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Amino Acid Substituted Guanidines as Organocatalysts

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Amino Acid Substituted Guanidines as Organocatalysts

PhD in Organic Chemistry

In the

School of Natural Sciences

By

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Contents

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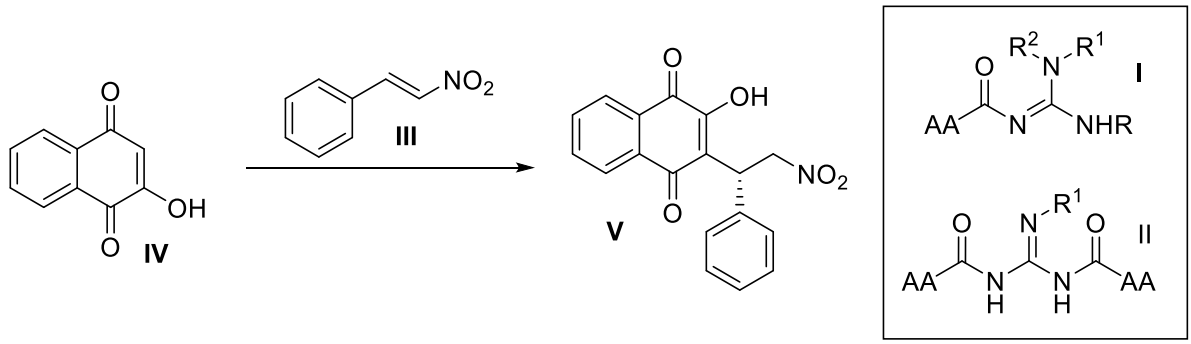
Presentations and awards

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.
4. The 32rd Annual Review Meeting: Hot Topic in Organic Synthesis at SCI, London, UK on 1st December 2016, presentation of a 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, R^1, R^2 = 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 temprature
T	Temperature (degree centigrade)
TLC	Thin layer chromatography
TM	target molecule
Cons.	Conditions

Reagents

BA	Benzoin acid
CbzCl	Benzyl chloroformate
CDI	Carbonyldiimidazole
$SOCl_2$	Thionyl chloride
CAN	Ceric ammonium nitrate

(-)-CSA	Camphorsulfonic acid
$(CH_2O)_n$	Paraformaldehyde
EDCI	3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine
Et_3N	triethylamine
DEPC	diethylphosphorocyanidate
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DIAD	diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
HOBT	Hydroxybenzotriazole
HBTU	(2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
NHS	*N*-Hydroxysuccinimide
^{i}PrNEt	*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	$^{t-}$Butyloxycarbonyl
Cbz	Carbobenzyloxy
Cy	Cyclohexyl
Et	Ethyl
*i*Pr	i-Propyl
Me	Methyl
Ph	Phenyl
PBB	*p*-bromobenzyl
PMP	paramethoxphenyl
TBS	tert-Butyldimethylsilyl ethers

Solvents

^{t}BuOH	^{t}Butyl alcohol
CF	Chloroform
DCM	Dichloromethane
DE	Diethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EA	Ethyl acetate
EtOH	Ethanol
Hex	hexane
IPA	Isopropyl alcohol
ME	Methanol
PE	Petroleum ether
PhH	Benzene
PhMe	Toluene
THF	Tetrahydrofuran

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.[1] 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.[2] 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". [3] 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***[1]

> "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*** [4]

> "Organocatalysis is catalytic reactions mediated by small organic molecule in absence of metals or metal ions." ***Carlos F. Barbas, III***[5]

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*© 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**)

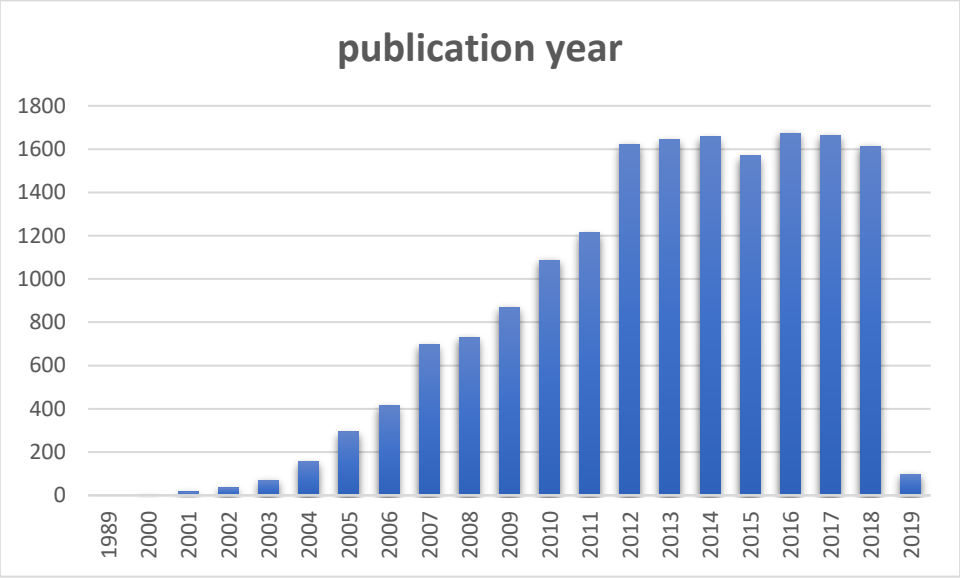


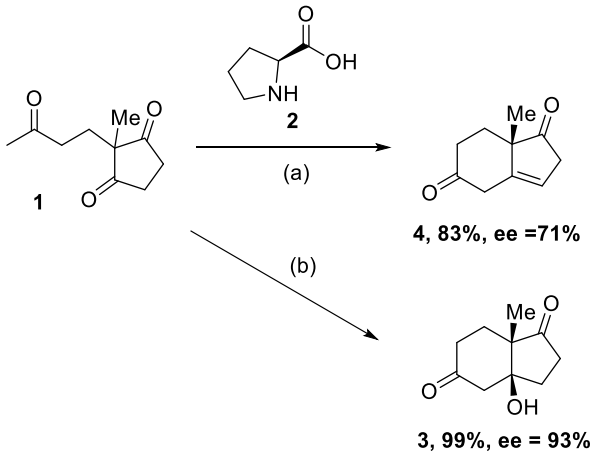
Figure 1: Annual publications containing the keyword "Organocatalysis"

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[10] 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**.[11] 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_3CN, 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) [12a] involving iminium ion (**5** and **7**), and enamine (**6**) intermediates. This mechanism is essentially identical to the accepted mechanism of class I aldolases.[12a] 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".

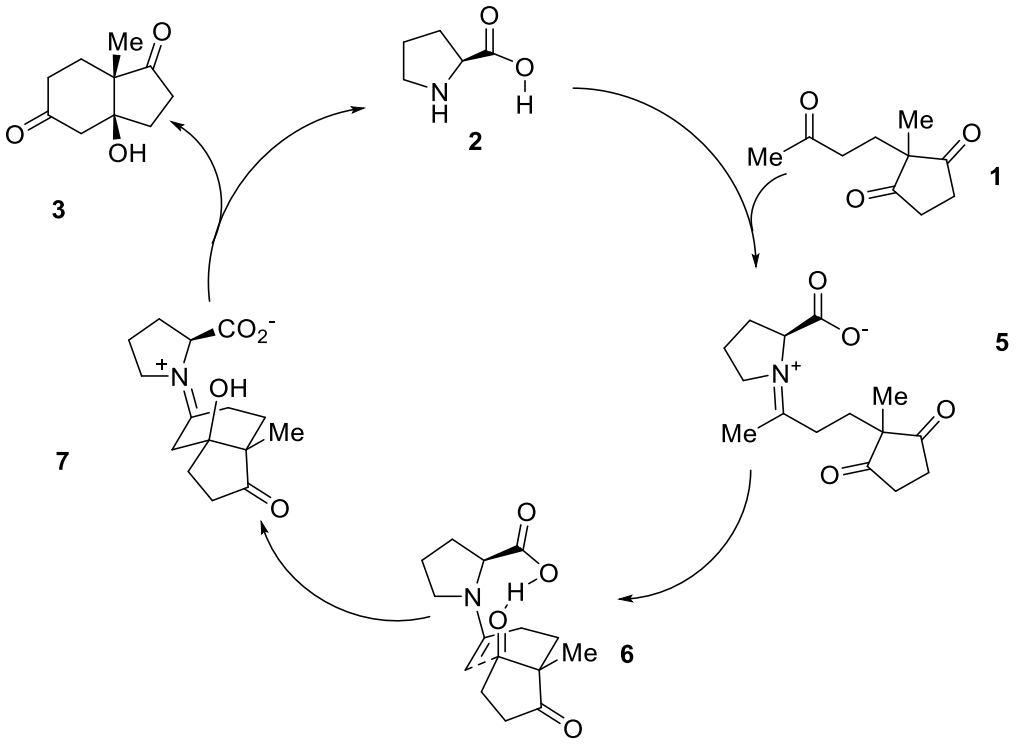
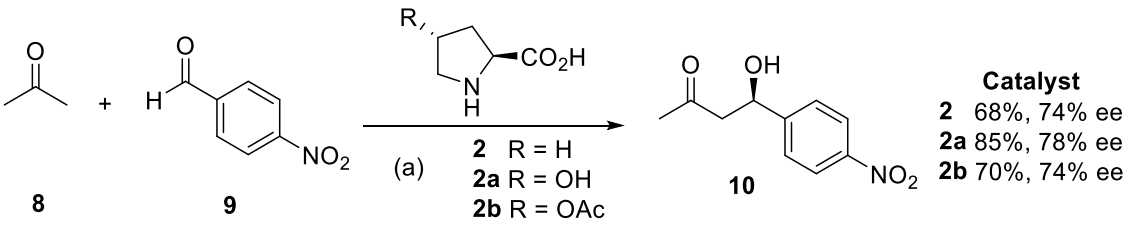


Figure 2: Proposed mechanistic cycle of the L-proline catalysed intermolecular aldol reaction.

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 authors[12b] 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.

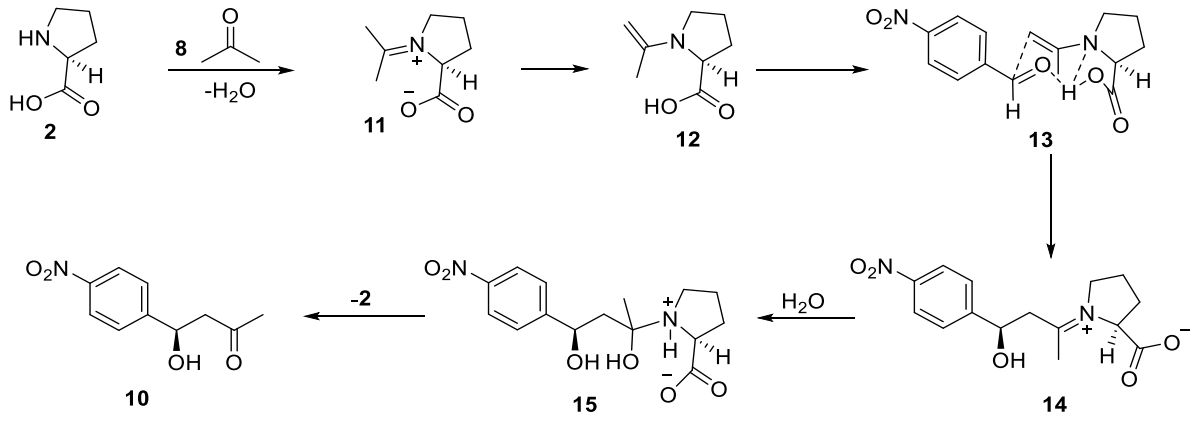


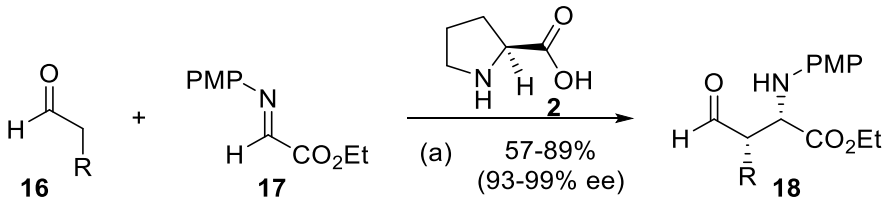
Figure 3: Proposed enamine mechanism of the proline-catalysed asymmetric aldol reaction.

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

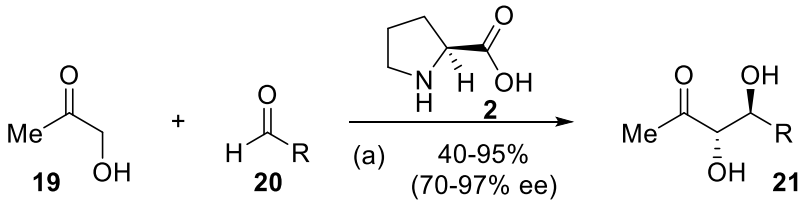
reaction partner through either hydrogen bonding or via an electrostatic interaction attraction. This mode of activation has been used in a wide range of enantioselective processes.[14]

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.[15, 16] A one-pot imine formation/Mannich reaction is also possible, although, in some cases, the enantiomeric excess is moderate.[17] Notz *et al.* 2004, and Cordova 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 = Me < Et < *i*-Pr < *n*-Pent. In five of the cases studied, excellent *syn*-stereoselectivities were achieved.[15, 16]



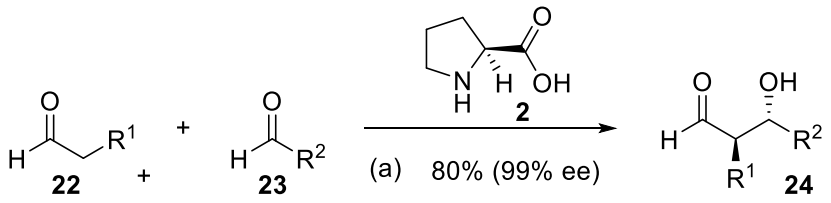
Scheme 3: (a) Catalyst **2** (0.05 equiv.) dioxane, 2-24 h, rt, R = Me, Et, *i*Pr, *n*-pentyl.

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[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)



Scheme 4: (a) Catalyst **2** (0.2-0.3 equiv.) DMSO, rt, 24-72 h; R = Cy, 3,3-dimethyl butyl, 2-chlorobenzyl, α-oxygenated *D*-isopropylidene-glyceryl.

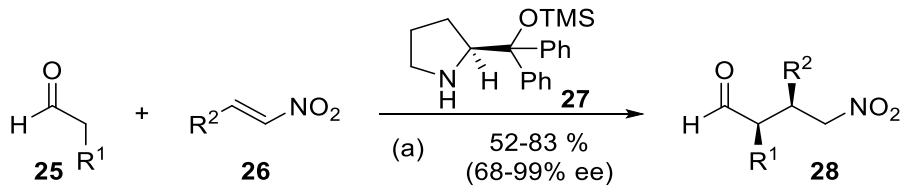
MacMillan and co-workers, who describe a crossed aldehyde aldol coupling, have reported an impressive development of this process. (Scheme 5)[19] A requirement of this reaction is that a given aldehyde can be defined clearly as donor and acceptor. This means that only one aldehyde should be able to form 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.[20]



Scheme 5: (a) Catalyst **2** (0.1-0.2 equiv.), DMF, 4 °C, 11 h, R^1 = Me, *n*-Bu, Bn, R^2 = Et, *i*-Bu, C_6H_{11}, Ph, $_i$-Pr.

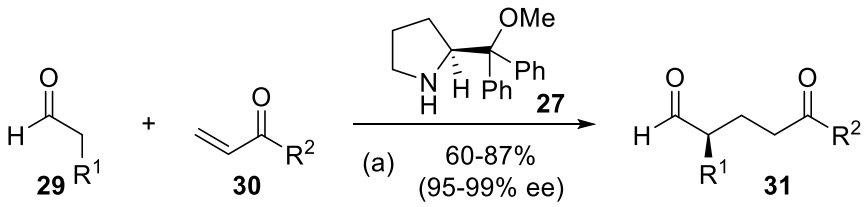
1.2.2 Michael reactions

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,[21] this research accelerated the search for proline alternatives.[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)[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.



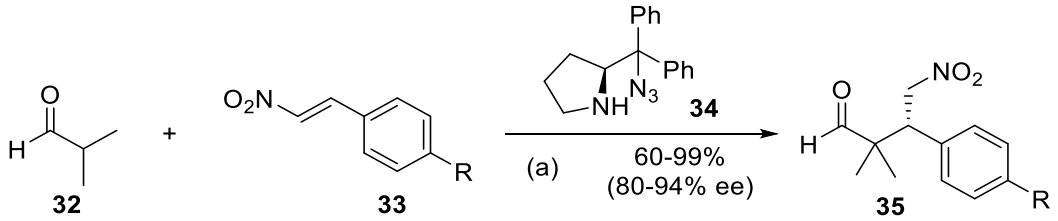
Scheme 6: (a) Catalyst **27** (0.1-0.2 equiv.), MeCN, (0-23) °C, 1-96 h; R^1 = Me, ^{i}Pr, n-Pr, R^2 = Ph, Ar, Het, Cy.

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]



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]



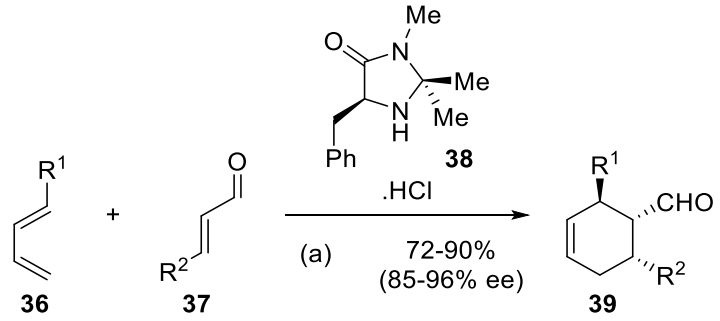
Scheme 8: (a) Catalyst **34** (0.2 equiv.), 10 °C -rt, 3-12 d, IPA-H_2O (3:1);
R = H, CH_3, CH_3O, Br, Cl, F, NO_2

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 research[12]

and MacMillan's iminium ion catalysis[29] 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.[29] They were first evaluated using substituted dienes **36** with enals **37** and the chiral secondary amine HCl salt **38** as the catalyst. This LUMO-lowering strategy was successful using only catalytic quantities of **38** providing the Diels-Alder adduct **39** in excellent yield and stereo-selectivity. (Scheme 9)



Scheme 9: (a) Catalyst **38** (0.2 equiv.), MeOH-H_2O, 23 °C, 14-42 h;
R_1 = Me, H; R_2 = Me, Ph, OAc.

The mechanism of this reaction involves the formation of the intermediate iminium species **40** (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.

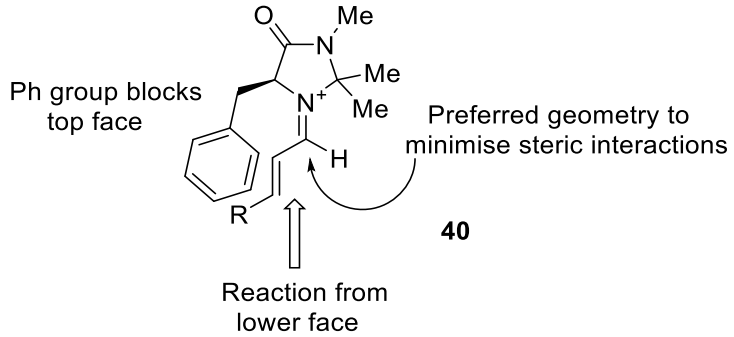
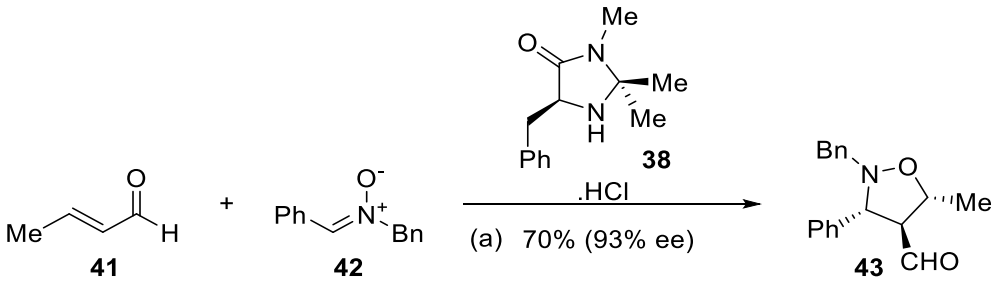


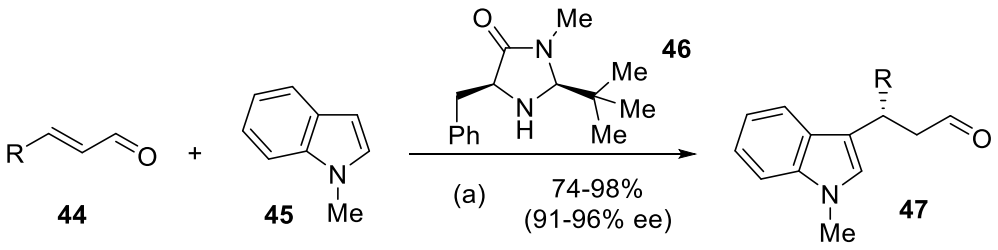
Figure 4: Stereocontrol elements in the iminium ion

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.[30] Moreover, this study further documents that chiral amines can be employed as asymmetric catalysts for a range of transformations that traditionally utilise metal salts.[31]



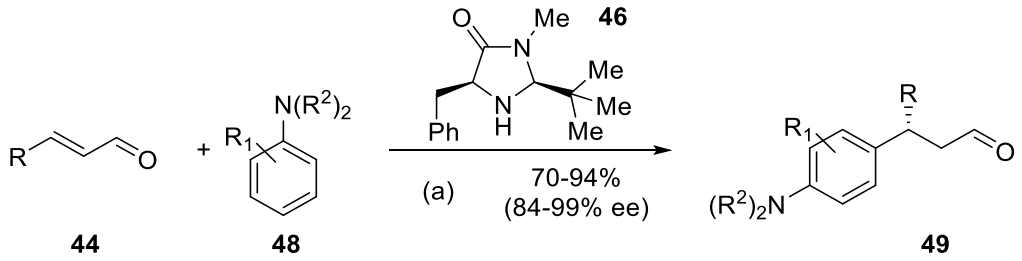
Scheme 10: (a) Catalyst **38** (0.2 equiv.), $MeNO_2$-H_2O (1:10), 40 °C, 72 h.

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).[32,33]



Scheme 11: (a) Catalyst **46** (0.2 equiv.), CH_2Cl_2-IPA, - 83 to - 55 °C, 6-45 h,
R = Me, Pr, *i*Pr, CH_2OBz, Ph, CO_2Me.

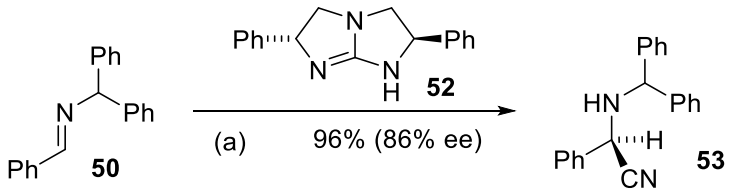
A similar reaction was reported for the reaction of anilines **48** to give **49** which can be modified to synthetically useful compounds. (Scheme 12)[32,33]



Scheme 12: (a) Catalyst **46** (0.1 equiv.) CH_3Cl, - 20 °C-rt, 0.1-80 h; R = Me, CH_2OBz, CO_2Me, 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.

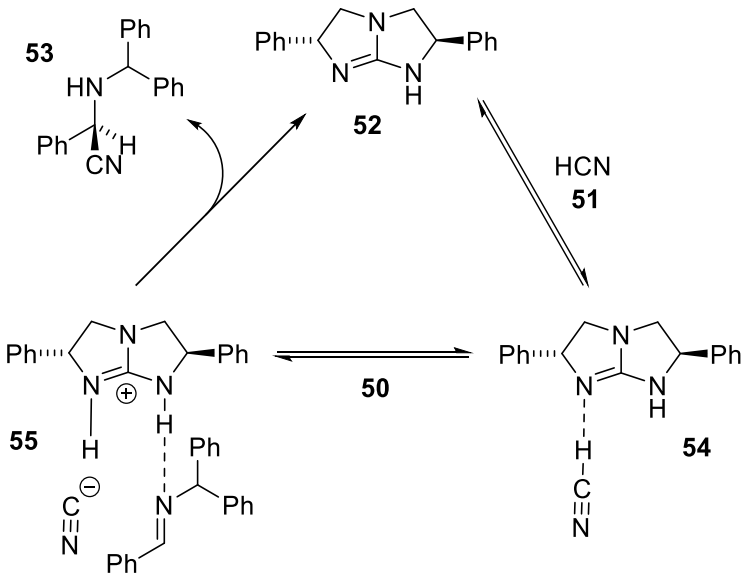
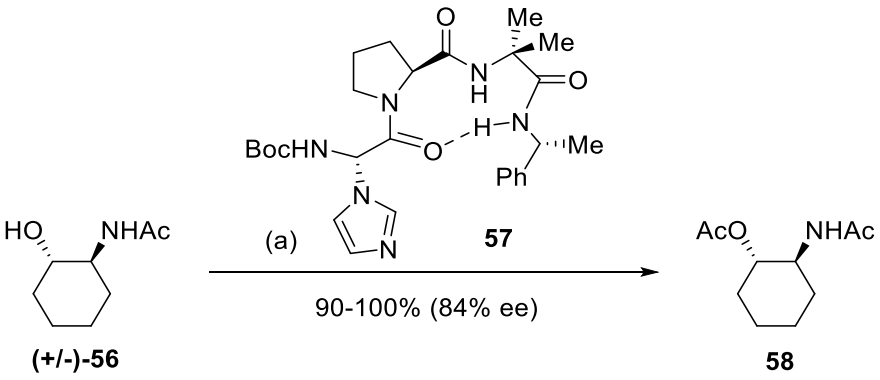


Figure 5: Mechanism proposed for the Strecker reaction

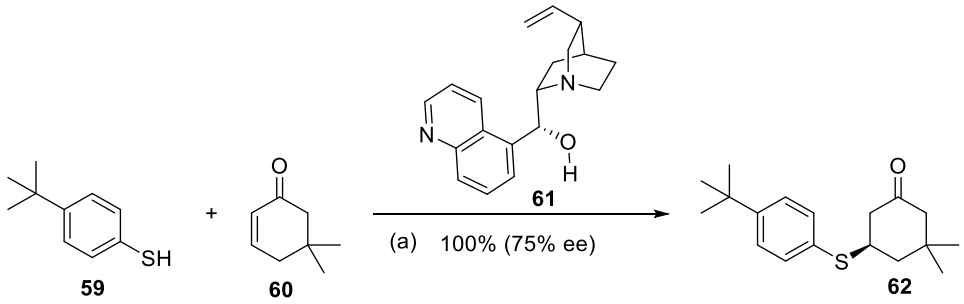
Along similar lines, Miller *et al*. reported the design and synthesis of new functional peptides **57** that catalyse the kinetic resolution of secondary alcohols.[39] The design of the catalyst mimics structural features found in enzymes and the *N*-alkyl-imidazole fragment of the catalyst was found 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 α-*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**.

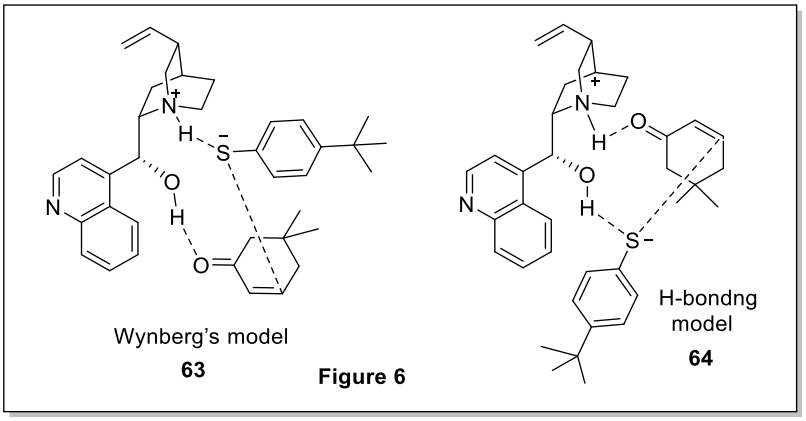


Scheme 14: (a) Catalyst **57** (0.05 equiv.), **56** (10 equiv.), Ac_2O (1.0 Equiv.), toluene, 0 °C.

Several early examples of hydrogen bonding catalysis were reported, for example in 1981, Wynberg reported[34] the Michael-addition of aromatic thiols, such as **59** to conjugated

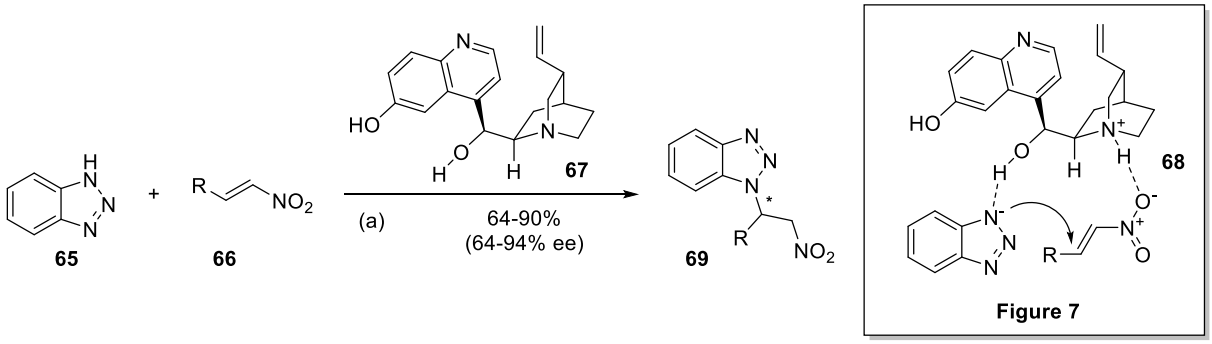
cycloalkenone **60**, was catalyses by alkaloids such as cinchonidine **61** to give **62** in quantitative yield and 75% ee. (Scheme 15) Wynberg proposed that the reaction proceeded via the formation of a thiolate-alkyl ammonium tight ion pair **63** and activation of the enone electrophile occurs by 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]





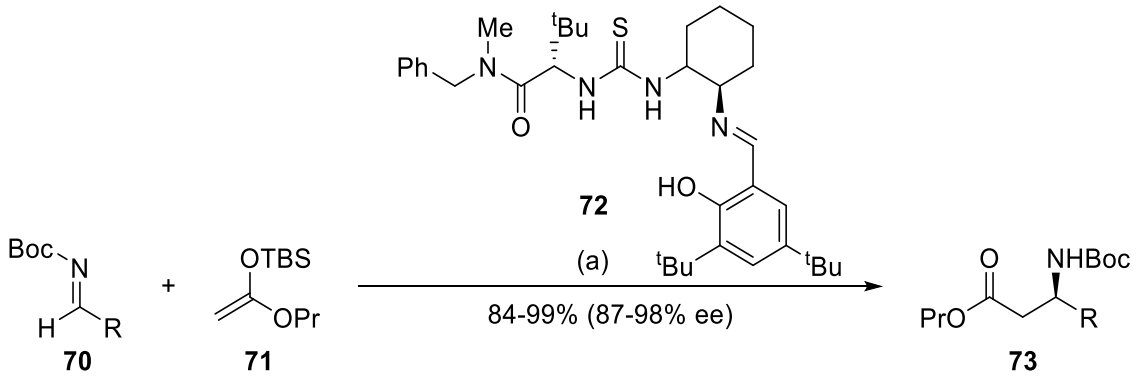
Scheme 15: (a) Catalyst **61** (0.01 equiv.), PhH, rt.

Similarly Wang *et al*. reported the Michael-addition of benzotriazole **65** to a variety of nitroolefins **66** catalyses 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)



Scheme 16: (a) Catalyst **67** (0.1 equiv.), - 25 °C, DCM, 24-96 h;
R = Ph, Aryl, 2-naphthyl, 2-thienyl, alkyl.

Possibly the most significant discovery in this area was made by Jacobsen in 2002.[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.



Scheme 17: (a) Catalyst **72** (0.05 equiv.), toluene, - 40-4 °C, 48 h;
R = aryl, 1-naphthyl, 2-naphthyl, 2-furyl, 2-thienyl, 3-quinolinyl, 3-pyridyl.

Ureas and thioureas are small organic molecules capable of reliable catalysis of a variety of reactions through dual hydrogen bonding interactions.[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.[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.[47,48,49] Subsequently Wilcox and Curran reported significant substituent effects in the hydrogen bonding abilities of aryl urea **75**[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.[52,53]

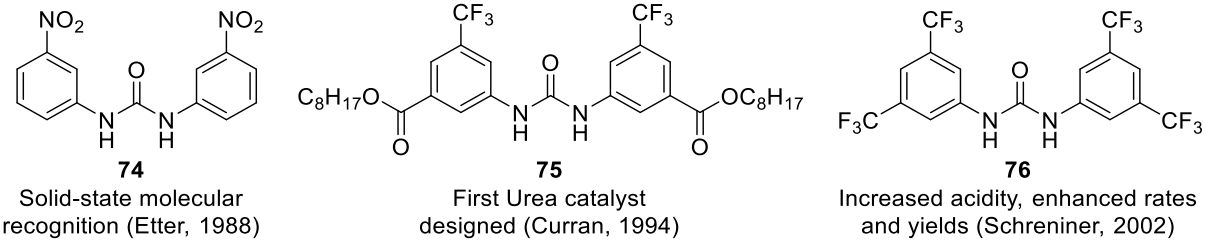
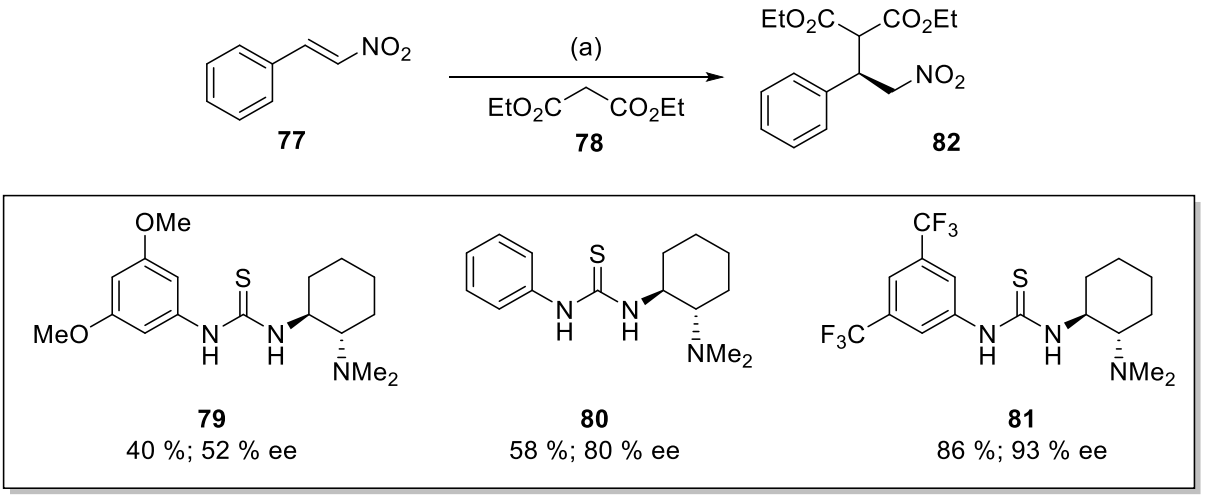


Figure 8: Evolution of the 3,5-bis(trifluoromethyl)phenyl functionality in urea catalysts.

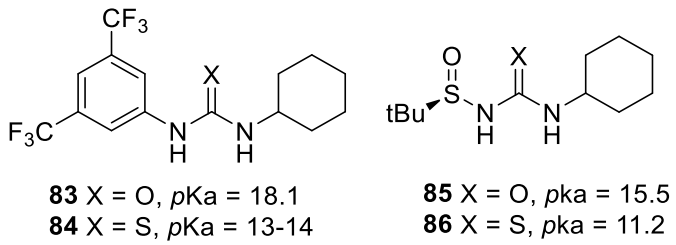
Takemoto and co-workers reported that the 3,5-bis(trifluoromethyl) phenyl group improved yield and stereoselectivity in the series of thiourea catalysts **79-81**, when applied to the enantioselective addition of diethyl malonate **78** to *trans-β*-nitrostyrene **77**.[54,55] They reported that the 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.

Ellman and co-workers reported the synthesis of a class of ureas and thioureas containing chiral *N*-sulfinyl substituents as auxiliaries.[56] They prepared a range of organocatalysts in which the electron-withdrawing nature of the *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 p*K*a 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)

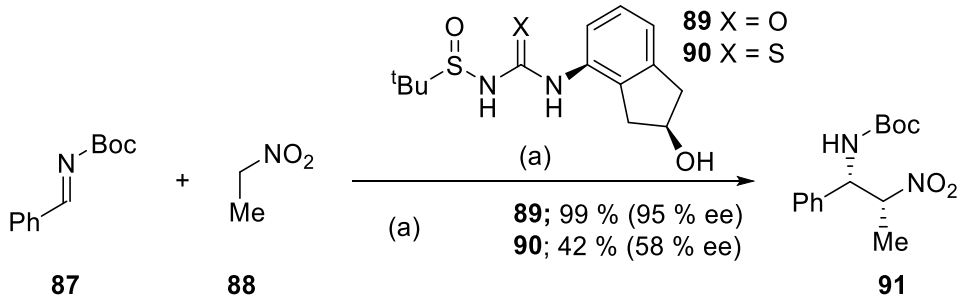


83 X = O, *p*Ka = 18.1
84 X = S, *p*Ka = 13-14

85 X = O, *p*ka = 15.5
86 X = S, *p*ka = 11.2

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

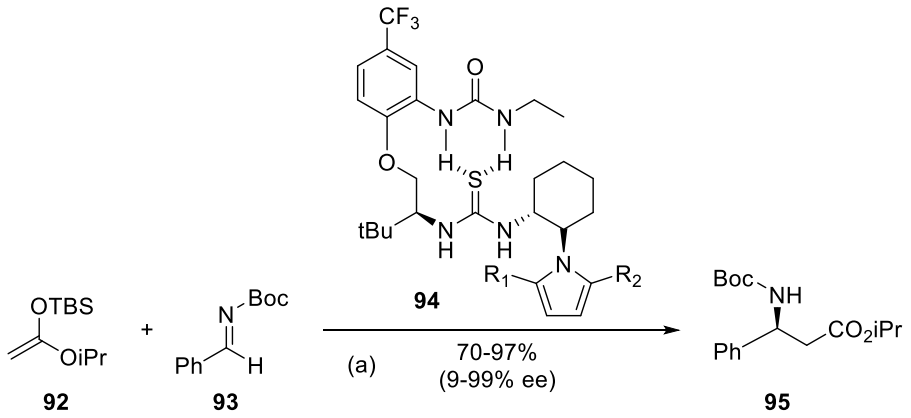
They reported that the *N*-sulfinylurea catalysts **89** and **90** were used in the stereoselective aza-Henry reaction between the aromatic *N*-Boc imine **87** and nitroethane **88** to give **91**. It was reported, that the urea **89** was the best catalyst leading to **91** in 95% ee with a 95% conversion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



87 **88** **91**

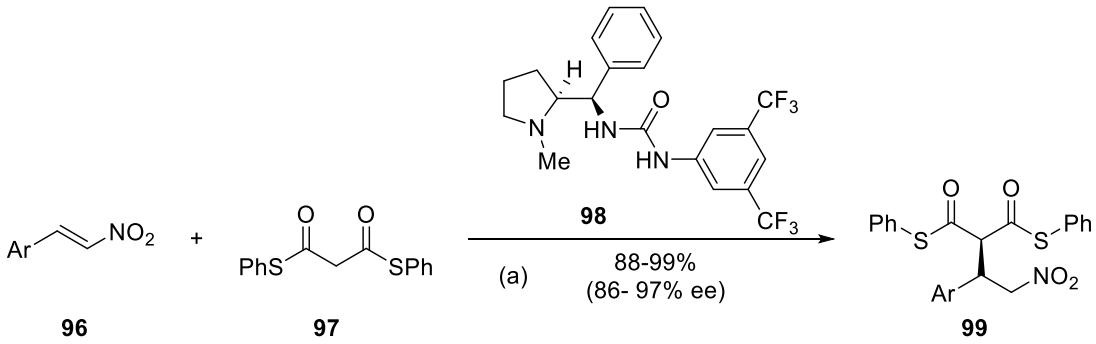
Scheme **19:** (a) Catalyst **89** or **90** (0.1 equiv.), ^{i}PrNEt (0.5 equiv.), MeCN, - 40 °C, 32 h.

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-*trans*-diaminopyrrolyl substituent was most the effective substituent.[57] (Scheme 20).



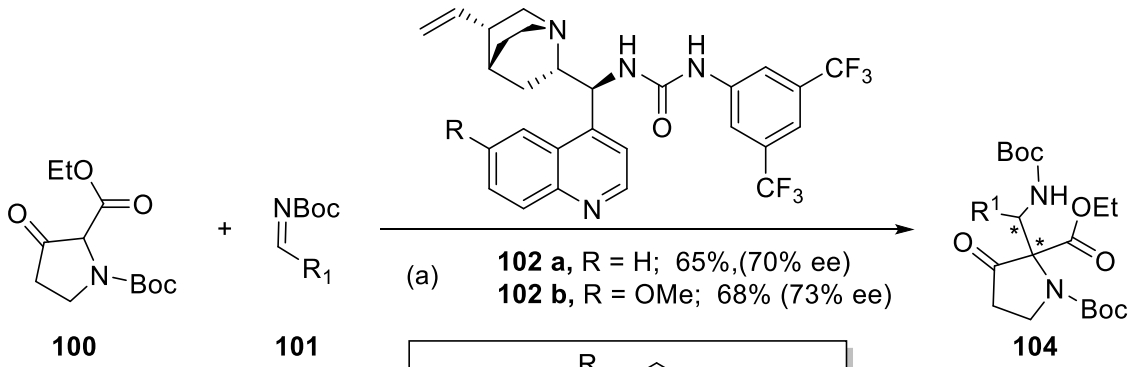
Scheme **20:** (a) Catalyst **94** (0.1 equiv.), Toluene, - 40 °C, 15-96 h;
R^1 = Alkyl, R^2 = Ph, aryl, 2-naphthyl, 2-furyl.

