)) which on accurate mass measurement gave a mass of 441.2132 (\([\text{M+H}]^+\)) Daltons which corresponds closely to the required value of 441.2134 Daltons for \(\text{C}_{22}\text{H}_{25}\text{NaOs}^+\) (\([\text{M+H}]^+\)).

Following this, \(N\)-Cbz-L-phenylalanine 304 was activated using CDI in DMF and coupled with \(N\)-Boc-guanidine 207, to give the catalyst 305 in 84% yield. (Scheme 123)

\[\text{CbzHN} \quad \text{O} \quad \text{Bn} \quad \text{304} \quad \text{a} \quad \text{CbzHN} \quad \text{O} \quad \text{NH} \quad \text{Boc} \quad \text{305}\]

**Scheme 123:** (a) i) 304, CDI, DMF, rt, 30 min; ii) 207, DMF, rt, 72 h.

The analytical data obtained for 305 confirmed its structure. The compound gave a negative specific rotation value of \([\alpha]D^21\) -32 whilst the proton NMR spectrum gave two signals at \(\delta_H 8.34-10.29\) (2H, br s, 2 \(\times\) NH) and 8.65 (1H, br s, NH) ppm for the guanidine NH protons and a signal at \(\delta_H 5.58\) (1H, d, \(J 7.0\) Hz, NH) ppm for the carbamate NH proton. The aromatic protons were observed as three signals at \(\delta_H 7.26-7.41\) (5H, m, Ph) 7.15-7.25 (3H, m, 3 \(\times\) CH), and 7.06 (2H, br d, \(J 6.6\) Hz, CH) ppm, whilst the methylene of the Cbz-group appeared as two doublet signals at \(\delta_H 5.12\) (1H, d, \(J 12.7\) Hz, CH) and 5.08 (1H, d, \(J 12.7\) Hz, CH) ppm. The methylene of the phenylalanine residue appeared as a double doublet at \(\delta_H 3.25\) (1H, dd, \(J 13.6, 5.0\) Hz, CH) and 3.11 (1H, dd, \(J 13.6, 5.2\) Hz, CH) ppm, whilst the methine proton was a
multiplet at δH 4.57-4.62 (1H, m, CH) ppm. The t-butyl signal of the Boc-group was observed as a singlet at δH 1.48 (9H, s, 3 × Me) ppm. The 13C NMR spectrum gave the required 15 non-equivalent signals with two quaternary carbons not detected, with the methine carbon in the phenylalanine resonating at δC 58.2 ppm. Finally, analysis by mass spectrometry gave an ion at 441.2 ([M+H]+) Daltons, which on accurate mass measurement gave an ion at 441.2132 Daltons which corresponds closely to the required value of 441.2136 Daltons for C23H29N4O5+ ([M+H]+).

Finally, N-Cbz-phenylalanine 304 was activated with CDI in DMF over 30 mins after which N-Cbz-guanidine 224 was added. After 48 h at rt, no reaction was observed and the mixture was then heated at 40 °C for 48 h. At this point, an aqueous work up, chromatography and recrystallization (from ethanol/petroleum ether) gave 306 in 19% yield as a white solid.

(Scheme 124)

![Scheme 124](image)

Scheme 124: (a) i) 304, CDI, DMF, 0 °C, 30 min; ii) 224, DMF, rt, 72 h then 40 °C, 48 h.

The analytical data obtained for 306 confirmed its structure. The compound gave a negative specific rotation value of [α]D25 -19.6, whilst the 1H NMR spectrum gave two signals at δH 7.71-9.79 (3H, br s, 3 × NH), and 5.20-5.31 (1H, br s, NH) ppm for the guanidine and carbamate protons respectively. The aromatic protons were a complex multiplet at δH 7.17-7.43 (13H, m, 13 × CH) and 7.09 (2H, d, J 6.8 Hz, 2 × CH) ppm. The methylenes of the protecting groups were observed as singlet at δH 5.16 (2H, br s, CH2) ppm and a multiplet at δH 5.01-5.13 (2H, m, 2 × CH) ppm, whilst the methylene of the amino acid residue was observed at δH 2.85-3.35 (2H, m, CH2) ppm. The distinctive methine proton of the phenylalanine was observed as a broad multiplet at δH 4.28-4.59 (1H, br m, CH) ppm. The 13C NMR spectrum gave the 13 non-equivalent signals in the DEPT-135 spectrum, with the methine carbon observed at δC 57.5 ppm. Finally, analysis by mass spectrometry gave an ion at 475.2 (100%, [M+H]+), which on accurate mass measurement gave a mass of 475.1977 Daltons which corresponded very closely to the required value of 475.1976 Daltons for C26H26N4O5+ ([M+H]+).
2.9.4 C$_2$-symmetric L-alanine and L-phenylalanine catalysts.

We next prepared the C$_2$-symmetric N-Cbz-L-alanine 298 derived catalyst 307. Firstly, 0.5 equivalents of guanidinium chloride 206 was added a suspension of hexane washed NaH in DMF. After 2 h a DMF solution of 3 equivalents of CDI activated N-Cbz-L-phenylalanine 298 was added and after stirring for 2 days, an aqueous work up and silica gel chromatography gave the catalyst 307 in 51% yield as a white solid. (Scheme 125)

Scheme 125: (a) i) 298, CDI, DMF, rt, 2 h, ii) 206 (0.5 equiv.), NaH, DMF, 24 h. iii) combine then stir 2 d.

The analytical data obtained for 307 confirmed its structure. The compound gave a negative specific rotation value of [α]$_D$-22.7 and NMR spectroscopy indicated the possibility of rotamers or a non-equivalence of the two L-alanine residues due to doubling up of signals. The proton NMR spectrum gave signals at δ$_H$ 7.63-10.64 (1H, br s, NH) and 1.82-5.78 (2H, br s, 2 × NH) ppm for the guanidine NH protons, whilst the NH of the amide group appeared as a broad singlet at δ$_H$ 5.41-5.62 (2H, br s, 2 × NH). The aromatic protons appeared at δ$_H$ 7.20-7.24 (10H, m, 2 × Ph) ppm, whilst the benzyl methylene appeared as two double doublets at δ$_H$ 5.14 (2H, d, J 12.3, 2 × CH) and 5.10 (2H, d, J 12.3, 2 × CH) ppm. The methyl groups appeared as doublets at δ$_H$ 1.34/1.35 (6H, 2 × d, J 7.0 Hz, 2 × Me) and the methine protons were observed as a complex multiplet at δ$_H$ 4.11-4.41 (2H, m, 2 × CH) ppm. The $^{13}$C NMR spectrum gave the required 9 non-equivalent signals with one quaternary carbon not detected, with the methine carbon appearing at δ$_C$ 52.8 ppm. Finally, analysis by mass spectrometry gave a mass at 470.2 Daltons for [M+H]$^+$ which on high resolution mass spectrometry gave a mass of 470.2042 Daltons which is in good agreement with the theoretical value of 470.2034 Daltons required for C$_{23}$H$_{28}$N$_5$O$_6$$^+$ ([M+H]$^+$).

The C$_2$-symmetric N-Cbz-L-phenylalanine derived catalyst 308 was prepared in the same manner and after purification by chromatography was obtained in 47% yield as a white solid. (Scheme 126)
Scheme 126: (a) i) 304, CDI, DMF, rt, 90 min, ii) 206 (0.5 equiv.), NaH, DMF, 90 min. iii) combine then stir 4 d.

The analytical data obtained for 308 confirmed its structure. The compound gave a negative specific rotation value of \([\alpha]_{D}^{20} -12.8\) and again, NMR spectroscopy indicated the possibility of rotamers or a non-equivalence of the two L-phenylalanine residues due to doubling up of signals. The proton NMR spectrum gave signals at \(\delta_H 8.30-10.68\) (3H, br s, 3 × NH) ppm for the guanidine NH protons and 5.24-5.48 (2H, br s, 2 × NH) for the amide NH. The aromatic protons appeared as two multiplet signals at \(\delta_H 7.16-7.39\) (16H, m, 16 × CH), and 7.04-7.14 (4H, m, 4 × CH) ppm. The methylenes of the protection groups appeared at \(\delta_H 4.96-5.14\) (4H, m, 2 × CH₂) while the phenylalanine methylenes appeared as a multiplet at \(\delta_H 2.80-3.23\) (4H, m, 2 × CH₂) ppm. The aliphatic methine proton was observed as a broad multiplet at \(\delta_H 4.31-4.59\) (2H, m, 2 × CH) ppm. The \(^{13}\)C NMR spectrum gave 12 non-equivalent signals with one quaternary signal not detected, whilst the methine carbon was at \(\delta_C 57.8\) ppm. Finally, analysis by high resolution mass spectrometry gave a mass at 622.3 Daltons for \([M+H]^+\) which on high resolution mass spectrometry gave a mass of 622.2660 Daltons which is in good agreement with the theoretical value of 622.2667 Daltons required for \(C_{35}H_{36}N_5O_6^+\) ([M+H]+).

The corresponding \(C_2\)-symmetric \(N\)-Boc-protected catalysts 309 and 310 were similarly prepared. Thus, \(N\)-Boc-L-alanine 295 was activated with CDI over 90 min and reacted with guanidine 206 in DMF. After stirring for 72 h, an aqueous work up followed by chromatography gave the catalyst 309 in 54 % yield as a white solid. (Scheme 127)

Scheme 127: (a) i) 295, CDI, DMF, rt, 90 min; ii) 206 (0.5 equiv.), NaH, DMF, 90 min; iii) Combine then stir 72 h.
The analytical data obtained for 309 confirmed its structure. The compound gave a negative specific rotation value of \([\alpha]_D^{21} -30.0\) with NMR spectroscopy indicating the possibility of rotamers or a non-equivalence of the two L-alanine residues due to doubling up of signals. The proton NMR spectrum gave signals at \(\delta_H 8.42-10.88\) (3H, br s, 3 \(\times\) NH) ppm for the guanidine NH protons and at \(\delta_H 5.30-5.70\) (2H, m, 2 \(\times\) NH) ppm for the amide NH. The methine proton of the alanine residue was observed as a complex broad multiplet at \(\delta_H 3.94-4.36\) (2H, m, 2 \(\times\) CH) ppm, whilst the t-butyl groups appeared as two singlets at \(\delta_H 1.42\) (9H, s, 3 \(\times\) Me) and 1.42 (9H, s, 3 \(\times\) Me) ppm. The methyl signals appeared as a doublet at \(\delta_H 1.37\) (3H, d, \(J\) 6.8 Hz, 2 \(\times\) Me) ppm. The \(^{13}\)C NMR spectrum gave the required 6 non-equivalent signals with one quaternary carbon not detected, whilst the methine carbon was at \(\delta_C 52.3\) ppm.

Finally, analysis by high resolution mass spectrometry gave a mass at 402.2 Daltons for \([M+H]^+\) which on high resolution mass spectrometry gave a mass of 402.2348 Daltons which is in good agreement with the theoretical value of 402.2347 Daltons required for \([C_{17}H_{32}N_5O_6]^+\) (\([M+H]^+\)).

Similarly, \(N\)-Boc-L-phenylalanine 301 was activated with CDI over 90 min and reacted with guanidine 206 in DMF; after stirring for 48 h, an aqueous work up followed by chromatography gave the catalyst 310 in 74\% yield as a white solid. (Scheme 128)

\[
\begin{align*}
\text{BocHNN} & \text{COOH} \quad \text{(a)} \quad \text{BocHNN} & \text{CONH} \text{NH} \text{CONH} \text{NH}{\text{Boc}} \\
301 & \quad \quad \quad & 310
\end{align*}
\]

**Scheme 128:** (a) i) 301, CDI, DMF, rt, 90 min, ii) 206 (0.5 equiv.), NaH, DMF, 90 min. iii) combine, stir 48 h.

The analytical data obtained for 310 confirmed its structure. The compound gave a negative specific rotation value of \([\alpha]_D^{27} -21.4\) with NMR spectroscopy indicating the possibility of rotamers or a non-equivalence of the two L-phenylalanine residues due to doubling up of signals. The proton NMR spectrum gave signals at \(\delta_H 8.22-11.13\) (3H, br s, 3 \(\times\) NH) ppm for the guanidine NH protons and at \(\delta_H 5.05-5.70\) (2H, m, 2 \(\times\) NH) ppm for the amide NH. The aromatic protons appeared as two multiplets at \(\delta_H 7.21-7.38\) (6H, m, 6 \(\times\) CH), and 7.13-7.21 (4H, m, 4 \(\times\) CH) ppm. The benzyl methylenes appeared as a multiplet at \(\delta_H 2.97-3.31\) (4H, m, 2 \(\times\) CH\(_2\)) ppm, whilst the aliphatic methine proton was observed at \(\delta_H 4.18-4.24\) (2H, m, 2 \(\times\) CH) ppm. The t-butyl groups were observed as a singlet at \(\delta_H 1.42\) (18H, s, 6 \(\times\)
Me) ppm. The $^{13}$C NMR spectrum gave the required 9 non-equivalent signals with one quaternary not detected, whilst the methine carbon was found at $\delta_{C}$ 57.5 ppm. Finally, analysis by high resolution mass spectrometry gave a mass at 554.3 Daltons ([M+H]$^+$) which on high resolution mass spectrometry gave a mass of 554.2982 Daltons which is in good agreement with the theoretical value of 554.2973 Daltons required for $\text{C}_{29}\text{H}_{40}\text{N}_{5}\text{O}_{6}$ ([M+H]$^+$).

2.9.5 Glycine based Catalysts.

We wished to prepare a $N,N$-disubstituted glycine catalyst in which the source of chirality was found in the guanidine and the glycine was present as the basic moiety. ($R$)-1-(1-phenylethyl)guanidine 312 was used as the source of the chirality which was prepared form commercially available ($R$)-(+)-1-phenylethylamine 311. Thus amine 311 was dissolved in a minimum volume of dioxane and a slight excess of HCl (conc.) was added at 15–20 °C. After evaporation under vacuum, the solid was triturated with diethyl ether before then being dissolved in water. Cyanamide was then added and the reaction mixture was adjusted to pH 8-9 by the addition a few drops of ($R$)-(+-1-phenylethylamine 311. The reaction was subsequently refluxed for 24 h, then evaporated and triturated with diethyl ether. Purification of the residue was achieved using a Dowex 500 ion exchange column to give 312 as a colourless gum in 38% yield. Spectroscopic data was in agreement with the literature.\textsuperscript{116} (Scheme 129)

![Scheme 129](image_url)

\textbf{Scheme 129:} (a) 311, HCl (conc.), 15-20 °C, 30 min. (b) NH$_2$CN, reflux, 24 h.

(c) Dowex 500 ion exchange column

The coupling of guanidine 312 with commercially available dimethylglycine 313, was attempted by firstly activating 1.2 equivalents of 313 with 2.5 equivalents of CDI over 30 min, then adding an equivalent of 312. The reaction was stirred for 6 days at rt, then diluted with water and extracted with ethyl acetate. Analysis of the product by $^1$H NMR indicated the presence of a promising product but this appeared to be contaminated with a large amount of dimethylglycine 313. Attempts were made to remove this material by washing with aqueous NaOH (1M) which seemed to result in the loss of most of the material. The reaction was
repeated using one molar equivalents of the starting materials, with the acid 313 being activated with 2 equivalents of CDI and again the reaction was stirred at rt for 24 h and at 45-50 °C for 18 h. Again, after work-up, analysis by 1H NMR indicated the presence of unreacted dimethylglycine 313 which could not be separated by column chromatography. We repeated this reaction using triethylamine (3.0 equiv.) to act as a competitive base, which seemed to increase the material yield, however again the presence of unreacted 313 hindered purification by column chromatography. We reasoned that the product 314 and dimethylglycine 313 were forming a salt, which was co-eluting as the product. We thus repeated the reaction using 1.2 equivalents of the guanidine 312 and unfortunately achieved the same result as the formation of what appeared to be a 1:1 mixture of 314 and dimethylglycine 315. (Scheme 130) We attempted to purify the mixture by stirring with basic ion exchange resin (Dowex® 50W X8), which led to the decomposition of the product even over short reaction times. We tried using weaker bases and thus dissolved the product in THF and stirred with solid potassium carbonate, which also led to complete decomposition.

One interesting observation was that the products of this reaction were quite polar as chromatography in 20% methanol in ethyl acetate was required to achieve elution from silica gel. We hoped that by using dibenzylglycine, the lower polarity of this compounds derivatives might aid purification. We thus took N-N-dibenzylglycine 197 and attempted to activate it using CDI and observed that under our usual conditions (DMF, rt, 24 h) the reaction did not proceed as the starting material appeared to be completely insoluble in DMF. This was also the case on heating to 60-80 °C or with the addition of triethylamine as no reaction was apparent. We added an excess of allyl amine 316 to these reaction to test for amide formation and on work up, no coupled product 317 was isolated. (Scheme 131)
2.10 Catalytic studies of the $N$-Boc and $N$-Cbz protected amino acid catalysts.

The $N$-proline derived catalysts 292, 293 and 294 catalysts were utilised in the Michael reaction to form 170. (Scheme 132, Table 10) The first (unsurprising) result is that the yields for these catalytic reactions were all low and the reaction times relatively long which must arise the low basicity of the catalysts. The $N$-Boc-proline catalyst 293 gave poor ee’s (1-5% ee) over the range of solvents studied, whilst the $N$-Cbz-proline catalyst 292 gave better ee’s 8-18% ee but slow reaction times. Interestingly the $C_2$-symmetric catalyst 294 gave the best ee’s (12-22% ee) which is surprising as the corresponding Boc-protected catalyst 293 gave poorer results. The best ee’s for this process were observed when benzene and toluene were used as solvents (both 22% ee).

**Scheme 132:** Formation of 170 using catalysts 292, 293 and 294: Conditions: See Table 10, Catalyst (0.1 equiv.), 0 °C, 7-8 h then rt.

**Table 10:** Entries and results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>DCM</th>
<th>PhMe</th>
<th>Xylenes</th>
<th>PhH</th>
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<td>292</td>
<td>18 (120/55)</td>
<td>13 (120/31)</td>
<td>8 (120/32)</td>
<td>8 (48/30)</td>
</tr>
<tr>
<td>2</td>
<td>293</td>
<td>5 (24/38)</td>
<td>4 (24/22)</td>
<td>1 (72/30)</td>
<td>4 (24/25)</td>
</tr>
<tr>
<td>3</td>
<td>294</td>
<td>18 (24/38)</td>
<td>22 (48/30)</td>
<td>12 (23/41)</td>
<td>22 (48/25)</td>
</tr>
</tbody>
</table>

i) Results are given as: ee (time (h)/yield (%))
The N-Boc and N-Cbz protected L-alanine and L-phenylalanine derived catalysts were next utilised in the Michael reaction to form 170. (Scheme 133, Table 11) Again, the reaction times for all of these catalysts were slow requiring several days to reach a reasonable yield. Again, most of these catalysts gave very poor ee’s with the best catalysts being 297 (entry 2) and 299 (entry 3), which gave 16% and 14% ee in toluene, but as stated, the reactions were very slow and yields poor.

Scheme 131: Formation of 170 using catalysts 296, 297, 299, 300, 302, 305 and 306:

Conditions: Table 11, (a) Catalyst (0.1 equiv.) then i) 0 °C, 7-8 h then rt

Table 11: Entries and results

<table>
<thead>
<tr>
<th>Entry</th>
<th>AA</th>
<th>AAPG</th>
<th>GPG</th>
<th>Catalyst</th>
<th>DCM</th>
<th>PhMe</th>
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<td>Ala</td>
<td>Boc</td>
<td>Boc</td>
<td>296</td>
<td>2</td>
<td>2 (160/81)</td>
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<tr>
<td>2</td>
<td>Ala</td>
<td>Boc</td>
<td>Cbz</td>
<td>297</td>
<td>6</td>
<td>14 (286/11)</td>
</tr>
<tr>
<td>3</td>
<td>Ala</td>
<td>Cbz</td>
<td>Boc</td>
<td>299</td>
<td>12</td>
<td>16 (265/37)</td>
</tr>
<tr>
<td>4</td>
<td>Ala</td>
<td>Cbz</td>
<td>Cbz</td>
<td>300</td>
<td>6</td>
<td>10 (240/24)</td>
</tr>
<tr>
<td>5</td>
<td>Phe</td>
<td>Boc</td>
<td>Boc</td>
<td>302</td>
<td>5</td>
<td>0 (214/84)</td>
</tr>
<tr>
<td>6</td>
<td>Phe</td>
<td>Boc</td>
<td>Cbz</td>
<td>303</td>
<td>6</td>
<td>12 (255/18)</td>
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<td>Phe</td>
<td>Cbz</td>
<td>Boc</td>
<td>305</td>
<td>3</td>
<td>2 (190/73)</td>
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<td>Cbz</td>
<td>Cbz</td>
<td>306</td>
<td>5</td>
<td>0 (50/56)</td>
</tr>
</tbody>
</table>

i) Results are given as ee (time (h)/yield (%))  
ii) Amino acid.  
iii) Amino acid protecting group  
iv) Guanidine protecting group
$N$-Boc and $N$-Cbz protected L-alanine and L-phenylalanine $C_2$-symmetric catalysts were next utilised in the Michael reaction to form 170. Initially the catalysts 307, 308, 309 and 310 were studied under the standard conditions (Table 12, Entries 1, 3, 4 and 5) and it was found that in all cases the reactions were very slow in all cases, with the catalysts 307 and 310 not showing any appreciable reaction over several days. Repeating these two reactions in the presence of benzoic acid (Entries 2 and 6) did effect reaction, however the time scale of the reaction particularly in dichloromethane was 10-25 days. Of these reactions, the most successful catalyst was 308, which gave a 26% ee in dichloromethane and a 15% ee in toluene (Entry 3).

**Scheme 134:** Preparation of 170 using catalysts 307, 308, 309 and 310: Conditions: See table 12; Catalyst (0.1 equiv.) with either (a) 0 °C, 7-8 h then rt or (b) 0 °C, 7-8 h then rt with benzoic acid (BA).

