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How to cite:

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Organocatalysis using Bifunctional Aminoboronic Acids – Application to the Asymmetric Aldol Reaction

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Department of Chemistry
Durham University
March 2012

Declaration

The work described in this thesis was carried out in the Department of Chemistry at Durham University between October 2008 and October 2011, under the supervision of Prof. Andy Whiting. The material contained has not been previously submitted for a degree at this or any other university. The research reported within this thesis has been conducted by the author unless indicated otherwise.

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Abstract

The organocatalytic iminium activation strategy acting cooperatively with a Lewis acidic group has been applied to the development of a novel generation of proline-based aminoboronic acid catalysts.

Key steps for their synthesis included (-)-sparteine mediated asymmetric deprotonation of *N*-Boc-pyrrolidine, copper(I) catalysed borylation of alkylhalides and catalysed hydroboration of alkenes. The evaluation of the first proline-based aminoboronic acids is described in the context of organocatalysed aldol reactions between *p*-nitrobenzaldehyde and acetone. Enhanced reactivity and enantioselectivity observed in the presence of a boronate ester analogue of the catalyst resulted in further examination regarding the role of the esterification diol in these organocatalytic reactions. Notably, ^{11}B NMR studies have been assessed, allowing the evaluation of different diols in terms of stability and Lewis acid tuning, and plausible identification of the catalytic species present.

The feasibility of the catalyst under optimised reaction conditions was demonstrated in the aldol reaction of different substrates. Extended mechanistic studies lead to the proposal of a catalytic cycle in which a highly organised transition state plays a key role for both the reactivity and enantioselectivity observed. Finally, strategies employed to further examine both reactivity and asymmetric induction of the free boronic acid catalyst are discussed, examing the carbon length chain between the secondary amine moiety and the boronic acid group of the catalyst.

"Σαν βγεις στο πηγαιμό για την Ιθάκη,
να εύχεσαι νάναι μακρύς ο δρόμος,
γεμάτος περιπέτειες γεμάτος γνώσεις.
Τους Λαιστρυγόνας και τους Κύκλωπας,
τον θυμωμένο Ποσειδώνα μη φοβάσαι ...
Πολλά τα καλοκαιρινά πρωιά να είναι
που με τι ευχαρίστησι, με τι χαρά
θα μπαίνεις σε λιμένας πρωτοειδωμένους ..."

Κ .Π.Καβάφης, Ιθάκη, 1911

"As you set out on the way to Ithaca
hope that the road is long one,
filled with adventures, filled with understanding.
The Laestrygonians and the Cyclopes,
Poseidon in his anger: do not fear them ...
Many may the summer mornings be
when-with what pleasure, with what joy-
you first put in to harbors new to your eyes ..."

K. P. Cavafy, Ithaca, 1911

To my parents and Aggelos

Acknowledgments

First of all, I would like to express my profound gratitude to my supervisor Prof. Andy Whiting for his invaluable guidance, support, suggestions and repeated explanations throughout my research work. His passion for research and active encouragement the last three years will always be an inspiration to me.

I am grateful for the cooperation of the analytical services at Durham University. In particular, Dr. Alan Kenwright, Mr. Ian McKeag and Mrs. Catherine Hefferman of the NMR service; Dr. Jackie Mosely of the mass spectroscopy service; Dr. Andrei Batsanov of the single X-ray crystallography service; and Dr. Ritu Kataky and Mrs. Judith Magee from elemental analysis. My special thanks are given to Dr. Aileen Congreve and Dr. Ellie Hurst for their invaluable and much appreciated help with the HPLC instruments. In addition, I would like to thank the National Mass Spectrometry Centre in Swansea for carrying out some high resolution mass spectroscopy analysis.

Moreover, I would like to acknowledge One North East and the Department of Chemistry at Durham University for funding my project.

I would also like to take this opportunity to thank all the people who made up our research group, past and present. I have been benefited working in a unique environment of not only highly dedicated scientists but also friends. In particular, I would like to thank Dr. Jonathan Knowles and Dr. Alexander Gehre for providing useful comments and sharing their experience and knowledge with me during my studies. A big thank you goes to Ricardo Girling whose contribution in both the experimental section and writing up procedure of my thesis proved to be invaluable. My special thanks are due also to Dr. Genaddiy Ilyashenko, Dr. Craig McNair, Andy Henderson, Fathia Mosa, Garr-Layy Zhou, Adam Calow, Farhana Ferdousi and Nim Chaiyaveij. I wish them all the best for the future.

But above all, within the group, I was fortunate to make amazing friends such as Hayley Charville, Benjamin Smith and Vicki O’Connor. Their support has been unwavering; they have been my strength when times were hard, the greatest fan when days were bright and the family away from home. A special thank you also

goes to Dimitris, who convinced me in the first place to apply for a Ph.D and supported me all the way through.

Finally, and most importantly, I would like to thank my parents, Nicos and Leda Georgiou. They have done their best so that Aggelos and I could understand and appreciate the value of family. Their high expectations for us were always accompanied with their support, encouragement and love.

Abbreviations

aq.	Aqueous
ASAP	Atmospheric Solids Analysis Probe
Boc	*N*-*tert*-Butoxycarbonyl
bp	Boiling point
brd	Broad doublet
brs	Broad singlet
n-BuLi	*n*-Butyllithium
s-BuLi	*sec*-Butyllthium
t-BuLi	*tert*-Butyllithium
n-BuOH	*n*-Butanol
t-Bu	*tert*-Butyl
c	Concentration
cod	Cyclooctadiene
d	Doublet
dd	Doublet of doublets
DCM	Dichloromethane
de	Diastereomeric excess
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMS	Dimethyl sulphide
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
DoE	Design of Experiment
dppe	Diphos; 1,2-Bis(diphenylphosphino)ethane
dr	Diastereoselectivity
ee	Enantiomeric excess
EI	Electron impact ionization
Et	Ethyl
ES	Electrospray ionization
FTMS	Fourier Transform Mass Spectroscopy
GC	Gas Chromatography
HPLC	High-Performance Liquid Chromatography

HRMS	High Resolution Mass Spectroscopy
IPA	Isopropanol
IR	Infra-Red
J	Coupling constant
LSF	Least Square Fitting
m	Multiplet
Mp	Melting point
MS	Mass Spectroscopy
M.S.	Molecular sieves
Me	Methyl
MeCN	Acetonitrile
n.r.	No reaction
NMP	*N*-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
Np	Neopentyl
Ph	Phenyl
i-Pr	*iso*-Propyl
quin	Quintet
rt	Room temperature
s	Singlet
sat.	Saturated
sep	Septet
Tf	Triflyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
t_R	Retention time
Ts	Tosyl

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Chapter 1: Introduction

1 Introduction

One of the ultimate goals in organic chemistry is the synthesis of complex natural products with multiple chiral centres. Enantiomerically pure compounds are of great importance not only in fine chemicals and material science but also in pharmaceutical companies. In addition, the development of stereospecific carbon-carbon bond forming reactions is one of the most challenging fields in organic chemistry. As a result, over recent decades the area has been dominated by groups interested in asymmetric organocatalysis. This is not only due to the versatile character of small organic molecules to function as efficient and selective catalysts but it is also attributed to their important role in the construction of complex and enantiopure molecular skeletons.[1]

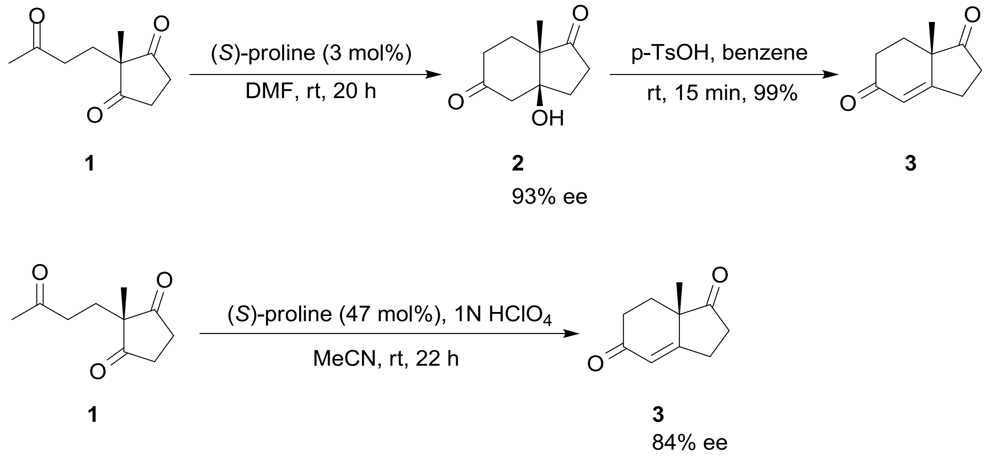
A variety of organic molecules have been employed as asymmetric organocatalysts but proline and its derivatives are among the most successful catalysts studied to date.[2] The first part of this introduction will focus on the application of proline in the aldol reaction. Moreover, an effort has been made to uncover and report novel organocatalysts that are superior to proline and are effective in the aldol reaction. Most importantly the main aim is to provide an overview on the recently developed field of proline-based aminoboronic acids and their ability to act as organocatalysts, providing reactivities and selectivities beyond those of proline and its derivatives.[3-4]

1.1 Proline as a Powerful Catalyst in the Aldol Reaction

The ability of proline not only to catalyse organic reactions but to favour the formation of a single enantiomer was first noted more than 35 years ago.[5] Unfortunately, limited interest was observed until the beginning of the year 2000 when its potential was rediscovered by Barbas and List.[6] Since then an impressive number of catalytic applications have been reported, improving the so-called organocatalysis field.[1] One of the most important features of this small, natural, inexpensive amino acid, is its availability in both enantiomeric forms, giving rise to the possible synthesis of an unlimited number of chiral compounds. Similar to enzymatic catalysis, proline can be characterised as a bifunctional catalyst since the amine moiety and the carboxylic acid act simultaneously. The increased pK_a value rising from the presence of the secondary amine functional group enhances the nucleophilicity allowing it to react more easily with carbonyl compounds, leading to the formation of iminium ions or enamines.

1.1.1 The Hajos-Parrish-Eder-Sauer-Wiechert reaction

In the early 1970s, in an attempt to develop new methods for the synthesis of steroids, two industrial groups independently discovered that a small amount of (*S*)-proline can catalyse an asymmetric intramolecular aldol reaction (Scheme 1.1). According to Hajos and Parrish, the optically active bicyclic diketone **3** can be generated in good yields and enantioselectivity by the proline-catalysed intramolecular aldol reaction of triketone **1**, followed by the dehydration of aldol **2**.[5a] Analogous results were achieved by Eder, Sauer and Wiechert who proposed the *in situ* dehydration of **2** using perchloric acid as a co-catalyst in order to form the aldol condensation product **3**.[5b]

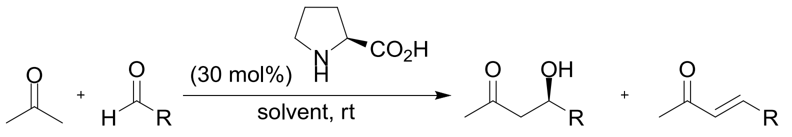


Scheme 1.1 First proline-catalysed intramolecular aldol reaction.

Taking into consideration the enantioselectivity observed, a number of experimental and theoretical studies have followed, mainly focusing their research on the mechanism of the specific reaction.[5a,7-9] Nevertheless, the only synthetic utility of this methodology before the beginning of the new century was only illustrated by the synthesis of a variety of steroids and terpenes.[10]

1.1.2 Proline-catalysed intermolecular aldol reactions

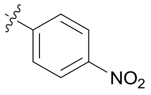
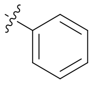
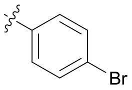
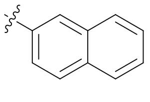
The first proline-catalysed direct intermolecular aldol reaction between acetone and a variety of aldehydes **4** was reported (eqn. 1.1) by List and Barbas.[6] High yields and enantioselectivities were observed, not only when α-branched aldehydes (entries 1-4, Table 1.1) were used, but also when using tertiary aldehydes such as isobutylaldehyde (entry 5, Table 1.1). Unfortunately, unbranched aldehydes were unreactive. This difficulty is due to the weakness of proline to distinguish between the α-protons of the aldehyde and the ketone, leading to the formation of the self-aldolisation product **6**. As a result, further studies changing the reaction temperature and the solvent were carried out using α-unbranched aldehydes.[11] Even though the cross-aldol products were obtained in poor yields, the enantioselectivities were good (entries 6-8, Table 1.1).

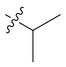
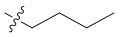
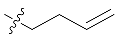
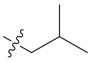


4 **5** **6**

(1.1)

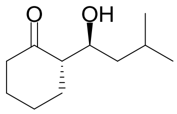
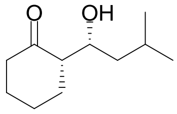
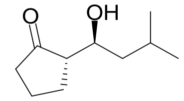
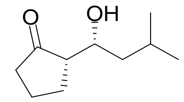
Table 1.1 Enantioselective aldol reaction catalysed by proline, between acetone and a variety of aldehydes.

Entry	R	Solvent	Yield [%]	ee [%]
1		DMSO	68	76
2		DMSO	62	60
3		DMSO	74	65
4		DMSO	54	77

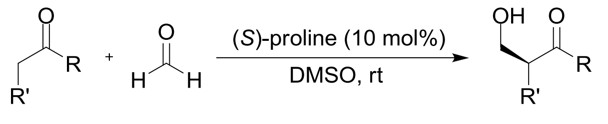
5		DMSO	97	96
6		$CHCl_3$	29	70
7		$CHCl_3$	34	72
8		$CHCl_3$	23	61

In the same context, List *et al.* developed the aldol reaction (Table 1.2) between isovaleraldehyde and cyclic ketones such as cyclopentanone and cyclohexanone, giving a mixture of both diastereoisomers.[11]

Table 1.2 Proline-catalysed aldol reaction using cyclic ketones.

Entry	Product	ee [%]	Yield [%]	dr
1		86	41	7:1
		89		
2		95	75	2.5:1
		20		

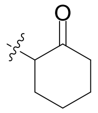
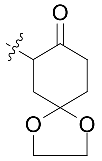
In addition to the previous examined aldol reaction using cyclic ketones, Córdova *et al.* also described the reaction of formaldehyde with a series of cyclic ketones **7** (eqn. 1.2).[12] This reaction enabled the asymmetric α-hydroxymethylation of the ketones in high enantioselectivities, albeit in moderate yields (Table 1.3).



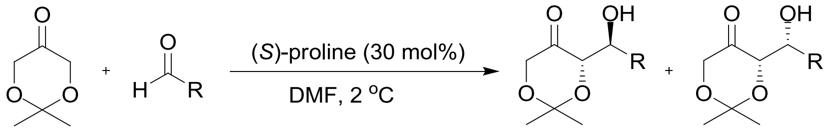
7

(1.2)

Table 1.3 Proline-catalysed α-hydroxymethylation of ketones.

Entry	R,R'	Yield [%]	ee [%]
1		45	>99
2		40	95

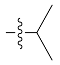
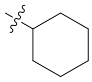
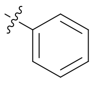
The (*S*)-proline–catalysed aldol reaction between a variety of aldehydes **4** and dioxanones (eqn. 1.3) was applied by Enders *et al.* to 2,2-dimethyl-1,3-dioxan-5-one in the presence of the catalyst in DMF at 2 °C.[13] Similar results were observed in the previous reported work of Córdova. In particular, when α-branched aldehydes were used the aldol product **8** was obtained in excellent yields and diastereoselectivities (entries 1-2, Table 1.4). This contrasted with α-unsubstituted and aromatic aldehydes which showed lower yields (entries 3-6, Table 1.4).

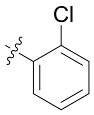
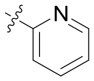
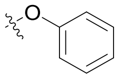
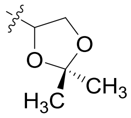
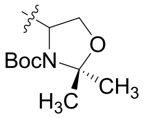


4 **8** **8'**

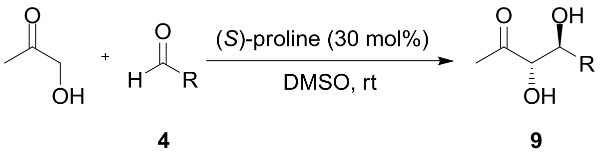
(1.3)

Table 1.4 Proline-catalysed aldol reaction of dioxanone analogue.

Entry	R	Yield [%]	ee [%]	*anti/syn* [%]
1		97	94	>98:2
2		86	90	>98:2
3		57	76	1.5:1

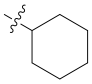
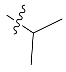
4		73	86	4:1
5		61	25	4:1
6		40	>96	>98:2
7		76	>98	>98:2
8		80	>96	>98:2

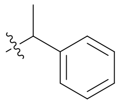
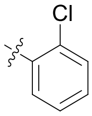
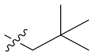
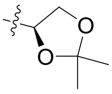
It is noteworthy to mention that highly regio- and diastereo-selective aldol reactions between hydroxyacetone and aldehydes **4** are possible when using (*S*)-proline as the catalyst (Table 1.5).[14] The desired *anti*-1,2-diols **9** had been obtained in moderate yields, although with excellent enantioselectivities in the presence of 30 mol% of the catalyst in DMSO at room temperature. In contrast to the impressive enantioselectivities observed, the diastereomeric ratio when 2-chlorobenzaldehyde, α-unsubstituted aldehyde and α-oxygenated D-isopropylidene-glyceraldehyde were used was low (entries 4-6, Table 1.5).



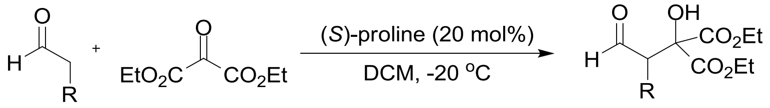
(1.4)

Table 1.5 Proline-catalysed asymmetric aldol reaction between hydroxyacetone and several aldehydes.

Entry	R	Yield [%]	ee [%]	dr
1		60	>99	>20:1
2		62	>99	>20:1

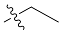
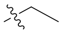
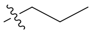
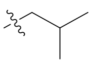
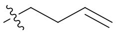
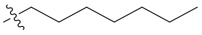
3		51	>95	>20:1
4		95	67	1.5:1
5		38	>97	1.7:1
6		40	>97	2:1

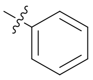
The first direct proline-catalysed aldol reaction of aldehydes with activated carbonyl compounds was reported by Jørgensen *et al.* in 2002.[15] A catalyst loading, solvent and temperature screen was investigated with proline and optimum results were observed in dichloromethane at -20 °C, where excellent yield (94%) and enantioselectivity (93%) were obtained. The reaction between a range of aldehydes **4** and diethyl 2-oxomalonate was then explored (eqn. 1.5). Excellent yields and enantioselectivities were observed for all aliphatic aldehydes, although the use of phenylethanol provided the aldol product in 97% yield as a racemic mixture.



4 **10** (1.5)

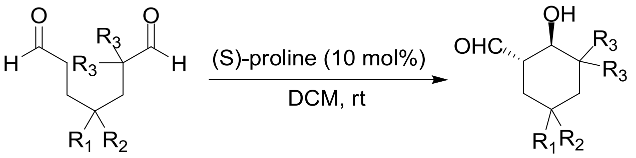
Table 1.6 Proline-catalysed asymmetric aldol reaction between diethyl 2-oxomalonate and several aldehydes.

Entry	R	T [°C]	t [h]	Yield [%]	ee [%]
1		-20	4	94	93
2		25	3	90	90
3		25	1.25	91	85
4		25	2	88	85
5		25	3	94	88
6		25	1.5	91	84

7		25	1	97	0

1.1.3 Proline catalysed intramolecular aldol reactions

The rediscovery of the proline-catalysed strategy has initiated an exponential growth of research for both the inter- and intra-molecular aldol reaction. In 2003 List *et al.* developed a new method for the organocatalytic synthesis of *trans*-1,2-disubstituted cyclohexanones **12** through an enol exo aldolization (eqn. 1.6).[16] The reaction scope was evaluated by treating several pentane-1,5-dialdehydes **11** with (*R*)- and (*S*)-proline using dichloromethane as solvent. The absence or presence of the two substituents in the 4-position of the starting aldehyde gave the desired products in moderate to good yields but in excellent enantioselectivities and diastereoselectivities (entries 1-3, Table 1.7). It is worth mentioning that the presence of a single substituent led to the formation of all four possible diastereomeric aldols, indicating the undesired effect on the stereoselectivity of the cycloaldolisation (entry 4, Table 1.7).



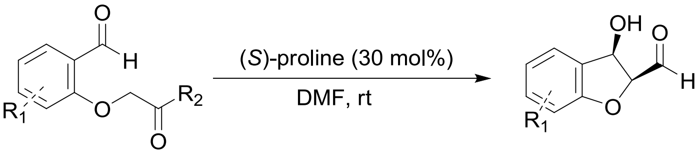
11 **12**

(1.6)

Table 1.7 Intramolecular aldolisation of dicarbonyl compounds catalysed by proline.

Entry	R_1	R_2	R_3	Yield [%]	ee [%]	dr [%]
1	H	H	H	95	99	10:1
2	H	H	Me	74	98	>20:1
3	Me	Me	H	75	97	>20:1
4	Me	H	H	76	75,89,95,8	22:5:5.1

In 2006 Enders *et al.* established elegant approaches for the synthesis of *cis*-substituted dihydrobenzofuranols **14** *via* intramolecular aldol reactions (eqn. 1.7).[17] Their initial studies were focused on the intramolecular reaction of aldehyde ketone **13**. Under the optimised conditions a variety of aldehyde ketones **13** were transformed into the desired 3-hydroxy-2,3-dihydrobenzofurans **14**. The bulkiness of the R_2 substituent played an important role in the stereoselectivity of the final product. In contrast, the R_1 aryl substituent had no effect (Table 1.8).



13 **14**

(1.7)

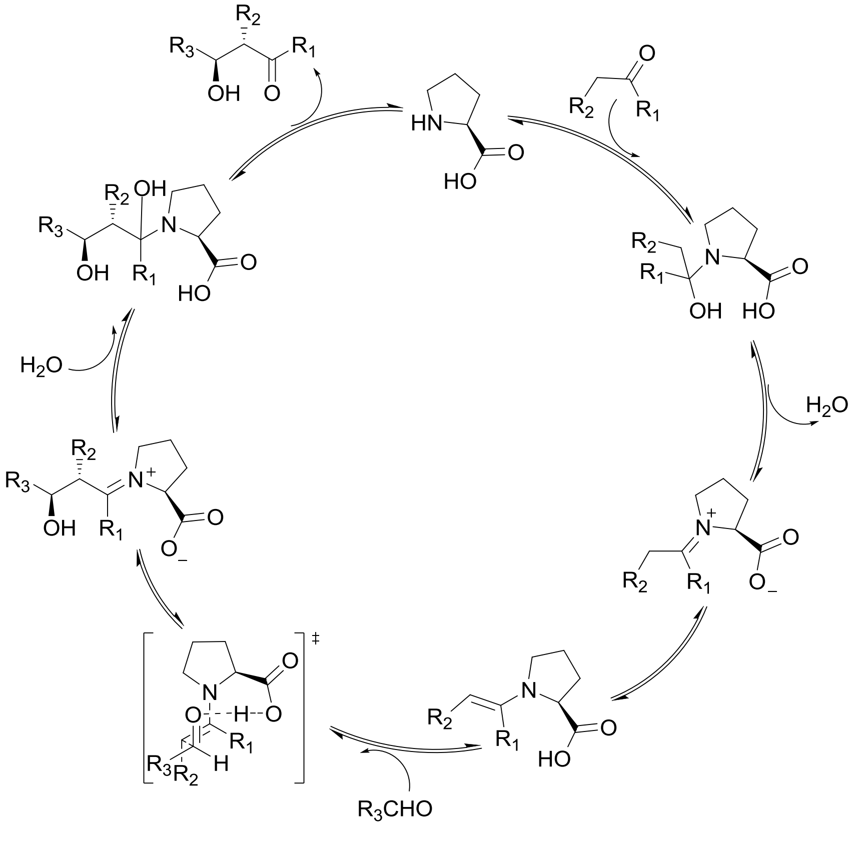
Table 1.7 Intramolecular proline-catalysed aldolisation of dihydrobenzofuranols.

Entry	R_1	R_2	Yield [%]	de [%]	ee [%]
1	H	Me	91	94	94/76
2	H	Et	74	88	88/77
3	2-Me	Me	89	97	97/86
4	2,3-OMe	Me	87	71	71/87
5	2,3-OMe	Me	85	73	73/87

1.1.4 Mechanism of the proline-catalysed intermolecular aldol reaction

The details of the mechanism of the proline-catalysed aldol reaction are generally the subject of much debate and discussion. However, it is likely that proline acts the same way as enzymes do in the aldolase type I reaction mechanism, without the presence of a metal cofactor. Early work by Houk *et al.* developed elegant approaches understanding the catalytic acid-catalysed enamine mechanism, using quantum mechanical calculations.[9] As a result, the proton transfer from the proline carboxylic acid moiety and the nucleophilic addition of the neutral enamine to the carbonyl group is simultaneous. These results are consistent with the kinetic, stereochemical and dilution experiments by List *et al.*, who reinforced the proposal of a one proline mechanism[18] since non-linear effects do not exist, this contrasts with Agamis proposal of a second proline molecule participating.[8]

The general catalytic cycle of proline mediated aldol reactions initiates with the secondary amine moiety acting as a nucleophilic enamine catalyst in order to form a positive iminium ion.[1b,2c,19] As a result, the acidity of the adjacent α-proton increases leading to the formation of the enamine. Recent experimental studies showed that the enamine is formed through an oxazolidinone intermediate.[20] Moreover, the enamine will attack the carbonyl group of the acceptor with the high enantiofacial selectivity due to the carboxylic acid acting as a Brønsted catalyst. Finally, hydrolysis of the iminium ion affords the aldol product and regeneration of proline.

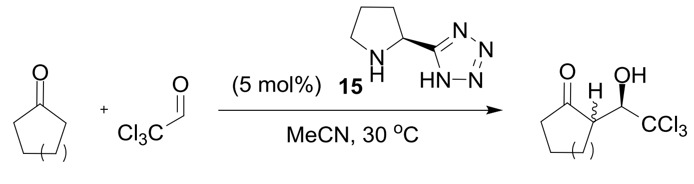


Scheme 1.2 Enamine mechanism for the proline-catalysed intermolecular aldol reaction.

1.2 Proline Derivatives as Catalysts in the Aldol Reaction

The interesting enantioselective transformations of the proline-catalysed aldol reaction which was rediscovered by Barbas and List[6] has emerged as a simple, yet powerful method for the synthesis of aldol products. Unfortunately, the excess nucleophile and high catalyst loading required in most cases led to the synthesis of proline derivatives. The majority of proline derivatives are increasingly attracting interest as asymmetric catalysts due to unquestionable advantages over other organocatalysts used to generate a wide range of products: all are obtained in high enantiomeric excess. In this respect, a series of proline derivatives such as prolinamides, bisprolinamides, prolinethiamides and proline sulphonamides have been synthesised in order to potentially overcome some of the inherent issues in asymmetric organocatalysis.[1-2] Due to the large number of reviews providing an overview on both the synthesis and application of proline derivatives, the aim of the following part is to present two distinct examples that found application in the synthesis of complex molecules.

In 2004, Yamamoto *et al.*, taking into consideration the similar pK_a value of tetrazole and carboxylic acids in water, provided the first indication that tetrazole proline derivative **15** can act as a catalyst.[21] Proline triazole **15** was first screened for its ability to catalyse the asymmetric aldol reaction between cyclic ketones and chloral in MeCN (eqn. 1.8). Initially they observed that when the amount of water added was increased to 500 mol% from 100 mol%, the enantioselectivity of the reaction could be increased from 84% to 94%. Further studies on the same reaction using a variety of ketones showed that aromatic and methyl ketones exhibit high enantioselectvities with moderate yields.



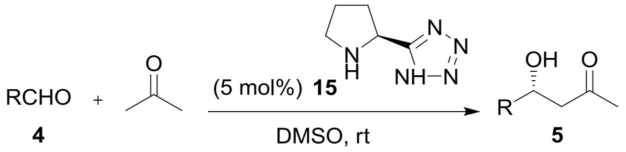
(1.8)

n = 1,2
16

n = 1,2
17

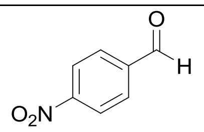
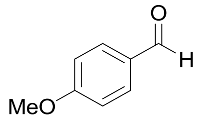
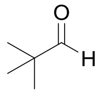
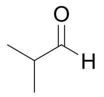
n = 1; 85%, 84% ee, 80% de
n = 2; 78%, 98% ee, 92% de

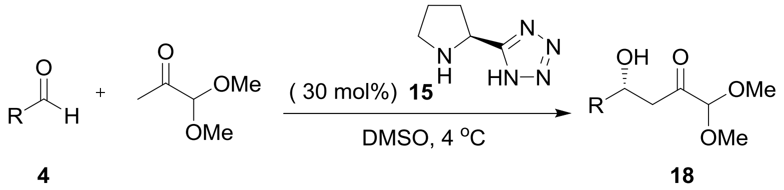
Shortly after, Arvidsson *et al.* investigated a variety of solvents and found pronounced effects on both the yield and enantiomeric excess, compared with the proline-catalysed reaction.[22] Even in the presence of 10% water the yield and enantioselectivity had no effect, which contrast with proline-catalysed asymmetric aldol reactions. To test the substrate generality of this catalyst, the reaction of various aldehydes **4** and acetone was studied in DMSO at room temperature (eqn. 1.9). Aromatic aldehydes led to slightly better yields compared with aliphatic ones (Table 1.8). The reaction between pyruvic aldehyde dimethyl acetal and a series of aldehydes **4** in the presence of catalyst **15** was examined recently by Enders *et al.* (eqn. 1.10).[22] It was observed that even though the yields were moderate, the diastereomeric excess of the desired aldol product was excellent (Table 1.9).



(1.9)

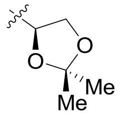
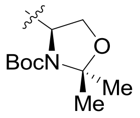
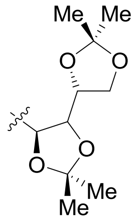
Table 1.8 Direct asymmetric aldol reaction catalysed by tetrazole proline analogue **15**.

Entry	Aldehyde	Yield [%]	ee [%]
1		82	79
2		65	62
3		69	99
4		79	99

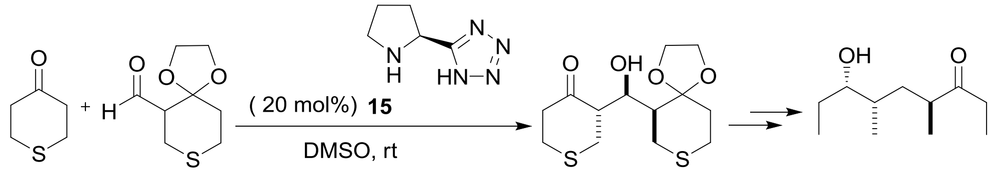


(1.10)

Table 1.9 Direct asymmetric aldol reaction catalysed by tetrazole proline analogue **15**.

Entry	R	Yield [%]	ee [%]	de [%]
1		38	>99	91
2		31	>99	90
3		35	>99	92

In 2006 Ward *et al.* extended the scope of catalyst **15** for the synthesis of serricornin, a sex pheromone produced by the female cigarette beetle.[24] This was achieved in seven steps, whereby reacting ketone **19** with the readily available aldehyde **20** in the presence of 0.2 equivalents of catalyst **15**. This afforded the aldol product **21** in good yield and excellent enantiomeric excess (eqn. 1.11). Through the above mentioned example it is clear that organocatalysed asymmetric transformations are able to grant access to natural products in high asymmetric induction, whilst also reducing also the total amount of synthetic steps needed.

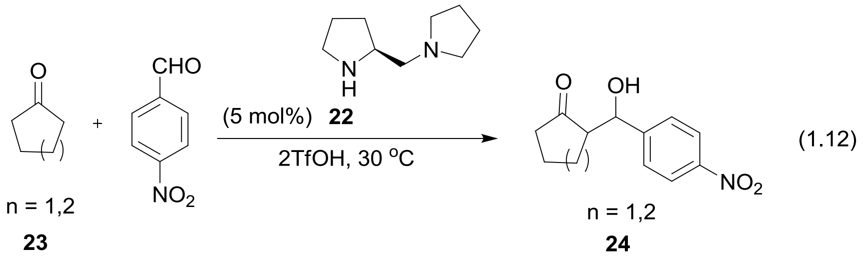


(1.11)

20 **21**

75%, 98% ee serricornin (31% overall yield)

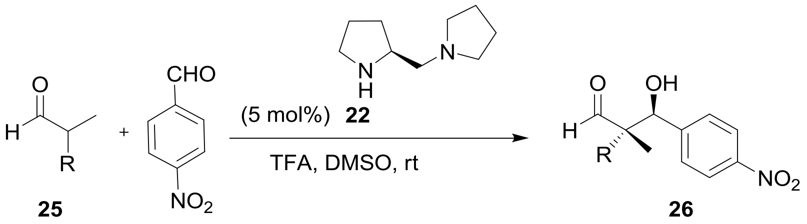
Efforts to further explore the catalytic activity of proline derivatives led to the synthesis and screening of a variety of proline derived diamines.[25] Secondary prolinamine **22** exhibited superior reactivity in the "benchmark" aldol reaction in the presence of TfOH, proving the influence of the acid to both selectivity and reactivity of the reaction.[26] In the same report, the initial test of the specific catalyst was focused on the reaction of *p*-nitrobenzaldehyde and different ketones **23** (eqn. 1.12). Remarkably, when cyclohexanone and cyclopentanone were used, the yields ranged from 88 to 97%, but the enantioselectivity was moderate.



(1.12)

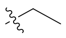
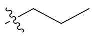
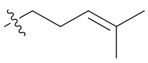
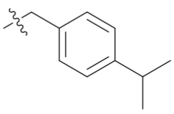
n = 1: 88% *anti* (ee)/*syn* (ee): 43 (84)/57 (5)
n = 2: 97% *anti* (ee)/*syn* (ee): 74 (96)/26 (61)

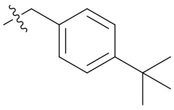
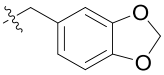
In 2004, Barbas *et al.* reported their first investigations with organocatalyst **22** in the direct aldol reaction between *p*-nitrobenzaldehyde and a variety of aryl aldehydes **25** (eqn. 1.13).[27] Notably, the enantioselectivity of the aldol product was significantly improved using TFA. In contrast with other proline derivatives, high yields and enantioselectivities were observed in most of the reactions even when deactivated aldehydes were used.



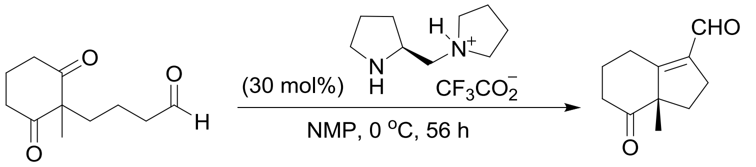
(1.13)

Table 1.10 Asymmetric aldol reaction catalysed by secondary prolinamine **22**.

Entry	R	Yield [%]	*anti*:*syn* [%]	ee of *anti* [%]	ee of *syn* [%]
1		96	62:38	91	75
2		92	66:34	89	66
3		96	65:35	89	52
4		97	84:16	95	74

5		91	85:15	96	68
6		91	77:23	90	53

Recently, the synthetic utility of the specific catalyst was illustrated by the synthesis of bicyclo[4.3.0]nonene derivatives with the creation of a quaternary carbon centre in an intramolecular aldol reaction of a tricarbonyl compound (eqn. 1.14).[28] After screening the catalyst using a model tricarbonyl compound in different reaction conditions Hayashi *et al.* were able to determine the best ones and use them in order to synthesise the desired bucyclonone derivative **27**.



(1.14)

27
89%, 89% ee

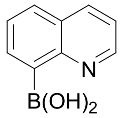
1.3 Aminoboronic Acids as Catalysts

Even though extended research has been appended to the amine function of proline-based catalysts, a Lewis acidic group has never been added. Taking into consideration that boronic acids are one of the most successful Lewis acidic catalysts studied to date,[29] then aminoboronic acids were proposed to act as organocatalysts. The catalytic reactivity of the specific bifunctional catalyst is based on the cooperative relationship between the Lewis acidic boronic acid and the nucleophilic amine moiety. Although there are a number of useful general approaches to the synthesis of aminoboronic acids, their catalytic applications are relatively undeveloped.[3] The focus of the following section will be on the application of these novel catalysts in order to show reactivities and selectivities that go beyond those of proline and its derivatives and the potential of developing an excellent catalyst.