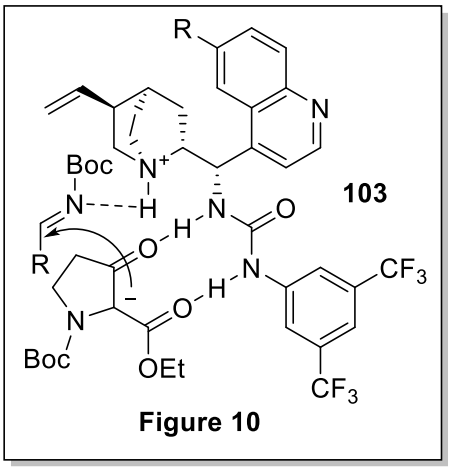
In a more recent example, Jin *et al*. reported the use of L-proline-urea bifunctional organocatalysts, which were applied to the Michael addition of dithiomalonates **97** to trans-*β*-nitroolefins **96**. Using catalyst **98**, the reaction gave high yields of **99** (88-99%) with high ee's (86-97% ee) over 12 examples. (Scheme 21).[58]



Scheme 21: (a) Catalyst **98** (0.05 equiv.), 0.5-2 h, PhMe, 25 °C. Ar = Ph, Aryl, 2-thienyl, 2-furyl, 2-naphthyl, 4-F-C_6H_4, 2-F-C_6H_4, 4-Br-C_6H_4, 2-Br-C_6H_4, 4-CF_3-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 2-MeO-C_6H_4.

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 *β*-ketoester as well as forming a hydrogen-bonded intermediate with both reactants.[59]

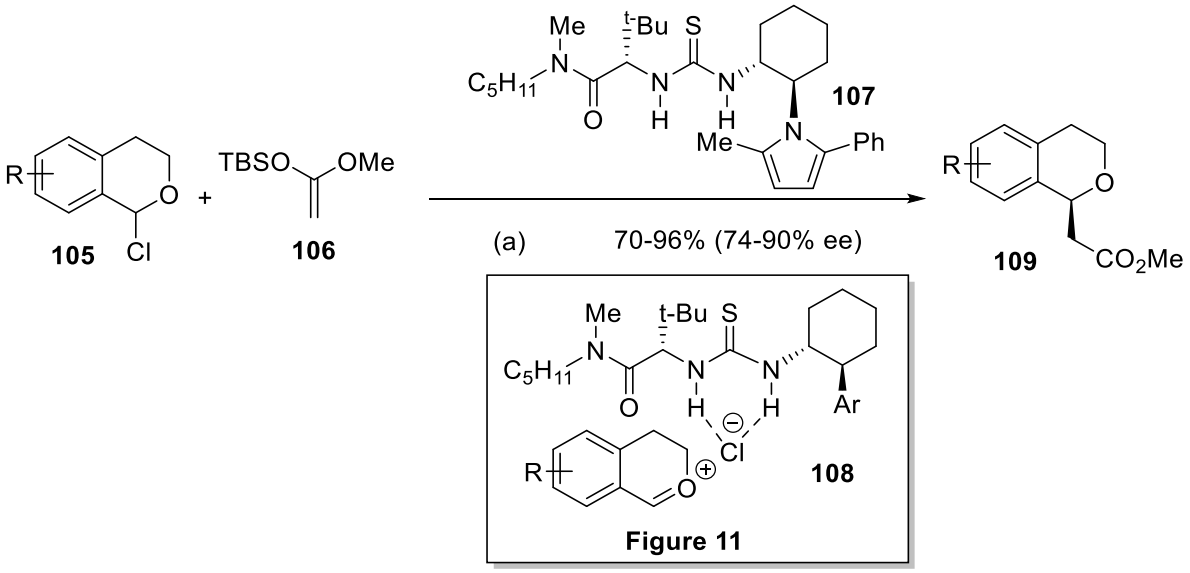




Scheme **22:** (a) catalyst **102a,b** (0.2 equiv.), DCM/THF/ACN/Toluene, 20 °C, 36 h;
R_1 = Ph, 4-NO_2-C_6H_4, 4-CF_3-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 2-furyl, 2-benzofuryl.

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.[60, 61] 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-arylpyrrolidine derivatives.[61] (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.[62] 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**.[63,64] 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).[62]

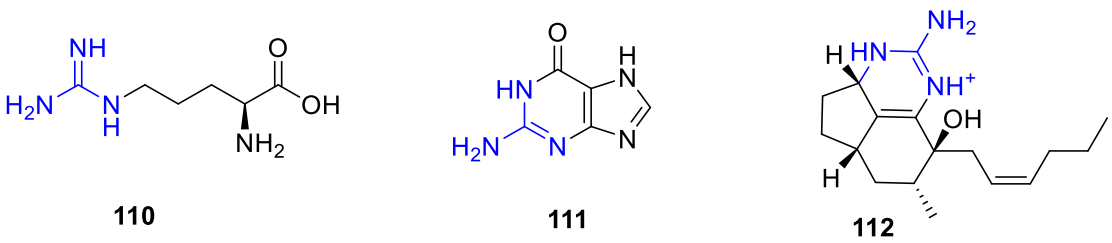


Figure 12: Some natural products containing the guanidine functionality.

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]

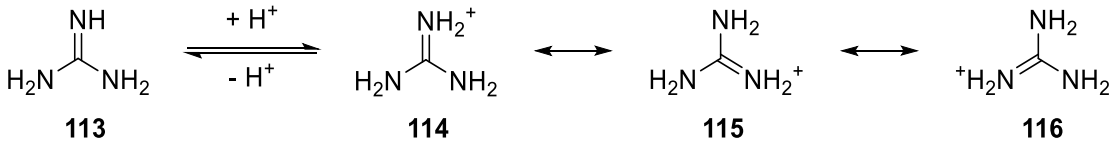


Figure 13: Guanidine and the guanidinium cation.

Due to the high stability of the conjugated acid of guanidine **113**, the pKa 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]

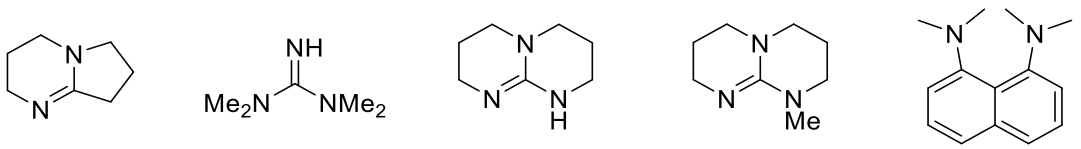
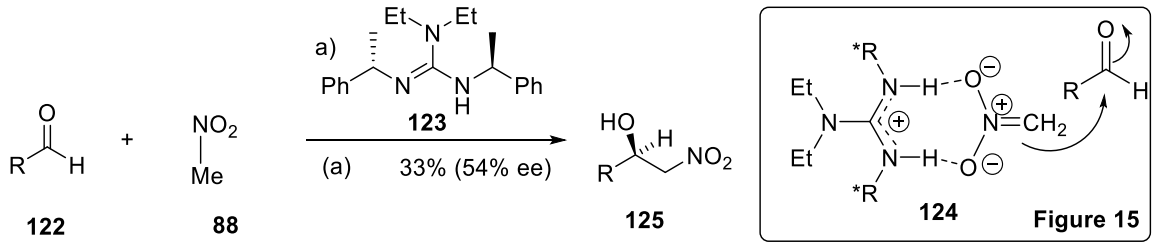


Figure 14: *p*K$_a$ values (in acetonitrile) of (DMAN) and guanidine superbases.

1.6.2 Guanidines and the guanidine motif in organocatalysts.

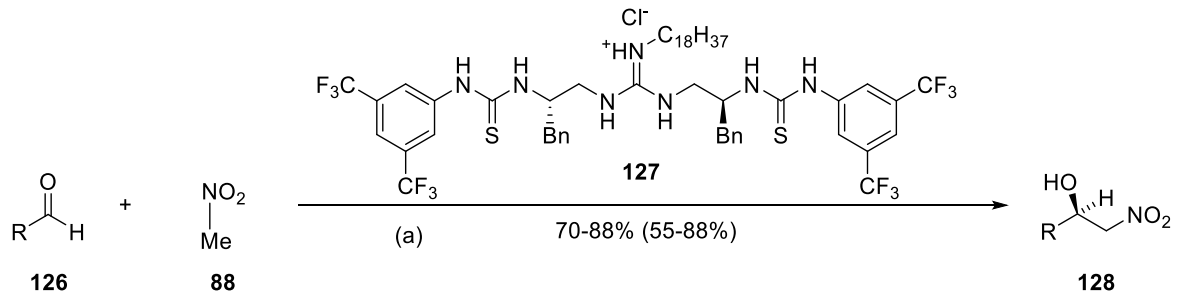
The basicity of guanidine and the ability of the guanidinium ion to undergo hydrogen-bonding interactions has resulted in the use of guandines as both basic catalysts but also as motifs for hydrogen bonding interactions with anions in organocatalysis.

An early use of chiral guanidines in asymmetric catalysts was the report by Najera *et al.* of the asymmetric nitro-aldol (Henry) reaction.[71] They reported the nitro-aldol reaction took place with good chemical yields especially using the chiral guanidine **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 **124**.



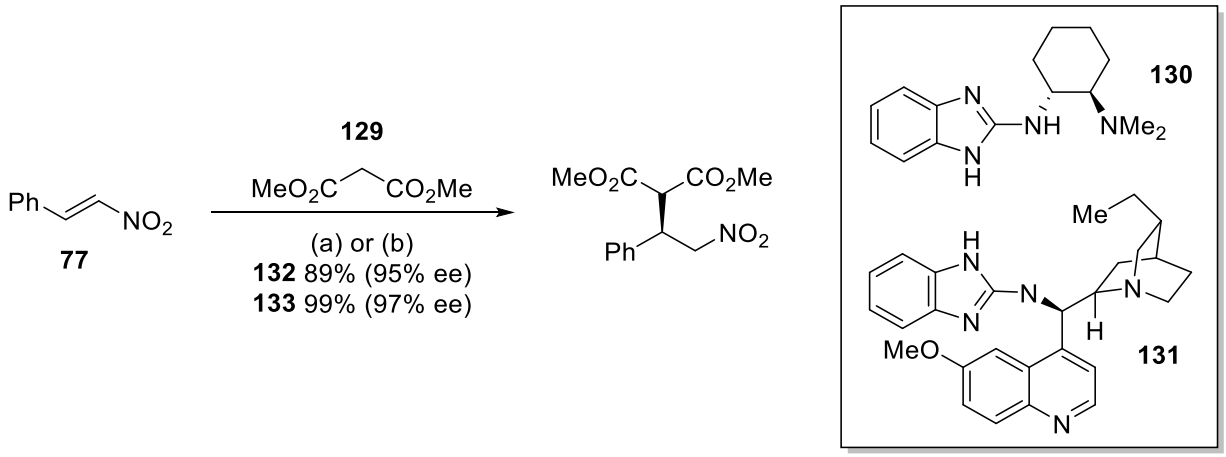
Scheme 24: (a) Catalyst **123** (0.1 equiv.), - 65 °C to rt, 9-72 h; THF, R = Bu, Ph.

Following this work, in 2005 Nawasaga *et al*. designed the novel bifunctional catalyst **127** bearing guanidine and thiourea moieties within the same molecule.[72,73,74] This was found to catalyze the reaction of nitromethane **88** with α-branched aldehydes **126** giving the product **128** in up to 88% ee.



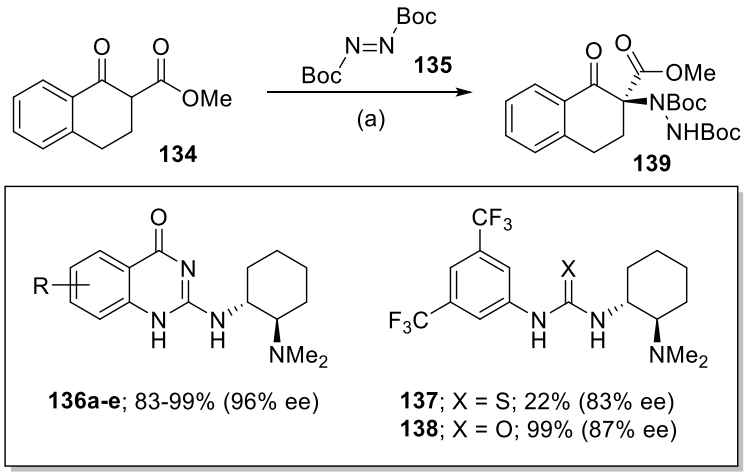
Scheme 25: (a) Catalyst **127** (0.1 equiv.), PhMe/H_2O (1:1), KOH, KI, 0 °C, 5-45 h.
R = cyclopentyl, 2,2-dimethylpropanyl, isopentenyl, 2-ethyl-2-methylbutan-yl, ethylbenzene.

Following on from this work, both Nájera *et al.*[75] and Park *et al.*[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)



Scheme 26: (a) Catalys **130** (0.1 equiv.), CF_3CO_2H (0.1 equiv), toluene, 23 °C, 48 h.
(b) Catalyst **131** (0.02 equiv.), DCM, - 20 °C, 40 h.

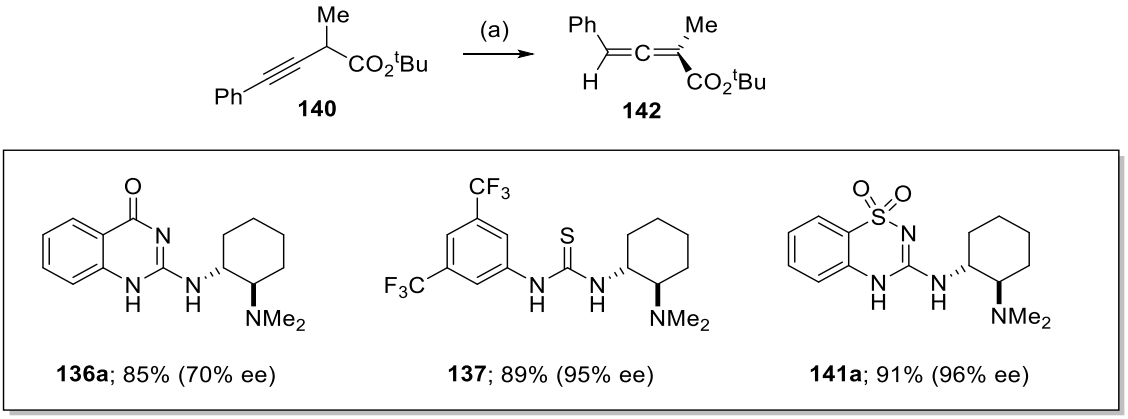
Takemoto and co-workers have capitalised on covalent intramolecular activation of HBDs in their design of catalyst scaffolds containing electron-withdrawing group bridges that link the HBD functionalities to their parent aryl substituents.[77] They reported the two HBD catalyst scaffolds that displayed 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)[77]



Scheme 27: (a) Catalyst (0.1 equiv.), toluene, 23 °C, 5 h,

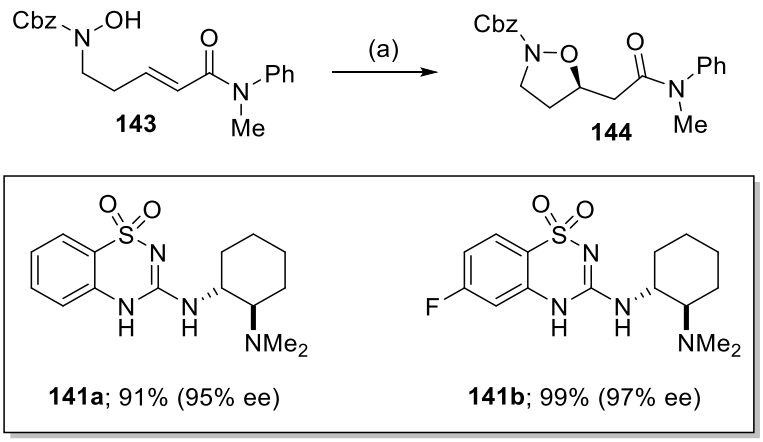
136a-e: R = H, 8-F, 7-F, 6-F, 5-F.

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)[78] 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.



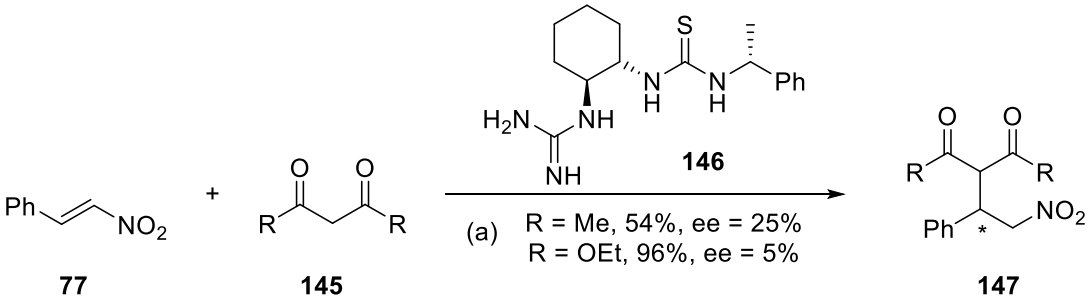
Scheme 28: (a) Catalyst (0.1 equiv.), 60 °C, DCM, 168 h.

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]



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

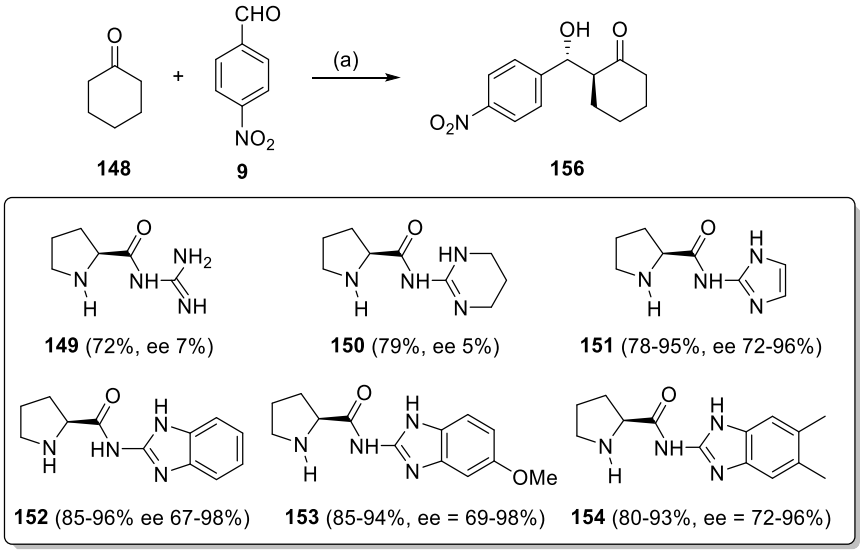
Shubina later reported that the guanidine derived chiral thiourea **146** catalysed the asymmetric nitro-Michael addition of dialkyl malonate **145** to trans-*β*-nitrostyrene **77**, giving high yields (up to 96%) of adduct **147** but with quite low enantioselectivities. (Scheme 30) The authors reported 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 enentioselectivity.[81]

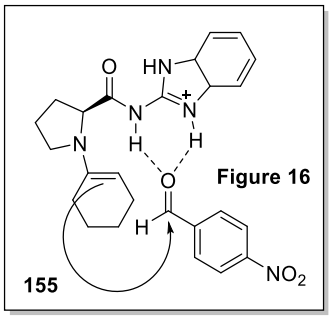


Scheme 30: (a) Catalyst **146** (0.2 equiv.), toluene, rt; R = Me, 120 h; R = OEt, 2 h.

In 2012, Tang *et al*. prepared a range of novel aminoimidazole derived L-proline derived organocatalysts **149-154** and applied them to aldol reactions.[82] Of these compounds the catalyst **152** was the most successful which was catalytic in the presence of an appropriate acid (succinic acid, AcOH, CF_3COOH, CF_3SO_2OH or HCl) which serves to control and activate the acceptor carbonyl group **9**. Under optimized reaction conditions using catalyst **152** (**152** (0.1 equiv)/TFA (0.1 mol of TFA)/H_2O/EtOAc) a high yield (86%) and an ee of 98% was achieved for the product **156**.[82] The reaction is thought to proceed via the intermediate enamine

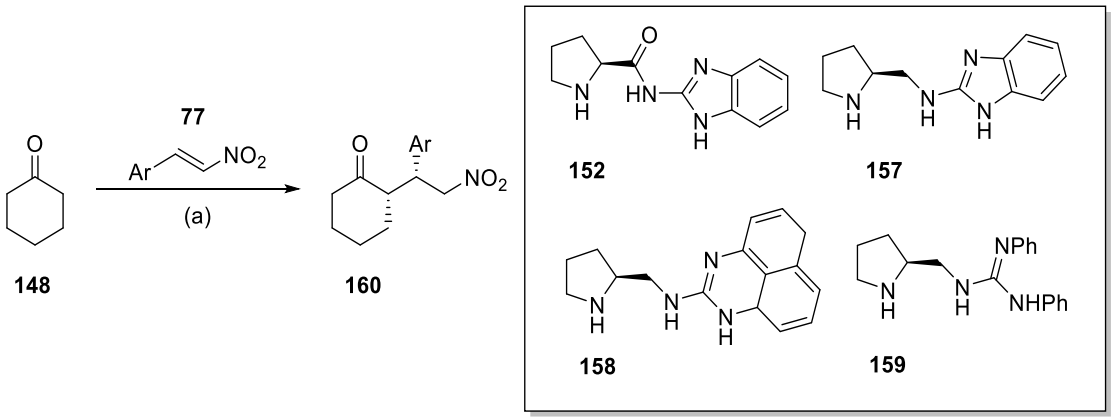
155 in which the protonated guanidine, hydrogen bonds with the incoming aldehyde and directs the reaction of the enamine in the transition state. (Scheme 31)





Scheme 31: (a) Catalyst (0.01-0.1 equiv.), acid catalyst (0.01- 0.05 equiv.), Solvent (DMSO, EtOAc, MeOH, DCM, THF or H_2O), rt, 18-72 h.

J. Lin et.al reported the synthesis of a four similar L-proline derived pyrrolidine-aminobenzimidazoles **152-(157-159)**[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 diastereoselectivies (to 88-99/1) were observed for catalyst **157**. (Scheme 32)



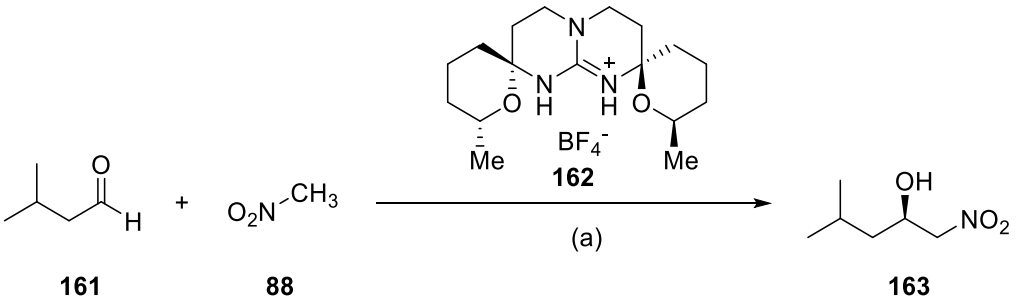
Scheme 32: Conditions (a) Catalyst **152-(157-159**) (10 mol %), *p*-methoxybenzoic acid (10 mol %), brine, rt (25 °C) and 7-10 h.

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.[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.

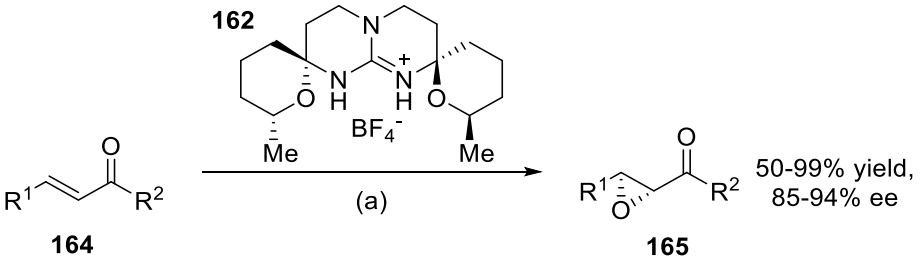
1.8 Previous work with guanidine catalysts in the Murphy research group.

Early work within the group focused on the synthesis and use of 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]



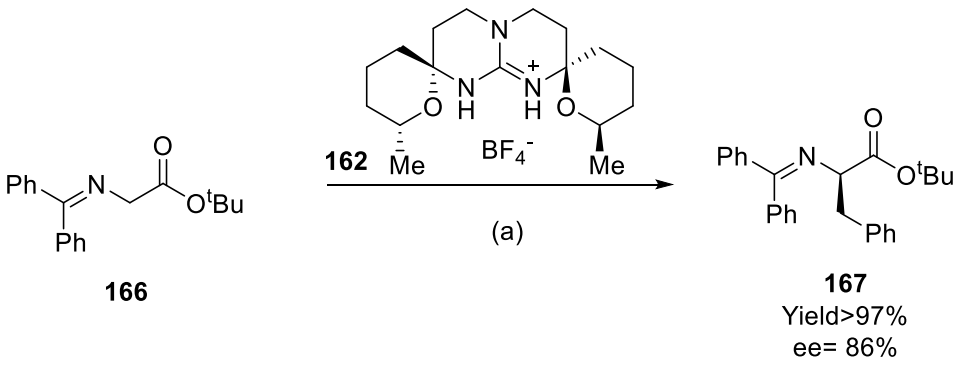
Scheme 33: (a) i) Catalyst **162** (0.1 equiv.), NaOMe (0.09 equiv.), MeOH, 30 min then remove solvent; ii) CCl_4, rt, **88**, **161**, 16 h.

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]



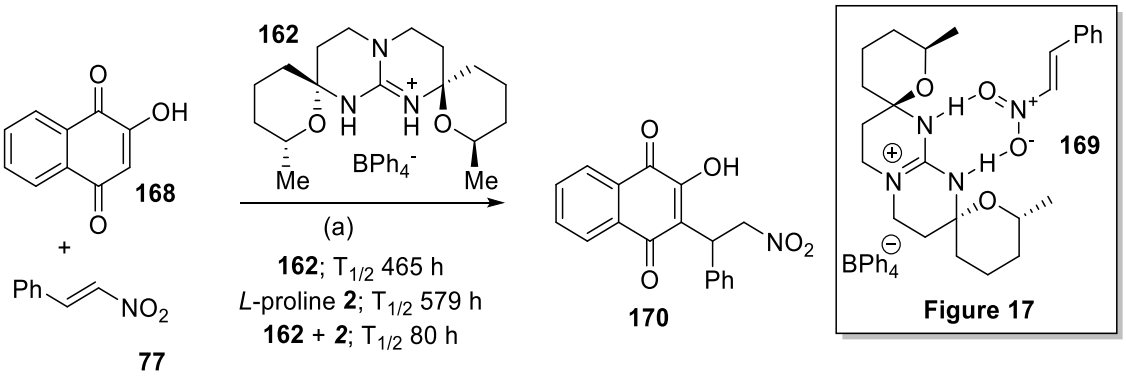
Scheme 34: (a) Catalyst **162** (0.1-0.025 equiv.), MOCl (aq), toluene, 16-72 h, 0 °C-rt; M = Li, Na, K; R^1, R^2 = Ph, C_6H_{13}, 4-(Cl)-Ph

Similarly, phase transfer benzylation 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.

Guanidinum 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-*β*-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 R^1 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.

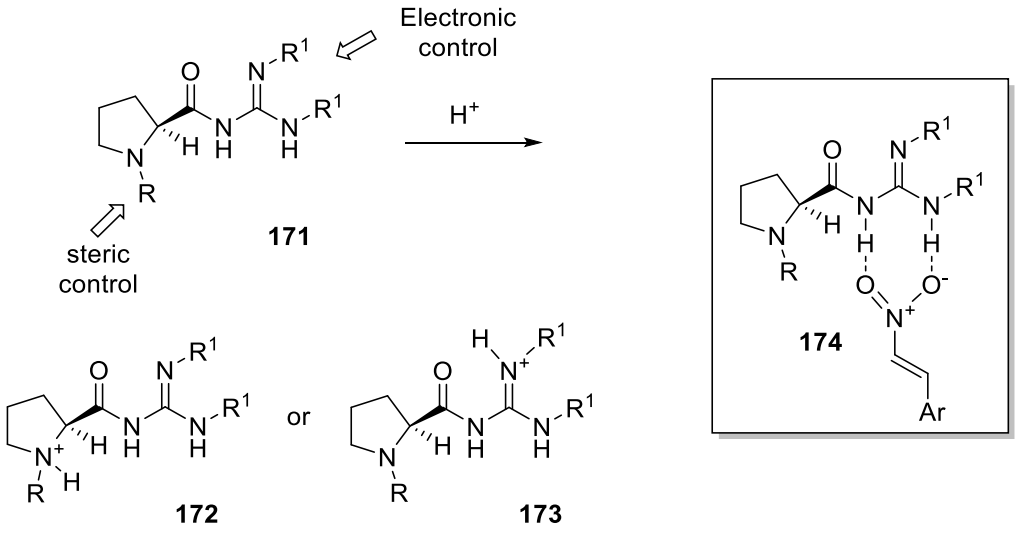
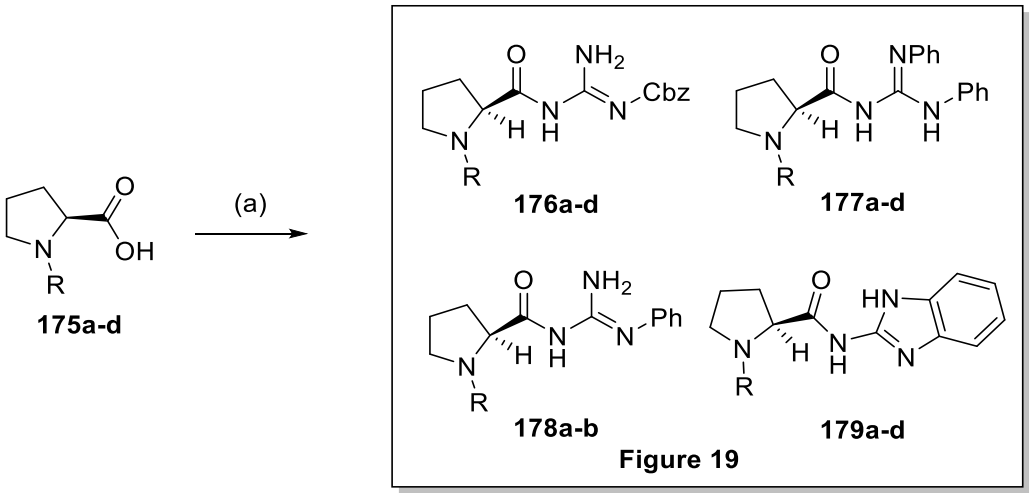


Figure 18: Proposed catalyst **171**.

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) *i*Pr (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 ($PhCH_2$-), isopropyl ($(CH_3)_2$ CH-) or cyclohexyl (Cy-) gave appreciably lower selectivity leading to the conclusion that increasing steric bulk at the N-substituent was detrimental to catalyst efficiency.

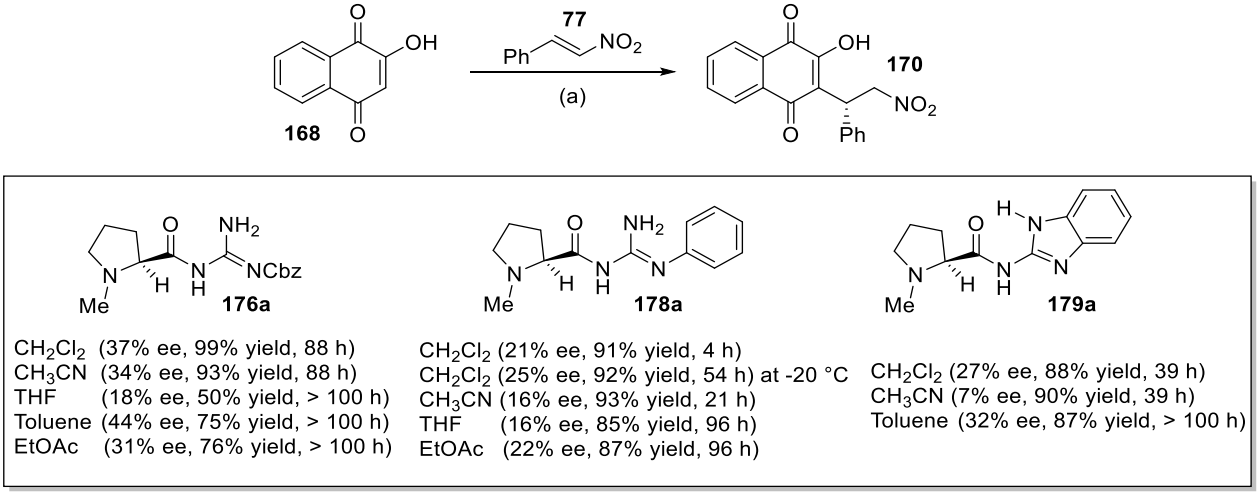


Figure 20: Michael reaction catalysed by **176a**, **178a** and **179a**.

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 enantioselctive 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[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)

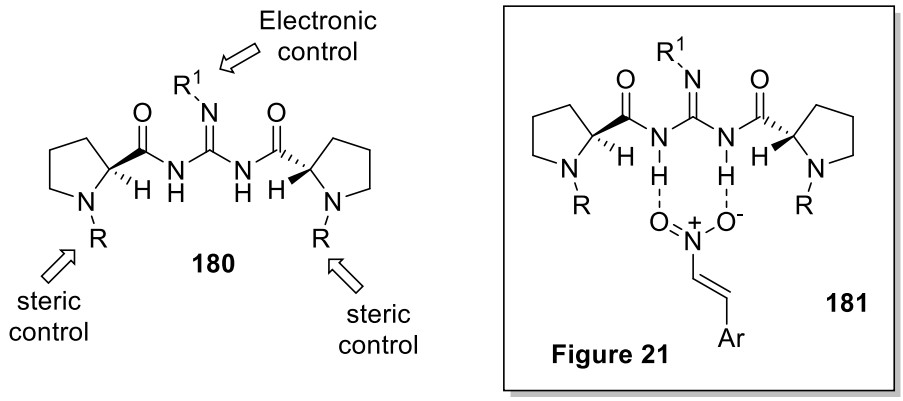
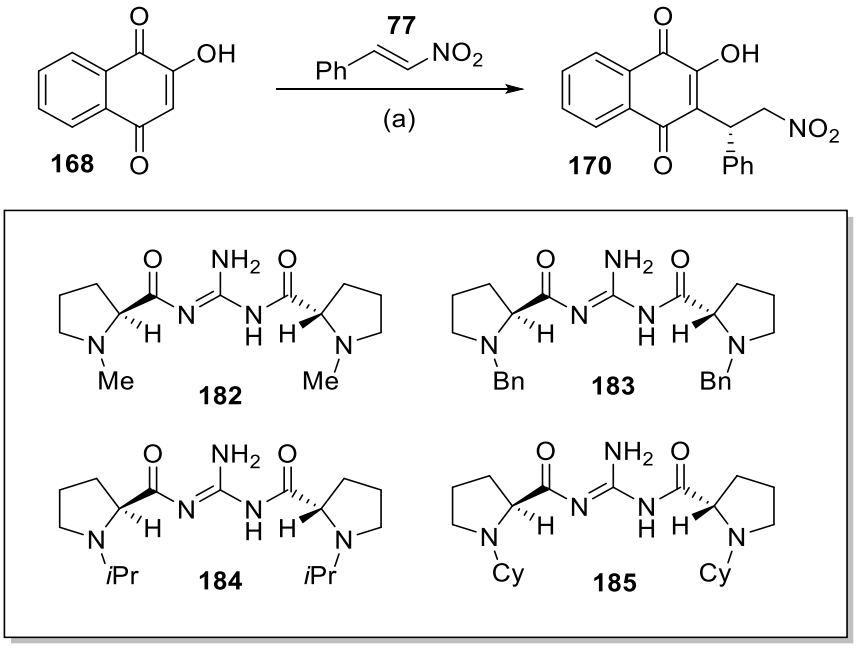


Figure 21: Rational behind the design of the second-generation catalysts **180**.

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.

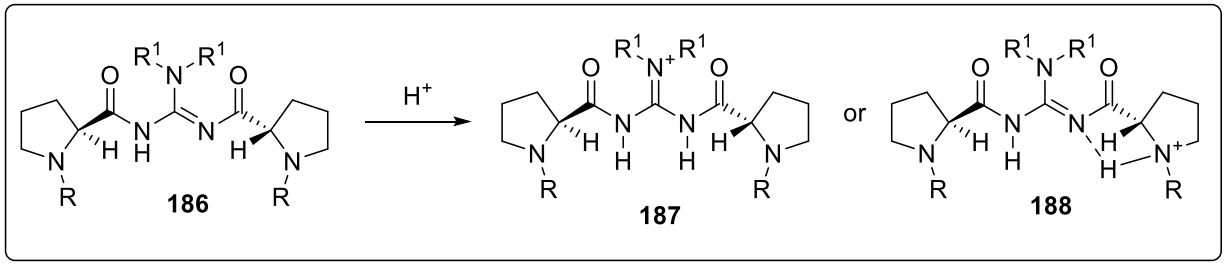


Figure 22: Third generation catalysts **187** and **188**.

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.[97] 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.

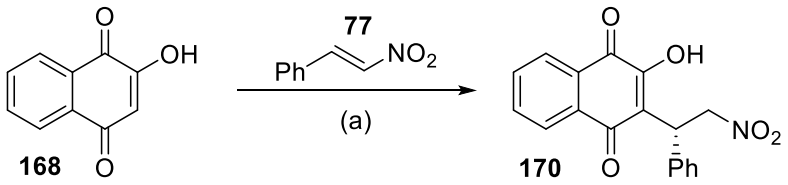
ii) Discussion of enantioselective reactions attempted.

iii) Mechanistic and X-ray crystallographic studies.

iv) Conclusions and further work.

Chapter 2: Results and Discussion.

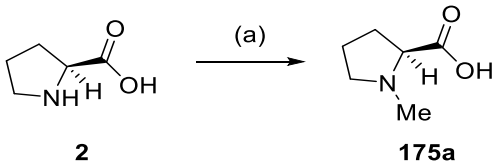
As stated previously, the initial aim of this project was to prepare a range of C_2-symmetrical catalysts and to study their application to asymmetric transformations. It was intended to study the Michael reaction between *β*-nitrostyrene **77** with 2-hydroxy-1,4-naphthoquinone **168** which in the 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 *β*-nitrostyrene **77** and 2-hydroxy-1,4-naphthoquinone **168**.

2.1 Preparation of *N*-substituted amino acids.

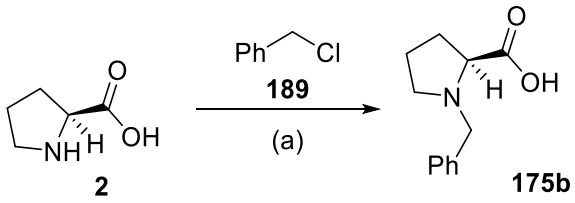
The first requirement was to prepare *N*-methyl-L-proline **175a**, which is a key compound in these investigations and was achieved using a literature method.[87] Thus L-proline **2** was dissolved in methanol with aqueous 40% formaldehyde under hydrogenation conditions using 10 % Pd/C. After 24 h, 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 δ_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)).[88] (Scheme 40)



Scheme 40: (a) CH_2O (40%, aq), H_2, 10% Pd/C, MeOH, 24 h.

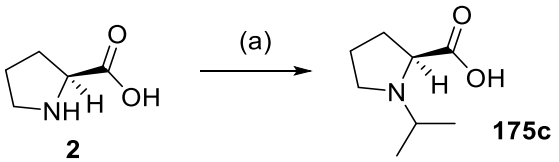
The next precursor *N*-benzyl-L-proline **175b** was prepared in a different manner, by the dropwise addition of BnCl **189** to a solution of **2** and KOH in *i*PrOH at 40 °C over 3 h. After

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)



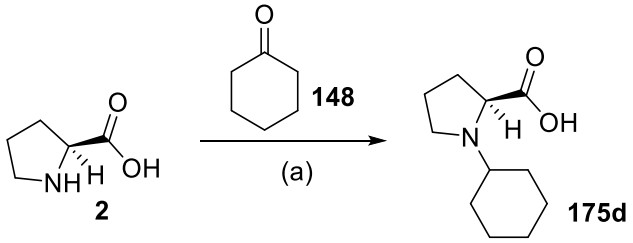
Scheme 41: (a) **189**, KOH, *i*PrOH, HCl, 40 °C, 20 h.

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]



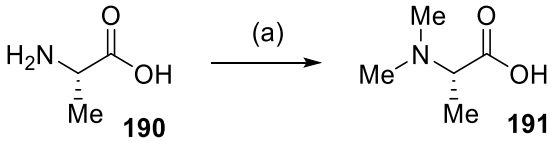
Scheme 42: (a) acetone, H_2, 10% Pd/C, rt, MeOH, 24 h.

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 δ_H 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).



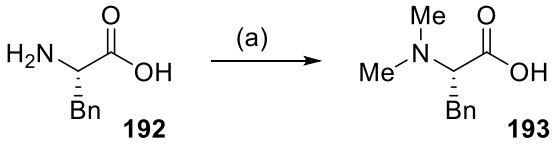
Scheme 43: (a) **148**, H_2, MeOH, 10% Pd/C, 24 h.

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.[92,93] 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 δ_H 2.84 (6H, s, 2 × 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_2O), which was in agreement with literature data.[93] (Scheme 44)



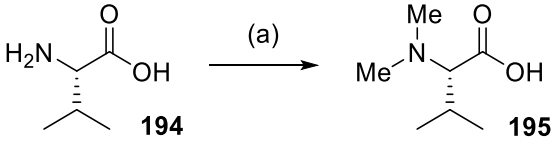
Scheme 44: (a) CH_2O (40%, aq), H_2, 10% Pd/C, MeOH, 24 h.

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.[94] 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 δ_H 2.83 (6H, s, 2 × 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_2O)) were in good agreement with the literature values.[93, 94] (Scheme 45)



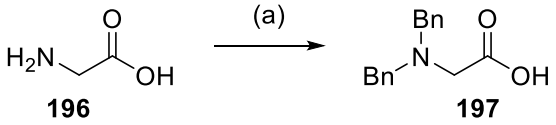
Scheme 45: (a) CH_2O (40%, aq), H_2, Pd/C, MeOH, 24 h.