<table>
<thead>
<tr>
<th>Entry</th>
<th>AA</th>
<th>PG</th>
<th>Cat.</th>
<th>Conds.</th>
<th>DCM</th>
<th>PhMe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phe</td>
<td>Boc</td>
<td>310</td>
<td>(a)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Phe</td>
<td>Boc</td>
<td>310</td>
<td>(b)</td>
<td>5 (565/48)</td>
<td>8 (216/32)</td>
</tr>
<tr>
<td>3</td>
<td>Phe</td>
<td>Cbz</td>
<td>308</td>
<td>(a)</td>
<td>26 (527/22)</td>
<td>15 (285/46)</td>
</tr>
<tr>
<td>4</td>
<td>Ala</td>
<td>Boc</td>
<td>309</td>
<td>(a)</td>
<td>3 (216/85)</td>
<td>3 (216/70)</td>
</tr>
<tr>
<td>5</td>
<td>Ala</td>
<td>Cbz</td>
<td>307</td>
<td>(a)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Ala</td>
<td>Cbz</td>
<td>307</td>
<td>(b)</td>
<td>10 (565/95)</td>
<td>6 (255/70)</td>
</tr>
</tbody>
</table>

i) Results are given as ee (time (h)/yield (%))
ii) Amino acid.
iii) Amino acid protecting group
2.11 X-rays structures of the catalysts 297 and 303.

We were able to obtain X-ray structures for the catalysts 297 and 303 and pleasingly neither of these appeared to be racemised in the crystal form.

Catalyst 297, derived from L-alanine, had a structure which had an E-amide arrangement with the carbonyl of the amide having a E-bc type H-bonding type (bond b; N2(HN2B)...O3 = 1.978 Å and bond c; N3(HN3)...O2 = 1.972 Å). Additionally an H-bond was observed between the guanidine NH and the Boc-protecting group (bond f; N3(HN3)...O4 = 3.041 Å) and possibly a weaker H-bond between the Boc-protecting group NH and the Cbz-protecting group carbonyl (bond g; N4(HN4)...O2 = 3.403 Å). This is an E-amide-bcf(g) pattern. (Figure 44)

On examination of the structure of compound 303, it again possessed an E-amide arrangement but with the amide N-H not involved in any intramolecular H-bonds to the carbamate protecting group of the guanidine. Instead there was a long distance interaction between the Boc-carbonyl and the amide N-H (bond f; N3(HN3)...O4 = 3.488 Å) was observed. The guanidine NH$_2$ had two H-bonds of the E-bd) type (bond b; N2(HN2B)...O3 = 2.169 Å and bond d; N2(HN2A)...O2 = 1.969 Å) and a H-bond between the NH of the Boc protecting group and the amide oxygen was also observed (bond e; N4(HN4)...O3 = 3.166 Å). Overall this is an E-amide-bde(f) pattern. (Figure 45)
Unfortunately, we could not obtain suitable crystals of the best catalysts 294, 299 and 308 for X-ray analysis and no rationale for the higher ee’s observed with these catalysts can be offered.

2.12 Conclusions.

The overall conclusion from the reactions of the N-protected amino acids is that these processes are typically slower than the corresponding N-alkyl catalysts and that there is no appreciable increase in ee’s. There is no apparent correlation between the different general types of the catalysts however, two of the better catalysts of this class were the $C_2$-symmetric examples 294 and 308, which were encouraging results. (Figure 46)
2.13 Conclusion and further work.

Within this work the preparation of a range of L-proline-guanidine based catalysts has been achieved and their application to the addition of the enolate of 168 to nitrostyrene 77 to give the Michale adduct 170. The initial catalyst 176a was studied previously and a reinvestigation has shown that the catalyst had probably undergone some level of racemisation during its preparation. The catalyst was prepared in an enantiomerically pure form and reapplication of this catalyst to the formation of 176a gave an improved ee of 56%, which equates to a 78:22 selectivity for the process. Unfortunately modifications of this structure (Figure 47) led to no marked improvement of this result and in some cases the reaction times were longer and yields poorer.

![Figure 47: The most successful catalysts used in this work.](image)

A mechanistic rationale for this reaction is difficult to determine and even with X-ray crystallographic data we can only speculate as to the nature of any intermediates present in the reaction. It is apparent from the preference of the (R)-stereochemistry in the product, a the reaction must be occurring as shown below with the enol adding to the top face of the alkene as depicted below. (Figure 48)
Our goal was to have an associative mechanism where potentially the enol/enolate was bound to the molecule via a hydrogen bonding interaction with the proline or guanidine motif. If the association of the enolate is the first process occurring in this reaction then the mode of approach of nitrostyrene 77 is obviously dependent on the structure of the intermediate. An alternate mode of interaction in which the nitrostyrene 77 first associates with the catalyst is less convincing. This is because the mode of hydrogen bonding of the nitro-group would most likely be a bidentate one 318, and many of the structures (from X-ray) of the un-protonated catalysts do not appear to be able to allow this. However if protonation were to happen, the bidentate mode of this interaction might be possible, but the nature of any protonation is not known. (Figure 49)

Our overall conclusion from this work is the goal of developing a tunable range of catalysts is still not within reach. Our work has unfortunately focused on one reaction, as the previous study seemed to indicate that other Michael processes were robust suffered from deactivation of the catalysts and the formation of complex mixtures. The modifications made to the catalysts have not lead to any improvement in ee and one conclusion from this work is that the H-bonding patterns observed are not predictable. This might suggest that the ability of the guanidine to form multiple strong H-bonds is not a favorable one and a more simplistic range of basic catalysts might be more advantageous.

Inspection of the literature indicated that Koga et al.\textsuperscript{117} reported the preparation of compound 319 in his studies on chiral lithium amide bases. This derivative was prepared from dimethylglycine 313 and the commercially available chiral amine 312 using
diethylphosphorocyanidate (DEPC) and triethylamine as the coupling agents. This compound was prepared in the latter stages of the project and was found to catalyse the reaction to give \( 319 \) in 75% yield over 24 h, however the ee of the product was 6-8%. (Scheme 135)

\[
\begin{align*}
\text{Me}^+ & \text{N} & \text{O} \quad \text{Me} \\
\text{313} & \quad & \\
\text{Me}^+ & \text{N} & \text{O} \\
\text{312} & \quad & \text{Me} \\
\text{(a)} & \rightarrow & \\
\text{Me}^+ & \text{N} & \text{O} \quad \text{Me} \\
\text{319} & \quad & \\
\end{align*}
\]

Scheme 135: (a) DEPC, NEt\(_3\), DMF, 3 h, 66%.

Despite the problems encountered with racemisation of the activated amino acids under CDI coupling, the increased nucleophilic strength of the amine in this reaction should limit racemisation and allow access to a range of simpler catalysts 320. Indeed access to both enantiomers of the chiral amine might allow the investigation of matched and mismatched pairs of catalysts using the structure 321.

\[
\begin{align*}
\text{Me} & \quad \text{N} & \text{O} \\
\text{320} & \quad & \text{Me} \\
\text{Me} & \quad \text{N} & \text{O} \\
\text{321} & \quad & \text{Me} \\
\end{align*}
\]

Figure 50: \( R = \text{Me, Bn, } i\text{-Pr} \).

Interesting, the \( C_2 \)-symmetric compound 322 and the related structures 323 and 324 have been reported in the literature.\(^{118}\) The catalysts were prepared using a mixed anhydride coupling method and ytterbium complexes of these compounds have been utilised in asymmetric tandem aldol/reduction reactions. Compound 322 gave no enantioselectivity in the reaction studied whilst compounds 323 and 324 gave 50% and 48% ee respectively.
Figure 51: (a) (i) Yb(OTf)$_3$/catalyst (10 mol %), THF, rt, 4 h; (ii) MeOH, MeONa

Whilst compound 322 was unsuccessful in the above reaction the added H-bonding capability of these relatively simple compounds might offer some advantages in base catalyses processes and are worth investigating.

Shortly after the onset of this work, Liu et al. reported the use of chiral bi-functional guanidine catalyses aza-Henry reactions of the isatin derived ketimines 326 with nitromethane 88. This reaction led to the amines 327 in 81-99% yield and 85-94% ee. (Scheme 13) The authors put forward a model where the strong H-bond (2.260 Å) between the guanidine and the amide is broken by the deprotonation of nitromethane 88. When this intramolecular hydrogen bonding is removed by this chelation, the amide groups is thought to act as a Brønsted acid to activate ketimine 325 (Figure 52), eventually leading to the formation of the product 327.\textsuperscript{119}

Scheme 136: (a) i) 326 (10 mol %), 88, PhMe, -30 °C, 72 h.
R$^1$ = Me, Bn; R$^2$ = Boc, EtO$_2$C; R$^3$ = H, F, Cl, Br, I, Me, F$_3$CO, CF$_3$.

Figure 52 reproduced from reference.\textsuperscript{119}
This work seems to suggest that the H-bonding within our catalysts might be a key factor in the success of these reactions and perhaps attempting one or more of these examples with our catalysts might be of interest.

The original premise of this work was to avoid complexity in the design of our catalysts. Whilst other have achieved considerable success in the field of organocatalysis, particularly in the use of structurally complex peptide\textsuperscript{120,121} and peptide cluster\textsuperscript{122} catalysts, much of this work has been via an iterative design approach. This might be considered to be a “reaction in search of a catalyst” approach, very much like our own work. We hoped to design a range of catalysts, which would have a more general application to Michael reactions and as such have not succeeded. A major failing of this work has been the lack of scope of the catalysts, however as we have currently a good candidate molecule (176a) which gives reasonable enantioselectivity (56% ee), it might be possible to apply this catalyst to other reactions. This is obviously a “catalyst in search of a reaction” approach, which is another popular strategy. This work has encountered several pitfalls in the preparation and design of these catalysts, however some insight was gained on structural limitations and this work might point the way for future developments in this area.
Chapter Three Experimental

3.1 General Procedures:

Unless otherwise noted, reactions were stirred and monitored by TLC. TLC plates were visualized using iodine, phosphomolybdic acid or under UV light. All anhydrous reactions were conducted under a static argon atmosphere using oven dried glassware that had previously been cooled under a constant stream of nitrogen.

3.2 Materials

Reagents and starting materials were purchased from commercial suppliers and used without further purification unless otherwise noted. All anhydrous solvents used in reactions were distilled over either sodium wire and benzophenone (THF/DE) or calcium hydride (DCM), and used either immediately or stored over molecular sieves prior to use. Flash column chromatography was performed on Davisil® silica gel (35-70 microns) with the eluent specified in each case, TLC was conducted on precoated E.Merck silica gel 60 F_{254} glass plates.

3.3 Instrumentation

Melting points were determined using a Gallenkamp MF370 instrument. \(^1^H\) and \(^1^3^C\) NMR spectra were recorded on a Bruker Avance 400 or 500 spectrometer with an internal deuterium lock at ambient temperature at 400 or 500 MHz with internal references of \(\delta_H\) 7.26 and \(\delta_C\) 77.016 ppm for CDCl\(_3\), \(\delta_H\) 3.31 and \(\delta_C\) 49.0 ppm for CD\(_3\)OD and \(\delta_H\) 2.54 ppm and \(\delta_H\) 39.52 ppm for DMSO. Mass spectra were acquired at the EPSRC National Mass Spectrometry Service Centre based in Swansea University (Low-resolution Chemical Ionisation (CI) and Electrospray Ionisation (ESI) mass spectra were recorded on a Micromass Quattro II spectrometer and high resolution mass spectra were recorded on either a Finnigan MAT 900 XLT or a Finnigan MAT 95 XP) or in house (Low-resolution Electrospray Ionisation (ESI) mass spectra were recorded on a Thermo Scientific Q Exactive Plus spectrometer). Infrared samples were prepared as thin films or solutions using sodium chloride plates or KBr discs on a Bruker Tensor 37 FT-IR on as thin films on a Bruker Alpha spectrometer.
3.4 General Methods for the Preparation of catalysts.

**Method A:** The N-alkyl-L-proline (1.0-1.6 equiv.) was dissolved in DMF (1-2.5 mL per mmol), CDI (1.2 equiv.) was added and the mixture stirred for 5 min to 24 h. After cooling (0 °C) the mixture, the required guanidine (1.0 equiv.) was added as a solid and the mixture stirred to rt over 16-168 h. After evaporation under reduced pressure (freeze dryer) or dilution with water and extracting with ethyl acetate, drying (MgSO₄), filtering and evaporation under reduced pressure, the product was obtained and was purified by column chromatography (DE/PE or EA/PE), or recrystallization or trituration.

**Method B:** (C₂-catalysts): The N-alkyl-L-amino acid (1 equiv.) and CDI (1.20 equiv.) were added sequentially to dry DMF (0.5-2.5 mL per mmol) and the mixture stirred for 1-16 h. In a separate flask, NaH (0.60 equiv.) was suspended in dry DMF (1.0-2.0 mL per mmol) and dried (P₂O₅) guanidinium chloride (0.50 equiv.) was added. After stirring for 1 h the activated amino acid solution was transferred into this flask via cannula and the mixture stirred for 24-48 h. The mixture was diluted with water (100 mL) and EA (100 mL), separated and the aqueous layer extracted with further EA (2 × 100 mL) and the combined extracts washed with water (2 × 100 mL). After drying (MgSO₄), filtering and evaporation under reduced pressure the residue was co-evaporated with heptane to remove residual DMF and purified by silica gel chromatography (EA in PE).
3.4.1 Preparation of N-methyl-L-proline 175a.\textsuperscript{88}

L-proline 2 (10.0 g, 86.7 mmol) was dissolved in methanol (100 mL) together with formaldehyde (37 % aqueous, 7.6 mL, 95.5 mmol) and the mixture was stirred. The flask was purged with N\textsubscript{2} gas and 10% Pd/C (0.43 g) was added following which the flask was purged with hydrogen gas (balloon) and stirred overnight. The solution was filtered through Celite\textsuperscript{©} and evaporated to dryness and the solid obtained dissolved in a minimum of methanol (ca 50 mL) and diethyl ether was added to the cloud point (ca 1 mL). The solution was cooled overnight in a freezer to give crystal of 175a, which were removed by decanting the mother liquor. After drying under high vacuum, the title compound 175a (11.1 g, 85.9 mmol) was obtained as a white crystalline solid in 99% yield.

\textbf{Rf} 0.23 (90% ME/DE); \textbf{Mp} 142-144 °C; (lit.\textsuperscript{88} Mp 142-145 °C); [\textalpha]D\textsuperscript{22} = -75.0 (MeOH, c = 2.0); (lit.\textsuperscript{88} [\textalpha]D\textsuperscript{23} = -78.0 (MeOH, c = 2.0)); \textbf{8H} (D\textsubscript{2}O) 3.78 (1H, dd, J 9.0, 7.2 Hz, CH), 3.56-3.52 (1H, m, CH), 2.99-2.90 (1H, m, CH), 2.75 (3H, s, Me), 2.35-2.29 (1H, m, CH), 2.00-1.79 (3H, m, CH); \textbf{8C} (D\textsubscript{2}O) 173.6, 70.6, 56.3, 40.6, 28.7, 22.7; \textbf{v}_{\text{max}} (KBr disk) 2900, 1668, 1611, 1467, 1400, 1353, 1326, 1233, 1182, 1112, 1055, 1024, 807, 774 cm\textsuperscript{-1}; \textbf{MS (EI, -ve ion) m/z} 128.01 (100%, [M-H]); HRMS m/z found 128.0720, C\textsubscript{6}H\textsubscript{10}NO\textsubscript{2} ([M-H]') requires 128.0717.

3.4.2 Preparation of N-benzyl-L-proline 175b.\textsuperscript{89}

L-Proline 2 (10.0 g, 86.86 mmol) and KOH (14.7 g, 262.1 mmol, 3.0 equiv.) were dissolved in i-PrOH (100 mL) and heated with stirring to 40 °C. As soon as the solution became transparent, benzyl chloride (12.0 g, 10.9 mL, 95.02 mmol, 1.1 equiv.) was added in a dropwise fashion over 3 h. After 24 h, the reaction was cooled rt and neutralized using HCl (conc.) to 5-6 pH and chloroform (100 mL) was added and the mixture stirred overnight. The reaction was then filtered and the residue washed with CHCl\textsubscript{3}. The filtrate was evaporated to give the crude product which was triturated with acetone (100 mL) and filtered and the solid product washed with further small portions of acetone. The solid obtained was dried under vacuum (P\textsubscript{2}O\textsubscript{5}) for two days to give the product 175b (8.20 g, 40.0 mmol) as a pale yellow solid in 46% yield.
Rf 0.36 (80% ME/EA); Mp 170-171 °C (lit. Mp 174-175 °C\(^8\)); [\(\alpha\)]\(\text{D}\)\(^{19}\) -22.5 (EtOH, c = 1.0; lit. [\(\alpha\)]\(\text{D}\)\(^{20}\) -25.8 (EtOH, c = 1.0)); \(\delta\)\(_{\text{H}}\) (CDCl\(_3\)) 7.51-7.44 (2H, m, 2 × CH), 7.41-7.35 (3H, m, 3 × CH), 5.84 (1H, br s OH), 4.39 (1H, d, J 12.9 Hz, CH), 4.31 (1H, d, J 12.9 Hz, CH), 3.98-3.85 (1H, m, CH), 3.71-3.60 (1H, m, CH), 3.10-2.93 (1H, m, CH), 2.42-2.21 (2H, m, 2 × CH), 2.10-1.88 (2H, m, 2 × CH); \(\delta\)\(_{\text{C}}\) (CDCl\(_3\)) 171.1, 130.7, 130.6, 129.6, 129.2, 67.0, 57.6, 53.3, 28.7, 22.8; \(\nu\)\(_{\text{max}}\) (KBr disk) 3432, 3036, 2873, 1745, 1634, 1394, 1321, 1203, 1005 cm\(^{-1}\); MS(ES, -ve) m/z 204.1 (100%, [M-H]-); MS(ES) m/z 206.1 (100%, [M+H]+); HRMS(ESI) m/z found 204.1030, C\(_{12}\)H\(_{14}\)NO\(_2\)- ([M-H]-) requires 204.1030.

3.4.3 Preparation of N-isopropyl-L-proline 175c.\(^{90}\)

\begin{equation*}
\text{N-Isopropyl-L-proline}
\end{equation*}

Acetone (16.6 g, 19.0 mL, 260.57 mmol, 5.0 equiv.) was added to L-proline 2 (6.0 g, 52.1 mmol) and stirred for 1 h, following which dry MeOH (10 mL) was added and the mixture stirred for a further 1 h. 10% Pd/C (0.5 g, 4.53 mmol) was cautiously added and the mixture purged with hydrogen gas and was stirred for 42 h replenishing the hydrogen as needed. The reaction was filtered through Celite\(©\) and evaporated to dryness to give a crude product which was re-dissolved in a minimum amount of methanol and the product precipitated by the addition of diethylether to give 175c (7.78 g, 49.5 mmol) as yellow crystals in 95% yield.

Rf 0.21 (50% ME/DE); Mp 189 °C; [\(\alpha\)]\(\text{D}\)\(^{18}\) -68.1 (MeOH, c 1.28; Lit.\(^{90}\) [\(\alpha\)]\(\text{D}\)\(^{20}\) -55.0 (MeOH, c = 1.28)); \(\delta\)\(_{\text{H}}\) 3.67 (1H, dd, J 8.1, 4.7 Hz, CH), 3.50 (1H, ddd, J 11.0, 7.1, 2.7 Hz, CH), 3.37 (1H, septet, J 6.4 Hz, CH), 2.97 (1H, app dt, J 11.0, 6.6 Hz, CH), 1.96-2.05 (2H, m, CH\(_2\)), 1.79-1.89 (1H, m, CH), 1.52-1.67 (1H, m, CH), 1.19 (3H, d, J 6.4 Hz, Me), 1.17 (3H, d, J 6.4 Hz, Me); \(\delta\)\(_{\text{C}}\) 70.7, 66.0, 55.5, 51.3, 30.4, 24.3, 18.4, 18.1; \(\nu\)\(_{\text{max}}\) (KBr disk) 3432, 3036, 2873, 1634, 1394, 1321, 1203, 1005 cm\(^{-1}\); MS(ESI -ve) m/z 156.1 (100%, [M-H]-); MS(ESI) m/z 158.1 (100%, [M+H]+); HRMS(ESI) m/z found 156.1032, C\(_8\)H\(_{14}\)NO\(_2\)- ([M-H]-) requires 156.1030.
3.4.4 Preparation of N-cyclohexyl-l-proline 175d.\(^{91}\)

![Chemical Structure](image)

Methanol (100 mL) was added to 10% Pd/C (10 %, 0.5 g) in a dry 500 mL RBF under a nitrogen atmosphere. L-Proline 2 (11.5 g, 99.9 mmol, 1.0 equiv.) and cyclohexanone (10.8 g, 11.4 mL, 109.9 mmol, 1.1 equiv.) were then added and the reaction flask evacuated under reduced pressure and hydrogen gas was introduced (balloon). The mixture was vigorously stirred under a hydrogen atmosphere (balloon replaced as needed) overnight. The reaction was filtered through a Celite\(^{\text{©}}\) pad which was washed with further methanol (excess). The filtrate was evaporated under reduce pressure to give 175d (18.95 g, 96.1 mmol) as an off-white solid in 96% yield.

**Rf** 0.25 (5% MeOH/EtOAc); **Mp** 180-183 °C; [\(\alpha\)]\(D\)\(^{19}\) - 36.5 (MeOH, c = 2.8); \(\delta\)\(H\) (D\(_2\)O) 4.06 (1H, dd, \(J\) 10.0, 4.7 Hz, CH), 3.74-3.69 (1H, m, CH), 3.27-3.19 (2H, m, CH), 2.43-3.33 (1H, m, CH), 1.14-1.99 (4H, m, 4 \times CH), 1.93-1.83 (3H, m, 3 \times CH), 1.68-1.63 (1H, m, CH), 1.50-1.11 (5H, m, 5 \times CH); \(\delta\)\(C\) (D\(_2\)O) 174.8, 66.2, 64.4, 52.5, 29.5, 28.3, 24.4, 24.3, 23.6; \(\nu\)\(_{\text{max}}\) 3401, 3027, 2967, 2874, 2812, 1656, 1385; **MS**(EI-ve) m/z 196.1 (100%, [M-H]^{-}); **HRMS**(ES-ve) m/z found 196.1343, C\(_{11}\)H\(_{18}\)NO\(_2\)^{-} ([M-H]^{-}) requires 196.1343.