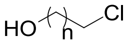
1.3.1 Chloroalcohol hydrolysis and alcoholysis

Letsinger *et al.* elegantly initiated the use of aminoboronic acids in catalytic (and stoichiometric) reactions of simple chloroalcohol substrates.[30] Preliminary studies using 8-quinolineboronic acid **28** as catalyst in a range of reactions with a variety of chlorohydrins in DMF solution were examined, where by the rate of formation of chloride ion indicated the rate of the reaction. In the presence or absence of quinoline, or a mixture of quinoline and benzeneboronic acid, the reactions of all the chloroalcohols used were slow. In contrast, in the presence of 8-quinolineboronic acid **28** the rate of liberation of chloride ion was increased. For example, in chloroethanol the rate rose by a factor of 60 (entry 1 *versus* 4, Table 1.11). The mechanism of the reaction was not initially investigated, however, the formation of hydrogen chloride indicated the initial esterification or complexation of the chloroalcohol to boron, with the bifunctional participation of the basic nitrogen assisting chloride displacement.

Table 1.11 Hydrolysis of chloroalcohols using different boronic acid catalysts.

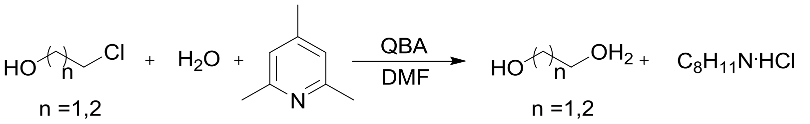


28

Entry		**Additive**	**Conversion [%]**
1	n = 1	-	4.0
2	n = 1	C_9H_7N[a]	4.3
3	n = 1	C_9H_7N[a], $C_6H_7O_2B$[b]	3.4
4	n = 1	QBA[c]	44.3
5	n = 2	-	2.9
6	n = 2	C_9H_7N	3.6
7	n = 2	QBA	44.5
8	n = 4	-	3.6
9	n = 4	C_9H_7N	2.2
10	n = 4	QBA, n-BuOH	3.5

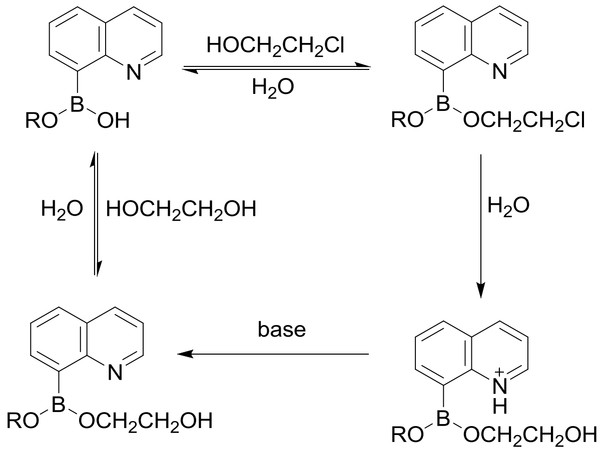
[a]Quinoline; [b]Benzeneboronic acid; [c]8-Quinolineboronic acid **28**.

Further results from the same group suggested that rather than the nitrogen atom of the bifunctional catalyst being alkylated, it could be protonated.[31] As a consequence, the same methodology was applied using a stronger base than the catalyst (e.g. collidine) in order to ensure the catalyst nitrogen remained unprotonated. This resulted in the rates of the reactions being increased, demonstrating the ability of collidine to aid catalyst turnover (eqn. 1.15). Moreover, glycols, collidine hydrochloride and the recovered catalyst were the major products isolated from the reaction. The importance of water was also investigated, with the same reactions being carried out with varying water varied content, showing that its presence was important at lower concentrations.



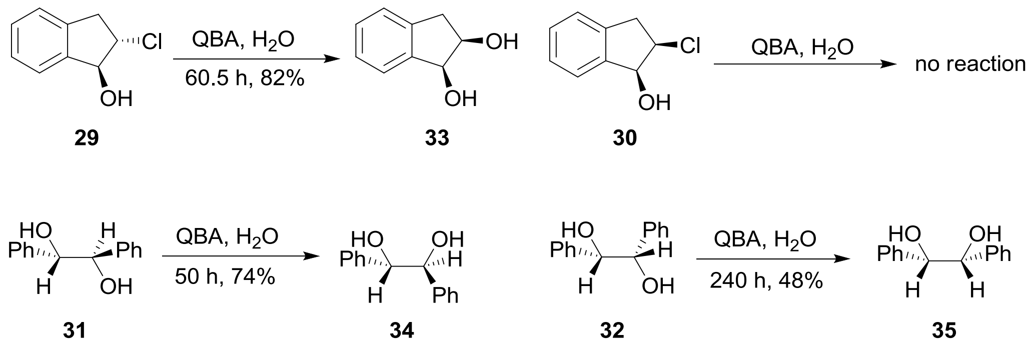
(1.15)

These studies indicated that 8-quinolineboronic acid **28** was esterified by the chloroalcohols. This was followed by displacement of chloride and the protonation of the quinoline nitrogen. Importantly, the glycol was formed and the aminoboronic catalyst was regenerated by boron ester hydrolysis (Scheme 1.3).



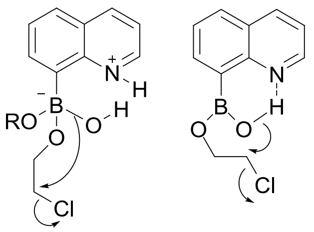
Scheme 1.3 Proposed mechanism for the formation of glycols involving the QBA catalyst.

Further mechanistic studies on the above reaction focussed on the important carbon-halogen bond breaking step.[32] Initially, Letsinger *et al.* proposed two mechanistic routes: the first involved the displacement of halogen by nitrogen; the second by oxygen. Investigation of the potential for retention or inversion of configuration that could take place in the reactions shown in Scheme 1.4 was examined. As a result, using 8-quinolineboronic acid **28** was reacted with two pairs of isomers: *trans*-2-chloro-1-indanol **29** and *cis*-2-chloro-1-indanol **30**, and *erythro*-2-chloro-1,2-diphenylethanol **31** and *threo*-2-chloro-1,2-diphenylethanol **32** (Scheme 1.4).



Scheme 1.4 Proposed intermediates in the 8-quinolineboronic acid **28** catalysed reactions of chloroethanol.

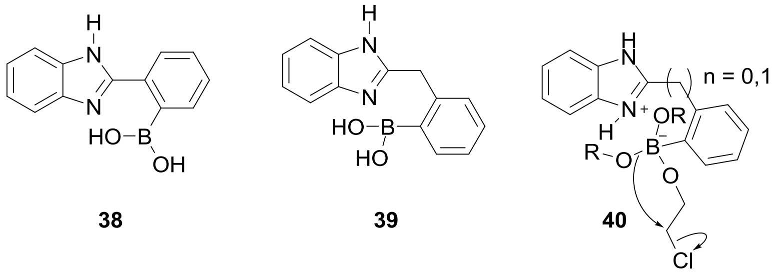
The reaction involving *trans*-2-chloro-1-indanol **29** provided an 82% yield of *cis*-1,2-indandiol **33**, whereas *cis*-2-chloro-1-indanol **30** did not react. Furthermore, in the hydrolysis of the second pair or isomers **31** and **32**, *dl*-hydrobenzoin **34** was obtained in 74% yield from the *erythro*-isomer reaction (run for 50 h), whereas from the *threo*-isomer, the *meso*-hydrobenzoin **35** was detected after 240 h, although in low yield. The observation that the displacement in the stereoselective hydrolysis occurred with inversion of configuration led to the conclusion that the halogen was displaced by the oxygen. Unfortunately, the exact intermediate in which the oxygen was activated was not determined, however, some possibilities were proposed, including **36** (N.B. this is shown as a hydroxide-‘ate’-complex rather than as a water complex being deprotonated by the quinoline nitrogen as originally reported) and **37** (Scheme 1.5).[47]



36 **37**

Scheme 1.5 Proposed intermediates in the 8-quinolineboronic acid **28** catalysed reactions of chloroethanol.

The bifunctional nature of another two aminoboronic acids containing an imidazole ring was exploited by the same group, by developing alcoholysis of chloroethanol using 1-butanol.[33a] Thus, 2-(2-boronophenyl)-benzimidazole **38** and 2-(2-boronobenzyl)-benzimidazole **39** were used with different bases to catalyse this reaction, providing the rapid formation of 2-butoxyethanol as the major product with catalyst recovery. The main reason for the reactivity of catalysts **38** and **39** was proposed to be the same as that for 8-quinolineboronic acid **28**, *i.e.* that the boronic acid undegoes reversible esterification, resulting in increasing nucleophilicity of the oxygen due to the nitrogen proximity in an analogous manner to that outlined in Scheme 1.5. However, given the observed formation of 2-butoxyethanol with these catalysts, one might reconsider Letsinger’s original mechanistic proposals by discounting **37**, updating the process depicted by **36** and propose that species such as **40** are likely to be involved (Scheme 1.6).

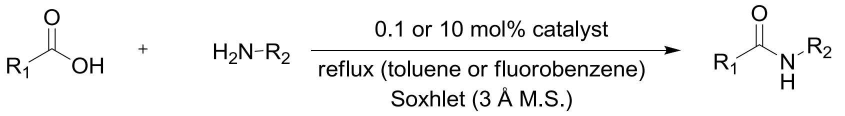


38 **39** **40**

Scheme 1.6 Proposed intermediate **40** involved using the benzimidazole catalysts **38** and **39** with chloroethanol.

1.3.2 Direct Amide formation catalysed by bifunctional aminoboronic acids

Over the last few years, the direct formation of amides from carboxylic acids and amines involving aminoboronic acid catalysts has been demonstrated. Initially, Whiting *et al.* reported the first comparative kinetic studies of the uncatalysed (thermal), boric acid, boronic acids **44** and **45** and amino-boronic **46** catalysed reactions in refluxing toluene, and later at a lower temperature in refluxing fluorobenzene.[34] In this solvent, it was shown that proto-deboronation of arylboronic acids did not take place and that catalytic effects assisted the reactions considerably above background uncatalysed reactions. One of the most attractive features of this study was the demonstrated utility of the bifunctional catalyst **46a** for less reactive substrate combinations, such as aryl carboxylic acids and less electron rich amines. Moreover, applying soft ionization electrospray mass spectrometric techniques provided information on the possible acylating species involved in the amidation reaction. Knowing that the carboxylate activation, and not the amine acylation, was the rate-determining step, the formation of either a monoacyloxyboronic acid or a diacyloxyboronate were thought to be the most likely species involved in the acylation. The latter would be more reactive, and hence, proposed to be the most likely species involved in amide formation (Table 1.12).



(1.16)

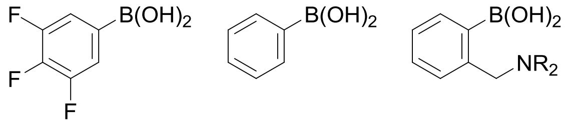
41 **42** **43**

a; R_1 = $Ph(CH_2)_3$
b; R_1 = Ph

a; R_2 = $PhCH_2$
b; R_2 = $Ph(CH_2)_4$

a; R_1 = $Ph(CH_2)_3$, R_2 = $PhCH_2$
b; R_1 = $Ph(CH_2)_3$, R_2 = $Ph(CH_2)_4$
c; R_1 = Ph, R_2 = $PhCH_2$
d; R^1 = Ph, R_2 = $Ph(CH_2)_4$

Catalysts: $B(OH)_3$



44 **45** **46**

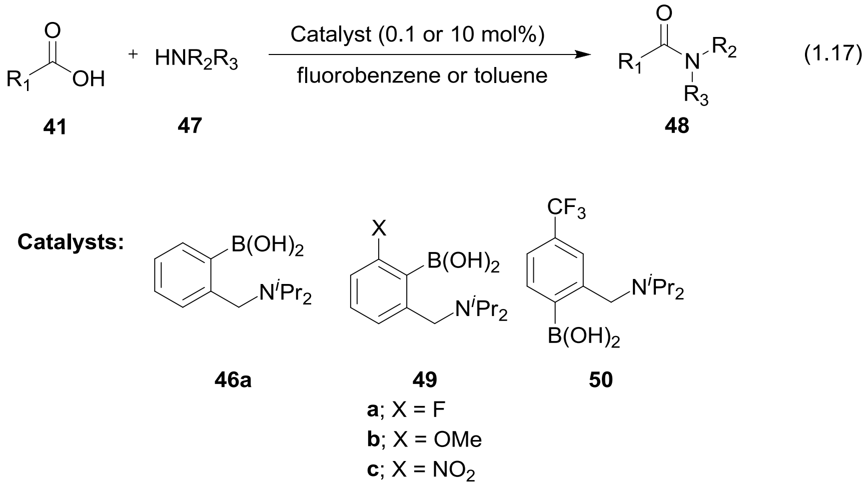
a; R = ^{i}Pr
b; R = Me

Table 1.12 Rate constants for the direct amide formation.

Entry	**41**	**42**	**43**	**Solvent**	**Catalyst**	**k**
1	**a**	**a**	**a**	toluene	**-**	$(2.91 \pm 0.20)\times10^{-5}\ s^{-1}$
2	**b**	**a**	**c**	toluene	**-**	$(2.20 \pm 0.04)\times10^{-7}\ moldm^{-3}s^{-1}$
3	**a**	**a**	**a**	toluene	**46a**	$(4.49 \pm 0.35)\times10^{-5}\ s^{-1}$
4	**b**	**a**	**c**	toluene	Boric acid	$(2.16 \pm 0.03)\times10^{-5}\ moldm^{-3}s^{-1}$
5	**b**	**a**	**c**	fluorobenzene	**46a**	$(1.24 \pm 0.11)\times10^{-5}\ s^{-1}$
6	**b**	**b**	**d**	fluorobenzene	**46a**	$(8.26 \pm 0.15)\times10^{-7}\ moldm^{-3}s^{-1}$
7	**a**	**a**	**a**	fluorobenzene	**46a**	$(7.90 \pm 0.48)\times10^{-5}\ s^{-1}$
8	**a**	**b**	**b**	fluorobenzene	**46a**	$(3.97 \pm 0.31)\times10^{-5}\ s^{-1}$
9	**a**	**a**	**a**	fluorobenzene	**-**	$(1.04 \pm 0.05)\times10^{-5}\ s^{-1}$
10	**b**	**a**	**c**	fluorobenzene	**-**	$0\ moldm^{-3}s^{-1}$
11	**a**	**a**	**a**	fluorobenzene	**62**	$(2.47 \pm 0.08)\times10^{-4}\ s^{-1}$
12	**b**	**a**	**c**	fluorobenzene	**46b**	$(7.83 \pm 0.17)\times10^{-7}\ moldm^{-3}s^{-1}$
13	**a**	**b**	**b**	fluorobenzene	**46a**	$(3.97 \pm 0.31)\times10^{-5}\ s^{-1}$
14	**b**	**a**	**c**	fluorobenzene	Boric acid	$(5.95 \pm 0.07)\times10^{-7}\ moldm^{-3}s^{-1}$
15	**b**	**a**	**c**	toluene	**45**	$(3.02 \pm 0.05)\times10^{-7}\ moldm^{-3}s^{-1}$
16	**a**	**b**	**a**	toluene	**45**	$(5.60 \pm 0.31)\times10^{-5}\ s^{-1}$

17	**a**	**a**	**a**	fluorobenzene	**45**	$(2.47 \pm 0.08)\times10^{-5}\ s^{-1}$
18	**b**	**a**	**c**	fluorobenzene	**45**	$(8.92 \pm 0.11)\times10^{-7}$ $moldm^{-3}s^{-1}$

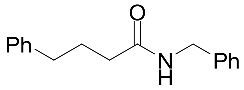
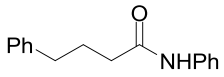
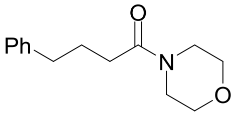
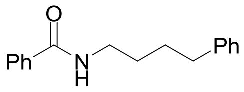
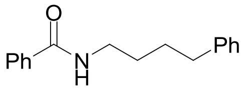
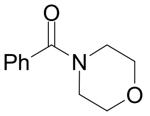
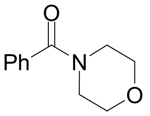
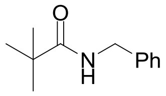
In addition, it was proposed that a combination of a more basic and hindered bifunctional system such as **46a**, together with an electron withdrawing group to further activate the boronic acid, resulted in a more useful bifunctional catalyst. Consequently, the catalytic activity of the *ortho*-*N*,*N*-di-*iso*propylbenzylaminoboronic acid derivatives **49** and **50** was examined (eqn. 1.17).[35] The use of an electron donating group such as methoxy **49b** decreased the reactivity of the catalyst compared with **46a**. In contrast, the addition of a *para*-trifluoromethyl group **50** increased the rate of direct amide formation, especially under the lower temperature fluorobenzene conditions.

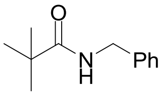


Taking into consideration that catalyst loading, concentration and time were the important optimisation factors from DoE studies, the reaction was extended to the use of phenyl-substituted carboxylic acids and various amines using catalyst **46a** (eqn. 1.17). The reaction was found to be effective for the formation of amides from more reactive substrates when fluorobenzene was used (entries 1, 3 and 4, Table 1.13). In contrast, toluene was necessary for less reactive substrates (entries 2, 4 and

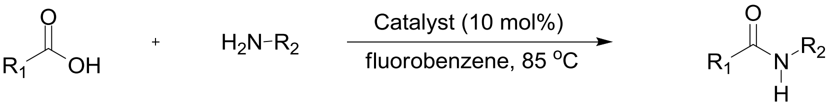
9, Table 1.13). One of the most important aspects of these direct amide formation reactions is the ability to recover the solvent and molecular sieves used, hence, the only by-product is water which makes this type of process potentially *the* most clean and green approach to amide formation.

Table 1.13 Direct amide formation using catalyst **46a**.

Entry	**Solvent**	**46a [mol%]**	**t [h]**	**Product**	**Yield [%]**
1	PhF	0	24		16
		10			68
2	Toluene	0	22		0
		1			46
3	PhF	0	24		4
		10			67
4	PhF	0	48		0
		10			55
5	Toluene	5	24		71
		10			75
6	PhF	0	24		0
		10			11
7	Toluene	0	24		0
		5	24		16
		10	30		21
8	PhF	0	24		0
		10			15

9	Toluene	0	30		7
		5			42
		10			59

The use of bifunctional aminoboronic acids for direct amide formation was extended by the first report of an enantioselective synthesis of amides **52** using a planar chiral ferrocene-derived catalyst **53** to achieve kinetic resolution (eqn. 1.18).[36] Catalyst **53** provided the amide **52a** in 41% ee (entry 2, Table 1.14) using benzoic acid **41b**. However, when the more reactive carboxylic acid **41a** was used the asymmetric induction was reduced (entries 4-12, Table 1.14). In addition, proto-deboronation of the catalyst **53** led to competitive side-reactions from boric acid. Proto-deboronation was reduced when a lower boiling point solvent was used (entries 13 and 14, Table 1.14). It was proposed that the nitrogen-boron distance had a major impact on the enantioselectivity of the final product, since the reaction may involve the benzimidazole function hydrogen-bonding the incoming ammonium salt to react with a diacylboronate intermediate.[34] Hence, kinetic resolution might occur at the ammonium group hydrogen-bonding stage.



(1.18)

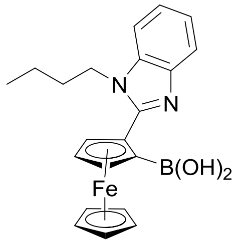
41 **51** **52**

a; R_1 = $(CH_2)_3$Ph
b; R_1 = Ph

a; R_2 = CH(Me)Ph
b; R_2 = CH(Me)Np
c; R_2 = CH(Et)Ph

a; R_1 = Ph, R_2 = CH(Me)Ph
b; R_1 = $(CH_2)_3$Ph, R_2 = CH(Me)Ph
c; R_1 = $(CH_2)_3$Ph, R_2 = CH(Me)Np
d; R_1 = $(CH_2)_3$Ph, R_2 = CH(Et)Ph

Catalyst:



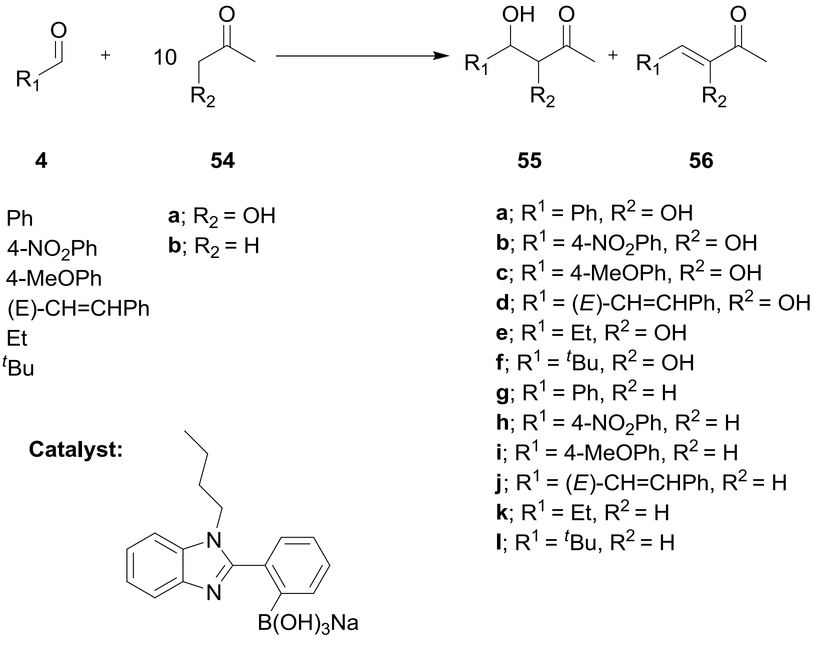
53

Table 1.14 Direct amide formation as outlined in Equation 1.18.

Entry	Catalyst	Solvent	41	51 (equiv.)	52	Conversion [%]	ee [%]
1	**-**	PhF	**b**	**a** (1)	**a**	0	n/a
2	**53**	PhF	**b**	**a** (1)	**a**	21	41 (*S*)
3	**53**	PhF	**b**	**a** (2)	**a**	13	18 (*S*)
4	**-**	PhF	**a**	**a** (1)	**b**	11	n/a
5	**53**	PhF	**a**	**a** (1)	**b**	34	29 (*S*)
6	**53**	PhF	**a**	**a** (2)	**b**	67	15 (*S*)
7	**-**	PhF	**a**	**b** (1)	**c**	13	n/a
8	**53**	PhF	**a**	**b** (1)	**c**	85	9 (*S*)
9	**53**	PhF	**a**	**b** (2)	**c**	64	6 (*S*)
10	**-**	PhF	**a**	**c** (1)	**d**	12	n/a
11	**53**	PhF	**a**	**c** (1)	**d**	65	7 (*S*)
12	**53**	PhF	**a**	**c** (2)	**d**	63	8 (*S*)
13	**-**	$i\mathrm{Pr_2O}$	**a**	**a** (1)	**b**	<1	n/a
14	**53**	$i\mathrm{Pr_2O}$	**a**	**a** (1)	**b**	21	16 (*S*)

1.3.3 Aminoboronic acid-catalysed aldol reaction

Recently, in an attempt to show for the first time that boron enolates could be generated catalytically *in situ* from ketone compounds, it has been shown that the 'ate'-complex of benzimidazolphenylboronic acid **57** could catalyse direct aldol reactions in water (eqn. 1.19).[37] Initially, hydroxyacetone was reacted with various aldehydes **4** providing the aldol adducts **55** (entries 1-6, Table 1.15) with high *syn*-selectivity. In contrast, the reaction of acetone with the aldehydes **4** formed primarily condensation products **56**, whereas with some aldehydes a complex mixture was observed (entries 7-10, Table 1.15). The reactivity and stereoselectivity of the 'ate'-catalyst **57** was proposed to be dependent upon intramolecular cooperation between the benzimidazole and boronate groups,[37] *i.e.* the formation of the boron enolate 'ate'-complex occured due to the intramolecular nitrogen increasing the effective basicity of a boronate-hydroxy group. The resulting boron-bound enolate was then proposed to be strategic for the *syn*-selectivity observed in the aldol addition of hydroxyacetone. Furthermore, in the aldol addition of acetone, an analogous mechanism was proposed following deprotonation of the ketone, and elimination occurs due to the higher reactivity of the boronate-bound intermediate aldol adduct.



(1.19)

4 **54** **55** **56**

a; R_1 = Ph
b; R_1 = 4-NO_2Ph
c; R_1 = 4-MeOPh
d; R_1 = (E)-CH=CHPh
e; R_1 = Et
f; R_1 = ^{t}Bu

a; R_2 = OH
b; R_2 = H

a; R^1 = Ph, R^2 = OH
b; R^1 = 4-NO_2Ph, R^2 = OH
c; R^1 = 4-MeOPh, R^2 = OH
d; R^1 = (*E*)-CH=CHPh, R^2 = OH
e; R^1 = Et, R^2 = OH
f; R^1 = ^{t}Bu, R^2 = OH
g; R^1 = Ph, R^2 = H
h; R^1 = 4-NO_2Ph, R^2 = H
i; R^1 = 4-MeOPh, R^2 = H
j; R^1 = (*E*)-CH=CHPh, R^2 = H
k; R^1 = Et, R^2 = H
l; R^1 = ^{t}Bu, R^2 = H

Catalyst:

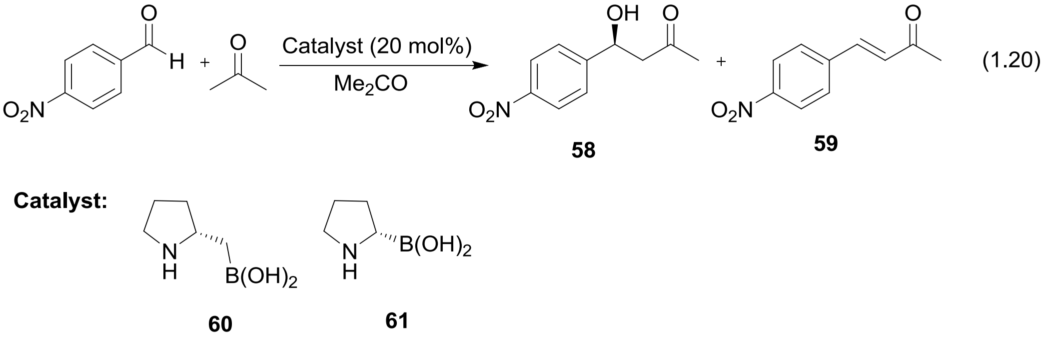
57

Table 1.15 Product ratios and yields of the aldol reaction outlined in Equation 1.19.

Entry	4	54	t [h]	Conversion [%]	Yield 55 [%] (*syn:anti*)	Yield 56 [%]
1	**a**	**a**	7	>99	97(2.75:1)	0
2	**b**	**a**	7	>99	76(5.5:1)	0

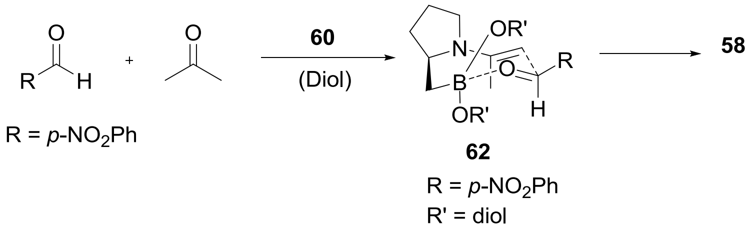
3	**c**	**a**	9	*ca.* 70	46(2.2:1)	0
4	**d**	**a**	7	>99	64(1.3:1)	0
5	**e**	**a**	7	>99	68(2:1)	0
6	**f**	**a**	7	>99	62(1:0)	0
7	**a**	**b**	7	>99	19	77
8	**b**	**b**	7	>99	0	64
9	**c**	**b**	9	>93	10	81
10	**d**	**b**	7	>85	10	75

The novel report of the *in situ* formation of boron enolates in water was followed for the first demonstration of the utility and catalytic compatibility of an enamine and intramolecular boronic acid. Hence, an asymmetric aldol reaction of acetone with *para*-nitrobenzaldehyde was developed (eqn. 1.20), catalysed by homoboroproline **60** and its ester derivatives, producing mainly the β-hydroxycarbonyl compound (aldol adducts) with moderate to high enantioselectivity.[38]



Catalyst **60** was difficult to prepare as a neutral compound, and was therefore produced *in situ* by neutralisation of its HX salts using either Et_3N or $i$$Pr_2NEt$ (entries 1-8, Table 1.6). The neutral homoboroproline **60** provided the aldol adduct

58 as the major enantiomer in up to 43% ee, whereas its shorter homologue boroproline **61** was a sluggish catalyst and provided no asymmetric induction. The contrast between boroproline **61** and homoboroproline **60** supported the idea that catalyst **60** worked by *in situ* formation, followed by aldehyde activation by the boronic acid function, as outlined in Scheme 1.7 (R´ = H).



Scheme 1.7 Proposed enamine transition state involving catalyst **60** and its ester derivatives as an aldol catalyst.

This analysis was further supported by *in situ* esterification of the boronic acid function of **60** with chiral and achiral diols (entries 9-13, Table 1.6) which allowed probing of the proposed transition state **62**. Tartrate esters increased boronate Lewis acidity, tightening the transition state **62** and increasing the asymmetric induction to 90% (from a 96% ee catalyst) independently of the absolute stereochemistry or sterics or stereochemistry of the tartrate (entries 9-11, Table 1.6). Catechol could also be used to increase the effective Lewis acidity of catalyst **60**, however, its additional hydrolytic susceptibility led to compromised results, *i.e.* 80% ee (entry 12, Table 1.6). In addition, the importance of drying the reaction mixture to favour boronate ester formation was demonstrated by entry 13, where the ee dropped from 90% to 82% in the absence of molecular sieves due to competition between the boronic acid **60** *versus* its corresponding tartrate ester mediating the reaction. However, although the ee was increased by drying of the reaction mixture, the rate of reaction dropped, showing the importance of catalyst turnover due to iminium ion hydrolysis and hence, catalyst regeneration.

Table 1.6 Yields of the aldol reaction outlined in Equation 1.20.

Entry	**Conditions**	**Additive (s)**	**t [h]**	**Conversion [%]**	**Yield 58 [%]**	**ee [%]**	**Yield 59 [%]**
1	(*S*)-**60**.TFA	Et_3N	6	>99	92	40	7
2	(*S*)-**60**.TFA	*i*Pr_2NEt	6	92	71	43	21
3	(*S*)-**60**.HCl	Et_3N	6	>99	90	38	10
4	(*S*)-**60**.HCl	*i*Pr_2NEt	6	95	92	40	3
5	(*S*)-**60**.HBr	Et_3N	24	97	93	43	4
6	(*S*)-**60**.HBr	*i*Pr_2NEt	24	97	92	43	5
7	(*S*)-**60**.HI	Et_3N	40	86	81	38	5
8	(*S*)-**60**.HI	*i*Pr_2NEt	24	63	61	37	2
9	(*S*)-**60**.HCl, (R,R)-diisopropyl tartrate	Et_3N, 4Å M.S.	20	65	58	90	7
10	(*S*)-**60**.HCl, (S,S)-diisopropyl tartrate	Et_3N, 4Å M.S.	20	76	63	90	13
11	(*S*)-**60**.HCl, (*R*,*R*)-diethyl tartrate	Et_3N, 4Å M.S.	20	87	78	90	9
12	(*S*)-**60**.HCl, catechol	Et_3N, 4Å M.S.	20	14	11	70	3
13	(*S*)-**60**.HCl, (*R*,*R*)-diisopropyl tartrate	Et_3N	20	98	94	82	4

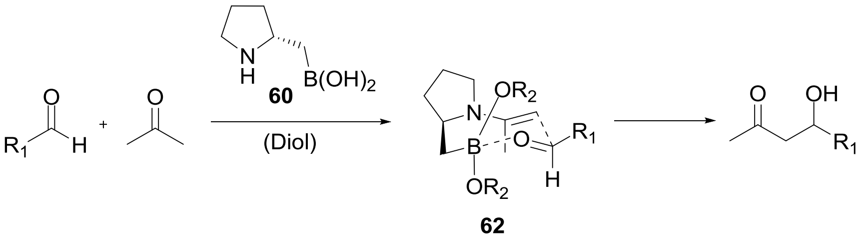
1.4 Conclusions

A central goal of many chemical companies, the pharmaceutical industries and academia is to produce compounds, with a reduction of waste products, non-toxic components and improved efficiency. This goal continues to grow in parallel to the demand of an economical mean to generate large amounts of enantioenriched compounds. Even though the first 30 years following the initial report of a proline-catalysed reaction witnessed only scattered examples of organocatalytic reactions, an intense interest has been observed in the last decade. In its present form, the field of organocatalysis has provided a huge range of single-enantiomer building blocks, important for the synthesis of complex natural products. As a result, the initial aim of the current introduction was to highlight this discipline by demonstrating one of the most notable of these catalytic systems, iminium catalysis through proline and its derivatives. Close inspection of the different functions being appended to the secondary amine-containing proline-based catalysts revealed that the use of Lewis acidic groups acting cooperatively was not considered so far. This observation led to the synthesis of a privileged yet still under developed class of Lewis acidic organocatalysts; aminoboronic acids. The resulting systems and in particular homoboroproline **60** has shown catalytic activities beyond those of proline. With regard to the former, further studies on the synthesis, application and mode of action of proline-based aminoboronic acids were necessary in order to achieve a broadly applicable platform for asymmetric organocatalysis.

Chapter 2: Results and Discussion

2 Results and Discussion

As already mentioned in the introduction, our approach towards the development of an asymmetric organocatalytic aldol reaction was based on iminium catalysis and Lewis acid activation through boronic acids. Previous work in our group had demonstrated that the salt of chiral aminoboronic acid **60** efficiently promoted asymmetric aldol reaction of *p*-nitrobenzaldehyde with acetone *via* iminium ion intermediate **62**.[38] In these transformations, improved enantioselectivity and reaction rate (58%, 90% ee) result from *in situ* formation of the boronate ester. It was reasoned that the enhanced reactivity and enantioselectivity was partly due to an increased boron Lewis acidity of the boronate ester, in comparison to the free boronic acid and partly due to a highly organised transition state **62**.



Scheme 2.1 Proposed enamine transition state involving catalyst **60** and its ester derivatives as an aldol catalyst.

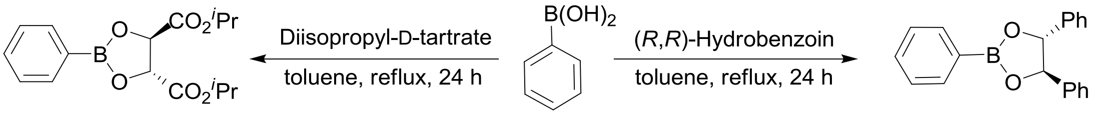
These initial results and assumptions required further investigation in order to both optimise the organocatalysed aldol reaction conditions and furthermore, understand its mechanistic pathway. Therefore, the initial aim of this research project was to synthesise boron analogue of proline **60** and then examine in-depth the correlation between the nature of the diol used for the esterification and the influence of the resulting boronate ester towards the yield and asymmetric induction in the aldol reaction. Following the first tests for the catalytic efficiency, further reaction optimisation, for example temperature and solvent screening, would be performed. The above studies would determine the best reaction conditions in order to achieve high reaction rates, asymmetric induction and relative stereocontrol. Moreover, the catalytic activity of **60** was determined in a single aldehyde and ketone aldol reaction. As a consequence, further aldol reactions would be carried out between a variety of aldehydes and ketones in an attempt to analytically explore the catalytic capability of **60** towards a range of substrates. In addition to the approaches which mainly focus on the synthesis and evaluation of catalyst **60**, studies would need to include the understanding of its mode of action. Thus, taking into consideration the proposed transition state **62** and the assumption that the chiral centre on the pyrrolidine ring plays a crucial role in the enantiomeric excess of the resulting product, the next aim would be the synthesis and application of the opposite enantiomer of **60** (Scheme 2.1). On the other hand, the influence of the carbon length chain between the secondary amine moiety and the boronic acid would be examined in a hope to collect information regarding the mechanistic aspect of the proline-based boronic acid-catalysed aldol reaction.

This chapter will review and describe the experimental work carried out in order to probe the scope and limitations of a series of proline-based aminoboronic acids. Furthermore, an evaluation and discussion of both the followed procedure and the obtained results will be mentioned.