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 δ_H 2.83 (6H, s, 2 × 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.[93, 95] (Scheme 46)



Scheme 46: (a) CH_2O (40%, aq), H_2, 10% Pd/C, MeOH, 24 h.

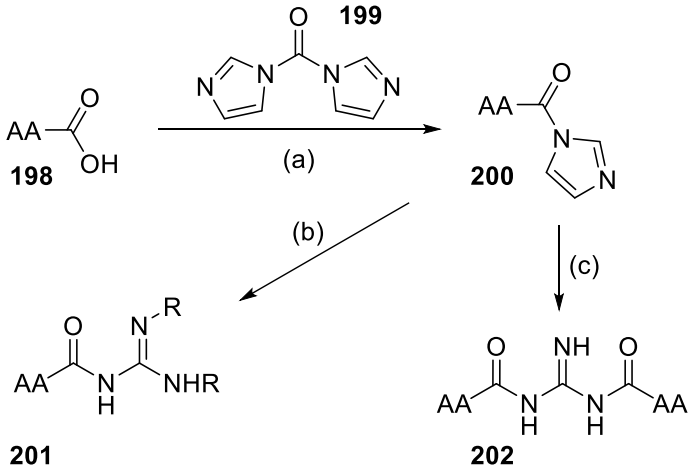
We also prepared *N*,*N*-dibenzylglycine **197** by conversion of glycine **196** to its Schiff's base with benzaldehyde under basic condition and in situ reduction of the imine formed with $NaBH_4$. The step was repeated with the addition of excess benzaldehyde and $NaBH_4$ reduction again. Isolation of the product was achieved by neutralisation to pH 6.5, which on standing gave **197** in 59% yield as a white precipitate with a melting point of 192-194 °C (lit.[96] 200 °C). ^1H NMR data for **197** gave diagnostic signals at δ_H 7.42 (10H, s, CH), 3.90 (4H, s, CH_2) and 3.14 (2H, s, CH_2) ppm.[96]



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.

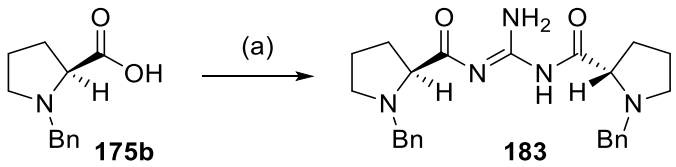
With the required amino acids available, we proceeded onto the coupling of these compounds with the desired substituted guanidines. In previous cases[97] carbonyldiimidazole (CDI) **199** was used as the amino acid activating agent as this has been shown to be an effective peptide-coupling reagent. It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



Scheme 48: Schematic plan for catalysts synthesis. Conditions
(a) **199**, DMF; (b) substituted guanidine; (c) guanidine. R = H, alkyl, aryl, acyl.

2.2.1 Preparation of the C_2-symmetric L-proline catalysts.

With the amino acid derivatives available, we embarked upon the synthesis of the di-substituted C_2-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)

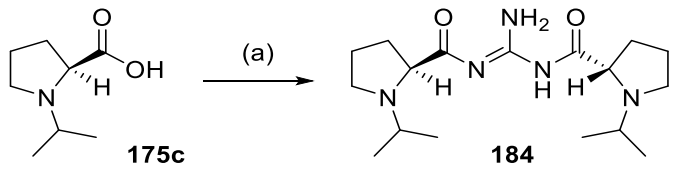


Scheme 49: (a) i) CDI, DMF, 24 h; ii) guanidine.HCl (0.5 equiv.), NaH, 1 h; iii) combine.

The analytical data obtained for **183** confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{20}$ -83.3 whilst the proton NMR spectrum gave a signal at δ_H 8.17-11.43 (3H, br s, 3 × NH) ppm for the guanidine NH protons and a complex multiplet at δ_H 7.19-7.39 (10H, m, 2 × Ph) ppm for the aromatic protons. The benzyl methylene was observed as two signals at δ_H 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 δ_H 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 δ_H 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 × CH_2) ppm. The ^{13}C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon in the proline ring appearing at δ_C 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 $[C_{25}H_{32}N_5O_2]^+$ 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.

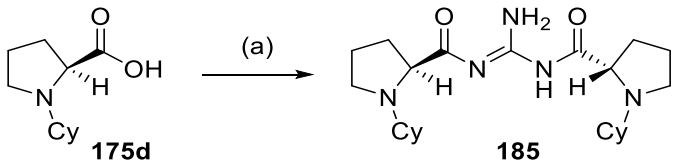
After aqueous work up and silica gel chromatography the catalyst **184** was obtained in 93% yield as an off-white solid. (Scheme 50)



Scheme 50: (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 $CDCl_3$ gave a broad signal at δ_H 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 δ_H 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 δ_H 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 × CH_2) ppm whilst the dimethyl signal was observed as a doublet at δ_H 1.01 (12H, d, *J* 6.4 Hz, 4 × Me). The ^{13}C NMR spectrum gave the required 10 non-equivalent signals with the methyl carbons in the isopropyl group appearing as two signals at δ_C 21.2 and 19.9 ppm, whilst the two methine carbons of the proline and isopropyl groups appeared at δ_C 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 $[C_{17}H_{32}N_5O_2]^+$ ($[M+H^+]$).

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)

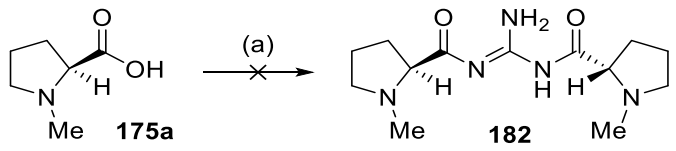


Scheme 51: (a) i) CDI, DMF, 24 h; ii) Guanidine. HCl (0.5 equiv.) , NaH, 1 h; iii) combine.

Analysis of the proton NMR spectrum of the product illustrated the presence of a broad singlet signals at δ_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 δ_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 δ_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 δ_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 δ_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 $[C_{23}H_{40}N_5O_2]^+$ corresponding to $M+H^+$. An X-ray structure was also obtained for **185** (*vide infra*).

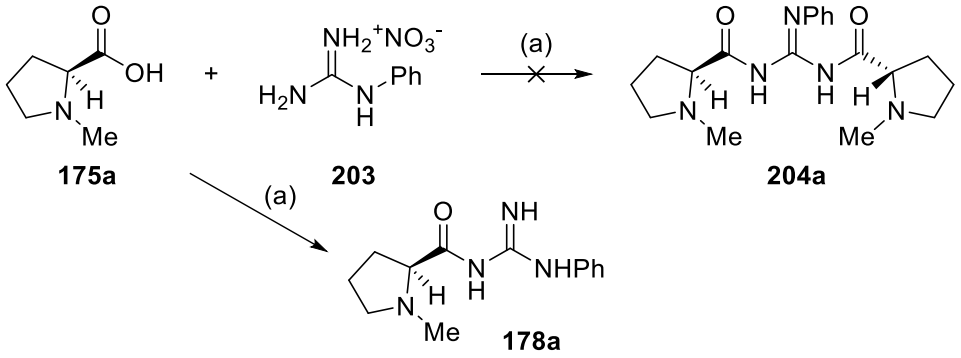
With the successful preparation of these three catalysts, we envisaged the preparation of the corresponding *N*-methyl substituted catalyst **182** to be relatively straightforward. We thus repeated the reaction as detailed above but were disappointed to observe only a low mass yield of material from 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.



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

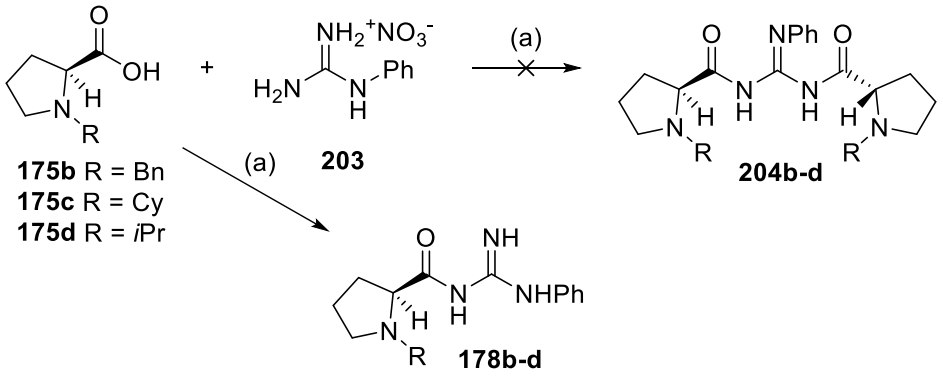
As we intended to investigate the substitution pattern of the guanidine in these catalysts, we wished to prepare the *N*-substituted guanidine catalyst **204a** from phenyl guanidinium nitrate **203**. We thus reacted *N*-methyl-L-proline **175a** under our standard conditions by activating it using 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.



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**.

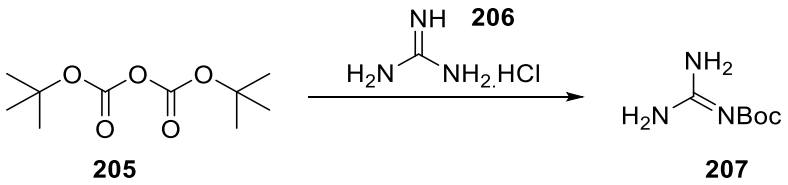


Scheme 54: Attempted preparation of **204b-d**. (a) (i) CDI, DMF, 24-72 h, (ii) Add to **203** (0.5 equiv.) treated with NaH for 3 h, then rt, 2 d.

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.

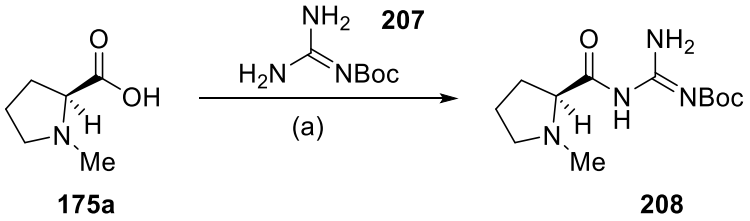
2.2.2 Preparation of L-proline derived catalysts

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

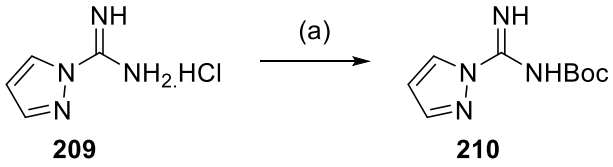
The Boc-protected guanidine **207** was coupled with *N*-methyl-L-proline **175a** by activating with CDI coupling agent in dry DMF for 24 h, followed by the addition of guanidine **207**. After 24 h, extractive work up and column chromatography gave **208** in 38% yield as a white solid. (Scheme 56)



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 $[\alpha]_D^{20}$ -46 whilst the proton NMR spectrum gave a signal at δ_H 8.21-10.03 (3H, br s, NH, NH_2) ppm for the guanidine NH protons. The methine proton of the proline was observed as double doublet at δ_H 2.95 (1H, dd, *J* 10.5, 4.8 Hz, CH) ppm, whilst the *N*-methyl signal was observed at δ_H 2.31 (3H, s, Me) ppm, with the tert-butyl appearing at δ_H 1.46 (9H, s, 3 × Me) ppm. Other signals for the methylenes of the proline ring were observed at δ_H 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 ^{13}C NMR spectrum gave the required 10 non-equivalent signals with the methine carbon in the proline ring resonating at δ_C 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 $C_{12}H_{23}N_4O_3^+$ ($[M+H^+]$). An X-ray structure was also obtained for **208** (*vide infra*).

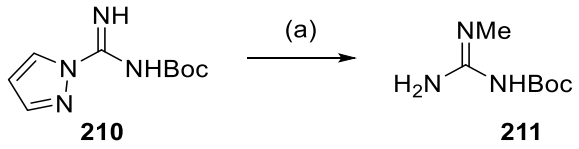
It was intended to study more highly substituted guanidines in these catalysts and in order to prepare the required substituted guanidines we prepared *N*-Boc-1*H*-pyrazole-1-carboxamide **210** by the reaction of 1*H*-pyrazole-1-carboxamidine hydrochloride **209** and di-*tert*-butyl dicarbonate **205** 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)



209 **210**

Scheme 57: (a) Boc_2O, THF, 24 h.

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)

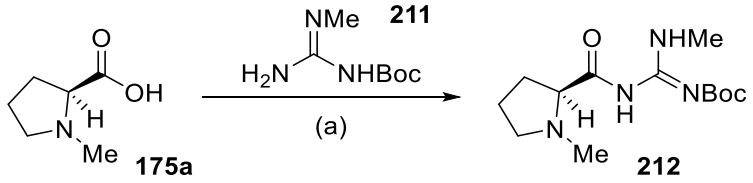


210 **211**

Scheme 58: (a) CH_3NH_2, THF, 24 h.

Literature data were not available for **211**[99] however the proton NMR spectrum gave a broad signal at δ_H 5.93 (3H, br s, 3 × NH) ppm for the guanidine NH protons, whilst the proline *N*-methyl signal was observed at δ_H 2.85 (3H, s, Me) ppm and the *t*-butyl signal was at δ_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 δ_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 $C_7H_{16}N_3O_2^+$ ($[M+H^+]$).

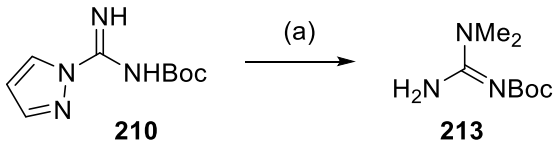
With **211** in hand, the catalyst **212** was prepared by treating *N*-methyl-L-proline **175a** with CDI in DMF for 24 h, followed the addition of **211**, followed by stirring for 5 days. After an aqueous work up, trituration with diethyl ether gave the target product **212** in 94% yield as an off-white 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 $[\alpha]_D^{18}$ -36.4 whilst the proton NMR spectrum gave signals at δ_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 δ_H 2.99 (1H, dd, *J* 4.6, 9.9 Hz, CH) ppm. The *N*-methyl guanidine signal appeared as a doublet at δ_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 δ_H 2.41 (3H, s, Me) and 1.51 (9H, s, 3 × Me) ppm. Other signals for the proline appeared at δ_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 × CH) ppm. The ^{13}C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon in the proline ring appearing at δ_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 $C_{13}H_{25}N_4O_3^+$ ($[M+H^+]$). An X-ray structure was also obtained for **212** (*vide infra*).

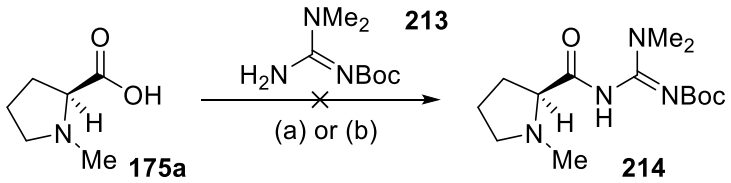
We next investigated the synthesis of a *N*,*N*-dimethylguanidine catalyst **214** and prepared *N*,*N*-dimethyl-Boc-guanidine **213** by treatment of *N*-Boc-*H*-pyrazole-carboxamide **210** with excess (4 equivalent) aqueous dimethylamine in THF. The reaction was monitored by TLC and after 24 h there 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_2HN (aq., 6 equiv.), THF, 3d.

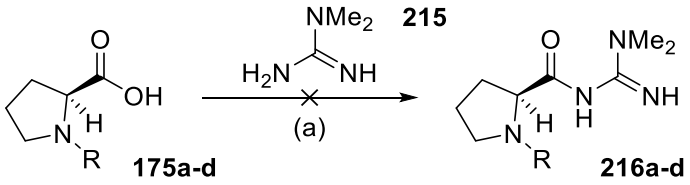
The formation of **213** was confirmed by NMR and incorporation of the dimethyl group was evident by a six hydrogen singlet at δ_H 3.01 (6H, s, 2 × Me) ppm and a nine hydrogen singlet at δ_H 1.49 (9H, s, 3 × Me) ppm corresponded to the Boc-protecting group. The ^{13}C NMR spectrum displayed the expected 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 $C_8H_{18}N_3O_2^+$ ($[M+H]^+$).

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_2CO_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)



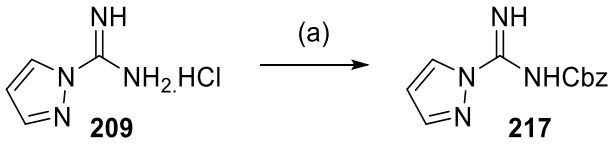
Scheme 61: Attempted preparation of **214**. (a) (i) CDI, DMF, 24 h; ii) **213**, rt, 3 d, 40 °C, 2 d. (b) i) CDI, DMF, 24 h. ii) NaH, DMF, rt, 4 d.

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)



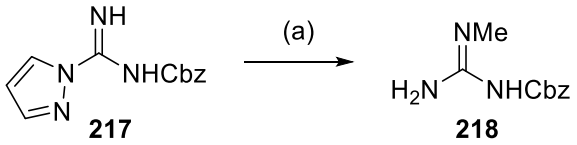
Scheme 62: Previous attempts at preparing catalysts **216a-d**. Conditions (a) i) CDI, DMF, 24-72 h; ii) Add to **215** treated with NaH for 3 h, then rt, 2 d; R = Me, Bn, Cy, *i*Pr.

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-1*H*-pyrazole-1-carboxamide **217** by the reaction of 1*H*-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.[98] (Scheme 63)



Scheme 63: Preparation of **217**: (a) CbzCl, THF, 24 h.

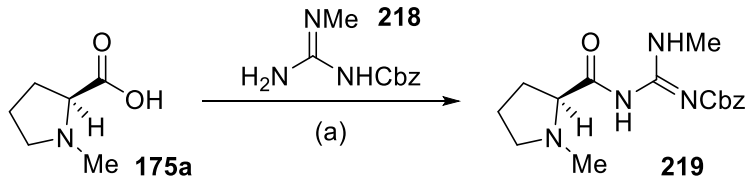
This guanidine **217** was stirred with two equivalent of solid methylamine hydrochloride and triethylamine in THF under anhydrous conditions. After stirring for 17 h, starting material was still present and a further three equivalents of methylamine hydrochloride and triethylamine were added. Again, 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)



Scheme 64: Preparation of **218**: (a) $MeNH_2$ (aq., 2 equiv.) THF, 1.5 h.

Incorporation of the new methyl group was evident by the appearance of a singlet at δ_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)

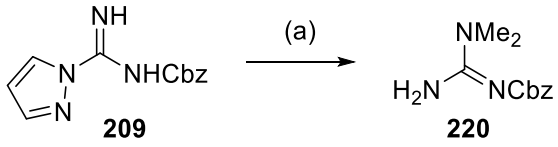


Scheme 65: Preparation of catalyst **219**. (a) i) CDI, DMF, 24 h, rt, ii) **218**, rt, 4 d.

Catalyst **219** gave a negative specific rotation value of $[\alpha]_D^{20}$ -54.0 whilst the proton NMR spectrum gave two signals at δ_H 12.81 (1H, s, NH), and 8.99 (1H, s, NH) ppm for the guanidine NH protons. Signals at δ_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 δ_H 5.16 ppm. Signals for the proline methylenes were observed at δ_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 δ_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 δ_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 δ_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*-

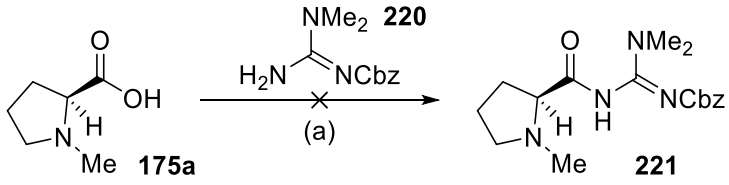
Cbz-*H*-pyrazolecarboxamide **209** with 3 equivalents of aqueous dimethylamine in THF. After 24 h TLC indicated a trace of starting material present and so a further equivalents of dimethyl amine was added. After a further 24 h, an extractive work-up followed by column chromatography gave guanidine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



Scheme 66: Preparation of **220**: (a) Me_2NH (aq., 4 equiv.), THF, 24 h.

Incorporation of the dimethyl group was evident by the appearance of a singlet at δ_H 3.04 (6H, s, 2 × Me) ppm in the ^1H NMR as well as a corresponding signal at δ_C 36.9 ppm in the ^{13}C NMR. The ^{13}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 $C_{11}H_{16}N_3O_2^+$ ([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)

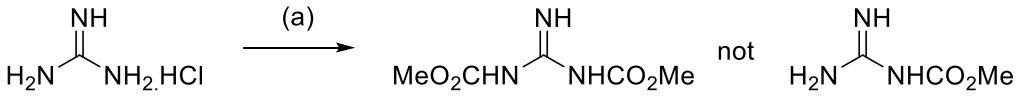


Scheme 67: Attempted preparation of **221**. (a) i) CDI, DMF, rt, 24 h. ii) **220**, rt, 6 d.

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.[100] 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 δ_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, NH_2) 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)



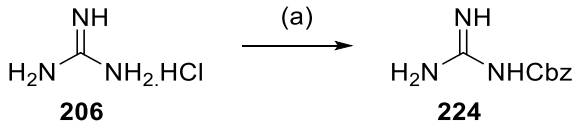
206 **223** **222**

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.

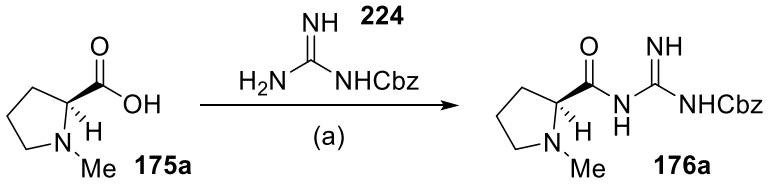
We wished to investigate the deprotection of the previously prepared catalyst **176a**[97] as the free guanidine might be of interest as a catalyst. The required *N*-Cbz-guanidine **224**, was prepared by the addition of a solution of benzyl chloroformate dissolved in dioxane to a solution of guanidine 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)



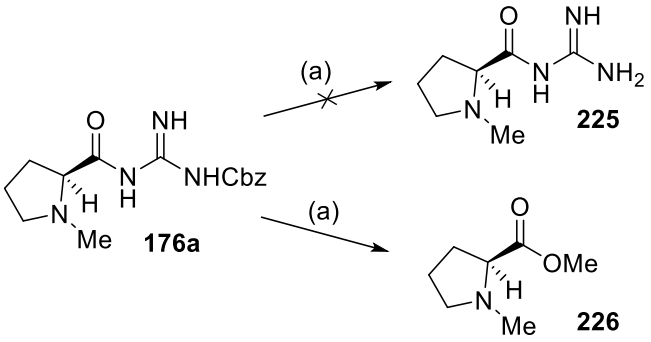
Scheme 69: Preparation **224**: (a) CbzCl, NaOH, Dioxane, water, 22 h.

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)



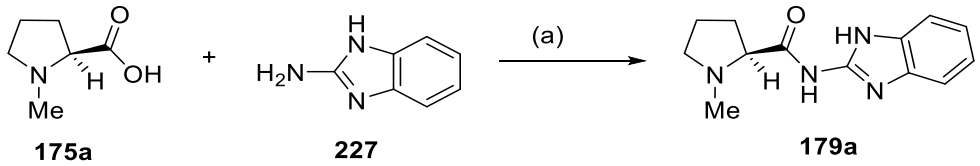
Scheme 70: Preparation of **176a**. (a) i) CDI, DMF, 0 °C, 4 h. (ii) **224**, rt, 5 d

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 δ_H 3.86 (3H, s, Me) ppm whist the second which was assumed to be the *N*-methyl of the proline was observed as a singlet at δ_H 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 $C_7H_{13}NONa^+$ ($[M+Na]^+$). This evidence seems to suggest the formation of methyl *N*-methyl-L-prolinate **226**, a conclusion supported by the NMR data. The compound gave a negative specific rotation value of $[\alpha]_D^{40}$ -72.2 (c = 3.3, CF) which corresponds very closely to the reported value of $[\alpha]_D^{22}$ -70.8 (c = 3.3, CF). [102] (Scheme 71)



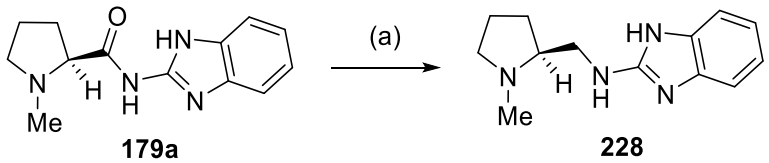
Scheme **71:** Synthesis of **226**. (a) H_2, 10% Pd/C, MeOH, rt, 2 h.

We wished to continue the studies on the *N*-methyl-L-proline-2-aminobenzimidazole catalyst **179a**, previously prepared in the group.[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.[97] (Scheme 72)



Scheme 72: Preparation of **179a**. (a) i) CDI, DMF, 24 h; ii) **227**, rt, 72 h.

The amide **179a** was subsequently reduced in dry diethyl ether using $LiAlH_4$. 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)

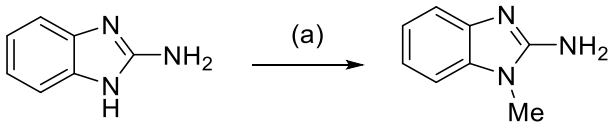


Scheme 73: Preparation of **228**. (a) $LiAlH_4$, dry Et_2O, 0 °C, then reflux 5 h, then 24 h rt.

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 δ_H 7.13-7.23 (2H, m, 2 × CH), and 6.94-7.00 (2H, m, 2 × CH) ppm for the aromatic ring protons. Two double doublets at δ_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 δ_H 2.67-2.76 (1H, m, CH) ppm, whilst the *N*-methyl signal was observed as a singlet at δ_H 2.53 (3H, s, CH_3) ppm. The remaining signals for the pyrrolidine ring were at δ_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 δ_C 45.7 ppm and the methine carbon of the pyrrolidine ring at δ_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-1*H*-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, where upon CH_3I 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)



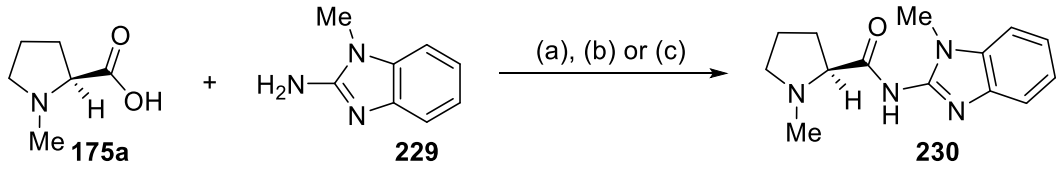
227 **229**

Scheme 74: Preparation of **229**. (a) CH_3I, KOH, 30 min

Data was not given in the literature,[103] however incorporation of the methyl group was evident by the appearance of a singlet at δ_H 3.35 (3H, s, Me) ppm in the ^{1}H NMR, together with a corresponding signal at δ_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 $C_8H_{10}N_3^+$ ([M+H$^+$]).

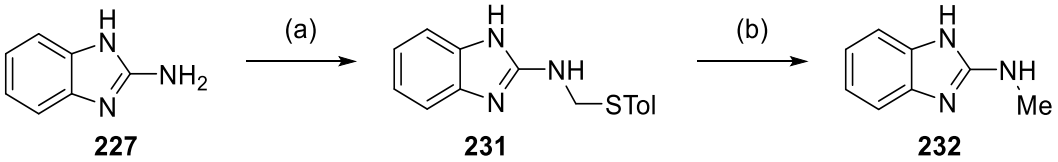
We next attempted the coupling of **229** with one equivalent of *N*-methyl-L-proline **175a** which was activated with CDI in dry DMF for 2 h at rt followed by the addition of **229**. After 5 days, an aqueous workup extracting with ethyl acetate followed by column chromatography gave the catalyst **230** 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 ^{1}H 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% $CHCl_3$ 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-1*H*-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 triturates 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_3N, THF, 3 h. (ii) **229**, rt, 3 d.

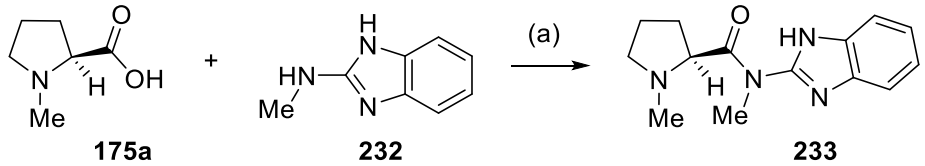
The analytical data obtained for **230** confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{23}$ -32.2 whilst the proton NMR spectrum gave a broad signal at δ_H 9.40-11.24 (1H, br s, NH) ppm for the guanidine NH protons and two signal at δ_H 7.53 (1H, br d, *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 $C_{14}H_{19}N_4O^+$ ($[M+H^+]$).

We similarly wanted to prepare the *N*-methyl-1*H*-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-1*H*-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, CH_2O (39%, aq), ethanol, reflux 7 h, (b) $NaBH_4$, 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)



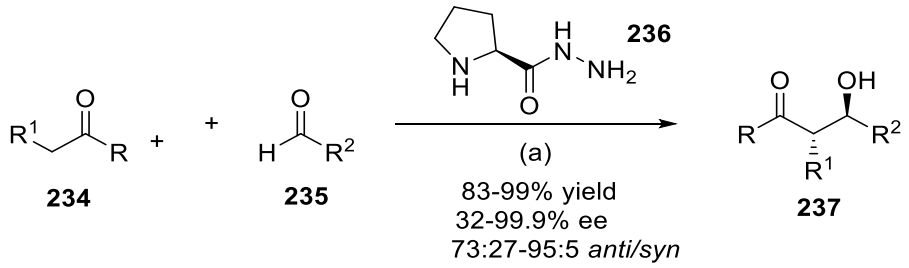
Scheme 77: Preparation of **233**. (a) i) CDI, DMF, 8 h; ii) **232**, rt, 72 h.

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}H NMR spectrum gave a broad signal at δ_H 11.60 (1H, s, NH) ppm for the guanidine NH proton. Signals at δ_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 × CH) ppm correspond to the aromatic ring protons. The methine proton of the proline ring was observed as a multiplet at δ_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 δ_H 3.78 (3H, s, Me), and at δ_H 2.44 (3H, s, Me) respectively. The remaining signals for the proline ring were at δ_H 3.39 (1H, dd, *J* 8.6, 7.2 Hz, CH), 2.25-2.47 (2H, m, 2 × CH), and 1.82-2.08 (3H, m, 3 × 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 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 $C_{14}H_{19}N_4O^+$ ($[M+H^+]$).

2.2.3 Hydrazine catalysts

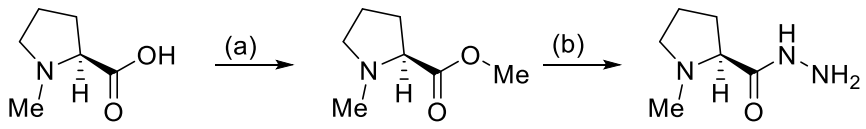
Following a report by Bhowmick *et al*. who reported that the L-proline hydrazide **236** was the smallest and, most importantly, one of the best organocatalysts reported thus far in the literature.[105] The existence of a suitable hydrogen-bonding pocket (two hydrogen bonds within a short space) in 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**. (a) **236** (0.1 equiv.), PTSA, (0.05 eqv.) in H_2O; 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.

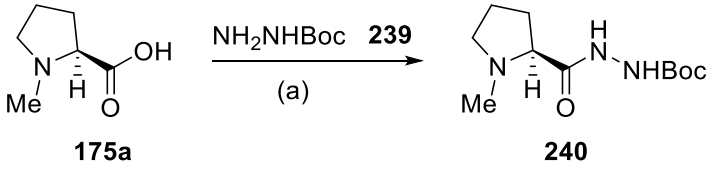
The first catalyst was prepared by initially converting *N*-methyl-L-proline **175a** into its methyl ester **226** using acetyl chloride and methanol under reflux for 12 h, then reacting this compound with an excess of hydrazine monohydrate in methanol. Work up gave the desired catalyst **238** as a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



Scheme 79: (a) AcCl, MeOH, reflux, 12 h. (b) $NH_2NH_2.H_2O$, 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 $[\alpha]_D^{20}$ -121.6 whilst the proton NMR spectrum gave a broad signal at δ_H 8.25 (1H, br s, NH) and 3.74 (2H, br s, NH_2) ppm for the hydrazine NH protons. The methine proton of the proline ring was observed as a doublet of doublets at δ_H 2.93 (1H, dd, *J* 10.3, 5.1 Hz, CH) ppm, whilst the *N*-methyl signal was observed as a singlet at δ_H 2.32 (3H, s, Me). The remaining signals for the proline ring were at δ_H 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, CH_2) ppm. The ^{13}C NMR spectrum gave the desired 6 non-equivalent signals with the methine carbon in the proline ring at δ_C 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 $C_6H_{14}N_3O^+$ ($[M+H^+]$).

We next prepared the Boc-substitued 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)

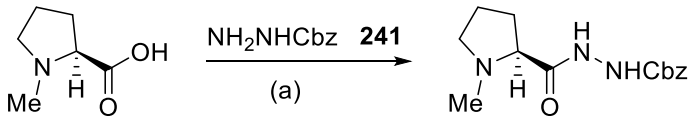


Scheme 80: Preparation of **240**. (a) i) CDI, DMF, 8 h; ii) **239**, rt, 72 h.

The analytical data obtained for **240** confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{20}$ -73.3 whilst the proton NMR spectrum gave a signals at δ_H 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 δ_H 3.00 (1H, dd, *J* 10.2, 4.4 Hz, CH) ppm whilst the methyl signal was observed at δ_H 2.42 (3H, s, Me) ppm and the tert-

butyl at δ_H 1.47 (9H, s, 3 × Me) ppm. The proline methylene was observed at δ_H 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, CH_2) ppm. The ^{13}C NMR spectrum gave the required 9 non-equivalent signals with the methine carbon in the proline ring at δ_C 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 $C_{11}H_{22}N_3O_3^+$ ([$M+H^+$]). 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)



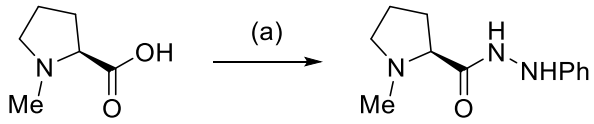
175a **242**

Scheme 81: Preparation of **242**. (a) i) CDI, DMF, 8 h; ii) **241**, rt, 72 h.

The analytical data obtained for **242** confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{21}$ -61.3 whilst the proton NMR spectrum gave signals at δ_H 8.82 (1H, s, NH), and 6.75 (1H, s, NH) ppm for the two NH protons and signals at δ_H 7.41-7.29 (5H, m, CH) ppm for the aromatic ring. The benzyl methylene was observed at δ_H 5.16 (2H, s, CH_2) ppm, whilst the methine proton for the proline was observed as a multipet at δ_H 3.05-2.95 (1H, m, CH) ppm. The methyl signal was observed at δ_H 2.42 (3H, s, Me) ppm, whilst the other proline protons were observed at δ_H 3.15-3.06 (1H, m, CH_5), 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, CH_2) ppm. The ^{13}C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon of the proline appearing at δ_C 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 $C_{14}H_{20}N_3O_3^+$ ([$M+H^+$]).

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)



175a **244**

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 δ_H 8.90 (1H, s, NH) and 6.15 (1H, s, NH) ppm for the NH protons. Signals at δ_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 δ_H 3.07 (1H, dd, *J* 10.2, 4.8 Hz, CH) ppm. The *N*-methyl signal was observed at δ_H 2.47 (3H, s, CH_3) ppm, whilst the remaining signals for the proline ring were at δ_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 δ_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 $C_{12}H_{18}N_3O^+$ ($[M+H^+]$). An X-ray structure was also obtained for **244** (*vide infra*).

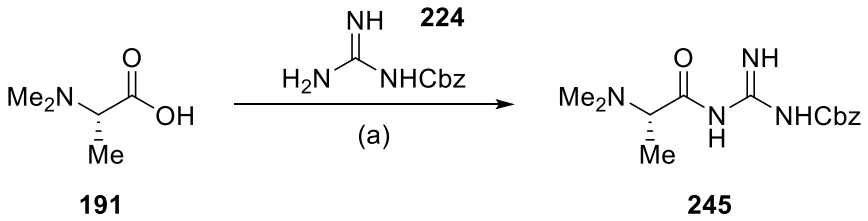
2.2.4 L-Alanine, L-phenylalanine and L-valine catalysts

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

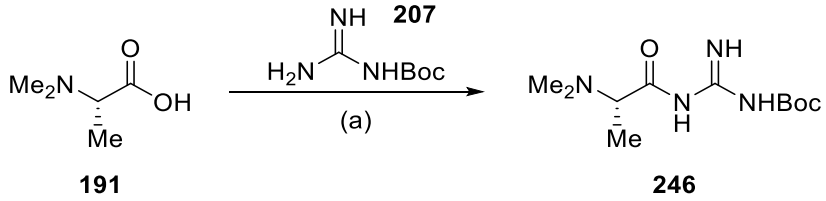
Cbz-guanidine substituted catalyst **245**. Activation of *N*,*N*-dimethyl-L-alanine **191** with CDI in dry DMF over 24 h was followed by the addition of *N*-Cbz-guanidine **224**. After stirring for 4 days at rt an aqueous extraction and purification by column chromatography gave the catalyst **245** 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 δ_H 8.45-10.94 (3H, br s, 3 × NH) ppm for the guanidine NH protons. A multiplet signal at δ_H 7.23-7.41 (5H, m, CH) ppm corresponded to the aromatic ring, whilst the benzyl methylene was observed as a singlet at δ_H 5.11 (2H, s, CH_2) ppm. The methine proton of the alanine was observed as a quartet at δ_H 3.13 (1H, q, *J* 7.0 Hz, CH) ppm, the *N*,*N*-dimethyl amine was observed as singlet at δ_H 2.21 (6H, s, 2 × CH_3) ppm and the methyl signal appeared as a doublet at δ_H 1.19 (3H, d, *J* 7.0 Hz, CH_3) ppm. The ^{13}C NMR spectrum gave the required 11 non-equivalent signals with the methine carbon appearing at δ_C 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 $C_{14}H_{21}N_4O_3^+$ ($[M+H^+]$). An X-ray structure was also obtained for **245** (*vide infra*).

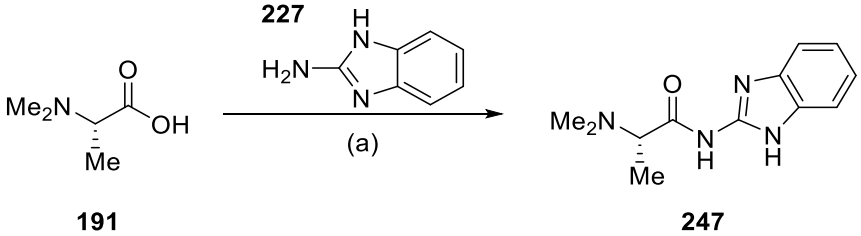
The corresponding *N*,*N*-dimethyl-Boc protected catalyst **246** was prepared in a similar manner, by reaction *N*,*N*-dimethyl alanine **191** with CDI in dry DMF for 6 h at rt followed by the addition of *N*-Boc-guanidine **207**. After stirring for 4 days, aqueous work up and column chromatography 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 δ_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 δ_H 3.12 (1H, q, *J* 6.9 Hz, CH) ppm with the dimethyl groups appearing at δ_H 2.22 (6H, s, 2 × Me) ppm. The *t*-butyl singlet appeared at δ_H 1.49 (3H, s, 3 × Me) ppm whilst the methyl of the alanine residue was a doublet at δ_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 δ_C 64.9 ppm. Finally analysis by mass spectrometry gave ions at 275.2 (100%, [M+H_2O-H]) and 259.2 (43%, $[M+H]^+$), which on accurate mass measurement gave a mass of 259.1768 Daltons which corresponded closely to the required mass of 259.1765 Daltons for $C_{11}H_{23}N_4O_3^+$ ([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)

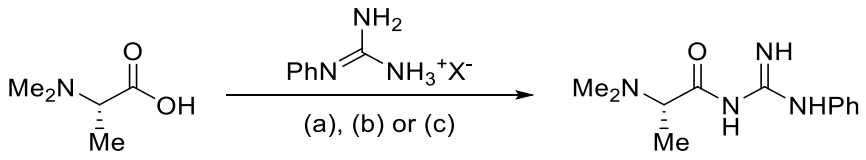


Scheme 85: Preparation of **247**. (a) i) CDI, DMF, rt, 24 h; ii) **227**, rt, 24 h.

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 δ_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 δ_H 7.37-7.50 (2H, m, 2 × CH), and 7.07-7.09 (2H, m, 2 × CH) ppm, whilst the methine proton for alanine was observed as a quartet at δ_H δ 3.32 (1H, q, *J* 6.8 Hz, CH) ppm. The dimethyl group was observed at δ_H 2.28 (6H, s, 2 × CH_3) ppm whilst that of the other methyl group was a doublet at δ_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 δ_C 62.2 ppm. Finally analysis by mass spectrometry gave an ion 233.1 (100%) for $[M+H]^+$, which on accurate mass measurement gave a mass of 233.1404 Daltons which corresponded closely to the required mass of 233.1402 Daltons for $C_{12}H_{17}N_4O^+$ $[M+H^+]$).

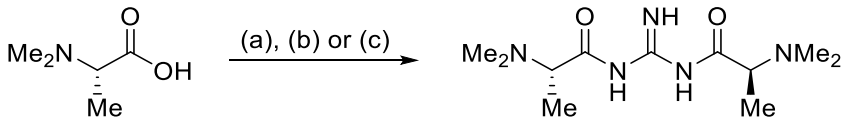
We next attempted the preparation of the corresponding phenyl substituted catalyst **250**. Thus, phenylguanidinium nitrate **203**[106] was added to a suspension of petroleum ether washed NaH in dry DMF and the mixture stirred for 1 h. At this point activated *N*,*N*-dimethyl-L-alanine **191** in DMF 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_2O_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)



191 **250**

Scheme 86: Attempted preparation of **250**. (a) i) CDI, DMF, rt, 24 h; ii) **203**, X = NO_2; NaH, DMF, 1 h; iii) Combine, stir for 4 d. (b) i) CDI, DMF, rt, 6 h; ii) **248**, X = ½.CO_2; NaH, DMF, rt, 6 h; iii) Combine, stir for 12 d. (c) i) CDI, DMF, rt, 24 h; ii) **249**, X = Cl; NaH, DMF, rt, 24 h; iii) then combine, stir for 6 d.