3.4.5 Preparation of N,N-dimethyl-l-alanine 191.\(^{92,93}\)

![Chemical Structure](image)

To a suspension of L-alanine 190 (20.0 g, 0.225 mmol, 1.0 equiv.) dissolved in water (100 mL) was added aqueous formaldehyde 37% w/w (52.8 g, 0.65 mol, 64.8 mL, 2.9 equiv.) and palladium on charcoal (6.0 g, 10%). The flask was purged with nitrogen and then saturated with hydrogen under balloon pressure. After purging and back-filling with hydrogen three times, the reaction mixture was stirred under hydrogen at rt and atmospheric pressure for 7 days. Upon completion, the resulting aqueous slurry was heated to reflux for 30 min and then filtered while hot. The filtrate was concentrated in vacuo and water removed as its azeotrope with toluene to afford a white solid. The crude product was dissolved in a hot EtOH/acetone (20 mL/150 mL) mixture, then cooled overnight in a freezer. The cooled mixture was then...
diluted with PE until the cloud point, then kept in the freezer overnight. An initial crop of 191 (15.4 g) was obtained as a white solid. After evaporation and recrystallization of the product in the same manner a second crop (8.53 g) was obtained. Repetition of this gave a third crop (5.33 g, 20%) to give an overall yield of 79% (29.3 g).

**Mp** 184-185 °C (Lit. 184 °C); [α]D23 +8.3 (H2O, c = 5.0, Lit. 7.8 (H2O, c = 5); δH (CD3OD) 3.63 (1H, q, J 7.2 Hz, CH), 2.84 (6H, s, 2 × CH3), 1.49 (3H, d, J 7.2 Hz, CH3); δC (CD3OD) 173.4, 67.4, 41.5, 13.0; \( \nu_{\text{max}} \) 2939, 1596, 1329; **MS (ESI -ve) m/z** 59.0 (100%), 116.1 ([M-H]-, 6%); **HRMS (ESI -ve) m/z** found 116.0718, C5H10NO2- ([M-H]-) requires 116.0717.

### 3.4.6 Preparation of N,N-dimethyl-L-phenylalanine 193

Aqueous formaldehyde (37% w/w, 6.42 g, 79.7 mmol, 5.9 mL, 6.5 equiv.) was added to a solution of L-phenylalanine 192 (2.0 g, 12.1 mmol, 1.0 equiv.) dissolved in water (100 mL) and the mixture stirred for 10 min. The reaction flask was evacuated under reduced pressure, purged with nitrogen gas and 10% Pd/C (10%, 0.60 g) was added. The reaction flask was purged with hydrogen gas (balloon), then vigorously stirred under a hydrogen atmosphere (balloon replaced as needed) for 5 days. The reaction was heated at reflux for 30 min, then filtered whilst hot through a pad of Celite. The filtrate was concentrated in vacuo, then redissolved in a small volume of water (ca. 20 mL) and evaporated again to remove excess ethanol and formaldehyde. This process was repeated until a greyish solid was obtained which was then dissolved in a minimum amount of hot EtOH (ca. 35 mL), cooled to rt and left in the freezer overnight to give 193 (1.99 g, 10.3 mmol) as an off white crystals in 85% yield.

**Mp** 214-216 °C (Lit. 218 °C); [α]D19 +76.8 (H2O, c = 1.98), (lit. 77.5 (H2O, c = 1.98); δH (CD3OD) 7.30-7.38 (4H, m, 4 × CH), 7.25 (1H, br t, J 7.2 Hz, CH), 3.84 (1H, dd (app triplet), J 7.1, 6.5 Hz, CH), 3.31 (1H, dd, J 14.5, 6.5 Hz, CH), 3.21 (1H, dd, J 14.5, 7.1 Hz, CH), 2.83 (6H, s, 2 × CH3); δC (CD3OD) 172.0, 137.7, 130.3, 129.8, 128.2, 73.1, 42.4, 35.1; \( \nu_{\text{max}} \) 3402, 3029, 2921, 1609, 1516, 1335; **MS (ESI) m/z** 194.1 (100%, [M+H]+), 161.1 (36%), **HRMS (ESI) m/z** found 194.1183, C11H16NO2+ ([M+H]+), requires 194.1176.

34.6

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**Note:** The numbers 3.4.6 and 193 are likely indicating sections or identifiers within the document, possibly referring to specific methods or compounds. The text is formatted to mirror the layout of a scientific paper, with sections, tables, and chemical formulas. The content seems to describe the preparation of N,N-dimethyl-L-phenylalanine, including reaction conditions, yields, and characterization data such as melting points, optical rotations, and spectroscopic data.
3.4.7 Preparation of \( \text{N}_2\text{N}-\text{dimethyl-}\text{L-}

\text{valine} \) \(195\).\(^{93,95}\)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{OH} \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{OH}
\end{align*}
\]

Chemical Formula: \( \text{C}_7\text{H}_{16}\text{NO}_2 \)

Exact Mass: 145.11

Molecular Weight: 145.20

(5.0 g, 42.68mmol, 1 equiv) of \( \text{L-valine} \) was weighed and added to a 250 mL round-bottomed flask. The \( \text{L-valine} \) \(194\) was solved in 110 mL of water and a stirring bar was added. 15 mL of 37w% formaldehyde solution in water (149.38mmol, 3.5 equivalents) was added to flask. The flask was purged three times using a vacuum pomp and refilling the flask using nitrogen. 1.04 g of 10% palladium on charcoal was weighed and added. The flask was purged six times to create a hydrogen atmosphere. The hydrogen balloon was refilled several times. After a reaction of approximately 68 hours, the reaction mixture was heated for 30 minutes to dissolve all the products. The reaction mixture was filtrated over Celite© and the Celite© was washed with water. To the combined aqueous layers was added methylated spirit and the mixture was evaporated using rotary evaporation and high vacuum evaporation. The product was obtained as a yellow solid in 98% yield.

\text{Rf} \ 0.35 \ (\text{MeOH}); \ \text{Mp} \ 148-150 \ (\text{lit.:153 °C})^{95}; \ [\alpha]_D^{24} \ 34.9° \ (\text{MeOH}, \ c = 1.0); \ \delta_H \ (\text{CD}_3\text{OD}) \ 3.34 \ (1H, d, J 4.4 Hz, CH), 2.87 \ (6H, s, CH_3), 2.34-2.27 \ (1H, m, CH), 1.15 \ (3H, d, J 6.8 Hz, CH_3), 1.01 \ (3H, d, J 6.7 Hz, CH_3) \ ppm. \ \delta_C \ (\text{CD}_3\text{OD}) \ 91.1, 77.7, 42.4, 27.6, 20.8, 16.9 ppm. \ \nu_{\text{max}} \ 3271-3076, 2999, 2841, 1600, 1399-1325, 1153, 1105, 1039, 1012.

3.4.8 Preparation of \( \text{N}_2\text{N}-\text{dibenzyl-glycine} \) \(197\).\(^{96}\)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{OH} \quad \text{OH} \\
\text{Bn} & \quad \text{Bn} \\
\text{O} & \quad \\
\text{H}_2\text{N} & \quad \text{OH}
\end{align*}
\]

Chemical Formula: \( \text{C}_{12}\text{H}_{17}\text{NO}_2 \)

Molecular Weight: 255.32

Glycine \(196\) (7.50 g, 0.10 mol) and 10 mL of 10 N NaOH were each added to 40 mL of H\(_2\)O. Benzaldehyde (10.1 mL, 0.1 mol) was added, and the mixture was stirred for 20 min. NaBH\(_4\), (1.14 g, 0.03 mol) was then added in small portions over a period of 30 min while maintaining the temperature of the solution below 15 °C in an ice bath. The benzylation procedure was repeated twice more by the successive addition of 10.0 mL (0.1 mol) of benzaldehyde and 1.1 g of NaBH\(_4\), (0.03 mol). The final solution was extracted twice with ether and then neutralized to pH 6.5. As the pH of the solution approached neutrality a white
solid precipitated. After the mixture had stood for 3 hr, this solid was filtered off and dried to give (15.16 g, 59.38 mmol, 59 %) of the N,N-dibenzylglycine 197.

\[ \text{Mp} 192-194 \degree \text{C (Lit.} 200 \degree \text{C); } \delta_H (\text{D}_2\text{O}) 7.42 (10\text{H, s, CH}), 3.90 (4\text{H, s, CH}_2), 3.14 (2\text{H, s, CH}_2); \delta_C (101 \text{MHz, D}_2\text{O}) \delta 180.5, 130.2, 128.5, 127.80, 57.2, 55.4. \]

3.4.9 Attempted synthesis of (2S,2'S)-N,N'- (iminomethylene)bis(1-methylpyrrolidine-2-carboxamide) 182.

Method B N-methyl-L-proline 175a (2.0 g, 15.5 mmol, 1.0 equiv.); DMF (5 mL); CDI (3.01 g, 18.58 mmol, 1.50 equiv.); 1 h; guanidinium hydrochloride 206 (1.33 g, 7.74 mmol, 0.50 equiv.); DMF (3 mL); NaH (60%, 370.0 mg, 9.29 mmol, 0.60 equiv.); 48 h. Co-evaporation with heptane and chromatography (15-25% ME in CF). MS and \(^1\)H NMR analysis indicated the presence of only recovered imadizole. This reaction was repeated three times with an extended coupling time (96 hours), longer activation times (24h and 48h) and extended time for the NaH step (48 hr) with only imadizole being recovered.

3.4.10 Preparation of (2S,2'S)-N,N'-(Iminomethylene)bis(1-benzylpyrrolidine-2-carboxamide) 183.

Method B: N-benzyl-L-proline 175b (2.0 g, 9.74 mmol, 1.0 equiv.); CDI (1.92 g, 11.7 mmol, 1.2 equiv.); DMF (6 mL); 16 h; NaH (60%, 0.234 g, 5.85 mmol, 0.60 equiv.); DMF (10 mL); guanidinium chloride 206 (0.97 g, 4.87 mmol, 0.50 equiv.); 48 h. Extraction and column chromatography (25-27% EA in PE) gave 183 (1.66 g, 3.84 mmol) as an off-white solid in 79% yield.

\[ \text{Rf} 0.25 (30\% \text{ EA in PE); } \text{Mp} 125-127 \degree \text{C; } [\alpha]_D^{19} -83.3 (\text{CH}_2\text{Cl}_2, c = 1.2); \delta_H (\text{CDCl}_3) 8.17-11.43 (3\text{H, br s, } 3 \times \text{NH}), 7.19-7.39 (10\text{H, m, } 2 \times \text{Ph}), 3.86 (2\text{H, d, } J 12.8 \text{ Hz, } 2 \times \text{CH}), 3.61 (2\text{H, d, } J 12.7 \text{ Hz, } 2 \times \text{CH}), 3.22 (2\text{H, dd, } J 9.7, 5.9 \text{ Hz, } 2 \times \text{CH}), 3.11-3.15 (2\text{H, m, } 2 \times \text{CH}), 2.38-2.44 (2\text{H, m, } 2 \times \text{CH}), 2.17-2.28 (2\text{H, m, } 2 \times \text{CH}), 1.91-2.02 (2\text{H, m, } 2 \times \text{CH}), 1.76-1.82 (10\text{H, m, } 2 \times \text{CH}) \]
1.90 (4H, m, 2 × CH₂); δC (CDCl₃) 176.0, 147.8, 137.8, 129.5, 128.4, 127.4, 68.9, 59.5, 53.9, 30.6, 23.8; νmax 3354, 3027, 2964, 2875, 2805, 1701, 1604, 1494, 1260; MS (ESI) m/z 434.3 (100%. [M+H]⁺), 160.1 (72%); HRMS (ESI) found 434.2540, C₂₅H₃₂N₅O₂⁺ ([M+H]⁺) requires 434.2551.

3.4.11 Preparation of (2S,2′S)-N,N′-(Iminomethylene)bis(1-isopropylpyrrolidine-2-carboxamide) 184.

Method B: N-Isopropyl-L-proline 175c (1.0 g, 6.36 mmol, 1.0 equiv); DMF (5 mL); CDI (1.24 g, 7.36 mmol, 1.2 equiv); 24 h; guanidine hydrochloride 206 (303.8 mg, 3.18 mmol, 0.5 equiv); DMF (10 mL); NaH (60%, 0.38 g, 9.54 mmol, 1.0 equiv.); 48 h. Extraction and column chromatography (50-100% EA in PE) gave 184 (1.07 g, 3.17 mmol) in 93% yield as an off-white solid.

Rf 0.13 (100% EA); Mp 121-123 °C; [α]D²³ -129.7 (CH₂Cl₂, c = 1.2); δH (CDCl₃) 10.22-12.70 (1H, br s, NH), 8.05-10.22 (2H, br s, 2 × NH), 3.25-3.28 (1H, m, CH), 3.04-3.16 (2H, m, 2 × CH), 2.70-2.80 (2H, m, 2 × CH), 2.46-2.52 (2H, m, 2 × CH), 2.00-2.10 (2H, m, 2 × CH), 1.83-1.94 (2H, m, 2 × CH), 1.64-1.77 (4H, m, 2 × CH₂), 1.01 (12H, d, J 6.4 Hz, CH₃); δC (CDCl₃) 177.3, 148.3, 94.5, 64.9, 53.0, 50.5, 31.8, 24.9, 21.2, 19.9; νmax 3365, 2967, 2874, 1698, 1636, 1611, 1555, 1497, 1308, 1145 cm⁻¹; MS (ESI) m/z 338.3 ([M+H]⁺); HRMS (ESI) m/z found 338.2553, C₁₇H₃₁N₅O₂⁺ ([M+H]⁺) requires 338.2551.

3.4.12 Preparation of (2S,2′S)-N,N′-(Iminomethylene)bis(1-cyclohexylpyrrolidine-2-carboxamide) 185.

Method B: N-cyclohexyl-L-proline 175d (3.0 g, 15.21 mmol, 1.0 equiv.); CDI (2.96 g, 18.25 mmol, 1.20 equiv.); DMF (6 mL) 1 h; NaH (60%, 0.36 g, 9.12 mmol, 0.6 equiv.) DMF (10 mL); guanidinium chloride 206 (0.73 g, 7.60 mmol, 0.5 equiv.) 24 h. Extraction and column
chromatography (50-100% EA in PE) to give 185 (0.50 g, 16% pure, and 1.87 g, 46% as impure) as pale yellow crystals.

Rf 0.30 (5% ME in EA); Mp 157-159 °C; [α]D17 -53.9 (CH2Cl2, c = 1.0); δH (CDCl3) 10.44-12.71 (1H, br s, NH), 8.26-10.44 (2H, br s, 2 × NH), 3.37 (2H, dd, J 3.2, 10.3 Hz, 2 × CH), 3.15-3.25 (2H, m, 2 × CH), 2.52-2.62 (2H, m, 2 × CH), 2.32-2.45 (2H, m, 2 × CH), 2.04-2.17 (2H, m, 2 × CH), 1.87-1.98 (4H, m, 4 × CH), 1.69-1.85 (10H, m, 10 × CH), 1.61 (2H, br d, J 12.1 Hz, 2 × CH), 1.03-1.31 (10H, m, 10 × CH); δC (CDCl3) 177.2, 150.6, 65.3, 62.0, 50.8, 31.7, 31.5, 30.6, 26.1, 25.6, 25.5, 24.5; νmax 3348, 2965, 2926, 2851, 1693, 1660, 1605, 1660, 1605, 1462, 108; MS (ESI) m/z 418.3 (100%, [M+H]+), 152.2 (49%); HRMS (ESI) m/z found 418.3168, C23H40N5O2+ ([M+H]+), requires 418.3177.

3.4.13 Attempted preparation of the phenyl substituted catalysts 204a-d.

Compound 240a (Method B): N-methyl-L-proline 175a (700 mg, 5.42 mmol, 1.0 equiv.); DMF (3 mL); CDI (1.05 g, 6.05 mmol, 1.20 equiv.); 3 h; phenyl guanidinium nitrate 203 (549.0 mg, 2.77 mmol, 0.51 equiv.); DMF (3 mL); NaH (60%, 130.0 mg, 3.25 mmol, 0.6 equiv.); 2.5 h; then combine; 5 d. Extraction with EA; washed with water (3 × 500 mL) and brine (2 × 100 mL); chromatography (4-6% Me in CF) gave the previously isolated 178a (500.0 mg, 1.44 mmol, 27% yield)97

Compound 240b (Method B): N-Benzyl-L-proline 175b (700 mg, 3.41 mmol equiv.); DMF (3 mL); CDI (663.60 mg, 4.09 mmol, 1.20 equiv.); 2 h; phenyl guanidinium nitrate 203 (337.9 mg, 1.71 mmol, 0.5 equiv.); DMF (4 mL); NaH (82.0 mg, 2.05 mmol, 0.6 equiv.); 1 h; the combine; 3 d. Extraction with EA; washed with water (3 × 500 mL) and brine (2 × 100 mL); chromatography (10-25% EA in PE) gave the previously isolated 178b (560.0 mg, 1.10 mmol, 32%) yield 97

Compound 240c (Method B): N-Isopropyl-L-proline 175c (700.0 mg, 4.45 mmol, 1.0 equiv.); DMF (4 mL); CDI (866.4 mg, 5.34 mmol, 1.20 equiv.); 12 h; phenyl guanidinium nitrate 203 (441.2 mg, 2.23 mmol, 0.5 equiv.); DMF (3 mL); NaH (213.70 mg, 5.34 mmol, 1.20 equiv.); 1 h; then combine; 3 d. Extraction with EA; washed with water (3 × 500 mL) and brine (2 × 100 mL); chromatography (10-100% DE in PE) gave the previously isolated 178c (420.0 mg, 1.02 mmol, 23% yield)97
**Compound 240d (Method B):** N-Cyclohexyl-L-proline 175d (700.0 mg, 3.55 mmol, 1.0 equiv.); DMF (3 mL); CDI (690.4 mg, 4.26 mmol, 1.20 equiv.); 2 h; phenyl guanidinium nitrate 203 (352.0 mg, 1.77 mmol, 0.5 equiv.); DMF (3 mL); NaH (60%, 85.2 mg, 2.13 mmol, 0.6 equiv.); 1.5 h; then combain; 4 d. Extraction with EA; washed with water (3 × 500 mL) and brine (2 × 100 mL); chromatography (20-30% EA in PE) gave the previously isolated 178d (320.0 mg, 0.65 mmol, 18% yield)

### 3.4.14 Preparation of N-Boc-Guanidine 207

A solution of Boc₂O (6.0 g, 6.3 mL, 27.5 mmol, 1.0 equiv.) in dioxane (50 mL) was added dropwise over 8 h with vigorous stirring to a cooled (0 °C) solution of guanidinium chloride 206 (13.2 g, 137.7 mmol, 5.0 equiv.) and sodium hydroxide (6.1 g, 151.4 mmol, 5.5 equiv.) in water (25 mL). The resulting suspension was stirred at rt for an additional 20 h and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (3 × 50 mL), dried (MgSO₄) and evaporated under reduced pressure to give a crude compound, which was dissolved in hot EA to which PE was added to the cloud point. Overnight cooling in the freezer gave 207 (4.3 g, 27.0 mmol) as a white solid in 98% yield. Data was in agreement with the literature.

**Rf** 0.25 (20% DCM in ME, with 1% NEt₃); **Mp** 167 °C (dec.) (lit 165 °C (dec.)); δH ((CD₃)₂SO) 5.49-8.06 (4H, br s, 2 × NH, NH₂), 1.34 (9H, s, 3 × CH₃); δC ((CD₃)₂SO) 163.4, 162.7, 75.5, 28.3; νmax 3441, 3402, 3315, 3139, 2975, 2935, 1656, 1533, 1308 cm⁻¹; **MS (ESI)** m/z 319.2 (100%, [2M+H]⁺), 341.2 (40%, [2M+Na]⁺), 160.1 (60%, [M+H]⁺). **HRMS (ESI)** m/z found 160.1077, C₆H₁₄N₃O₂⁺ ([M+H]⁺) requires 160.1081.

### 3.4.15 Preparation of (S)-N’-Boc-N-carbamidoyl-1-methylpyrrolidine-2-carboxamide 208

**Method A:** N-Methyl-L-proline 175a (2.0 g, 15.5 mmol, 1.0 equiv.); DMF (10 mL); CDI (3.0 g, 18.6 mmol, 1.2 equiv.); 24 h; N-Boc-guanidine 207 (2.5 g, 15.48 mmol, 1.0 equiv.);
Extraction and silica gel chromatography (70-100% EA in PE) gave 208 (1.6 g, 5.85 mmol) as a white solid in 38% yield.

**Rf** 0.3 (5% ME in CF); [α]D20 -46 (CH2Cl2, c = 1.0); **Mp** 134 °C; δH (CDCl3) 8.21-10.03 (3H, br s, NH, NH2), 3.00-3.07 (1H, m, CH), 2.95 (1H, dd, J 10.5, 4.8 Hz, CH), 2.31 (3H, s, CH3), 2.30-2.38 (1H, m, CH), 2.15-2.26 (1H, m, CH), 1.79-1.89 (1H, m, CH), 1.64-1.97 (2H, m, 2 × CH), 1.46 (9H, s, 3 × Me); δC (CDCl3) 178.0, 163.4, 158.5, 79.4, 69.0, 56.5, 41.7, 31.3, 28.2, 24.6; vmax 3381, 3293, 2974, 2871, 2794, 1704, 1649, 1619, 1430, 1135, 1048 cm⁻¹; **MS (ESI)** m/z 171.1 (82%), 271.2 (100%, [M+H]+), 293.2 (13 %, [M+Na]+), 563.3 (27%, [2M+Na]+); **HRMS (ESI)** m/z found 271.1765, C12H23N4O3+ ([M+H]⁺) requires 271.1765.

### 3.4.16 Preparation of N-Boc-1H-Pyrazole-1-Carboxamide 210

![Chemical diagram](image)

N-Hydroxy-N-(1-pyrazolyl)-carboxamidine 209 (10.0 g, 68 mmol) and di-tert-butyl dicarbonate (22.2 g, 102 mmol) were dissolved in anhydrous THF (40 mL) and N,N-diisopropylethylamine (23.6 mL, 136 mmol) was added. After stirring for 24 h, the reaction was diluted with water (50 mL), extracted with dichloromethane (4 × 50 mL) and the combined organic extracts washed with brine (50 mL). After drying (MgSO4), and filtering, the solvent was removed under reduced pressure and the crude product re-crystallised from a minimum volume of warm DE to give 210 (10.80 g, 51.4 mmol) as a white crystalline solid in 75% yield. Data was in agreement with the literature.