2.1 Importance of Bifunctionality – Synthesis of Benzeneboronate Esters

During the initial studies regarding the homoboroproline-catalysed aldol reaction, it was proposed that catalyst **60** functions intramolecularly as a synergic system of two distinct functionalities (Scheme 2.1). Operating under this mechanistic hypothesis, a strategy for proving the necessity of the cooperative functional reactivity was required. Particularly, it was necessary to determine that for cooperative catalysis to take place, the secondary pyrrolidine-amine and the boronate moiety needed to be within the same molecule. As a result, we considered examining the aldol reaction between *p*-nitrobenzaldehyde and acetone in the presence of pyrrolidine and a boronate ester compound.

Thus, these studies began by forming both the diisopropyl-D-tartrate **63** and (*R*,*R*)-hydrobenzoin **64** esters of benzeneboronic acid. The synthesis of benzeneboronate ester **63** was initially carried out by reacting benzeneboronic acid and diisopropyl-D-tartrate in the presence of molecular sieves in dry DCM. Unfortunately, the yield of the reaction was only 57%. Hence, the reaction was repeated in toluene using Dean-Stark conditions, affording the desired product after recrystallisation in an improved yield of 81%.[39] The same procedure using (*R*,*R*)-hydrobenzoin as the diol was followed for the synthesis of boronate ester **64**. Nevertheless the lower yield observed was due to difficulties during purification, since residual diol co-recrystallised with the product. After several recrystallisations **64** was isolated in a pure form in 52% yield. In addition, leaving a small sample of **64** in a hexane and EtOAc solution to evaporate slowly provided crystals suitable for single crystal X-ray analysis (see Appendix).

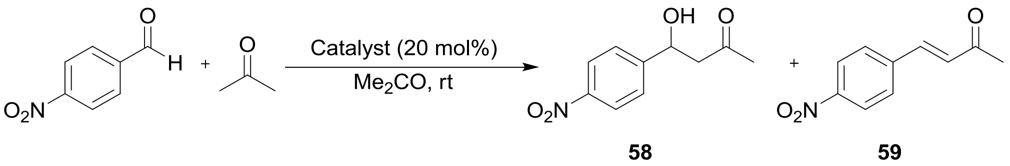


63
81%

64
52%

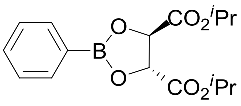
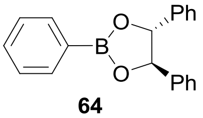
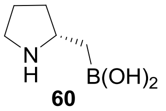
Scheme 2.2 Phenylboronic acid esterification to give boronate esters **63** and **64**.

Having made boronate esters **63** and **64**, it was now possible to probe the influence of bifunctionality in the aldol reaction. Thus, a screening study was performed in the reaction between *p*-nitrobenzaldehyde and acetone in the presence of 20 mol% of different species in order to determine their catalytic reactivity or otherwise. As already mentioned in the literature, pyrrolidine proved to be catalytically active by itself, resulting in a racemic mixture of the desired aldol product.[40] In this case, the secondary amine acts as a nucleophile affording an iminium ion species, which can easily react with the present aldehyde to furnish the aldol addition product. In contrast, benzeneboronic acid was found to be unreactive (entry 1 *versus* 2, Table 2.1). In addition, neither benzeneboronate ester **63** nor **64** led to any reaction conversion, demonstrating also their lack of catalytic activity. Notably, a substantially reduced reactivity compared to using pyrrolidine alone resulted, when the reaction was conducted in the presence of both pyrrolidine and benzeneboronate ester **63** (entry 5, Table 2.1). Moreover, the product mixture from the reaction displayed no enantiomeric excess. These observations clearly revealed the importance of the intramolecular mode of action between the pyrrolidine ring nitrogen and the boronate function of catalyst **60** since the reaction of homoboroproline tartrate ester of **60** (entry 6, Table 2.1) not only efficiently catalyses the reaction, but also provided 90% asymmetric induction in the resulting product.



(2.1)

Table 2.1 Catalysed aldol reaction of *p*-nitrobenzaldehyde and acetone.

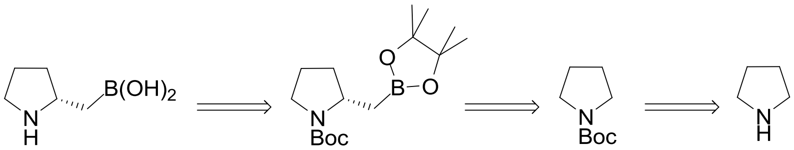
Entry	Catalyst	Conversion [%][a]	Yield of 58 [%][b]	Yield of 59 [%][b]
1	Pyrrolidine	>99	>99	<1
2	PhB(OH)$_2$	n.r.	-	-
3	 **63**	n.r.	-	-
4	 **64**	n.r.	-	-
5	Pyrrolidine + **63**	38	36	>2
6[38]	 **60** + diisopropyl-D-tartrate	65	58 (90% ee, *S*)	7

[a]Reaction time was 24 h. [b]Isolated yield after SiO$_2$ column chromatography.

2.2 Studies towards the Synthesis of the Homoboroproline Catalyst

Having proved the importance of the intramolecular bifunctional nature of homoboroproline **60** and its esterified derivatives, investigations were directed back to the catalyst itself. Specifically, the next goal of the project, before being able to focus on optimisation of the enantioselective aldol reactions, was to synthesise catalyst **60** and access both enantiomeric forms.[38] Our strategy for the synthesis of

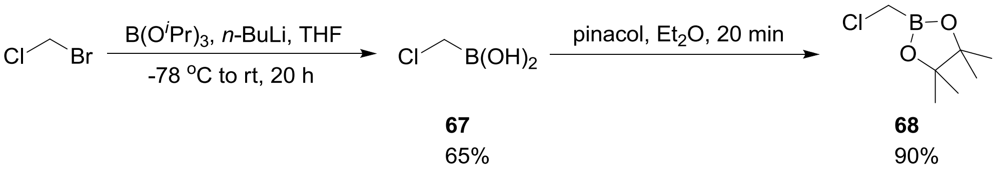
60 was based on the enantioselective formation of 2-substituted *tert*-butoxycarbonyl-pyrrolidines through asymmetric deprotonation (Scheme 2.3). The access to optically active proline derivatives was initially reported by Beak *et al.*[41] and valuably complemented by the work of O'Brien *et al*.[42] In these transformations, *s*-BuLi and (-)-sparteine promoted the enantioselective lithiation of *N*-(*tert*-butoxycarbonyl)-pyrrolidine, which was followed by the addition of a variety of electrophiles in order to afford 2-substituted analogues. It was believed that such a platform would provide the desired product **60** if a suitable chloromethylboronate ester was used as the electrophile.



60 **65** **66**

Scheme 2.3 Retrosynthetic route for the synthesis of pyrrolidine boronic acid-based catalyst **60**.

The synthesis of **60** commenced with a lithium-halogen exchange of bromochloromethane with triisopropylborate, which allowed the isolation of chloromethylboronic acid **67** (Scheme 2.4).[43] The boronic acid **67** was subsequently transformed to the boronate ester **68** using pinacol, as shown in Scheme 2.4. Attempts to purify the pinacol boronate ester **68** using silica gel chromatography was not feasible since residual pinacol co-eluted with the product in any solvent combination. Instead, short-path fractional distillation *in vacuo* was carried out, providing pure chloromethylboronate ester **68** in good overall yield. In addition, the reaction was repeated treating bromochloromethane with trimethylborate instead of triisopropylborate, however, the yield of the isolated boronic acid was not improved.

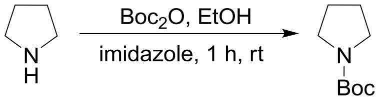


67
65%

68
90%

Scheme 2.4 Synthetic route towards the formation of chloromethylboronate ester **68**.

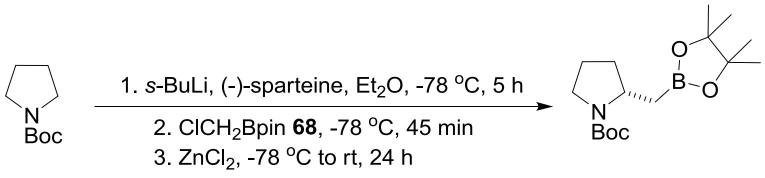
The second step of the synthesis of **60** involved a simple protection of the nitrogen atom of pyrrolidine as a *tert*-butoxycarbonyl group (eqn. 2.2).[44] The reaction was carried out in ethanol in the presence of imidazole using di-*tert*-butyl dicarbonate. The crude product was purified by *in vacuo* distillation over calcium hydride to give *N*-Boc-pyrrolidine **66** in high yield.



66
95%

(2.2)

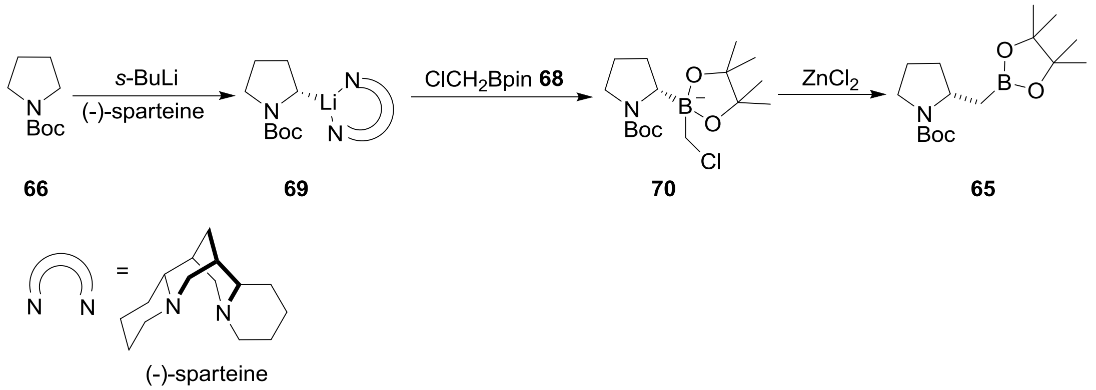
On the basis of similar reported reactions, a (-)-sparteine-mediated lithiation of *N*-Boc-pyrrolidine **66** in the presence of chloromethylboronate ester **68** afforded the desired compound **65** in 62% yield after purification by silica gel chromatography (eqn. 2.3).[42] The first key step for the successful conversion was the dropwise addition at low temperature of electrophile **68** to the intermediate boronate complex **69**, which resulted from the asymmetric deprotonation of *N*-Boc-pyrrolidine **66** driven by the presence of (-)-sparteine (Scheme 2.5). This was followed by the addition of anhydrous $ZnCl_2$ solution, promoting the rearrangement of the 'ate'-complex **70** and providing the 2-substituted *N*-Boc-pyrrolidine **65** in 96% enantiomeric excess.[38,45] This methodology was firstly indroduced by Matteson *et al.* in an attempt to form chiral α-chloroboronates through asymmetric homologation by using $ZnCl_2$-promoted addition of dichloromethyllithium to boronates.[45] It is believed that $ZnCl_2$ acts as a Lewis acid inducing a facile boron-promoted displacement.



66

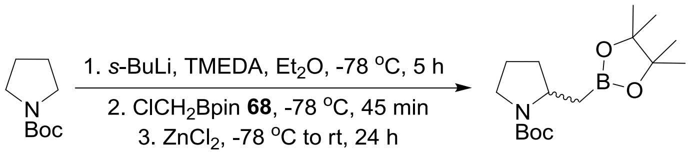
65
62%

(2.3)



Scheme 2.5 (-)-Sparteine-mediated lithiation of *N*-Boc-pyrrolidine **66** using chloromethylboronate ester **68** as electrophile.

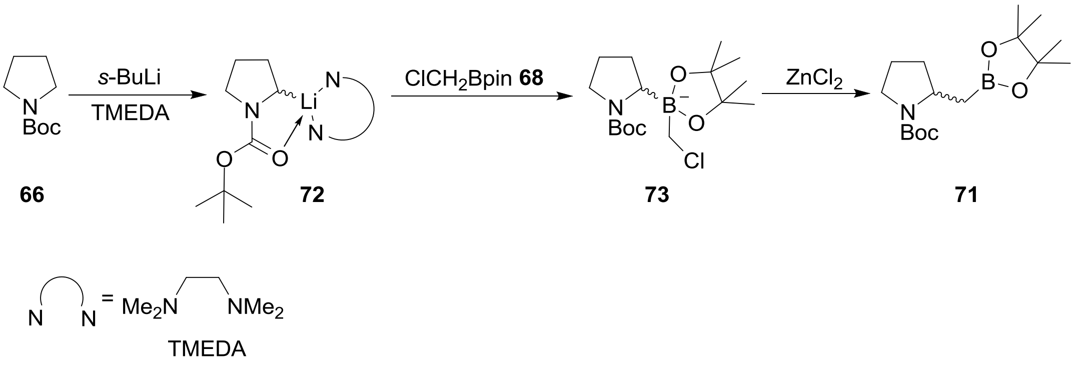
In addition, in order to prove the origin of the chirality present in the resulted product of the homoboroproline-catalysed aldol reaction, an attempt to synthesise a racemic mixture of compound **68** was made. Initially, the same methodology used for the enantiopure derivative **68** was followed, replacing (-)-sparteine with TMEDA (eqn. 2.4).[46] Unfortunately, no conversion was observed and both starting materials were recovered in almost 100%, even though early work by Whiting *et al.* developed approaches for the specific reaction.[38,47]



(2.4)

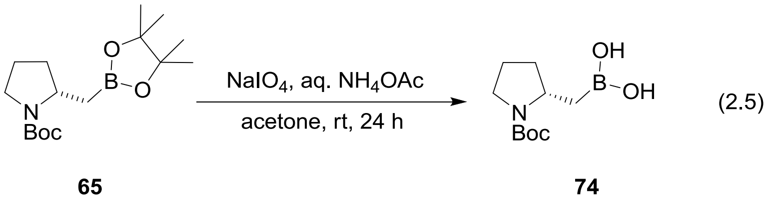
66 **71**

In order to understand and overcome the problem, several attempts were made by changing the reaction conditions. Firstly we assumed that the boronate complex **73** had been formed but the amount of $ZnCl_2$ was not sufficient to break down the 'ate'-complex. As a result, the reaction was quenched with 3 equivalents of $ZnCl_2$. Nonetheless, the product was still not formed and again *N*-Boc-pyrrolidine and chloromethylboronate **68** were recovered. Moreover, considering that the reaction of the electrophile with the TMEDA-coordinated lithium intermediate **72** could be slow, the addition of **68** was carried out dropwise at -78 ^{o}C and then warmed to room temperature for 1 h before adding the $ZnCl_2$. Once more, only the starting material **66** and **68** were isolated. In addition, the reaction was repeated using THF instead of Et_2O as the solvent, but without any improvements. In a competition experiment study by O'Brien *et al.*, evidence was provided that the diamine-mediated lithiation of *N*-Boc-pyrrolidine **66** using TMEDA is more reactive than (-)-sparteine.[48] Hence, the lithium-mediated deprotonation should have been occurring but presumably, intermediate complex **72** was too hindered and stable due to the Li atom being fully coordinated both by the TMEDA ligand and the carbonyl oxygen as shown in Scheme 2.6. In addition, the bulkiness of the electrophile **68** contributed to the lack of the 'ate'-complex **73** to be formed.



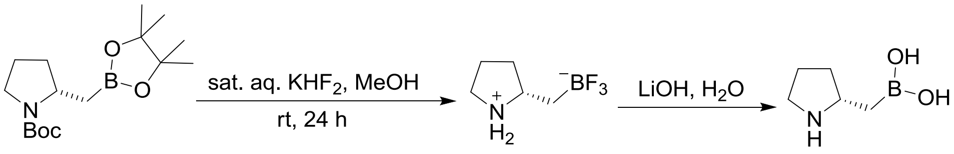
Scheme 2.6 TMEDA-mediated lithiation of N-Boc-pyrrolidine using chloromethylboronate etser **68** as electrophile.

Having prepared enantiomerically enriched **65**, the deprotection of this species to provide catalyst **60** was examined. The first deprotection methods examined were based on the desire to isolate catalyst **60** in its neutral form, if at all possible. Therefore, removal of the pinacol ester was attempted using sodium metaperiodate in an aqueous solution of NH_4OAc in acetone (eqn. 2.5).[49] Unfortunately, even when increasing the amount of the oxidizing agent to 10 equivalents, free pinacol was still present indicating that the diol was not oxidised to acetone. This made the purification of the desired boronic acid **74** from pinacol a hard task to achieve.



(2.5)

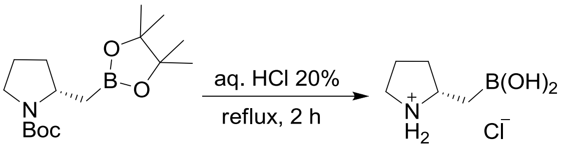
Furthermore, an alternative method for pinacol boronate ester **65** deprotection using a two step process that proceeds *via* formation of a potassium trifluoroboronate was examined (Scheme 2.7).[50] The boronate ester **65** was dissolved in methanol and treated with saturated KHF_2. After 2 h stirring at room temperature, a white precipitate was formed presumably being trifluoroborate **75**. The solid was isolated, although it was not easy to characterise due to the fact that it was insoluble in chloroform and partially soluble in water and MeCN; a mixture of the two was used for NMR analysis. The peak at δ_B 0.21 in the ^{11}B NMR spectrum indicated the trifluoroboronate **75** formation. However a peak at δ_F -159.3 in the ^{19}F NMR spectrum showed that a large amount of the solid was excess KHF_2. Attempts to purify and characterise the resulting product by recrystallisation proved to be difficult since the removal of the excess KHF_2 proved to be impossible.



65 **75** **60**

Scheme 2.7 Deprotection of pinacol boronate ester **65** using KHF_2.

Since the attempts for selective deprotection of the pinacol boronate ester were unrewarding due to purification difficulties, a previous reported method was examined using aqueous solution of HCl as outlined in equation 2.6.[38] Hence boronate ester **65** was reacted with 20 mol% of HCl under refluxing conditions. The resultant isolated brown oil, was azeotroped with toluene and water, resulting in the simultaneous deprotection of the pinacol boronate ester and the *N*-Boc group and affording the desired product **76** as a brown oil in 88% yield.



(2.6)

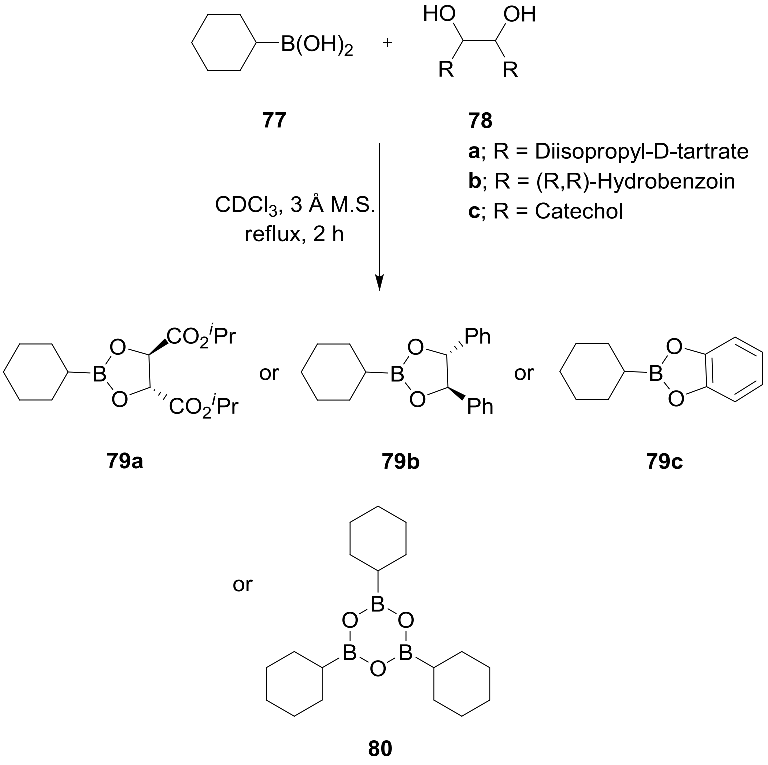
65 **76**
88%

2.3 Lewis Acid Tuning and ^{11}B NMR Analysis

The remarkable efficiency with which the diisopropyl-D-tartrate boronate ester of homoboroproline **60**, compared to the free boronic acid, catalyses the aldol reaction of *p*-nitrobenzaldehyde and acetone in high asymmetric induction (58% yield, 90% ee *vs* 90% yield, 38% ee) promoted us to investigate further the effect of the esterification diol.[38] The main aim of this study was to reveal the dependence of both the stability of the boronate ester and the Lewis acidity of the resulting boron atom on the reactivity and enantioselectivity of the organocatalysed aldol reaction. As a result, examination of the relative stabilities and determination of the possible isolation of cyclohexyl- and cyclopentyl-boronate esters was initiated.[51]

Firstly, a conventional strategy towards the synthesis of the boronate esters was investigated. The relevant boronic acid **77** or **81** were reacted in refluxing toluene using azeotropic water removal with diol **78**. While this procedure afforded the desired boronate esters, the scope for characterisation was limited due to difficulties observed in the purification process. This was the result of some of the boronate esters being particularly sensitive to hydrolysis and hence impossible to purify by column chromatography. In order to circumvent the necessity of isolation, a new approach to prove the formation or otherwise of the boronate esters was needed. Particularly, boronic acids **77** and **81** were reacted with either diisopropyl-D-tartrate **78a**, (*R*,*R*)-hydrobenzoin **78b** or catechol **78c** under dehydrating conditions in refluxing $CDCl_3$ in order to form the boronate esters *in situ* (Scheme 2.8 and 2.9). This was then followed by *in situ* filtration and ^{11}B NMR analysis was carried out for each boronic acid and diol reaction combination.[29,52]

The above protocol was firstly applied to cyclohexylboronic acid **77**, *i.e.* in an attempt to form the corresponding esters **79a**, **79b**, and **79c** (Scheme 2.8). This resulted in the ^{11}B NMR spectra which are shown in Figure 2.1. Surprisingly, when diisopropyl-D-tartrate **78a** and (*R*,*R*)-hydrobenzoin **78b** were reacted in order to generate boronate esters **79a** and **79b**, two ^{11}B NMR peaks were observed in each case (δ_B 36 and 23, and 35 and 23 respectively). Nevertheless, on treatment with catechol **78c**, a single peak was observed at δ_B 23. In accordance with previous reports in the literature regarding ^{11}B NMR analysis, the recurrent signal in all three cases was the peak at δ_B 23 which is diagnostic of boroxine formation, presumably with either water or the diol acting as a nucleophile to create a partial tetrahedral geometry.[29,52-53] These results clearly indicated that catechol **78c** does not result in esterification to the boronate ester **79c**, instead it encourages boronic acid dehydration in order to form boroxine **80**.[54] In addition, use of diisopropyl-D-tartrate **78a** and (*R*,*R*)-hydrobenzoin **78b** also resulted in the formation of boroxine **80** although not exclusively. The boronate esters **79a** and **79b** were also observed presumably in equilibrium. This observation, in addition with the low intensity of the boronate ester peaks compared to the boroxine, revealed that boronate esters **79a** and **79b** are relatively unstable though not to the same extent as the corresponding catechol boronate ester **79c**. Hence, it can be proposed that with the cyclohexylboronic acid **77**, there is a surprising level of instability for the corresponding tartrate **79a** and hydrobenzoin **79b** esters and that they exist in equilibrium with boroxine **80**. On the other hand, catechol clearly causes complete dehydration; a process encouraged by the instability of boronate ester **79c**.



Scheme 2.8 *In situ* formation of cyclohexylboronate esters **79a**, **79b** and **79c**.

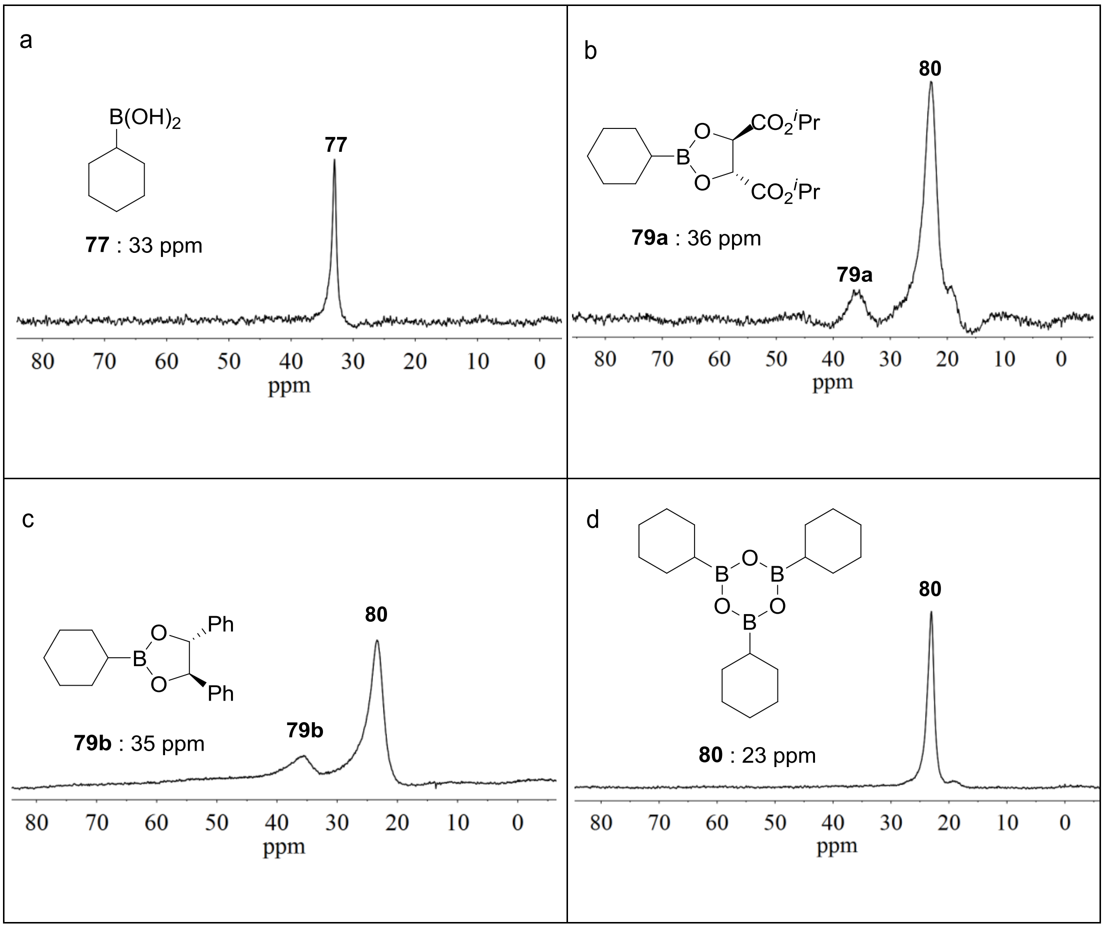
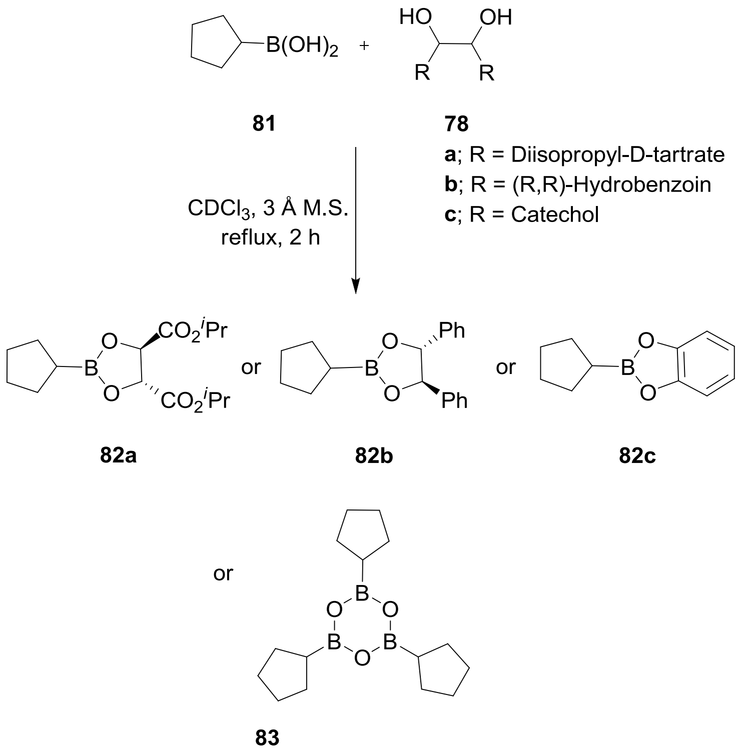


Figure 2.1 ^{11}B NMR spectra of cyclohexylboronic acid **77** esterified with diisopropyl-D-tartrate **78a**, (*R*,*R*)-hydrobenzoin **78b** or catechol **78c**.

Next, attention was turned to the esterification of cyclopentylboronic acid **81**, using the same diols **78** as mentioned above (Scheme 2.9). The reason for repeating this study using boronic acid **81** was to examine whether there were any major effects arising as a result of ring size that affected boronic acid esterification and stability of the resulting boronate ester. Hence, esterification was carried out using the same azeotropic conditions as discussed above, and again, reaction process was monitored by ^{11}B NMR.

As can be seen in ^{11}B NMR spectrum d (Figure 2.2), in the presence of catechol **78c**, exclusive boroxine **83** formation still occurred, as evidenced by the major δ_B 23 signal. In contrast, minimal boroxine formation was observed when the two other diols **78a** and **78b** were used. In particular, the major peak at δ_B 34 in spectrum b in which diol **78a** was used shows that the formation of the boronate ester **82a** is favoured over boroxine **83** formation. However, around 20% boroxine was still present. These results also indicate that the cyclopentylboronate ester **82a** is more stable than its cyclohexyl counterpart **79a**, which showed a greater preference to form boroxine **80**, *i.e.* in approximately 90% compared to boronate ester **79a**. Similar observations were noted when (*R*,*R*)-hydrobenzoin **78b** was used for the esterification of boronic acid **81**. Indeed, boronate ester **82b** appears to be even more stable than the corresponding ester **82a**, since only a very minor boroxine peak at δ_B 23 was observed in the ^{11}B NMR spectrum. On the basis of the above observations, it can be proposed that cyclopentylboronate esters appear to be more stable than the six-ring analogues, and that hydrobenzoin boronate esters are more stable esters than the tartrate esters. If this speculation is generally correct, it can be proposed that increased asymmetric induction and improved catalytic activity performance over those reported previously might be obtained with the (*R*,*R*)-hydrobenzoin analogue of homoboroproline **60** as a catalyst in the aldol reactions, rather than the tartrate esters used to date. To address this hypothesis, further studies were aimed at examining the effect of the nature of the diol on the asymmetric aldol reaction.



Scheme 2.9 *In situ* formation of cyclopentylboronate esters **82a**, **82b** and **82c**.

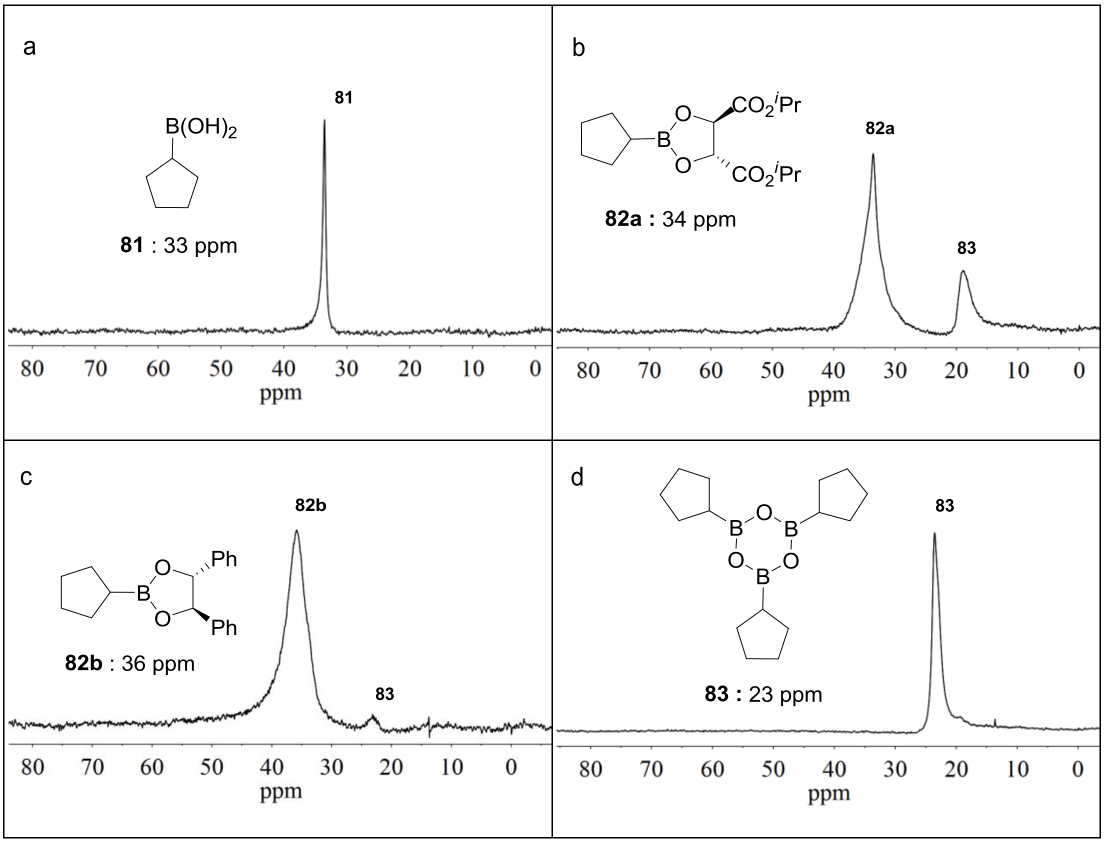
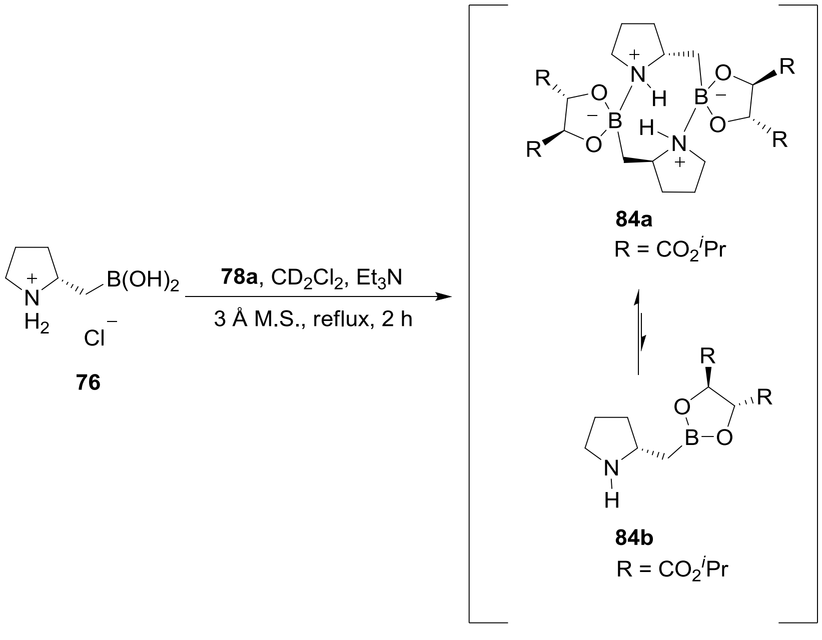


Figure 2.2 ^{11}B NMR spectra of cyclopentylboronic acid **81** esterified with diisopropyl-D-tartrate **78a**, (*R*,*R*)-hydrobenzoin **78b** or catechol **78c**.

Furthermore, it is also important to note that the relative peak intensities and chemical shifts of the different ^{11}B NMR spectra signals in Figures 2.1 and 2.2 do not change when the ^{11}B NMR spectra were repeated using longer reaction times, showing that the equilibrium had been reached. This is worthy of note as enantioselectivity in the homoboroproline **60** catalysed aldol reaction is significantly improved through boronate Lewis-acidity tuning. As a result, a boronate ester suitable for longer reaction times due to its stability should result in an increased asymmetric induction and a reliable, reproducible catalytic reaction. In addition, when some of the above mentioned ^{11}B NMR spectra were repeated using an increasing relaxation time, identical spectra were obtained in every case, showing that the intensity of the signals is proportional to the concentration of the relevant species. Hence, integration of the two signals observed in the ^{11}B NMR spectra could give an accurate ratio between the two species present, *i.e.* boronate ester to boroxine.