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)



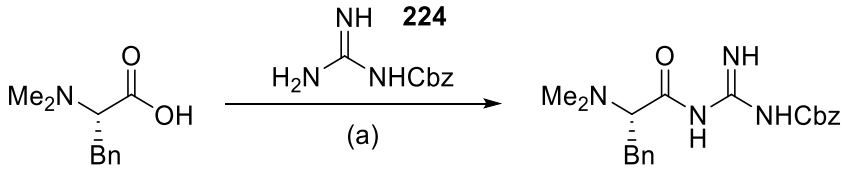
191 **251**

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 *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 *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 *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)

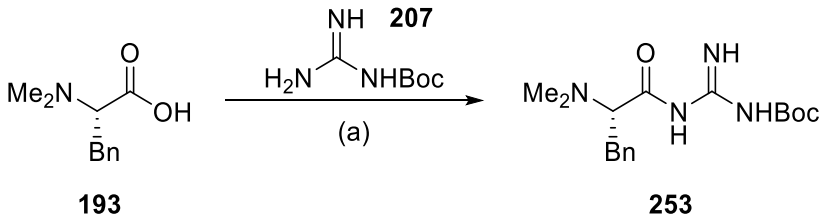


193 **252**

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 δ_H 7.99-10.49 (3H, br s, 3 × NH) ppm for the guanidine NH protons and a complex multiplet at δ_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 δ_H 5.05 (2H, s, CH_2) ppm whilst the benzyl methylene of alanine was observed as of two double doublets at δ_H 3.04 (1H, dd, *J* 14.0, 7.4 Hz, CH), and 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 δ_H 3.36 (1H, dd, *J* 7.4, 5.8 Hz, CH) ppm, whilst the *N,N*-dimethyl signals were at δ_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 δ_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 $C_{20}H_{25}N_4O_3^+$ ($[M+H^+]$). An X-ray structure was also obtained for **252** (*vide infra*).

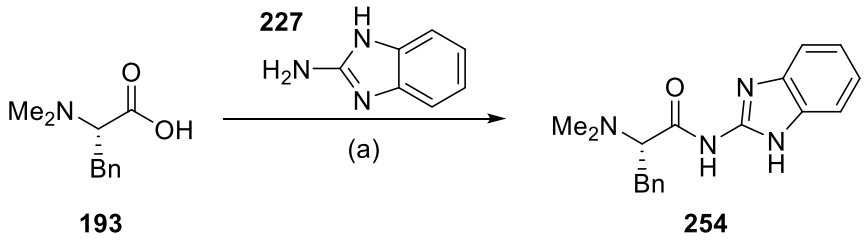
Similarly the Boc-protected catalyst was prepared by activating the *N*,*N*-dimethyl-L-phenylalanine **193** with CDI in dry DMF over 24 h followed by the addition of *N*-Boc-guanidine **207**. After 13 days, an extractive work-up and column chromatography gave **253** in 87% yield as a white solid.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



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

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 δ_H 8.95 (3H, br s, 3 × NH) ppm for the guanidine NH protons and a signals at δ_H 7.30-7.15 (5H, m, CH) ppm for aromatic protons. The methine proton for the phenylalanine was observed as a multiplet at δ_H 3.42-3.35 (1H, m, CH) ppm whilst the benzyl methylene of phenylalanine was observed as two double doublets signals at δ_H 3.08 (1H, dd, *J* 14.0, 7.4 Hz, CH), and 2.88 (1H, dd, *J* 14.1, 5.9 Hz, CH_2) ppm. The *N*,*N*-dimethyl was observed at δ_H 2.27 (6H, s, 2 × CH_3) ppm whilst the tert-butyl was a singlet at δ_H 1.47 (3H, s, 9H) ppm. The ^{13}C NMR spectrum gave the required 12 non-equivalent signals with the methine carbon observed at δ_C 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 $C_{17}H_{27}N_4O_3^+$ ($[M+H^+]$).

The 2-aminobenzimidazole catalyst, **254** was similarly prepared by activating *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)

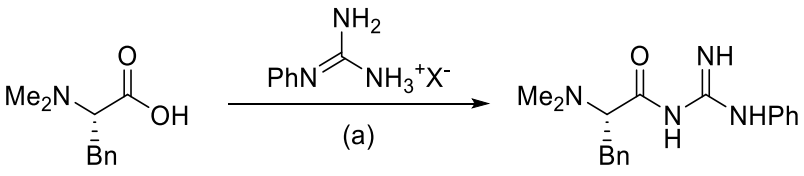


193 254

Scheme 90: Preparation of **254**. (a) i) CDI, DMF, rt, 24h; ii) **227**, rt, 7 days.

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 δ_H 10.32 (2H, br s, 2 × NH) ppm for the guanidine NH protons. Signals at δ_H 7.44-7.46 (2H, m, 2 × CH), and 7.13-7.25 (7H, m, Ph, 2 × CH) ppm corresponded to the aromatic protons, whilst the methine proton for the phenylalanine was observed as a double doublets at δ_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 δ_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 δ_H 2.35 (6H, s, 2 × CH_3) ppm. The ^{13}C NMR spectrum gave the 11 non-equivalent signals with the methine in the proline ring at δ_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 $C_{18}H_{21}N_4O^+$ ($[M+H^+]$).

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)

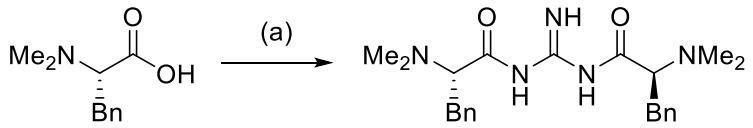


193 255

Scheme 91: Preparation of **255**. (a) i) CDI, DMF, rt, 24 h; ii) **248**, X = ½ CO_2, NaH, DMF, rt, 24 h; iii) Combine, stir 4 d.

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 δ_H 7.09-7.51 (11H, m, NH, NH_2, Ph, 3 × CH) ppm for both the guanidine NH protons with the other aromatic protons at δ_H 7.02 (2H, br d, *J* 8.0 Hz, 2 × CH) ppm. The aliphatic methine proton was observed as a double doublet at δ_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 δ_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 δ_H 2.38 (6H, s, 2 × CH_3) ppm. The ^{13}C NMR spectrum gave the required 13 non-equivalent signals with the aliphatic methine carbon appearing at δ_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** (*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)



193 **256**

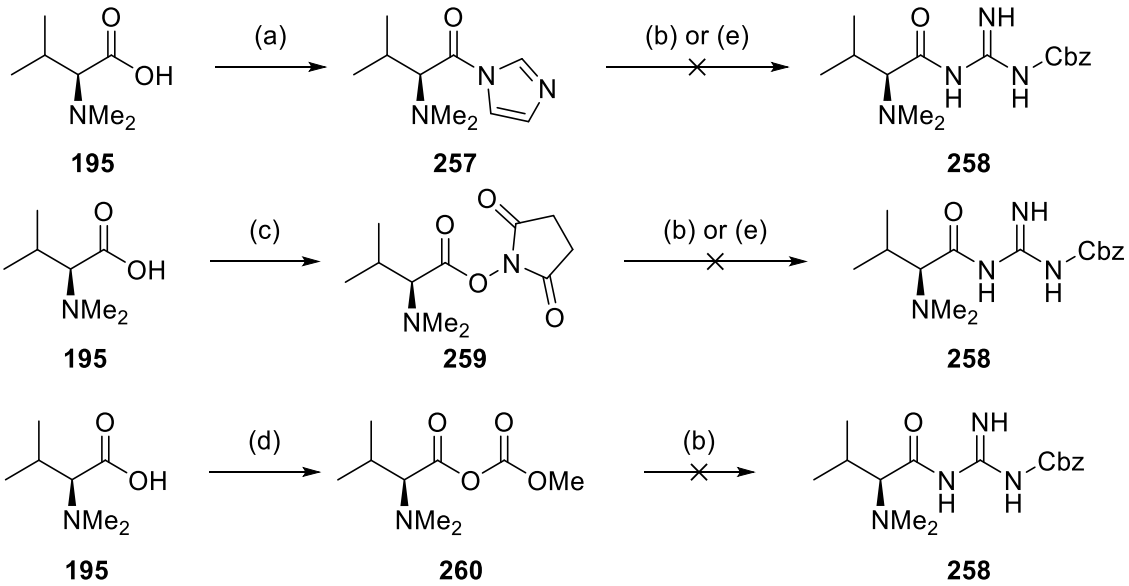
Scheme 92: Preparation of **256**. (a) i) CDI, DMF, rt, 24 h; ii) Guanidine hydrochloride **206** (0.5 equiv.), NaH, DMF, 24 h; iii) combine, stir, 7 d.

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 δ_H 8.06-10.70 (3H, br s, 3 × NH) ppm for the guanidine NH protons and signals at δ_H 7.20-7.24 (10H, m, 2 × Ph) ppm for the aromatic protons. The aliphatic methine proton was observed at δ_H 3.39 (2H, dd, *J* 8.5, 5.3 Hz, 2 × CH) ppm, whilst benzyl methylene appeared as two double doublets at δ_H 3.12 (2H, dd, *J* 13.6, 8.6 Hz, 2 × CH), 2.98 (2H, dd, *J* 13.6, 5.3 Hz, 2 × CH)

ppm. The dimethyl phenylalanine groups appear as a singlet at δ_H 2.41 (6H, s, 2 × Me). The ^{13}C NMR spectrum gave the required 9 non-equivalent signals with the methine carbon appearing at δ_C 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 $[C_{23}H_{32}N_5O_2]^+$ ($[M+H]^+$).

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)

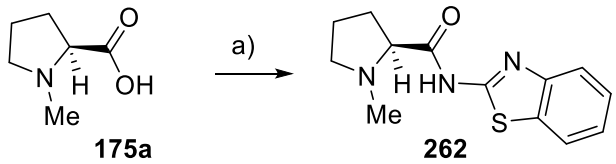


Scheme **93:** Attempted preparation of **258**. (a) CDI, DMF, 24 h. (b) **224**, 48 h. (c) NHS, HBTU, DMF, 0 °C . 30 min. (d) Methyl chloroformate, THF, Et_3N, 0 °C, 2 h. (e) **207**, **224** or **227**, THF, reflux 48 h.

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)



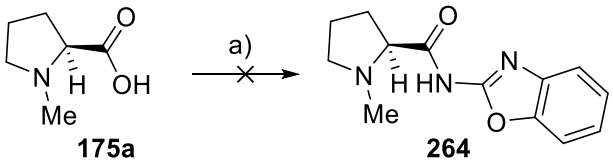
175a **262**

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

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 δ_H 9.82-11.72 (1H, br s, NH) ppm for the NH proton. The aromatic protons appeared at δ_H 7.82 (1H, d, *J* 7.9 Hz, CH), 7.78 (1H, d, *J* 8.1 Hz, CH), 7.44 (1H, dd, *J* 8.1, 7.5 Hz, CH), and 7.31 (1H, dd, *J* 7.9, 7.5 Hz, CH), whilst the methine proton of the proline was observed as a multiplet at δ_H 3.17-3.30 (2H, m, 2 × CH) ppm. The *N*-methyl group was observed at δ_H 2.49 (3H, s, CH_3) ppm, whilst the methylene protons appeared at δ_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, CH_2) ppm. The ^{13}C NMR spectrum gave the required 13 non-equivalent signals with the methine carbon in the proline ring at δ_C 68.5 ppm. Finally analysis by mass spectrometry gave an ion 262.1 (98%, $[M+H]^+$), which on accurate mass measurement gave a mass of 262.1011 Daltons which corresponded well to the required mass of 262.1009 Daltons for $C_{13}H_{16}N_3OS^+$ ($[M+H^+]$).

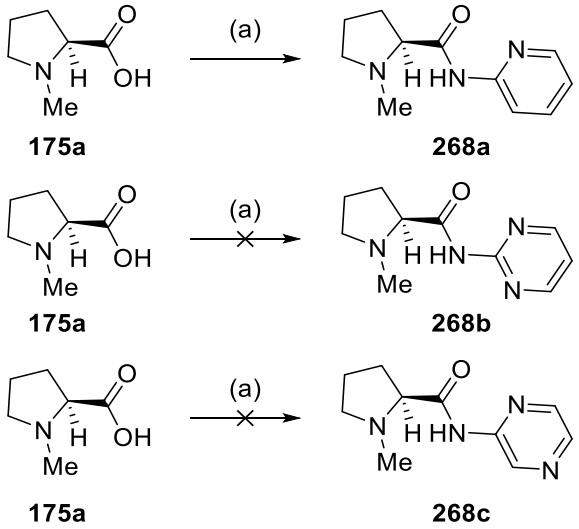
We also attempted to prepare the analogous benzoxazole catalyst **264** under identical conditions, however treatment of a CDI activated solution of *N*-methyl-L-proline **175a** with 2-aminobenzoxazole **263** did not lead to the formation of the desired product. Repeating the reaction under longer 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 nucleophilicitiy 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 nucleophilicitiy 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)

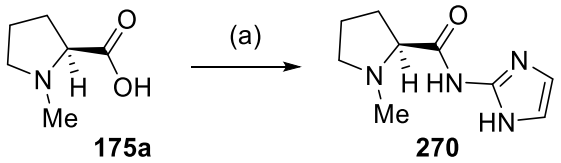


Scheme 96: Preparation of **268a-c**. (a) i) CDI, DMF, 24 h; ii) **265**, **266** or **267**, rt, 7 d.

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 δ_H 9.85 (1H, br s, NH) ppm for the NH proton. The aromatic ring protons signals were observed

at δ_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 δ_H 2.99-3.10 (1H, m, CH) ppm, whilst the *N*-methyl signal was at δ_H 2.46 (3H, s, Me) ppm. The remaining signals for the proline ring were observed at δ_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 δ_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 $C_{11}H_{16}N_3O^+$ ($[M+H]^+$).

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)



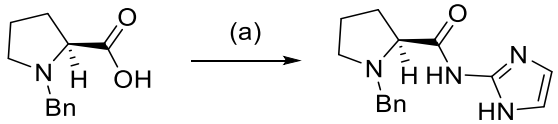
175a **270**

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 δ_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 δ_H 6.82 (2H, s, 2 × CH) ppm, whilst the methine proton for the proline was observed as double of doublets at δ_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 δ_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 δ_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 $C_9H_{15}N_4O^+$ ($[M+H^+]$).

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)



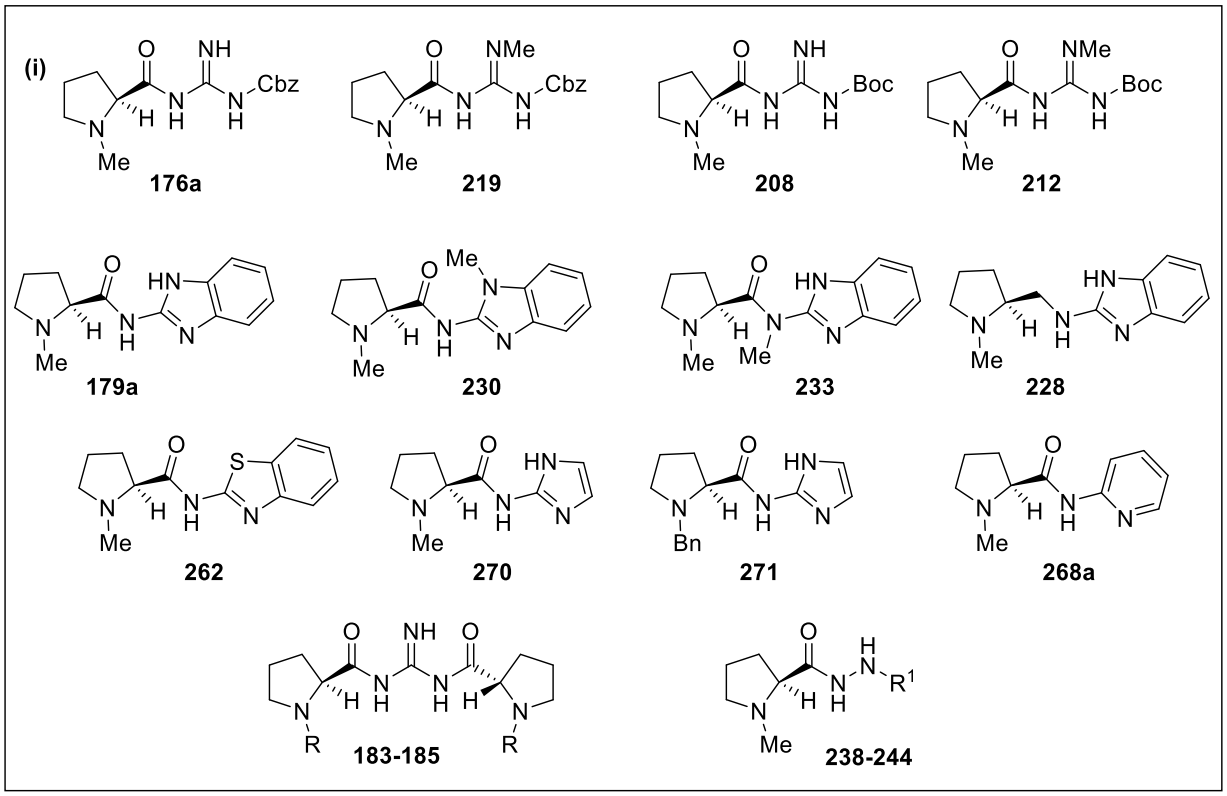
175b **271**

Scheme 98: Preparation of **271**. (a) i) CDI, DMF, 24 h; ii) **269**, NEt_3, rt, 2 h; iii) rt, 24 h

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 δ_H 9.38-11.51 (2H, br m, 2 × NH) ppm for the imidazole NH protons. The aromatic ring protons for the benzyl groups were observed at δ_H 7.15-7.31 (5H, m, Ph) ppm, whilst the imidazole CH protons were a singlet at δ_H 6.76 (2H, s, 2 × CH). Signals at δ_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 δ_H 3.31 (1H, dd, *J* 10.4, 4.2 Hz, CH) ppm. The remaining signals of the proline ring were at δ_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 × 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 δ_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 $C_{15}H_{18}N_4ONa^+$ ($[M+Na]^+$). 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.



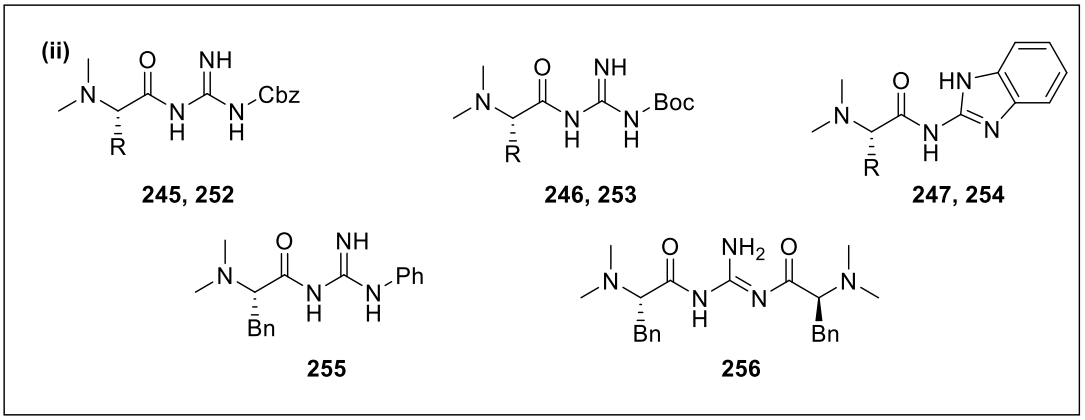
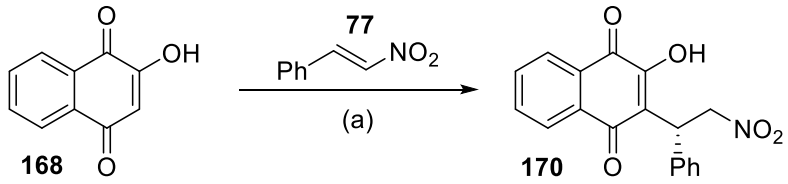


Figure 23: Catalysts prepared in this chapter

2.4 The Michael addition reaction of 2-hydroxy-1,4-naphthoquinone to *β*-nitrostyrene

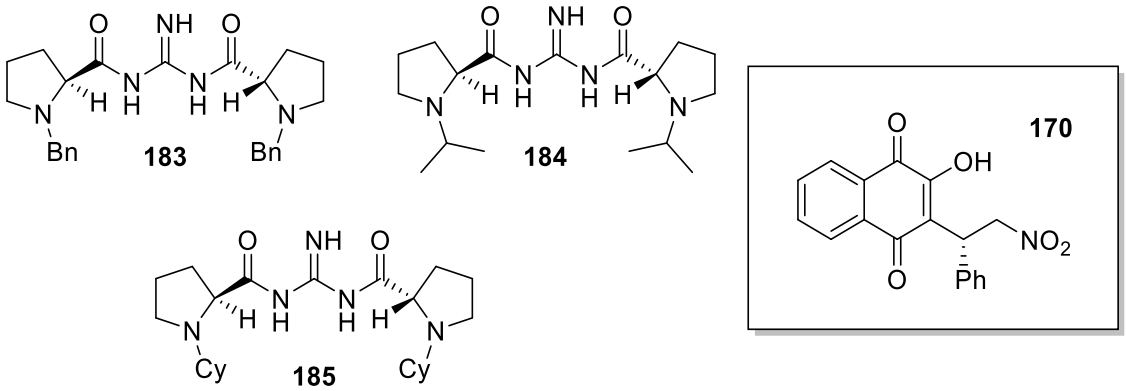
As previously stated, the initial aim of this project was to prepare a range of C_2-symmetrical catalysts to study their application to asymmetric transformations. To this end, the Michael reaction between *β*-nitrostyrene **77** with 2-hydroxy-1,4-naphthoquinone **168** was found to be a robust reaction 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.[85,86] 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 ^{1}H 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.[85, 86]



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

We firstly investigated the C_2-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 ^{1}H 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

1, entries 3c). The reasons for the low ee in these reactions probably stems from observations made in the previous study[97] that increasing the steric hindrance at the *N*-substituient 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**

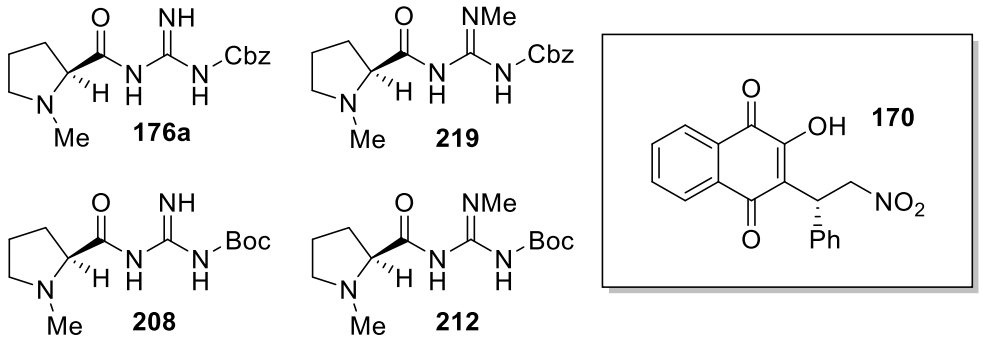
Table 1: Entries and results.

Entry[i]	Cat.	Cons.	DCM	MeCN	THF	PhMe	Xylenes	PhH
1	**183**	a	6 (96/91)	----	----	----	7 (24/82)	----
		b	4 (48/92)	----	----	----	----	----
2	**184**	a	4 (29/81)	4 (5/60)	4 (72/80)	4 (5/48)	4 (5/67)	4 (5/37)
		b	3 (5/48)	----	----	4 (5/53)	----	----
3	**185**	a	1(46/100)	2 (24/87)	1 (144/91)	2 (72/39)	2 (48/65)	2 (72/75)
		b	7 (48/89)	----	----	----	----	----
		c	1 (24/63)	----	----	1 (24/41)	1 (24/53)	----

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[97] 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.

Entry[i]	Cat.	Cons.	DCM	PhMe	Xylene	Et_2O	PhH	CCl_4
1	**176a**	a	37 (88/99)	44 (100/75)	----	----	26 (72/48)	----
		b	13 (61/50)	17 (2/45)	9 (18/81)	----	28 (18/36)	----
2	**219**	a	5 (120/65)	4 (46/7)	----	1 (120/22)	----	----
3	**208**	a	19 (28/75)	22 (2/89)	22 (2/80)	19 (124/80)	17 (4/90)	21 (28/64)
		b	28 (168/63)	37 (48/90)	----	----	----	----
		c	----	18 (24/38)	----	----	----	----
4	**212**	a	9 (120/86)	7 (48/70)	4 (48/91)	5 (120/54)	7 (48/85)	3 (120/55)

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

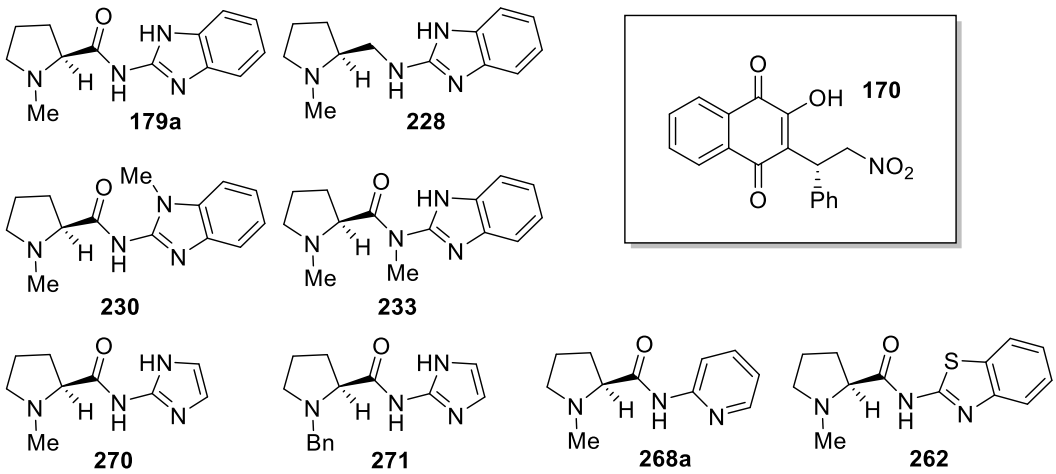
The analogous Boc-substituted catalyst **208** was also studied, which gave broadly comparative results with catalyst **208** (Table 2, entry 3a-c), however in dichloromethane and toluene reactions the ee's were lower at 19% and 22% respectively. Despite this we observed that the rate of reaction appeared 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 study[97] (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).

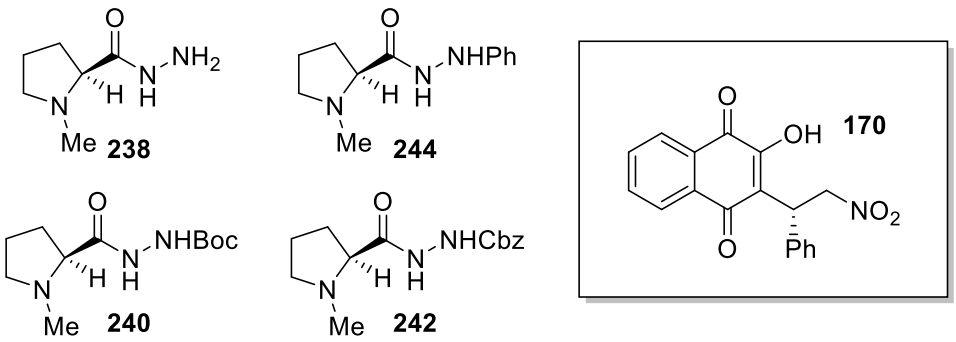
Table 3: Entries and results.

Entry[i]	Cat.	Cons.	DCM	PhMe	Xylenes	Et_2O	PhH
1	**179a**	a	27 (38/88)	32 (100/87)	----	----	----
2	**230**	a	4 (48/91)	5 (49/86)	----	3 (120/55)	----
3	**233**	a	6 (120/75)	14 (48/19)	10 (22/48)	8 (48/48)	10 (48/80)
4	**228**	a b	5 (21/82) 21 (28/54)	7 (3.5/66) 21 (21/74)	---- ----	---- ----	---- ----
5	**270**	a	16 (100/69)	16 (120/54)	----	----	----
6	**271**	a	13 (96/70)	5 (96/67)	----	----	----
7	**268a**	a	2 (48/78)	2 (48/16)	----	----	0 (48/87)
8	**262**	a	3 (48/25)	0 (48/14)	----	----	4 (48/37)

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

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)



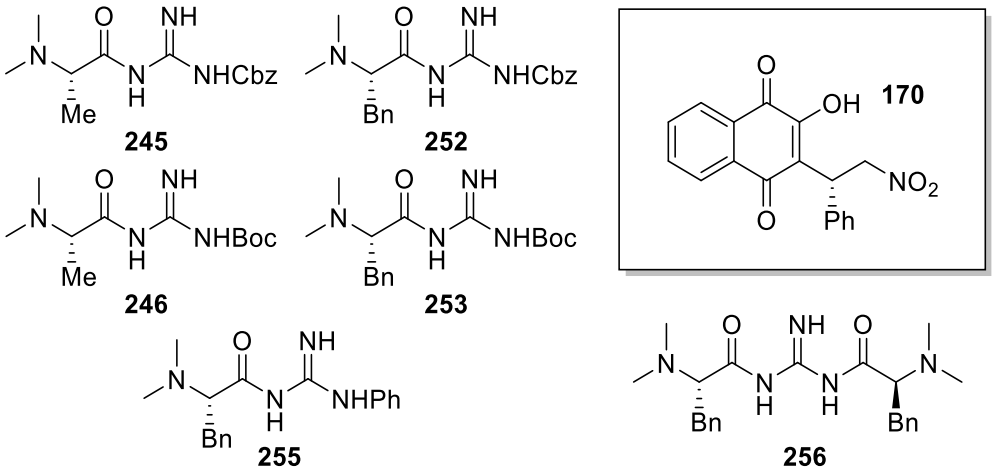
Scheme 103: Formation of **170** using catalysts **238**, **240**, **242** and **244**: Conditions: Catalyst (0.1 equiv.) then either (a) 0 °C, 7-8 h then rt or (b) -78 °C - -20 °C, see table 4

Table 4: Entries and results.

Entry[i]	Cat.	Conds.	DCM	PhMe	Xylenes	Et_2O	PhH
1	**238**	a	3 (100/70)	5 (2/71)	4 (72/68)	4 (124/41)	NR
2	**244**	a	3 (48/87)	3 (1/86)	3 (1/59)	----	2 (1/56)
		b	----	17 (24/63)	----	----	----
3	**240**	a	4 (168/42)	13 (168/19)	10 (168/10)	2 (168/28)	9 (168/71)
4	**242**	a	2 (10/66)	10 (10/27)	5 (48/74)	4 (96/36)	8 (10/72)
		b	3 (48/80)	----	----	----	----

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)



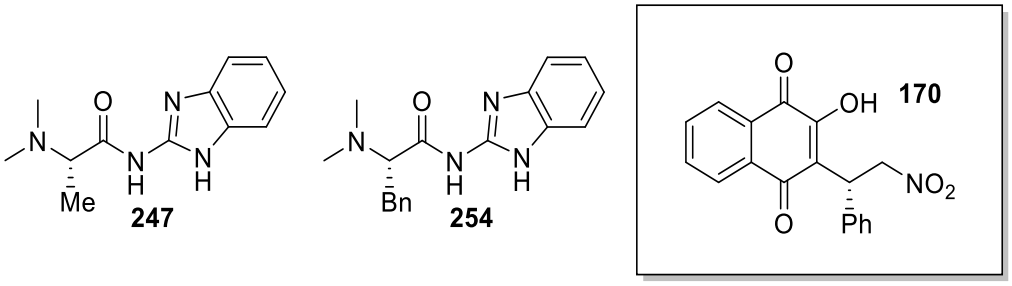
Scheme 104: Formation of **170** using catalysts **245**, **252**, **246**, **253**, **255** and **256**: Conditions: Catalyst (0.1 equiv.) then either (a) 0 °C, 7-8 h then rt, or (b) with (BA); or (c); -78 °C - -20 °C; see table 5

Table 5: Entries and results.

Entry[i]	Cat.		DCM	PhMe	Xylenes	THF	Et_2O	PhH	CCl_4
1	**245**	a b	7 (96/88) 7 (96/88)	13 (18/88) ----	10 (40/65) ----	9 (96/60) ----	8 (96/69) ----	10(18/75) ----	7 (96/67) ----
2	**252**	a b c	4 (28/92) 7(120/34)	15 (72/43) 25 (2/67) 22 (10/54)	15 (72/33) 21 (2/44) ----	6 (72/99) ---- ----	6 (48/43) ---- ----	9 (2/97) ---- ----	7 (99/75) ---- ----
3	**246**	a b	10 (44/65) 8 (24/75)	11 (20/40) -----	15 (20/39) ----	10 (72/77) ----	10 (20/44) ----	11 (20/54) ----	11 (44/76) ----
4	**253**	a b c	9 (8/49) ---- -----	18 (1/46) 30 (48/91) 31(10/40)	20 (15/41) ---- ----	15 (10/85) ---- --------	11 (10/57) ---- ----	13 (15/63) ---- ----	6 (8/89) ---- ----
5	**255**	a	18 (8/81)	21 (10/96)	21 (8/100)	21 (10/66)	----	21 (10/76)	18 (10/36)
6	**256**	a c	21 (2/67) 25(24/33)	23 (2/59) 25 (72/42)	24 (2/61) ----	21 (18/95) ----	---- ----	25 (2/54) ----	---- ----

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.

Entry[i]	Cat.	DCM	PhMe	Xylenes	THF	Ether	PhH	CCl_4
1	**247**	10 (168/88)	16 (168/37)	14 (168/48)	10 (168/54)	9 (168/88)	----	9 (168/67)
2	**254**	10 (120/79)	20 (120/57)	28 (120/41)	17 (120/75)	9 (120/81)	9 (72/65)	15 (72/49)

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

2.5 Conclusions.

The previous work in this area[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 **183**, **184** and **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 **208** + BA, **184** + BA, **185** + BA, **244**, **252** + BA, **253** and **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.[107] Jeffrey[108] 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 it 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 NH_2. In the case of **177a** and **179a** where no carbamate is present there is an *E*-ab 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 ^{13}C 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)

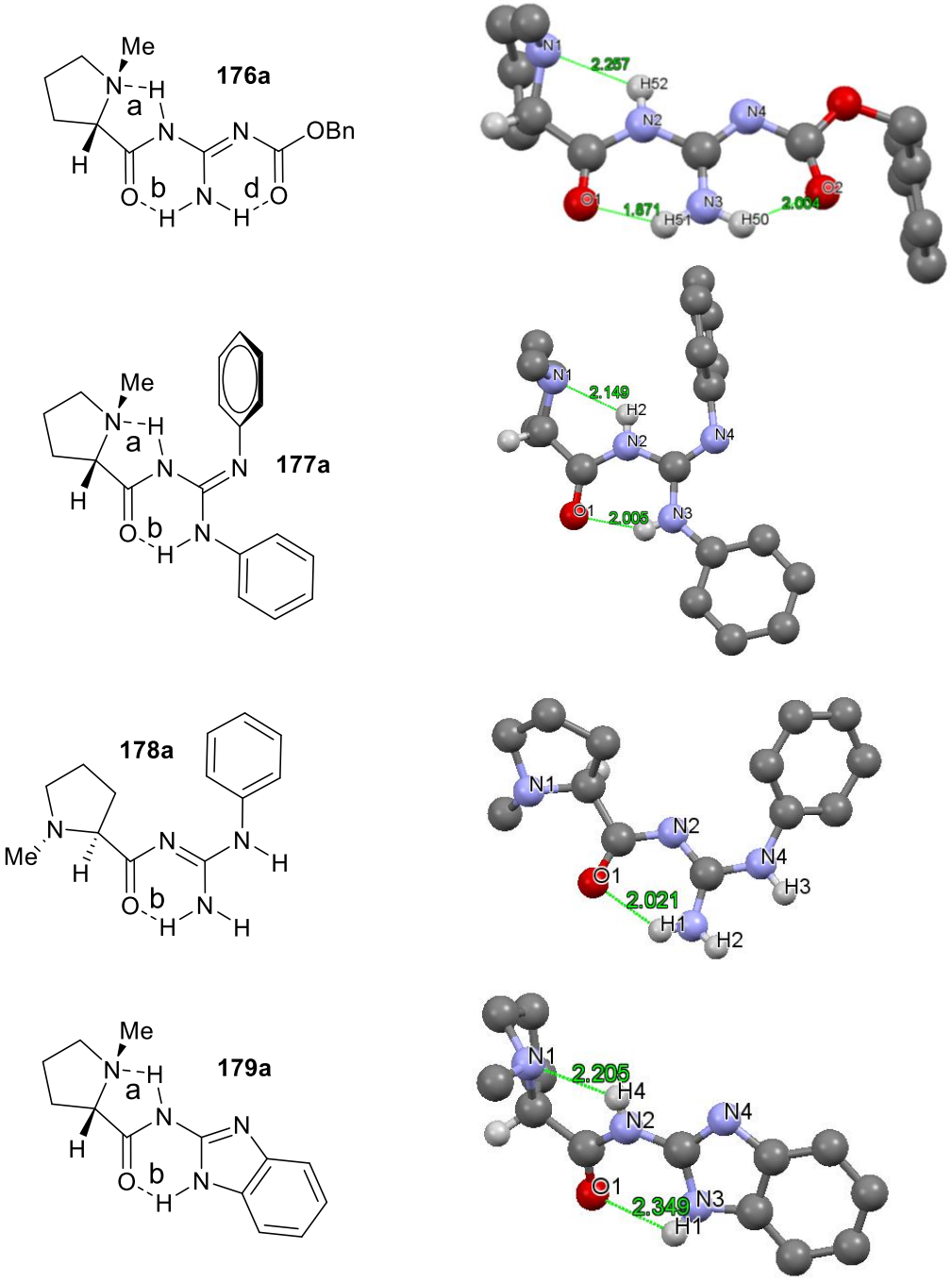


Figure 24: X-Ray structure of compounds **176a**, **177a**, **178a** and **179a**.[97]

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).

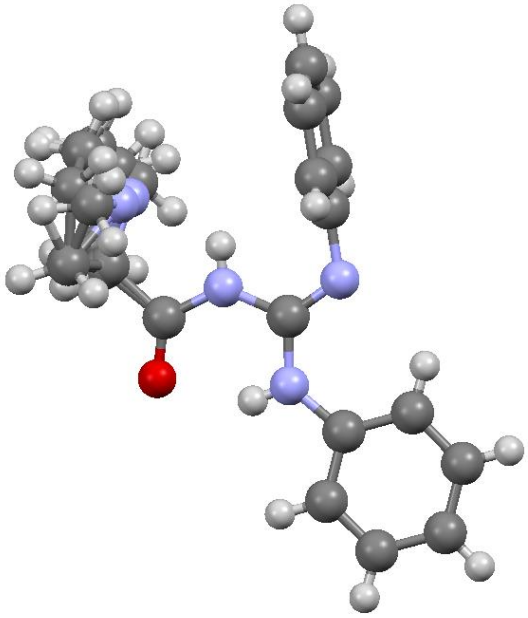


Figure 25: The *S*:*R* epimeric mixture observed for **177a**.[97]

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)

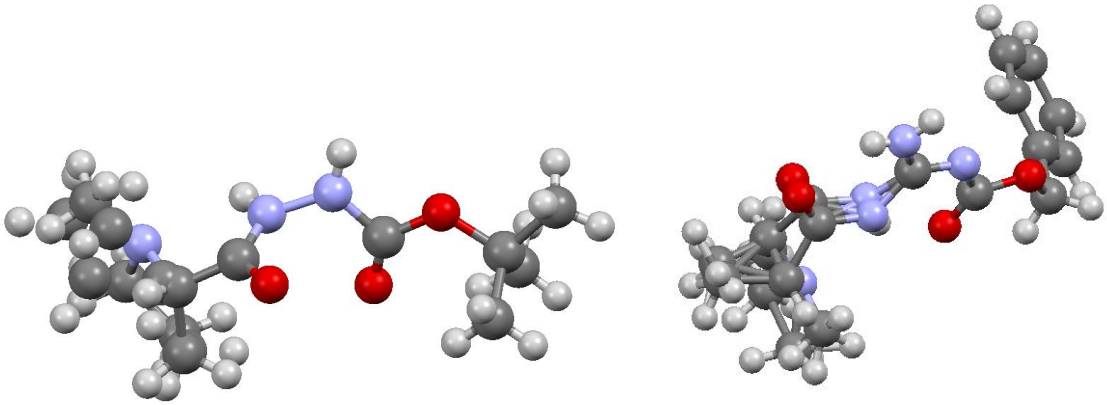
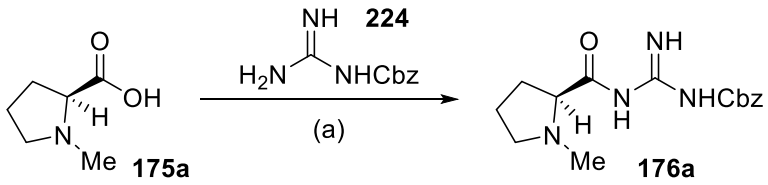


Figure 26: X-Ray structure of compounds **240** and **245**.