**Mp** 100-102 °C (Lit. 98 98-99 °C); δH (CDCl3) 9.05 (1H, br. s, NH), 8.46 (1H, br d, J 2.7 Hz, CH), 7.68 (2H, m, CH, NH), 6.40 (1H, d, J 1.5 Hz, CH), 1.55 (s, 9H, ‘Bu); δC (CDCl3) 163.6, 155.3, 143.5, 129.0, 109.1, 80.3, 28.3; vmax 3432, 3316, 3144, 3126, 2977, 2964, 1655, 1606, 1510, 1364, 1308; **MS (ESI)** m/z 210.1 ([100%, M]+), 211.1 ([91%, M+H]+), 155.1 (51); **HRMS (ESI)** found 210.1123, C9H14N4O2+ ([M]⁺) requires 210.1117; found 211.1197, C9H15N4O2 ([M+H]⁺) requires 211.1190.
3.4.17 Preparation of N-methyl-\(N'\)-Boc-guanidine 211. 99

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{Boc} \\
\text{N} & \quad \text{N} \\
\text{NHMe} & \quad \text{Boc} \\
\text{H}_2\text{N} & \quad \text{N} \\
\end{align*}
\]

Chemical Formula: \(\text{C}_7\text{H}_{15}\text{N}_5\text{O}_2\)
Exact Mass: 173.12
Molecular Weight: 173.22

Methylamine (aq. 40%, 3.5 mL, 2.77 g, 35.7 mmol, 3 equiv.) was added to a solution of 210 (2.5 g, 11.9 mmol, 1.0 equiv.) in THF (25 mL) and stirring for 24 h. Water (100 mL) was added and the mixture extracted with EA (2 \times 100 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL) then dried (\(\text{MgSO}_4\)), filtered and evaporated under vacuum. The residue was purified by silica gel chromatography (gradient elution (70-100% EA/PE) to give 211 (1.69 g, 82%, 0.96 mmol) as an off-white crystalline solid. Data not reported in the literature.

Rf 0.09 (50% EA/PE); Mp 176-178 °C; \(\delta\)H (CDCl\(_3\)) 5.93 (3H, br s, 3 \times NH), 2.85 (3H, s, CH\(_3\)), 1.47 (9H, s, CH\(_3\)); \(\delta\)C (CDCl\(_3\)) 162.4, 78.1, 28.6, 27.7; v\(_{\text{max}}\) 3245, 3440, 2975, 2931, 1638, 1589, 1362, 1136 cm\(^{-1}\); MS (ESI) m/z 174.1(100%, [M+H]\(^+\)). HRMS (ESI) m/z found 174.1237, \(\text{C}_7\text{H}_{16}\text{N}_3\text{O}_2\)\(^+\) ([M+H]\(^+\)) requires 174.1237.

3.4.18 Preparation of (S)-N-\(N'\)-Boc-N-methylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 212.

\[
\begin{align*}
\text{N} & \quad \text{H} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{Boc} \\
\text{NHMe} & \quad \text{Boc} \\
\end{align*}
\]

Chemical Formula: \(\text{C}_{13}\text{H}_{24}\text{N}_4\text{O}_3\)
Exact Mass: 284.18
Molecular Weight: 284.36

Method A: \(\text{N-methyl-L-proline 175a}\) (1.12 g, 8.66 mmol, 1.0 equiv.); DMF (12 mL); CDI (2.42 g, 14.94 mmol, 2.0 equiv.); 24 h; \(\text{N-Boc-N'}\)-methylguanidine 211 (750.0 mg, 4.33 mmol, 3.45 equiv.); 5 d. Extraction and trituration with DE (2 \times 50 mL) gave 212 (1.15 g, 4.04 mmol) in 94% yield as an off white solid.

Rf 0.13 (50% EA in PE); \([\alpha]_D^{18}\) -6.4 (CH\(_2\)Cl\(_2\), c = 1.1); Mp 130-132 °C; \(\delta\)H (CDCl\(_3\)) 12.80 (1H, s, NH), 8.81 (1H, s, NH), 3.21-3.28 (1H, m, CH), 2.99 (1H, dd, J 9.9, 4.6 Hz, CH), 2.95 (3H, d, J 4.9 Hz, CH\(_3\)), 2.41 (3H, s, CH\(_3\)), 2.36-2.44 (1H, m, CH), 2.16-2.29 (1H, m, CH), 1.75-1.93 (3H, m, 3 \times CH), 1.51 (9H, s, 3 \times Me); \(\delta\)C (CDCl\(_3\)) 177.7, 167.2, 156.0, 79.3, 69.5, 56.5, 41.5, 31.4, 28.4, 27.9, 24.5; v\(_{\text{max}}\) 3312, 2975, 1727, 1434, 1152, 1046 cm\(^{-1}\); MS (ESI) m/z 285.2 (100%, M+H\(^+\)), HRMS (ESI) found 285.1919, m/z \(\text{C}_{13}\text{H}_{25}\text{N}_3\text{O}_3\)\(^+\) ([M+H]\(^+\)) requires 285.1921.
3.4.19 Preparation of \(N,N\)-dimethyl-\(N'\)-Boc-guanidine 213.

\[
\text{Dimethylamine (aq. 40\%, 8.04 g, 71.4 mmol, 9.0 mL, 6.0 equiv.) was added to a solution of 208 (2.5 g, 11.89 mmol, 1.0 equiv) in THF (25 mL) and the mixture stirred for 24 h. Water (150 mL) was added and the mixture extracted with EA (2 \times 100 mL). The combined extracts washed with water (50 mL), brine (50 mL) and then dried (MgSO}_4. After evaporation under vacuum, purification by silica gel chromatography (70-100\% EA/H) gave 213 (2.19 g, 11.7 mmol) as an off-white crystalline solid in 98\% yield.}
\]

\[\text{M}p \quad 176^\circ \text{C; Rf 0.27 (100\% EA); } \delta \text{H (CDCl}_3) \quad 6.50-7.45 (2H, br s, NH}_2, 3.01 (6H, s, 2 \times \text{CH}_3), 1.49 (9H, s, 3 \times \text{CH}_3); \delta \text{c (CDCl}_3) \quad 164.2, 161.4, 78.1, 36.9, 28.6; \nu_{\text{max}} 3370, 3231, 2976, 2933, 1651, 1589, 1317, 1268; \text{MS (ESI) m/z} \quad 188.1 (48\%, [M+H]^+); \text{HRMS (ESI) found 188.1393, C}_8\text{H}_{18}\text{N}_3\text{O}_2^+ ([M+H]^+) requires 188.1394.}\]


\[
\text{Method A: } N\text{-Methyl-L-proline 175a (1.03 g, 8.01 mmol, 1.50 equiv.); DMF (15 mL); CDI (2.25 g, 13.9 mmol, 2.6 equiv.); 24 h; } N,N\text{-dimethyl-\(N'\)-Boc-guanidine 213 (1.0 g, 5.34 mmol, 1.0 equiv.); 6 d, rt; 40^\circ \text{C 2 d; diluted with K}_2\text{CO}_3 \text{ solution (aq. 10\%, 100 mL). Extraction with EA; washed with water (3 \times 150 mL) and brine (2 \times 50 mL); column chromatography (0-65\% EA in PE) gave recovered 213 (790.0 mg, 4.22 mmol). (100\% EA).}\]
3.4.21 Attempted preparation of methyl N-carbamimidoylcarbamate 222; preparation of \(N,N'\)-di(methyloxy formyl)guanidine 223.\(^{100}\)

\[
\begin{align*}
\text{HN} & \text{NH} \quad \text{MeO} & \text{NH} & \text{O} & \text{Me} \\
\text{H}_2\text{N} & \text{NH}_2\text{HCl} & \text{HN} & \text{O} & \text{NH} & \text{O} & \text{HN} & \text{MeO}
\end{align*}
\]

Guanidinium chloride 206 (12.0 g, 125.6 mmol, 1.0 equiv.) was dissolved in NaOH (aq, 10 M, 9 mL) then cooled (0 °C) and stirred for 30 min. Dioxane (100 mL) was then added and the mixture cooling (0 °C). A solution of methyl chloroformate (11.9 g, 125.6 mmol, 9.7 mL, 1.0 equiv.) in dioxane (100 mL), together with an aqueous solution of NaOH (10 M, 12 mL) were simultaneously added. The reaction formed a thick white precipitate over 30 min, whereupon further dioxane (100 mL) was added and was stirred for a further 90 mins. Water (500 mL) was added and the mixture extracted with EA (3 × 250 mL) and the extracts washed with water (200 mL) and brine (200 mL), then dried (MgSO\(_4\)) and evaporated under reduced pressure to give \(N,N'\)-di(methyloxy formyl)guanidine 223 (5.10 g, 43.55 mmol, 35%) as white crystals.\(^{100}\)

\[\text{M}p\ 214-215 \degree C, (\text{lit.}\ 206 \degree C); \delta_{\text{H}} ((\text{CD}_3)_2\text{SO}) 10.76 (1\text{H, br s, NH}), 8.65 (2\text{H, br s, } 2 \times \text{NH}), 3.61 (6\text{H, br s, } 2 \times \text{CH}_3); \delta_{\text{C}} ((\text{CD}_3)_2\text{SO}) 159.4, 158.7, 52.2; \nu_{\text{max}} 3392, 3255, 2958, 1732, 1655, 1219; \ MS (\text{ESI}) m/z 176.1 (100%, [M+H]\(^+\)); \ HRMS (\text{ESI}) \text{found 176.0665} \ C_5\text{H}_{10}\text{N}_3\text{O}_4^{+} ([\text{M+H}]^{+}) \text{requires 176.0666.}
\]

3.4.22 Preparation of N-Cbz-Guanidine 224.\(^{101}\)

\[
\begin{align*}
\text{HN} & \text{NH} \quad \text{H}_2\text{N} & \text{NH}_2\text{HCl} & \quad \text{HN} & \text{NH}_2\text{HCl} \\
\text{H}_2\text{N} & \text{NH}_2\text{HCl} & \quad \text{HN} & \text{NH}_2\text{HCl} & \quad \text{HN} & \text{NH}_2\text{HCl}
\end{align*}
\]

A solution of benzyl chloroformate (13.1 g, 10.9 mL, 76.5 mmol, 1.0 equiv.) in dioxane (25 mL) was added slowly (15 h) at 5 °C under vigorous stirring to a mixture of guanidine hydrochloride 206 (45.7 g, 0.48 mol, 6.25 equiv.) and sodium hydroxide (19.1 g, 0.48 mol, 6.25 equiv.) dissolved in water (100 mL). The resulting suspension was stirred at rt for an additional 10 h, then extracted with ethyl acetate (4 × 100 mL). The combined organic layers were washed with brine (2 × 50 mL), dried (MgSO\(_4\)) and evaporated under vacuum to give a crude product. Recrystallization from EA/PE gave 224 (13.5 g, 69.8 mmol) as white crystals in 91% yield. Data was in agreement with the literature.
M.p 139-142 °C (Lit 101 140-142 °C); δH ((CD3)2SO) 7.25-7.60 (5H, m, Ph), 6.07-8.01 (4H, br s, 2 × NH, NH2), 4.96 (2H, s, CH2); δC ((CD3)2SO) 163.3, 163.0, 138.2, 128.2, 127.3, 64.8; vmax 3450, 3405, 3306, 3065, 2954, 1621, 1591, 1522, 1290 cm⁻¹; MS (ESI) m/z 194.1 (100% [M+H]+); HRMS (ESI) m/z found 194.0922, C9H12N3O2⁺ ([M+H]+) requires 194.0924.

3.4.23 Preparation of (S)-N-Cbz-N’-carbamimidoyl-1-methylpyrrolidine-2-carboxamide 176a.

\[
\begin{align*}
\text{Me} & \quad \text{O} \quad \text{H} \quad \text{OH} \\
\text{Me} & \quad \text{O} \quad \text{H} \quad \text{NH} \quad \text{NH} \quad \text{Cbz}
\end{align*}
\]

**Chemical Formula:** C15H20N4O3

**Exact Mass:** 304.15

**Molecular Weight:** 304.35

**Method A:** N-Methyl-L-proline 175a (0.50 g, 3.87 mmol, 1.0 equiv.); DMF (10 mL); CDI (0.75 g, 4.65 mmol, 1.2 equiv.); 5-10 min; 0 °C; N-Cbz-guanidine 224 (0.74 g, 3.87 mmol, 1.0 equiv.); 24 h. Evaporation then column chromatography (0-60% DE in PE) gave 176a (0.86 g, 2.82 mmol) as a white solid in 48% yield.

Rf 0.17 (10% DE/PE); M.p 117 °C; [α]D²¹-75 (CHCl₃, c = 1.0); δH (CDCl₃) 8.24-10.8 (3H, br. s, 2 × NH), 7.38-7.44 (2H, m, 2 × CH), 7.26-7.38 (3H, m, 3 × CH), 5.16 (H, d, J 12.9 Hz, CH), 5.12 (H, d, J 12.9 Hz, CH), 3.05-3.08 (1H, m, CH), 3.01 (1H, dd, J 10.5, 4.8 Hz, CH), 2.42 (1H, dd, J 10.1, 6.5 Hz, CH), 2.38 (3H, s, Me), 2.2-2.32 (1H, m, CH), 1.71-1.96 (3H, m, CH, CH₂); δC (CDCl₃) 178.0, 163.9, 158.8, 136.6, 128.4, 128.2, 128.0, 68.9, 67.0, 56.5, 41.7, 31.3, 24.6; vmax (KBr disk) 3395, 3279, 3086, 2945, 1704, 1656, 1611, 1375, 1090 cm⁻¹; MS (EI) m/z 305.2 (100%, M+H⁺); HRMS (ESI) m/z, found 305.1610, C15H21N3O3⁺ ([M+H]+) requires 305.1608.

3.4.24 Preparation of N-Cbz-1H-Pyrazole-1-Carboxamide 217. ⁹⁸

\[
\begin{align*}
\text{HN} & \quad \text{NH} \quad \text{Cl} \\
\text{HN} & \quad \text{NH} \quad \text{Cbz}
\end{align*}
\]

1H-pyrazole-1-carboxamidine hydrochloride 209 (10.0 g, 68.2 mmol, 1.0 equiv.) and benzyl chloroformate (17.5 g, 14.6 mL, 20.6 mmol, 1.5 equiv.) were dissolved in dry THF (50 mL) and N,N-diisopropylethylamine (16.8 g, 22.6 mL, 129.6 mmol, 1.9 equiv.) was added drop-wise over 5 minutes. After 24 h the reaction was diluted with water (120 mL), extracted with dichloromethane (3 × 200 mL) and the organic phase combined and washed with brine.
(200 mL). After drying (MgSO₄), filtering and evaporation, recrystallisation from dichloromethane yielded 217 (13.3 g, 54.5 mmol) as rectangular transparent crystals in 80% yield. Data was in agreement with the literature.

Mₚ 109 °C (lit. 98 107-108 °C); Rf 0.31 (30% EtOAc in Petrol); δH (CDCl₃) 9.05 (1H, br s, NH), 8.46 (1H, d, J 2.7 Hz, CH), 7.70 (1H, br d, J 1.6, CH), 7.65 (1H, br s, NH), 7.44 (2H, br d, J 7.0 Hz, 2 × CH), 7.29-7.39 (m, 3H, 3 × CH), 6.42 (1H, dd, J 2.7, 1.6 Hz, CH), 5.22 (s, 2H, CH₂); δC (CDCl₃) 163.9, 155.4, 143.9, 136.4, 129.1, 128.6, 128.4, 128.3, 109.5, 67.8; vₘₐₓ 3442, 3308, 3144, 3067, 2963, 1664, 1607, 1530, 1272; MS (ESI) m/z 245.1 (100%, [M+H]⁺), 130.2 (23%); HRMS (ESI) found 245.1041, C₁₂H₁₃N₄O₂⁺ ([M+H]⁺) requires 245.1039.

3.4.25 Preparation of N-methyl-N’-Cbz-guanidine 218.

\[
\begin{align*}
\text{HN} & \quad \text{N} \\
\text{H₂N} & \quad \text{N}=\text{NCbz} \\
\end{align*}
\]

Chemical Formula: C₁₀H₁₄N₃O₂
Exact Mass: 207.10
Molecular Weight: 207.23

Methylamine (aq. 40%, 1.27 g, 16.4 mmol, 1.6 mL, 2.0 equiv.) was added to a solution of 217 (2.0 g, 8.19 mmol, 1.0 equiv.) in THF (25 mL). The reaction was vigorously stirred for 90 min, at which point TLC indicated the complete consumption of 217. The reaction was diluted with water (50 mL), extracted with CF (3 × 100 mL) and the combined organic extracts washed with water (2 × 50 mL) and brine (2 × 50 mL). After drying (MgSO₄), filtering and evaporation under vacuum, the crude product was dissolved in the minimum volume of DCM and hexane was added to the cloud point. After standing for 24 h, filtration gave 218 (1.39 g, 6.71 mmol) as a white crystalline solid in 82% yield.

Mₚ 164 °C; Rf 0.15 (EA); δH (CDCl₃) 8.75-7.93 (1H, br s, NH), 7.24-7.38 (5H, m, Ph), 5.76-6.92 (2H, br s, NH₂), 5.08 (2H, s, CH₂), 2.73 (3H, s, CH₃); δC (CDCl₃) 163.5, 162.4, 137.5, 128.5, 128.0, 127.9, 66.4, 27.4; vₘₐₓ 3391, 3305, 3164, 2984, 2925, 1622, 1578, 1494, 1291, 1016; MS (ESI) m/z 208.1 (100% [M+H]⁺), 164.1 (67%); HRMS (ESI) found 208.1091, C₁₀H₁₄N₃O₂⁺ ([M+H]⁺) requires 208.1081.

**Method A**: N-Methyl-L-proline 175a (935.0 mg, 7.24 mmol, 1.5 equiv.); DMF (12 mL); CDI (1.96 g, 12.06 mmol, 2.5 equiv.); 24 h; N-methyl-N-Cbz-guanidine 218 (1.0 g, 4.83 mmol, 1.0 equiv.); 4 d. Extraction and recrystallization from methanol gave 219 (1.37 g, 4.30 mmol) in 89% yield as a white solid.

**Rf** 0.23 (50% EA/PE); [α]D20 -54.0 (CH3Cl, c = 1.1); Mp 100-102 °C, δH (CDCl3) 12.81 (1H, s, NH), 8.99 (1H, s, NH), 7.42 (2H, d, J 7.0 Hz, 2 × CH), 7.28-7.37 (3H, m, 3 × CH), 5.16 (2H, s, CH2), 3.25-3.32 (1H, m, CH), 3.00 (1H, dd, J 4.7, 10.0 Hz, CH), 2.97 (3H, d, J 4.9 Hz, CH3), 2.43 (3H, s, CH3), 2.37-2.43 (1H, m, CH), 2.20-2.32 (1H, m, CH), 1.77-1.94 (3H, m, 3 × CH); δC (CDCl3) 178.0, 163.0, 156.6, 137.0, 128.5, 128.4, 128.0, 69.6, 67.2, 56.6, 41.6, 31.5, 27.9, 24.5; νmax 3298, 3130, 2946, 2851, 2793, 1691, 1642, 1618, 1562, 1497, 1436, 1124, 1082, 874 cm⁻¹; MS (ESI) m/z 319.2 (100%, [M+H]+). HRMS (ESI) m/z found 319.1767, C16H23N4O3+ ([M+H]+) requires 319.1765.

3.4.27 Preparation of N,N-dimethyl-N'-Cbz-guanidine 220.

Dimethylamine (aq., 40%, 1.27 g, 16.4 mmol, 1.6 mL, 2.0 equiv.) was added to a solution of 217 (2.50 g, 10.24 mmol, 1.0 equiv.) dissolved in THF (25 mL) and the mixture vigorously stirred for 48 h, at which point TLC indicated the complete consumption of 217. Water (150 mL) was added, the mixture extracted with CF (3 × 100 mL) and the combined extracts washed with water (2 × 50 mL) and brine (2 × 50 mL), then dried (MgSO4) and evaporated under reduced pressure. The resulting residue was dissolved in the minimum amount of DCM and hexane was added to the cloud point. After standing for 24 h, the product was collected by filtration to give 220 (2.20 g, 9.94 mmol) as a pale yellow crystalline solid in 97% yield.
Mp 79-81 °C; Rf 0.09 (50% EA in PE); δH (CDCl₃) 7.41 (2H, br d, J 7.3 Hz, 2 × CH), 7.32 (2H, br t, J 7.3 Hz, 2 × CH), 7.24-7.28 (1H, m, CH), 6.61-7.24 (2H, br s, NH₂), 5.13 (2H, s, CH₂), 3.04 (6H, s, 2 × CH₃); δC (CDCl₃) 163.8, 161.3, 137.7, 128.3, 128.0, 127.6, 66.6, 36.9; νmax 3376, 3285, 3037, 2957, 2894, 1575, 1479, 1442; MS (ESI) m/z 222.1 (100% [M+H]⁺); HRMS (ESI) found 222.1237, C₁₁H₁₆N₂O₂⁺ (100% [M+H]⁺) requires 222.1237.

3.4.28 Attempted preparation of (S,Z)-N-(N'-Cbz)-N,N-dimethylcarbamidoyl)-1-methylpyrrolidine-2-carboxamide 221.

Method A: N-Methyl-L-proline 175a (875.6 mg, 6.78 mmol, 1.5 equiv.); DMF (10 mL); CDI (1.47 g, 9.04 mmol, 2.0 equiv.); 24 h; N,N-dimethyl-N'-Cbz-guanidine 220 (1.0 g, 4.52 mmol, 1.0 equiv.); 6 d, rt. Extraction with EA; washed with water (3 × 150 mL) and brine (2 × 50 mL); column chromatography (0-50% EA in PE) gave recovered 220 (940.0 mg).