With the objective of understanding the mode of action of the homoboroproline catalysed aldol reaction, an attempt to synthesise and characterise the diisopropyl-D-tartrate boronate ester analogue of **60** was undertaken *in situ*. Hence, homoboroproline HCl salt **76** was dissolved in CD_2Cl_2, followed by the addition of diisopropyl-D-tartrate **78a** and triethylamine. After refluxing the mixture for 2 h, Et_3NHCl was removed by filtration upon cooling. Surprisingly, the ^{11}B NMR spectrum of the resulting mixture showed a single peak at δ_B 10, with no sign of any boroxine species in δ_B 23 region. The observed shift revealed the possible formation of a dimer **84a**, since it does not correspond to either the free boronic acid **60** (~δ_B 30) or boroxine (~δ_B 23). This is in agreement with the absence of free diol in the ^1H NMR spectrum, since the indicative shift of the α-H of diisopropyl-D-tartrate is shifted form a singlet at δ_H 4.48 to the region of δ_H 4.30, where the CH_2N hydrogen of **84a** appear too. These results strongly suggest that even though only the dimer **84a** is observed in the absence of a substrate, it probably exists in equilibrium with its monomer form **84b** in order for the aldol reaction to take place. In addition, the lack of any boroxine signal, strongly suggests that the presence of the anionic function in **76** serves to stabilise the tartrate ester formation compared to unsubstituted boronic acids. While it is not absolutely clear how this works, one might speculate that the tetrahedral 'ate'-complex **84a** is favoured substantially over the boroxine because of a possible B-N complexation.



Scheme 2.10 *In situ* formation of the di*iso*propyl-D-tartrate etser of homoboroproline **76**.

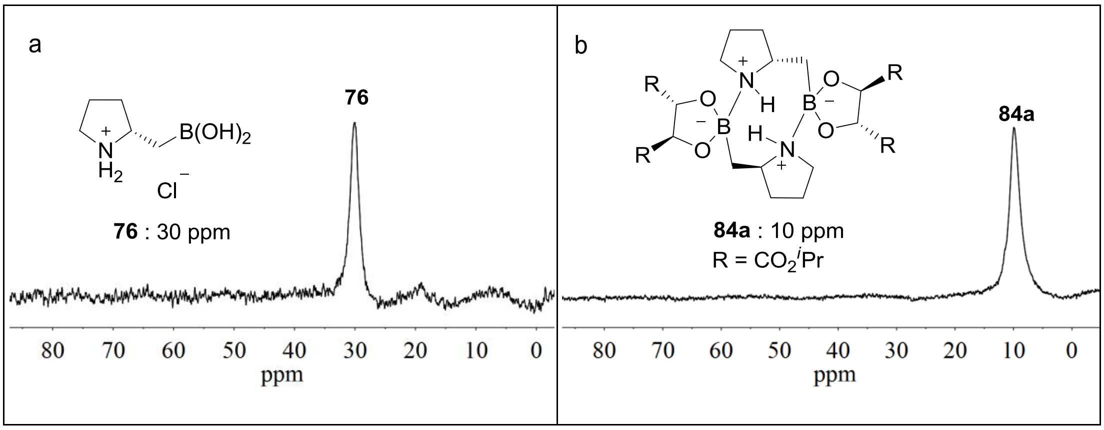
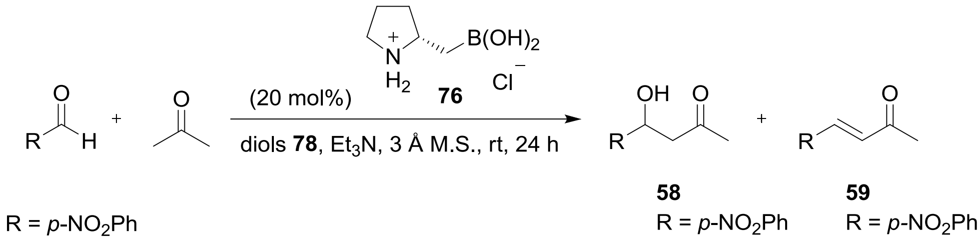


Figure 2.3 ^{11}B NMR spectra: (a) pyrrolidine-based boronic acid **76**; (b) condensation reaction of **76** with diisopropyl-D-tartrate **78a**.

2.4 Reaction Optimisation of the Homoboroproline-Catalysed Aldol Reaction

Taking into consideration the results of the ^{11}B NMR analysis and having identified the tartrate boronate ester **84b** as an effective catalyst for the enantioselective aldol reaction, the catalytic activity of different boronate ester derivatives of catalyst **60** was examined next. Hence, once the catalysts were prepared by reacting homoboroproline **74** with the relevant diol in the presence of molecular sieves at room temperature for 2 h, they were tested in the classic model aldol reaction between acetone and *p*-nitrobenzaldehyde, to examine their efficiency and asymmetric induction (eqn. 2.7).

This preliminary work revealed that in the presence of 20 mol% of the diisopropyl boronate ester catalyst **84a** in acetone, the aldol product **58** was afforded in 85% yield and 80% enantioselectivity (Table 2.2). To our surprise, the observed result was not in accordance with that previously reported by our group.[38] Even though the asymmetric induction had decreased to 80% from a claimed 90%, the conversion had increased to 95%, compared to 65%. A closer study revealed that the only variation in reaction conditions between this work and that of Whiting *et al.*[38] was the use of different adsorption capability molecular sieves. Nevertheless, even when 4 Å molecular sieves were used instead of 3 Å, neither the enantioselectivity nor the conversion changed. Bearing in mind that the final step for the synthesis of homoboroproline **76** involves a water-toluene azeotropic procedure, perhaps residual water could have resulted in a lower catalyst loading, and hence, lower conversion in the same reaction time period. However, replacement of the tartrate boronate ester **84b** with the hydrobenzoin catalyst **85** improved the ee to 90%, though the yield of the chalcone by-product **59** arising from dehydration of the aldol product **58** also increased (Table 2.2, entry 2) over the same reaction time period. Interestingly, use of catechol had a negative impact on both the reaction conversion and asymmetric induction (Table 2.2, entry 3).



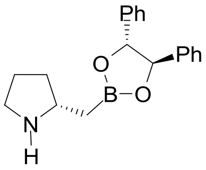
(2.7)

Table 2.2 Catalysed aldol reaction of *p*-nitrobenzaldehyde in neat acetone.

Entry	Catalyst	Yield of 58 [%][a]	ee [%][b]	Yield of 59 [%][a]
1	**76** + Diisopropyl-D-tartrate **78a**	85	80	10
2	**76** + (*R*,*R*)-Hydrobenzoin **78b**	63	90	20
3	**76** + Catechol **78c**	11	70	3

[a]Isolated yield after SiO_2 column chromatography.[b]Determined by HPLC analysis.

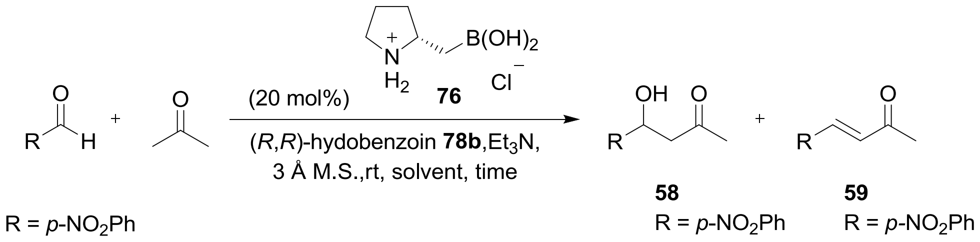
This observation is consistent with the results of the ^{11}B NMR analysis, *i.e.* that the use of catechol **78c** as a boronate tuning diol mostly result in boroxine formation which presumably explains the poor conversion and lower ee. Presumably, the boroxine is a sluggish catalyst, although it does result in relatively high ee, compared to the free boronic acid (70% ee *vs* 38% ee). On the other hand, one can claim that the asymmetric induction observed could be due to some extent to the catechol boronate ester formation. A clear answer as to whether the origin of the ee in the aldol product arises from a catalytic species in the form of boroxine or boronate ester cannot be given in the case of catechol esterification. Hence, the use of hydrobenzoin as a boronate esterification diol, serves to form a more stable boronate ester with an increased Lewis acidity. Such stabilisation and activation has two consequences: firstly, the acceleration of the reaction rate; and secondly, improvement in the asymmetric induction of the desired aldol product **58**. Hence, the increased yield of the aldol condensation product **59** observed may also be due to the increased reaction rate, which results in the consumption of the aldol product. On the other hand, in the case of catechol, boroxine and not the boronate ester is the major species formed and hence, a poor yield observed.



85

Figure 2.4 Boronate ester **85**, resulting from aminoboronic acid **76** and diol **78b**.

As indicated above, initial studies demonstrated the effect of the diol used for the boronate ester formation upon both the reactivity and enantioselectivity of the aldol reaction. Moreover, it was anticipated that by analysing a different reaction parameter, it would be possible to achieve the optimal reaction conditions. In particular, solvent screening was necessary since it was likely to significantly influence the yield and enantioselectivity of the organocatalysed reactions. To investigate this, the aldol reaction between acetone and *p*-nitrobenzaldehyde was performed in various solvents (eqn. 2.8). As revealed in Table 2.3, the highest enantioselectivities were obtained using either acetone or DMF as solvent for the catalysed aldol reaction. On the other hand, when THF or DMSO was used, a decrease was observed in both the yield and asymmetric induction. It is worth mentioning that in the case of DMF, homoboroproline salt **76** was fully soluble, in contrast with the use of acetone, DMSO and THF, where a homogeneous solution occured when the boronate ester starts to form after the addition of the diol. Hence, presumably the increased polarity of the solvent accelerates the formation of the boronate ester, minimising the possibility of boroxine formation and enhancing the enantioselectivity. Nonetheless, in DMF, a greater aldol condensation product **59** was observed, suggesting that the reaction in DMF is faster. Indeed, as seen in Table 2.3 (entry 5), when the reaction was run only until complete consumption of the aldehyde, 100% conversion was achieved in only 6 h and there was only minor chalcone **59** formation, suggesting that chalcone formation tends to occur after the formation of aldol product **58**. As a result, the yield of the aldol product **58** increased to 88% with an additional improvement of the ee at 95%.



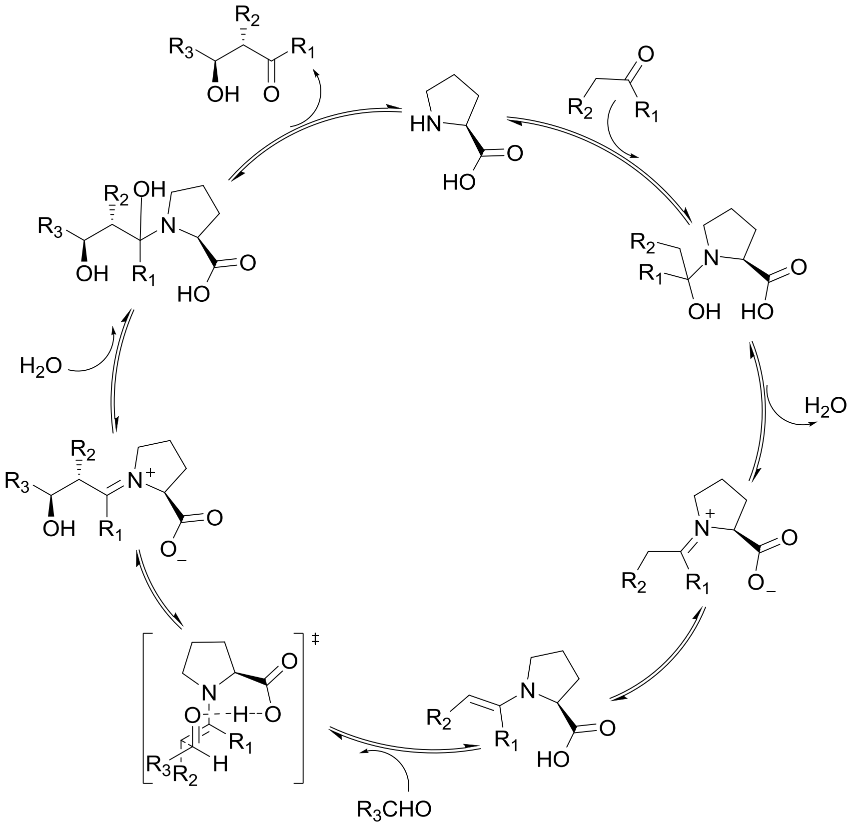
(2.8)

Table 2.3 Solvent screening of the catalytic reaction between *p*-nitrobenzaldehyde and acetone.

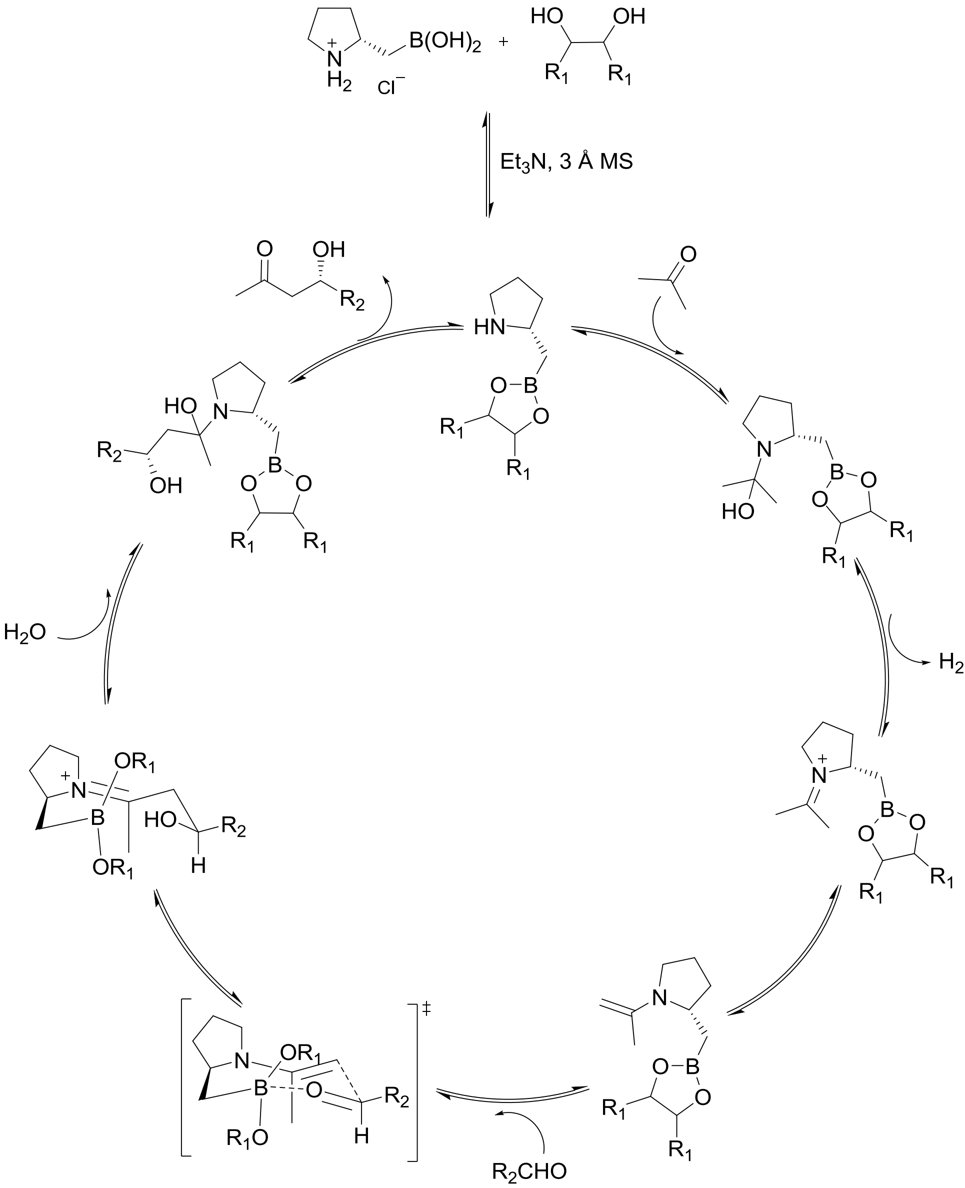
Entry	**Solvent**	**Time [h]**	**Yield of 2 [%][a]**	**ee [%][b]**	**Yield of 3 [%][a]**
1	Acetone	20	87	93 (*S*)	10
2	THF	20	45	88 (*S*)	41
3	DMF	20	54	93 (*S*)	34
4	DMSO	20	74	81 (*S*)	18
5	DMF	6	88	95 (*S*)	4

[a]Isolated yield after SiO_2 column chromatography.[b]Determined by HPLC analysis.

During the course of these mechanistic and optimisation studies, it was found that the use of DMF as the solvent enhanced the formation of the aldol product **58** essentially in 99% asymmetric induction, considering that the enantiomeric excess of homoboroproline **76** used was 96%. Thus, the hydrobenzoin boronate ester **85** proved to be a better catalyst than (*S*)-proline, regarding both the yield and enantioselectivity of the desired product.[6] The (*S*)-proline catalysed reaction between *p*-nitrobenzaldehyde and acetone has been reported to provide the aldol product **58** in 68% yield and 76% ee in DMSO under optimised reaction conditions. It is notable that again, polar solvents are preferred with proline, as with our catalyst, and this clearly relates to the ease of formation of the relevant enamine/iminium species. The two proposed catalytic cycles are shown in Schemes 2.11 and 2.12 respectively for comparison between the two systems. In addition, considerable excess of donor (enamine precursor) usually used in organocatalysed aldol reactions was significantly improved at 5 equivalents allowing us to consider that the optimised conditions could be beneficial when the amount of ketone needs to be at least stoichiometric.



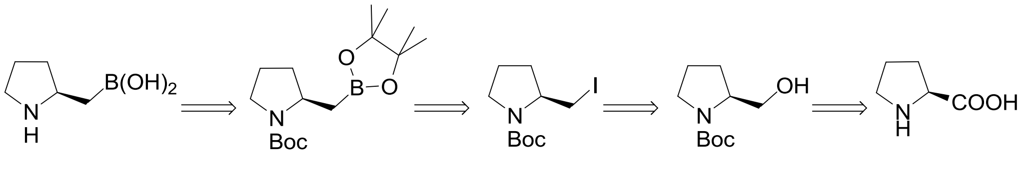
Scheme 2.11 Enamine mechanism for the proline-catalysed intermolecular aldol reaction.[9]



Scheme 2.12 Proposed mechanism for the homoboroproline-catalysed aldol reaction.

2.5 Studies towards the Asymmetric Synthesis of the opposite Enantiomer of the Homoboroproline Catalyst

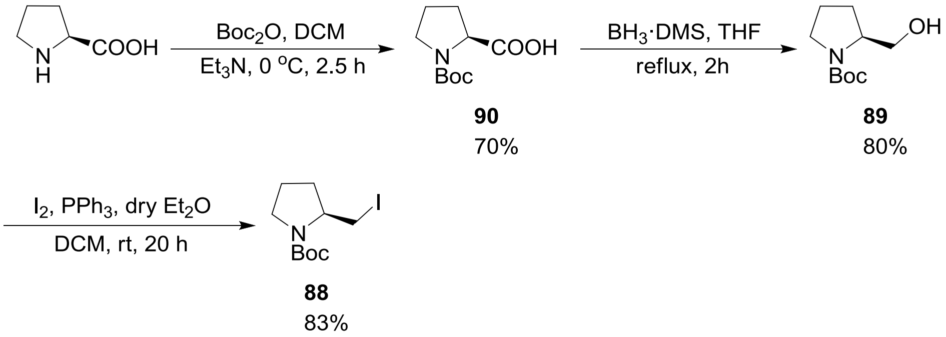
In the initial report on catalyst **60**, it was reasoned that part of the increased reactivity was due to a highly organised transition state occurring from the additional single carbon length chain between the pyrrolidine moiety and the boronic acid.[38] This results in catalytic activity which is superior to (*S*)-proline, and usefully readily provides access to the opposite enantiomer of the aldol product compared with (*S*)-proline, as outlined in Schemes 2.11 and 2.12. Having achieved success in improving the enantioselectivity, rate of reaction and stereoselectivity, the investigation was turned from the *in situ* esterification of the boronic acid to further applications. Specifically, the influence of the Lewis acidity of the boron atom has been examined systematically using various tartrate diols and had been noted that the *in situ* esterification promoted the aldol reaction to proceed with high enantioselectivities independently of the absolute stereochemistry or sterics of the tartrate.[38] Consequently, it was claimed that the stereochemistry of the aldol product is exclusively dependant on the stereochemistry of the chiral centre adjacent to the pyrrolidine moiety of catalyst **60**. Hence, it was thought that the synthesis of the opposite enantiomer of homoboroproline **60** would be a logical extension of these studies to both prove the origin of the stereoselectivity and to enable access to either enantiomeric series. Equally important to note is that the external ligand [(-)-sparteine] used for the asymmetric deprotonation of *N*-Boc-pyrrolidine in order to synthesise homoboroproline **60** had become almost impossible to acquire. The main reason provided from suppliers was the lack of availability of the usual plant source providing this lupin-derived alkaloid product commercially available.[55] Hence, attention was then focused on the synthesis of the homoboroproline enantiomer **86** in order to both confirm the origin of the stereocontrol in the aldol reaction and present an alternative route for formation of enantiomeric aldol products. A retrosynthetic plan to catalyst **86** was formulated in which the use of (*S*)-proline as the initial building block was exploited using the chiral centre already present as outlined in Scheme 2.13.



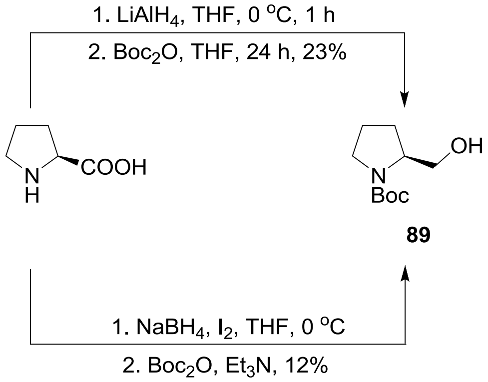
Scheme 2.13 Retrosynthetic route for the synthesis of pyrrolidine boronic acid-based catalyst **86**.

The first synthetic attempt started with a known protection of the nitrogen atom of (*S*)-proline using Boc$_2$O anhydride, followed by reduction with BH$_3$·DMS, which afforded the *N*-Boc-prolinol **89** in 56% overall yield (Scheme 2.14).[56-57]

Although this method involved a two step pathway, the relative ease and good overall yield made it preferable over attempted one-step procedures. Particularly, reduction of proline using $LiAlH_4$ at 0 °C, followed by *in situ* addition of Boc_2O, upon filtration furnished the desired product **89** in only 23% yield (Scheme 2.15).[58] In addition, even when (*S*)-proline was treated with $NaBH_4$ in an iodine-THF solution, followed by Boc_2O, the yield was poor (Scheme 2.15).[59] Unidentified impurities formed made the procedure complicated in terms of purifying the desired product. Furthermore, *N*-Boc-prolinol **89** was successfully converted to iodine **88** in 83% yield in the presence of iodine, triphenylphosphine and imidazole, as outlined in Scheme 2.14.[57]

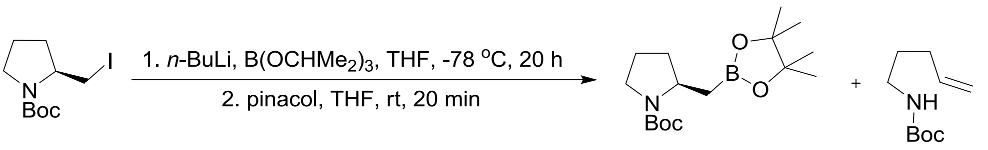


Scheme 2.14 Synthetic route for the formation of iodomethyl-pyrrolidine **88** starting from (*S*)-proline.



Scheme 2.15 Alternative one-pot Boc-protection and reduction of (*S*)-proline.

Having prepared iodide **88**, it was then necessary to convert the iodide function to the corresponding boronate, *i.e.* **87**. Borylation of alkylhalides is theoretically accomplished by trapping such reactive species as organolithium intermediates with a borate electrophile. However, initial attempts to form the alkylboronic acid derivative **86** were unsuccessful using lithium-halogen exchange methods.[60] In a preliminary experiment, a solution of compound **88** and trimethylborate in THF was treated with *n*-BuLi at -78 °C. Surprisingly, the reaction did not give the expected product but a mixture of the starting material **88** and its ring opening analogue **91** in a ratio of 3:1 (eqn. 2.9). This result suggested that the intermediate organolithium reagent was unstable towards β-elimination and thus gives rise to unsaturated compound **91**, rather than being trapped by the electrophile.[57,61] In an attempt to optimise the reaction conditions, the same type of procedure was carried out whilst increasing the amount of boron electrophile source to 3, and then to 10 equivalents, however this did not lead to any improvements. On the other hand, quantitive conversion to compound **91** was observed when the equivalents of the lithiating agent were increased and when *t*-BuLi was used instead.



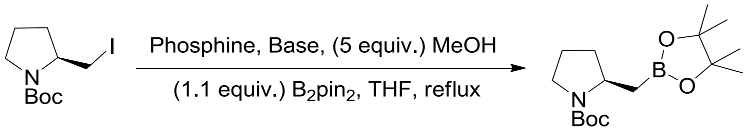
(2.9)

88 **87** **91**

23%

Despite the variety of borylation protocols that have been developed for the synthesis of aryl- and alkenyl-boronic acids, a general and reliable method for the synthesis of alkylboronic acids remains elusive apart from the trapping of organomagnesium or organolithium intermediates with borates or catalytic hydroboration of alkenes.[29] As eluded to above, in this case, the direct conversion of **88** to **87** was not successful.

In 2010, metal-free boration of α,β-unsaturated compounds emerged as a new strategy for the enantioselective catalytic construction of β-borated carbonyl compounds. Fernández *et al.* were able to obtain β-pinacolboronated carbonyl compounds when they treated α,β-unsaturated esters or ketones with B_2pin_2, Cs_2CO_3, PPh_3 and MeOH.[62] They argued that the phosphine promoted the cleavage of the B-B bond of B_2pin_2, resulting in the plausible nucleophilic attack of the boron moiety to the substrate. As a result, this reaction became of interest for the potential borylation of compound **88** as outlined in equation 2.10. Unfortunately, subjecting iodomethyl-pyrrolidine **88** to react with B_2pin_2, 0.15 equivalents of Cs_2CO_3, 20 mol% of PPh_3 and MeOH did not furnish the desired product **87** (eqn. 2.10). All attempts to modify the reaction conditions, including the use of KO^tBu instead of Cs_2CO_3 or the absence of PPh_3 proved fruitless in our hands, providing full recovery of the starting material as summarised in Table 2.4.



88 **87**

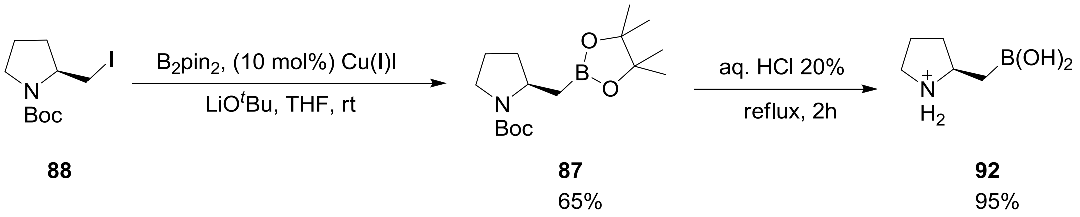
(2.10)

Table 2.4 Reaction conditions carried out for the attempted conversion of compound **88** to boronate ester **87**.

Entry	Phosphine	Base	Conversion [%][a]
1	0.2 equiv. PPh_3	0.15 equiv. Cs_2CO_3	0
2	-	0.15 equiv. Cs_2CO_3	0
3	0.2 equiv. PPh_3	1.1 equiv K^tOBu	0
4	-	1.1 equiv K^tOBu	0

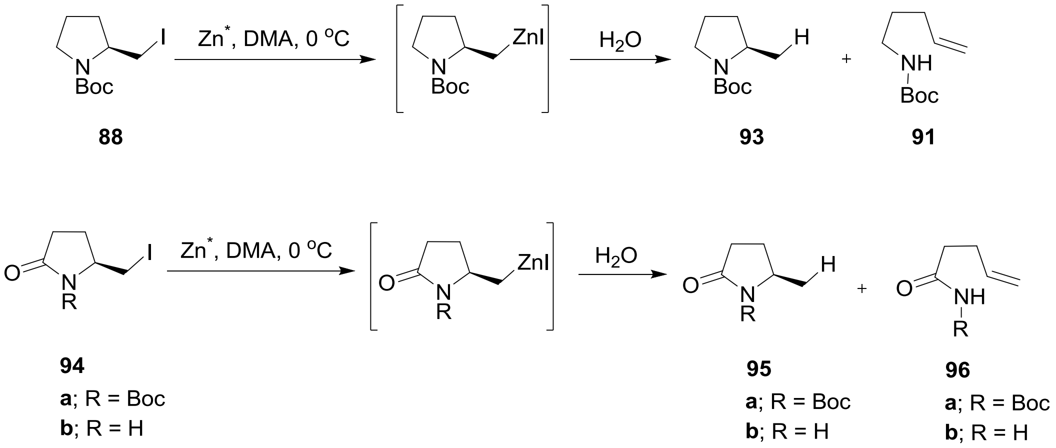
[a]Almost 100% recovery of the starting material **88**.

The prospect of using diboronyl esters such as B_2pin_2 in the cross-coupling of aryl halides and triflates under palladium catalysis was introduced in 1995 by Miyara and co-workers.[63] Since then, the development of modified conditions has expanded the scope of transition metal-catalysed coupling reactions between aryl halides and diboronyl reagents.[29] While the use of transition metal catalysis in order to access arylboronate esters has been accomplished, the synthesis of alkylboronates through transmetalation is much more underdeveloped. Liu *et al.* reported the first example of cross-coupling reactions between organoboron compounds and primary alkyl halides using copper-catalysed conditions.[64] These authors were able to obtain cross-coupled adducts in up to 85% yield by treating unactivated alkyl electrophiles with arylboronic esters in the presence of CuI and LiO^{t}Bu. Based on earlier results on the copper-catalysed borylation of arylhalides, α,β-unsaturated carbonyl compounds and aldehydes,[65] Marder *et al.* achieved the selective borylation of primary and secondary alkylhalides.[66] This study demonstrated that borylation of sp^3-carbon atoms using B_2pin_2 in the presence of CuI, LiO^{t}Bu and PPh_3, highlighted a novel and general method for the synthesis of alkylboronate esters from simple alkyl halides. Encouraged by these results, these reaction conditions were applied to iodomethylpyrrolidine **88**. As a result, compound **88** was treated with B_2pin_2, LiO^{t}Bu and 10 mol% of CuI in THF at room temperature to yield pinacol boronate ester **87** in 48% yield and 97% enantiomeric excess. The yield of the reaction improved to 65% when an acidic work-up was carried out prior to purification, even though the literature procedure suggested a simple filtration. The development of this simple, high yielding and reproducible reaction meant that enantiomeric series to catalyst **86** could be easily achieved through this sequence from (*S*)-proline. Finally, cleavage of the Boc-group and pinacol boronate ester of **87** was readily conducted under the standard conditions to afford deprotected **92** in quantitive yield.



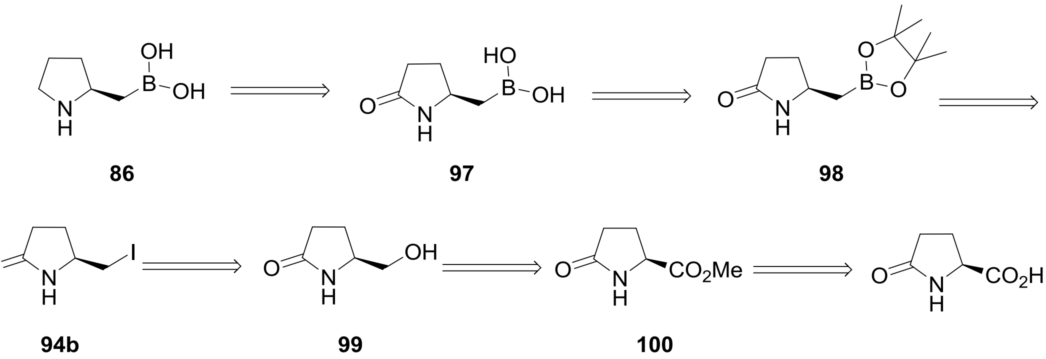
Scheme 2.16 Synthetic route towards the formation of homoboroproline catalyst **92**.

When the investigation into the synthesis of homoboroproline **86** was commenced, the recently reported paper on the borylation of alkyl halides using catalytic CuI had not been published.[66] As mentioned before, (*S*)-proline was *N*-Boc protected and reduced to give compound **89** which was subjected to iodination conditions affording the alkyl halide product **88**. However, the borylation using a lithium-halogen exchange method was hampered by the facility of **88** to undergo β-elimination. A literature search revealed a 2006 paper dealing with the cross-coupling of organozinc analogues of amino acids with acid chlorides[57] and in this report, Tanner *et al.* showed that the reaction of activated zinc with iodides **88** and **94a** did not afford the desired products **93** and **95a** (Scheme 2.17). In the case of **88** and **94a**, the generated organozinc intermediates perhaps not surprisingly β-eliminated to give the unsaturated compounds **91** and **96a** respectively. Nevertheless, zinc insertion, occurs when compound **94b** is used, yielding exclusively reduced product **95b** after an aqueous quench rather than the elimination product **96b**.



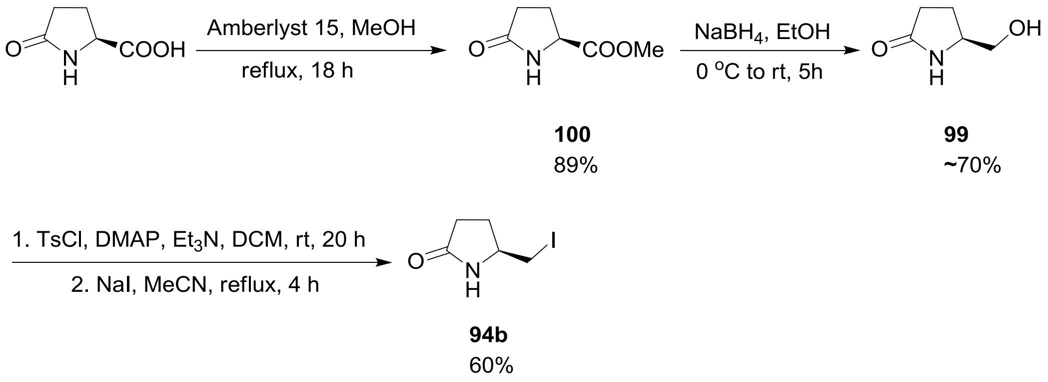
Scheme 2.17 Generation and possible products from aqueous quenching of organozinc reagents.

As a result of these reports, these observations were of interest in the case of the studies towards the synthesis of homoboroproline **86**. An alternative retrosynthetic plan was proposed in which the main idea was to use L-pyroglutamic acid as the starting material, hoping to achieve the borylation of iodide **94b** to boronate ester **98**, in an attempt to avoid the formation of the ring opening analogue **96b** (Scheme 2.18). In addition, this would be followed by the reduction of the amide carbonyl group of compound **97**, in an effort to furnish the desired aminoboronic acid **86**.



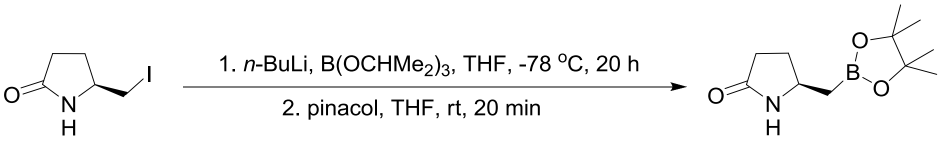
Scheme 2.18 Retrosynthetic plan towards the synthesis of homoboroproline **86**, starting from L-pyroglutamic acid.

Initially L-pyroglutamic acid was reacted with Amberlyst 15 in refluxing MeOH resulting in the isolation of methyl ester compound **100** in 89% yield (Scheme 2.19).[67] In a second step, treatment of **100** with $NaBH_4$ in EtOH afforded the primary alcohol **99**.[68] Even though 1 equiv. of acetic acid was used to quench the reaction, some of it was present in the crude product. Efforts to remove it were unsuccessful and as a result, compound **99** was used crude for the next step without any further purification. Further transformation to iodide **94b** was accomplished in a two-step sequence consisting of: 1) tosylation with TsCl in the presence of Et_3N and DMAP; and 2) iodination with NaI in MeCN resulting after purification in 60% iodide **94b**.[57]



Scheme 2.19 Synthetic route for the formation of iodide compound **94b** starting from L-pyroglutamic acid.