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

procedure.[88] We investigated the epimerization of several of the catalysts by NMR in deuterated methanol under neutral, weakly basic (NEt_3) and acidic ($PhCO_2H$) 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[109] 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)



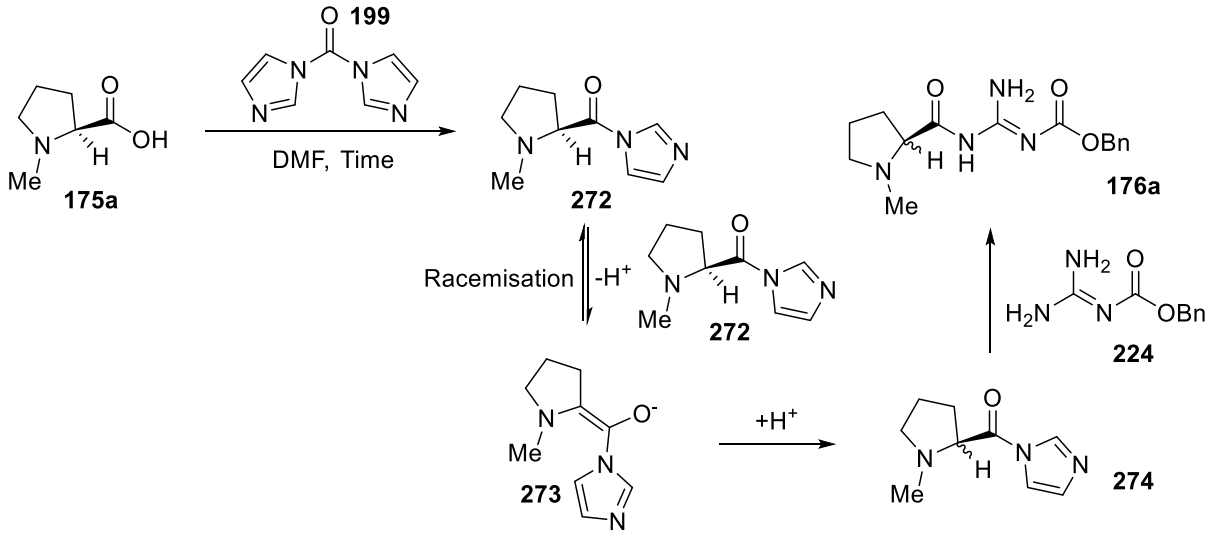
Scheme 106: (a) i) **175a**, CDI, DMF, 5 min/1 h/24 h, rt; ii) **224**, 24h.

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

Activation time	ee/%[i] (HPLC)	$[\alpha]_D$	% yield
5 min	87	-70	47
60 min	57	-41	48
24 h	33	-24	53

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 form 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)

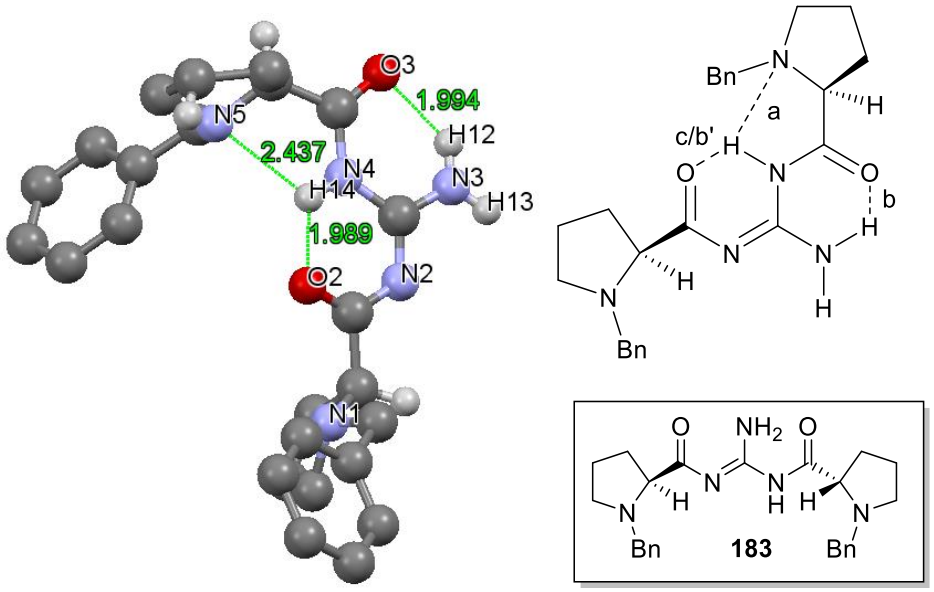


Figure 27: X-ray structure of **183** (2016ncs0617)

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)

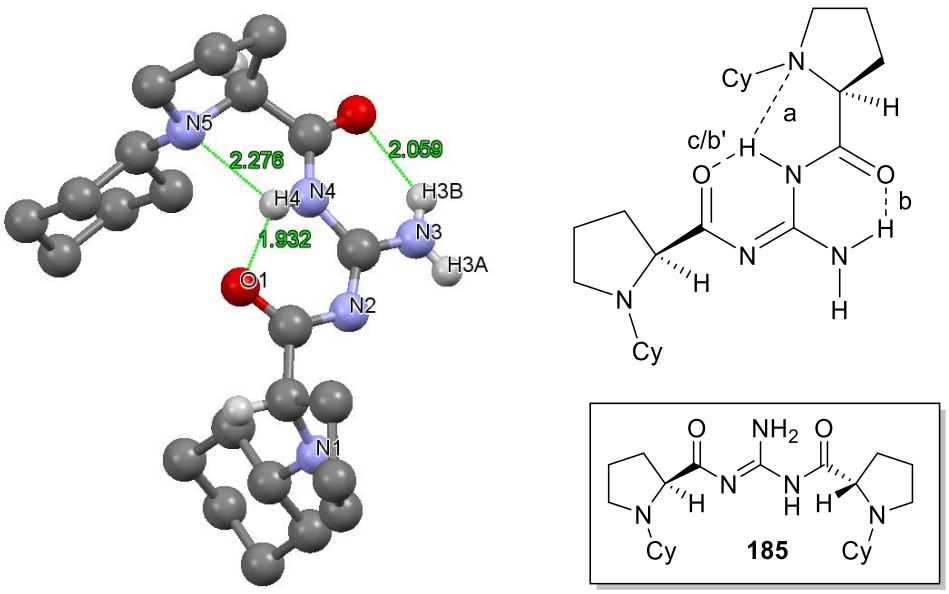


Figure 28: X-ray structure of **185** (2016ncs0616)

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.[97] 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)

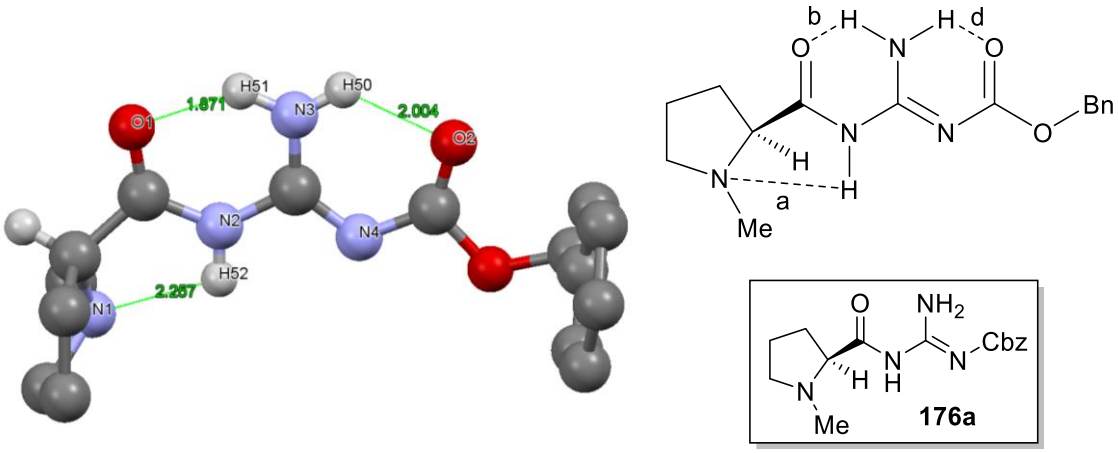


Figure 29: X-ray structure of **176a** (2016ncs0664)

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)

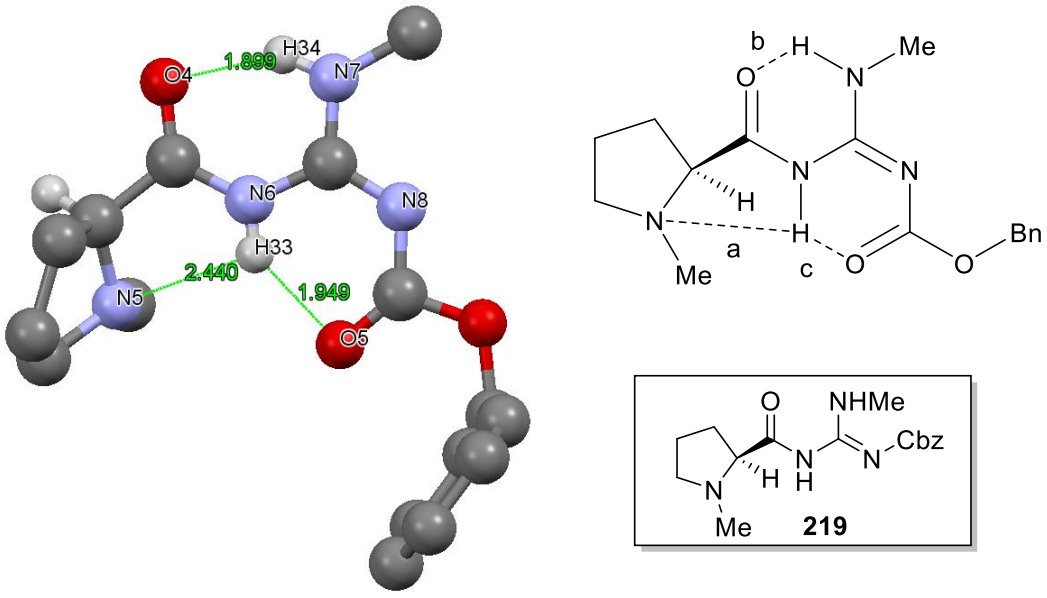


Figure 30: X-ray structure of **219** (2017ncs0425)

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 un-methylated case. (Figure 31)

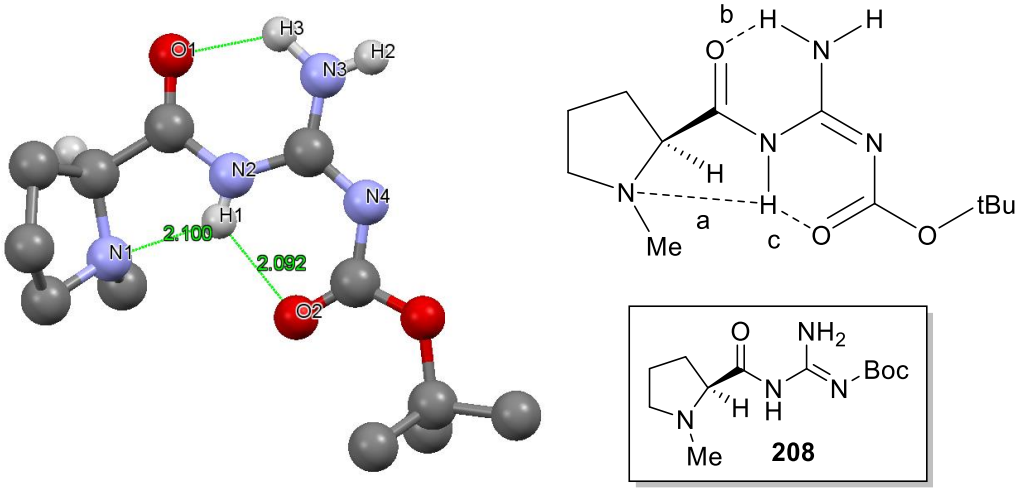


Figure 31: X-ray structure of **208** (2017ncs0423)

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)

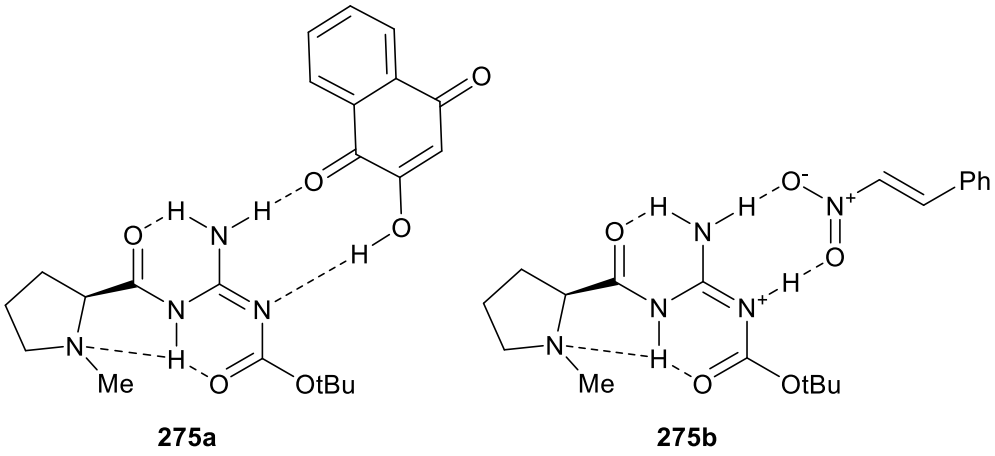


Figure 32: Possible H-bonding modes of catalyst **208**.

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)

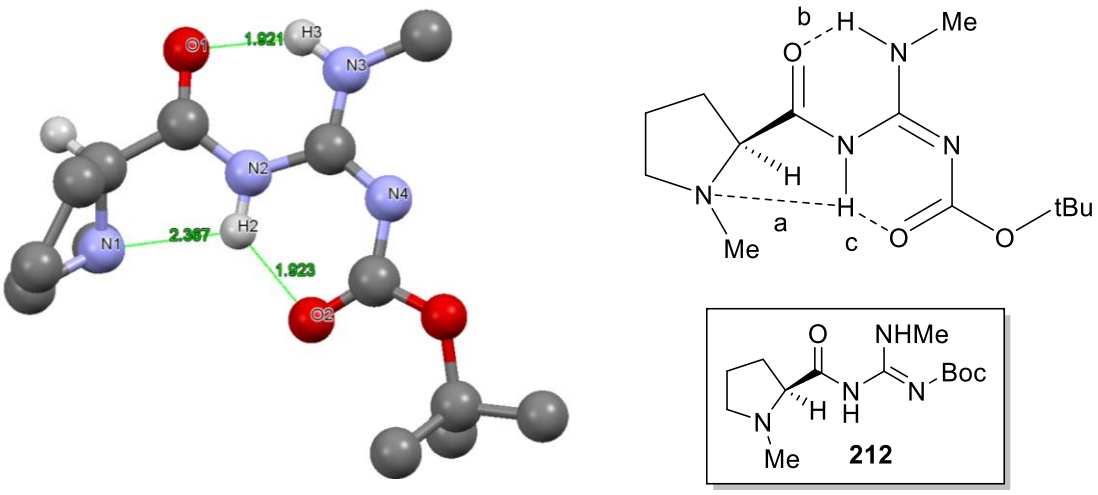


Figure 33: X-ray structure of **212** (2017ncs0528)

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)…01 = 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)

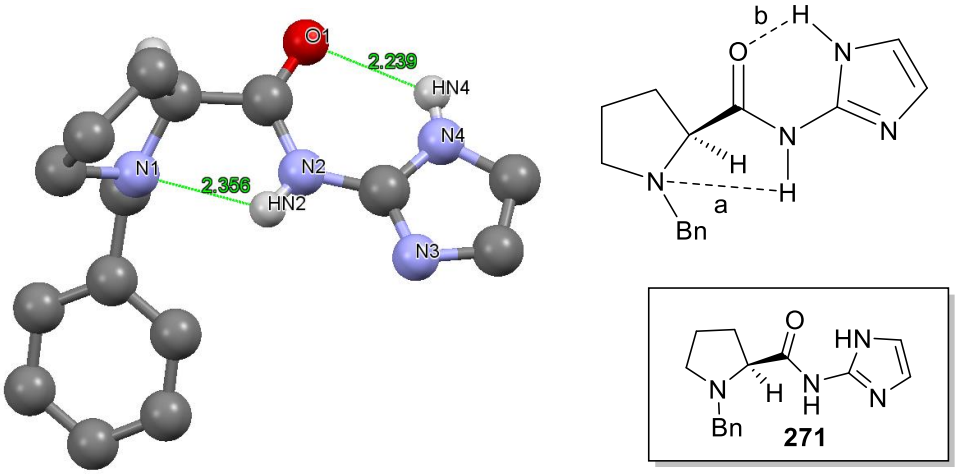


Figure 34: X-ray structure of **271** (2018ncs0156)

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).

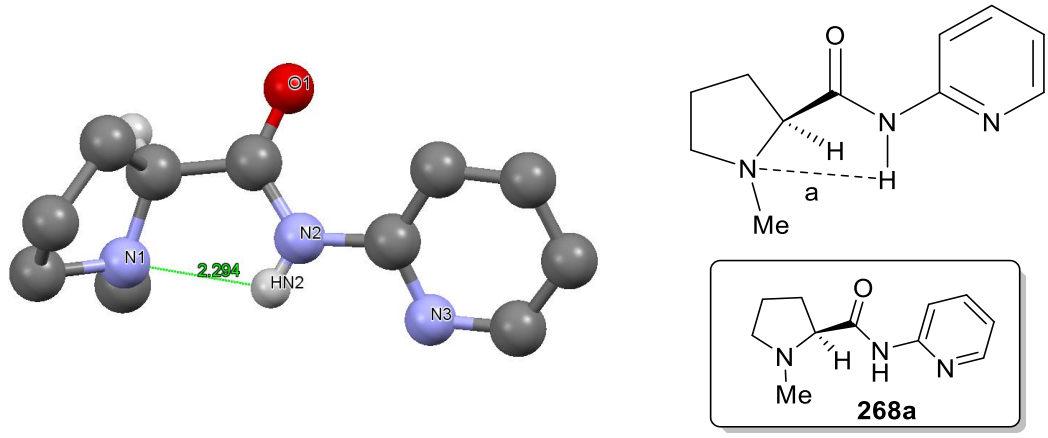


Figure 35: X-ray structure of **268a** (2017ncs0802)

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).

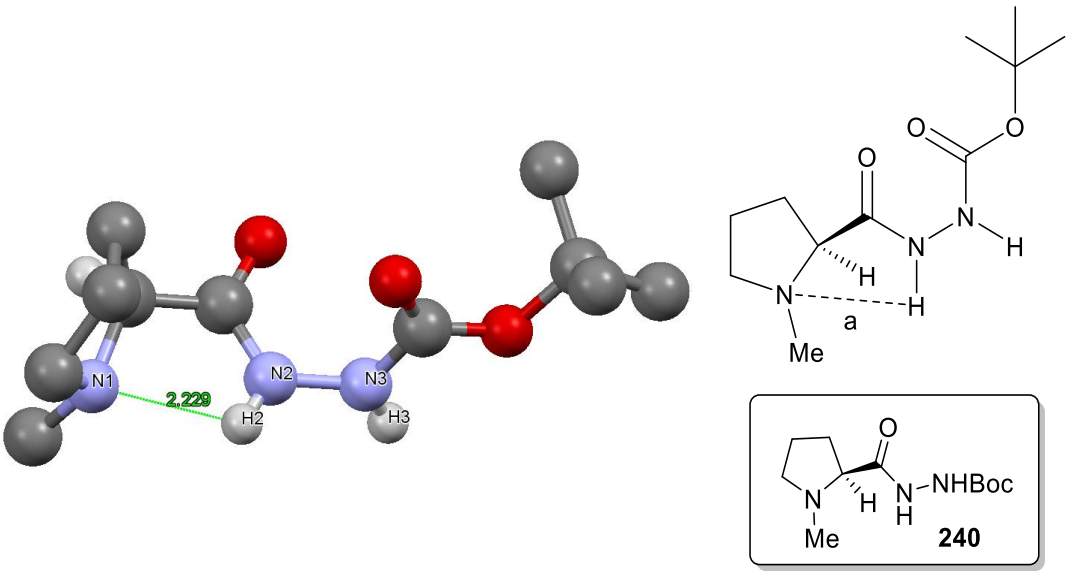


Figure 36: X-ray structure of **240** (2017ncs0860)

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).

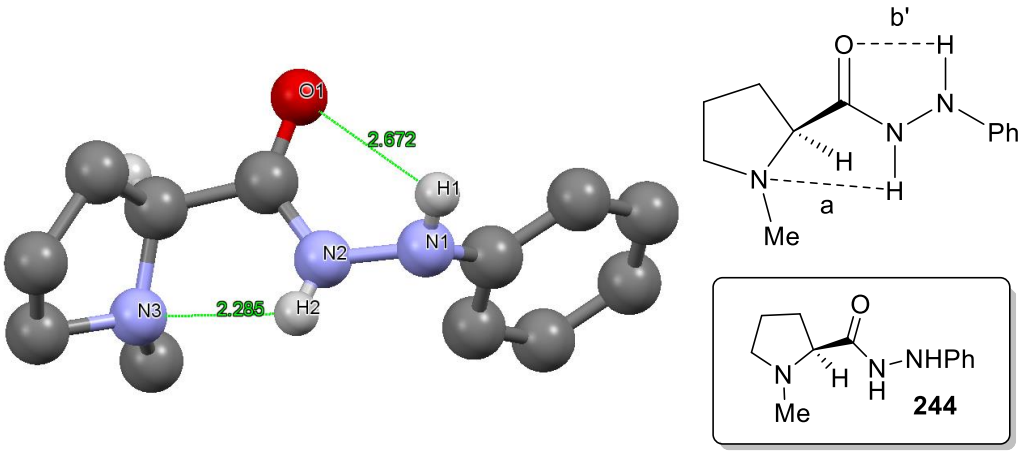


Figure 37: X-ray structure of **244** (2019ncs0081)

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)

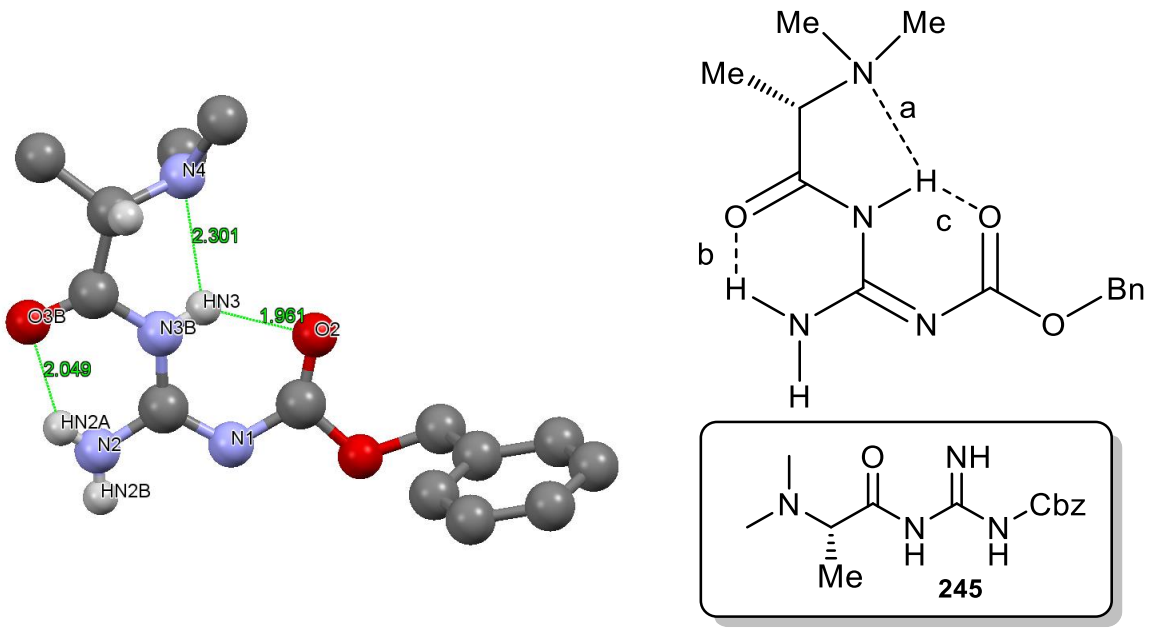


Figure 38: X-ray structure of **245** (2017ncs0681)

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 NH_2 and the Cbz-carbonyl (bond d; N2B(HN2A)…O2 = 1.977 Å), which again was the shortest H-bond of the three. (Figure 39)

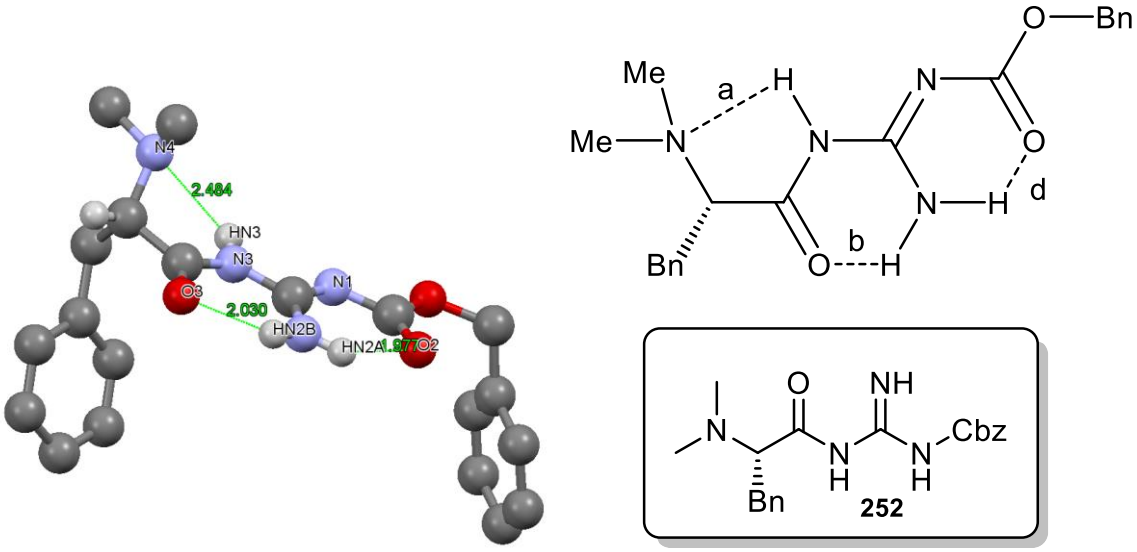


Figure 39: X-ray structure of **252** (2017ncs0682)

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)

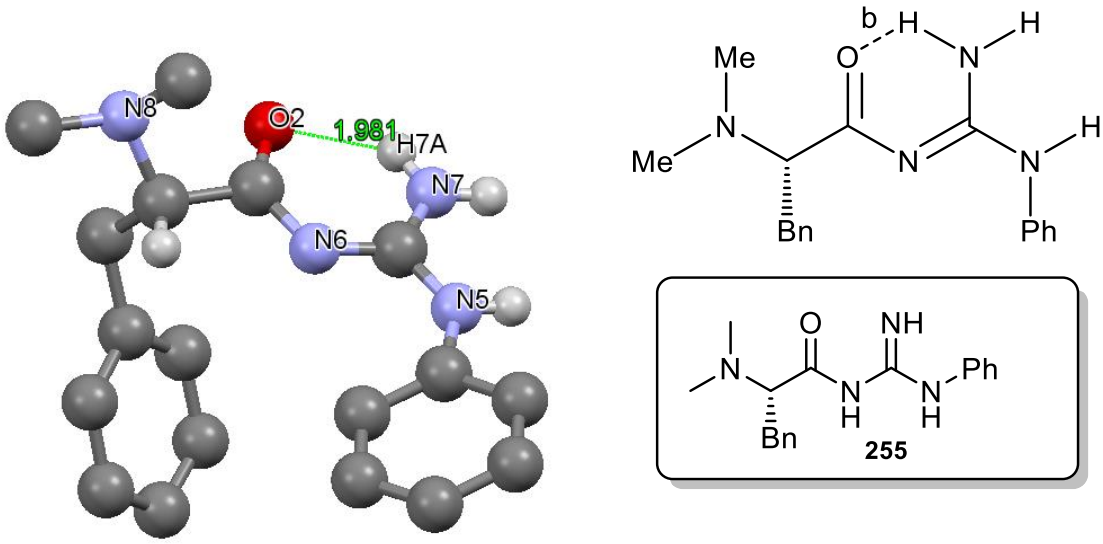
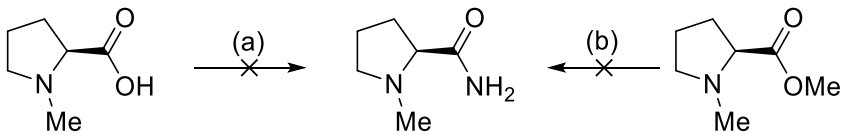


Figure 40: X-ray structure of **255** (2018ncs0072)

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

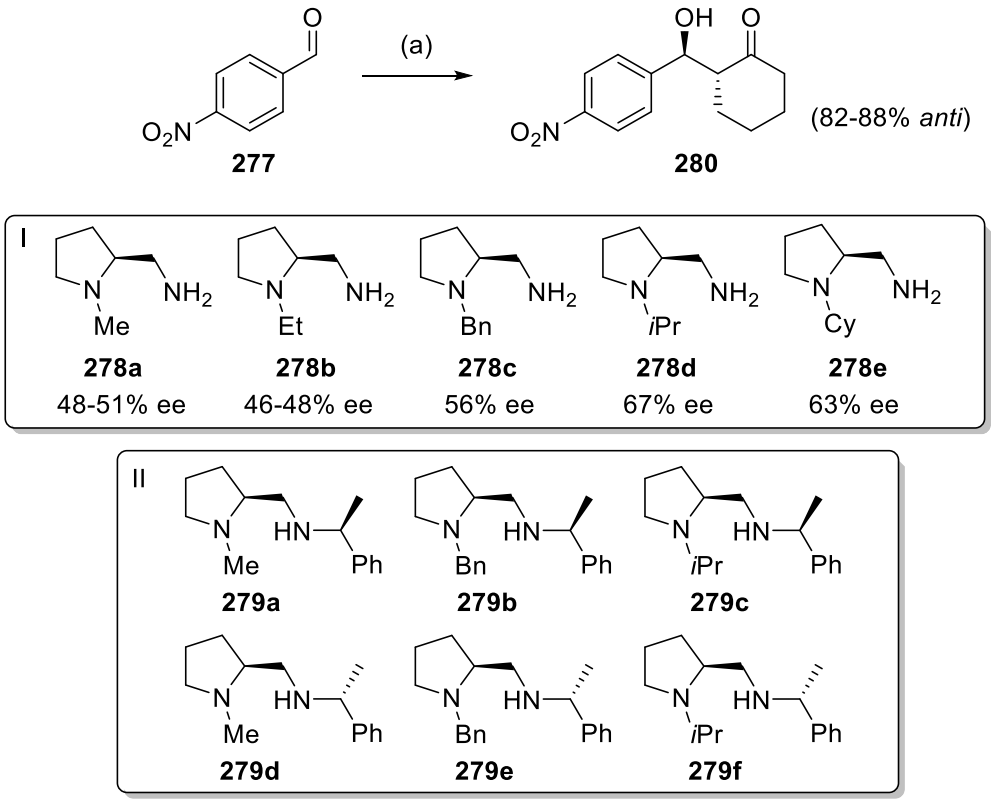
The first conclusion of note from the X-ray structures is that the presence of racemisation is likely to prevent the catalysts from being effective and if this problem cannot be overcome their utility is limited. Some unpublished work was performed by Professor Barry Lygo and Graham Moore, and was reported in a thesis in 2013,[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)



175a **276** **226**

Scheme 108: (a) i) EtO_2CCl or $SOCl_2$ or $tBuO_2CCl$, DCM, NEt_3. ii) NH_3 in MeOH, rt, 17 h; (b) NH_3 in MeOH, 60 °C, 24 h.

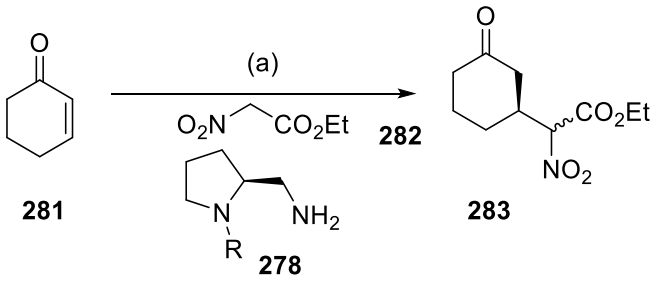
No reasoning was given for the poor yields, however high water solubility might be proposed as the synthesis of the corresponding *N*-ethyl, *N*-benzyl and *N*-isopropyl proline amides **278a-e**, **279a-f** were relatively easy to achieve via the direct coupling method. Lygo and Moore applied these 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[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, *i*Pr, 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.

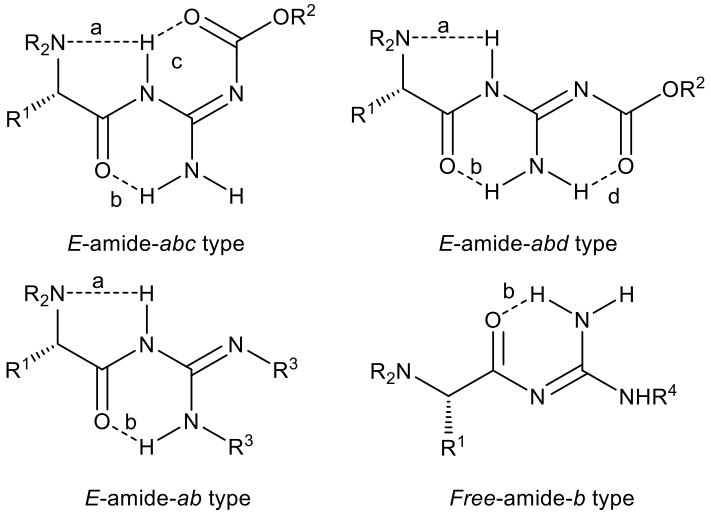
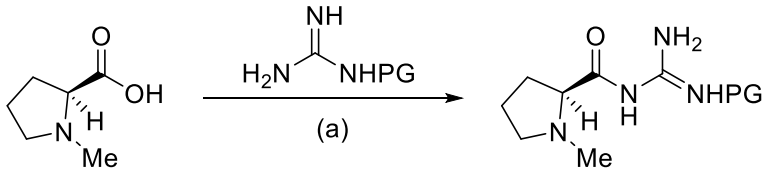


Figure 41: Observed common H-bonding types.
R = Me, Bn, Cy, *i*Pr, alkyl; R^1 = Me, Bn, alkyl; R^2 = Bn, *t*-Bu; R^3 = H, Ph; R^4 = Me, Ph.

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 gel[112] (entry 10).



175a **176a, 208**

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

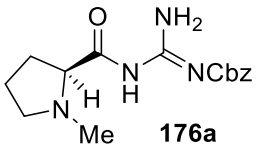
Table 8: Entries and results[i]

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

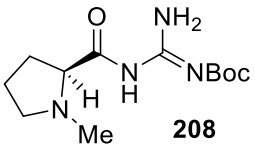
i) Estimated errors of +/- 3%
ii) Estimated errors of +/- 3%
iii) From compounds prepared by previous workers

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.[97] 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 dichlromethane 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

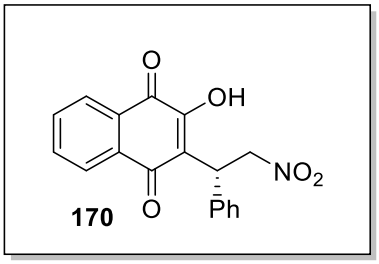
gave a slightly increase in ee but not of any significance. There is a considerable variance of reaction yield and reaction time with the toluene results but this might be due to solubility problems encountered in these reactions in toluene.



176a



208



170

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[i]

Entry	Cat.	Additive	DCM	Previous DCM	PhMe	Previous PhMe
1	**176a**	---	12 (24/92)	37 (99/88)	56 (48/49)	44 (100/75)
2	**208**[ii]	---	22 (10/97)	19 (28/75)	41 (10/42)	22 (2/89)
3	**208**[ii]	BA	23 (10/98)	28 (186/63)	38 (10/45)	37 (48/90)
4	**208**	---	15 (10/71)	19 (28/75)	32 (10/46)	22 (2/89)
5	**208**	BA	19 (10/76)	28 (186/63)	40 (10/41)	37 (48/90)

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-compouind 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)

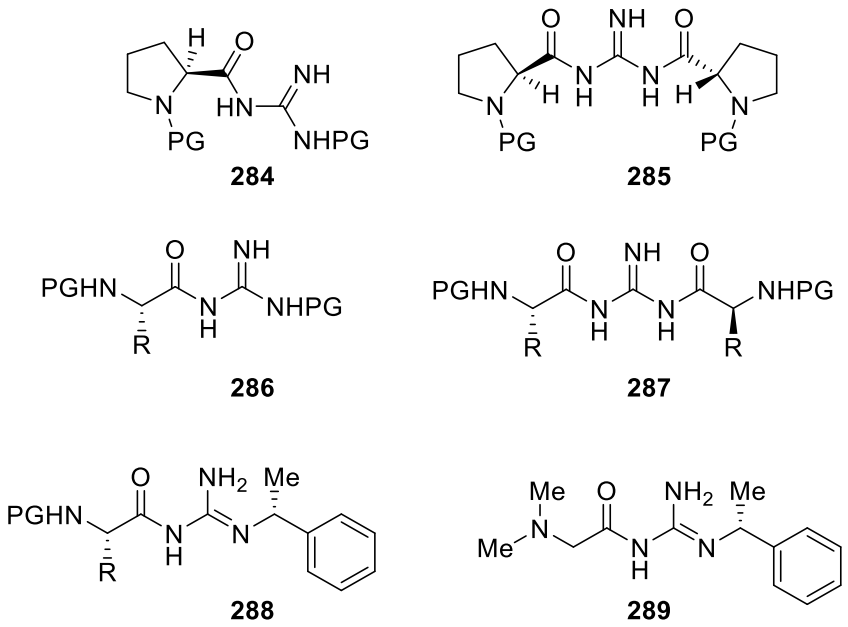
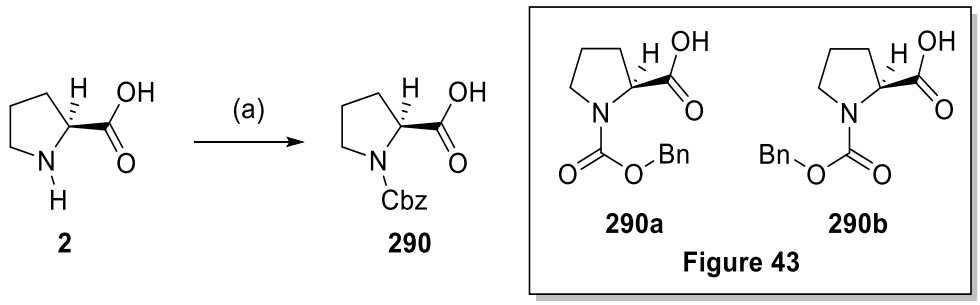


Figure 42: Proposed catalysts; PG = Boc, Cbz; R = Me, Bn.

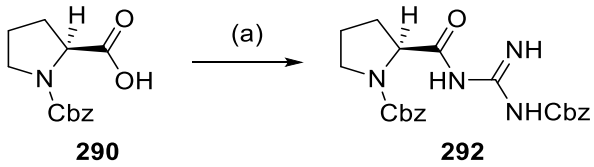
2.9.1 *N*-Cbz-L-proline and *N*-Boc-L-proline catalysts.

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}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}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).

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)

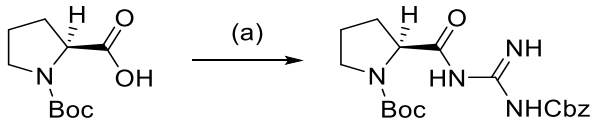


Scheme 114: Preparation of **292**. (a) i) **290**, CDI, DMF, rt, 24 h; ii), **224**, rt, 48 h.

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

up". The proton NMR spectrum gave a broad signal at δ_H 7.82-9.96 (3H, br s, 3 × NH) ppm for the guanidine NH protons and a multiplet signal at δ_H 7.16-7.45 (10H, m, 2 × Ph) ppm for the aromatic ring protons. The four doublets at δ_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 δ_H 4.24-4.47 (1H, m, CH) ppm. Other signals were observed corresponding to the remaining signals of the proline ring at δ_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 18 non-equivalent signals with the methine carbon in the proline ring at δ_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 $C_{22}H_{25}N_4O_5^+$ ($[M+H^+]$). 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)



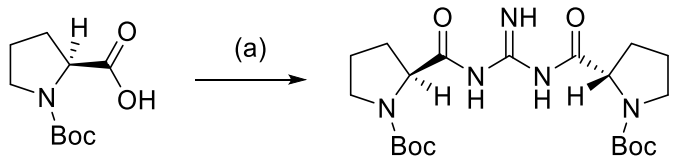
291 **293**

Scheme 115: Preparation of **293**. (a) i) **291**, CDI, DMF, rt, 24 h; ii), **224**, rt, 48 h

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 δ_H 7.63-10.22 (3H, br. s, 3 × NH) ppm for the guanidine NH protons, whilst the protons of aromatic ring were observed at δ_H 7.27-7.38 (5H, m, Ph). The methylene of the benzyl group appeared as singlet at δ_H 5.11 (2H, s, CH_2) ppm whilst the signals for the proline ring were observed at δ_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 δ_H 1.44/1.40 (9H, 2 × s, 3 × 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 δ_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 391.1980 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)



291 **294**

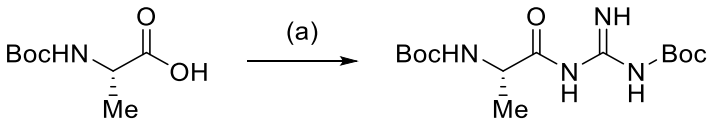
Scheme 116: Preparation of **294**. (a) i) **291**, CDI, DMF, rt, 24 h; ii) **206**, NaH, DMF, rt, 36 h; iii) Combine and stir, 48 h, rt.

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 δ_H 6.93-11.12 (3H, br s, 3 × NH) ppm for the guanidine NH protons whilst the broad signal at δ_H 4.13-4.48 (2H, m, 2 × CH) ppm corresponded to the methine proton of the prolines. The methylene protons of the proline were observed at δ_H 3.29-3.69 (4H, m, 2 × CH_2) and 1.70-2.35 (8H, m, 4 × CH_2) ppm. Finally the tert-butyl signals were observed as two singlets at δ_H 1.45 (9H, s, 3 × Me) and 1.39 (9H, s, 3 × Me) ppm. The ^{13}C NMR spectrum gave 9 non-equivalent signals with the methine of proline ring at δ_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 $C_{21}H_{36}N_4O^+$ ($[M+H^+]$).