3.4.29 Attempted preparation of methylpyrrolidine-2-carboxamide 225.

Pd/C (10%, 500.0 mg) was added to a solution of 176a (700.0 mg, 2.53 mmol) in dry methanol (15 mL) under a nitrogen atmosphere. The mixture was stirred at rt for 2 h under a hydrogen atmosphere and then the reaction was then filtered through Celite© and the filtrate concentrated in vacuum to give a white solid. Purification by silica gel chromatography eluting with (0-9% ME in DCM) gave methyl-L-prolinate 226 (290.0 mg, 1.70 mmol, 76%) as a yellow gum as the only identifiable product. Data was in agreement with the literature.¹⁰²

Rf 0.17 (10% DE/PE); δH [D₂O] 2.5-25.3 (CH₂Cl₂, c = 1.5); δH (CD₃OD) 4.34 (1H, dd, J 9.0, 8.0 Hz, CH), 3.86 (3H, s, Me), 3.75 (1H, ddd, J 11.3, 8.0, 4.3 Hz, CH), 3.20-3.30 (1H, m, CH), 3.02 (1H, s, Me), 2.53-2.64 (1H, m, CH), 2.14-2.27 (2H, m, 2 × CH), 1.99-2.13 (1H, m, CH); δC (CD₃OD) 169.8, 68.9, 57.7, 54.0, 41.4, 29.0, 23.2; νmax 3377, 2962, 2923, 1745, 1671, 1427, 1258 cm⁻¹; MS (ESI) m/z 309.2 (35%, [2M+Na⁺], 166.1 (100%, [M+Na]⁺), 144.1 (76%, [M+H]⁺); HRMS (ESI) found 166.0835, C₇H₁₄N₂O₂⁺ ([M+Na]⁺) requires 166.0838.
2.4.30 Preparation of (S)-N-(1H-benzo[d]imidazol-2-yl)-1-methylpyrrolidine-2-carboxamide 179a.

Method A; N-Methyl-L-proline 175a (1.0 g, 7.74 mmol, 1.0 equiv.); DMF (9 mL); CDI (1.51 g, 9.29 mmol, 1.2 equiv.); 24 h; 2-aminobenzimidazole 227 (1.05 g, 7.74 mmol, 1.0 equiv.); 72 h. Extraction and column chromatography (0-50% ME in EA) gave 179a (1.04 g, 4.25 mmol) in 55% yield as a pale yellow solid.

Rf 0.16 (20% ME in EA); Mp 242-244 °C; [α]D 16 ± 1; (CDCl3, c = 1.0); δH (CDCl3) 10.92 (1H, br s, NH), 10.47 (1H, br s, NH), 7.24-7.74 (2H, m, 2 × CH), 7.06-7.22 (2H, m, 2 × CH), 3.01-3.18 (2H, m, 2 × CH), 2.39 (3H, s, Me), 2.33-2.45 (1H, m, CH), 2.18-2.32 (1H, m, CH), 1.87-1.99 (1H, m, CH), 1.68-1.83 (2H, m, 2 × CH); δC (CDCl3) 175.3, 146.3, 138.3, 122.3, 122.3, 68.7, 56.7, 41.9, 31.4, 24.8; vmax (KBr disk) 3350, 3244, 3050, 2946, 1702, 1626, 1589, 1310, 1021, 861 cm⁻¹; MS (ESI) m/z 267.1 (100%, [M+Na]+), 245.1 (55%, [M+H]+), HRMS (ESI) found 245.1399, C13H17N4O+ ([M+H]+) requires 245.1397.

3.4.31 Preparation of (S)-N-((1-methylpyrrolidin-2-yl)methyl)-1H-benzo[d]imidazol-2-amine 228.

Lithium aluminum hydride (203.2 mg, 5.35 mmol, 4.36 equiv) was added in small portions to a cooled (0 °C) solution of amide 179a (300.0 mg, 1.23 mmol, 1.0 equiv.) in DE (20 mL) over 30 min. After 6 h at 0 °C, the reaction was stirred for 18 h at rt then at reflux for 5 h. The reaction was quenched by the sequential addition of EA (3 mL), then ME (2 mL) and after stirring for 30 min, filtered through a Celite© pad and the pad washed with DE (excess). The filtrate was evaporated under reduced pressure to give an off-white gum, which was purified by column chromatography (3% ME in CF + 0.05% TFA) to give 228 (230.0 mg) as a TFA salt. This was dissolved in KOH (MeOH, 5% w/v, 2 mL) and diluted with CF/ME (9:1,
10 mL) and the solution washed with brine (2 × 10 mL). Drying (MgSO₄), filtering and evaporation gave 228 (150 mg, 0.65 mmol, 78%) as a golden yellow viscous oil.

**Rf 0.39 (30% ME in DCM+TFA 0.05%); [α]D²⁰ -75.4 (CHCl₃, c = 1.02); δH (CD₃OD) 7.13-7.23 (2H, m, 2 × CH), 6.94-7.00 (2H, m, 2 × CH), 3.59 (1H, dd, J 13.6, 4.5 Hz, CH), 3.41 (1H, dd, J 13.6, 5.6 Hz, CH), 3.12-3.20 (1H, m, CH), 2.67-2.76 (1H, m, CH), 2.53 (3H, s, CH₃), 2.38-2.47 (1H, m, CH), 2.00-2.11 (1H, m, CH), 1.69-1.87 (3H, m, CH, CH₂); δC (CD₃OD) 157.1, 139.0 (HMBC), 121.4, 112.8, 67.0, 58.1, 45.7, 41.2, 29.3, 23.5; Vmax 3272, 3059, 2968, 2794, 1632, 1602, 1582, 1464, 1267, 740; MS (ESI) m/z 231.2 ([100, M+H]+), 461.3 ([5, 2M+H]+); HRMS (ESI) found 231.1604, C₁₃H₁₉N₄⁺ ([M+H]+) requires 231.1604.

### 3.4.32 Preparation of 1-Methyl-1H-benzo[d]imidazol-2-amine 229

Powdered KOH (10.5 g, 187.8 mmol, 5.0 equiv.) was added to a stirred solution of 1H-benzo[d]imidazol-2-amine 227 (5.0 g, 37.6 mmol, 1.0 equiv.) in acetone (200 mL). A thick white precipitate formed after 10 min; whereupon methyl iodide (2.6 mL, 5.86 g, 41.3 mmol, 1.1 equiv.) was added and the reaction mixture stirred vigorously for 30 min. At this point, the brown solution was transferred to a separating funnel containing toluene (250 mL) and the mixture washed with water (120 mL), brine (120 mL) and then dried (MgSO₄). After evaporation under reduced pressure, the residue was dissolved in a small volume of toluene and diluted with CHCl₃ to the cloud point then stored at -20 °C overnight. The solid was dissolved in dilute HCl (1M, adjusted to pH = 2) and extracted with CHCl₃ (3 × 100 mL). The aqueous acidic layer was made alkaline with NaOH (aq. 10% w/v) and extracted with DCM (3 × 50 mL). The DCM extract dried (MgSO₄) and evaporated under reduced pressure to give 229 (1.39 g, 25%) as light brown solid. Data was in agreement with the literature.

**Mp 203-204 °C (lit.¹⁰³ 202-204 °C); Rf 0.13 (20% ME in EA); δH (CD₃OD) 7.22 (1H, br dd, J 6.9, 1.2 Hz, CH), 7.12 (1H, br dd, J 7.1, 1.4 Hz, CH), 6.98-7.06 (2H, m, 2 × CH), 3.53 (3H, s, Me); δC (CD₃OD) 156.4, 142.4, 135.8, 122.3, 120.6, 115.7, 108.6, 28.7; Vmax 3448, 3307, 3024, 2727, 1648, 1541, 1317 cm⁻¹; MS (ESI) m/z 148.1, (100%, [M+H]+); HRMS (ESI) found 148.0872, C₈H₁₀N₃⁺ ([M+H]+) requires 148.0875.
3.4.33 Preparation of (S)-N-(1H-benzo[d]imidazol-2-yl)-1-methylpyrrolidine-2-carboxamide 230.

Method A: N-Methyl-L-proline 175a (658.2 mg, 5.10 mmol, 1.50 equiv.); DMF (12 mL); CDI (1.38 g, 8.49 mmol, 2.5 equiv.); 8 h; 1-methyl-2-aminobenzimidazole 229 (0.50 g, 3.40 mmol, 1.0 equiv.). 10 d. Extraction and silica gel chromatography, eluting with (2.5-6% ME in CF), gave 230 (357.0 mg, 0.138 mmol) in 41% yield as a tan coloured gum.

Rf 0.24 (50% CHCl3/MeOH); [α]D23 -32.2 (CH2Cl2, c = 1.6); δH (CDCl3) 9.40-11.24 (1H, br s, NH), 7.53 (1H, br d, J 6.0 Hz, CH), 7.22-7.30 (3H, m, 3 × CH), 3.69 (3H, s, CH3), 3.26 (1H, br t, J 7.5 Hz, CH), 3.10-3.18 (1H, m, CH), 2.54 (3H, s, CH3), 2.40-2.51 (1H, m, CH), 2.25-2.36 (1H, m, CH), 2.02-2.12 (1H, m, CH), 1.81-2.00 (2H, m, 2 × CH); δC (CDCl3) 175.1 (HMBC), 155.4 (HMBC), 135.5 (HMBC), 122.7, 109.3, 70.2, 56.9, 41.8, 31.1, 30.1, 24.2; νmax 3342, 2981, 2922, 2851, 1626, 1557, 1483, 1454, 1065 cm⁻¹; MS (ESI) m/z 259.2 (100%, [M+H]+), 539.3 (64%, [2M+Na]+), 281.1 (59%, [M+Na]+); HRMS (ESI) m/z found 259.1555; C14H19N4O⁺ ([M+H]+) requires 259.1553.

3.4.34 Preparation of N-Methyl-1H-benzo[d]imidazol-2-amine 232. 104

1H-Benzimidazol-2-amine 227 (4.00 g, 30.0 mmol, 1.0 equiv.), formaldehyde (aq. 37% w/v; 5.03 mL, 5.49 g, 67.6 mmol, 2.25 equiv.) and p-thiocresol (8.43 g, 68.0 mmol 2.26 equiv.) were dissolved in absolute ethanol (100 mL) and heated under reflux for 7 h. After cooling to rt, the precipitate was collected by filtration and washed with CF and recrystallized from hot ethanol to give 2-(p-tolylthiomethylamino)benzimidazole (6.90 g, 85%) as a white solid. This compound (6.90 g) was dissolved in ethanol (200 mL) and sodium borohydride (6.88 g, 0.19 mol, 7.5 equiv) was added in small portions over 1 h with stirring and the reaction was then heated under reflux for 1 h. After cooling, methanol (80 mL) was added, followed by HCl (aq. 1M, 160 mL) and the mixture concentrated under reduced pressure to give a white
solid. The solid was dissolved in HCl (aq. 1M, 200 mL) and this solution was washed with DE (4 × 150 mL) before it was neutralized (pH 7-8) with sodium hydroxide (aq. 10% w/w) and extracted with EA (3 × 150 mL). The combined EA extracts were dried (MgSO₄) and evaporated under reduced pressure to give 232 (3.0 g, 20.6 mmol) as a white solid in 69% yield over two steps.

Mp 170-173 °C (Lit. 104 167-168 °C); δH (CD3OD) 7.18-7.22 (2H, m, 2 × CH), 6.96-7.00 (2H, m, 2 × CH), 2.98 (3H, s, CH₃); δC (CD3OD) 157.3, 138.3, 121.5, 112.6, 79.4, 29.6; v_max 3425, 3050, 2905, 2878, 2848, 1638, 1601, 1327 cm⁻¹; MS (ESI) m/z 148.1 (100%, [M+H]+); HRMS (ESI) m/z found 148.0865, C₈H₁₀N₃⁺ ([M+H]+) requires 148.0869.

3.4.35 Preparation of (S)-N-(1H-Benz[d]imidazol-2-yl)-N,1-dimethylpyrrolidine-2-carboxamide 233.

![Chemical structure of 233](image)

**Method A:** N-Methyl-L-proline 175a (1.32 g, 10.19 mmol, 1.5 equiv.); DMF (11 mL); CDI (2.75 g, 16.99 mmol, 2.5 equiv.); 8 h; N-methyl-1H-benzo[d]imidazol-2-amine 232 (1.0 g, 6.79 mmol, 1.0 equiv.); 3 d. Extraction and recrystallization (DE/PE) gave 233 (970.0 mg, 3.06 mmol) in 45% yield as an off-white solid.

Rf 0.13 (3% MeOH in CHCl₃); Mp 112-114 °C; [α]D¹⁸ -84.4 (CH₂Cl₂, c = 1.3); δH (CDCl₃) 11.60 (1H, s, NH), 7.64 (1H, d, J 5.8 Hz, CH), 7.39 (1H, d, J 5.8 Hz, CH), 7.16-7.25 (2H, m, 2 × CH), 3.78 (3H, s, CH₃), 3.39 (1H, dd, J 8.6, 7.2Hz, CH), 3.22-3.29 (1H, m, CH), 2.44 (3H, s, CH₃), 2.25-2.47 (2H, m, 2 × CH), 1.82-2.08 (3H, m, 3 × CH); δC (CDCl₃) 174.9 (HMBC), 149.9, 122.3, 118.3, 110.8, 68.0, 56.2, 41.0, 33.9, 29.7, 23.4; v_max 3361, 3055, 2948, 2850, 2786, 1672, 1622, 1525, 1427, 1308 cm⁻¹; MS (ESI) m/z 259.2 (100%, [M+H]+) 539.3 (16%, [2M+Na]+), 281.1 (9%, [M+Na]+) HRMS (ESI) m/z found 259.1555, C₁₃H₁₉N₄O⁺ ([M+H]+) requires 259.1553.
3.4.36 Preparation of (S)-1-Methylpyrrolidine-2-carbohydrazide 238.

\[
\begin{array}{c}
\text{COOH} \\
\text{Me} \\
\text{HOH} \\
\end{array} \rightarrow \begin{array}{c}
\text{Cl} \\
\text{Me} \\
\text{H} \\
\text{OMe} \\
\end{array} \rightarrow \begin{array}{c}
\text{Me} \\
\text{N} \\
\text{H} \\
\text{OH} \\
\text{Cl} \\
\end{array}
\]

\[\text{Chemical Formula: C}_6\text{H}_{13}\text{N}_2\text{O}\]
\[\text{Exact Mass: 143.11}\]
\[\text{Molecular Weight: 143.19}\]

\(N\)-Methyl-L-proline 175a (2.30 g, 17.8 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), cooled (0 °C) and acetyl chloride (2 mL, 2.2 g, 28.0 mmol, 1.6 equiv.) was slowly added over 5 min. The mixture was heated at reflux for 12 h, cooled to rt and concentrated under reduced pressure. The residue was triturated with DE (3 × 50 mL) and dried under vacuum to give a brown gum in 79% yield. The crude ester (1.57 g, 8.77 mmol) was dissolved in MeOH (9 mL) and hydrazine hydrate (98%, 8.27 g, 0.165 mols, 9.3 equiv.) was added dropwise over 5 min. After stirring for 24 h, a white precipitate was removed by filtration and the filtrate concentrated under reduced pressure to give a yellow oily residue. Trituration of the residue with CHCl₃ (2 × 40 mL) followed by drying under vacuum gave the crude product as a yellow oil (1.75 g) which was purified by column chromatography (5-10% ME in CF with 1% NEt₃) to give 238 (1.15 g, 8.03 mmol) as a pale yellow oil in 93% yield (73% over 2 steps).

\(\text{Rf} 0.24 \ (5\% \ \text{ME in CF with 1\% NEt}_3);\ \ [\alpha]_{20}^{\circ} -121.6 \ \text{(CH}_2\text{Cl}_2, \ c = 1.28); \ \delta_\text{H} \ (\text{CDCl}_3) 8.25 \ (1\text{H, br s, NH}), 3.74 \ (2\text{H, br s, NH}_2), 3.04 \ (1\text{H, ddd, J 2.2, 6.5, 8.5 Hz, CH}), 2.93 \ (1\text{H, dd, J 10.3, 5.1 Hz, CH}), 2.32 \ (3\text{H, s, CH}_3), 2.25-2.32 \ (1\text{H, m, CH}), 2.12-2.22 \ (1\text{H, m, CH}, 1.66-1.84 \ (3\text{H, m, CH, CH}_2); \ \delta_\text{C} \ (\text{CDCl}_3) 174.6, 68.1, 56.7, 41.9, 30.9, 24.4; \ \nu_{\text{max}} 3297, 2967, 2884, 2785, 1650, 1464, 1085 \ \text{cm}^{-1}; \ \text{MS (ESI) m/z} 144.1 \ (51\% , [M+H]^+); \ \text{HRMS (ESI)} \ \text{found} 144.1128, \ \text{C}_6\text{H}_{14}\text{N}_3\text{O}^+ ([M+H]^+) \ \text{requires} 144.1131.\]

3.4.37 Preparation of tert-Butyl 2-(methyl-L-prolyl)hydrazine-1-carboxylate 240.

\[
\begin{array}{c}
\text{COOH} \\
\text{Me} \\
\end{array} \rightarrow \begin{array}{c}
\text{BocNHNH}_2 \\
\text{Me} \\
\end{array} \rightarrow \begin{array}{c}
\text{Me} \\
\text{N} \\
\text{H} \\
\text{Boc} \\
\end{array}
\]

\[\text{Chemical Formula: C}_{11}\text{H}_{21}\text{N}_3\text{O}_3\]
\[\text{Exact Mass: 243.16}\]
\[\text{Molecular Weight: 243.31}\]

\textbf{Method A:} \(N\)-methyl-L-proline 175a (1.47 g, 11.35 mmol, 1.5 equiv.); DMF (15 mL); CDI (3.07 g, 18.92 mmol, 2.5 equiv.); 8 h; tert-butyl hydrazine carboxylate (1.02 g, 7.57 mmol, 1.0 equiv.); 3 d. Extraction and recrystallization (ME/CF) gave 240 (1.1 g, 4.52 mmol) as a white solid in 60% yield.
Rf 0.10 (EA); [α]D20 73.3 (CH3Cl, c = 1.08); Mp 102-106 °C; δH (CDCl3) 8.74 (1H, br s, NH), 6.47 (1H, br s, NH), 3.05-3.13 (1H, m, CH), 3.00 (1H, dd, J 10.2, 4.4 Hz, CH), 2.42 (3H, s, CH3), 2.28-2.37 (1H, m, CH), 2.16-2.27 (1H, m, CH), 1.73-1.97 (3H, m, CH, CH2), 1.47 (9H, s, 3 × CH3); δC (CDCl3) 173.7, 155.2, 81.8, 68.3, 56.8, 41.9, 31.0, 28.3, 24.4; νmax 3268, 2967, 2885, 2788, 1726, 1680, 1476, 1391, 1160 cm⁻¹; MS (TOF ASAP) m/z 244.2 (100%, M+H]+); HRMS (ESI) found 244.1663, C11H22N3O3 ([M+H]+) requires 244.1656.

3.4.38 Preparation of Benzyl 2-(methyl-L-prolyl)hydrazine-1-carboxylate 242.

\[
\begin{align*}
\text{Me} & \quad \text{CbzNHNH}_2 & \quad \text{NMe} \\
\text{N} & \quad \text{O} & \quad \text{NHCbz}
\end{align*}
\]

**Method A:** N-methyl-L-proline 175a (1.17 g, 9.03 mmol, 1.5 equiv.); DMF (15 mL); CDI (2.44 g, 15.0 mmol, 2.5 equiv.); 8 h; benzyl hydrazinecarboxylate (1.0 g, 6.02 mmol, 1.0 equiv.); 3 d. Extraction and trituration (DE 3 × 50 mL) gave 242 (1.5 g, 5.41 mmol) as a pale yellow viscous liquid in 90% yield.

Rf 0.13 (EA); [α]D21 61.3 (CH3Cl, c = 0.45); δH (CDCl3) 8.82 (1H, s, NH), 7.41-7.29 (5H, m, Ph), 6.75 (1H, s, NH), 5.16 (2H, s, CH2), 3.15-3.06 (1H, m, CH), 3.05-2.95 (1H, m, CH), 2.42 (3H, s, CH3), 2.34 (1H, m, CH), 2.27-2.13 (1H, m, CH), 2.00-1.87 (1H, m, CH), 1.83-1.67 (2H, m, CH2); δC (CDCl3) 156.1, 135.7, 128.7, 128.5, 128.3, 68.3, 68.0, 56.7, 41.8, 31.0, 24.4; νmax 3265, 2967, 2885, 2791, 1735, 1685, 1466, 1385, 1025 cm⁻¹; MS (ASAP) m/z 278.2 (100%, [M+H]+), 220.2 (58%); HRMS (ASAP) found 278.1505, C14H20N3O3 ([M+H]+) requires 278.1499.

3.4.39 Preparation of (S)-1-methyl-N'-phenylpyrrolidine-2-carbohydrazide 244.

\[
\begin{align*}
\text{Me} & \quad \text{PhNHNH}_2 & \quad \text{NMe} \\
\text{N} & \quad \text{O} & \quad \text{NHPh}
\end{align*}
\]

**Method A:** N-methyl-L-proline 175a (1.79 g, 13.87 mmol, 1.50 equiv.); DMF (12 mL); CDI (3.75 g, 23.1 mmol, 2.5 equiv.); 24 h; phenyl hydrazine (1.0 g, 9.25 mmol, 1.38 mL, 1.0
equiv.) 2 d. Extraction and column chromatography (3-5% ME in CHCl₃), gave 244 (1.0 g, 4.56 mmol) as a yellow solid in 50% yield.

Rf 0.25 (5% ME in EA), [α]D²⁰ -64.6 (CH₃Cl, c = 1.05); Mp 101-103 °C; δH (CDCl₃) 8.90 (1H, s, NH), 7.21 (2H, d, J 7.6 Hz, CH), 6.89 (1H, t, J 7.3 Hz, CH), 6.81 (2H, d, J 8.0 Hz, CH), 6.15 (1H, s, NH), 3.14 (1H, m, CH), 3.07 (1H, dd, J 10.2, 4.8 Hz, CH), 2.47 (3H, s, CH₃), 2.38 (1H, m, CH), 2.33-2.19 (1H, m, CH), 1.98-1.76 (3H, m, CH + CH₂); δC (CDCl₃) 173.9, 148.2, 129.2, 121.1, 113.6, 68.3, 56.8, 42.2, 31.2, 24.6; νₘₚₐₓ 3267, 2965, 2849, 2788, 1672, 162, 1495, 1351, 1084 cm⁻¹; MS (TOF ASAP) m/z 220.2 (100%, [M+H]+); HRMS (TOF ASAP) found 220.1454, C₁₂H₁₈N₃O⁺ ([M+H]+) requires 220.1444.