As already mentioned above, attempts to obtain boronate ester **87** by lithium-halogen exchange of **88** were unrewarding, since they led to reductive ring opening with formation of **91**. Unfortunately, a similar outcome was observed when iodide **94b** was treated with triisopropyl borate and *n*-BuLi.[60] A complex mixture of unidentified products was obtained after the work up procedure, with strong implications that one of them was once again the ring opening analogue **96b**. Further optimisation of the reaction or characterisation of the resulting products was not carried out since by that time the synthesis of the desired boronic acid **92** was achieved through the initial proposed retrosynthetic plan, starting from (*S*)-proline.



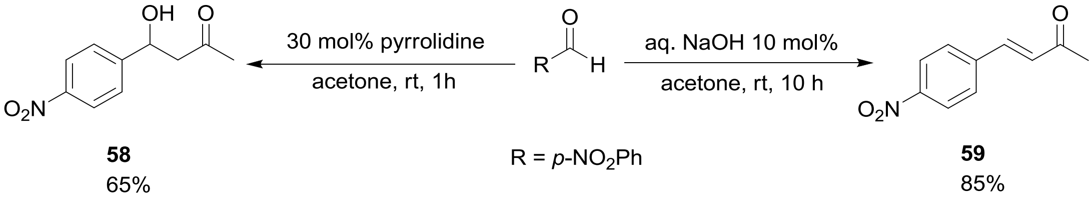
94b **98** (2.11)

In summary, the synthesis of the (*R*)-enantiomer of the homoboroproline catalyst **76** was achieved, with the CuI catalysed borylation of alkyl halide **88** being the key step of the synthetic strategy. Having in hand novel catalyst **92**, it was anticipated that further applications would result in an improvement towards attempts in understanding the mode of action of this type of catalyst.

2.6 Mechanistic Studies

At this stage, in an effort to better understand the mechanism of the homoboroproline catalysed aldol reaction, it was necessary to establish whether the reaction was proceeding, as envisioned, *via* a catalytically accessed iminium ion species in which the boronate forms a tetrahedral aldolate ‘ate’-complex **62** (Scheme 2.12). To explore these mechanistic questions, a series of experiments in which the standard aldol reaction between acetone and *p*-nitrobenzaldehyde needed to be monitored over time using chiral HPLC were carried out. Before being able to conduct these experiments, the formation of the relevant calibration curves was necessary. As a result, both the racemic aldol condensation product **58** and aldol elimination product

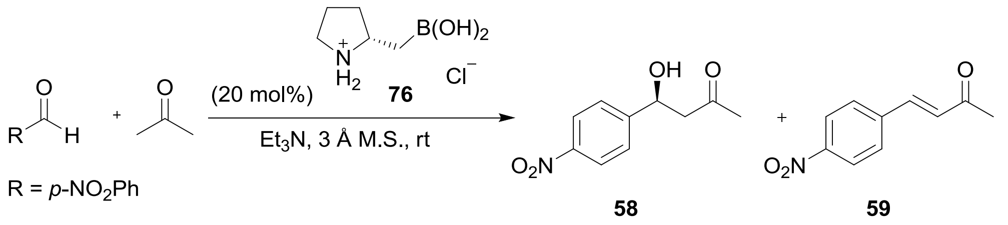
59 resulting from the reaction of acetone and *p*-nitrobenzaldehyde had to be synthesised. Both desired compounds were formed following previously reported literature procedures (Scheme 2.20).[37,69] Firstly, *p*-nitrobenzaldehyde was reacted in a mixture of water and acetone using 30 mol% of pyrrolidine as a catalyst, affording after purification the racemic aldol product **58** as a white solid.[69] In addition, chalcone **59** was furnished after reacting acetone and *p*-nitrobenzaldehyde in a 0.01 M aqueous solution of NaOH.[37]



Scheme 2.20 Synthetic route for the synthesis of racemic aldol condensation product **58** and aldol elimination product **59**.

Moreover, the calibration curves for the starting material (p-NO$_2$PhCHO), aldol condensation **58** and aldol elimination product **59** were formed using standard solutions of the above mentioned compounds. It is worth mentioning that for each concentration, the absorption was measured three times and the lowest concentration was 0.001 M reaching 0.005 M the highest. In addition, in each case, an identical amount of internal standard, *i.e.* naphthalene, was added in order to minimise the error factor. The calibration graphs and equations resulting from these experiments were used in order to calculate the concentrations of both reactants and products in the following reactions and can be found in the Appendix section for reference.

In the initial experiment, kinetic measurements were performed on the catalytic system which contained only homoboroproline **76**. As a model reaction, the aldol addition of *p*-nitrobenzaldehyde with acetone in the presence of Et_3N, and catalyst **76** was examined (eqn. 2.12). The reaction was carried out in neat acetone at room temperature and was monitored over time using HPLC. The results are summarised in Figure 2.5. According to Figure 2.5, the aldol reaction was complete in 8 h and aldol elimination product **59** remained at a relatively low level throughout. In addition, even though the enantioselectivity of the aldol condensation **58** was only 48%, the fact that it remained relatively constant over time gave the first indication of the absence of any non-linear effects.[70]



(2.12)

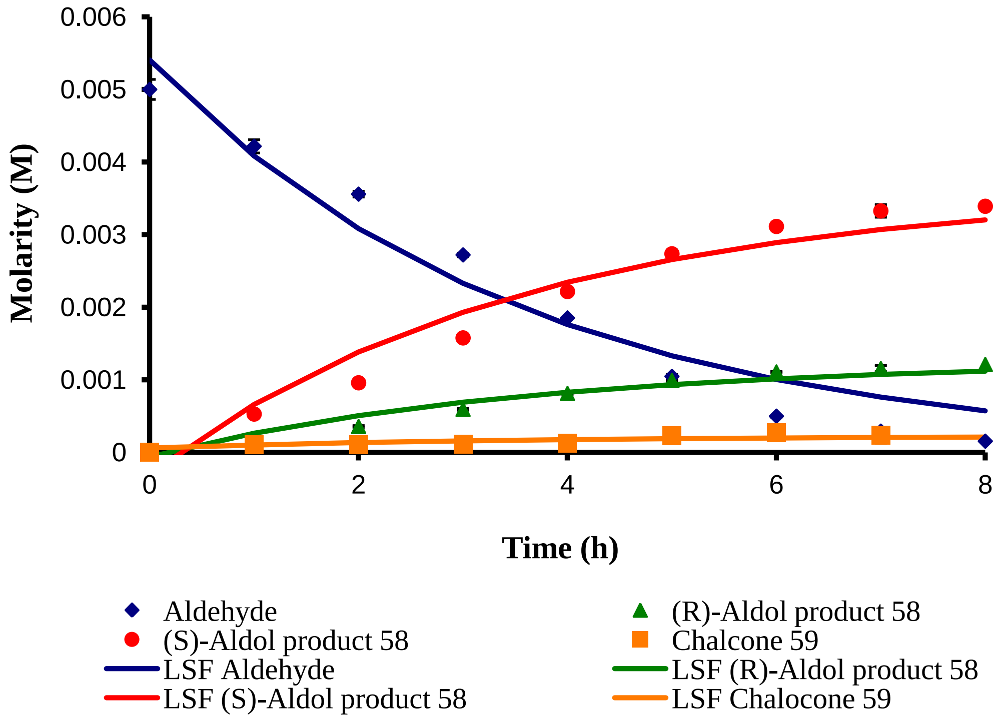
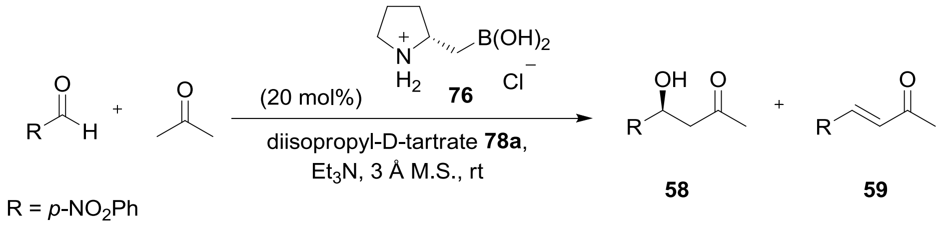


Figure 2.5 Molarity of the starting material, (*S*)-aldol product **58**, (*R*)-aldol product **58** and chalcone **59** when the reaction was carried out in the presence of catalyst **76**.

In a second set of experiments, the influence of the *in situ* formation of a boronate ester on the ‘benchmark’ aldol reaction was examined (eqn. 2.13). As a result, before the addition of the aldehyde, diisopropyl-D-tartrate catalyst **84b** was generated *in situ* by reacting the homoboroproline catalyst **76** with diol **78a** in the presence of molecular sieves in neat acetone for 1 h. Moreover, the catalytic reaction was further monitored every hour for a total period of 9 h, as shown in Figure 2.6. Notably, the reaction rate was not affected by the presence of the boronate ester instead of the boronic acid as the catalyst. Consequently, the reaction reached completion in about 8 h and once again the by-product **59** started to appear only when the starting material was almost totally consumed. Nevertheless, although we expected the enantiomeric excess to be constant over time, it started at 70% and by the end of the reaction reached 80%. At this point it was assumed that a possible explanation for this phenomenon involved the fact that there was an insufficient amount of time provided in order to form the boronate ester before the addition of the aldehyde. This would have resulted in a reaction where free boronic acid was still present in the first hours, acting as a catalyst, and therefore, decreasing the overall enantioselectivity.



(2.13)

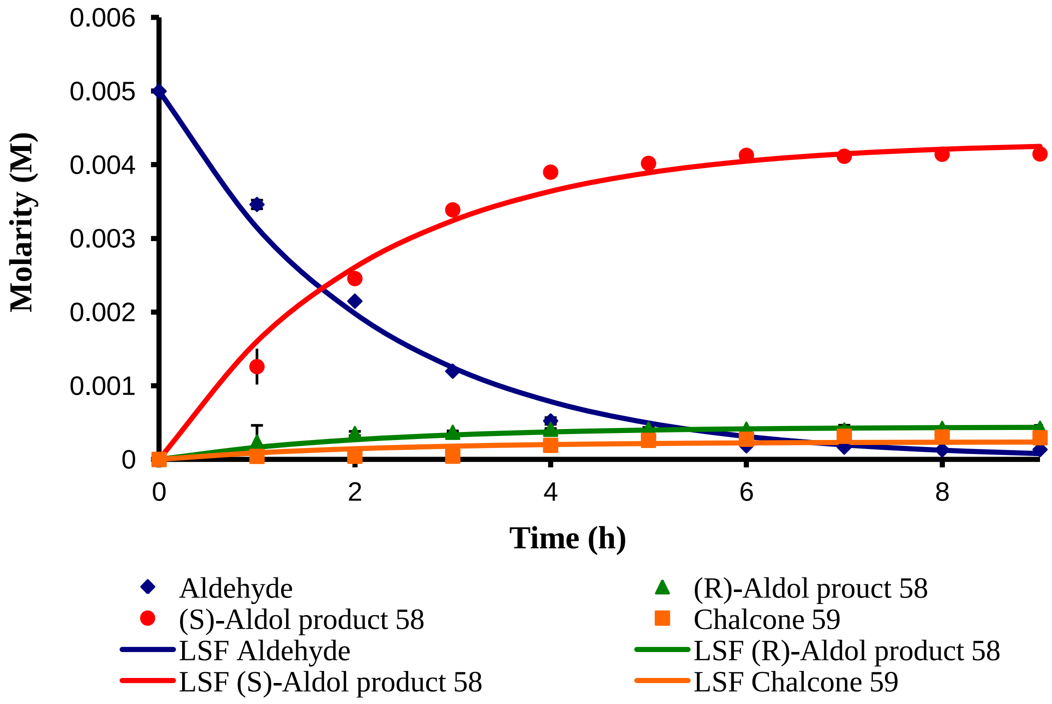
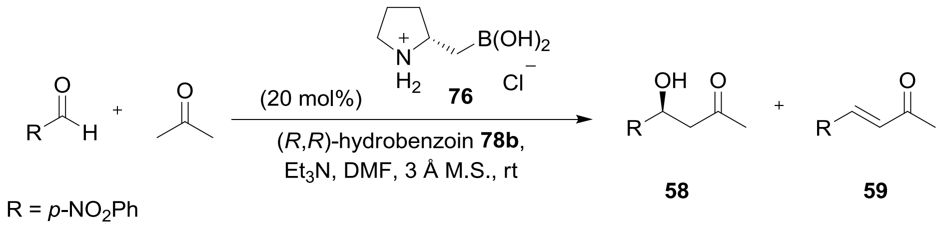


Figure 2.6 Molarity of the starting material, (*S*)-aldol product **58**, (*R*)-aldol product **58** and chalcone **59** when the reaction was carried out in neat acetone using catalyst **82b**.

To verify whether the lower ee observed at the start of the reaction was due to a lower boronate ester concentration, the reaction time for its formation was prolonged. When the reaction was repeated allowing a period of 20 h for the catalyst **84b** to be formed, 100% conversion was obtained at 8 h and the ee was constant at around 83%. This observation shows the necessity for a longer reaction time for the complete esterification of the boronic acid, before the aldol reaction is initiated.

Similar results were observed when the (*R*,*R*)-hydrobenzoin ester of homoboroproline **76**, *i.e.* **85**, was used as the catalytic species in the aldol reaction between *p*-nitrobenzaldehyde and acetone in DMF (eqn. 2.14). In this case, an enhanced reaction rate was observed, resulting in the completion of the reaction in 6 h, with minimal elimination product formation occurring (Figure 2.7). In addition, the formation of the boronate ester was achieved in 2 h and this is due to the increased solubility of the proline-based boronic acid **76** in DMF compared to acetone. Most importantly, the desired aldol product was obtained in 95% ee and 88% yield. Under the optimised reaction conditions, the enantioselectivity of the product was proportional to the enantiomeric excess of the catalyst. With regard to this, no sign of non-linear asymmetric induction was observed.[70] Despite indications that both catalysts **84b** and **85** could exist as dimeric species, they do react as monomeric entities in order for the aldol reaction to occur with invariably high asymmetric induction.

In an attempt to further elucidate the mechanism of the enantioselective aldol reactions catalysed by the boronate ester analogues of **76**, further studies were undertaken to prove the origin of the enhanced asymmetric induction observed. Specifically and as described in previous sections, it was argued that the enantioselectivity arises from the chiral centre present on the pyrrolidine ring of the catalyst and it is independent of the chirality of the diol used for the esterification of the boronic acid.[38] To check this to be the case, the aldol reaction between *p*-nitrobenzaldehyde and acetone in DMF was performed in the presence of (*meso*)-hydrobenzoin analogue **101** of homoboroproline **76** (eqn. 2.15). As expected, the rate of the reaction and the yield of the desired aldol product **58** were almost identical to the experiment where the (*R*,*R*)-hydrobenzoin analogue **85** of the catalyst was used (eqn. 2.14). On the other hand, the enantiomeric excess was decreased slightly from 95% to 89%. These results, in combination with the previously reported observations, revealed that the stereochemistry of the boronate ester does not affect the magnitude of the enantioselectivity or absolute configuration of the aldol condensation product **58**. The drop in the asymmetric induction when using the (*meso*)-diol is likely to be due to the formation of a less stable boronate ester resulting in some boroxine formation. However, more importanlty the use of the (*meso*)-hydrobenzoin as the diol in the catalytic aldol reaction proved to be a valuable strategy for confirming that the chirality of the diol has no effect on the asymmetric induction of the final aldol product **58**.



(2.14)

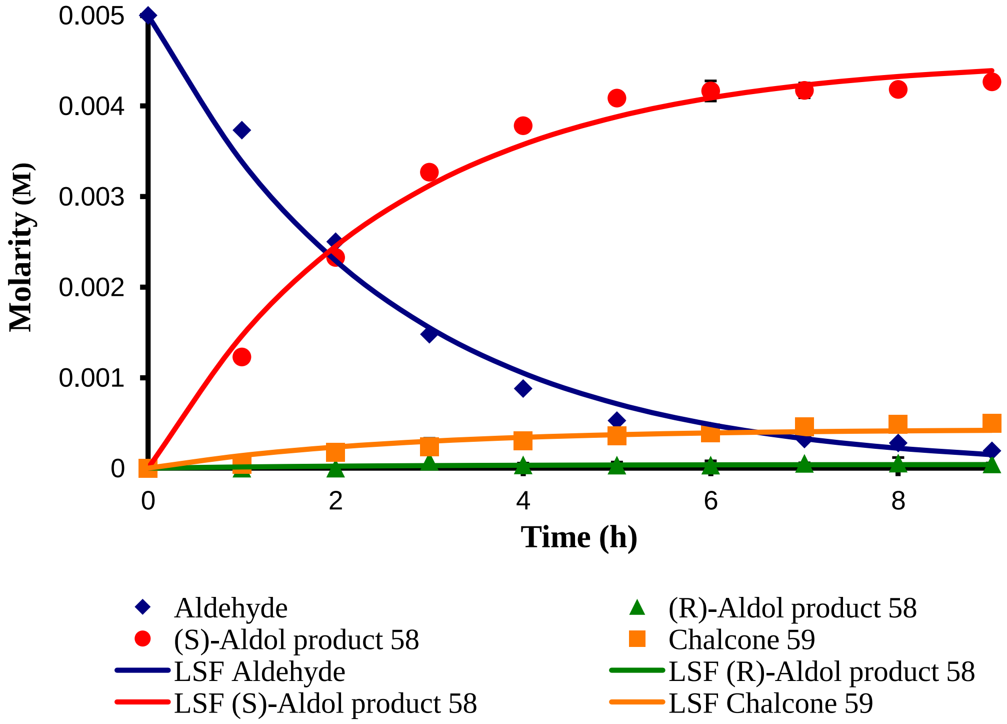
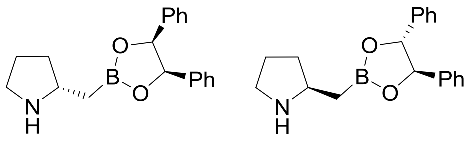
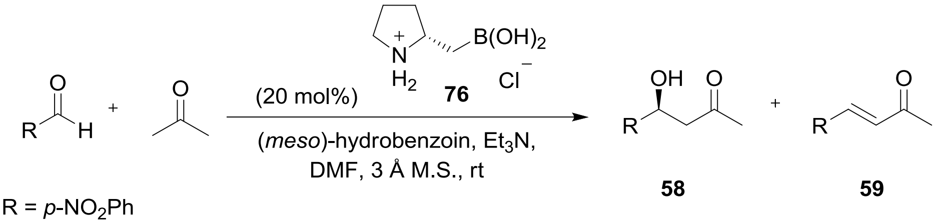


Figure 2.7 Molarity of the starting material, (*S*)-aldol product **58**, (*R*)-aldol product **58** and chalcone **59** when the reaction was carried out in DMF using the (*R*,*R*)-hydrobenzoin derived catalyst, *i.e.* **85**.



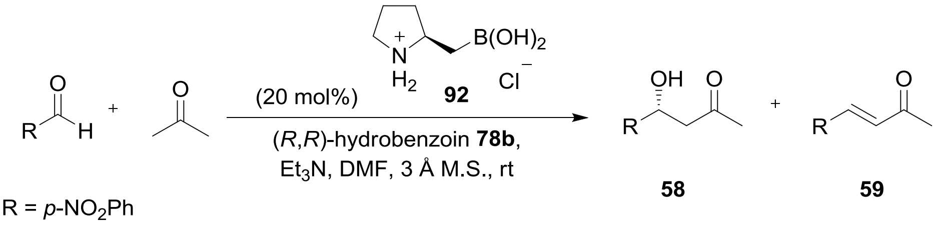
101 **102**

Figure 2.8 Catalytic species present in the reactions outlined in eqn. 2.15 and 2.16.



(2.15)

Further information regarding the orientation of the boronate ester analogue of homoboroproline catalyst **76** in the transition state (see Scheme 2.12) of the enantioselective aldol reaction needed to be obtained. In this context, the effect of the absolute stereochemistry of the chiral centre present on the pyrrolidine moiety was examined. Therefore, having in hand the opposite enantiomer of the homoboroproline catalyst, *i.e.* **92**, it was applied under the optimised reaction conditions to carry out the ‘benchmark’ aldol reaction. Specifically, the reaction of *p*-nitrobenzaldehyde and acetone in DMF was carried out in the presence of (*R*,*R*)-hydrobenzoin analogue **102** of proline-based boronic acid **92** (eqn. 2.16). In full agreement with our expectations, the aldol product **58** was obtained in its opposite enantiomeric form in 96% ee (see entry 6, Table 2.5).



(2.16)

Table 2.5 summarises the results obtained to date from the mechanistic studies. These studies have highlighted the significance of an increased Lewis acidic boron moiety in order to obtain high asymmetric induction in our organocatalytic methodology. In addition, they have given some insight into the transition state, demonstrating the utility of the chirality present in the pyrrolidine ring and also proving that the chirality of the diol plays no part; it simply contributes to ester stability.

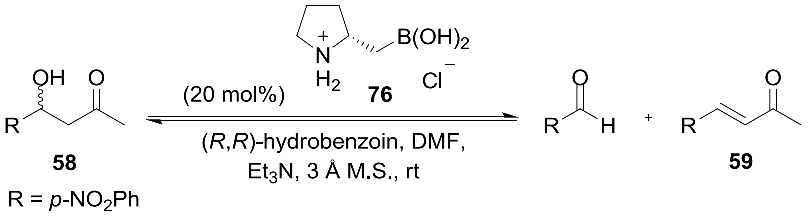
Table 2.5 Effect of catalytic system and solvent on the homoboroproline-catalysed aldol reaction.

Entry	**Catalyst**	**Diol**	**Solvent**	**Time [h][a]**	**Yield of 58 [%][b]**	**ee [%][b]**	**Yield of 59 [%][b]**
1	**76**	-	acetone	8	93	49 (*S*)	6
2[c]	**76**	diisopropyl-D-tartrate	acetone	8	89	80 (*S*)	6
3[d]	**76**	diisopropyl-D-tartrate	acetone	8	82	83 (*S*)	9
4[e]	**76**	(*R*,*R*)-hydrobenzoin	DMF	6	88	95 (*S*)	4
5[e]	**76**	(*meso*)-hydrobenzoin	DMF	8	85	89 (*S*)	7
6[e]	**92**	(*R*,*R*)-hydrobenzoin	DMF	7	89	93 (*R*)	7

[a] Time period for 100% conversion. [b] Determined by HPLC. [c] 2 h, [d] 20 h, [e] 3 h Reaction time for the formation of the boronate ester.

During the preliminary studies, it seemed that longer reaction times were the reason for the aldol condensation product **59** being formed. A closer look at Figures 2.5, 2.6 and 2.7 reveals that once the starting materials have been consumed, the aldol adduct **58** might undergo a slow elimination in the presence of the catalyst resulting in the formation of **59**. Efforts were then devoted towards investigating whether the racemic aldol product **58** could undergo kinetic resolution in the presence of catalyst **83** to provide aldol adduct **58** with high asymmetric induction and aldol elimination **59** as the by-product. Hence, herein are described results on precisely such a study, performed by reacting the racemic sample of aldol adduct **58** with catalyst **85** in both the absence and presence of acetone in DMF.

Initially, the fate of the racemic aldol **58** in the presence of the (*R*,*R*)-hydrobenzoin boronate ester **85** in DMF (eqn. 2.17) was monitored and the results are shown in Figure 2.9 and the corresponding enantiomeric excess in Figure 2.10. These show that the two enantiomers of the racemic aldol product **58** were consumed at different rates. Notably, the condensation product **59** appeared at a roughly similar rate to the starting aldehyde, both of which seemed to be levelling off after 24 h. In addition, the intriguing observation that a greater decrease in the concentration of the (*S*)-aldol product of **58** compared to the (*R*)-aldol was made. The former remained essentially constant and hence, an increase in the enantiomeric excess of the (*R*)-enantiomer of **58** from 0.15% to 21% was observed, as shown in Figure 2.10. As a result, there were a few points of direct evidence that a kinetic resolution process was occuring throughout the 48 h period, though the increase in enantiomeric excess of the aldol adduct **58** did level off.



(2.17)

With these results taken into account, it is possible to claim that the catalyst derived from **76** and (*R*,*R*)-hydrobenzoin consumes the (*S*)-aldol product **58** highly selectively. The outcome was both the formation of the chalcone **59** as a by-product through elimination, and the generation of the starting aldehyde by a retro-aldol-addition reaction. It should be noted that the slight reduction in the amount of the (*R*)-aldol product **58** can be explained by the fact that the asymmetric induction of the catalyst itself is 96%. Hence, the minor enantiomer of the catalyst resulted in the formation of the opposite aldol product. This fits well with the fact that the (*S*)-aldol product was preferably consumed, giving rise to an increase in the enantiomeric excess of the (*R*)-aldol product.

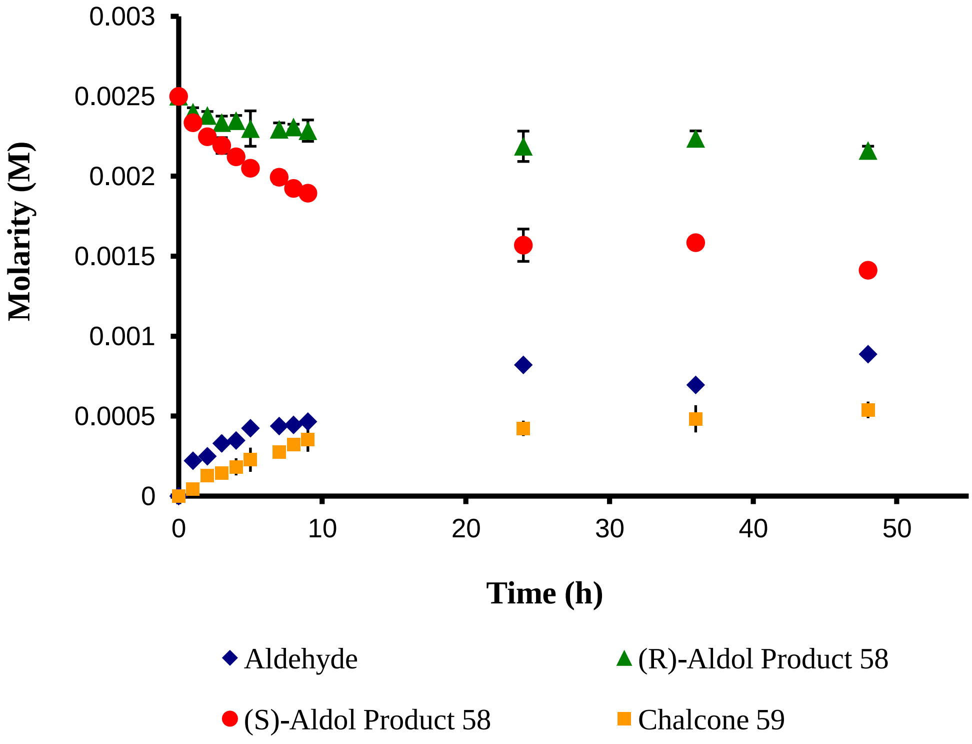


Figure 2.9 Molarity of the starting material, (*S*)-aldol product **58**, (*R*)-aldol product **58** and chalcone **59** over time for the reaction outlined in eqn. 2.17.

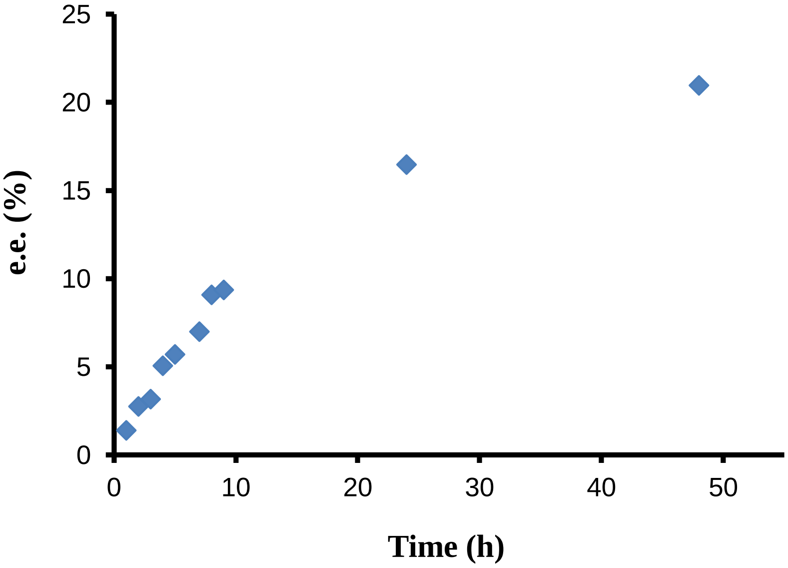
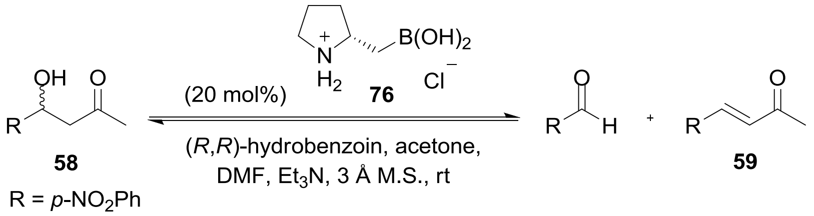


Figure 2.10 Enantiomeric excess of (*R*)-aldol product **58** over time for the reaction outlined in eqn. 2.17.

In a similar fashion, the racemic aldol product **58** was subjected to a catalytic amount of catalyst **85** in the presence of excess acetone in DMF with the idea of the acetone being present to react with any aldehyde turnover (eqn. 2.18). The first thing to note is that the release of the starting aldehyde was not observed, as expected with the excess acetone present (Figure 2.11). This seemed reasonable given that the aldehyde formed reacts rapidly again with acetone to furnish aldol product **58** in favour of the (*S*)-enantiomer. Hence, the asymmetric induction of the kinetic resolution process decreased to 10% after 24 h which was less compared to the reaction carried out without acetone (Figure 2.12). This study proved valuable in revealing key ideas about the mode of action of the homoboroproline catalyst, contributing to the proposed catalytic reaction mechanism described in the following section.



(2.18)

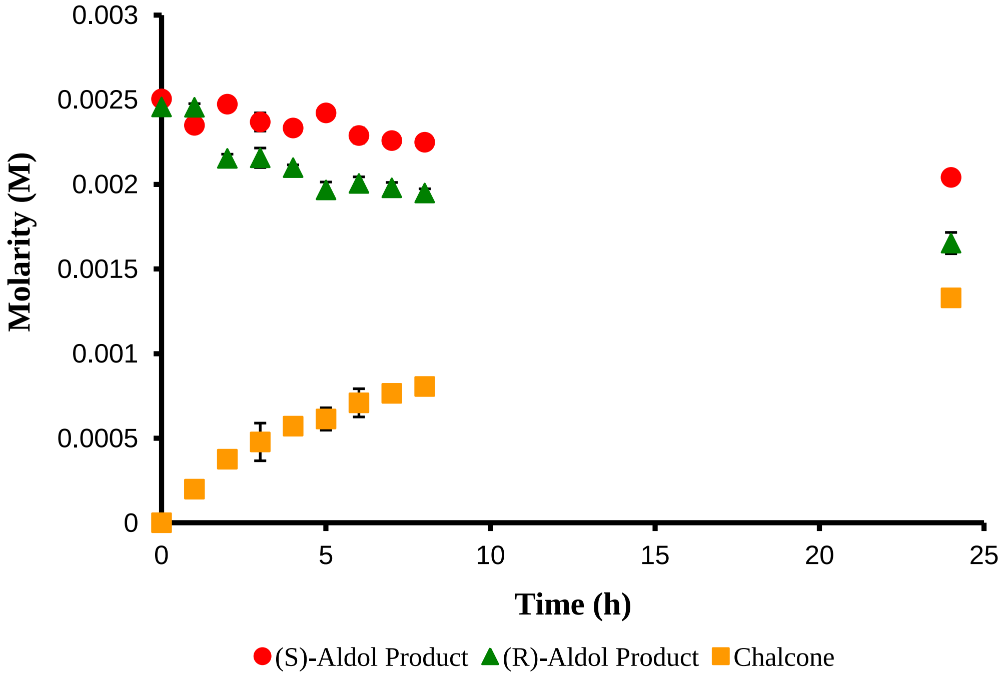


Figure 2.11 Molarity of the (*S*)-aldol product **58**, (*R*)-aldol product **58** and chalcone **59** over time for the reaction outlined in eqn. 2.18.

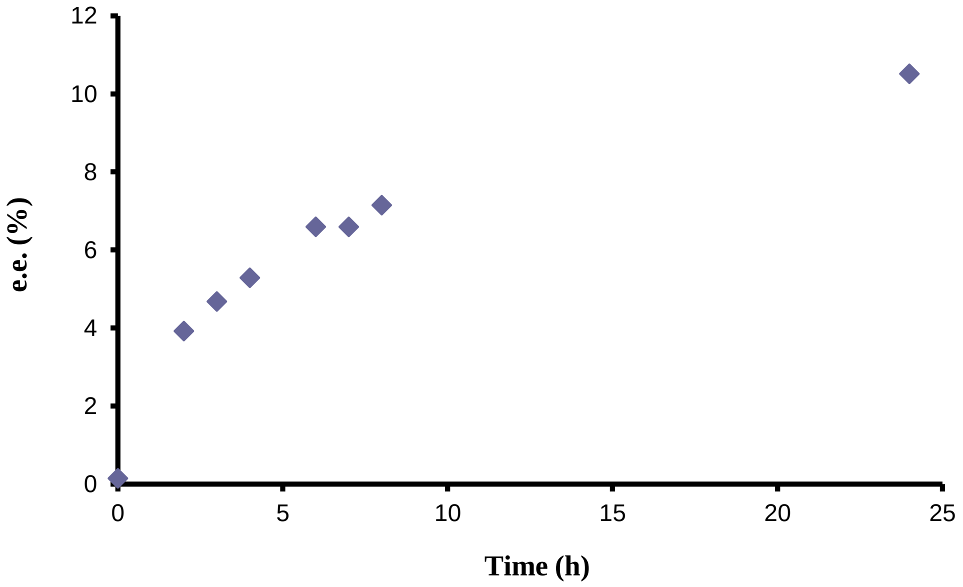
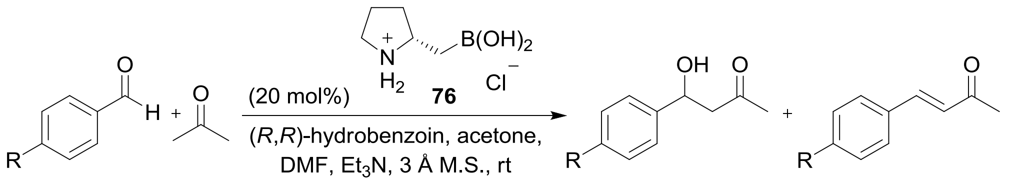


Figure 2.12 Enantiomeric excess of (*R*)-aldol product **58** over time for the reaction outlined in eqn. 2.18.

2.7 Application of the Homoboroproline Catalyst to Other Aromatic Aldehydes

The promising enantioselectivity (95%) in combination with the mechanistic studies suggested that the homoboroproline-catalysed aldol reaction warranted further development for the reaction of *p*-nitrobenzaldehyde with acetone. The key issue in developing a truly useful organocatalyst is the ability to perform the reactions on a range of different substrates. With optimal conditions in hand for the aldol reaction between *p*-nitrobenzaldehyde and acetone, a study of the scope of the reaction was undertaken to test the limitations of this new process examining different aldehyde substrates.

Since boronate ester **85** in DMF was found to provide the optimal mix of reactivity and selectivity, it was chosen for further study. In particular, using HPLC, the capacity of homoboroproline **85** to catalyse the aldolisation of *p*-anisaldehyde and benzaldehyde with acetone was next examined (eqn. 2.19).



(2.19)

103
a; R = p-NO$_2$
b; R = p-OMe
c; R = H

104
a; R = p-NO$_2$
b; R = p-OMe
c; R = H

105
a; R = p-NO$_2$
b; R = p-OMe
c; R = H

Table 2.7 Effect of substrate on the homoboroproline-catalysed aldol reaction outlined in eqn. 2.19.