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)

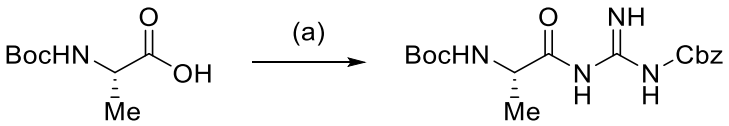


295 **296**

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 $[\alpha]_D^{25}$ -24 whilst the proton NMR spectrum a broad singlets at δ_H 7.77-9.70 (3H, br s, 3 × NH) ppm for the guanidine NH protons and a broad singlet at δ_H 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 δ_H 3.90-4.31 (1H, m, CH) ppm, whilst the *t*-butyl signals were at δ_H 1.49 (9H, s, 3 × Me), and 1.44 (9H, s, 3 × Me) ppm. Finally, the methyl signal was observed as doublet at δ_H 1.38 (3H, d, *J* 7.1 Hz, Me) ppm. The ^{13}C 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 δ_C 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 $C_{14}H_{27}N_4O_5^+$ ($[M+H]^+$). 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-guaindine **224**. After three days, an aqueous work-up followed by recrystallization from ethanol gave **297** in 71% yield. (Scheme 118)



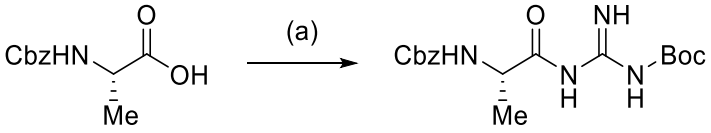
295 **297**

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 $[\alpha]_D^{25}$ -18.8, whilst the proton NMR spectrum gave two signals at δ_H 7.93-10.03 (3H, br. s, 3 × NH) ppm for the guanidine NH protons and at δ_H 5.10

(1H, br s, NH) ppm for the carbamate NH protons. The aromatic protons appeared as a multiplet at δ_H 7.29-7.42 (5H, m, Ph) ppm, whilst the methylene of the Cbz group was a singlet at δ_H 5.15 (2H, s, CH_2) ppm. The distinctive methine of the L-alanine residue was found as broad multiplets at δ_H 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 δ_H 1.33-1.46 (3H, m, CH_3) ppm and the *t*-butyl of the Boc-group was seen at δ_H 1.46 (9H, s, 3 × Me) ppm. The ^{13}C spectrum gave the required 12 non-equivalent signals with one quaternary carbon not detected. The methine carbon of the alanine appeared at δ_C 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 $C_{17}H_{25}N_4O_5^+$ ($[M+H]^+$).

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)



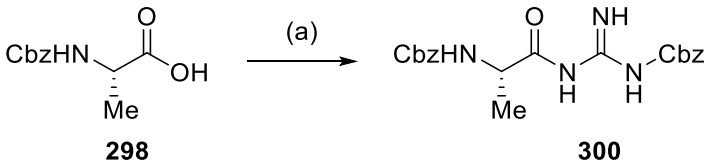
298 **299**

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 $[\alpha]_D^{28}$ -21.2, whilst the proton NMR spectrum a broad singlets at δ_H 8.16-10.21 (3H, br s, NH, NH_2) ppm for the guanidine NH protons and at δ_H 5.69-5.99 (1H, m, NH) ppm for the amide NH protons. The aromatic protons appeared as a multiplet at δ_H 7.24-7.39 (5H, m, Ph) ppm, whilst the methylene of the Cbz group was two doublets at δ_H 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 δ_H 4.10-4.33 (1H, m, CH) ppm, whilst the *t*-butyl signal was at δ_H 1.45 (9H, s, 3 × Me) ppm and finally the methyl signal was found at δ_H 1.38 (3H, d, *J* 7.0 Hz, Me) ppm. The ^{13}C NMR spectrum gave the required 11 non-equivalent signals with two quaternary carbons not detected, with the methine carbon of the alanine residue at δ_C 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 $C_{17}H_{25}N_4O_5^+$ ([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)



298 **300**

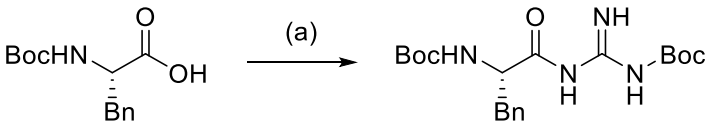
Scheme 120: Preparation of **300**. (a) i) **298**, CDI, DMF, rt, 30 min, ii) **224**, DMF, rt, 72 h.

The analytical data obtained for **300** confirmed its structure. The compound gave a negative specific rotation value of $[\alpha]_D^{25}$ -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, NH_2) 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 ^{13}C 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 339.2 ([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 $C_{20}H_{23}N_4O_5^+$ ([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)

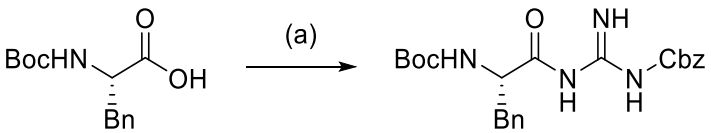


301 **302**

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 δ_H 8.60 (1H, br s, NH) and δ_H 7.57-10-34 (2H, br s, 2 × NH) ppm for the guanidine NH protons with the carbamate NH proton appearing at δ_H 5.09 (1H, br s, NH) ppm. The aromatic protons appeared as a multiplet at δ_H 6.99-7.24 (5H, m, Ph) ppm, whilst the benzyl methylene of the phenylalanine was observed as complex signals at δ_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 reside was observed as a complex set of signals at δ_H 4.42/4.14-4.27 (1H, dd, *J* 5.0, 5.5 Hz/br m, CH) ppm and the *t*-butyls were observes as singlets at δ_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 δ_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 $C_{20}H_{31}N_4O_5$ ($[M+H]^+$).

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)

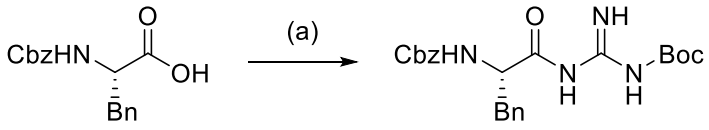


301 **303**

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 δ_H 8.28-9.38 (3H, br s, 3 × NH) ppm for the guanidine NH protons and at δ_H 4.90 (1H, br s, NH) ppm for the carbamate NH proton. The aromatic protons appeared as a multiplet at δ_H 7.20-7.41 (8H, m, 8 × CH) and as a doublet at δ_H 7.13 (2H, d, *J* 7.1 Hz, 2 × CH) ppm. The benzyl methylene for the Cbz group was observed as a singlet at δ_H 5.14 (2H, s, CH_2) ppm, whilst that of the phenylalanine residue was observed at δ_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 reside was observed as a broad multiplet at δ_H 4.39-4.56 (1H, m, CH) ppm, whilst the *t*-butyl signal was observed as a singlet at δ_H 1.38 (9H, s, 3 × 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 δ_C 56.9 ppm. Finally, analysis by mass spectrometry gave an ion at 441.2 (100%, $[M+H]^+$) which on accurate mass measurement gave a mass of 441.2132 ($[M+H]^+$) Daltons which corresponds closely to the required value of 441.2134 Daltons for $C_{22}H_{25}N_4O_5^+$ ($[M+H]^+$).

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)



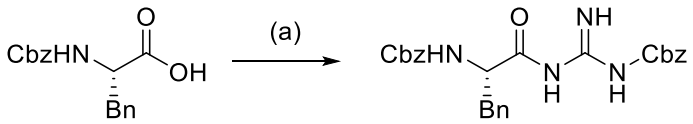
304 **305**

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 δ_H 8.34-10.29 (2H, br s, 2 × NH) and 8.65 (1H, br s, NH) ppm for the guanidine NH protons and a signal at δ_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 δ_H 7.26-7.41 (5H, m, Ph) 7.15-7.25 (3H, m, 3 × 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 δ_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 δ_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 δ_H 4.57-4.62 (1H, m, CH) ppm. The *t*-butyl signal of the Boc-group was observed as a singlet at δ_H 1.48 (9H, s, 3 × Me) ppm. The ^{13}C NMR spectrum gave the required 15 non-equivalent signals with two quaternary carbons not detected, with the methine carbon in the phenylalanine resonating at δ_C 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 $C_{23}H_{29}N_4O_5^+$ ($[M+H]^+$).

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)



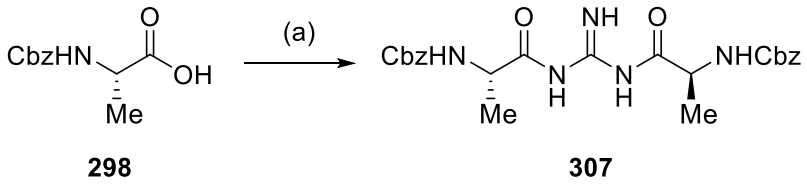
304 **306**

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 $[\alpha]_D^{25}$ -19.6, whilst the ^1H NMR spectrum gave two signals at δ_H 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 δ_H 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 δ_H 5.16 (2H, br s, CH_2) ppm and a multiplet at δ_H 5.01-5.13 (2H, m, 2 × CH) ppm, whilst the methylene of the amino acid residue was observed at δ_H 2.85-3.35 (2H, m, CH_2) ppm. The distinctive methine proton of the phenylalanine was observed as a broad multiplet at δ_H 4.28-4.59 (1H, br m, CH) ppm. The ^{13}C NMR spectrum gave the 13 non-equivalent signals in the DEPT-135 spectrum, with the methine carbon observed at δ_C 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 $C_{26}H_{26}N_4O_5^+$ ($[M+H^+]$).

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)

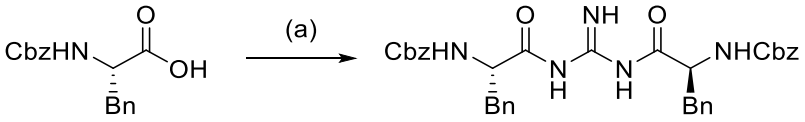


298 **307**

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 $[\alpha]_D^{16}$ -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 $C_{23}H_{28}N_5O_6^+$ ($[M+H]^+$).

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)

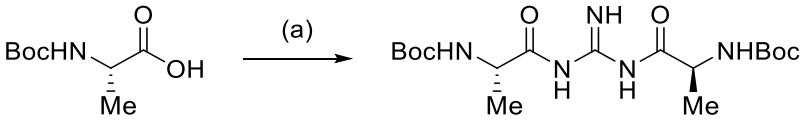


304 **308**

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 δ_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 δ_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 δ_H 4.96-5.14 (4H, m, 2 × CH_2) while the phenylalanine methylenes appeared as a multiplet at δ_H 2.80-3.23 (4H, m, 2 × CH_2) ppm. The aliphatic methine proton was observed as a broad multiplet at δ_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 δ_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)

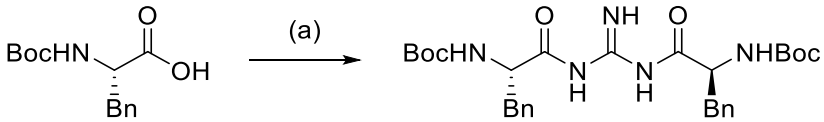


295 **309**

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 δ_H 8.42-10.88 (3H, br s, 3 × NH) ppm for the guanidine NH protons and at δ_H 5.30-5.70 (2H, m, 2 × NH) ppm for the amide NH. The methine proton of the alanine residue was observed as a complex broad multiplet at δ_H 3.94-4.36 (2H, m, 2 × CH) ppm, whilst the *t*-butyl groups appeared as two singlets at δ_H 1.42 (9H, s, 3 × Me) and 1.42 (9H, s, 3 × Me) ppm. The methyl signals appeared as a doublet at δ_H 1.37 (3H, d, *J* 6.8 Hz, 2 × 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 δ_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)



301 **310**

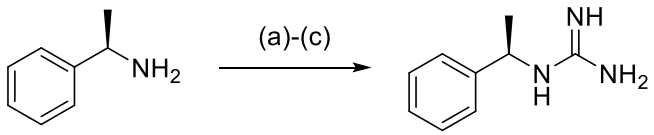
Scheme 128: (a) i) **301**, CDI, DMF, rt, 90 min, ii) **206** (0.5 equiv.), NaH, DMF, 90 min. iii) combine, stir 48 h.

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 δ_H 8.22-11.13 (3H, br s, 3 × NH) ppm for the guanidine NH protons and at δ_H 5.05-5.70 (2H, m, 2 × NH) ppm for the amide NH. The aromatic protons appeared as two multiplets at δ_H 7.21-7.38 (6H, m, 6 × CH), and 7.13-7.21 (4H, m, 4 × CH) ppm. The benzyl methylenes appeared as a multiplet at δ_H 2.97-3.31 (4H, m, 2 × CH_2) ppm, whilst the aliphatic methine proton was observed at δ_H 4.18-4.24 (2H, m, 2 × CH) ppm. The *t*-butyl groups were observed as a singlet at δ_H 1.42 (18H, s, 6 ×

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 δ_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 $C_{29}H_{40}N_5O_6^+$ ($[M+H]^+$).

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.[116] (Scheme 129)

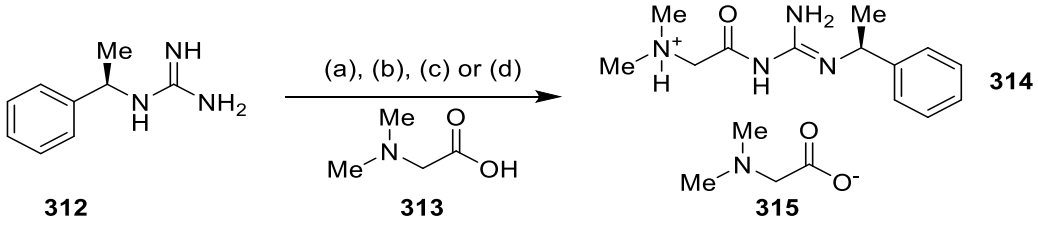


311 **312**

Scheme 129: (a) **311**, HCl (conc.), 15-20 °C, 30 min. (b) NH_2CN, reflux, 24 h. (c) Dowex 500 ion exchange column

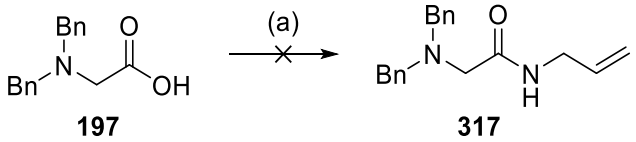
The coupling of guanidine **312** with commercially available dimethylglycine **313**, was attempted by firstly activating 1.2 equivalents of **313** with 2.5 equivalents of CDI over 30 min, then adding an equivalent of **312**. The reaction was stirred for 6 days at rt, then diluted with water and extracted with ethyl acetate. Analysis of the product by ^1H 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 ^{1}H 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.



Scheme 130. (a) (i) **313** (1.20 equiv.), CDI, DMF, 2 d, rt; (ii) **312** (1.0 equiv.), rt, 6 d; (b) (i) **313** (1.0 equiv.), CDI, DMF, 7 h, rt; (ii) **312** (1.0 equiv.), rt, 5 d; (c) (i) **313** (1.0 equiv.), CDI, DMF, 1 d, rt; (ii) Et_3N (1.0 equiv.), 10 min, (iii) **312** (1.0 equiv.), rt, 2 d, 45-55 °C, 18 h; (d) i) **313** (0.60 equiv.), CDI, DMF, 1 d, rt; (ii) Et_3N (3.0 equiv.), 10 min, (iii) **312** (1.20 equiv.), rt, 2 d, 70 °C, 1 d.

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)

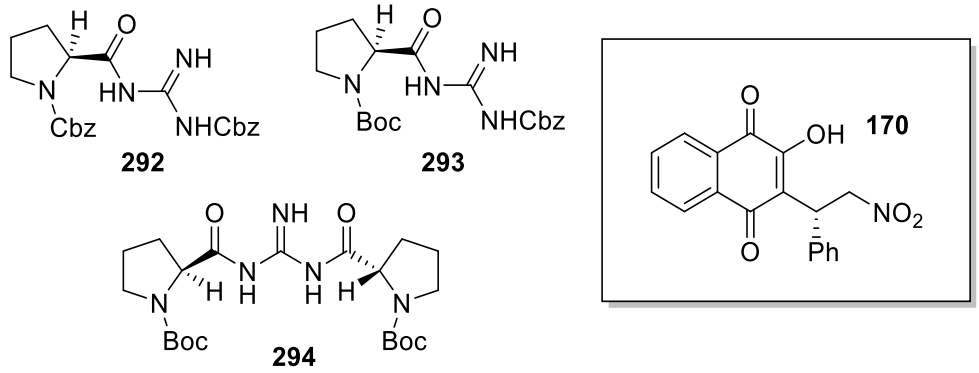


197 317

Scheme 131: (a) i) **197**, CDI, DMF, 24 h, rt; Et_3N, 1 h, (60-80 °C);
ii) **316**, 72 h, rt then 6 h at 45 °C.

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).



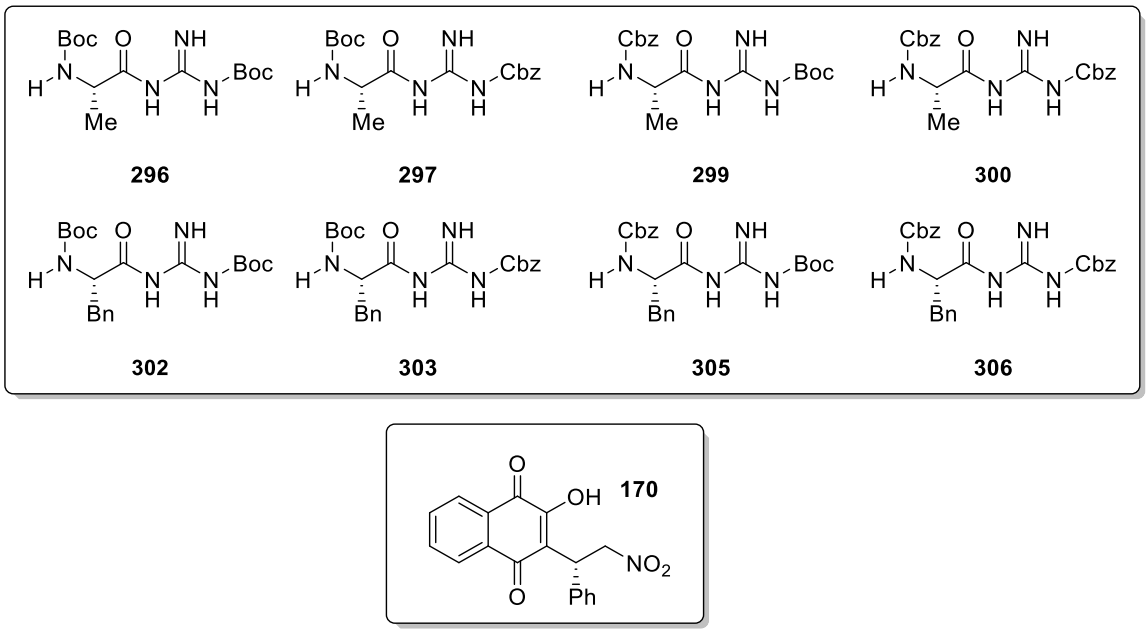
Scheme 132: Formation of **170** using catalysts **292**, **293** and **294**: Conditions: See Table **10**, Catalyst (0.1 equiv.), 0 °C, 7-8 h then rt.

Table 10: Entries and results

Entry[i]	Cat.	DCM	PhMe	Xylenes	PhH
1	**292**	18 (120/55)	13 (120/31)	8 (120/32)	8 (48/30)
2	**293**	5 (24/38)	4 (24/22)	1 (72/30)	4 (24/25)
3	**294**	18 (24/38)	22 (48/30)	12 (23/41)	22 (48/25)

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.



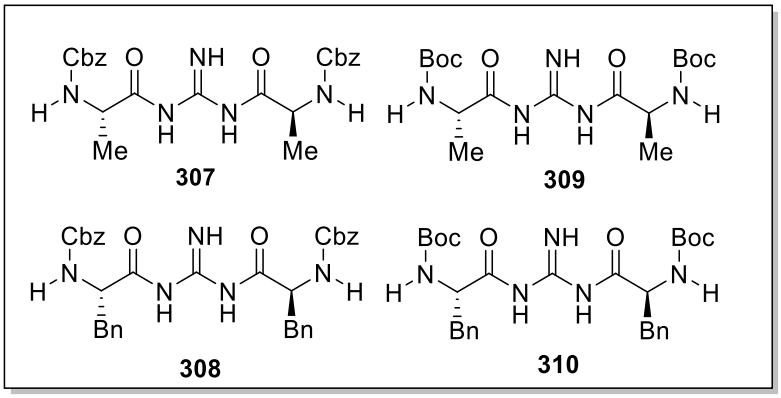
Scheme 131: Formation of **170** using catalysts **296**, **297**, **299**, **300**, **302**, **302**, **305** and **306**: Conditions: Table **11**, (a) Catalyst (0.1 equiv.) then i) 0 °C, 7-8 h then rt

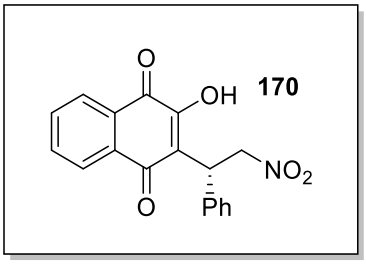
Table 11: Entries and results

Entry[i]	AA[ii]	AAPG[iii]	GPG[iv]	Catalyst	DCM	PhMe
1	Ala	Boc	Boc	**296**	2 (142/49)	2 (160/81)
2	Ala	Boc	Cbz	**297**	6 (428/47)	14 (286/11)
3	Ala	Cbz	Boc	**299**	12 (241/37)	16 (265/37)
4	Ala	Cbz	Cbz	**300**	6 (240/51)	10 (240/24)
5	Phe	Boc	Boc	**302**	5 (214/67)	0 (214/84)
6	Phe	Boc	Cbz	**303**	6 (400/68)	12 (255/18)
7	Phe	Cbz	Boc	**305**	3 (187/74)	2 (190/73)
8	Phe	Cbz	Cbz	**306**	5 (72/84)	0 (50/56)

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 12: Entries and results

Entry[i]	AA[ii]	PG[iii]	Cat.	Conds.	DCM	PhMe
1	Phe	Boc	**310**	(a)	NR	NR
2	Phe	Boc	**310**	(b)	5 (565/48)	8 (216/32)
3	Phe	Cbz	**308**	(a)	26 (527/22)	15 (285/46)
4	Ala	Boc	**309**	(a)	3 (216/85)	3 (216/70)
5	Ala	Cbz	**307**	(a)	NR	NR
6	Ala	Cbz	**307**	(b)	10 (565/95)	6 (255/70)

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)

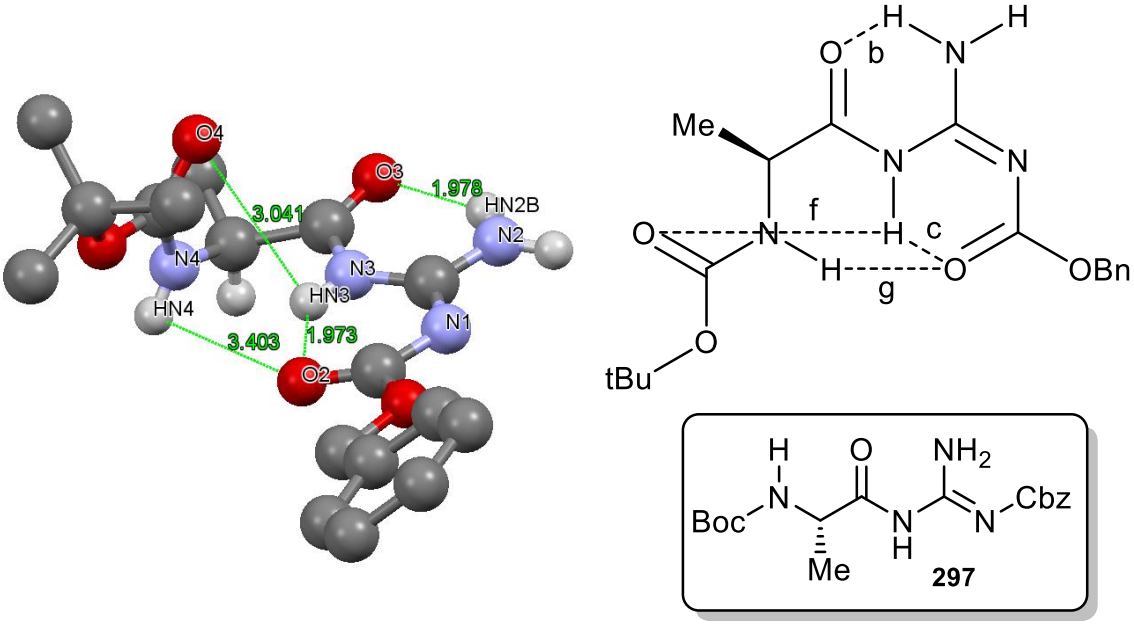


Figure 44: X-ray crystal structure of **297** (2018ncs0698)

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)

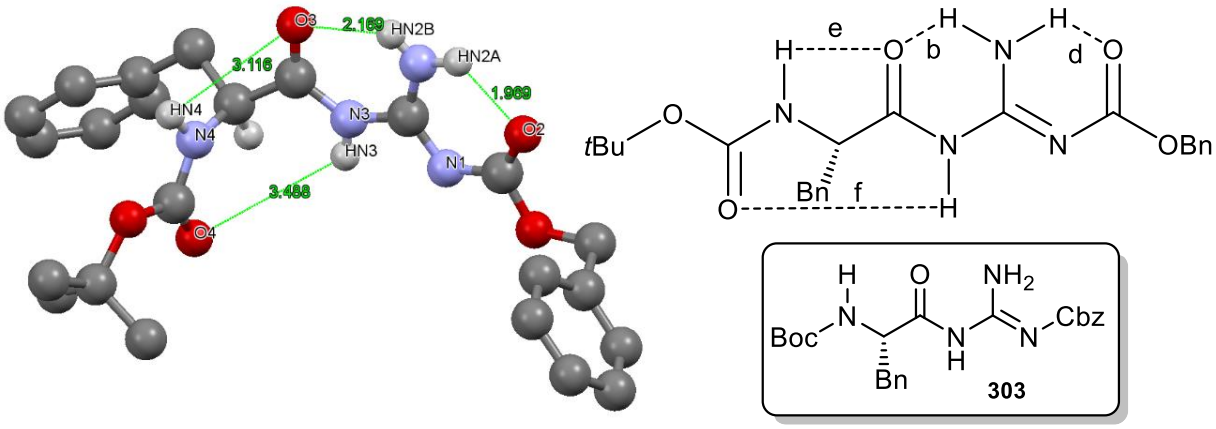
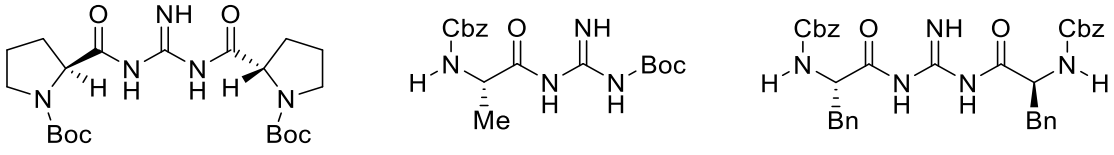


Figure 45: X-ray structure of **303** (2018 ncs0699)

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)



294 18% ee (DCM), 22% ee (PhMe) 22%ee (PhH)

299 12% ee (DCM), 16% ee (PhMe)

308 26% ee (DCM), 15% ee (PhMe)

Figure 46: Most successful *N*-protected catalysts

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[97] 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.

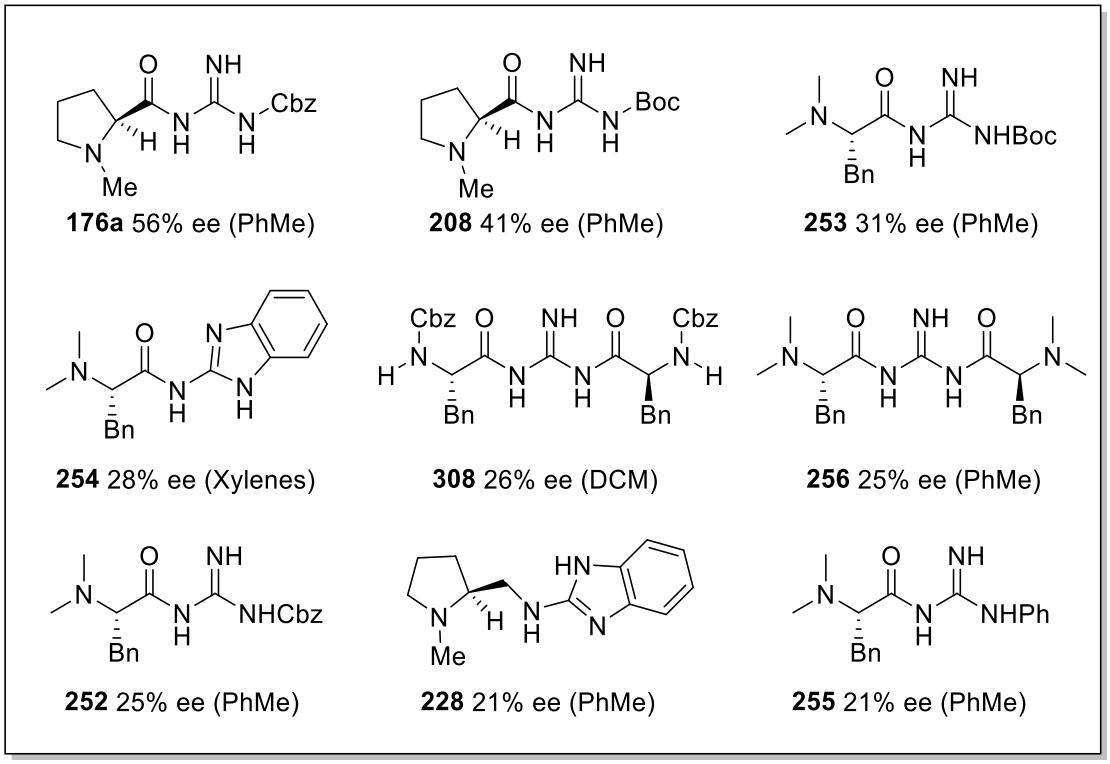


Figure 47: The most successful catalysts used in this work.

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)

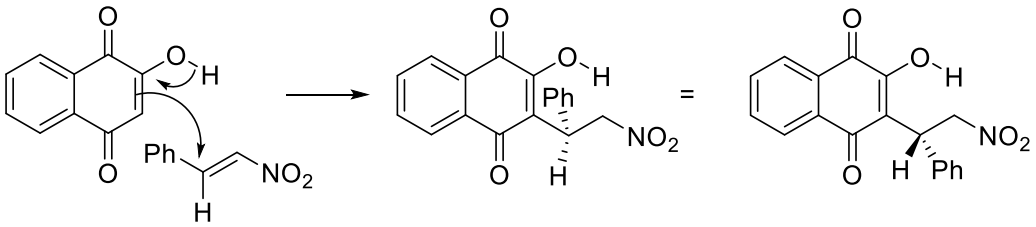
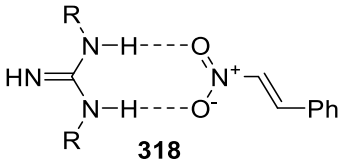


Figure 48: Mechanism of reaction.

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)



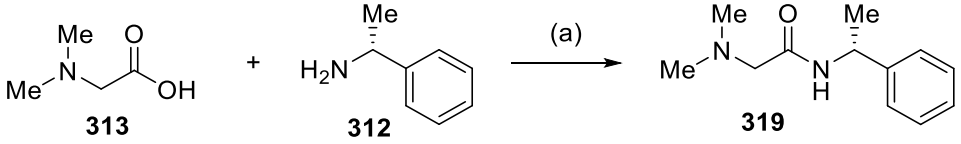
318

Figure 49: The observed H-bonding modes in the catalysts studied

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.*[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)



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**.

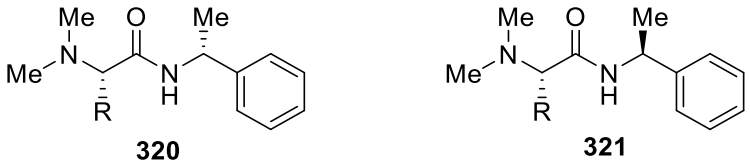


Figure 50: R = Me, Bn, *i*-Pr.

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.

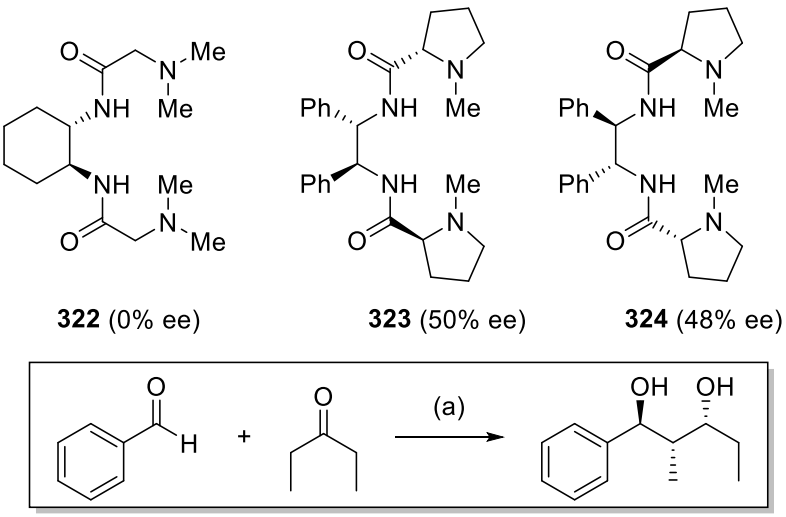


Figure 51: (a) (i)Yb(OTf)$_3$/catalyst (10 mol %), THF, rt, 4 h; (ii) MeOH, MeONa

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 136) 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**.[119]

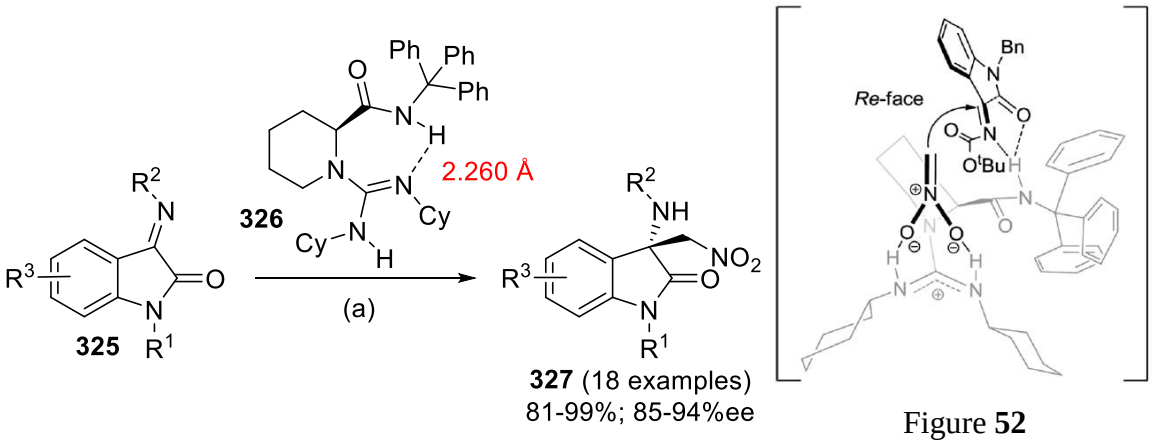


Figure **52**

Scheme 136: (a) i) **326** (10 mol %), **88**, PhMe, - 30 °C, 72 h.

R^1 = Me, Bn; R^2 = Boc, EtO_2C; R^3 = H, F, Cl, Br, I, Me, F_3CO, CF_3.

Figure 52 reproduced from reference.[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[120,121] and peptide cluster[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

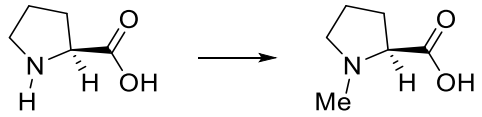
Melting points were determined using a Gallenkamp MF370 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 or 500 spectrometer with an internal deuterium lock at ambient temperature at 400 or 500 MHz with internal references of δ_H 7.26 and δ_C 77.016 ppm for $CDCl_3$, δ_H 3.31 and δ_C 49.0 ppm for CD_3OD and δ_H 2.54 ppm and δ_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 ($MgSO_4$), filtering and evaporation under reduced pressure, the product was obtained and was purified by column chromatography (DE/PE or EA/PE), or recrystallization or tritutation.

Method B: (C_2-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 (P_2O_5) 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 ($MgSO_4$), 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.[88]

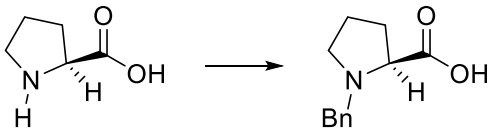


Chemical Formula: $C_6H_{11}NO_2$
Exact Mass: 129.0790
Molecular Weight: 129.1590

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_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© 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.

Rf 0.23 (90% ME/DE); **Mp** 142-144 °C; (lit.[88] Mp 142-145 °C); **$[\alpha]_D^{22}$** -75.0 (MeOH, c = 2.0); (lit.[88] $[\alpha]_D^{23}$ -78.0 (MeOH, c = 2.0)); **δ_H** (D_2O) 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); **δ_C** (D_2O) 173.6, 70.6, 56.3, 40.6, 28.7, 22.7; **ν_{max}** (KBr disk) 2900, 1668, 1611, 1467, 1400, 1353, 1326, 1233, 1182, 1112, 1055, 1024, 807, 774 cm^{-1}; **MS (EI, -ve ion) m/z** 128.01 (100%, $[M-H]^-$); **HRMS m/z** found 128.0720, $C_6H_{10}NO_2^-$ ($[M-H]^-$) requires 128.0717.

3.4.2 Preparation of *N*-benzyl-L-proline 175b.[89]

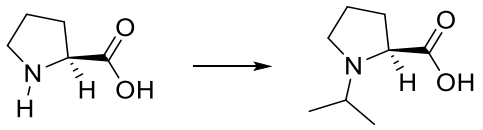


Chemical Formula: $C_{12}H_{15}NO_2$
Exact Mass: 205.11
Molecular Weight: 205.26

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 $CHCl_3$. 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_2O_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[89]); **[α]$_D^{19}$** -22.5 (EtOH, c = 1.0; lit. $[\alpha]_D^{20}$ -25.8 (EtOH, c = 1.0)); **δ_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); **δ_C** ($CDCl_3$) 171.1, 130.7, 130.6, 129.6, 129.2, 67.0, 57.6, 53.3, 28.7, 22.8; **ν_{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]

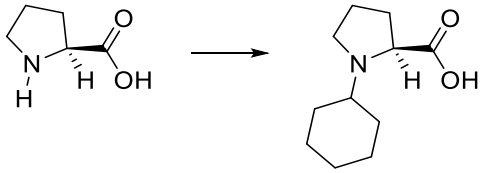


Chemical Formula: $C_8H_{15}NO_2$
Exact Mass: 157.11
Molecular Weight: 157.21

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; **[α]$_D^{18}$** -68.1 (MeOH, c 1.28; Lit.[90] **[α]$_D^{20}$** -55.0 (MeOH, c = 1.28)); **δ_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); **δ_C** 70.7, 66.0, 55.5, 51.3, 30.4, 24.3, 18.4, 18.1; ν_{max} (KBr disk) 3432, 3036, 2873, 1634, 1394, 1321, 1203, 1080, 1005 cm^{-1}; **MS(EI -ve) m/z** 156.1 (100%, $[M-H]^-$); **MS(ESI) m/z** 158.1 (100%, $[M+H]^+$); **HRMS(ESI) m/z** found 156.1032, $C_8H_{14}NO_2^-$ ($[M-H]^-$) requires 156.1030.

3.4.4 Preparation of *N*-cyclohexyl-L-proline 175d.[91]

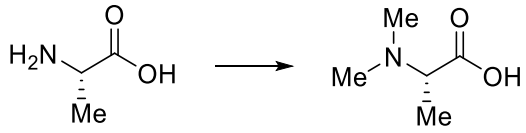


Chemical Formula: $C_{11}H_{19}NO_2$
Exact Mass: 197.14
Molecular Weight: 197.28

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© 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); **δ_H** (D_2O) 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 × CH), 1.93-1.83 (3H, m, 3 × CH), 1.68-1.63 (1H, m, CH), 1.50-1.11 (5H, m, 5 × CH); **δ_C** (D_2O) 174.8, 66.2, 64.4, 52.5, 29.5, 28.3, 24.4, 24.3, 23.6; **ν_{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]



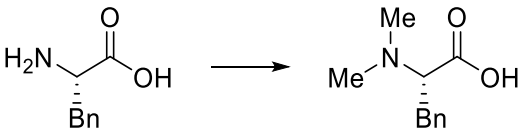
Chemical Formula: $C_5H_{11}NO_2$
Exact Mass: 117.08
Molecular Weight: 117.15

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.[93] 184 °C); **[α]$_D^{23}$** +8.3 (H_2O, c = 5.0, Lit[93] +7.8 (H_2O, c = 5); **δ_H** (CD_3OD) 3.63 (1H, q, *J* 7.2 Hz, CH), 2.84 (6H, s, 2 × CH_3), 1.49 (3H, d, *J* 7.2 Hz, CH_3); **δ_C** (CD_3OD) 173.4, 67.4, 41.5, 13.0; **ν_{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, $C_5H_{10}NO_2^-$ ([M-H]$^-$) requires 116.0717.

3.4.6 Preparation of *N*,*N*-dimethyl-L-phenylalanine 193.[93]

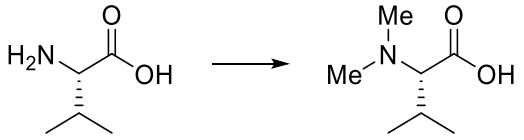


Chemical Formula: $C_{11}H_{15}NO_2$
Exact Mass: 193.11
Molecular Weight: 193.25

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.[93] 218 °C); **[α]$_D^{19}$ +** 76.8 (H_2O, c = 1.98), (lit. 77.5 [92] (H_2O, c = 1.98); **δ_H** (CD_3OD) 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 × CH_3); **δ_C** (CD_3OD) 172.0, 137.7, 130.3, 129.8, 128.2, 73.1, 42.4, 35.1; **ν_{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, $C_{11}H_{16}NO_2^+$ ([M+H]$^+$), requires 194.1176.

3.4.7 Preparation of *N*,*N*-dimethyl-L-valine 195.[93, 95]

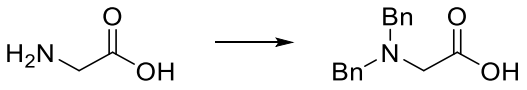


Chemical Formula: $C_7H_{15}NO_2$
Exact Mass: 145.11
Molecular Weight: 145.20

(5.0 g, 42.68mmol, 1 equiv) of L-valine was weight and added to a 250 mL round-bottomed flask. The 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 weight 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 30minutes 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.