3.4.40 Preparation of (S)-N-Cbz-N’-carbamimidoyl-2-(dimethylamino)propanamide 245.

Method A: N,N-dimethyl-L-alanine 191 (727.6 mg, 6.21 mmol, 1.2 equiv.); DMF (15 mL); CDI (1.43 g, 8.80 mmol, 1.7 equiv.); 24 h; N-Cbz-guanidine 224 (1.0 g, 5.18 mmol, 1.0 equiv.); 4 d. Extraction and column chromatography (30-50% EA in PE) gave 245 (1.50 g, 5.13 mmol) in 99% yield as a white solid.

Rf 0.15 (100% EA); [α]D²⁰ +31.3 (CH₂Cl₂, c = 1.8); Mp 112-114 °C, δH (CDCl₃) 8.45-10.94 (3H, br s, 3 × NH), 7.23-7.41 (5H, m, CH), 5.11 (2H, s, CH₂), 3.13 (1H, q, J 7.0 Hz, CH), 2.21 (6H, s, 2 × CH₃), 1.19 (3H, d, J 7.0 Hz, CH₃); δC (CDCl₃) 177.2, 163.8, 158.9, 136.6, 128.4, 128.1, 127.9, 66.9, 64.6, 41.8, 9.5; νₘₚₐₓ 3378, 3286, 3033, 2980, 2944, 2872, 2833, 2789, 1708, 1649, 1619, 1528, 1498, 1439, 1263, 1082 cm⁻¹; MS (ESI) m/z 293.2 (100%, [M+H]+); HRMS (ESI) found 293.1614, m/z C₁₄H₂₀N₄O₃⁺ [M+H]+ requires 293.1614.
3.4.41 Preparation of (S)-N-Boc-N’-Carbamimidoyl-2-(dimethylamino)propanamide 246.

Method A: N-Methyl-L-alanine 191 (883.1 mg, 7.54 mmol, 1.2 equiv.) DMF (20 mL); CDI (1.73 g, 10.68 mmol, 1.7 equiv.) 6 h; N-Boc-guanidine 207 (1.0 g, 6.28 mmol, 1.0 equiv.); 4 d. Extraction and column chromatography (0-0.5% ME in CF) gave 246 (0.65 g, 2.52 mmol) as a white solid in 40% yield.

Rf 0.14 (DE); [α]D18 + 27.8 (CH2Cl2, c = 1.05); Mp 119-120 °C; δH (CDCl3) 8.96 (3H, br s, 3 × NH), 3.12 (1H, q, J 6.9 Hz, CH), 1.49 (3H, s, 3 × Me), 1.20 (3H, d, J 7.0 Hz, CH3); δC (CDCl3) 177.3, 158.6, 79.5, 64.9, 41.9, 28.3, 9.8; vmax 3380, 3129, 2972, 2938, 2871, 2791, 1712, 1653, 1564, 1478, 1136, 1049 cm⁻¹; MS (ESI) m/z 275.2 (100%, [M+H+2O-H]+), 259.3 (43%, [M+H]+); HRMS (ESI) found 259.1768, C11H23N4O3+ ([M+H]+) requires 259.1765.

3.4.42 Preparation of (S)-N-(1H-Benz[d]imidazol-2-yl)-2-(dimethylamino)propanamide 247.

Method A: N,N-Dimethyl-L-alanine 191 (500.0 mg, 3.76 mmol, 1.0 equiv.); DMF (7 mL); CDI (1.52 g, 9.39 mmol, 2.5 equiv.); 24 h; 2-aminobenzimidazole 227 (659.8 mg, 5.63 mmol, 1.5 equiv.) 24 h. Extraction and column chromatography (60-90% EA in PE) gave 247 (800.0 mg, 3.44 mmol) as a white solid in 92% yield.

Rf 0.10 (EA); [α]D30 +24.3 (CH3Cl, c = 1.07); Mp 208-210 °C; δH ((CD3)2SO) 12.08 (1H, br s, NH), 11.20 (1H, br s, NH), 7.37-7.50 (2H, m, 2 × CH), 7.07-7.09 (2H, m, 2 × CH), 3.32 (1H, J 6.8 Hz, CH), 2.28 (6H, s, 2 × CH3), 1.20 (3H, d, J 6.8 Hz, CH3); δC (CDCl3) 172.5, 146.2, 140.5 (HMBC), 134.4 (HMBC), 121.0, 62.2, 41.2, 12.4; vmax 3335, 3100, 2978, 2942, 2870, 2826, 2782, 1683, 1562, 1520, 1455, 1222 cm⁻¹; MS (ESI) m/z 233.1 (100%,
[M+H]\(^{+}\)), 161.1 (44%); HRMS (ESI) found 233.1404, \(\text{C}_{12}\text{H}_{17}\text{N}_{4}\text{O}^{+}\) ([M+H]\(^{+}\)) requires 233.1402.

### 3.4.43 Attempted preparation of (S)-2-(dimethylamino)-N-(N’-phenylcarbamimidoyl)propanamide 250.

**Method B:** \(N\)-dimethyl-\(L\)-alanine 191 (0.50 g, 4.27 mmol, 1.0 equiv.); DMF (15 mL); CDI (1.38 g, 8.54 mmol, 2.0 equiv.); 24 h; NaH (60%, 170.0 mg, 4.27 mmol, 1.0 equiv.); DMF (15 mL); phenylguanidinium nitrate 203 (846.0 mg, 4.27 mmol, 1.0 equiv.); 4 d. Extraction with EA and repeated column chromatography (90-100% DE in PE) gave 250 as an inseparable mixture with 203 (900.0 mg, 3.84 mmol). Attempted recrystallization from DE/PE also failed to separate the two compounds. Repeats of this reaction varying the relative equivalents of the guanidine salt and the nature of the counterion gave similar mixtures of the two compounds. (Table 13)

<table>
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<tr>
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<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>HNO(_2)</td>
<td>1.0 (0.5g)</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.90 g</td>
</tr>
<tr>
<td>2</td>
<td>(\frac{1}{2}) H(_2)CO(_3)</td>
<td>1.0 (1.0g)</td>
<td>2.5</td>
<td>1.25</td>
<td>2.15</td>
<td>1.50 g</td>
</tr>
<tr>
<td>3</td>
<td>(\frac{1}{2}) H(_2)CO(_3)</td>
<td>1.0 (1.0g)</td>
<td>2.17</td>
<td>0.83</td>
<td>0.8</td>
<td>0.85 g</td>
</tr>
<tr>
<td>4</td>
<td>HCl</td>
<td>1.0 (1.0g)</td>
<td>2.17</td>
<td>0.96</td>
<td>1.25</td>
<td>1.23 g</td>
</tr>
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</table>

### 3.4.44 Attempted preparation of (S)-N-(amino((S)-2-(dimethylamino)propanamido)methylene)-2-(dimethylamino)propanamide 251.

**Method B:** Attempt 1: \(N,N\)-Dimethyl-\(L\)-alanine 191 (1.0 g, 8.54 mmol, 1.0 equiv.); DMF (15 mL); CDI (2.08 g, 12.80 mmol, 1.5 equiv.); 24 h; guanidinium hydrochloride 206 (404.0 mg, 4.12 mmol, 0.5 equiv.); DMF (10 mL); NaH (60%, 205.0 mg, 5.12 mmol, 0.6
equiv.); 24 h; 3 d. Extraction with EA, then column chromatography (50-100% EA in PE), gave 251 (120.0 mg) as an off-white wax, contaminated with imidazole.

**Attempt 2:** N,N-Dimethyl-L-alanine 191 (1.0 g, 8.54 mmol, 1.0 equiv.); EDCI (1.99 g, 12.80 mmol, 1.5 equiv.); DMF (10 mL); 24 h; guanidinium hydrochloride 206 (408.0 mg, 4.27 mmol, 0.50 equiv.); DMF (15 mL) NaH (60%, 205.0 mg, 5.12 mmol, 0.6 equiv.); 24 h; 3 d. Extraction with EA; washed with water (2 × 100 mL); co-evaporated with heptane. Analysis by $^1$H proton NMR indicated the presence of 251 contaminated with a number of impurities.

### 3.4.45 Preparation of (S)-N-Cbz-N'-Carbamimidoyl-2-(dimethylamino)-3-phenylpropanamide 252.

![Chemical Diagram]

Method A: N-dimethyl-L-phenylalanine 193 (800.2 mg, 4.14 mmol, 1.0 equiv.); DMF (15 mL); CDI (1.43 g, 8.28 mmol, 2.0 equiv.); 24 h; N-Cbz-guanidine 224 (800.0 mg, 4.14 mmol, 1.0 equiv.); 6 d. Extraction and column chromatography (33-42% EA in PE) gave 252 (1.20 g, 3.26 mmol) as a white solid in 79% yield.

Rf 0.1 (50% EA in PE); $[\alpha]_D^{23} + 30$ (CH$_2$Cl$_2$, c = 3.0); Mp 141-143 °C, $\delta_H$ (CDCl$_3$) 7.99-10.49 (3H, br s, 3 × NH) 7.11-7.32 (10H, m, 2 × Ph) 5.05 (2H, s, CH$_2$), 3.36 (1H, dd, J 7.4, 5.8 Hz, CH), 3.04 (1H, dd, J 14.0, 7.4 Hz, CH), 2.85 (1H, dd, J 14.0, 5.8 Hz, CH), 2.23 (6H, s, 2 × CH$_3$); $\delta_C$ (CDCl$_3$) 175.8, 163.6, 158.8, 138.9, 136.6, 129.1, 128.7, 128.5, 128.2, 128.0, 126.6, 71.3, 67.1, 42.0, 31.3; $\nu_{max}$ 3381, 3284, 3063, 3030, 2929, 2789, 1704, 1650, 1621, 1530, 1496, 1453, 1268, 1165 cm$^{-1}$; MS (ESI) m/z 385.2 (100%, [M+H$_2$O-H]+), 369.2 (43%, [M+H]+); HRMS (ESI) found 369.1926, C$_{20}$H$_{25}$N$_4$O$_3$ [M+H]+ requires 369.1921.

### 3.4.46 Preparation of (S)-N-Boc-N'-Carbamimidoyl-2-(dimethylamino)-3-phenylpropanamide 253.

![Chemical Diagram]

Method A: N-Methyl-L-phenylalanine 193 (1.00 g, 5.17 mmol, 1.0 equiv.); DMF (20 mL); CDI (1.30 g, 7.76 mmol, 1.55 equiv.); 24 h; N-Boc-guanidine 207 (823.8 mg, 5.17 mmol,
1.0 equiv.); 13 d. Extraction and column chromatography (17-28% EA in PE) gave 253 (1.5 g, 4.49 mmol) as a white solid in 87% yield.

**Rf** 0.16 (50% EA/PE); [α]D18 +37.0 (CH2Cl2, c = 1.9); **Mp** 101-103 °C; δH (CDCl3) 8.95 (3H, br s, NH), 7.30-7.15 (5H, m, CH), 3.42-3.35 (1H, m, CH), 3.08 (1H, dd, J 14.0, 7.4 Hz, CH2), 2.88 (1H, d, J 5.9 Hz, CH2), 2.27 (6H, s, CH3), 1.47 (9H, s, CH3); δC (CDCl3) 176.0, 162.9, 158.4, 138.9, 129.1, 128.6, 126.5, 79.5, 71.4, 42.0, 31.5, 28.2; νmax 3386, 3285, 2975, 2935, 2832, 2789, 1702, 1654, 1620, 1561, 1495, 1293 cm⁻¹; **MS (ESI) m/z** 351.2 (100%, [M+H2O-H]+), 335.2 (100%, [M+H]+); **HRMS (ESI)** found 335.2082, C17H27N4O3+ ([M+H]+), requires 335.2078.

### 3.4.47 Preparation of (S)-N-((1H-Benzod|d|imidazol-2-yl)-2-(dimethylamino)-3-phenylpropanamide 254.

![Chemical Structure of 254](image)

**Method A**: N,N-dimethyl-L-phenylalanine 193 (800.0 mg, 4.14 mmol, 1.0 equiv.); DMF (15 mL); CDI (1.64 g, 10.10 mmol, 2.44 equiv.); 24 h; 2-aminobenzimidazole 277 (551.2 mg, 4.14 mmol, 1.0 equiv.); 7 d. Brine (100 mL) was added, extraction and column chromatography (0-30% EA in DE) gave 254 (540.0 mg, 1.75 mmol) as a white solid in 42% yield.

**Rf** 0.06 (DE); [α]D20 +33.5 (MeOH, c = 2.6); **Mp** 133-136 °C; δH (CDCl3) 10.32 (2H, br s, 2 × NH), 7.44-7.46 (2H, m, 2 × CH), 7.13-7.25 (7H, m, Ph, 2 × CH), 3.57 (1H, dd, J 7.8, 5.7 Hz, CH), 3.21 (1H, dd, J 13.9, 7.8 Hz, CH), 2.97 (1H, dd, J 13.9, 5.7 Hz, CH), 2.27 (6H, s, 2 × CH3); δC (CDCl3) 172.9, 146.7, 141.0 (HMBC), 138.7, 129.0, 128.5, 126.5, 122.3, 70.6, 42.0, 32.5; νmax 3372, 3027, 2885, 2785, 1682, 1630, 1561, 1519, 1455, 1272 cm⁻¹; **MS (ESI) m/z** 309.2 (100%, [M+H]+); **HRMS (ESI)** found 309.1712, C18H20N4O+ ([M+H]+) requires 309.1710.
3.4.48 Preparation of (S)-2-(dimethylamino)-3-phenyl-N-(N’-phenylcarbamimidoyl)propanamide 255.

Method B: N,N-dimethyl-L-phenylalanine 193 (1.0 g, 5.17 mmol, 1.0 equiv.); DMF (15 mL); CDI (1.82 g, 11.21 mmol, 2.6 equiv.); 24 h; NaH (60%, 155.2 mg, 3.88 mmol, 1.0 equiv.); DMF (15 mL); phenylguanidinium carbonate 248 (850.4 g, 4.31 mmol, 1.0 equiv.); 4 d. Extraction and column chromatography (50-100% EA in PE) gave 255 (0.61 g, 1.97 mmol) pale yellow solid in 46% yield.

Rf 0.1 (EA); [α]D +5.7 (CH2Cl2, c = 2.15); δH (CDCl3) 7.09-7.51 (11H, m, NH, NH2, Ph, 3 × CH), 7.02 (2H, br d, J 8.0 Hz, 2 × CH), 3.50 (1H, dd, J 7.1, 6.2 Hz, CH), 3.22 (1H, dd, J 14.2, 7.1 Hz, CH), 2.95 (1H, dd, J 14.1, 6.2 Hz, CH), 2.38 (6H, s, 2 × CH3); δC (CDCl3) 175.3, 149.6, 144.6, 139.4, 129.8, 129.2, 128.7, 126.5, 124.2, 123.3, 71.5, 42.1, 31.8; νmax 3309, 3060, 3027, 2940, 2866, 2830, 2785, 1655, 1589, 1561, 1509, 1493, 1077 cm–1; MS (ESI–ve) m/z 345.2 (52%, [M+Cl]–), 309.2 (77%, [M–H]–), 264 (100%); HRMS (ESI–ve) found 309.1720, C18H21N4O–(M–H)– requires 309.1721.

3.4.49 Preparation of (S)-N-(Amino((S)-2-(dimethylamino)-3-phenylpropanamido)methylene)-2-(dimethylamino)-3-phenylpropanamide 256.

Method B: N,N-Dimethyl-L-phenylalanine 193 (1.0 g, 5.17 mmol, 1.0 equiv.); DMF (10 mL); CDI (1.43 g, 8.80 mmol, 1.7 equiv.); 24 h; guanidinium hydrochloride 206 (247.2 mg, 2.59 mmol, 0.5 equiv.); DMF (10 mL); NaH (60%, 124.1 mg, 9.54 mmol, 3.1 equiv.) 7 d. Extraction and column chromatography (90-100% DE in PE; 0-100% EA in DE with NH3 (3 drop per litre) gave 256 (820.0 mg, 2.00 mmol) as an off-white wax in 77% yield.

Rf 0.15 (100% EA + 3 drops NH3); [α]D+61.9 (CH2Cl2, c = 1.38); δH (CDCl3) 8.06-10.04 (2H, s, 2 × NH), 7.20-7.24 (10H, m, 2 × Ph), 3.39 (2H, dd, J 8.5, 5.3 Hz, 2 × CH), 3.12 (2H, dd, J 13.6, 8.6 Hz, 2 × CH), 2.98 (2H, dd, J 13.6, 5.3 Hz, 2 × CH), 2.41 (12H, s, 4 × CH3);
δc (CDCl3) 178.8, 157.9, 139.2, 129.3, 128.5, 126.4, 73.1, 42.4, 33.1; νmax 3365, 3062, 2965, 2935, 2829, 2785, 1703, 1633, 1602, 1450, 1453, 1078 cm⁻¹; MS (ESI) m/z 410.3 (100%, [M+H]+); HRMS (ESI) found 410.2543, \( \text{C}_{23}\text{H}_{32}\text{N}_{5}\text{O}_{2}^{+} \) ([M+H]+) requires 410.2551.

3.4.50 Preparation of (S)-N-(benzo[d]thiazol-2-yl)-1-methylpyrrolidine-2-carboxamide 262

![Chemical Structure](image)

**Chemical Formula:** \( \text{C}_{13}\text{H}_{15}\text{N}_{3}\text{O} \)

**Exact Mass:** 261.09

**Molecular Weight:** 261.34

**Method A:** N-Methyl-L-proline 175a (1.00 g, 7.74 mmol, 1.6 equiv.); CDI (2.93 g, 5.16 mmol, 3.5 equiv.); DMF (10 mL); 16 h; 2-aminobenzothiazole 261 (786.0 mg, 1.0 equiv.); 7 d.

Extraction and column chromatography (0-50% EA in PE with 0.1% NH₃) gave 262 (1.00 g, 3.81 mmol, 74%) as a white solid.

Rf 0.1 (30% EA in PE with 0.1% NH₃); mp 79-83 °C, \([\alpha]_D^{19} = -38.0\) (CHCl₃, c = 1.0); δH (CDCl₃) 9.82-11.72 (1H, br s, NH), 7.82 (1H, d, \( J = 7.9 \text{ Hz}, \text{CH} \)), 7.78 (1H, d, \( J = 8.1 \text{ Hz}, \text{CH} \)), 7.44 (1H, dd (apparent t), \( J = 8.1, 7.5 \text{ Hz}, \text{CH} \)), 7.31 (1H, dd (apparent t), \( J = 7.9, 7.5 \text{ Hz}, \text{CH} \)), 3.17-3.30 (2H, m, 2 × CH), 2.49 (3H, s, CH₃), 2.44-2.55 (1H, m, CH), 2.26-2.40 (1H, m, CH), 1.97-2.07 (1H, m, CH), 1.76-1.92 (2H, m, CH₂);

δc (CDCl₃) 173.7, 157.7, 148.6, 132.3, 126.4, 124.1, 121.6, 121.1, 68.5, 56.7, 42.0, 31.3, 24.9; νmax 3182, 2949, 2848, 2796, 1696, 1600, 1628, 1445, 1352, 1316, 1263, 1156, 1048, 1016, 779, 757, 730, 668 cm⁻¹; MS (ESI) m/z 284.1 (100%, [M+Na]+), 262.1 (95%, [M+H]+), 545.2 (42%, [2M+Na]+); HRMS (ESI) found 262.1011, \( \text{C}_{13}\text{H}_{16}\text{N}_{4}\text{OS}^{+} \) ([M+H]+) requires 262.1009.

3.4.51 Attempted preparation of (S)-N-(benzo[d]oxazol-2-yl)-1-methylpyrrolidine-2-carboxamide 264.

![Chemical Structure](image)

**Chemical Formula:** \( \text{C}_{13}\text{H}_{16}\text{N}_{3}\text{O}_{2} \)

**Exact Mass:** 245.12

**Molecular Weight:** 245.28

**Method A:** N-Methyl-L-proline 175a (1.00 g, 7.74 mmol, 1.5 equiv.); CDI (2.93 g, 18.04 mmol, 2.33 equiv.); DMF (10 mL); 16 h; 2-aminobenzoxazole 263 (692 mg, 5.16 mmol,
1.0 equiv.); 5 d. Extraction EA gave a crude compound (353 mg) which was composed of mainly 2-aminobenzoxazole 263.