Entry	**R**	**Conversion [%]**	**Time [h]**	**Yield of 104 [%]**	**ee [%][a]**	**Yield of 105 [%]**
1	p-NO$_2$	>98	6	88[a]	95 (*S*)	4[a]
2	p-OMe	15	20	3[b]	-	12[b]
3	H	10	20	5[b]	-	5[b]

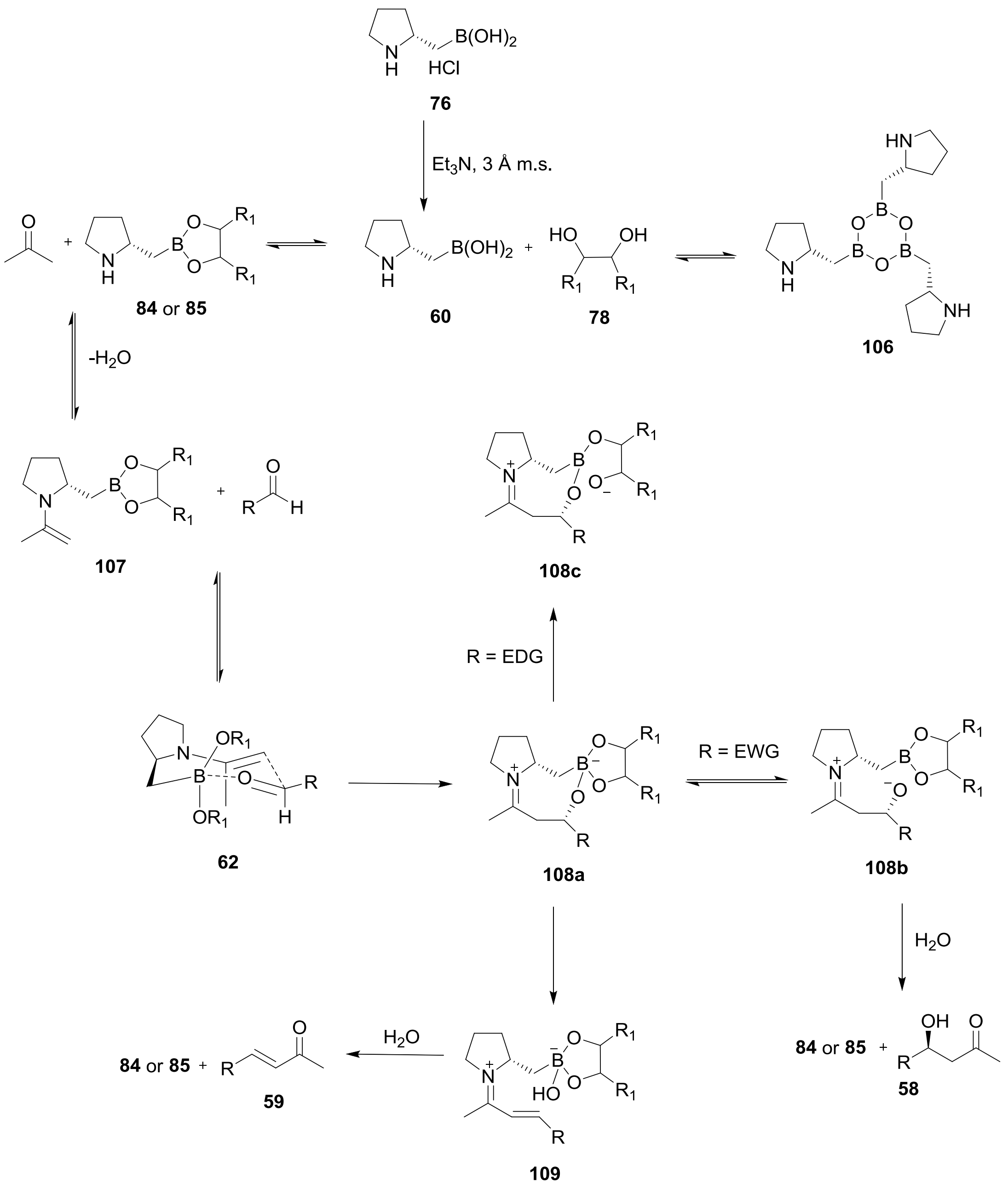
[a] Determined by HPLC.[b] Isolated yield after SiO$_2$ column chromatography.

However, as shown in entries 1 and 2 (Table 2.7) only trace reactivity was observed with these aldehydes, even after 20 h and there was no sign of enantiocontrol. It should be noted that the by-product arising from the aldolisation was generated from the start of the reaction, indicating that elimination was a faster competing process in these cases. These organocatalytic results stand in marked contrast to the homoboroproline-catalysed aldol reaction of *p*-nitrobenzaldehyde where excellent levels of enantiocontrol and reaction efficiency were obtained. One can explain the poorer reactivity of these substrates since they are more electron-rich and as a consequence of lower electrophilicity of the carbonyl group. In addition, the Lewis acidity of the boron atom present in catalyst **85** proves to be insufficient and therefore the aldehyde exists in an inactive form, unable to participate in the homoboroproline-catalysed aldol transformation. While increased electrophilicity afforded by an aldehyde with an electron-withdrawing group greatly enhances the reaction efficiency with high asymmetric induction too.

Based on these results that showed that less electrophilic aldehydes proved not to be amenable to the organocatalytic conditions of aldolisation, a new method was required in order to react these type of substrates. At this point and for the above mentioned reasons, studies on the homoboroproline catalyst **76** were abandoned, but provided a suggested lead as to how to approach further developments.

2.8 Proposed Mechanism of the Homoboroproline-Catalysed Aldol Reaction

Taking into account the experimental work regarding the homoboroproline-catalysed aldol reaction, a revised catalytic cycle reflecting all the results obtained to date can be proposed (Scheme 2.21). The absolute stereochemistry of the product obtained can be rationalised by a stereochemical model and a transition state **62** can be proposed. Commencing, the initial *in situ* esterification with the diol **78** of the boronic acid **76** after neutralisation results in the formation of boronate esters **84** or **85**, and to varying extents, boroxine **106** formation. As already proven, the equilibrium is dependent on the stability of the boronate ester formed. This is followed by the secondary amine of the pyrrolidine ring acting as a nucleophilic catalyst by reacting with acetone to form the corresponding enamine **107**. Lewis acid activation and coordination of the aldehyde by the boronate ester, enables it to react with the enamine through a highly organised transition state **62**. Presumably this results in the formation of an iminium ion species **108a**, in which the boronate forms a tetrahedral aldolate ‘ate’-complex. In the case of an electron deficient aldehyde the ‘ate’-complex **108a** is possible to be in an equilibrium with **108b** since the hydroxyl carbon atom is more electrophilic. Furthermore, hydrolysis of the iminium ion and protonation of the boronate ‘ate’-complex of **108b**, affords aldol product **58** with high asymmetric induction and regeneration of the catalyst. Control of the enamine geometry and the resulting absolute stereochemistry of the aldol product can be thought of as arising from the chiral centre present on the pyrrolidine ring. This control is crucial to high enantiocontrol since exposure to the opposite enantiomer of the catalyst leads to the opposite enantiomer of the product **58**. On the other hand, when an electron rich aldehyde is used instead, the ‘ate’-complex is likely to be in the form of **108c**, a species which cannot regenerate the catalyst and hence, leads to the unreactivity observed. In addition, β-elimination of complex **108a** could also give rise to the iminium ion analogue of the chalcone **109**, which after hydrolysis delivers the by-product **59**. Under normal conditions, the hydrolysis of complex **108a** is seemingly faster than the elimination reaction resulting in **109**, presumably as a result of a sufficient concentration of water despite the presence of molecular sieves. Indeed, it may be that water plays a direct part in the active catalytic cycle and could be directly associated with each of the species shown as key in the process.

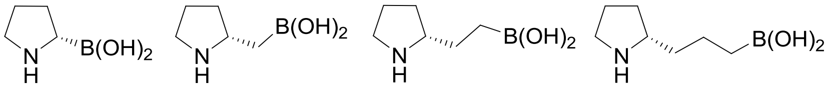


Scheme 2.21 Proposed catalytic cycle for the pyrrolidine-based boronate ester aldol reaction.

2.9 Studies towards the Synthesis of Optimised Homoboroproline Catalysts

Having secured optimised conditions for the enantioselective aldol reaction between *p*-nitrobenzaldehyde and acetone, the use of more electron-rich aldehydes such as *p*-anisaldehyde and benzaldehyde was investigated. As mentioned in Section 2.7, it was shown that the proposed enantioselective aldol union is inefficient due to the electronic nature of the aldehydes, which has a pronounced effect on the efficiency of the process. The poor reactivity of these aldehydes under optimised conditions that are well suited for *p*-nitrobenzaldehyde meant that the Lewis acidity of the homoboroproline boronate ester **85** was not sufficient to activate the less reactive carbonyl towards aldolisation or that aldol adducts deactivate the catalyst by alcoholic exchange (see Scheme 2.21).

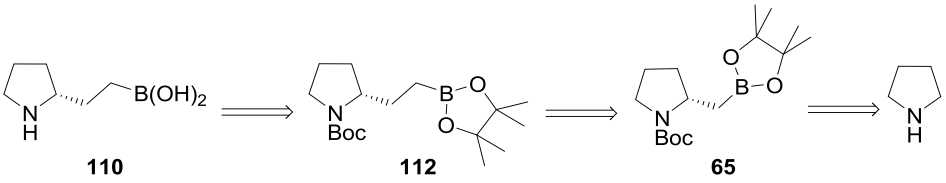
Taking into consideration that homoboroproline **60** and its boronate ester analogues have proved to be successful in the ‘benchmark’ aldol reaction, in contrast to boroproline **61** which was a sluggish catalyst, a new approach was envisioned. In particular, in order to overcome this limitation and achieve optimised aldol conditions applicable to a vast range of substrates, the synthesis of the longer chain homoboroproline **110** and **111** was proposed. This approach in theory would place the Lewis acidic boron atom in the ideal position to assist the aldol reaction and as a result perhaps overcome the poorer reactivity of the more electron-rich aldehydes, by possibly avoiding the need for *in situ* esterification.



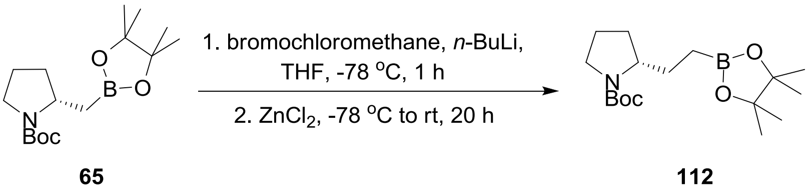
61 **60** **110** **111**

Figure 2.13 Proline-based aminoboronic acid catalysts.

Efforts toward the synthesis of catalyst **110** were commenced by using homologation methodology (Scheme 2.22).[71] This was based on analogy to similar reaction conditions developed in our lab for the synthesis of the one carbon length proline-based boronate ester **65** from its boroproline analogue.[38] As a result, compound **65** was treated with bromochloromethane and *n*-BuLi, followed by the addition of $ZnCl_2$ (eqn. 2.20). However, to our disappointment, these conditions did not furnish the desired product **112** but led to the full recovery of the starting material. Increasing the amount of bromochloromethane or $ZnCl_2$ did not change this outcome.

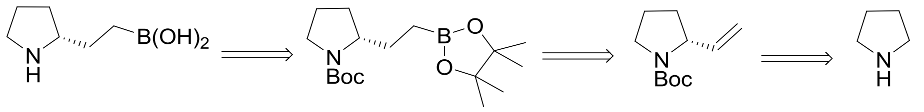


Scheme 2.22 Retrosynthetic route towards the synthesis of aminoboronic acid catalyst **110**.



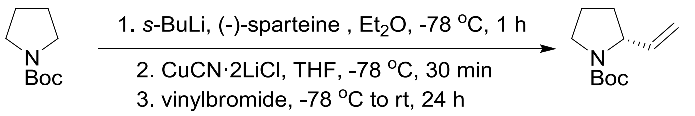
(2.20)

Moreover, taking inspiration from detailed studies concerning the asymmetric deprotonation and substitution of *N*-Boc-pyrrolidine, the design of a rapid synthesis for the two carbon length chain homoboroproline catalyst **110** taking advantage of this methodology was sought. It was envisioned that catalyst **110** could be accessed from *N*-Boc-pyrrolidine **66** by an asymmetric substitution with vinylbromide followed by hydroboration and deprotection (Scheme 2.23). This transformation provides tremendous simplification, as it would furnish the desired product **110** in only three steps, if the asymmetric substitution was highly selective. Key to this approach was the recognition that the (-)-sparteine catalysed enantioselective substitution of *N*-Boc-pyrrolidinylcuprates developed by Dieter *et al.* could be used to introduce the chiral centre of **113** enantioselectively.[72] As a result, the synthesis of **110** was initiated by reacting *N*-Boc-pyrrolidine with *s*-BuLi and (-)-sparteine, followed by treatment with CuCN·2LiCl and vinylbromide (eqn. 2.21). Unfortunately, even though this transformation had already been reported affording the desired product **110** in 70% ee in our hands, a lower enantioselectivity of 27% was obtained.



110 **112** **113**

Scheme 2.23 Second retrosynthetic route towards the synthesis of aminoboronic acid catalyst **110**.

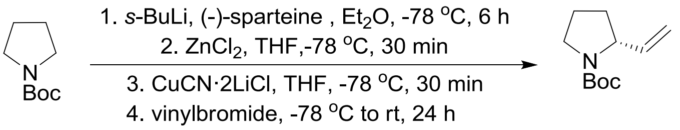


(2.21)

66

113
39%, 27% ee

However, encouraged by work from Coldman *et al.*[73] which demonstrated that the enantioselectivities of the products arising from the 2-substitution of *N*-Boc-pyrrolidine in such sparteine-mediated metallations could be improved by transmetallation with $ZnCl_2$/CuCN·2LiCl, further reactions were undertaken. In particular, the asymmetric induction for the synthesis of *N*-Boc-(2-propen-1-yl)-pyrrolidine was increased to 90% when the reaction mixture was treated with $ZnCl_2$ before the addition of CuCN·2LiCl, compared to 78% when the reaction was carried out in the absence of $ZnCl_2$. Nevertheless, in the case where the electrophile was vinylbromide, only a slight increase to 43% was observed using the same conditions (eqn. 2.22). Due to these limitations, an alternative synthetic pathway which could provide the desired product **110** in a higher enantiomeric excess was necessary.

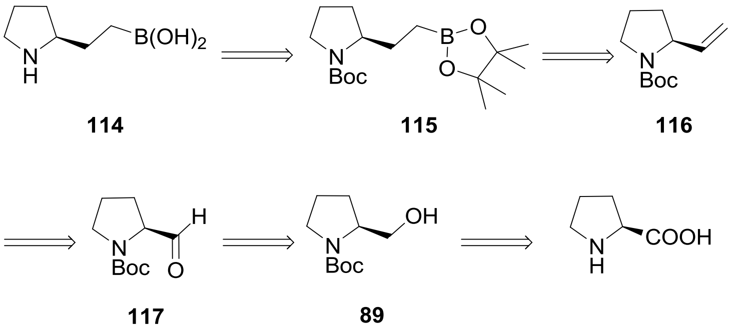


(2.22)

66

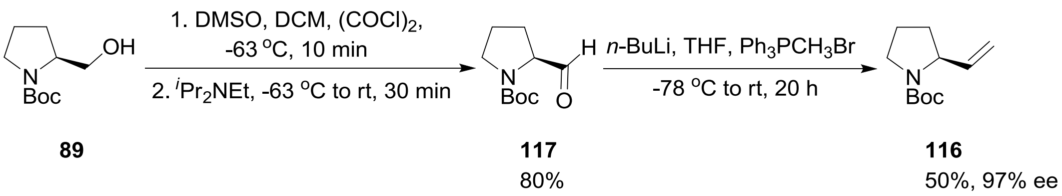
113
46%, 43% ee

As a result, a new strategy was derived for the synthesis of catalyst **110** that would make it possible to avoid the asymmetric substitution step and take advantage of synthetic chemistry that had already been developed by using (*S*)-proline as the starting material. Centred on the synthetic methodology used for the formation of homoboroproline **92**, the retrosynthetic plan proposed included the transformation of L-proline to the analogous vinylpyrrolidine derivative **116**, followed by hydroboration and deprotection (Scheme 2.24). Nevertheless, this plan posed the question as to whether the enantioselectivity of the chiral centre could be maintained, especially through an oxidation and a Wittig reaction involving aldehyde **117**.



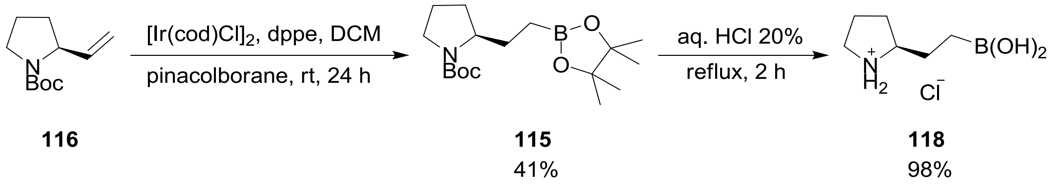
Scheme 2.24 Retrosynthetic route towards the synthesis of aminoboronic acid catalyst **114**.

Despite these concerns, alcohol **89** was furnished following the same procedure as reported in Section 2.5. Exposure of alcohol **89** to Swern oxidation conditions led to the isolation of the unstable aldehyde **117** in 80% yield.[74] It is worth mentioning that a more hindered amine was used instead of triethylamine for the Swern oxidation and no purification procedure was carried out in order to avoid epimerisation of the aldehyde **117** (Scheme 2.25). Furthermore, a Wittig reaction using methyltriphenylphosphinium bromide in Et_2O gave vinylpyrrolidine **116** in 50% yield.[75] The yield of this reaction improved when THF was used as the solvent instead of Et_2O. To our delight, chiral HPLC analysis of the isolated product **116** showed that the asymmetric induction was 97%. Even though this procedure did not allow a rapid access to vinylpyrrolidine **116**, the enantiomeric excess of the desired product was excellent, allowing the synthesis of catalyst **114** to continue.



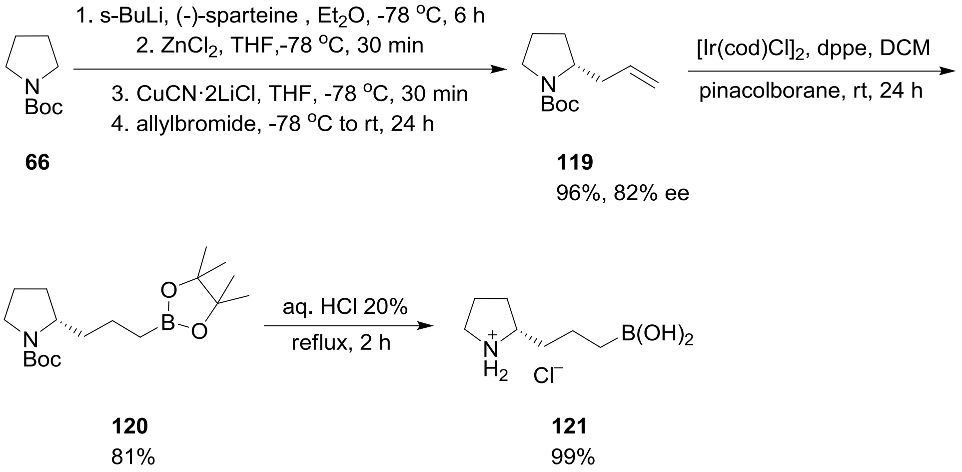
Scheme 2.25 Synthetic route for the formation of vinylpyrrolidine **116** starting from alcohol **89**.

With a procedure for the synthesis of vinylpyrrolidine **116** in place, a key remaining task was the synthesis of the pinacolboronate ester **115** through hydroboration. A wealth of catalysed or non-catalysed hydroboration reactions of terminal alkenes using a variety of both borane reagents and metal catalysts have been described in the literature.[29] However, the hydroboration of compound **116** employed in this case was based on methodology developed by Miyaura *et al.* using iridium-catalysed conditions (Scheme 2.26).[76] As a result, treatment of **116** with ½[Ir(cod)Cl]$_2$/dppe and pinacolborane in DCM produced boronate ester **115** in 41% yield. Finally, deprotection of **115** was effectively mediated by an aqueous solution of HCl, furnishing the target aminoboronic acid salt **118** in 98% yield.[38]



Scheme 2.26 Synthetic route for the formation of pyrrolidine-based boronic acid **118** starting from vinylpyrrolidine **116**.

In parallel with the synthesis of catalyst **118**, additional work to prepare the three carbon length aminoboronic acid catalyst **111** has been carried out by Ricardo Girling. A detailed discussion of these results will be published in due course, but a brief overview is described below. Conditions essentially identical to those attempted above were used (Scheme 2.27). The key issue to be addressed was the (-)-sparteine mediated asymmetric 2-substitution of *N*-Boc-pyrrolidine with allylbromide. Fortuitously, this was accomplished by using the ZnCl$_2$, CuCN·2LiCl catalysed conditions already discussed in this section.[73] The desired product **119** was furnished in 96% yield and 82% enantiomeric excess. The remaining steps to fulfil the synthesis of HCl salt **121** were an ½$[Ir(cod)Cl]_2$/dppe catalysed hydroboration, followed by the usual HCl-mediated deprotection.[76,38]



Scheme 2.27 Synthetic route for the formation of pyrrolidine-based boronic acid **121** starting from *N*-Boc-pyrrolidine **66**.

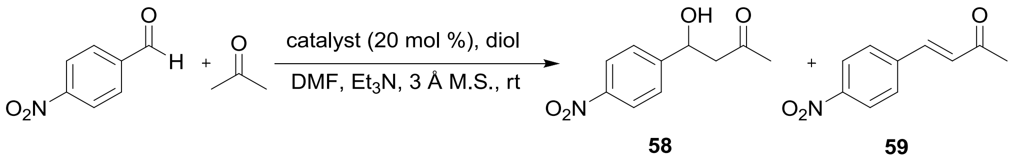
This work represents the combined efforts toward the first synthesis of novel proline-based boronic acids **118** and **121** and hence, each of these homologous catalysts were available to compare with the homoboroproline system.

2.10 Application of the Optimised Homoboroproline Catlysts on the Aldol Reaction

Having demonstrated the inability of chiral pyrrolidine-based esters of **76** to function as asymmetric catalysts for the aldol reaction between less reactive aldehydes and acetone, there was need to study the effect of chain length between the secondary amine and the boronic acid. It was envisaged that extra carbon atoms incorporated between the pyrrolidine ring and the boronic acid moiety of the catalyst could change the Lewis acidity of the boron atom, altough it would be unlikely to enhance it to a great extent. It would however, allow the determination of the ideal chain length to make the most of the existing reactivity and perharps remove the need for diol esterification. Prior to demonstrating the feasibility of this proposal, the synthesis of pyrrolidine-based aminoboronic acids **118** and **121** was accomplished as described in Section 2.9. As a result, preliminary investigations were focused on defining the reactivity of these potential catalysts **118** and **121** when participating in the optimised aldol reaction conditions reported above.

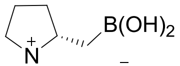
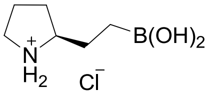
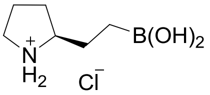
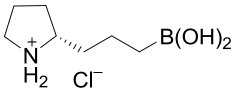
Hence, the impact of the carbon chain length part of compounds **118** and **121** was next examined on the organocatalytic 'benchmark' aldol reaction and compared with homoboroproline **76**. The initial experiment involved monitoring over time the reaction between *p*-nitrobenzaldehyde and acetone in DMF in the presence of catalyst **118**, after neutralisation with Et_3N (eqn. 2.23). Unfortunately, the reaction demonstrated diminished conversion to the aldol (21%) with no asymmetric induction, together with 9% of the chalcone formed; a total conversion of 30% over 48 h. This compares with 92% conversion for the homoboroproline catalyst (entry 1 *vs* 2, Table 2.8). At this juncture, it was hypothesised that there was inadequate Lewis acidity of the boron atom, resulting in the lower reaction conversion. To possibly improve both reactivity and enantioselectivity catalyst **118** was *in situ* esterified using (*R*,*R*)-hydrobenzoin under the optimised aldol reaction conditions and monitored over time. However, the reaction was completely suppressed, even when conducted after 48 h (entry 3, Table 2.8).

It was immediately apparent that the presence of an extra carbon atom had the effect of self-inhibiting the organocatalytic reaction, presumably *via* stronger B-N chelation. From the outset, it was hypothesised that the increased flexibility of the chain, due to the additional carbon atom, facilitates the intramolecular B-N coordination, thereby minimising the nitrogen ability to form the enamine and the ability of the boron atom to activate the substrate. Another interesting feature was the complete lack of reactivity observed when the hydrobenzoin boronate ester derivative of **118** was used. The key point is that the esterification leads to a more Lewis acidic boron atom, hence, causing a stronger B-N interaction despite the steric bulk of the phenyl groups.



(2.23)

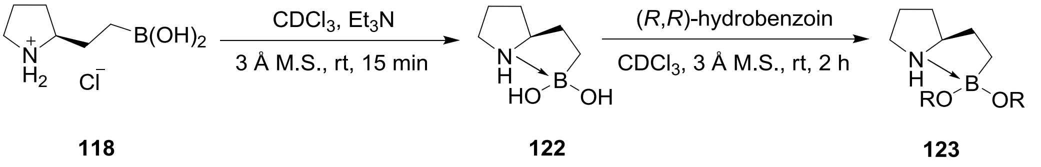
Table 2.8 Catalysed aldol reaction of *p*-nitrobenzaldehyde in neat acetone.

Entry	Catalyst	Diol	Time [h]	Yield of 58 [%][a]	ee [%][a]	Yield of 59 [%][a]
1	 **76**	(*R*,*R*)-hydrobenzoin	6	88	95 (*S*)	4
2	 **118**	-	48	21	1 (*R*)	9
3	 **118**	(*R*,*R*)-hydrobenzoin	48	0	0	0
4	 **121**	-	24	0	0	0

[a]Determined by HPLC analysis.

Having examined the possibility of using aminoboronic acid **118**, the use of pyrrolidine-based boronic acid **121** was next considered as a potential catalyst for the organocatalytic aldol reaction. An initial experiment was carried out on the standard optimised system, consisting of *p*-nitrobenzaldehyde and acetone in DMF in the presence of catalyst **121**. Disappointingly, once again the reaction did not afford the desired product **58** or any other by-products in a period of 24 h (entry 4, Table 2.8). This unexpected result again revealed the likely strong B-N interaction present in neutralised **121** similarly to **118**; a scenario that dramatically decreases the ability of both the boron atom and secondary amine to act as catalytic moieties and lead to greatly diminished conversions.

As revealed in Table 2.8, there is a clear correlation between the reaction conversion and carbon length chain of the catalysts. In order to probe this further, additional studies aimed at understanding and evaluating the catalytic profile of compound **118** and **121** for the aldol organocatalytic transformation were initiated. To gain insight into these initial results and justify the assumptions that the catalytic species present, the reaction needed to be thoroughly examined by ^{11}B NMR analysis. With this in mind, firstly, aminoboronic acid salt **118** was neutralised with Et_3N in $CDCl_3$ and ^{11}B NMR analysis was carried out on the resulting mixture. Secondly, the same procedure was repeated but with the addition of (*R*,*R*)-hydrobenzoin in order to achieve the *in situ* esterification (Scheme 2.28). The expectation was to be able to observe directly reactants occurring as outlined in Scheme 2.28.



118

122

123

R = (*R*,*R*)-hydrobenzoin

Scheme 2.28 *In situ* formation of the (*R*,*R*)-hydrobenzoin ester of homoboroproline **118**.

As shown in Figure 2.14, in the first case, by ^{11}B NMR analysis a shift at δ_B 18 was observed and the subsequent esterification led to a shift change to δ_B 13. These observations provide direct evidence to validate our hypothesis that the compound resulting from the neutralisation of the pyrrolidine-based boronic acid **118**, could indeed be in the form of **122**. A distorted tetrahedral geometry of the boron atom, originating from an intramolecular B-N coordination results in the observed shift.[77] One might then argue that a ^{11}B NMR shift in the range of δ_B 20-18 could correspond to the relevant boroxine. However, since some conversion is observed, the possibility of boroxine is most likely discounted. A closer look in the literature revealed that partial tetrahedral geometry at boron could result in compounds with a weaker B-N interactions resulting with similar ^{11}B NMR shifts.

Moreover, the addition of (*R*,*R*)-hydrobenzoin leads to a lower ^{11}B NMR shift, highlighting the presence of a stronger B-N interaction. Given that upon esterification the Lewis acidity of the boron atom should increase, a stronger interaction occurs between the nitrogen and boron atom. As a result, the boron atom is unable to activate the aldehyde since its electron density has been completely lost and of course, the nitrogen is similarly deactivated towards aldolisation with the ketone.

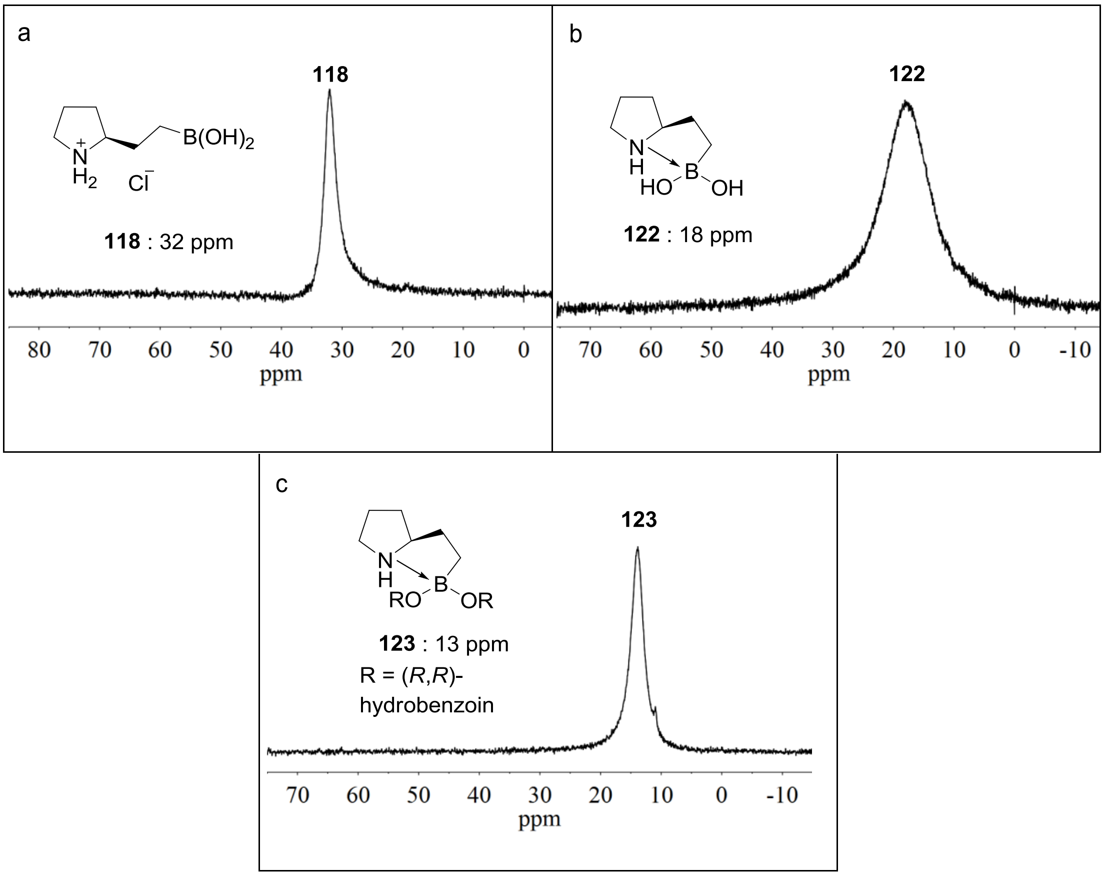
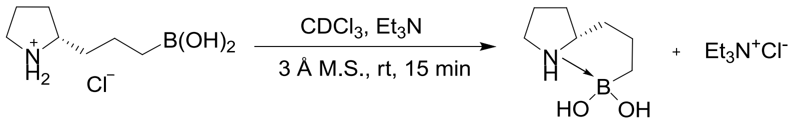


Figure 2.14 ^{11}B NMR spectra: (a) pyrrolidine-based boronic acid salt **118**; (b) neutralisation reaction of pyrrolidine-based boronic acid salt **118**; (c) condensation reaction of **118** with (*R*,*R*)-hydrobenzoin.

In this context, the pyrrolidine-based aminoboronic acid **121** was then examined by ^{11}B NMR of the resulting compound after neutralisation (eqn. 2.24). As revealed in Figure 2.15, the ^{11}B NMR analysis performed demonstrated a shift at δ_B

5. In this case, it is even more clear that the three carbon length chain offers a good facility for the boron atom to achieve a strong interaction with the nitrogen atom. Notably, a shift at δ_B 5 is indicative of an essentially 100% tetrahedral boron atom and hence, it is inactive and can not participate catalytically in the aldol reaction.[77]



(2.24)

121 **124**

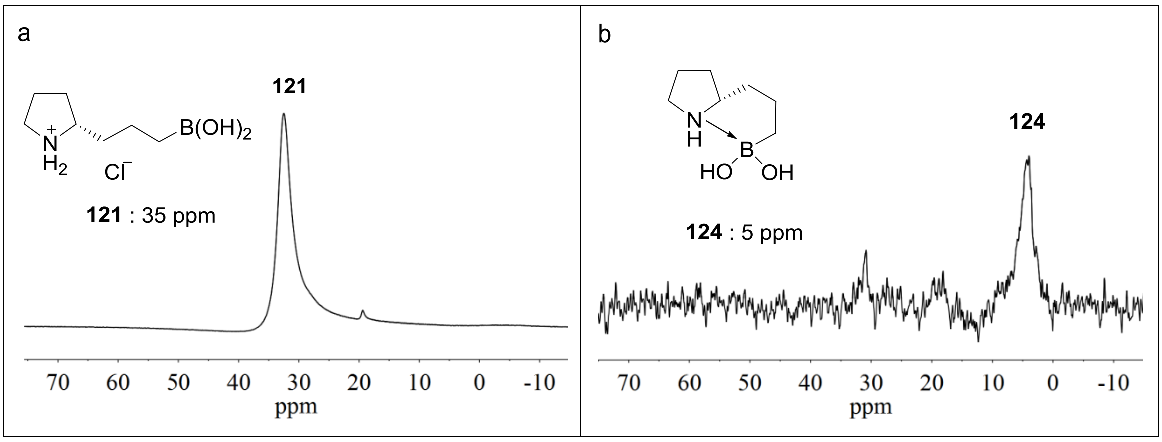


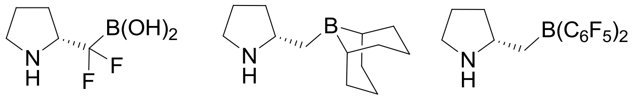
Figure 2.15 ^{11}B NMR spectra: (a) pyrrolidine-based boronic acid salt **121**; (b) neutralisation reaction of pyrrolidine-based boronic acid salt **121**.

2.11 Conclusions and Future Directions

The synthesis of both enantiomers of homoboroproline-catalyst **76** and **92** have been developed. Catalyst **76** is moderately effective in enamine-mediated aldol reactions, however, when esterified *in situ* with different diols the boron Lewis acidity can be tuned. This is not entirely straightforward since the facility of the diol to tune the boron Lewis acidity depends upon the stability of the boronate ester. Interestingly, ^{11}B NMR studies showed that cyclohexylboronic acid derived esters appear to be slightly less stable than the corresponding cyclopentylboronate esters, with the hydrobenzoin **82b** showing good stability compared to other systems examined. Applying this knowledge to the esterification of homoboroproline **76**, using hydrobenzoin as the esterification diol gives the highest boronate ester stability and catalyst **85** is believed to be the active species. Importantly, this ester essentially provides complete asymmetric control in the aldol reaction, *i.e.* 96% e.e. for a 96% ee catalyst when run under optimised reaction conditions. These conditions consist of running the reactions at room temperature in DMF in the presence of molecular sieves in order to maintain the boronate ester in equilibrium strongly in favour of the ester.

Application of boronate ester **102** highlighted the importance of the chiral centre present on the pyrrolidine ring for the enantiomeric excess achieved in the aldol product. In addition, the independence of the chirality of the diol used for the esterification upon the sense of asymmetric control has been proven. All these studies have also provided a foundation for understanding the mode of action of the catalyst. A highly organised transition state **62** resulting from the cooperative relationship between the enamine and the tetrahedral aldolate boron complex was proposed. Unfortunately, this methodology has not proven general for more electron rich substrates as yet. When aldehydes bearing an electron donating group were used, no aldol product formation was observed. Initial investigations have shown that electron deficient aldehydes such as ethyl glyoxylate and dimethoxyacetaldehyde, could be promising substrates. Hence, following work will involve the detail extension of this methodology, by applying boronate ester **85** on aldehydes with an electron-withdrawing group, allowing the rapid access to valuable products.