Rf 0.35 (MeOH); **Mp** 148-150 (lit.:153 °C)[95]; $\mathbf{[\alpha]_D^{24}}$ 34.9° (MeOH, c = 1.0); $\mathbf{\delta_H}$ (CD_3OD) 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. $\mathbf{\delta_C}$ (CD_3OD) 91.1, 77.7, 42.4, 27.6, 20.8, 16.9 ppm. $\mathbf{\nu_{max}}$ 3271-3076, 2999, 2841, 1600, 1399-1325, 1153, 1105, 1039, 1012.

3.4.8 Preparation of *N*,*N*-dibenzyl-glycine 197.[96]



Chemical Formula: $C_2H_5NO_2$
Molecular Weight: 75.07

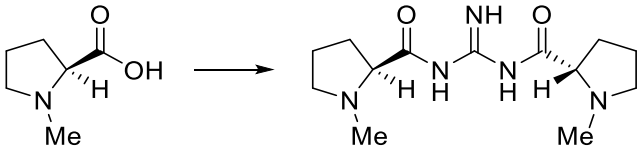
Chemical Formula: $C_{16}H_{17}NO_2$
Molecular Weight: 255.32

Glycine **196** (7.50 g, 0.10 mol) and 10 mL of 10 N NaOH were each added to 40 mL of H_2O. 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**.

Mp 192-194 °C (Lit.[96] 200 °C); δ_H (D_2O) 7.42 (10H, s, CH), 3.90 (4H, s, CH_2), 3.14 (2H, s, CH_2); δ_C (101 MHz, D_2O) δ 180.5,130.2, 128.5, 127.80, 57.2, 55.4.

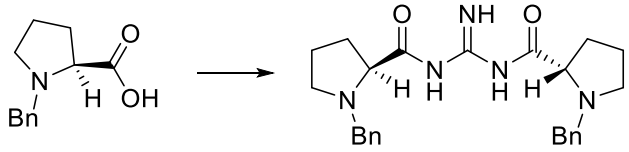
3.4.9 Attempted synthesis of (2*S*,2'*S*)-*N*,*N*'-(iminomethylene)bis(1-methylpyrrolidine-2-carboxamide) 182.



Chemical Formula: $C_{13}H_{23}N_5O_2$
Exact Mass: 281.19
Molecular Weight: 281.36

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.



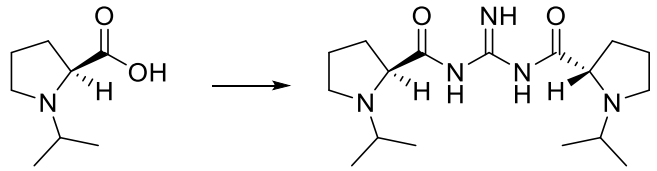
Chemical Formula: $C_{25}H_{31}N_5O_2$
Exact Mass: 433.25
Molecular Weight: 433.56

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.

Rf 0.25 (30% EA in PE); **Mp** 125-127 °C; $[\alpha]_D^{19}$ -83.3 (CH_2Cl_2, c = 1.2); δ_H ($CDCl_3$) 8.17-11.43 (3H, br s, 3 × NH), 7.19-7.39 (10H, m, 2 × Ph), 3.86 (2H, d, *J* 12.8 Hz, 2 × CH), 3.61 (2H, d, *J* 12.7 Hz, 2 × CH), 3.22 (2H, dd, *J* 9.7, 5.9 Hz, 2 × CH), 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), 1.76-

1.90 (4H, m, 2 × CH_2); **δC** ($CDCl_3$) 176.0, 147.8, 137.8, 129.5, 128.4, 127.4, 68.9, 59.5, 53.9, 30.6, 23.8; **ν_{max}** 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, $C_{25}H_{32}N_5O_2^+$ ($[M+H]^+$) requires 434.2551.

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

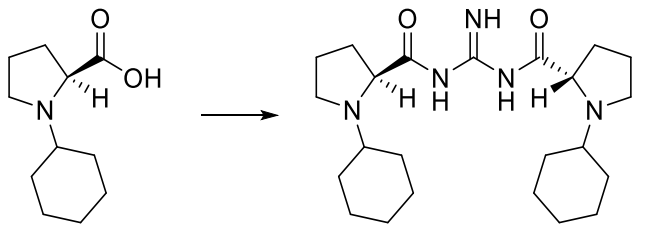


Chemical Formula: $C_{17}H_{31}N_5O_2$
Exact Mass: 337.25
Molecular Weight: 337.47

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; **$[\alpha]_D^{23}$** -129.7 (CH_2Cl_2, c = 1.2); **δH** ($CDCl_3$) 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 × CH_2), 1.01 (12H, d, *J* 6.4 Hz, CH_3); **δC** ($CDCl_3$) 177.3, 148.3, 94.5, 64.9, 53.0, 50.5, 31.8, 24.9, 21.2, 19.9; **ν_{max}** 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, $C_{17}H_{32}N_5O_2^+$ ($[M+H]^+$) requires 338.2551.

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



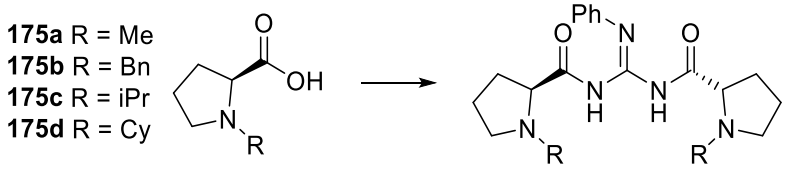
Chemical Formula: $C_{23}H_{39}N_5O_2$
Exact Mass: 417.31
Molecular Weight: 417.60

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; **$[\alpha]_D^{17}$** -53.9 (CH_2Cl_2, c = 1.0); **δ_H** ($CDCl_3$) 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); **δ_C** ($CDCl_3$) 177.2, 150.6, 65.3, 62.0, 50.8, 31.7, 31.5, 30.6, 26.1, 25.6, 25.5, 24.5; **ν_{max}** 3348, 2965, 2926, 2851, 1693, 1660, 1605, 1462, 108; **MS (ESI) m/z** 418.3 (100%, $[M+H]^+$), 152.2 (49%); **HRMS (ESI) m/z** found 418.3168, $C_{23}H_{40}N_5O_2^+$ ($[M+H]^+$), requires 418.3177.

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



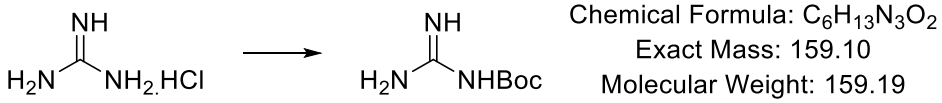
Compound 240a (Method B): *N*-methyl-L-proline **175a** (700 mg, 5.42 mmol, 1.0 equiv.); DMF (3 mL); CDI (1.05 g, 6.05 mmol, 1.20 equiv.); 3 h; phenyl guanidinium nitrate **203** (549.0 mg, 2.77 mmol, 0.51 equiv.); DMF (3 mL); NaH (60%, 130.0 mg, 3.25 mmol, 0.6 equiv.); 2.5 h; then combain; 5 d. Extraction 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 combin; 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 combain; 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)[97]

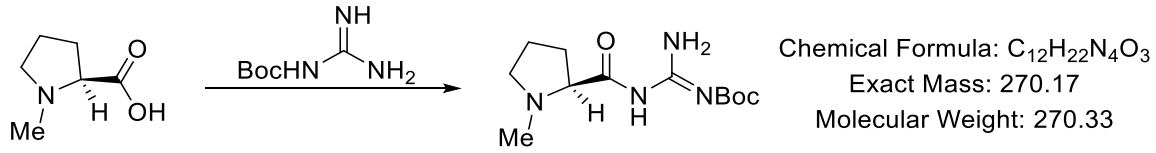
3.4.14 Preparation of *N*-Boc-Guanidine 207.[101]



A solution of Boc_2O (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 ($MgSO_4$) 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% NEt_3); **Mp** 167 °C (dec.) (lit [101] 165 °C (dec.)); **δ_H** ($(CD_3)_2SO$) 5.49-8.06 (4H, br s, 2 × NH, NH_2), 1.34 (9H, s, 3 × CH_3); **δ_C** ($(CD_3)_2SO$) 163.4, 162.7, 75.5, 28.3; **ν_{max}** 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, $C_6H_{14}N_3O_2^+$ ($[M+H]^+$) requires 160.1081.

3.4.15 Preparation of (*S*)-*N*'-Boc-*N*-carbamimidoyl-1-methylpyrrolidine-2-carboxamide 208

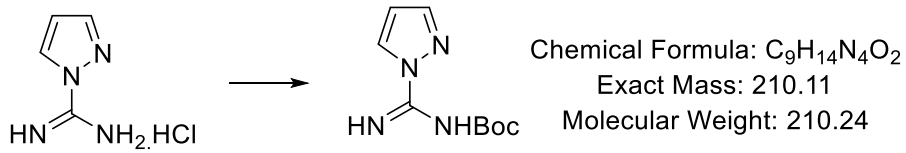


Method A: *N*-Methyl-L-proline **175a** (2.0 g, 15.5 mmol, 1.0 equiv.); DMF (10 mL); CDI (3.0 g, 18.6 mmol, 1.2 equiv.); 24 h; N-Boc-guanidine **207** (2.5 g, 15.48 mmol, 1.0 equiv.);

24 h. 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]$_D^{20}$** -46 (CH_2Cl_2, c = 1.0); **Mp** 134 °C; **δ_H** ($CDCl_3$) 8.21-10.03 (3H, br s, NH, NH_2), 3.00-3.07 (1H, m, CH), 2.95 (1H, dd, *J* 10.5, 4.8 Hz, CH), 2.31 (3H, s, CH_3), 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); **δ_C** ($CDCl_3$) 178.0, 163.4, 158.5, 79.4, 69.0, 56.5, 41.7, 31.3, 28.2, 24.6; **ν_{max}** 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, $C_{12}H_{23}N_4O_3^+$ ($[M+H]^+$) requires 271.1765.

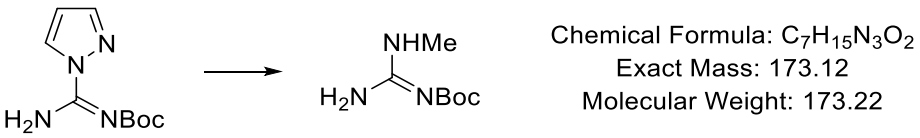
3.4.16 Preparation of *N*-Boc-1*H*-Pyrazole-1-Carboxamide 210.[98]



1*H*-Pyrazole-1-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 ($MgSO_4$), 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); **δ_H** ($CDCl_3$) 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, ^{t}Bu); **δ_C** ($CDCl_3$) 163.6, 155.3, 143.5, 129.0, 109.1, 80.3, 28.3; **ν_{max}** 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, $C_9H_{15}N_4O_2^+$ ($[M]^+$) requires 210.1117; found 211.1197, $C_9H_{15}N_4O_2$ ($[M+H]^+$) requires 211.1190

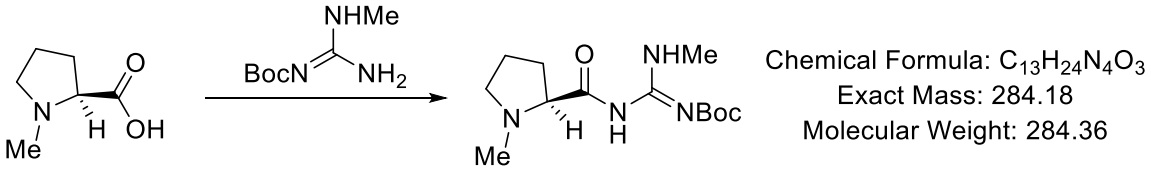
3.4.17 Preparation of *N*-methyl-*N'*-Boc-guanidine 211. [99]



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 × 100 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL) then dried ($MgSO_4$), 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; δ_H ($CDCl_3$) 5.93 (3H, br s, 3 × NH), 2.85 (3H, s, CH_3), 1.47 (9H, s, CH_3); δ_C ($CDCl_3$) 162.4, 78.1, 28.6, 27.7; ν_{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, $C_7H_{16}N_3O_2^+$ ($[M+H]^+$) requires 174.1237.

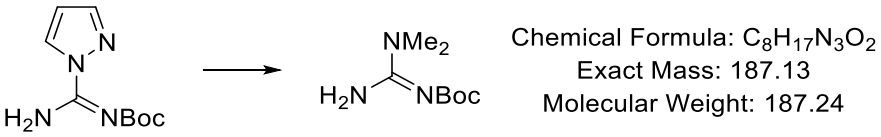
3.4.18 Preparation of (*S*)-*N*-(*N*'-Boc-*N*-methylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 212.



***Method A*:** *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; *N*-Boc-*N'*-methylguanidine **211** (750.0 mg, 4.33 mmol, 3.45 equiv.); 5 d. Extraction and trituration with DE (2 × 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_2Cl_2, c = 1.1); **Mp** 130-132 °C, δ_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 × CH), 1.51 (9H, s, 3 × Me); δ_C ($CDCl_3$) 177.7, 162.7, 156.0, 79.3, 69.5, 56.5, 41.5, 31.4, 28.4, 27.9, 24.5; ν_{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** $C_{13}H_{25}N_4O_3^+$ ($[M+H]^+$) requires 285.1921.

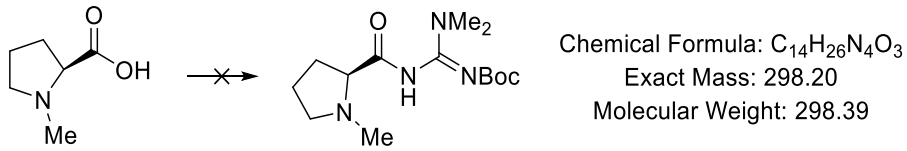
3.4.19 Preparation of *N,N*-dimethyl-*N'*-Boc-guanidine 213.



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 × 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.

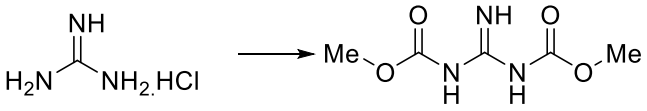
Mp 176 °C; **Rf** 0.27 (100% EA); **δ_H** ($CDCl_3$) 6.50-7.45 (2H, br s, NH_2), 3.01 (6H, s, 2 × CH_3), 1.49 (9H, s, 3 × CH_3); **δc** ($CDCl_3$) 164.2, 161.4, 78.1, 36.9, 28.6; **ν_{max}** 3370, 3231, 2976, 2933, 1651, 1589, 1317, 1268; **MS (ESI) m/z** 188.1 (48%, $[M+H]^+$); **HRMS (ESI)** found 188.1393, $C_8H_{18}N_3O_2^+$ ($[M+H]^+$) requires 188.1394.

3.4.20 Attempted preparation of (*S,Z*)-*N*-(*N*'-(Boc)-*N,N*-dimethylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 214.



Method A: *N*-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*-dimethyl-*N'*-Boc-guanidine **213** (1.0 g, 5.34 mmol, 1.0 equiv.); 6 d, rt; 40 °C 2 d; diluted with K_2CO_3 solution (aq. 10%, 100 mL). Extraction with EA; washed with water (3 × 150 mL) and brine (2 × 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]

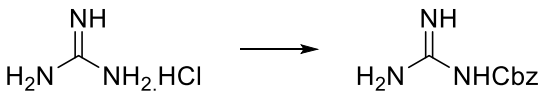


Chemical Formula: $C_5H_9N_3O_4$
Exact Mass: 175.06
Molecular Weight: 175.14

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]

Mp 214-215 °C, (lit.[100] 206 °C); δ_H ($(CD_3)_2SO$) 10.76 (1H, br s, NH), 8.65 (2H, br s, 2 × NH), 3.61 (6H, br s, 2 × CH_3); δ_C ($(CD_3)_2SO$) 159.4, 158.7, 52.2; ν_{max} 3392, 3255, 2958, 1732, 1655, 1219; **MS (ESI) m/z** 176.1 (100%, $[M+H]^+$); **HRMS (ESI)** found 176.0665 $C_5H_{10}N_3O_4^+$ ($[M+H]^+$) requires 176.0666.

3.4.22 Preparation of N-Cbz-Guanidine 224.[101]

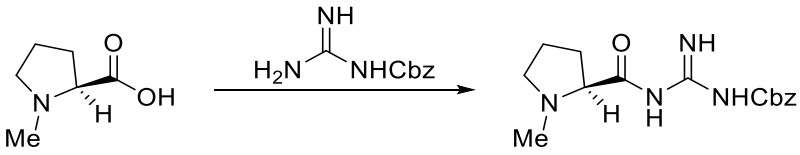


Chemical Formula: $C_9H_{11}N_3O_2$
Exact Mass: 193.09
Molecular Weight: 193.21

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.

Mp 139-142 °C (Lit [101] 140–142 °C); **δ_H** ($(CD_3)_2SO$) 7.25-7.60 (5H, m, Ph), 6.07-8.01 (4H, br s, 2 × NH, NH_2), 4.96 (2H, s, CH_2); **δ_C** ($(CD_3)_2SO$) 163.3, 163.0, 138.2, 128.2, 127.3, 64.8; **ν_{max}** 3450, 3405, 3306, 3065, 3040, 2954, 1621, 1591, 1522, 1290 cm^{-1}; **MS (ESI) m/z** 194.1 (100% $[M+H]^+$); **HRMS (ESI) m/z** found 194.0922, $C_9H_{12}N_3O_2^+$ ($[M+H]^+$) requires 194.0924.

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

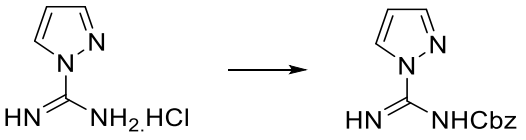


Chemical Formula: $C_{15}H_{20}N_4O_3$
Exact Mass: 304.15
Molecular Weight: 304.35

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); **Mp** 117 °C; **$[\alpha]_D^{21}$** -75 ($CHCl_3$, c = 1.0); **δ_H** ($CDCl_3$) 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, CH_2); **δ_C** ($CDCl_3$) 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; **ν_{max}** (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, $C_{15}H_{21}N_4O_3^+$ ($[M+H]^+$) requires 305.1608.

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



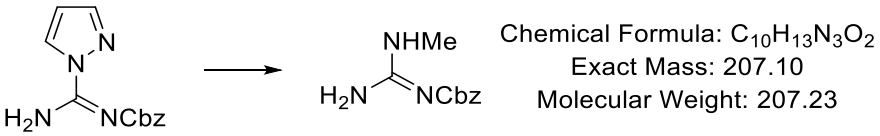
Chemical Formula: $C_{12}H_{12}N_4O_2$
Exact Mass: 244.10
Molecular Weight: 244.25

1*H*-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 ($MgSO_4$), 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); δ_H ($CDCl_3$) 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, CH_2); δ_C ($CDCl_3$) 163.9, 155.4, 143.9, 136.4, 129.1, 128.6, 128.4, 128.3, 109.5, 67.8; ν_{max} 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, $C_{12}H_{13}N_4O_2^+$ ($[M+H]^+$) requires 245.1039.

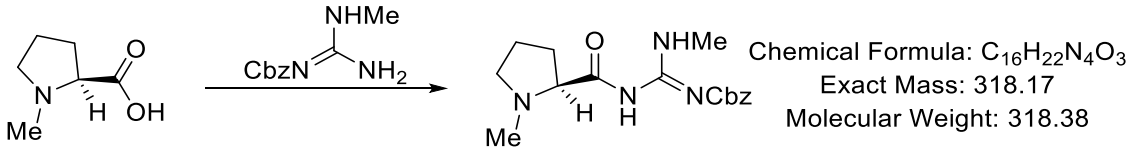
3.4.25 Preparation of *N*-methyl-*N'*-Cbz-guanidine 218.



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 ($MgSO_4$), 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); δ_H ($CDCl_3$) 8.75-7.93 (1H, br s, NH), 7.24-7.38 (5H, m, Ph), 5.76-6.92 (2H, br s, NH_2), 5.08 (2H, s, CH_2), 2.73 (3H, s, CH_3); δ_c ($CDCl_3$) 163.5, 162.4, 137.5, 128.5, 128.0, 127.9, 66.4, 27.4; ν_{max} 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, $C_{10}H_{14}N_3O_2^+$ ($[M+H]^+$) requires 208.1081.

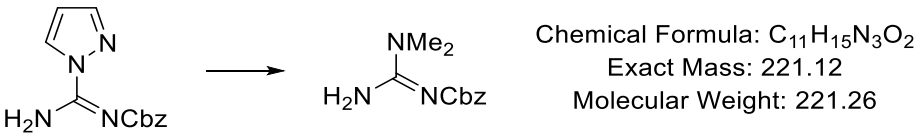
3.4.26 Preparation of (*S*)-*N*-(*N*'-Cbz-*N*-Methylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 219.



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); $[\alpha]_D^{20}$ -54.0 (CH_3Cl, c = 1.1); Mp 100-102 °C, δ_H ($CDCl_3$) 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, CH_2), 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, CH_3), 2.43 (3H, s, CH_3), 2.37-2.43 (1H, m, CH), 2.20-2.32 (1H, m, CH), 1.77-1.94 (3H, m, 3 × CH); δ_C ($CDCl_3$) 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; ν_{max} 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, $C_{16}H_{23}N_4O_3^+$ ($[M+H]^+$) requires 319.1765.

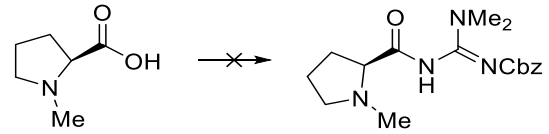
3.4.27 Preparation of *N*,*N*-dimethyl-*N*'-Cbz-guanidine 220.



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 ($MgSO_4$) 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); δ_H ($CDCl_3$) 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, NH_2), 5.13 (2H, s, CH_2), 3.04 (6H, s, 2 × CH_3); δ_C ($CDCl_3$) 163.8, 161.3, 137.7, 128.3, 128.0, 127.6, 66.6, 36.9; ν_{max} 3376, 3285, 3.037, 2957, 2894, 1575, 1479, 1442; **MS (ESI) m/z** 222.1 (100% $[M+H]^+$); **HRMS (ESI)** found 222.1237, $C_{11}H_{16}N_3O_2^+$ (100% $[M+H]^+$) requires 222.1237.

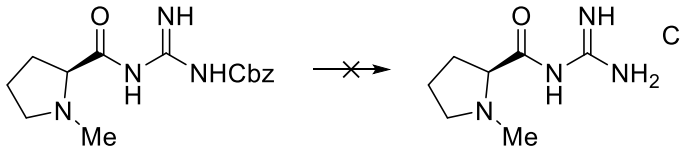
3.4.28 Attempted preparation of (*S*,*Z*)-*N*-(*N*'-(Cbz)-*N*,*N*-dimethylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 221.



Chemical Formula: $C_{17}H_{24}N_4O_3$
Exact Mass: 332.18
Molecular Weight: 332.40

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.

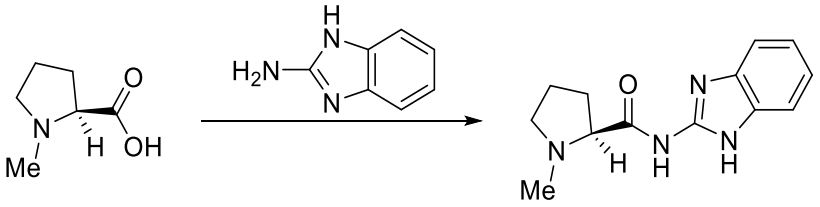


Chemical Formula: $C_7H_{14}N_4O$
Exact Mass: 170.12
Molecular Weight: 170.22

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); $[\alpha]_D^{18}$ -25.3 (CH_2Cl_2, c = 1.5); δ_H (CD_3OD) 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); δ_C (CD_3OD) 169.8, 68.9, 57.7, 54.0, 41.4, 29.0, 23.2; ν_{max} 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, $C_7H_{13}NaNO_2^+$ ($[M+Na]^+$) requires 166.0838.

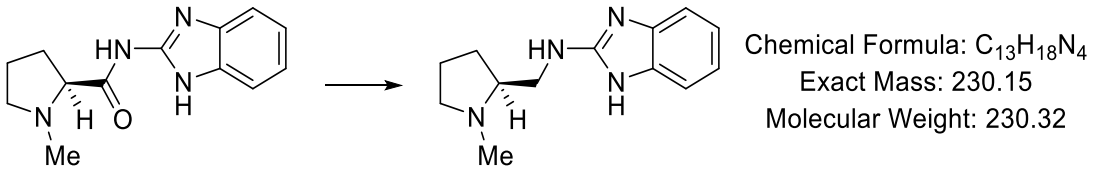
2.4.30 Preparation of (*S*)-*N*-(1*H*-benzo[d]imidazol-2-yl)-1-methylpyrrolidine-2-carboxamide 179a.



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; $[\alpha]_D^{16}$ -117 ($CDCl_3$, c = 1.0); δ_H ($CDCl_3$) 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); δ_C ($CDCl_3$) 175.3, 146.3, 138.3, 122.3, 122.3, 68.7, 56.7, 41.9, 31.4, 24.8; ν_{max} (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, $C_{13}H_{17}N_4O^+$ ($[M+H]^+$) requires 245.1397.

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

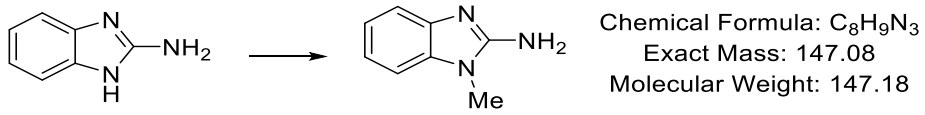


Lithium aluminum hydride (203.2 mg, 5.35 mmol, 4.36 equiv) was added in small portions to a cooled (0 °C) solution of amide **179a** (300.0 mg, 1.23 mmol, 1.0 equiv.) in DE (20 mL) over 30 min. After 6 h at 0 °C, the reaction was stirred for 18 h at rt then at reflux for 5 h. The reaction was quenched 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 ($MgSO_4$), filterting 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%);**$[\alpha]_D^{20}$** -75.4 ($CHCl_3$, c = 1.02); **δ_H** (CD_3OD) 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, CH_3), 2.38-2.47 (1H, m, CH), 2.00-2.11 (1H, m, CH), 1.69-1.87 (3H, m, CH, CH_2); **δ_C** (CD_3OD) 157.1, 139.0 (HMBC), 121.4, 112.8, 67.0, 58.1, 45.7, 41.2, 29.3, 23.5; **ν_{max}** 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, $C_{13}H_{19}N_4^+$ ($[M+H]^+$) requires 231.1604.

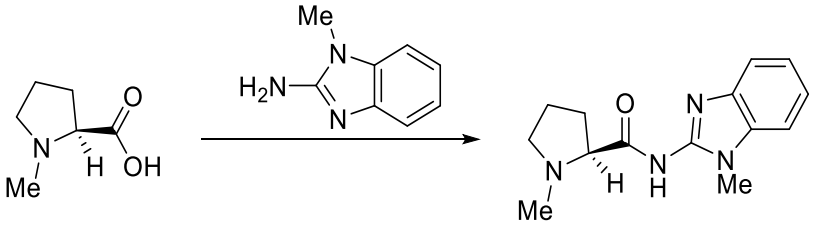
3.4.32 Preparation of 1-Methyl-1*H*-benzo[d]imidazol-2-amine 229.[103]



Powdered KOH (10.5 g, 187.8 mmol, 5.0 equiv.) was added to a stirred solution of 1*H*-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 ($MgSO_4$). After evaporation under reduced pressure, the residue was dissolved in a small volume of toluene and diluted with $CHCl_3$ 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 $CHCl_3$ (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 ($MgSO_4$) 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); **δ_H** (CD_3OD) 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); **δ_C** (CD_3OD) 156.4, 142.4, 135.8, 122.3, 120.6, 115.7, 108.6, 28.7; **ν_{max}** 3448, 3307, 3024, 2727, 1648, 1541, 1317 cm^{-1}; **MS (ESI) m/z** 148.1, (100%, $[M+H]^+$); **HRMS (ESI)** found 148.0872, $C_8H_{10}N_3^+$ ($[M+H]^+$) requires 148.0875.

3.4.33 Preparation of (*S*)-*N*-(1*H*-benzo[d]imidazol-2-yl)-1-methylpyrrolidine-2-carboxamide 230.

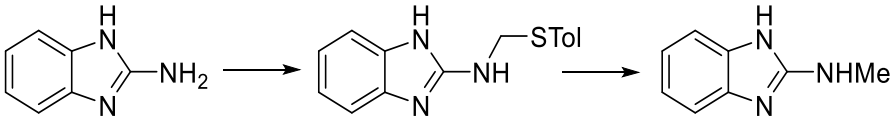


Chemical Formula: $C_{14}H_{18}N_4O$
Exact Mass: 258.15
Molecular Weight: 258.33

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% $CHCl_3$/MeOH); $\mathbf{[\alpha]_D^{23}}$ -32.2 (CH_2Cl_2, c = 1.6); $\mathbf{\delta_H}$ ($CDCl_3$) 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, CH_3), 3.26 (1H, br t, *J* 7.5 Hz, CH), 3.10-3.18 (1H, m, CH), 2.54 (3H, s, CH_3), 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); $\mathbf{\delta_C}$ ($CDCl_3$) 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; $\mathbf{\nu_{max}}$ 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; $C_{14}H_{19}N_4O^+$ ($[M+H]^+$) requires 259.1553.

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



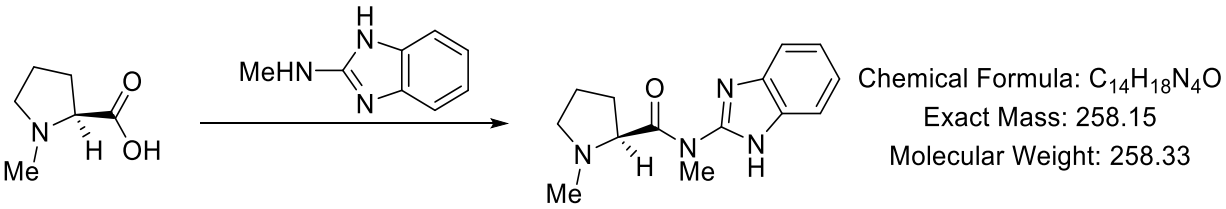
Chemical Formula: $C_8H_9N_3$
Exact Mass: 147.08
Molecular Weight: 147.18

1*H*-Benzo[*d*]imidazol-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 ($MgSO_4$) 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); **δ_H** (CD_3OD) 7.18-7.22 (2H, m, 2 × CH), 6.96-7.00 (2H, m, 2 × CH), 2.98 (3H, s, CH_3); **δ_C** (CD_3OD) 157.3, 138.3, 121.5, 112.6, 79.4, 29.6; **ν_{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, $C_8H_{10}N_3^+$ ($[M+H]^+$) requires 148.0869.

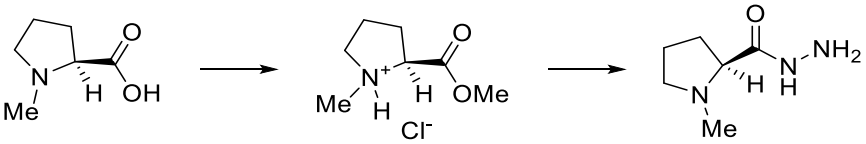
3.4.35 Preparation of (*S*)-*N*-(1*H*-Benzo[d]imidazol-2-yl)-*N*,1-dimethylpyrrolidine-2-carboxamide 233.



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-1*H*-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 $CHCl_3$); **Mp** 112-114 °C; **$[\alpha]_D^{18}$** -84.4 (CH_2Cl_2, c = 1.3); **δ_H** ($CDCl_3$) 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, CH_3), 3.39 (1H, dd, *J* 8.6, 7.2Hz, CH), 3.22-3.29 (1H, m, CH), 2.44 (3H, s, CH_3), 2.25-2.47 (2H, m, 2 × CH), 1.82-2.08 (3H, m, 3 × CH); **δ_C** ($CDCl_3$) 174.9 (HMBC), 149.9, 122.3, 118.3, 110.8, 68.0, 56.2, 41.0, 33.9, 29.7, 23.4; **ν_{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, $C_{13}H_{19}N_4O^+$ ($[M+H]^+$) requires 259.1553.

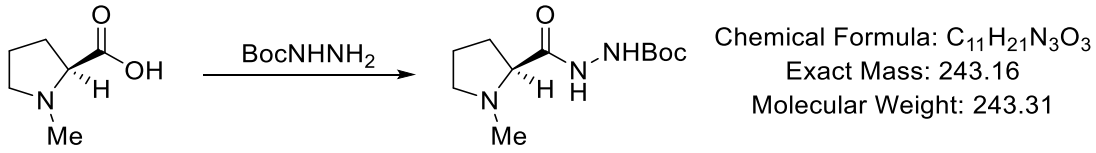
3.4.36 Preparation of (*S*)-1-Methylpyrrolidine-2-carbohydrazide 238.



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 (*2S*)-2-(methoxycarbonyl)-1-methylpyrrolidin-1-ium chloride (2.51 g, 14.0 mmol) as 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, 8.1 mL, 9.3 equiv.) was added drop wise 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 $CHCl_3$ (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% NEt_3) to give **238** (1.15 g, 8.03 mmol) as a pale yellow oil in 93% yield (73% over 2 steps).

Rf 0.24 (5% ME in CF with 1% NEt_3); $\mathbf{[\alpha]_D^{20}}$ -121.6 (CH_2Cl_2, c = 1.28); $\mathbf{\delta_H}$ ($CDCl_3$) 8.25 (1H, br s, NH), 3.74 (2H, br s, NH_2), 3.04 (1H, ddd, *J* 2.2, 6.5, 8.5 Hz, CH), 2.93 (1H, dd, *J* 10.3, 5.1 Hz, CH), 2.32 (3H, s, CH_3), 2.25-2.32 (1H, m, CH), 2.12-2.22 (1H, m, CH), 1.66-1.84 (3H, m, CH, CH_2); $\mathbf{\delta_C}$ ($CDCl_3$) 174.6, 68.1, 56.7, 41.9, 30.9, 24.4; $\mathbf{\nu_{max}}$ 3297, 2967, 2884, 2785, 1650, 1464, 1085 cm^{-1}; **MS (ESI) m/z** 144.1 (51%, $[M+H]^+$); **HRMS (ESI)** found 144.1128, $C_6H_{14}N_3O^+$ ($[M+H]^+$) requires 144.1131.

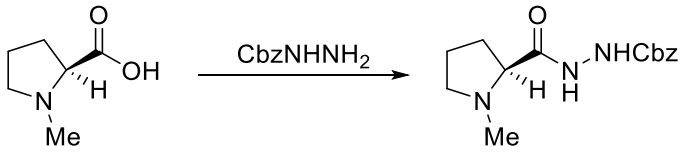
3.4.37 Preparation of *tert*-Butyl 2-(methyl-L-prolyl)hydrazine-1-carboxylate 240.



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]$_D^{20}$** -73.3 (CH_3Cl, c = 1.08); **Mp** 102-106 °C; **δ_H** ($CDCl_3$) 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, CH_3), 2.28-2.37 (1H, m, CH), 2.16-2.27 (1H, m, CH), 1.73-1.97 (3H, m, CH, CH_2), 1.47 (9H, s, 3 × CH_3); **δ_C** ($CDCl_3$) 173.7, 155.2, 81.8, 68.3, 56.8, 41.9, 31.0, 28.3, 24.4; **ν_{max}** 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, $C_{11}H_{22}N_3O_3^+$ ($[M+H]^+$) requires 244.1656.

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

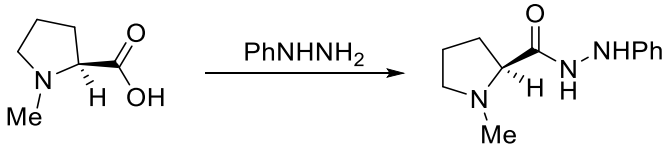


Chemical Formula: $C_{14}H_{19}N_3O_3$
Exact Mass: 277.14
Molecular Weight: 277.32

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]$_D^{21}$** -61.3 (CH_3Cl, c = 0.45); **δ_H** ($CDCl_3$) 8.82 (1H, s, NH), 7.41-7.29 (5H, m, Ph), 6.75 (1H, s, NH), 5.16 (2H, s, CH_2), 3.15-3.06 (1H, m, CH), 3.05-2.95 (1H, m, CH), 2.42 (3H, s, CH_3), 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, CH_2); **δ_C** ($CDCl_3$) 156.1, 135.7, 128.7, 128.5, 128.3, 68.3, 68.0, 56.7, 41.8, 31.0, 24.4; **ν_{max}** 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, $C_{14}H_{20}N_3O_3^+$ ($[M+H]^+$) requires 278.1499.

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



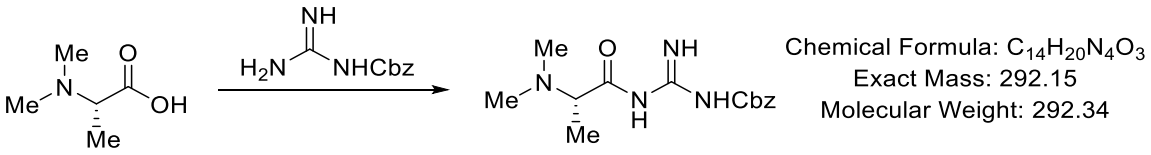
Chemical Formula: $C_{12}H_{17}N_3O$
Exact Mass: 219.14
Molecular Weight: 219.29

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 $CHCl_3$), gave **244** (1.0 g, 4.56 mmol) as a yellow solid in 50% yield.

Rf 0.25 (5% ME in EA), **$[\alpha]_D^{20}$** -64.6 (CH_3Cl, c = 1.05); **Mp** 101-103 °C; **δ_H** ($CDCl_3$) 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, CH_3), 2.38 (1H, m, CH), 2.33-2.19 (1H, m, CH), 1.98-1.76 (3H, m, CH + CH_2); **δ_C** ($CDCl_3$) 173.9, 148.2, 129.2, 121.1, 113.6, 68.3, 56.8, 42.2, 31.2, 24.6; **ν_{max}** 3267, 2965, 2849, 2788, 1672, 1602, 1495, 1351, 1084 cm^{-1}; **MS (TOF ASAP) m/z** 220.2 (100%, $[M+H]^+$); **HRMS (TOF ASAP)** found 220.1454, $C_{12}H_{18}N_3O^+$ ($[M+H]^+$) requires 220.1444.

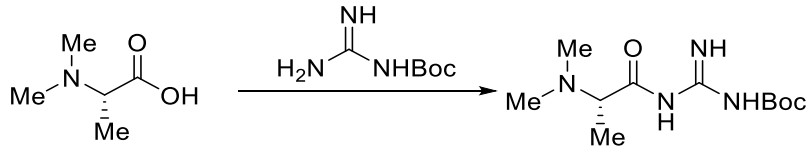
3.4.40 Preparation of (*S*)-*N*-Cbz-*N'*-carbamimidoyl-2-(dimethylamino)propanamide 245.



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); **$[\alpha]_D^{23}$** +31.3 (CH_2Cl_2, c = 1.8); Mp 112-114 °C, **δ_H** ($CDCl_3$) 8.45-10.94 (3H, br s, 3 × NH), 7.23-7.41 (5H, m, CH), 5.11 (2H, s, CH_2), 3.13 (1H, q, *J* 7.0 Hz, CH), 2.21 (6H, s, 2 × CH_3), 1.19 (3H, d, *J* 7.0 Hz, CH_3); **δ_C** ($CDCl_3$) 177.2, 163.8, 158.9, 136.6, 128.4, 128.1, 127.9, 66.9, 64.6, 41.8, 9.5; **ν_{max}** 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 $C_{14}H_{21}N_4O_3^+$ $[M+H]^+$ requires 293.1614.

3.4.41 Preparation of (*S*)-*N*-Boc-*N'*-Carbamimidoyl-2-(dimethylamino)propanamide 246.

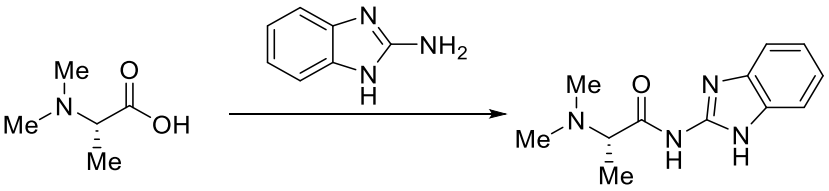


Chemical Formula: $C_{11}H_{22}N_4O_3$
Exact Mass: 258.17
Molecular Weight: 258.32

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); $[\alpha]_D^{18}$ + 27.8 (CH_2Cl_2, c = 1.05); **Mp** 119-120 °C; δ_H ($CDCl_3$) 8.96 (3H, br s, 3 × NH), 3.12 (1H, q, *J* 6.9 Hz, CH), 2.22 (6H, s, CH_3), 1.49 (3H, s, 3 × Me), 1.20 (3H, d, *J* 7.0 Hz, CH_3); δ_C ($CDCl_3$) 177.3, 158.6, 79.5, 64.9, 41.9, 28.3, 9.8; ν_{max} 3380, 3129, 2972, 2938, 2871, 2832, 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, $C_{11}H_{23}N_4O_3^+$ ($[M+H]^+$) requires 259.1765.

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



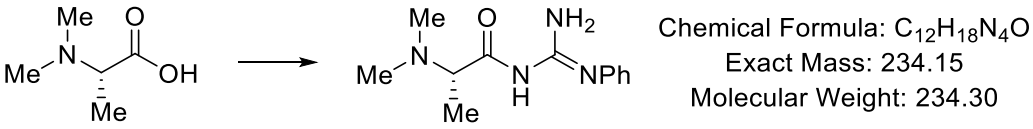
Chemical Formula: $C_{12}H_{16}N_4O$
Exact Mass: 232.13
Molecular Weight: 232.29

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); $[\alpha]_D^{20}$ +24.3 (CH_3Cl, c = 1.07); **Mp** 208-210 °C; δ_H ($(CD_3)_2SO$) 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, q, *J* 6.8 Hz, CH), 2.28 (6H, s, 2 × CH_3), 1.20 (3H, d, *J* 6.8 Hz, CH_3); δ_C ($CDCl_3$) 172.5, 146.2, 140.5 (HMBC), 134.4 (HMBC), 121.0, 62.2, 41.2, 12.4; ν_{max} 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, $C_{12}H_{17}N_4O^+$ ([M+H]$^+$) requires 233.1402.