3.4.52 Preparation of (S)-1-Methyl-N-(1H-imidazol-2-yl)pyrrolidine-2-carboxamide 270.

\[
\begin{align*}
\text{Method A: } N\text{-Methyl-L-proline } 175a & (1.00 \text{ g, 7.74 mmol, 1.6 equiv.}); \text{ CDI (2.26 g, 13.94 mmol, 1.8 equiv.); DMF (15 mL); 24 h; 2-aminomidazol hemisulfate (1.26 g, 14.98 mmol, 0.60 equiv.); Et}_3\text{N (3.04 mL, 34.84 mmol, 4.5 equiv); 24 h. Extraction and column chromatography (5-80% EA in PE with 0.1% NH}_3\text{) gave 270 (1.47 g, 7.57 mmol, 97\%)) as a off-white solid.} \\
\text{Rf 0.24 (10\% EA in ME); Mp 180-182 °C; } [\alpha]D -73.3 (c = 0.3, CHCl}_3); \delta (\text{CDCl}_3) 9.55-11.41 (2H, br s, 2 \times \text{NH}), 6.82 (2H, s, 2 \times \text{CH}), 3.15-3.19 (1H, m, CH), 3.08 (1H, dd, J 10.5, 4.6 Hz, CH), 2.44 (3H, s, Me), 2.40-2.47 (1H, m, CH), 2.23-2.33 (1H, m, CH), 1.91-1.98 (1H, m, CH), 1.74-1.86 (2H, m, CH}_2); \delta (\text{CDCl}_3) 174.3, 140.5, 68.5, 56.8, 42.0, 31.4, 24.8 (Imidazole 2 \times \text{CH not detected); } \nu \text{max} 3223, 2960, 2845, 2786, 1671, 1585, 1524, 1492 \text{ cm}^{-1}; \text{ MS (ESI) m/z 195.1 (100\%, [M+H]^+); HRMS (ESI) found 195.1240, C}_9\text{H}_{15}\text{N}_4\text{O}^+ ([M+H]^+) requires 195.1241.}
\end{align*}
\]

3.4.53 Preparation of (S)-1-Benzyl-N-(1H-imidazol-2-yl)pyrrolidine-2-carboxamide 271.

\[
\begin{align*}
\text{Method A: } N\text{-benzyl-L-proline } 175b & (1.0 \text{ g, 4.87 mmol, 1.0 equiv.}); \text{ CDI (1.44 g, 8.77 mmol, 1.80 equiv.); DMF (15 mL); 16 h; 2-aminomidazol hemisulfate (772.0 mg, 5.84 mmol, 1.2 equiv.); Et}_3\text{N (2.21 g, 21.9 mmols, 3.04 mL, 4.5 equiv.); 2 d. Extraction and column chromatography (5-80\% EA in PE) gave 171 (0.897 g, 3.32 mmol) in 68\% yield as a white solid.}
\end{align*}
\]
Rf 0.31 (50% EA in PE); Mp 64 °C; [α]D -198 (c = 1, CHCl₃); δ_H (CDCl₃) 9.38-11.51 (2H, br m, 2 × NH), 7.15-7.31 (5H, m, Ph), 6.76 (2H, s, 2 × CH), 3.82 (1H, d, J 12.7 Hz, CH), 3.57 (1H, d, J 12.7 Hz, CH), 3.31 (1H, dd, J 10.4, 4.2 Hz, CH), 3.00-3.07 (1H, m, CH), 2.37-2.46 (1H, m, CH), 2.16-2.27 (1H, m, CH), 1.87-1.97 (1H, m, CH), 1.66-1.82 (2H, m, 2 × CH); 174.1, 141.3, 137.6, 129.2, 128.7, 127.6, 66.7, 60.0, 54.0, 30.9, 24.3 (Imidazole 2 × CH not detected); v_max 3269, 3025, 2973, 29251, 2804, 1665, 1571, 1525, 1493 cm⁻¹; MS (CI) m/z 160.1 (100%), 269.1 (40%, [M-H]+) 293.1 (55% [M+Na]+); HRMS (CI) found 293.1376, C₁₅H₁₈N₄ONa ([M+Na]+) requires 293.1373.

3.4.54 Preparation of (S)-1-Methyl-N-(pyridine-2-yl)pyrrolidine-2-carboxamide 268a

\[
\text{Method A: N-methyl-L-proline 175a (1.00 g, 7.74 mmol, 1.5 equiv.); CDI (2.93 g, 18.07 mmol, 3.5 equiv.); DMF (10 mL); 16 h; 2-aminopyridine 265 (486.0 mg, 5.16 mmol, 1 equiv.); 7 d. Extraction, column chromatography (0-50% EA in PE with 0.1% NH₃) and recrystallization (CF) gave 268a (189.6 mg, 0.92 mmol, 18%) as pale yellow-green crystals.}
\]

Rf 0.26 (15% EA in PE); Mp 40-41 °C; [α]D²⁰ -78.9 (c = 1.0 in CF); δ_H (CDCl₃) 9.85 (1H, s, NH), 8.29 (H, br d, J 4.7 Hz, CH), 8.26 (1H, br d, J 8.4 Hz, CH), 7.69 (1H, ddd, J 8.4, 7.2, 1.6 Hz, CH), 7.02 (1H, t, J 7.2, 4.7 Hz, CH), 3.17-3.22 (1H, m, CH), 2.99-3.10 (1H, m, CH), 2.46 (3H, s, Me), 2.39-2.46 (1H, m, CH), 2.24-2.35 (1H, m, CH), 1.92-2.02 (1H, m, CH₂), 1.77-1.88 (2H, m, CH₂); δ_C (CDCl₃) 178.4, 151.4, 148.1, 138.4, 119.8, 113.9, 69.5, 56.7, 41.9, 31.3, 24.6; v_max 3301, 2950, 2850, 2711, 1705, 1570, 1508, 1433, 1271, 765 cm⁻¹; MS (CI) m/z 228.1 (100%, [M+Na]+), 206.1 (20%, [M+H]+); HRMS (CI) m/z found 206.1289, C₁₁H₁₆N₃O⁺ ([M+H]+) requires 206.1288.
3.4.55 Preparation of (S)-1-methyl-N-(pyrimidin-2-yl)pyrrolidine-2-carboxamide 268b

Method A: N-methyl-L-proline 175a (1.00 g, 7.74 mmol, 1.0 equiv.); CDI (2.95 g, 18.19 mmol, 2.35 equiv.); DMF (10 mL); 24 h; 2-aminopyrimidine 266 (736.0 mg, 7.74 mmol, 1.0 equiv.); 3 d. Extraction with EA gave a crude compound (425 mg) which was mainly composed of unreacted 2-aminopyrimidine 266.

3.4.56 Attempted preparation of (S)-1-methyl-N-(pyrazin-2-yl)pyrrolidine-2-carboxamide 268c

Method A: N-methyl-L-proline 175a (1.00 g, 7.74 mmol, 1.5 equiv.); CDI (2.93 g, 18.07 mmol, 3.5 equiv.); DMF (10 mL); 24 h; 2-aminopyrazine 267 (491.0 mg, 5.16 mmol, 1.0 equiv.); 7 d. Extraction with EA gave a crude compound (197 mg) which was mainly composed of unreacted 2-aminopyrazine 267.

3.4.57 Preparation of Synthesis of N-Cbz-L-proline 290

L-Proline 2 (2.87 g, 24.9 mmol, 1.0 equiv) was added to a solution of NaOH (aq., 12.5, 0.2 M) and the mixture cooled in an ice bath. Separately a solution of NaOH (aq., 8.75, 4 M) and benzyl chloroformate (4.7 mL, 33.0 mmol, 1.3 equiv) were added simultaneously in a dropwise manner over 15 min. After 1.5 hours, the reaction mixture was extracted with DE (2 × 10 mL, discarded) then acidified to a pH = 2 with HCl (6M) and saturated with sodium chloride. After extraction with EA (2 × 100 mL), the combined organic layers were dried (MgSO₄) then evaporated under reduced pressure. The residue was dissolved in hot EA (6 mL) which was diluted with hot PE (20 mL) to the cloud point. Cooling and filtration gave the
product 290 (4.86 g, 19.5 mmol) in 78% yield as a white solid. Data was in agreement with the literature.

\[ \text{Rf} \ 0.09 \ (\text{EA}); \ Mp. \ 74-76 \ ^\circ \text{C} \ (\text{Lit.} \ 69-75 \ ^\circ \text{C}); \ [\alpha]_D^{20} -70.0 \ (c = 1.3, \ CF, \ \text{Lit.}) \ [\alpha]_D^{20} -73.6 \ (c = 1.4, \ CF); \ \delta_H (\text{CDCl}_3) 9.35 \ (1H, \ br \ s, \ OH), 7.37-7.30 \ (5H, \ m, \ CH), 5.22-5.13 \ (2H, \ m, \ CH_2), 4.44-4.36 \ (1H, \ m, \ CH), 3.63-3.44 \ (2H, \ m, \ CH_2), 2.31-2.08 \ (2H, \ m, \ CH_2), 2.04-1.91 \ (2H, \ m, \ CH_2) \ \text{ppm}; \ \delta_C (\text{CDCl}_3) 178.3/176.3, 156.1/154.5, 136.6/136.4, 128.7/128.5, 128.3/128.1, 128.0/127.8, 67.8/67.3, 59.5/58.7, 47.0/46.8, 31.0/29.4, 24.4/23.6; \ \nu_{\text{max}} \ 3444, \ 3032, \ 2957, \ 2884, \ 1665, \ 1498, \ 1416, \ 1355, \ 1120, \ 1088, \ 1028; \ MS \ (\text{ESI}) \ m/z \ 248.1 \ (100\%, \ [M+H]^+); \ HRMS \ (\text{ESI}) \ m/z \ 248.0931, \ C_{13}H_{16}NO_4^+ \ ([M+H]^+) \ requires \ 248.0928.

3.4.58 Preparation of Benzyl (S)-2-((N-((benzyloxy)carbonyl)carbamimidoyl)carbamoyl)pyrrolidine-1-carboxylate 292.

![Chemical structure of compound 292]

**Method A**: N-Cbz-L-proline 290 (1.51 g, 6.07 mmol, 1.0 equiv.); DMF (10 mL), 0 \ ^\circ \text{C}; CDI (1.27 g, 7.83 mmol, 1.3 equiv.); 24 h; N-Cbz-guanidine 224 (1.17 g, 6.07 mmol, 1.0 equiv.); 2 d, rt. Extraction with EA; washed with water (3 x 150 mL) and brine (3 x 50 mL); column chromatography (0-30% EA in PE) gave 292 (1.73 g, 4.08 mmol) in 67% yield as a white solid.

\[ \text{Rf} \ 0.49 \ (\text{EA}); \ Mp. \ 47-49 \ ^\circ \text{C}; \ [\alpha]_D^{20} -60.1 \ (2.0, \ CF); \ \delta_H (\text{CDCl}_3) \ 7.82-9.96 \ (3H, \ br \ s, \ 3 \times \ NH), 7.16-7.45 \ (10H, \ m, \ 2 \times \ Ph), 5.19 \ (1H, \ br \ d, \ J \ 11.7 \ Hz, \ CH), 5.14 \ (1H, \ d, \ J \ 12.5 \ Hz, \ CH), 5.10 \ (1H, \ d, \ J \ 12.4 \ Hz, \ CH), 5.02 \ (1H, \ br \ d, \ J \ 11.7 \ Hz, \ CH), 4.24-4.47 \ (1H, \ m, \ CH), 3.37-3.65 \ (2H, \ m, \ CH_2), 1.98-2.32 \ (2H, \ m, \ CH_2), 1.81-1.97 \ (2H, \ m, \ CH_2); \ \delta_C (\text{CDCl}_3) \ mixture \ of \ rotamers; \ 162.8/162.7, \ 158.9/158.7, \ 155.7, \ 154.5, \ 136.4, \ 136.3/136.2, \ 128.5, \ 128.5, \ 128.2, \ 128.2, \ 128.2, \ 128.1, \ 67.7/67.5, \ 67.1, \ 61.8/61.7, \ 47.4/47.1, \ 31.3/29.6, \ 24.5/23.7; \ \nu_{\text{max}} \ 3383, \ 3274, \ 3032, \ 2957, \ 2886, \ 1703, \ 1662, \ 1627, \ 1539, \ 1498, \ 1446, \ 1414, \ 1379, \ 1355, \ 1277, \ 1170, \ 1116, \ 1090, \ 1026, \ 989, \ 914, \ 806, \ 748 \ \text{cm}^{-1}; \ MS \ (\text{ESI}) \ m/z \ 425.2 \ (100\%, \ [M+H]^+), \ HRMS \ (\text{ESI}) \ m/z \ found \ 425.1814, \ C_{22}H_{24}N_4O_5^+ \ ([M+H]^+) \ requires \ 425.1819.
3.4.59 Preparation of tert-Butyl (S)-2-((N-((benzyloxy)carbonyl)carbamimidoyl)carbamoyl)pyrrolidine-1-carboxylate 293.

Method A: N-Boc-L-proline 291 (1.52 g, 7.04 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (1.78 g, 10.1 mmol, 1.4 equiv.); 24 h; N-Cbz-guanidine 224 (1.35 g, 6.97 mmol, 1.0 equiv.); 2 d, rt. Extraction with EA; washed with water (150 mL × 3) and brine (50 mL × 2); column chromatography (0-20% EA in PE) gave 293 (1.1 g, 2.82 mmol) in 40% yield as a white solid. 

Rf 0.53 (EA); Mp 64-66 °C; [α]D20 -53.8 (2.1, CF); δH (CDCl3) 7.63-10.22 (3H, br. s, 3 × NH), 7.27-7.38 (5H, m, Ph), 5.11 (2H, s, CH2), 4.11-4.46 (1H, m, CH), 3.28-3.62 (2H, m, CH2), 1.94-2.30 (2H, m, CH2), 1.76-1.94 (2H, m, CH2), 1.44/1.40 (9H, 2 × s, 3 × CH3); δC (CDCl3) 163.1, 158.9, 136.5, 128.5, 128.1, 128.1, 81.0, 67.0, 62.0/61.5, 47.3/46.9, 31.3/29.7, 28.4, 24.6/23.9 (2 × C not detected); νmax 3380, 3275, 2976, 2883, 1697, 1661, 1628, 1541, 1497, 1477, 1446, 1392, 1367, 1279, 1161, 1120, 1090, 1045, 1026, 991, 927, 854, 806, 751, 698, 666, 583, 491 cm⁻¹; MS (ESI) m/z 391.2 (100%, [M+H]+); HRMS (ESI) found 391.1980, C19H27N4O5+ ([M+H]+) requires 391.1976

3.4.60 Preparation of Di-tert-butyl 2,2'-(((iminomethylene)bis(azanediyl))bis(carbonyl))(2S,2'S)-bis(pyrrolidine-1-carboxylate) 294.

Method B: N-Boc-L-proline 291 (950.0 mg, 4.40 mmol, 1.20 equiv.); DMF (10 mL); CDI (820.0 mg, 5.13 mmol, 1.40 equiv.); 24 h; guanidinium hydrochloride 206 (73.0 mg, 1.83 mmol, 0.50 equiv.); DMF (10 mL); NaH (60%, 180.0 mg, 1.87 mmol, 0.51 equiv.); 2 d. Extraction with EA; washed with water (100 mL × 3) and brine (100 mL × 2); column chromatography (25% EA in PE) gave 294 (500.0 mg, 1.10 mmol) as white solid in 25% yield.
3.4.61 Preparation of tert-Butyl (S)-(1-(3-(tert-butyloxy carbonyl) guanidino)-1-oxopropan-2-yl)carbamate 296.

**Chemical Formula:** C_{14}H_{26}N_{4}O_{5}

**Exact Mass:** 330.19

**Molecular Weight:** 330.39

**Method A:** N-Boc-L-alanine 295 (1.00 g, 5.29 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (940.0 mg, 6.66 mmol, 1.26 equiv.); 30 min; Boc-guanidine 207 (925.0 mg, 5.95 mmol, 1.12 equiv.); DMF (15 mL); 3 d, rt; 2 d; 40 °C. Extraction with EA (3 × 50 mL); washed HCl (0.1 M, 50 mL), NaHCO_{3} (aq. sat. 50 mL) and brine (2 × 50 mL); column chromatography (0-40% EA in PE) gave 296 (1.10 g, 3.33 mmol) in 63% as a white solid.

**Rf** 0.12 (25% EA/PE); [α]D^{23} -24.0 (CHCl_{3}, c = 1.0); **Mp** 113 °C; δ_{H} (CDCl_{3}) 7.77-9.70 (3H, br s, 3 × NH), 5.21 (1H, br s, NH), 3.90-4.31 (1H, m, CH), 1.49 (9H, s, 3 × Me), 1.44 (9H, s, 3 × Me), 1.38 (3H, d, J 7.1 Hz, Me); δ_{C} (CDCl_{3}) 159.0, 155.2, 60.5, 52.6, 28.5, 28.1, 19.4 (3 × C not detected); v_{max} 3382, 3282, 2978, 2934, 1712, 1643, 1539, 1496, 1447, 1148, 1047 cm^{-1}; **MS (ESI) m/z** 331.2 (100, [M+H]^+), **HRMS (ESI)** found 331.1973, C_{14}H_{27}N_{5}O_{5}^+ ([M+H]^+) requires 331.1976.

3.4.62 Preparation of tert-Butyl (S)-(1-(3-(benzyloxy carbonyl) guanidino)-1-oxopropan-2-yl)carbamate 297.

**Chemical Formula:** C_{17}H_{24}N_{4}O_{5}

**Exact Mass:** 364.17

**Molecular Weight:** 364.40

**Method A:** N-Boc-L-alanine 295 (1.00 g, 5.29 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (0.94 g, 6.66 mmol, 1.26 equiv.); 30 min; Cbz-guanidine 224 (1.12 g, 5.81 mmol, 1.1 equiv.); DMF (15 mL); 3 d, rt. Extraction with EA (3 × 50 mL); washed HCl (0.1 M, 50 mL), NaHCO_{3} (aq. sat. 50 mL) and brine (2 × 50 mL); Recrystallized from ethanol (ca. 15 mL) at -
20 °C (2 days) to form white needles which were washed with ice-cold DE and dried under vacuum to give 297 (1.37 g, 3.76 mmol) in 71% yield.

**Rf** 0.10 (25% EA/PE); [α]D25 -18.8 (CH3Cl, c = 1.15); **Mp** 138-140 °C; δ H (CDCl3) 7.93-10.03 (3H, br. s, 3 × NH), 7.29-7.42 (5H, m, Ph), 5.15 (2H, s, CH2), 5.10 (1H, br s, NH), 4.17-4.40/3.85-4.08 (1H, br m, CH), 1.46 (9H, s, 3 × Me), 1.33-1.46 (3H, m, CH3); δ C (CDCl3) 162.0, 159.1, 155.2, 136.2, 128.6, 128.3, 128.2, 80.5, 67.3, 51.8, 28.4, 18.3 (1 × C not detected); νmax 3383, 3282, 2978, 2928, 1695, 1629, 1542, 1498, 1436, 1165, 1069 cm⁻¹; **MS** (ESI) m/z 365.2 (100%, [M+H]⁺); **HRMS** (ESI) found 365.1819, C17H25N4O5⁺ ([M+H]⁺) requires 365.1820.

### 3.4.63 Preparation of Benzyl (S)-(1-(3-(tert-butyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 299.

![Chemical structure](image)

**Method A:** N-Cbz-L-alanine 298 (1.03 g, 4.48 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (910.0 mg, 5.60 mmol, 1.25 equiv.); 90 min; Boc-guanidine 207 (792.0 mg, 4.93 mmol, 1.1 equiv.); 24 h, rt. Extraction with CF (3 × 50 mL); washed HCl (0.1 M, 50 mL), NaHCO3 (aq. sat. 50 mL) and brine (2 × 50 mL). Purification was carried out using column chromatography (70% DE in Hex) to give 299 (1.37 g, 3.76 mmol) in 49% yield.

**Rf** 0.29 (75% DE/PE); [α]D28 -21.2 (CHCl3, c = 1.0); **Mp** 64-66 °C; δ H (CDCl3) 8.16-10.21 (3H, br s, 3 × NH), 7.24-7.39 (5H, m, Ph), 5.69-5.99 (1H, m, NH), 5.11 (1H, d, J 12.6, CH), 5.07 (1H, d, J 12.6, CH), 4.10-4.33 (1H, m, CH), 1.45 (9H, s, 3 × Me), 1.38 (3H, d, J 7.0 Hz, Me); δ C (CDCl3) 159.3, 155.7, 136.6, 128.6, 128.2, 128.1, 83.3, 66.7, 53.1, 28.0, 19.2 (2 × C not detected); νmax 3374, 3101, 2976, 1720, 1639, 1524, 1500, 1165, 1069 cm⁻¹; **MS** (ESI) m/z 365.2 (100%, [M+H]⁺); **HRMS** (ESI) found 365.1819, C17H25N4O5⁺ ([M+H]⁺) requires 365.1819.
3.4.64 Preparation of Benzyl (S)-(1-(3-(benzyloxy carbonyl)guanidino)-1-oxopropan-2-yl)carbamate 300.

Method A: Cbz-L-alanine 298 (1.00 g, 5.48 mmol, 1.0 equiv.); DMF (5 mL), 0 °C; CDI (0.88 g, 5.40 mmol, 1.20 equiv.); 3 h; Cbz-guanidine 224 (1.95 g, 4.93 mmol, 1.1 equiv.); DMF (5 mL); 3 d, rt. Extraction with CF (3 × 50 mL); washing with HCl (aq. 0.1 M, 50 mL), NaHCO₃ (aq. sat. 50 mL) and brine (2 × 50 mL); Recrystallized from DE (ca. 15 mL) at -20 °C (2 days) to form white needles which were washed with ice-cold DE and dried under vacuum to give 300 (1.34 g, 3.36 mmol) in 75% yield.

Rf 0.52 (DE); [α]D₂⁰ -17.5 (CHCl₃, c = 1.0); Mp 95-98 °C; δH (CDCl₃) 2 rotamers, 8.06-10.38 (3H, br s, 3 × NH), 7.27-7.40 (10H, m, 2 × Ph), 6.79-6.95/5.55 (1H, m and br d, J 6.3 Hz, NH), 5.13 (2H, s, CH₂), 5.12 (1H, d, J 12.3, CH), 5.07 (1H, d, J 12.3 Hz, CH), 4.24-4.40/4.02-4.16 (1H, 2 × m, CH), 1.37/1.23-1.30 (3H, d, J 6.8 Hz and m, Me); δC (CDCl₃) 159.0, 155.9, 136.2, 135.9, 128.6, 128.4, 128.3, 128.3, 67.5, 67.3, 52.3, 18.5 (2 × C not detected); νmax 3332, 3272, 3033, 2951, 1708, 1687, 1627, 1526, 1259 cm⁻¹; MS (ESI) m/z 399.17 (100, [M+H]⁺), HRMS (ESI) found 399.1664, C₂₀H₂₃N₄O₅⁺ ([M+H]⁺) requires 399.16630.

3.4.65 Preparation of tert-Butyl (S)-(1-(3-(tert-butyloxy carbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 302.

Method A: N-Boc-L-alanine 301 (1.01 g, 3.77 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (774.0 mg, 4.71 mmol, 1.25 equiv.); 90 min; Boc-guanidine 207 (672.0 mg, 4.15 mmol, 1.1 equiv.); DMF (15 mL); 2 d, rt. Extraction with CF (3 × 50 mL); washed with (3 × 50 mL), and brine (2 × 50 mL); column chromatography (30% DE in Hex) gave 302 (680.0 mg, 1.67 mmol) in 44% as a white solid which was contaminated with an impurity from the ethyl acetate.