The following efforts were then concentrated on the synthesis and application of potential catalysts **118** and **121**. Nevertheless, both catalysts were unreactive when applied on the optimised aldol reaction conditions; however, this was due to an increased facility of B-N chelation. Even though these aminoboronic acids were synthesised to see if they could provide enhanced enantiocontrol, faster reaction rates and avoid the need for *in situ* esterification, the design principle was not ideal since the extended carbon length chain permitted stronger B-N coordination, deactivating the boron and nitrogen atoms. Subsequent future work will involve the design and development of proline-based aminoboronic acid catalysts with a more Lewis acidic boron atom. Potential catalysts may involve compound **125** with incorporated fluorine atoms, boronate ester **126** or even **127**.



125 **126** **127**

Figure 2.16 Potential proline-based boronate catalysts.

Chapter 3: Experimental Section

3 Experimental Section

3.1 General Information

All chemicals and materials were purchased from standard chemical suppliers and reagents were tested for purity before use. Glassware was oven dried (130 ^{o}C) as required and cooled under a positive pressure of argon. Dry solvents were prepared using the Innovative Technology Inc. solvent purification system and analysed with Metrohm 831 KF coulometer. Chromatographic purification of products was accomplished using medium pressure column chromatography on 35-70 mesh silica gel. Thin-layer chromatography was performed on Polygram SIL G/UV$_{254}$ plastic backed silica gel plates. Visualisation of the developed chromatogram was achieved by using fluorescence quenching, or by staining either with potassium permanganate or anisaldehyde. All organic solvents were concentrated under reduced pressure at 20 mmHg on a Büchi rotary evaporator, followed by drying *in vacuo* (<2 mmHg). Molecular sieves were activated by heating at 250 °C.

All ^{1}H NMR were recorded with either of Varian Mercury-400, Bruker Avance-400, Varian Inova-500 or Varian VNMRS-700 spectrometers. ^{13}C NMR were recorded on Varian Mercury-400, Bruker Avance-400, Varian Inova-500 or Varian VNMRS-700 spectrometers at frequencies of 100, 126 or 176 MHz. ^{11}B NMR were recorded with the Bruker Avance-400 at a frequency of 128 MHZ. ^{19}F NMR were recorded with the Varian Inova-500 at a frequency of 500 MHz. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration and assignment. Data for ^{13}C, ^{11}B and ^{19}F NMR are reported in terms of chemical shift (δ ppm). Mass spectra were obtained using a Water Xevo QTOF equipped with Atmospheric Solids Analysis Probe (ASAP) or a Thermo-Finnigan Trace GCMS with an EI ion source. High resolution ASAP or EI mass spectra were recorded by the National Mass Spectrometry Service at Swansea. Chiral HPLC analyses were performed on a Perkin Elmer system equipped with a Perkin Elmer Series 200 pump, a Perkin Elmer Series 200 autosampler and a Perkin Elmer Series 200 Diode array detector. Elemental analysis was performed using an Exeter Analytical E-440 Elemental Analyser. IR spectra were recorded with a Perkin-Elmer melting point apparatus. Optical rotations were taken using a JASCO P-1020 polarimeter and $[\alpha]_D$ values are given in deg cm^2g^{-1} .

3.2 General Procedures

3.2.1 General procedure for the catalysed aldol reaction outlined in eqn. 2.1

To a solution of *p*-nitrobenzaldehyde (151 mg, 1 mmol) in acetone (10 mL), 20 mol% of the examined catalyst (0.2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and then quenched with saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted into EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Silica gel chromatography (petroleum ether:EtOAc, 5:4) afforded the aldol product **58**[69] as a yellow oil and the chalcone **59**[78] as a yellow solid. All spectroscopic and analytical properties were identical to those reported in sections *3.3.15* and *3.3.16*.

3.2.2 General procedure for the in situ formation of the cyclohexylboronate esters as outlined in Scheme 2.8

To a solution of cyclohexylboronic acid (15 mg, 0.12 mmol) in $CDCl_3$ (2 mL), the relevant diol (0.12 mmol) was added. The reaction mixture was refluxed for 2 h in the presence of 3 Å molecular sieves and then filtrated *in situ*. A ^{11}B NMR analysis was carried out for the residue.

3.2.3 General procedure for the in situ formation of the cyclopentylboronate esters as outlined in Scheme 2.9

To a solution of cyclopentylboronic acid (15 mg, 0.13 mmol) in $CDCl_3$ (2 mL), the relevant diol (0.13 mmol) was added. The reaction mixture was refluxed for 2 h in the presence of 3 Å molecular sieves and then filtrated *in situ*. A ^{11}B NMR analysis was carried out for the residue.

*3.2.4 Procedure for the in situ formation of the pyrrolidine-based boronate ester **84** as outlined in Scheme 2.10*

To a solution of compound **76** (15 mg, 0.09 mmol) in CD_2Cl_2 (1.5 mL), diisopropyl-D-tartrate (19 μL, 0.09 mmol) and triethylamine (12.5 μL, 0.09 mmol) were added. The reaction mixture was refluxed for 1 h in the presence of 3 Å molecular sieves, then cooled at -78 °C and filtrated *in situ*. A ^{11}B NMR analysis was carried out for the residue.

3.2.5 General procedure for the aldol reaction with the in situ formation of catalytic boronate esters as outlined in eqn. 2.7

Compound **76** (16.5 mg, 0.1 mmol) and the relevant diol (0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in acetone (5 mL) for 2 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol) and triethylamine (13.9 μL, 0.1 mmol) were added. The reaction mixture was stirred at 25 ^{o}C for 24h and then quenched with sat. aq. solution of NH_4Cl (5 mL). The aqueous layer was extracted into EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Silica gel chromatography (petroleum ether:EtOAc, 5:4) afforded the aldol product **58**[69] as a yellow oil and the chalcone **59**[78] as a yellow solid. All spectroscopic and analytical properties were identical to those reported in sections *3.3.15* and *3.3.16*.

*3.2.6 General procedure for the aldol reaction with the in situ formation of the boronate ester **85** using different solvents as outlined in eqn. 2.8*

Compound **76** (16.5 mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred in 4 mL of the relevant solvent for 3 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol) and acetone (0.37 mL, 5 mmol) were added. After stirring at 25 ^{o}C for 20 h in the presence of 200 mg of 3 Å molecular sieves, the reaction was quenched with sat. aq. solution of NH_4Cl (5 mL) and extracted into EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Silica gel chromatography (hexane:EtOAc, 1:1) afforded the aldol product **58**[69] as a yellow oil and the chalcone **59**[78] as a yellow solid. All spectroscopic and analytical properties were identical to those reported in sections *3.3.15* and *3.3.16*.

3.2.7 General procedure for the formation of the calibration curves

Standard solutions with concentrations from 0.1 M to 0.02 M were prepared by dissolving the appropriate amount of the relevant compound (*p*-nitrobenzaldehyde, recemic aldol condensation product **58** and aldol elimination product **59**) in acetone. From each concentrated standard solution 50 μL were dissolved in 95 μL of a hexane and IPA (9:1) solution, forming diluted solutions with the lowest concentration being 0.001 M and the highest 0.005 M. In each sample (10 mol%) of naphthalene was added as an internal standard. The absorption of every concentration was measured three times using chiral HPLC (See Appendix for graphs and equations).

3.2.8 General procedure for monitoring the reaction outlined in eqn. 2.12 over time using chiral HPLC

Compound **76** (16.5 mg, 0.1 mmol) was dissolved at 25 °C in the presence of 200 mg of 3 Å molecular sieves in acetone (5 mL), before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), triethylamine (13.9 μL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 μL were sampled from the reaction mixture, filtered and extracted with 200 μL of sat. aq. solution of NH_4Cl. Then 50 μL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

3.2.9 General procedure for monitoring the reaction outlined in eqn. 2.13 over time using chiral HPLC

Compound **76** (16.5 mg, 0.1 mmol) and diisopropyl-D-tartrate (21 μL, 0.1 mmol) were stirred at 25 °C in the presence of 200 mg of 3 Å molecular sieves in acetone (5 mL) for 2 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), triethylamine (13.9 μL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 μL were sampled from the reaction mixture, filtered and extracted with 200 μL of sat. aq. solution of NH_4Cl. Then 50 μL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

3.2.10 General procedure for monitoring the reaction outlined in eqn. 2.14 over time using chiral HPLC

Compound **76** (16.5 mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL of sat. aq. solution of NH_4Cl. Then 50 µL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

3.2.11 General procedure for monitoring the reaction outlined in eqn. 2.15 over time using chiral HPLC

Compound **76** (16.5 mg, 0.1 mmol) and (*meso*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL of sat. aq. solution of NH_4Cl. Then 50 µL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

3.2.12 General procedure for monitoring the reaction outlined in eqn. 2.16 over time using chiral HPLC.

Compound **92** (16.5 mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL of sat. aq. solution of NH_4Cl. Then 50 µL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

*3.2.13 Procedure for investigating possible kinetic resolution of racemic aldol product **58** in the absence of acetone as outlined in eqn. 2.17*

Compound **76** (16.5 mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 °C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2 h before racemic aldol condensation product **58** (104.6 mg, 0.5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL of sat. aq. solution of NH_4Cl. Then 50 µL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

*3.2.14 Procedure for investigating possible kinetic resolution of racemic aldol product **58** in the presence of acetone as outlined in eqn. 2.18*

Compound **76** (16.5 mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 °C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2 h before racemic aldol condensation product **58** (104.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL of sat. aq. solution of NH_4Cl. Then 50 µL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

*3.2.15 General procedure for monitoring the catalysed aldol reaction outlined in eqn. 2.19 using **103b** as the aldehdye.*

Compound **76** (16.5 mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 °C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2 h before *p*-anisaldehyde (68.1 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL of sat. aq. solution of NH_4Cl. Then 50 µL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC. After stirring at 25 °C for 20 h the reaction was quenched with sat. aq. solution of NH_4Cl (5 mL) and extracted into EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Silica gel chromatography (hexane:EtOAc, 1:1) afforded the aldol product **104b** as a colourless oil and the chalcone **105b** as a white solid. All spectroscopic and analytical properties were identical to those reported in the literature.[79,80]

*3.2.16 General procedure for monitoring the catalysed aldol reaction outlined in eqn. 2.19 using **103c** as the aldehdye.*

Compound **76** (16.5 mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2 h before benzaldehyde (53.1 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL of sat. aq. solution of NH_4Cl. Then 50 µL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC. After stirring at 25 ^{o}C for 20 h the reaction was quenched with sat. aq. solution of NH_4Cl (5 mL) and extracted into EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Silica gel chromatography (hexane:EtOAc, 1:1) afforded the aldol product **104c** as a colourless oil and the chalcone **105c** as a yellow solid. All spectroscopic and analytical properties were identical to those reported in the literature.[80,81]

*3.2.17 General procedure for monitoring the reaction outlined in eqn. 2.23 using catalyst **118** over time using chiral HPLC*

Compound **118** (17.9 mg, 0.1 mmol) was dissolved at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL), before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL of sat. aq. solution of NH_4Cl. Then 50 µL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

*3.2.18 General procedure for monitoring the reaction outlined in eqn. 2.23using boronate ester of **118** over time using chiral HPLC.*

Compound **118** (17.9 mg, 0.1 mmol) and (*R,R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 μL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 μL were sampled from the reaction mixture, filtered and extracted with 200 μL of sat. aq. solution of NH_4Cl. Then 50 μL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

*3.2.19 General procedure for monitoring the reaction outlined in eqn. 2.23 using catalyst **121** over time using chiral HPLC*

Compound **121** (19.3 mg, 0.1 mmol) was dissolved at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL), before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 μL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 μL were sampled from the reaction mixture, filtered and extracted with 200 μL of sat. aq. solution of NH_4Cl. Then 50 μL of the organic phase were dissolved in 0.95 mL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

*3.2.20 Procedure for the neutralisation of the aminoboronic acid salt **118** as outlined in Scheme 2.27*

To a solution of compound **118** (22 mg, 0.12 mmol) in $CDCl_3$ (1.5 mL), triethylamine (17 μL, 0.12 mmol) was added. The reaction mixture was stirred for 15 min at 25 ^{o}C in the presence of 3 Å molecular sieves and filtrated *in situ*. A ^{11}B NMR analysis was carried out for the residue.

*3.2.21 Procedure for the in situ formation of the pyrrolidine-based boronate ester of **118** as outlined in Scheme 2.27*

To a solution of compound **118** (22 mg, 0.12 mmol) in $CDCl_3$ (1.5 mL), (*R*,*R*)-hydrobenzoin (25.7 mg, 0.12 mmol) and triethylamine (17 μL, 0.12 mmol) were added. The reaction mixture was stirred for 2 h in the presence of 3 Å molecular sieves at 25 °C and filtrated *in situ*. A ^{11}B NMR analysis was carried out for the residue.

*3.2.22 Procedure for the neutralisation of the aminoboronic acid salt **121** as outlined in Equation 2.24*

To a solution of compound **121** (22 mg, 0.12 mmol) in $CDCl_3$ (1.5 mL), triethylamine (17 µL, 0.12 mmol) was added. The reaction mixture was stirred for 15 min at 25 ^{o}C in the presence of 3 Å molecular sieves and filtrated *in situ*. A ^{11}B NMR analysis was carried out for the residue.

*3.2.23 General HPLC method used for analysing the aldol product **58**, and monitoring the reactions involving aldol **58** and chalcone **59***

The enantiomeric ratio of the aldol product **58** was determined by chiral HPLC using OJ-Chiralcel column (250 × 4.6 mm), 15 ^{o}C, 1 mL/min, hexane:IPA (9:1), t_R (*S*-aldol product) = 39.7 min; t_R (*R*-aldol product) = 45.9 min, t_R (chalcone) = 51.6.

*3.2.24 General HPLC method used for monitoring the reactions involving aldol **104b** and chalcone **105b***

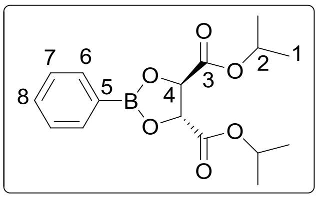
The enantiomeric ratio of the aldol product **104b** was determined by chiral HPLC using AS-H-Chiralpak column (250 × 4.6 mm), 25 ^{o}C, 1 mL/min, hexane:IPA (9:1), t_R (*S*-aldol product) = 30.2 min; t_R (*R*-aldol product) = 33.3 min, t_R (chalcone) = 39.1.

*3.2.25 General HPLC method used for monitoring the reactions involving aldol **104c** and chalcone **105c***

The enantiomeric ratio of the aldol product **104c** was determined by chiral HPLC using AS-H-Chiralpak column (250 × 4.6 mm), 25 ^{o}C, 1 mL/min, hexane:IPA (9:1), t_R (*S*-aldol product) = 12.6 min; t_R (*R*-aldol product) = 14.7 min, t_R (chalcone) = 10.4.

3.3 Synthetic Procedures

3.3.1 (4R,5R)-Diisopropyl-2-phenyl-1,3,2-dioxoborolane-4,5-dicarboxylate **63**



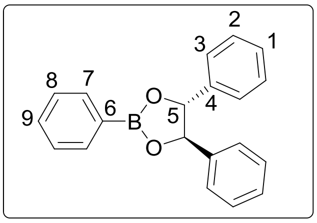
Procedure A

To a solution of benzeneboronic acid (750 mg, 6.15 mmol) in dry DCM (10 mL) was added diisopropyl-D-tartrate (1.08 mL, 5.13 mmol). The reaction was carried out in the presence of 3 Å molecular sieves (0.92 g), under argon and stirred overnight at room temperature. The mixture was then filtrated, washed with EtOAc (20 mL) and dried. Filtration and evaporation *in vacuo* furnished the crude product, which was purified by recrystallization with a mixture of hexane and EtOAc to give the boronate ester **63**[51a] as a pale brown solid (940 mg, 57%). Mp 73-74 °C; ^{1}H NMR ($CDCl_3$, 700 MHz) δ_H 1.32 (d, J = 6.3 Hz, 12H, H_1), 4.96 (s, 2H, H_4), 5.16 (sep, J = 6.3 Hz, 2H, H_2), 7.40-7.42 (m, 2H, H_7), 7.51-7.54 (m, 1H, H_8), 7.90-7.91 (dd, J_1 = 1 Hz, J_2 = 7 Hz, H_6); ^{13}C NMR ($CDCl_3$, 176 MHz) δ_C 21.8 (C_1), 70.2 (C_2), 78.3 (C_4), 128.0 (C_7), 132.3 (C_8), 135.4 (C_6), 169.1 (C_3); ^{11}B ($CDCl_3$, 128.4 MHz) δ_B 33.1; IR ν_{max} (neat)/cm^{-1} 3287, 3028, 1627, 1490; ASAP-MS (positive ion mode) *m/z*: 321 $[M+H]^+$, 279 $[M+H-C_3H_6]^+$, 237 $[M+H-C_6H_{12}]^+$, 193 $[M+H-C_7H_{12}O_2]^+$; HRMS-ASAP: Calcd for $C_{16}H_{22}BO_6$ 321.1504. Found 321.1500; Anal. Calcd for $C_{16}H_{21}BO_6$: C, 60.03; H, 6.61. Found: C, 59.71; H, 6.48.

Procedure B

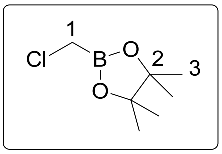
To a solution of benzeneboronic acid (750 mg, 6.15 mmol) in toluene (100 mL) under argon was added diisopropyl-D-tartrate (1.08 mL, 5.13 mmol). The mixture was heated under reflux for 24 h using a Dean-Stark apparatus. After cooling to room temperature, the solution was dried, filtered and the solvent was removed *in vacuo* to give a crude brown solid. The solid was then recrystallized from hexane to give the boronate ester **63** as a white solid (1.34 g, 81%). All spectroscopic and analytical properties were identical to those reported in procedure A of section 3.3.1.

3.3.2 (4R,5R)-2,4,5-Triphenyl-1,3,2-dioxoborolane ***64***



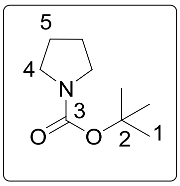
To a solution of phenylboronic acid (250 mg, 2.05 mmol) in toluene (40 mL) was added (*R*,*R*)-hydrobenzoin (439 mg, 2.05 mmol). The mixture was heated to reflux for 24 h using a Dean-Stark apparatus. After cooling to room temperature, the solution was dried, filtered and the solvent was evaporated to give the crude solid. The solid was then recrystallised from hexane to afford the boronate ester **64**[82] as a white solid (312 mg, 52%). Mp 92-95 ˚C; ^{1}H NMR ($CDCl_3$, 700 MHz) δ_H 5.34 (s, 2H, H_5), 7.35-7.37 (m, 6H, H_{Ar}), 7.40-7.42 (m, 4H, H_{Ar}), 7.44-7.46 (m, 2H, H_{Ar}), 7.54-7.56 (m, 1H, H_{Ar}), 7.99-8.00 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 176 MHz) δ_C 87.1 (C_5), 126.0, 128.1, 128.5, 129.0, 132.0, 135.4, 140.5 (C_{Ar}); ^{11}B ($CDCl_3$, 128.4 MHz) δ_B 31.5; IR ν_{max} (neat)/cm^{-1} 3080, 2941, 1602, 1497; ASAP-MS (positive ion mode) *m/z*: 318 $[M+NH_4]^+$; HRMS-ASAP: Calcd for $C_{20}H_{17}BO_2NH_4$ 318.1660. Found 318.1659; Anal. Calcd for $C_{20}H_{17}BO_2$: C, 80.03; H, 5.71. Found: C, 79.98; H, 5.74.

3.3.3 2-Chloromethyl-4,4,5,5-tetramethyl-1,2,3-dioxaborolane ***68***



To a stirred solution of bromochloromethane (2 mL, 31 mmol) and triisopropyl borate (6.46 mL, 28 mmol), in dry THF (28 mL) under argon at -78 ˚C, *n*-BuLi (13.4 mL, 2.5 M, 34 mmol) was added dropwise. The mixture was allowed to stir at -78 ˚C for 1 h, warmed to room temperature overnight (20 h) and then quenched with 20% (w/v) HCl (6 mL). The mixture was extracted into ether (3 × 10 mL) and the organic extracts washed with brine (10 mL), dried over and concentrated *in vacuo* providing the boronic acid **67**[83] (1.71 g, 65%). The white solid was redissolved in Et_2O, followed by the addition of pinacol (1.30 g, 10.98 mmol). The reaction mixture was stirred for 20 min. After drying and solvent removal, the yellow oil residue was distilled *in vacuo* (bp 80 ˚C/ 20 mmHg) to yield **68** as a colourless oil (1.75 g, 90%, 59% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.30 (s, 12H, H_3), 2.97 (s, 2H, H_1); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ_C 24.9 (C_3), 84.7 (C_1); ^{11}B NMR (128.4 MHz; $CDCl_3$) δ_B 31.5; IR ν_{max} (neat)/cm^{-1} 2980, 1343, 1140, 967, 888, 846; ASAP-MS (positive ion mode) *m/z*: 177.1 $[M+H]^+$, 161.1 $[M-Me]^+$, 91.1 $[M-C_6H_{11}]^+$; Anal. Calcd for $C_7H_{14}BO_2Cl$: C, 47.73; H, 8.03. Found: C, 47.65; H, 8.00.

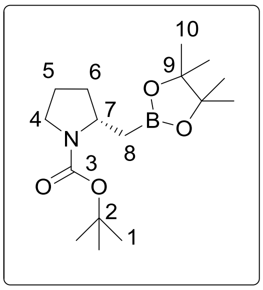
3.3.4 *N-tert-butylcarbonyl pyrrolidine **66***



To a stirred solution of pyrrolidine (11.5 mL, 137.5 mmol) in 200 mL of EtOH, Boc_2O (40 g, 206.2 mmol) was added dropwise. The reaction was stirred at room temperature for 30 min, followed by the addition of imidazole (9.36 g, 137.5 mmol). The resulting solution was allowed to stir for 30 min. $CHCl_3$ (100 mL) was added and the volatiles removed *in vacuo*. The residue was dissolved in DCM (200 mL) and washed with 1% aq. HCl (2 × 100 mL). The organic layer was dried and concentrated *in vacuo*. The crude was distilled over CaH_2 *in vacuo* (bp 110-112 ˚C/ 20 mm Hg) and **66**[84] was isolated as a colourless liquid (22.3 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.46 (s, 9H, H_1), 1.82-1.83 (m, 4H, H_5), 3.28-3.33 (m, 4H, H_4); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 25.2 (C_5), 25.9 (C_5), 28.7 (C_1), 45.8 (C_4), 46.1

(C_4), 79.0 (C_2), 154.9 (C_3); IR ν_{max} (neat)/cm^{-1} 2973, 2874, 1690 (s, C=O), 1396 (s, C-O); ASAP-MS (positive ion mode) *m/z*: 116.1 [M-C_4H_7]$^+$; HRMS-ASAP: Calcd for $C_5H_{10}NO_2$ 116.0712. Found 116.0709.

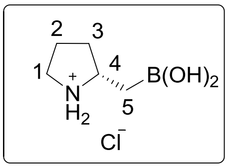
3.3.5 (S)-2-(Pinacolato)borylmethyl-N-tert-butoxycarbonyl-pyrrolidine ***65***



To a stirred solution of (-)-sparteine (0.87 mL, 3.8 mmol) in dry Et_2O (20 mL) under argon at -78 ˚C, *s*-BuLi (2.9 mL, 1.3 M, 3.8 mmol) was added dropwise and the solution was stirred for 20 min. Furthermore to the above solution *N*-Boc-pyrrolidine **66** (0.5 g, 2.9 mmol) in Et_2O (3 mL) was added dropwise and the reaction mixture was stirred at -78 ˚C for 2 h. 2-Chloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **68** (0.62 g, 3.5 mmol) was added dropwise followed by the addition of $ZnCl_2$ (5.6 mL, 1.0 M in Et_2O, 5.6 mmol) after 45 min. The mixture was stirred at -78 ˚C for 45 min and then warmed to room temperature and stirred overnight (24 h). The reaction was then quenched with 5% (w/v) aq. HCl (10 mL) filtered through Celite and washed with 5% w/v aq. HCl (5 mL). The phases were separated and the aqueous phase extracted into Et_2O (3 × 8 mL). The combined organic extracts were dried and concentrated *in vacuo*. Flash column chromatography (EtOAc:hex, 4:1) afforded boronate **65**[38] as a colourless oil (0.73 g, 62%). 96% ee; $[\alpha]_D$ = +33.2 (c = 1.00, DCM); ^{1}H NMR ($CDCl_3$, 700 MHz) δ_H 0.84-1.00 (m, 2H, H_8), 1.22 (s), 1.23 (s, 12H in total, H_{10}), 1.45 (s, 9H, H_1), 1.15 (brs, 1H, H_6), 1.70-1.75 (m, 1H, H_5), 1.81-1.87 (m, 1H, H_5), 2.02 (brs, 1H, H_6), 3.30-3.38 (brd, 2H, H_4), 3.90-3.99 (brm, 1H, H_7); ^{13}C NMR ($CDCl_3$, 176 MHz) δ_C 18.5 (C_8), 23.4, 23.9 (C_5), 24.9, 25.1 (C_{10}), 28.7 (C_1), 33.1, 33.4 (C_6), 46.3, 46.6 (C_4), 54.3 (C_7), 79.0 (C_2), 83.1 (C_9), 154.7 (C_3); ^{11}B ($CDCl_3$, 128.4 MHz) δ_B 33.2; IR ν_{max} (neat)/cm^{-1} 2975 (CH_2, CH_3), 1694 (NCO), 1389 (BO), 1165 (C-O); FTMS-MS *m/z* 645.44 [2M+Na]$^+$, 3324.22

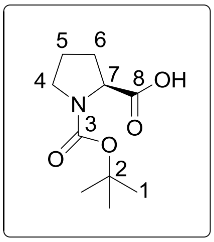
$[M+Na]^+$, 311.22 $[M+H]^+$, 256.17 $[M-C_4H_7]^+$, 212.18 $[M-C_6H_{11}O]^+$; HRMS-FTMS: Calcd for $C_{16}H_{31}BNO_4$ 312.2341. Found 312.2338. The enantiomeric ratio was determined by GC using CP-Chiralsil-Dex-CB column (35 m × 0.25 mm × 0.25 μm), 128 °C, FID, t_R (*S*) = 124 min; t_R (*R*) = 127 min.

3.3.6 *(S)-N-(1,1-Dimethylethoxycarbonyl)-(pyrrolidin-2-yl)methylboronic acid **76***



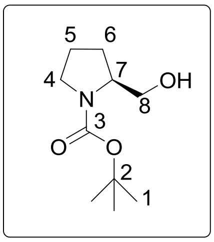
A stirred solution of boronate ester **65** (280 mg, 0.90 mmol) in 20% (w/v) aq. HCl (5 mL) was refluxed for 2 h. The mixture was cooled to room temperature, washed with Et_2O (3 × 10 mL) and concentrated *in vacuo*. The residue was redissolved in a water:toluene solution (1:10) and the mixture was concentrated *in vacuo*. Azeotroping with toluene was repeated a further five times affording **76**[38] as a pale brown oil (150 mg, 88%). $[\alpha]_D$ = +30.0 (c = 1.00, DCM); ^{1}H NMR ($CDCl_3$, 700 MHz) δ_H 1.27 (unsymmetrical dd, J = 15.4, 9.1 Hz, 1H, H_5), 1.39 (unsymmetrical dd, J = 15.4, 7 Hz, 1H, H_5), 1.64-1.68 (m, 1H, H_3), 2.00-2.12 (m, 1H, H_2), 2.25-2.29 (m, 1H, H_3), 3.29-3.37 (m, 2H, H_4), 3.73-3.77 (m, 1H, H_4); ^{13}C NMR($CDCl_3$, 176 MHz) δ_C 18.2 (C_5), 23.1, 23.6 (C_2), 31.5 (C_3), 44.8, 45.6 (C_1), 58.2 (C_4); ^{11}B ($CDCl_3$, 128.4 MHz) δ_B 30.9; IR ν_{max} (neat)/cm^{-1} 2979 (CH_2, CH_3), 1624 (NCO), 1364 (BO), 1217, 1165 (C-O).

3.3.7 *N-(tert-butoxycarbonyl)-(S)-proline **90***



To an ice-cold suspension of (*S*)-proline (1.5g, 13.03 mmol) in DCM (30 mL), triethylamine (2.36 mL, 16.94 mmol) was added, followed by a solution of di-*tert*-butyl-dicarbonate (3.98 g, 18.24 mmol) in 1.5 mL of DCM. The reaction mixture was stirred at room temperature for 2.5 h and then quenched with 8 mL of saturated aq. citric acid. The organic layer was washed with (2 × 10 mL) of brine, water (10 mL) and dried. Removal of the solvent yielded the crude product, which was dissolved in hot EtOAc, followed by the addition of 40 mL of hexane. The desired product **90**[56] was crystallised and collected by filtration as a white solid in 70% yield (1.93 g).Mp 123-126 ^{o}C; ^{1}H NMR ($CDCl_3$, 700 MHz, mixture of rotamers) δ_H 1.43 (brs), 1.49 (brs, 9H in total, H_1), 1.90-2.04 (m, 3H, CH_2Pro), 2.28-2.41 (m, 1H, CH_2Pro), 3.34-3.55 (m, 2H, H_4), 4.25-4.36 (m, 1H, H_7); ^{13}C NMR ($CDCl_3$, 176 MHz, mixture of rotamers) δ_C 23.9, 24.5 (C_5 + C_6), 28.3, 28.6 (C_1), 46.5, 47.3 (C_4), 59.0, 59.5 (C_7), 80.4, 82.0 (C_2), 154.0, 157.2, (C_8), 173.9, 178.3 (C_3); IR ν_{max} (neat)/cm^{-1} 2968, 1736, 1633; ES-MS (70 eV) *m/z* 429 [2M-H]$^+$, 214 [M-H]$^+$; HRMS-ES: Cald for $C_{10}H_{16}NO_4$ 214.1085. Found 214.1081; Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N,6.51. Found: C, 55.73; H, 7.92, N, 6.35.

3.3.8 (2S)-N-(tert-butoxycarbonyl)-2-(hydroxymethyl)pyrrolidine **89**



Procedure A

To a solution of (*S*)-*N*-(*tert*-Butoxycarbonyl)proline **90** (0.60 g, 2.79 mmol) in dry THF (5 mL) at room temperature under argon, BH_3·DMS (10.0-10.2 M as BH_3, 306 µL, 3.06 mmol) was added dropwise. The reaction mixture was refluxed for 2 h. After cooling to rt, ice (2.5 g) was added and the aqueous layer was extracted with (2 × 15 mL) DCM. The solution was filtrated through Celite and the solvent was removed affording a white solid. The desired product **89**[56] was recrystallised from

Et_2O (5 mL) and isolated as a white solid (0.45 g, 80%). Mp 55-60 ˚C; ^1H NMR ($CDCl_3$, 700 MHz) δ_H 1.47 (brs, 9H, H_1), 1.56-1.59 (m, 1H, CH_2Pro), 1.74-1.86 (m, 2H, CH_2Pro), 1.98-2.03 (m, 1H, CH_2Pro), 3.29-3.32 (m, 1H, H_8), 3.43-3.46 (m, 1H, H_8), 3.56-3.64 (m, 2H, H_4), 3.95 (brs, 1H, H_7), 4.74 (brs, 1H, -OH), (addition of D_2O caused the signal at δ_H 4.74 to disappear); ^{13}C NMR ($CDCl_3$, 126 MHz) δ_C 24.2 (CH_2Pro), 28.6 (C_1), 28.9 (CH_2Pro), 47.7 (C_8), 60.3 (C_7), 67.9 (C_4), 80.4 (C_2), 157.1 (C_3); IR ν_{max} (neat)/cm^{-1} 3435 (-OH), 2979 (CH_2, CH_3), 1660 (s, C=O), 1403, 1129, 1055, 903; ES-MS (70 eV) *m/z*: 321 425 [2M+Na]$^+$, 224 [M+Na]$^+$, 146 [2M-CMe_3+Na]$^+$; HRMS-ES: Calcd for $C_{10}H_{23}N_2O_3$ 224.1257. Found 224.1262; Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.48; H, 9.50; N, 6.87.

Procedure B

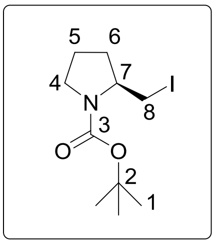
To a stirred solution of $LiAlH_4$ (0.74 g, 19.54 mmol) in dry THF (25 mL) under argon at 0 °C, (*S*)-proline (1.50 g, 13.03 mmol) was added portionwise. The reaction mixture was stirred for 1 h at 0 °C and for an extra 1 h at 25 °C. The reaction was then quenched with 5 mL of 20% (w/v) aq. KOH solution and filtered under inert atmosphere through celite and magnesium sulphate. The solution was diluted with dry THF (35 mL) and this was followed by the addition of di-*tert*-butyl-dicarbonate (4.27 g, 19.54 mmol) in a solution of THF (10 mL). The reaction mixture was further stirred overnight and then quenched with 15 mL of sat. aq. $NaHCO_3$ solution. The aqueous layer was extracted with (3 × 25 mL) Et_2O and the combined organic layers were washed with brine (25 mL) and dried. Removal of the solvent afforded the crude product, which was purified by flash column chromatography (EtOAc:hex, 3:1) and afforded compound **89** as a white solid (0.59 g, 23%). All spectroscopic and analytical properties were identical to those reported in procedure A of section 3.3.8.

Procedure C

To a suspension of $NaBH_4$ (1.58 g, 41.69 mmol) in dry THF (30 mL), a solution of iodine (4.41 g, 17.37 mmol) in dry THF (8 mL) was added dropwise. The I_2-THF solution was added at such a rate that it reacts instantly so that the reaction mixture remains white. The reaction mixture was stirred under argon at 0 °C. (*S*)-Proline

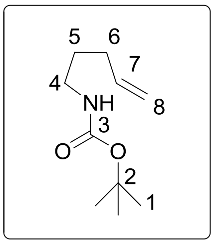
(2.0 g, 17.37 mmol) was added portionwise and the reaction mixture was refluxed overnight. After this period, the solution was cooled to 0 °C and methanol (4 mL) was added. The reaction mixture was diluted with THF (20 mL), followed by the addition of triethylamine (2.54 mL, 18.24 mmol) and di-*tert*-butyl-dicarbonate (3.83 g, 17.54 mmol) in dry THF (13 mL). After stirring the reaction for 3 h at rt, the solvent was removed *in vacuo* and the resulting white solid was suspended in 30 mL of EtOAc and 20 mL of water. This was followed by the addition of a 1:1 solution of 1.2 M aq. HCl and brine (26 mL). The aqueous layer was extracted in (3 × 15 mL) of EtOAc and the combined organic layers were washed with a 1:1 solution of 1.2 M aq. HCl and brine (15 mL), sat. aq. solution of $NaHCO_3$ (8 mL), brine (8 mL) and water (15 mL). The organic layer was dried and concentrated *in vacuo*. The desired product **89** was isolated after flash column chromatography (EtOAc:hex, 2:1) as a white solid (0.42 g, 12%). All spectroscopic and analytical properties were identical to those reported in procedure A of section 3.3.8.

*3.3.9 (2S)-N-(tert-butoxycarbonyl)-2-(iodomethyl)pyrrolidine **88***



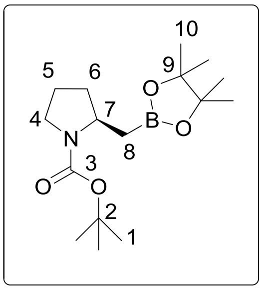
To a suspension of imidazole (0.20 g, 2.98 mmol) and PPh_3 (0.59 g, 2.24 mmol) in Et_2O (4 mL) at 0 °C under argon, iodine (0.57 g, 2.24 mmol) was added portionwise. The reaction mixture was stirred for 10 min, followed by the addition of (*S*)-N-(*tert*-butoxycarbonyl)prolinol **89** (0.30 g, 1.49 mmol) in Et_2O and 2 mL of DCM. The resulting mixture was stirred overnight at rt, filtrated and concentrated. The crude product was purified by flash column chromatography (hex:EtOAc, 6:1) and compound **88**[85] was isolated as a white solid (0.39 g, 83%). Mp 38-40 ˚C; ^{1}H NMR ($CDCl_3$, 700 MHz, mixture of rotamers) δ_H 1.46 (brs), 1.48 (brs, 9H in total, H_1), 1.81-1.91 (m, 3H, CH_2Pro), 2.04-2.06 (m, 1H, CH_2Pro), 3.14-3.52 (m, 4H, H_8+H_4), 3.86-3.89 (m, 1H, H_7); ^{13}C NMR ($CDCl_3$, 176 MHz, mixture of rotamers) δ_C 10.8, 11.2 (C_8), 23.0, 23.7 (C_6), 28.6 (C_1), 31.2, 31.8 (C_5), 47.2, 47.7 (C_4), 58.1, 58.3 (C_7), 79.74, 80.06 (C_2), 154.8 (C_3); IR ν_{max} (neat)/cm^{-1} 2972, 2869 (CH_2), 1674 (CONH), 1391, 1364 (CMe_3); ASAP-MS (positive ion mode) *m/z*: 255.9 $[M+H-CMe_3]^+$, 128.1 $[M+H-MeI]^+$; Anal. Calcd for $C_{10}H_{18}NIO_2$: C, 38.60; H, 5.83; N, 4.50. Found: C, 38.77; H, 5.88; N, 4.44.