3.4.43 Attempted preparation of (*S*)-2-(dimethylamino)-*N*-(*N*'-phenylcarbamimidoyl)propanamide 250.

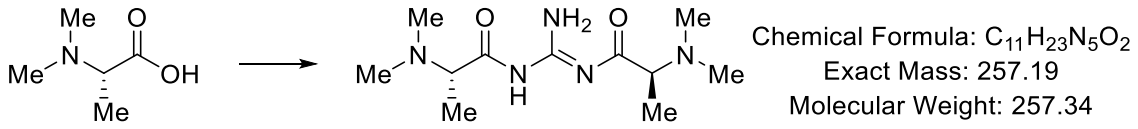


Method B: *N*-dimethyl-L-alanine **191** (0.50 g, 4.27 mmol, 1.0 equiv.); DMF (15 mL); CDI (1.38 g, 8.54 mmol, 2.0 equiv.); 24 h; NaH (60%, 170.0 mg, 4.27 mmol, 1.0 equiv.); DMF (15 mL); phenylguanidinium nitrate **203** (846.0 mg, 4.27 mmol, 1.0 equiv.); 4 d. Extraction with EA and repeated column chromatography (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 equivavlents of the guanidine salt and the nature of the counterion gave similar mixtures of the two compounds. (Table 13)

Table 13

Entry	HX	191	CDI	G.HX/equiv.	NaH/equiv.	Yield
1	HNO_2	1.0 (0.5g)	2.0	1.0	1.0	0.90 g
2	½ H_2CO_3	1.0 (1.0g)	2.5	1.25	2.15	1.50 g
3	½ H_2CO_3	1.0 (1.0g)	2.17	0.83	0.8	0.85 g
4	HCl	1.0 (1.0g)	2.17	0.96	1.25	1.23 g

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

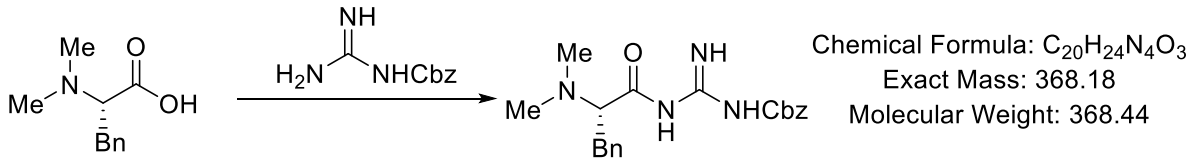


Method B: *Attempt* 1: *N*,*N*-Dimethyl-L-alanine **191** (1.0 g, 8.54 mmol, 1.0 equiv.); DMF (15 mL); CDI (2.08 g, 12.80 mmol, 1.5 equiv.); 24 h; guanidinium hydrochloride **206** (404.0 mg, 4.12 mmol, 0.5 equiv.); DMF (10 mL); NaH (60%, 205.0 mg, 5.12 mmol, 0.6

equiv.); 24h; 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.

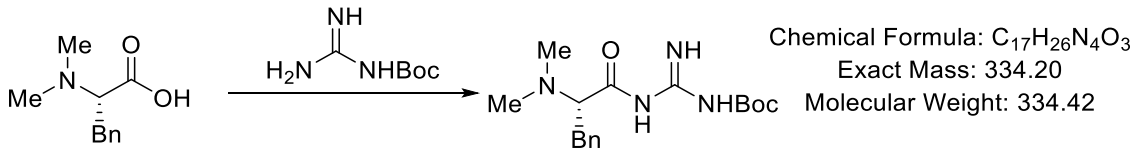
3.4.45 Preparation of (*S*)-*N*-Cbz-*N'*-Carbamimidoyl-2-(dimethylamino)-3-phenylpropanamide 252.



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_2Cl_2, c = 3.0); **Mp** 141-143 °C, **δ_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); **δ_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; **ν_{max}** 3381, 3284, 3063, 3030, 2929, 2789, 1704, 1650, 1621, 1530, 1496, 1453, 1268, 1165 cm^{-1}; **MS (ESI) m/z** 385.2 (100%, $[M+H_2O-H]^+$), 369.2 (43%, $[M+H]^+$); **HRMS (ESI)** found 369.1926, $C_{20}H_{25}N_4O_3^+$ $[M+H]^+$ requires 369.1921.

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

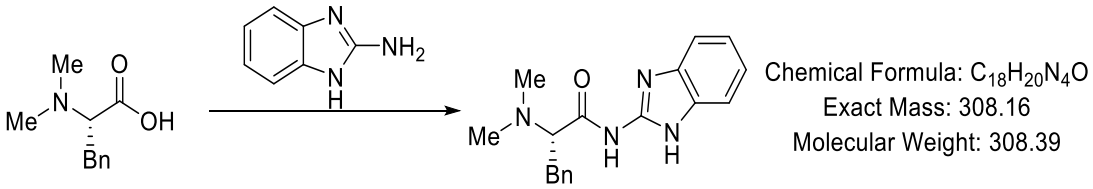


Method A: *N*-Methyl-L-phenylalanine **193** (1.00 g, 5.17 mmol, 1.0 equiv.); DMF (20 mL); CDI (1.30 g, 7.76 mmol, 1.55 equiv.); 24 h; *N*-Boc-guanidine **207** (823.8 mg, 5.17 mmol,

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); **$[\alpha]_D^{18}$** +37.0 (CH_2Cl_2, c = 1.9); **Mp** 101-103 °C; **δ_H** ($CDCl_3$) 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, CH_2), 2.88 (1H, d, *J* 5.9 Hz, CH_2), 2.27 (6H, s, CH_3), 1.47 (9H, s, CH_3); **δ_C** ($CDCl_3$) 176.0, 162.9, 158.4, 138.9, 129.1, 128.6, 126.5, 79.5, 71.4, 42.0, 31.5, 28.2; **ν_{max}** 3386, 3285, 2975, 2935, 2832, 2789, 1702, 1654, 1620, 1561, 1530, 1495, 1293 cm^{-1}; **MS (ESI) m/z** 351.2 (100%, $[M+H_2O-H]^+$), 335.2 (100%, $[M+H]^+$); **HRMS (ESI)** found 335.2082, $C_{17}H_{27}N_4O_3^+$ ($[M+H]^+$), requires 335.2078.

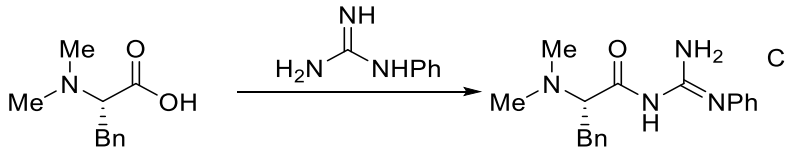
3.4.47 Preparation of (*S*)-*N*-(1*H*-Benzo[*d*]imidazol-2-yl)-2-(dimethylamino)-3-phenylpropanamide 254.



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); **$[\alpha]_D^{20}$** +33.5 (MeOH, c = 2.6); **Mp** 133-136 °C; **δ_H** ($CDCl_3$) 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), 2.35 (6H, s, 2 × CH_3); **δ_C** ($CDCl_3$) 172.9, 146.7, 141.0 (HMBC), 138.7, 129.0, 128.5, 126.5, 122.3, 70.6, 42.0, 32.5; **ν_{max}** 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, $C_{18}H_{21}N_4O^+$ ($[M+H]^+$) requires 309.1710.

3.4.48 Preparation of (*S*)-2-(dimethylamino)-3-phenyl-*N*-(*N'*-phenylcarbamimidoyl)propanamide 255.

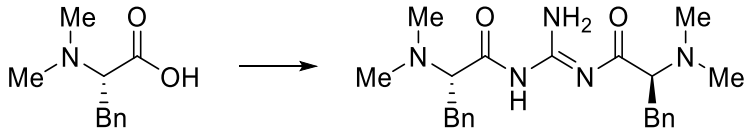


Chemical Formula: $C_{18}H_{22}N_4O$
Exact Mass: 310.18
Molecular Weight: 310.40

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); **$[\alpha]_D^{19}$** + 49.7 (CH_2Cl_2, c = 2.15); **δ_H** ($CDCl_3$) 7.09-7.51 (11H, m, NH, NH_2, 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 × CH_3); **δ_C** ($CDCl_3$) 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; **ν_{max}** 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, $C_{18}H_{21}N_4O^-$ ($[M-H]^-$) requires 309.1721.

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



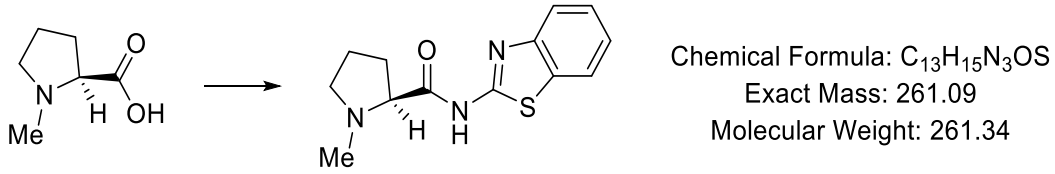
Chemical Formula: $C_{23}H_{31}N_5O_2$
Exact Mass: 409.25
Molecular Weight: 409.53

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 NH_3 (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 NH_3); **$[\alpha]_D^{21}$** +61.9 (CH_2Cl_2, c = 1.38); **δ_H** ($CDCl_3$) 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 × CH_3);

δC ($CDCl_3$) 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, $C_{23}H_{32}N_5O_2^+$ ($[M+H]^+$) requires 410.2551.

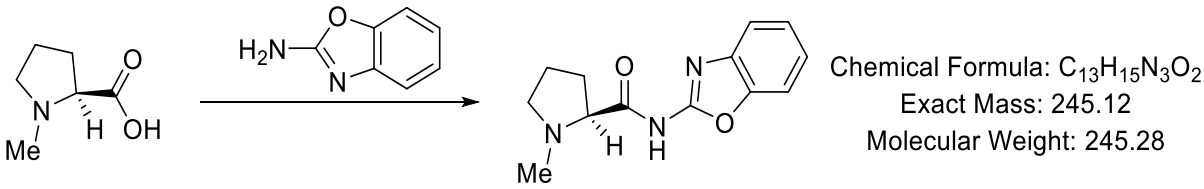
3.4.50 Preparation of (*S*)-*N*-(benzo[*d*]thiazol-2-yl)-1-methylpyrrolidine-2-carboxamide 262



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% NH_3) gave **262** (1.00 g, 3.81 mmol, 74%) as a white solid.

Rf 0.1 (30% EA in PE with 0.1 % NH_3); **mp** 79-83 °C, **[α]D19** -38.0 ($CHCl_3$, c = 1.0); **δH** ($CDCl_3$) 9.82-11.72 (1H, br s, NH), 7.82 (1H, d, *J* 7.9 Hz, CH), 7.78 (1H, d, *J* 8.1 Hz, CH), 7.44 (1H, dd (apparent t), *J* 8.1, 7.5 Hz, CH), 7.31 (1H, dd (apparent t), *J* 7.9, 7.5 Hz, CH), 3.17-3.30 (2H, m, 2 × CH), 2.49 (3H, s, CH_3), 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, CH_2); **δC** ($CDCl_3$) 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, $C_{13}H_{16}N_4OS^+$ ($[M+H]^+$) requires 262.1009.

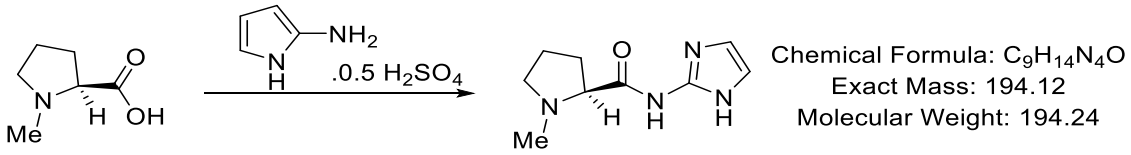
3.4.51 Attempted preparation of (*S*)-*N*-(benzo[d]oxaazol-2-yl)-1-methylpyrrolidine-2-carboxamide 264.



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**.

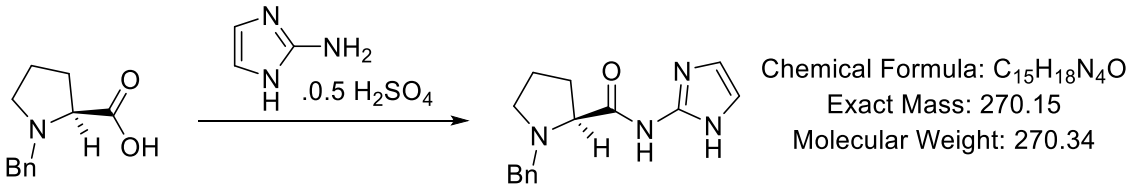
3.4.52 Preparation of *(S)*-1-Methyl-*N*-(1*H*-imidazol-2-yl)pyrrolidine-2-carboxamide 270.



Method A: *N*-Methyl-L-proline **175a** (1.00 g, 7.74 mmol, 1.6 equiv.); CDI (2.26 g, 13.94 mmol, 1.8 equiv.); DMF (15 mL); 24 h; 2-aminoimidazole hemisulfate (1.26 g, 14.98 mmol, 0.60 equiv.); Et_3N (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) gave **270** (1.47 g, 7.57 mmol, 97%) as a off-white solid.

Rf 0.24 (10% EA in ME); **Mp** 180-182 °C; **$[\alpha]_D$** -73.3 (c = 0.3, $CHCl_3$); **δ_H** ($CDCl_3$) 9.55-11.41 (2H, br s, 2 × NH), 6.82 (2H, s, 2 × 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); **δ_C** ($CDCl_3$) 174.3, 140.5, 68.5, 56.8, 42.0, 31.4, 24.8 (Imidazole 2 × CH not detected); **ν_{max}** 3223, 2960, 2845, 2786, 1671, 1585, 1524, 1492 cm^{-1}; **MS (ESI) m/z** 195.1 (100%, $[M+H]^+$); **HRMS (ESI)** found 195.1240, $C_9H_{15}N_4O^+$ ($[M+H]^+$) requires 195.1241.

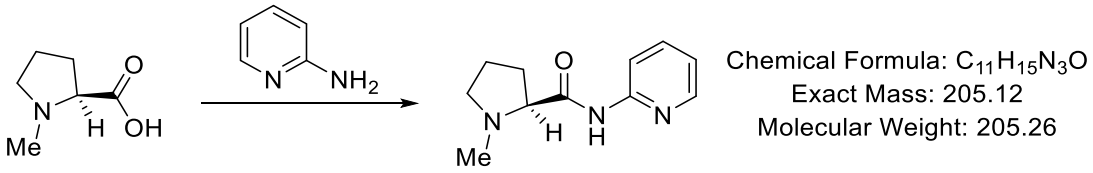
3.4.53 Preparation of *(S)*-1-Benzyl-*N*-(1*H*-imidazol-2-yl)pyrrolidine-2-carboxamide 271.



Method A: *N*-benzyl-L-proline **175b** (1.0 g, 4.87 mmol, 1.0 equiv.); CDI (1.44 g, 8.77 mmol, 1.80 equiv.); DMF (15 mL); 16 h; 2-aminoimidazole hemisulfate (772.0 mg, 5.84 mmol, 1.2 equiv.); Et_3N (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.

Rf 0.31 (50% EA in PE); **Mp** 64 °C; **[α]$_D$** -198 (c = 1, $CHCl_3$); **δ$_H$** ($CDCl_3$) 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); **ν$_{max}$** 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, $C_{15}H_{18}N_4ONa$ ($[M+Na]^+$) requires 293.1373.

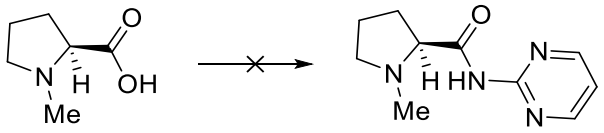
3.4.54 Preparation of (S)-1-Methyl-*N*-(pyridine-2-yl)pyrrolidine-2-carboxamide 268a



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% NH_3) 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]$_D^{20}$** -78.9 (c = 1.0 in CF); **δ$_H$** ($CDCl_3$) 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, CH_2), 1.77-1.88 (2H, m, CH_2); **δ$_C$** ($CDCl_3$) 178.4, 151.4, 148.1, 138.4, 119.8, 113.9, 69.5, 56.7, 41.9, 31.3, 24.6; **ν$_{max}$** 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, $C_{11}H_{16}N_3O^+$ ($[M+H]^+$) requires 206.1288.

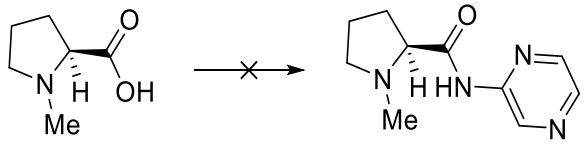
3.4.55 Preparation of (*S*)-1-methyl-*N*-(pyrimidin-2-yl)pyrrolidine-2-carboxamide 268b



Chemical Formula: $C_{10}H_{14}N_4O$
Exact Mass: 206.12
Molecular Weight: 206.25

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**.

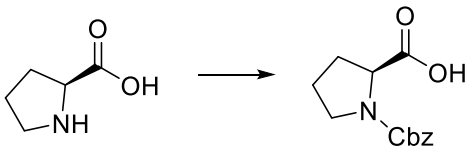
3.4.56 Attempted preparation of (*S*)-1-methyl-*N*-(pyrazin-2-yl)pyrrolidine-2-carboxamide 268c



Chemical Formula: $C_{10}H_{14}N_4O$
Exact Mass: 206.12
Molecular Weight: 206.25

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 [113]



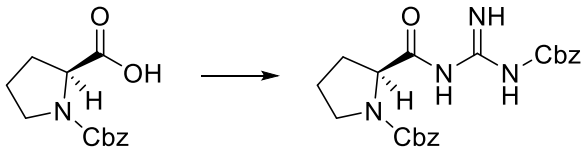
Chemical Formula: $C_{13}H_{15}NO_4$
Exact Mass: 249.1001
Molecular Weight: 249.2660

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 ($MgSO_4$) 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.

Rf 0.09 (EA); **Mp**. 74-76 °C (Lit.[113] 69-75 °C); **[α]$_D^{20}$** -70.0 (c = 1.3, CF, Lit.[113] **[α]$_D^{20}$** -73.6 (c = 1.4, CF); **δ_H** ($CDCl_3$) 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) ppm; **δ_C** ($CDCl_3$) 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; **ν_{max}** 3444, 3032, 2957, 2884, 1665, 1498, 1416, 1355, 1120, 1088, 1028; **MS (ESI) m/z** 248.1 (100%, $[M+H]^+$); **HRMS (ESI)** found 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.

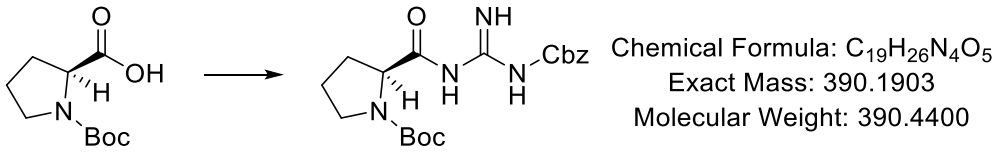


Chemical Formula: $C_{22}H_{24}N_4O_5$
Exact Mass: 424.17
Molecular Weight: 424.46

Method A: *N*-Cbz-L-proline **290** (1.51 g, 6.07 mmol, 1.0 equiv.); DMF (10 mL), 0 °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 × 150 mL) and brine (3 × 50 mL); column chromatography (0-30% EA in PE) gave **292** (1.73 g, 4.08 mmol) in 67% yield as a white solid.

Rf 0.49 (EA); **Mp** 47-49 °C; **[α]$_D^{20}$** -60.1 (2.0, CF); **δ_H** ($CDCl_3$) 7.82-9.96 (3H, br s, 3 × NH), 7.16-7.45 (10H, m, 2 × 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); **δ_C** ($CDCl_3$) 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; **ν_{max}** 3383, 3274 , 3032, 2957, 2886, 1703, 1662, 1627, 1539, 1498, 1446, 1414, 1379, 1355, 1277, 1170, 1116, 1090, 1026, 989, 914, 806, 748 cm^{-1}; **MS (ESI) m/z** 425.2 (100%, $[M+H]^+$), **HRMS (ESI) m/z** found 425.1814, $C_{22}H_{25}N_4O_5^+$ ($[M+H]^+$) requires 425.1819.

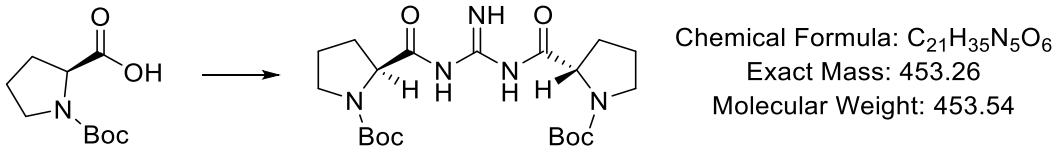
3.4.59 Preparation of *tert*-Butyl (*S*)-2-((*N*-((benzyloxy)carbonyl)carbamimidoyl)carbamoyl)pyrrolidine-1-carboxylate 293.



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; $\mathbf{[\alpha]_D^{20}}$ -53.8 (2.1, CF); $\mathbf{\delta_H}$ ($CDCl_3$) 7.63-10.22 (3H, br. s, 3 × NH), 7.27-7.38 (5H, m, Ph), 5.11 (2H, s, CH_2), 4.11-4.46 (1H, m, CH), 3.28-3.62 (2H, m, CH_2), 1.94-2.30 (2H, m, CH_2), 1.76-1.94 (2H, m, CH_2), 1.44/1.40 (9H, 2 × s, 3 × CH_3); $\mathbf{\delta_C}$ ($CDCl_3$) 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); $\boldsymbol{\nu_{max}}$ 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, $C_{19}H_{27}N_4O_5^+$ ($[M+H]^+$) requires 391.1976

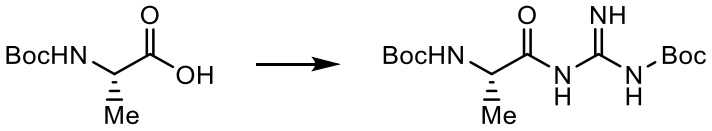
3.4.60 Preparation of Di-*tert*-butyl 2,2'-(((iminomethylene)bis(azanediyl))bis(carbonyl))(2*S*,2'*S*)-bis(pyrrolidine-1-carboxylate) 294.



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

Rf 0.35 (EA); **Mp** 65-69 °C; **[α]$_D^{20}$**-77.1 (2.3, CF); **δ_H** ($CDCl_3$) 6.93-11.12 (3H, br s, 3 × NH), 4.13-4.48 (2H, m, 2 × CH), 3.29-3.69 (4H, m, 2 × CH_2), 1.70-2.35 (8H, m, 4 × CH_2), 1.45 (9H, s, 3 × Me), 1.39 (9H, s, 3 × Me); **δ_C** ($CDCl_3$) 158.3, 145.9, 138.5, 80.2, 62.9/62.0, 47.1/46.9, 31.3/31.2, 28.5, 24.5/23.8; **ν_{max}** 3366, 3231, 2976, 2932, 2879, 1692, 1643, 1520, 1477, 1451, 1392, 1365, 1249, 1158, 1122; **MS (ESI) m/z** 454.3 (100% $[M+H]^+$); **HRMS (ESI)** found 454.2654, $C_{21}H_{36}N_5O_6^+$ ($[M+H]^+$) requires 454.2660.

3.4.61 Preparation of *tert*-Butyl (*S*)-(1-(3-(*tert*-butyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 296.

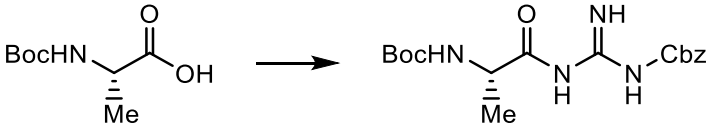


Chemical Formula: $C_{14}H_{26}N_4O_5$
Exact Mass: 330.19
Molecular Weight: 330.39

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); **ν_{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, $C_{14}H_{27}N_4O_5^+$ ($[M+H]^+$) requires 331.1976.

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



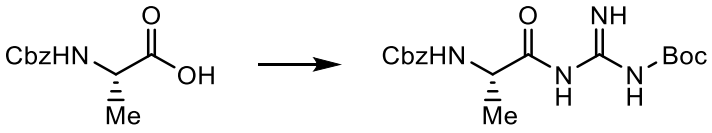
Chemical Formula: $C_{17}H_{24}N_4O_5$
Exact Mass: 364.17
Molecular Weight: 364.40

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, 5.81mmol, 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]$_D^{25}$** -18.8 (CH_3Cl, c = 1.15); **Mp** 138-140 °C; **δ_H** ($CDCl_3$) 7.93-10.03 (3H, br. s, 3 × NH), 7.29-7.42 (5H, m, Ph), 5.15 (2H, s, CH_2), 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, CH_3); **δ_C** ($CDCl_3$) 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); **ν_{max}** 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, $C_{17}H_{25}N_4O_5^+$ ($[M+H]^+$) requires 365.1820.

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

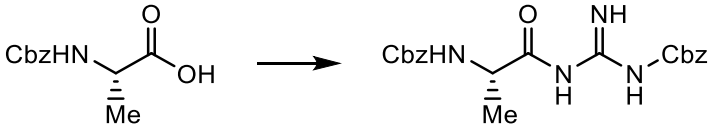


Chemical Formula: $C_{17}H_{24}N_4O_5$
Exact Mass: 364.17
Molecular Weight: 364.40

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), $NaHCO_3$ (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]$_D^{28}$** -21.2 ($CHCl_3$, c = 1.0); **Mp** 64-66 °C; **δ_H** ($CDCl_3$) 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** ($CDCl_3$) 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); **ν_{max}** 3374, 3101, 2976, 1720, 1639, 1524, 1500, 1236, 1146 cm^{-1}; **MS (ESI) m/z** 365.2 (100, $[M+H]^+$), **HRMS (ESI)** found 365.1819, $C_{17}H_{25}N_4O_5^+$ ($[M+H]^+$) requires 365.1819.

3.4.64 Preparation of Benzyl (*S*)-(1-(3-(benzyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 300.

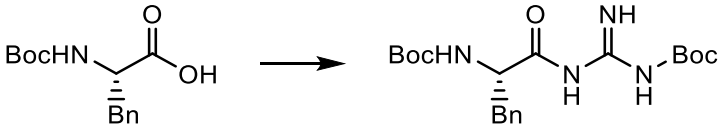


Chemical Formula: $C_{20}H_{22}N_4O_5$
Exact Mass: 398.16
Molecular Weight: 398.42

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, 4.93mmol, 1.1 equiv.); DMF (5 mL); 3 d, rt. Extraction with CF (3 × 50 mL); washing with HCl (aq. 0.1 M, 50 mL), $NaHCO_3$ (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); **$[\alpha]_D^{23}$** -17.5 ($CHCl_3$, c = 1.0); **Mp** 95-98 °C; **δ_H** ($CDCl_3$) 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, CH_2), 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); **δ_C** ($CDCl_3$) 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); **ν_{max}** 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, $C_{20}H_{23}N_4O_5^+$ ($[M+H]^+$) requires 399.16630.

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



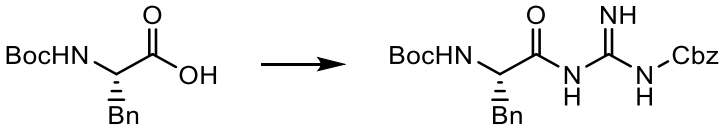
Chemical Formula: $C_{20}H_{30}N_4O_5$
Exact Mass: 406.22
Molecular Weight: 406.48

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); **$[\alpha]_D^{21}$** -21.0 (CH_3Cl, c = 1.0); **Mp** 64-66 °C; **δ_H** ($CDCl_3$; 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, CH_2), 1.42 (9H, s, 3 × Me), 1.34 (9H, s, 3 × Me); **δ_C** ($CDCl_3$) 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); **ν_{max}** 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, $C_{20}H_{31}N_4O_5^+$ ($[M+H]^+$), requires 407.2289.

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

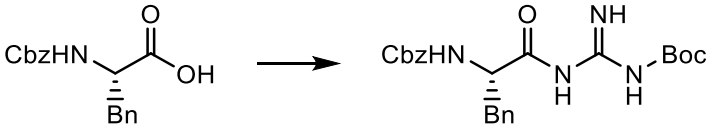


Chemical Formula: $C_{23}H_{28}N_4O_5$
Exact Mass: 440.2060
Molecular Weight: 440.5000

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), $NaHCO_3$ (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); **$[\alpha]_D^{25}$** -20.8 (CH_3Cl, c = 1.27); **Mp** 151-154 °C; **δ_H** ($CDCl_3$) 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, CH_2), 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); **δ_C** ($CDCl_3$) 158.7, 155.2, 136.0, 135.8, 129.2, 128.7, 128.5, 128.2, 128.2, 127.1, 80.7, 67.3, 56.9, 37.8, 28.2 (1 × C not detected); **ν_{max}** 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, $C_{23}H_{29}N_4O_5^+$ ($[M+H]^+$), requires 441.2132.

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



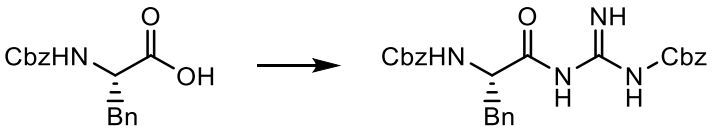
Chemical Formula: $C_{23}H_{28}N_4O_5$
Exact Mass: 440.21
Molecular Weight: 440.50

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), $NaHCO_3$

(aq. sat. 50 mL) and brine (2 × 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]$_D^{21}$** -32.2 (CH_3Cl, c = 1.54); **Mp** 123-125 °C; **δ_H** ($CDCl_3$) 8.34-10.29 (2H, br s, 2 × NH), 8.65 (1H, br s, NH), 7.26-7.41 (5H, m, Ph) 7.15-7.25 (3H, m, 3 × CH), 7.06 (2H, br d, *J* 6.6 Hz, CH) 5.58 (1H, d, *J* 7.0 Hz, NH), 5.12 (1H, d, *J* 12.7 Hz, CH), 5.08 (1H, d, *J* 12.7 Hz, CH), 4.57-4.62 (1H, m, CH), 3.25 (1H, dd, *J* 13.6, 5.0 Hz, CH), 3.11 (1H, dd, *J* 13.6, 5.2 Hz, CH) 1.48 (9H, s, 3 × Me); **δ_C** ($CDCl_3$) 159.1, 155.7, 136.7, 129.6, 129.6, 128.5, 128.4, 128.2, 128.1, 126.8, 83.6, 66.7, 58.2, 38.5, 28.0 (2 × C not detected); **ν_{max}** 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, $C_{23}H_{29}N_4O_5^+$ ($[M+H]^+$), requires 441.2133.

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

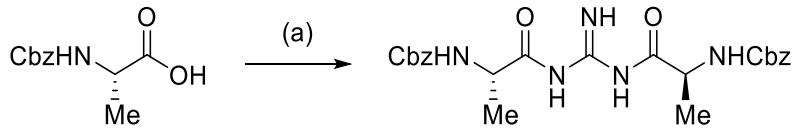


Chemical Formula: $C_{26}H_{26}N_4O_5$
Exact Mass: 474.19
Molecular Weight: 474.52

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 × 50 mL); washed with HCl (0.1 M, 50 mL), $NaHCO_3$ (aq. sat. 50 mL) and brine (2 × 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]$_D^{25}$** -19.6° ($CHCl_3$, c = 1.0); **Mp** 83-86 °C; **δ_H** ($CDCl_3$) 7.71-9.79 (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 , CH_2), 5.01-5.13 (2H, m, 2 × CH), 4.28-4.59 (1H, br m, CH), 2.85-3.35 (2H, m, CH_2); **δ_C** (DEPT-135, $CDCl_3$) 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; **ν_{max}** 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)** $C_{26}H_{27}N_4O_2^+$ $[M+H]^+$), requires 475.1976, found 475.1977.

3.4.69 Preparation of Dibenzyl ((2*S*,2'*S*)-((iminomethylene)bis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate 307.

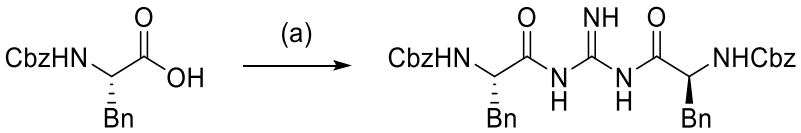


Chemical Formula: $C_{23}H_{27}N_5O_6$
Exact Mass: 469.1961
Molecular Weight: 469.4980

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.); 24h; 2 d. Extraction with CF and column chromatography (90-100% Et_2O in hexane) gave **307** (0.45 g, 0.95 mmol) in 51% yield as a white solid.

Rf 0.37 (DE); **$[\alpha]_D^{27}$** -22.7 ($CHCl_3$, c = 1.0); **Mp** 90-93 °C; **δ_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); **δ_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); **ν_{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, $C_{23}H_{28}N_5O_6^+$ ($[M+H]^+$) requires 470.2034.

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



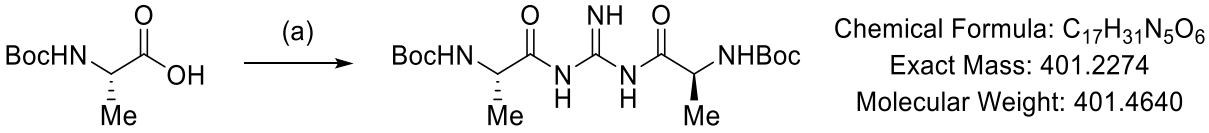
Chemical Formula: $C_{35}H_{35}N_5O_6$
Exact Mass: 621.2587
Molecular Weight: 621.6940

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.

Rf 0.30 (75% DE in PE), **$[\alpha]_D^{28}$** -12.8 ($CHCl_3$, c = 1.0); **Mp** 150-152 °C; **δ_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 ×

CH); 5.24-5.48 (2H, br s, 2 × NH), 4.96-5.14 (4H, m, 2 × CH_2), 4.31-4.59 (2H, m, 2 × CH), 2.80-3.23 (4H, m, 2 × CH_2); **δ_C** 158.3, 156.1, 136.2, 136.0, 129.4, 128.7, 128.6, 128.3 128.2, 127.2, 67.3, 57.8, 38.2 (1 × C missing); **ν_{max}** 3351, 3063, 3030, 2952, 1689, 1644, 1604, 1496, 1212 cm^{-1}; **MS (ESI) m/z** 622.3 (100, $[M+H]^+$), **HRMS (ESI)** found 622.2660, $C_{35}H_{36}N_5O_6^+$ ($[M+H]^+$) requires 622.2667.

3.4.71 Preparation of Di-*tert*-butyl ((2*S*,2'*S*)-((iminomethylene)bis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate 309.

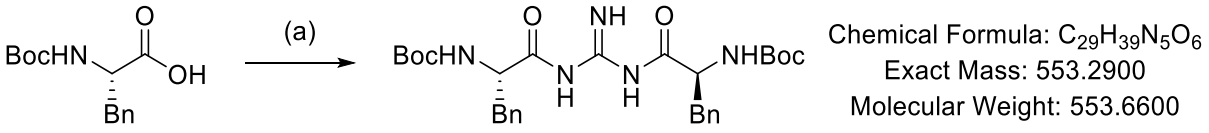


Chemical Formula: $C_{17}H_{31}N_5O_6$
Exact Mass: 401.2274
Molecular Weight: 401.4640

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, 3.98 mmol, 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); **$[\alpha]_D^{21}$** -30.0 (CF, c = 1.0); **Mp** 76-78 °C; **δ_H** 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); **δ_C** ($CDCl_3$) 158.8, 155.6, 80.2, 52.3, 28.4, 18.7 (1 × C not detected); **ν_{max}** 3245, 3219, 3001, 2977, 2932, 1690, 1644, 1603, 1509, 1247; cm^{-1}; **MS (ESI) m/z** 402.23 (100, $[M+H]^+$); **HRMS (ESI)** found 402.2348, $C_{17}H_{32}N_5O_6^+$ ($[M+H]^+$) requires 402.2347.

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



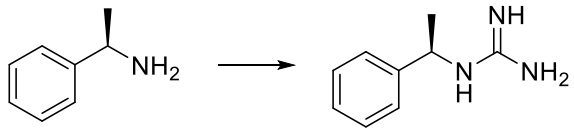
Chemical Formula: $C_{29}H_{39}N_5O_6$
Exact Mass: 553.2900
Molecular Weight: 553.6600

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% Et_2O 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 ($CHCl_3$, c = 1.0); **Mp** 83-86 °C; **δ_H** 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 × CH_2), 1.42 (18H, s, 6 × Me); **δ_C** 158.3, 155.6, 136.5, 129.5, 128.7, 127.0, 80.3, 57.5, 28.4, (1 × C not detected); **ν_{max}** 3368, 3008, 2977, 2932, 1689, 1645, 1604, 1496 cm^{-1}; **MS (ESI) m/z** 554.30 (100, $[M+H]^+$), **HRMS (ESI)** found 554.2982, $C_{29}H_{40}N_5O_6^+$ ($[M+H]^+$) requires 554.2973.

3.4.73 Preparation of Preparation of (*R*)-1-(1-phenylethyl)guanidine 312.[116]

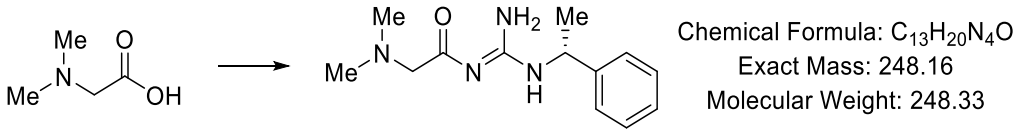


Chemical Formula: $C_9H_{13}N_3$
Exact Mass: 163.11
Molecular Weight: 163.22

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 (NH_2CN, 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 Et_2O (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 elluant 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]

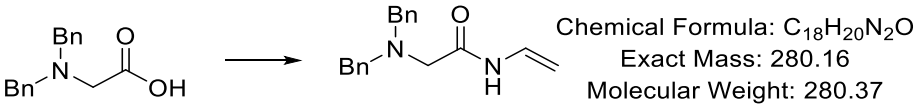
[α]$^{22}_D$ +28.9 (c 1.0, EtOH); (Lit. [116] **[α]$^{22}_D$** +28.9 (c = 1.00, EtOH); **δ_H** ($(CD_3)_2SO$) 7.36 (2H, d, *J* 7.3 Hz, 2 × CH), 7.29 (2H, t, *J* 7.3 Hz, 2 × CH), 7.18 (1H, t, *J* 7.3 Hz, CH), 3.97 (1H, q, *J* 6.7 Hz, CH), 1.24 (3H, d, *J* 6.7 Hz, CH_3); **δ_C** ($(CD_3)_2SO$) 148.8, 128.0, 126.1, 125.8, 50.7, 26.3; **ν_{max}** 3320, 3135, 2977, 2929, 1625, 1551, 1214, 755, 700 cm^{-1}.

3.4.74 Attempted preparation of (*R*)-*N*-(amino((1-phenylethyl)amino)methylene)-2-(dimethylamino)acetamide 314.



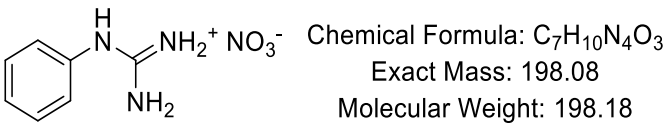
Method A: *N*-*N*-dimethylglycine **313** (348.0 mg, 3.37 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (1.09 g, 6.74 mmol, 2.0 equiv.); 24 h; Et_3N (341.0 mg, 3.37 mmol, 1.0 equiv.); 10 min, rt. Then (*R*)-1-(1-phenylethyl)guanidine **312**, 24 h at rt follow with stir for 18 h at (45-50) °C. Extraction with EA; washed with water (150 mL × 3) and brine (50 mL × 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.



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_3N (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 × 3) and brine (50 mL × 2); gave (85.0 mg) as a yellow wax, which was mainly the amine with impurities.

3.4.76 Preparation of Phenylguanidinium nitrate 203.[106]

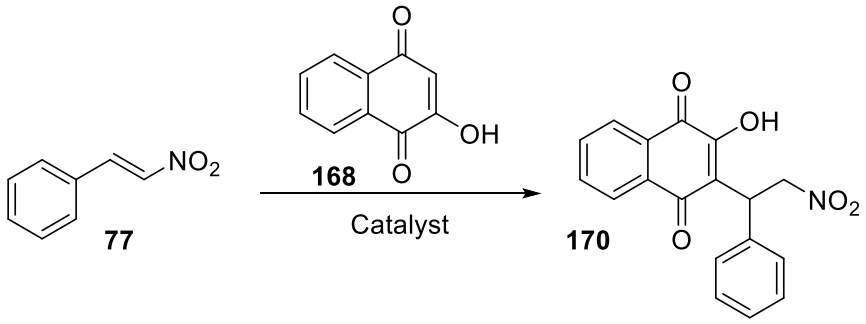


Aniline (9.3 g, 9.12 mL, 99.9 mmol, 1.0 equiv.) was dissolved in EtOH (75 mL) and an aqueous solution of HNO_3 (9.0 mL, 131.2 mmol, of a 65% w/w solution prepared from 90% w/w nitric acid by slow addition to water; **CAUTION!**) was then cautiously added. An aqueous solution of cyanamide (50% w/v, 12.6 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.[106] Data was in agreement with the literature.

Rf 0.28 (10% MeOH/EA); **Mp** 112-115 °C (lit.[106] Mp 120-122 °C); δ_H ($(CD_3)_2SO$) 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); δ_C ($(CD_3)_2SO$) 155.7, 135.3, 129.7, 126.5, 124.5; ν_{max} 3332, 3189, 3055, 1614, 1598, 1584, 1312 cm^{-1}; **MS (ESI) m/z** 136.1 $[M+H]^+$, **HRMS (ESI)** found 136.0867, $C_7H_{10}N_3^+$ ($[M+H]^+$) requires 136.0869.

3.4.77 Reaction *β*-nitrostyrene 77 with 2-hydroxy-1,4-napthoquinone 168



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). *β*-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, $[\alpha]_D^{25}$ -16.0 (acetone, c = 1.46); Lit. $[\alpha]_D^{17}$ -44.8 (acetone, c = 1.0);[123] Lit. $[\alpha]_D^{25}$ -34.0 (acetone, c = 1.46).[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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