Rf 0.20 (50% EA in PE); [α]D₂⁰ -21.0 (CH₃Cl, c = 1.0); Mp 64-66 °C; δH (CDCl₃; 2 rotamers), 8.60 (1H, br s, NH), 7.57-10-34 (2H, br s, 2 × NH), 6.99-7.24 (5H, m, Ph), 5.09 (1H, br s, NH), 4.42/4.14-4.27 (1H, dd, J 5.0, 5.5 Hz/br m, CH), 3.15/3.00/2.72-2.91 (2H, dd J 5.0,
13.6/dd, J 5.6, 13.6/br m, CH₂), 1.42 (9H, s, 3 × Me), 1.34 (9H, s, 3 × Me); δc (CDCl₃) 159.3, 155.1, 136.6, 129.5, 128.3, 126.7, 80.3, 79.4, 57.6, 38.5, 28.4, 28.0 (2 × C not detected); νmax 3378, 3005, 2977, 2933, 1709, 1641, 1542, 1493, 1240, 1146 cm⁻¹; MS (ESI) m/z 407.23 (100, [M+H⁺]); HRMS (ESI) found 407.2291, C₂₀H₃₁N₄O₅⁺ ([M+H⁺]), requires 407.2289.

3.4.66 Preparation of tert-butyl (S)-(1-(3-(benzyloxy carbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 303.

Method A: N-Boc-L-phenylalanine 301 (1.00 g, 3.77 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (672.0 mg, 4.75 mmol, 1.26 equiv.); 30 min; Cbz-guanidine 224 (801.0 mg, 4.15 mmol, 1.10 equiv.); DMF (15 mL); 3 d, rt, 2 d, 40 °C. Extraction with EA (3 × 50 mL); washed HCl (0.1 M, 50 mL), NaHCO₃ (aq. sat. 50 mL) and brine (2 × 50 mL); Recrystallized from ethanol (ca. 15 mL) at -20 °C (12 h) to form white needles which were washed with ice-cold DE and dried under vacuum to give 303 (1.20 g, 2.72 mmol) in 72% yield. Rf 0.21 (25% EA in PE); [α]D²⁵ -20.8 (CH₃Cl, c = 1.27); Mp 151-154 °C; δh (CDCl₃) 8.28-9.38 (3H, br s, 3 × NH), 7.20-7.41 (8H, m, 8 × CH), 7.13 (2H, d, J 7.1 Hz, 2 × CH), 5.14 (2H, s, CH₂), 4.90 (1H, br s, NH), 4.39-4.56 (1H, m, CH), 3.20 (1H, dd, J 14.2, 4.7 Hz, CH), 2.79-3.13 (1H, br s, CH), 1.38 (9H, s, 3 × Me); δc (CDCl₃) 158.7, 155.2, 136.0, 135.8, 129.2, 128.7, 128.5, 128.2, 127.1, 80.7, 67.3, 56.9, 37.8, 28.2 (1 × C not detected); νmax 3395, 3350, 3271, 3059, 3033, 2985, 2956, 1708, 1684, 1620, 1543, 1511, 1439, 1378, 1316, 1294, 1252, 1201 cm⁻¹; MS (ESI) m/z 441.2 (100, [M+H⁺]); HRMS (ESI) found 441.2134, C₂₃H₂₈N₄O₅⁺ ([M+H⁺]), requires 441.2132.

3.4.67 Preparation of Benzyl (S)-(1-(3-(tert-butyloxy carbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 305.

Method A: N-Boc-L-phenylalanine 304 (1.00 g, 3.34 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (600 mg, 3.74 mmol, 1.12 equiv.); 30 min; Boc-guanidine 207 (0.585 g, 4.14 mmol, 1.24 equiv.); DMF (15 mL); 3 d, rt. Extraction with EA; washed HCl (0.1 M, 50 mL), NaHCO₃
(aq. sat. 50 mL) and brine (2 x 50 mL); column chromatography (0-50% EA in PE) gave 305 (1.23 g, 2.79 mmol) in 84% yield as a white solid.

Rf 0.15 (25% EA in PE); [α]D21 -32.2 (CH3Cl, c = 1.54); Mp 123-125 °C; δH (CDCl3) 8.34-10.29 (2H, br s, 2 × NH), 8.65 (1H, br s, NH), 7.26-7.41 (5H, m, Ph), 7.06 (2H, d, J 6.6 Hz, CH), 5.08 (1H, d, J 12.7 Hz, CH), 5.01-5.13 (2H, m, 2 × CH), 4.28-4.59 (1H, br m, CH); δC (DEPT-135, CDCl3) 159.1, 155.7, 136.7, 129.6, 129.6, 129.4, 128.4, 128.2, 128.1, 126.8, 83.6, 66.7, 58.2, 38.0; vmax 3378, 3031, 2977, 1721, 1641, 1542, 1497, 1145, 1081 cm⁻¹; MS (ESI) m/z 441.2 (100%, [M+H]+); HRMS (ESI) found 441.2136, C23H29N4O5+ ([M+H]+), requires 441.2133.

3.4.68 Preparation of Benzyl (S)-(1-(3-(benzyloxy carbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 306.

Method A: N-Cbz-phenylalanine 304 (1.00 g, 3.34 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (701.0 mg, 4.98 mmol, 1.49 equiv.); 30 min; Cbz-guanidine 224 (701.0 mg, 3.67 mmol, 1.10 equiv.); DMF (15 mL); 3 d, rt; 2 d, 40 °C. Extraction with EA (3 x 50 mL); washed with HCl (0.1 M, 50 mL), NaHCO3 (aq. sat. 50 mL) and brine (2 x 50 mL); Column chromatography (0-50% EA in PE) and recrystallized from cold ethanol/petroleum ether to give 306 (300.0 mg, 0.632 mmol) in 19% as a white solid.

Rf 0.14 (25% EA in PE); [α]D25 -19.6° (CHCl3, c = 1.0); Mp 83-86 °C; δH (CDCl3) 7.71-7.99 (3H, br s, 3 × NH), 7.17-7.43 (13H, m, 13 × CH), 7.09 (2H, d, J 6.8 Hz, 2 × CH), 5.20-5.31 (1H, br s, NH), 5.16 (2H, s, CH2), 5.01-5.13 (2H, m, 2 × CH), 4.28-4.59 (1H, br m, CH), 2.85-3.35 (2H, m, CH2); δC (DEPT-135, CDCl3) 129.3, 128.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 127.1, 67.6, 67.1, 57.5, 38.0; vmax 3390, 3338, 3278, 3063, 3031, 2962, 1687, 1664, 1630, 1523, 1497, 1268, 1111, 1087; MS (ESI) m/z 475.2 ([100, M+H]+); HRMS (ESI) C26H27NaO5+ [M+H]+, requires 475.1976, found 475.1977.
3.4.69 Preparation of Dibenzyl ((2S,2'S)-((iminomethylene)bis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate 307.

Method B: \(N\)-Cbz-L-alanine 298 (930 mg, 4.16 mmol, 2.2 equiv.); DMF (5 mL); CDI (920.0 mg, 5.67 mmol, 3.0 equiv.); 2 h; guanidine hydrochloride 206 (180 mg, 1.92 mmol, 1.0 equiv.); DMF (5 mL); NaH (60%, 70.0 mg, 3.08 mmol, 0.96 equiv.), 24 h; 2 d. Extraction with CF and column chromatography (90-100% Et\(_2\)O in hexane) gave 307 (0.45 g, 0.95 mmol) in 51% yield as a white solid. 

\(R_f\) 0.37 (DE); \(\left[\alpha\right]_D^{27}\) -22.7 (CHCl\(_3\), c = 1.0); \(M_p\) 90-93°C; \(\delta\)\(_H\) (CDCl\(_3\)) 2 rotamers, 7.63-10.64 (1H, br s, NH), 7.22-7.46 (10H, m, 2 × Ph), 5.41-5.62 (2H, br s, 2 × NH), 5.14 (2H, d, J 12.3 Hz, 2 × CH), 5.10 (2H, d, J 12.3 Hz, 2 × CH), 4.11-4.41 (2H, m, 2 × CH), 1.82-5.78 (2H, br s, 2 × NH), 1.34/1.35 (6H, 2 × d, J 7.0 Hz, 2 × Me); \(\delta\)\(_C\) (CDCl\(_3\)) 158.6, 156.0, 136.2, 128.7, 128.4, 128.3, 67.3, 52.8, 18.7 (1 × C not detected); \(\nu\)\(_{max}\) 3338, 3031, 2977, 1693, 1643, 1605, 1508, 1213 cm\(^{-1}\); MS (ESI) \(m/z\) 470.20 (100, [M+H]+). HRMS (ESI) found 470.2040, \(C_{23}H_{29}N_5O_6^+\) ([M+H]+) requires 470.2034.

3.4.70 Preparation of Dibenzyl ((2S,2'S)-((iminomethylene)bis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate 308.

Method B: \(N\)-Cbz-L-phenylalanine 304 (1.24 g, 4.15 mmol, 2.2 equiv.); DMF (5 mL); CDI (918.0 mg, 5.65 mmol, 3.0 equiv); 0°C, 90 min; guanidine hydrochloride 206 (180.0 mg, 1.88 mmol, 1.0 equiv); DMF (5 mL); NaH (60%, 73.0 mg, 1.97 mmol, 0.95 equiv.), 24 min; 4 d. Extraction with CF and column chromatography (60% DE in Hex) gave 308 (1.20 g, 1.93 mmol) in 47% yield as a white solid. 

\(R_f\) 0.30 (75% DE in PE), \(\left[\alpha\right]_D^{28}\) -12.8 (CHCl\(_3\), c = 1.0); \(M_p\) 150-152°C; \(\delta\)\(_H\) (CDCl\(_3\)) 2 rotamers, 8.30-10.68 (3H, br s, 3 × NH), 7.16-7.39 (16H, m, 16 × CH), 7.04-7.14 (4H, m, 4 ×
3.4.71 Preparation of Di-tert-butyl ((2S,2'S)-
((iminomethylene)bis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate 309.

\[
\text{BocHN} \quad \text{OH} \quad \text{Me} \quad \text{a} \quad \text{BocHN} \quad \text{Me} \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{NH} \quad \text{Boc} \quad \text{Chemical Formula: C}_{17}H_{32}N_{5}O_{6} \quad \text{Exact Mass: 401.2274} \quad \text{Molecular Weight: 401.4640}
\]

**Method B:** N-Boc-L-alanine 295 (1.78 g, 9.21 mmol, 2.2 equiv); DMF (5 mL); CDI (2.04 g, 12.65 mmol, 3.0 equiv); 0 °C, 90 min; guanidine hydrochloride 206 (405.0 mg, 4.19 mmol, 1.0 equiv); DMF (5 mL); NaH (60%, 160.0 mg, 0.95 equiv.), 24 h; 5 d. Extraction with EA and column chromatography (60% DE in Hex) gave 309 (2.05 g, 5.11 mmol) in 54% yield as a white solid.

Rf 0.30 (75% DE/PE); [α]D\text{2} 1 -30.0 (CF, c = 1.0); Mp 76-78 °C; δH 2 rotamers 8.42-10.88 (3H, br s, 3 × NH), 5.30-5.70 (2H, br m, 2 × NH), 3.94-4.36 (2H, m, 2 × CH), 1.42 (9H, s, 3 × Me), 1.42 (9H, s, 3 × Me), 1.37 (6H, d, J 6.8 Hz, 2 × Me); δC (CDCl\text{3}) 158.8, 155.6, 80.2, 52.3, 28.4, 18.7 (1 × C not detected); \ν\text{max} 3245, 3219, 3001, 2977, 2932, 1690, 1644, 1603, 1509, 1247 cm\textsuperscript{-1}; MS (ESI) m/z 402.23 (100, [M+H]+); HRMS (ESI) found 402.2348, C\textsubscript{17}H\textsubscript{32}N\textsubscript{5}O\textsubscript{6}+ ([M+H]+) requires 402.2347.

3.4.72 Preparation of Di-tert-butyl ((2S,2'S)-
((iminomethylene)bis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate 310.

\[
\text{BocHN} \quad \text{OH} \quad \text{Bn} \quad \text{OH} \quad \text{Bn} \quad \text{a} \quad \text{BocHN} \quad \text{Bn} \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{NH} \quad \text{Boc} \quad \text{Chemical Formula: C}_{25}H_{39}N_{5}O_{6} \quad \text{Exact Mass: 553.2900} \quad \text{Molecular Weight: 553.6600}
\]

**Method B:** Boc-L-phenylalanine 301 (1.00 g, 4.15 mmol, 2.2 equiv); DMF (5 mL); CDI (918.0 mg, 5.66 mmol, 3.0 equiv); 2 h; guanidine hydrochloride 206 (0.19 g, 1.94 mmol,
1.0 equiv); DMF (5 mL); NaH (60%, 71.0 mg, 2.96 mmol, 0.96 equiv.); 2 d. Extraction CF and column chromatography (60-75% Et₂O in hexane) gave 310 (0.78 g, 1.40 mmol) in 74% yield as a white solid.

**Rf** 0.39 (70% DE/Hex); [α]D^27 -21.4 (CHCl₃, c = 1.0); **Mp** 83-86 °C; δH 2 rotamers, 8.22-11.13 (3H, br s, 3 × NH), 7.21-7.38 (6H, m, 6 × CH), 7.13-7.21 (4H, m, 4 × CH), 5.05-5.70 (2H, m, 2 × NH), 4.18-4.24 (2H, m, 2 × CH), 2.97-3.31 (4H, m, 2 × CH₂), 1.42 (18H, s, 6 × Me); δC 158.3, 155.6, 136.5, 129.5, 128.7, 127.0, 80.3, 57.5, 28.4, (1 × C not detected); νmax 3368, 3008, 2977, 2932, 1689, 1645, 1604, 1496 cm⁻¹; **MS (ESI)** m/z 554.30 (100, [M+H]+), **HRMS (ESI)** found 554.2982, C_{29}H_{40}N_{5}O_{6}+ ([M+H]+) requires 554.2973.

### 3.4.73 Preparation of Preparation of (R)-1-(1-phenylethyl)guanidine 312

Concentrated HCl (2.1 mL) was added dropwise over a period of 10 min to a cooled (15–20 °C) solution of (R)-(+) 1-phenylethylamine 311 (2.4 g, 19.8 mmol) in dioxane (3 mL) and the mixture stirred for 15 min. The solvent was evaporated under reduced pressure and the white crystalline residue was triturated with DE (3 × 10 mL) to give a hydrochloride salt (3.1 g, 99%) as white crystals. This salt was dissolved in water (12 mL) and then cyanamide (NH₂CN, 0.82 g, 19.5 mmol) was added and the solution was adjusted to pH 8–9 by the addition of (R)-(+) 1-phenylethylamine (a few drops). This mixture was heated under reflux and after 24 the reaction was cooled, evaporated under reduced pressure and the resultant sticky mass was triturated with Et₂O (3 × 20 mL) to give a white solid. This was dissolved in a minimum volume of distilled water and was passed through a Dowex 500 ion exchange column (120 g, hydroxide ion form, eluted with water). The eluant was evaporated and freeze-dried to give 312 (1.23 g, 6.61 mmol, 38%) as a colourless oil. Data was in agreement with the literature.¹¹⁶

[α]^[2]D +28.9 (c 1.0, EtOH); (Lit.¹¹⁶ [α]^[2]D +28.9 (c = 1.00, EtOH); δH ((CD₃)₂SO) 7.36 (2H, d, J 7.3 Hz, 2 × CH), 7.29 (2H, t, J 7.3 Hz, 2 × CH), 7.18 (1H, t, J 7.3 Hz, CH), 3.97 (1H, q, J 6.7 Hz, CH), 1.24 (3H, d, J 6.7 Hz, CH₃); δC ((CD₃)₂SO) 148.8, 128.0, 126.1, 125.8, 50.7, 26.3; νmax 3320, 3135, 2977, 2929, 1625, 1551, 1214, 755, 700 cm⁻¹.
3.4.74 Attempted preparation of \((R)-N-(\text{amino}((1\text{-}\text{phenylethyl})\text{amino})\text{methylene})-2-(\text{dimethylamino})\text{acetamide}\) 314.

\[
\begin{align*}
\text{Me}^+\text{N} &\text{COOH} \\
\longrightarrow \\
\text{Me}^+\text{N} &\text{COONH}_2\text{NH}_2\text{Me} \quad \text{Chemical Formula: } \text{C}_{13}\text{H}_{20}\text{N}_4\text{O} \\
\text{Exact Mass: } 248.16 \\
\text{Molecular Weight: } 248.33
\end{align*}
\]

**Method A:** \(N-N\)-dimethylglycine 313 (348.0 mg, 3.37 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (1.09 g, 6.74 mmol, 2.0 equiv.); 24 h; Et\(_3\)N (341.0 mg, 3.37 mmol, 1.0 equiv.); 10 min, rt. Then \((R)-1-(\text{1-phenylethyl})\text{guanidine}\) 312, 24 h at rt follow with stir for 18 h at (45-50) °C. Extraction with EA; washed with water (150 mL \(\times\) 3) and brine (50 mL \(\times\) 2); column chromatography (33-42% EA in PE) gave 314 (1.20 g, 3.26 mmol) in 79% yield as a yellow waxy solid. However, the desired product was made but the purity was 100% because it was difficult to purify form glycine even many trial was done by change the equivalent organic base.

3.4.75 Attempted Preparation of 2-(dibenzylamino)-N-vinylacetamide 317.

\[
\begin{align*}
\text{Bn} &\text{N} \text{COOH} \\
\longrightarrow \\
\text{Bn} &\text{N} \text{COON Nh} \text{L} \quad \text{Chemical Formula: } \text{C}_{18}\text{H}_{20}\text{N}_2\text{O} \\
\text{Exact Mass: } 280.16 \\
\text{Molecular Weight: } 280.37
\end{align*}
\]

**Method A:** \(N-N\)-dibenzylglycine 197 (1.00 g, 3.92 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (953.0 mg, 5.88 mmol, 1.5 equiv.); 24 h; Et\(_3\)N (341.0 mg, 3.37 mmol, 1.0 equiv.); 1 h, (60-80) °C. Then allyl amine (0.32 mL, 246.0 mg, 4.341 mmol, 1.10 equiv.), 72 h at rt follow with stir for 6 h at (45-55) °C. Extraction with DCM; washed with water (150 mL \(\times\) 3) and brine (50 mL \(\times\) 2); gave (85.0 mg) as a yellow wax, which was mainly the amine with impurities.

3.4.76 Preparation of Phenylguanidinium nitrate 203.

\[
\begin{align*}
\text{H} &\text{N} \text{NH}_2^+ \text{NO}_3^- \\
\quad \text{Chemical Formula: } \text{C}_{7}\text{H}_{10}\text{N}_4\text{O}_3 \\
\text{Exact Mass: } 198.08 \\
\text{Molecular Weight: } 198.18
\end{align*}
\]

Aniline (9.3 g, 9.12 mL, 99.9 mmol, 1.0 equiv.) was dissolved in EtOH (75 mL) and an aqueous solution of HNO\(_3\) (9.0 mL, 131.2 mmol, of a 65% w/w solution prepared from 90% w/w nitric acid by slow addition to water; **CAUTION!**) was then cautiously added. An aqueous solution of cyanamide (50% w/v, 12.6 g, 11.5 mL, 148.0 mmol, 1.48 equiv.) was then added and the mixture heated at reflux for 16 h. The mixture was cooled (ice), DE (800 mL) was
added and the mixture stirred vigorously for 1 h. The grey precipitate formed was removed by filtration washed with DE (excess) and dried under vacuum to give 203 (11.7 g, 85.9 mmol) as a grey solid in 86% yield.\textsuperscript{106} Data was in agreement with the literature.

RF 0.28 (10\% MeOH/EA); Mp 112-115 °C (lit.\textsuperscript{106} Mp 120-122 °C); $\delta_{\text{H}} ((\text{CD}_3)_2\text{SO})$ 9.62 (1H, s, NH) 7.45 (2H, br t, $J$ 7.8 Hz, 2 × CH), 7.33-7.40 (4H, br s, 2 × NH$_2$), 7.29 (1H, br t, $J$ 7.8 Hz, CH), 7.24 (2H, br d, $J$ 7.8 Hz, 2 × CH); $\delta_{\text{C}} ((\text{CD}_3)_2\text{SO})$ 155.7, 135.3, 129.7, 126.5, 124.5; $\nu_{\text{max}}$ 3332, 3189, 3055, 1614, 1598, 1584, 1312 cm$^{-1}$; MS (ESI) m/z 136.1 [M+H$^+$], HRMS (ESI) found 136.0867, C$_7$H$_{10}$N$_3^+$ ([M+H]$^+$) requires 136.0869.

3.4.77 Reaction $\beta$-nitrostyrene 77 with 2-hydroxy-1,4-napthoquinone 168

![Chemical Structure](image)

2-Hydroxy-1,4-napthoquinone 168 (100 mg, 0.574 mmol) and the required catalyst (0.04-0.1 equiv.) were dissolved in the requisite solvent and cooled to the required temperature (-20 to 0 °C). $\beta$-Nitrostyrene 77 (128.5 mg, 0.861 mmol, 1.5 equiv) was then added and the mixture stirred for the required time and temperature. Reaction progress was determined by sampling and determination by $^1$H NMR. On completion the solvent was evaporated to give a deep red residue which was purified by aqueous extraction with DCM then column chromatography eluting firstly with 2-4\% EA in petrol to remove excess 77 then followed with DCM to give the product 170 as a yellow solid. Illustrative example from catalyst 176a; 56% ee, $[\alpha]_b^{25}$ -16.0 (acetone, c = 1.46); Lit. $[\alpha]_b^{17}$ -44.8 (acetone, c = 1.0);\textsuperscript{123} Lit. $[\alpha]_b^{25}$ -34.0 (acetone, c = 1.46).\textsuperscript{124} Enantiomeric excesses were determined either on Chiralcel AS-H (250 × 4.6 mm, mobile phase 96\% hexane, 4\% isopropanol, 0.1\% TFA, 1.5 mL/min at 40 °C, detecting at 254 nm; R enantiomer 23.5 min, S enantiomer 26.2 min); or Phenomenex Lux Amylose-1 (250 × 4.6 mm, mobile phase 70\% hexane, 30\% isopropanol, 0.5 mL/min at 40 °C, detecting at 254 nm; R enantiomer 13.2 min, S enantiomer 14.3 min).
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