3.3.10 *tert-Butyl pent-4-enylcarbamate* ***91***



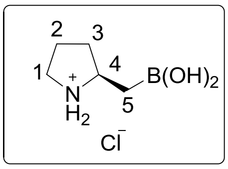
To a stirred solution of iodide **88** (100 mg, 0.32 mmol) and triisopropyl borate (74 µL, 0.32 mmol) in dry THF under argon at -78 °C, *n*-BuLi (0.26 mL, 2.5 M, 0.64 mmol) was added dropwise. The reaction was stirred at -78 °C for 1 h and then warmed up to room temperature overnight. The reaction mixture was quenched with 20% (w/v) aq. HCl (3 mL) and the aqueous layer was extracted in EtOAc (3 × 5 mL). The organic extracts were combined, dried and concentrated *in vacuo*. The resulting yellow solution was purified by flash column chromatography (hex:EtOAc, 10:1) and compound **91** was isolated as a colourless liquid (56 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.44 (s, 9H, H_1), 1.54-1.61 (m, 2H, H_6), 2.04-2.11 (m, 2H, H_5), 3.10-3.14 (m, 2H, H_4), 4.52 (brs, 1H, H_7), 4.96-5.05 (m, 2H, H_8), 5.75-5.85 (m, 1H, H_7). All spectroscopic and analytical properties were identical to those reported in the literature.[86]

3.3.11 *(R)-2-(Pinacolato)borylmethyl-N-tert-butoxycarbonyl-pyrrolidine* ***87***



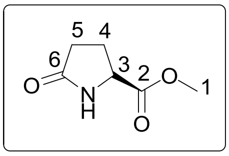
To a stirred solution of (2S)-N-(tert-butoxycarbonyl)-2-(iodomethyl)pyrrolidine **88** (0.50 g, 1.6 mmol) in dry THF (8 mL) under argon at room temperature, B_2pin_2 (0.41 g, 1.6 mmol) and LiO^{t}Bu (0.26 g, 3.2 mmol) were added, followed by CuI (17.5 mg, 0.16 mmol). The reaction mixture was stirred for 20 h and then quenched with 5% (w/v) aq. HCl (5 mL). The aqueous phase was extracted into Et_2O (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc:hex, 4:1) and **87**[38] was isolated as a colourless oil (0.32 g, 65%). 97% ee; $[\alpha]_D$ = -36.4 (c = 1.00, DCM). All spectroscopic and analytical properties were identical to those reported in section *4.3.5*. The enantiomeric ratio of the product was determined by GC using CP-Chiralsil-Dex-CB column (35 m × 0.25 mm × 0.25 μm), 128 ^oC, FID, t_R (*S*) = 124 min; t_R (*R*) = 127 min.

3.3.12 *(R)-N-(1,1-Dimethylethoxycarbonyl)-(pyrrolidin-2-yl)methylboronic acid* ***92***



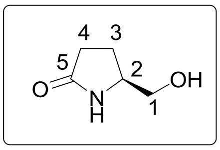
A stirred solution of boronate ester **87** (300 mg, 0.96 mmol) in 20% (w/v) aq. HCl (5 mL) was refluxed for 2 h. The mixture was cooled to room temperature, washed with Et_2O (3 × 10 mL) and concentrated *in vacuo*. The residue was redissolved in a water:toluene solution (1:10) and the mixture was concentrated *in vacuo*. Azeotroping with toluene was repeated a further five times affording **92**[38] as a pale brown oil (162 mg, 95%). $[\alpha]_D$ = -33.1 (c = 1.00, DCM). All spectroscopic and analytical properties were identical to those reported in Section *4.3.6*.

3.3.13 (S)-Methyl-5-oxo-pyrrolidine-2-carboxylate **100**



To a stirred solution of L-pyroglutamic acid (6.0 g, 46.5 mmol) and MeOH (25 mL) was added Amberlyst 15 resin (2.3 g). The reaction mixture was refluxed for 24 h, cooled, filtered and concentrated *in vacuo* affording compound **95**[67] as a brown oil (5.92 g, 89%). No further purification was carried out; the material was used directly in the next reaction. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.23-2.51 (m, 4H, CH_2Pro), 3.77 (s, 3H, H_1), 4.24-4.28 (m, 1H, H_3), 6.33 (s, 1H, -NH), (addition of D_2O caused the signal at 6.33 to disappear); ^{13}C NMR ($CDCl_3$, 126 MHz,) δ_c 24.9 (C_4), 29.3 (C_5), 52.7 (C_1), 55.5 (C_3), 172.5 (C_2), 178.1 (C_6); IR ν_{max} (neat)/cm^{-1} 3248 (CONH), 1686 (CONH), 1207, 1180 (OMe); ASAP-MS (positive ion mode) *m/z* 144.06 $[M+H]^+$, 84.04 $[M-CH_3COO]^+$; HRMS-ASAP: Calcd for $C_6H_{10}NO_3$ 144.0661. Found 144.0623.

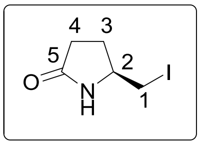
3.3.14 (S)-5-Hydroxymethyl-2-pyrrolidinone **99**



To a stirred solution of methyl-(*S*)-2-pyrrolidinone-5-carboxylate **100** (2.5 g, 17.5 mmol) and dry EtOH (60 mL) at 0 °C under argon was added portionwise $NaBH_4$ (1.32 g, 34.9 mmol). The reaction was allowed to warm to rt and monitored by TLC (EtOH:MeOH, 4:1). After 3 h the reaction was quenched with acetic acid (1 mL, 17.5 mmol) and stirred for further 30 min. The reaction mixture was then filtered through a glass fiber filter and the solvent was evaporated to afford the crude product was a white solid. To the product EtOAc (2 mL) and silica gel (2 g) were added. The suspension was concentrated and dried *in vacuo*. The silica gel mixture was added to the top of a short silica gel column and eluted using EtOAc:MeOH

(4:1), yielding **99**[68] as a white solid (1.36 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.76-1.84 (m, 1H, H_3), 2.14-2.21 (m, 1H, H_3), 2.30-2.42 (m, 2H, H_4), 3.48 (dd, J = 11.5, 7 Hz, 1H, H_1), 3.68 (dd, J = 11.5, 3.5 Hz, 1H, H_1), 3.78-3.83 (m, 1H, H_2), 7.10 (s, 1H), (addition of D_2O caused the signal at 7.10 to disappear); ^{13}C NMR ($CDCl_3$,126 MHz) δ_c 22.7 (C_3), 30.3 (C_4), 56.5 (C_2), 66.1 (C_1), 179.5 (C_5); IR ν_{max} (neat)/ cm^{-1} 3264 (CONH), 2934 (OH), 1656 (CONH), 1262, 1054.

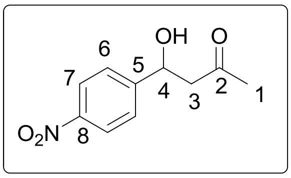
3.3.15 *(S)-5-Iodomethylpyrrolidin-2-one* ***94b***



To a stirred solution of (*S*)-5-(Hydoroxymethyl)-2-pyrrolidinone **99** (0.40 g, 3.5 mmol) in dry DCM (12 mL) under argon at rt, TsCl (0.79 g, 4.2 mmol) and Et_3N (1.45 mL, 10.4 mmol) were added, followed by DMAP (43 mg, 0.35 mmol). The reaction mixture was then stirred overnight at rt and then diluted with DCM (8 mL) and finaly acidified with 0.6 M aq. HCl (20.4 mL). The aqueous phase was extracted with DCM (2 × 10 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to afford the crude tosylate (0.83 g) as a pale yellow solid. To a solution of NaI (1.56 g, 10.4 mmol) in dry MeCN (20 mL) under argon at rt the crude tosylate product was added. The reaction was refluxed for 5 h, then cooled and concentrated *in vacuo*. The resulting dark orange oil was acidified with 1M aq. HCl (6 mL) and extracted with $CHCl_3$ (10 × 10 mL). The combined organic phases were washed with 10% (w/v) aq. solution of $Na_2S_2O_3$ (10 mL) and the aqueous phase was then extracted with $CHCl_3$ (2 × 20 mL). Silica gel (2.0 g) was added to the combined organic phases and then concentrated *in vacuo*. The silica gel mixture was added to the top of a short silica gel column and eluted using EtOAc, affording **94b**[85] as a yellow solid (0.47 g, 60%). Mp 76 ^{o}C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.80-1.86 (m, 1H, CH_2Pro), 2.30-2.52 (m, 3H, CH_2Pro), 3.18 (dd, J = 10, 7 Hz, 1H, H_1), 3.25 (dd, J = 10, 5.5 Hz, 1H, H_1), 3.84-3.89 (m, 1H, H_2), 5.99 (brs, 1H, -NH), (addition of D_2O caused the signal at 5.99 to disappear); ^{13}C NMR ($CDCl_3$, 126 MHz) δ_c 11.1 (C_1), 27.7 (C_3), 30.3 (C_4), 55.3 (C_2), 177.4 (C_5); IR ν_{max} (neat)/cm^{-1}

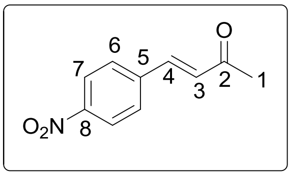
3165 (CONH), 1684 (CON); ASAP-MS (positive ion) *m/z* 226.0 [M+H]$^+$, 99.1 [M-I]$^+$; HRMS-ASAP: Cald for C_5H_9NIO 225.9729. Found 225.9714.

*3.3.16 4-Hydroxy-4-(4-nitrophenyl)-butan-2-one **58***



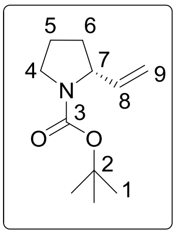
To a stirred solution of *p*-nitrobenzaldehyde (1.0 g, 6.62 mmol) in acetone (9.7 mL) and water (10 mL), pyrrolidine (0.17 mL, 2 mmol) was added. The reaction was stirred at room temperature for 2 h and then quenched with 5% (w/v) aq. HCl (20 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL). The organic layer was then washed with 5% w/v HCl (2 × 20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (hex:EtOAc, 1:1) and afforded the desired product **58**[69] as a white solid (0.89 g, 65%). Mp 55-66 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.23 (s 3H, H_1), 2.80-2.91 (m, 2H, H_3), 3.55 (d, J = 3.2 MHz, 1H, -OH), 5.26 (qui, J = 3.9 MHz, 1H, H_4), 7.53-7.55 (m, 2H, CH_{Ar}), 8.21-8.23 (m, 2H, CH_{Ar}), (addition of D_2O caused the signal 3.55 to disappear); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 30.9 (C_1), 51.8 (C_3), 69.3 (C_4), 123.9 (C_{Ar}), 208.8(C_2), 126.6 (C_{Ar}), 150.1 (C_8); IR ν_{max} (neat)/cm^{-1} 3452 (b, -OH), 1712 (s, C=O), 1519 (s), 1339 (s, $-NO_2$); ASAP-MS (positive ion) *m/z* 208.1 [M-H]$^+$, 192.1 [M-OH]$^+$, 144.1 [M- H_2NO_3]$^+$; Anal. Calcd for $C_{10}H_{11}O_3N$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.34; H, 5.14; N, 6.43.

*3.3.17 4-(4-Nitrophenyl)-3-buten-2-one **59***



To a stirred solution of *p*-nitrobenzaldehyde (500 mg, 3.31 mmol) in acetone (2.97 mL) was added 0.1 M aqueous solution of NaOH (33 mL). The reaction mixture was allowed to stir at room temperature for 10 h and then diluted in EtOAc (20 mL). The aqueous layer was extracted into EtOAc (3 × 15 mL) and then the organic layers were combined, dried and concentrated *in vacuo*. Silica gel chromatography (hexane: EtOAc, 2:1) afforded the desired product **59**[78] as a yellow solid (539 mg, 85%). Mp 88-90 ˚C; ^{1}H NMR ($CDCl_3$, 700 MHz) δ_H 2.42 (s, 3H, H_1), 6.81 (d, J = 16 Hz, 1H, H_3), 7.54 (d, J = 16 Hz, 1H, H_4), 7.69 (d, J = 9.1 MHz, 1H, H_6), 8.26 (d, J = 8.4 Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$, 176 MHz) δ_C 28.2 (C_1), 124.4 (C_7), 128.9 (C_6), 130.5 (C_3), 140.2 (C_4), 140.8 (C_5), 148.8 (C_8), 197.6 (C_2); IR ν_{max} (neat)/cm^{-1} 1691 (C=O, α,β-unsaturated), 1509 (NO_2), 1339 (NO_2); ASAP-MS (positive ion mode) *m/z*: 192.1 $[M+H]^+$, 161.1 $[M-Me]^+$ 144.0 $[M-HNO_2]^+$; HRMS-ASAP: Calcd for $C_{10}H_{10}NO_3$ 192.0661. Found 192.0655.

3.3.18 (2R)-N-(tert-Butoxycarbonyl)-2-vinylpyrrolidine ***113***



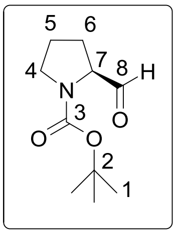
Procedure A

To a stirred solution of (-)-sparteine (1.77 mL, 7.70 mmol), *N*-Boc-pyrrolidine **66** (1.32 g, 7.70 mmol) in Et_2O (30 mL) under argon at -78 ^{o}C, *s*-BuLi (5.50 mL, 1.4 M, 7.70 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 1 h. In a second flask, a solution of CuCN (0.31 g, 3.50 mmol), LiCl (0.33 g, 7.70 mmol) in 30 mL of THF was stirred at room temperature under argon for 20 min. The second solution was added to the *N*-Boc-pyrrolidine solution and stirred for 1 h at room temperature. Vinyl bromide (7.70 mL, 1 M, 7.70 mmol) was added to the reaction mixture at -78 ^{o}C and allowed to warm to room temperature overnight. The reaction was then quenched with 24 mL of sat. aq. solution of NH_4Cl and diluted with 18 mL of Et_2O. The aqueous phase was extracted with (3 × 30 mL) of Et_2O and the combined organic extracts were dried, filtrated and concentrated *in vacuo*. The crude product was purified using flash column chromatography (pet. ether:EtOAC, 9:1), affording the desired vinyl pyrrolidine **113**[72] as a colourless oil (0.59 g, 39%). 27% ee; ^{1}H NMR ($CDCl_3$, 700 MHz) δ_H 1.68-1.71 (m, 1H, H_6), 1.78-1.86 (m, 2H, H_5), 2.00 (m, 1H, H_6), 3.39 (brs, 2H, H_4), 4.23-4.34 (brd, 1H, H_7), 5.04 (brs, 2H, H_9), 5.73 (brs, 1H, H_8); ^{13}C NMR ($CDCl_3$, 176 MHz) δ_C 22.9 (C_5), 28.6 (C_1), 32.2 (C_6), 46.3 (C_4), 59.3 (C_7), 79.2 (C_2), 113.8 (C_9), 139.2 (C_8), 154.9 (C_3); IR ν_{max} (neat)/ cm^{-1} 2947 (CH_2), 1690 (NCO), 1388, 1364 (CMe_3), 1166, 1112, 987, 913 ($CH{=}CH_2$); ASAP-MS (positive ion mode) *m/z*: 142.08 $[M-C_4H_7]^+$, 98.09 $[M-C_5H_7O_2]^+$; HRMS-ASAP: Calcd for $C_7H_{12}NO_2$ 142.0783. Found 142.0818. The enantiomeric ratio of the product was determined by HPLC analysis using a column t_R (*S*) = 28.7 min; t_R (*R*) = 31.1 min.

Procedure B

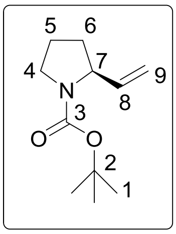
To a stirred solution of (-)-sparteine (2.4 mL, 10.51 mmol) in Et_2O (42 mL) under argon at -78 °C, was added *s*-BuLi (7.51 mL, 1.4 M, 10.51 mmol) dropwise and the solution was stirred for 30 min. Furthermore, to the above solution *N*-Boc-pyrrolidine **66** (1.50g, 8.76 mmol) was added and the reaction mixture was stirred at -78 °C. After 6 h a solution of $ZnCl_2$ (1.55 g, 11.39 mmol) in 14 mL of THF was added dropwise. The reaction mixture was stirred for additional 30 min before a solution of CuCN (0.94 g, 10.51 mmol), LiCl (0.92 g, 21.02 mmol) in 35 mL of THF was added dropwise. The mixture was allowed to warm to room temperature overnight and quenched with 10% (w/v) aq. solution of NH_4OH. The organic layer was then washed with brine, dried, filtrated and concentrated *in vacuo*. The residue was purified by flash column chromatography (pet. ether:EtOAc, 9:1) affording the vinyl pyrrolidine **111** as a colourless oil (0.74 g, 46%). 43% ee. All spectroscopic and analytical properties were identical to those reported in procedure A of section 3.3.18. The enantiomeric ratio of the product was determined by HPLC analysis using a column t_R (*S*) = 28.7 min; t_R (*R*) = 31.1 min.

3.3.19 (2S)-N-(tert-Butoxycarbonyl)pyrrolidine-2-carboxaldehyde ***117***



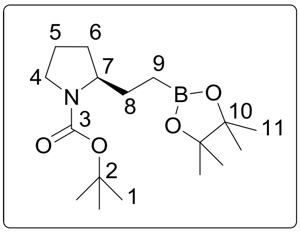
A solution of DMSO (1.64 mL, 16.40 mmol) dissolved in DCM (4 mL) was added dropwise over a 10 min period to a stirred cooled at -63 ^{o}C solution of oxalyl chloride (0.75 mL, 8.94 mmol) dissolved in 20 mL of DCM. After 10 min, a solution of alcohol **87** (1.50 g, 7.45 mmol) dissolved in 7.5 mL of DCM was added dropwise and the reaction mixture was stirred for 30 min. Diisopropylethylamine (5.20 mL, 29.80 mmol) was then added and the mixture was then washed with (3 × 10 mL) of 5% (w/v) aq. solution HCl, (3 × 10 mL) of H_2O and (2 × 10 mL) of brine, dried, filtrated and concentrated *in vacuo*. The desired aldehyde **115**[74] was stored under argon in a freezer without further purification (1.19 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ_H 1.43 (brs), 1.48 (brs, 9H in total, H_1), 1.84-2.15 (m, 4H, CH_2Pro), 3.42-3.59 (m, 2H, H_4), 4.02-4.21 (m, 1H, H_7), 9.45-9.56 (m, 1H, CHO). All other spectroscopic and analytical properties were identical to those reported in the literature.[74]

3.3.20 (2S)-N-(tert-Butoxycarbonyl)-2-vinylpyrrolidine ***116***



To a stirred solution ice-cold solution of methyl triphenylphosphonium bromide (1.80 g, 5.00 mmol) in 28 mL of THF under argon, *n*-BuLi (2.00 mL, 2.5 M, 5.00 mmol) was added dropwise. The mixture was allowed to warm to room temperature, stirred for 3 h and was then added dropwise to cold solution at -78 ^{o}C of aldehyde **117** (1.00 g, 5.00 mmol) in THF (28 mL). The reaction was allowed to warm to room temperature, stirred overnight and quenched with 8 mL of sat. aq. solution of NH_4Cl. The aqueous layer was then extracted with (3 × 30 mL) of EtOAc. The combined organic extracts were dried, filtrated and concentrated *in vacuo* affording the crude product as a brown oil, which was then purified by flash column chromatography (hex:EtOAc, 8:1) **114**[72] (0.99 g, 50%). 97% ee All spectroscopic and analytical properties were identical to those reported in procedure A of section 3.3.18. The enantiomeric ratio of the product was determined by HPLC analysis using a column t_R (*S*) = 28.7 min; t_R (*R*) = 31.1 min.

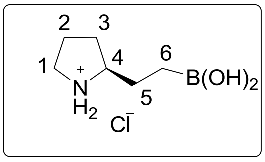
*3.3.21 (R)-tert-Butyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl) pyrrolidine-1-carboxylate **115***



To a stirred solution of $[Ir(cod)Cl]_2$ (15.3 mg, 0.03 mmol) and dppe (18.3 mg, 0.046 mmol) in DCM (4 mL), pinacol borane (0.26 mL, 1.82 mmol) and *N*-Boc-vinylpyrrolidine **116** (0.30 g, 1.52 mmol) were added. The reaction mixture was stirred at room temperature under argon for 20 h, and then quenched with MeOH (1.5 mL) and H_2O (4 mL). The aqueous layer was extracted with (3 × 5 mL) of Et_2O and the combined organic extracts were dried, filtrated and concentrated *in vacuo*. Flash column chromatography (hex:EtOAc, 3:1) resulted in the isolation of **115** as a colourless oil (0.20 g, 41%). $[\alpha]_D = -41.2$ (c = 0.25, DCM); ^1H NMR ($CDCl_3$, 700 MHz) δ_H 0.70-0.71 (m, 2H, H_9), 1.23 (s, 12H, H_{11}), 1.31-1.39 (m, 1H, H_6), 1.45 (m, 9H, H_1), 1.64-1.83 (m, 5H, H_5+H_6), 3.27-3.39 (brd, 2H, H_4), 3.65-3.72 (brd, 1H, H_7); ^{13}C NMR ($CDCl_3$, 176 MHz) δ_C ($CDCl_3$, 176 MHz) δ_C 7.7 (C_9), 23.2, 23.8 (C_6), 25.0 (C_{11}), 28.7 (C_1), 29.3, 30.2 (C_5), 46.3, 46.6 (C_4), 59.2 (C_7), 79.0 (C_2), 83.1 (C_{10}), 154.9 (C_3); ^{11}B ($CDCl_3$, 128.4 MHz) δ_B 34.1; IR ν_{max} (neat)/cm^{-1} 2975 (CH_2, CH_3), 1690 (NCO), 1389 (BO), 1165 (C-O); FTMS-MS *m/z* 673.47 $[2M+Na]^+$, 348.23

$[M+Na]^+$, 326.25 $[M+H]^+$, 270.19 $[M-C_4H_7]^+$, 226.20 $[M-C_6H_{11}O]^+$; HRMS-FTMS: Calcd for $C_{17}H_{33}BNO_4$ 326.2497. Found 326.2497.

3.3.22 (R)-2-(2-Boronoethyl)pyrrolidinium chloride ***118***



A stirred solution of boronate ester **118** (300 mg, 0.92 mmol) in 20% (w/v) HCl (5 mL) was refluxed for 2 h. The mixture was cooled to room temperature, washed with Et_2O (3 × 10 mL) and concentrated *in vacuo*. The residue was redissolved in a water:toluene solution (1:10) and the mixture was concentrated *in vacuo*. Azeotroping with toluene was repeated a further five times affording **118** as a pale brown oil (162 mg, 98%). $[\alpha]_D$ = -39.3 (c = 0.25, DCM); ^1H NMR (D_2O, 700 MHz) δ_H 0.87 (t, J = 8.4 Hz, 2H, H_6), 1.64-1.67 (m, 1H, H_3), 1.74-1.86 (m, 2H, H_5), 1.99-2.09 (m, 2H, H_2), 2.22-2.24 (m, 1H, H_3), 3.27-3.34 (m, 2H, H_1), 3.50 (qui, J = 8.4 Hz, 1H, H_4); ^{13}C NMR (D_2O, 176 MHz) δ_C 11.3 (C_6), 23.0 (C_2), 26.4 (C_5), 29.3 (C_3), 45.0 (C_1), 62.6 (C_4); ^{11}B ($CDCl_3$, 128.4 MHz) δ_B 32.0; IR ν_{max} (neat)/cm^{-1} 2979, 1624, 1364, 1217, 1015; ES-MS (70 eV) *m/z*: 124.0 $[M-Cl-H_2O]^+$, 97.0 $[M-Cl-2H_2O-B]^+$, 70.0 $[M-C_2H_8O_2BCl]^+$.

Chapter 4: References

4 References

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Chapter 5: Appendix

5 Appendix

5.1 List of Publications

I. Georgiou, G. Ilyashenko, A. Whiting, "Synthesis of Aminoboronic Acids and their Applications in Bifunctional Catalysis.", *Acc. Chem. Res.* **2009**, *42*, 756-768.

I. Georgiou, A. Whiting, "Synthesis and Application of Aminoboronic Acids as Bifunctional Catalysts. Clean, Green and Asymmetric.", *Chimica Oggi/Chemistry Today*, **May/June 2010**, *28*.

I. Georgiou, A. Whiting, "Mechanism and Optimisation of the Homoboroproline Bifunctional Catalytic Asymmetric Aldol Reaction: Lewis Acid Tuning Through *In situ* Esterification.", *Org. Biomol. Chem.***2012**, **DOI:** 10.1039/C2OB06872A.

5.2 List of Conferences Attended

Date	Meeting	Presentation
13/01/2009	Sheffield Stereochemistry	-
01/04/2009	RSC Organic Division North East Regional Meeting - Leeds	-
30/06/2009	2nd NEPIC Organic Chemistry and Catalysis Symposium	Poster
13-17/07/2009	Liverpool Summer School in Catalysis	Poster
11/09/2009	Symposium in Honor of Professor Bernard Golding –University of Newcastle	-
12/01/2010	Sheffield Stereochemistry	-
15/04/2010	RSC Organic Division North East Regional Meeting – Durham	Poster
13-19/09/2010	6th EFCATS Summer School –Izmir, Turkey- (Bursary)	Talk
18/10/2010	1st NORSC Meeting –York	Talk

11/01/2011	Sheffield Stereochemistry	-
24-25/03/2011	CATFLU.OR Symposium-Bologna, Italy-(Ustinov College Travel Award)	Talk
06/04/2011	SCI Postgraduate Symposium-Manchester	Talk
13/04/2011	RSC Organic Division North East Regional Meeting – Northumbria	Poster
22/09/2011	RSC Heterocyclic & Synthesis Group postgraduate meeting at AstraZeneca	Poster

5.3 Calibration Curves Used for the Aldol Reactions Outlined in Section 2.6

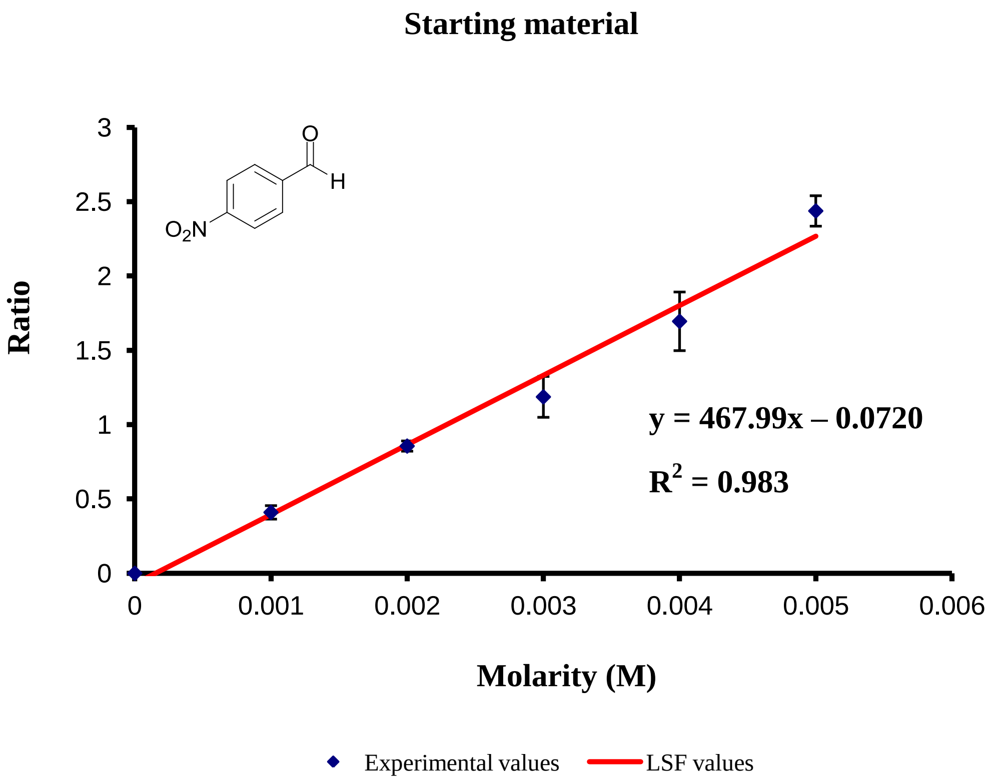

Figure 5.1 Calibration curve of the starting material, *p*-nitrobenzaldehyde.

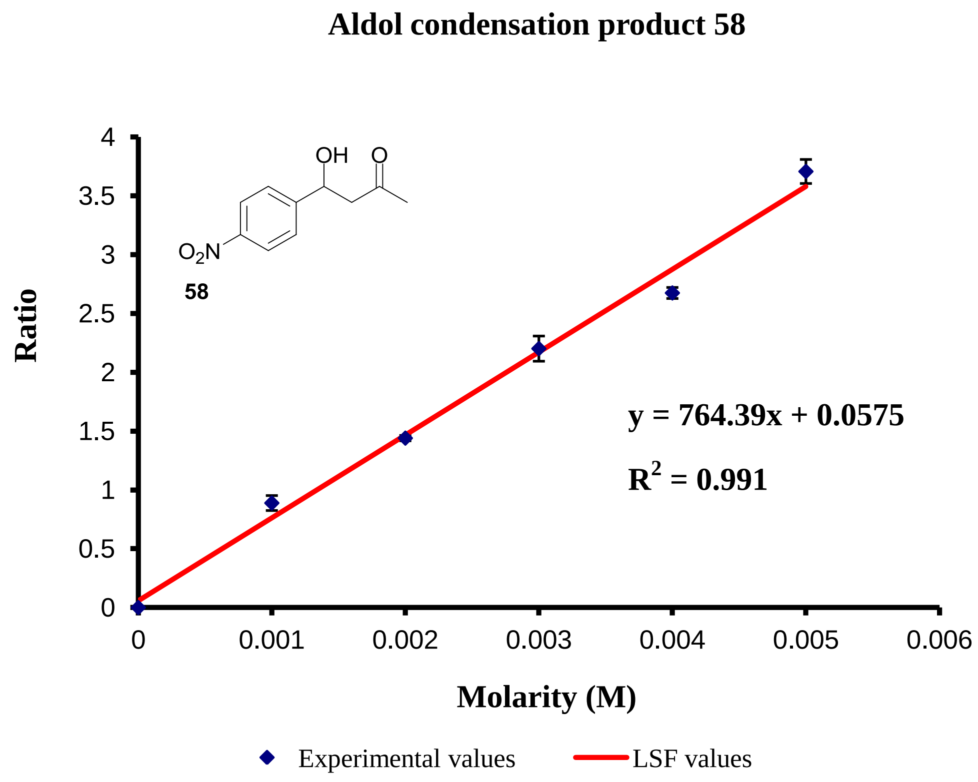

Figure 5.2 Calibration curve of the aldol condensation product **58**.

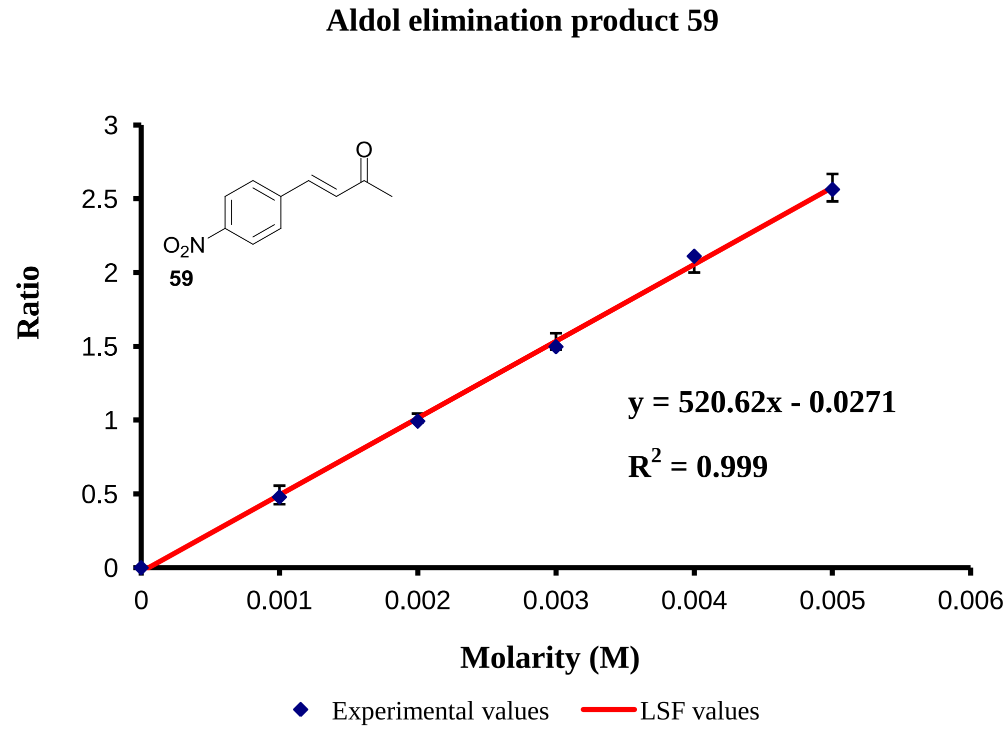

Figure 5.3 Calibration curve of the aldol elimination product **59**.

5.4 HPLC Spectra

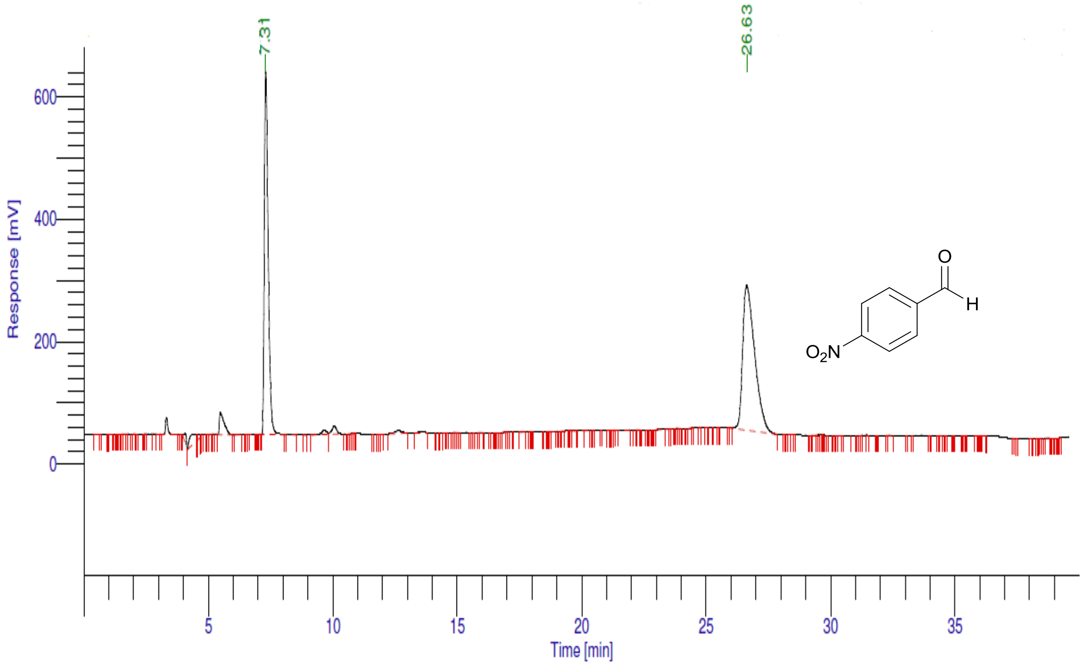

Figure 5.4 Example of HPLC spectrum of *p*-nitrobenzaldehyde (t_R = 26.63 min) used for the calibration curve outlined in Figure 5.1.

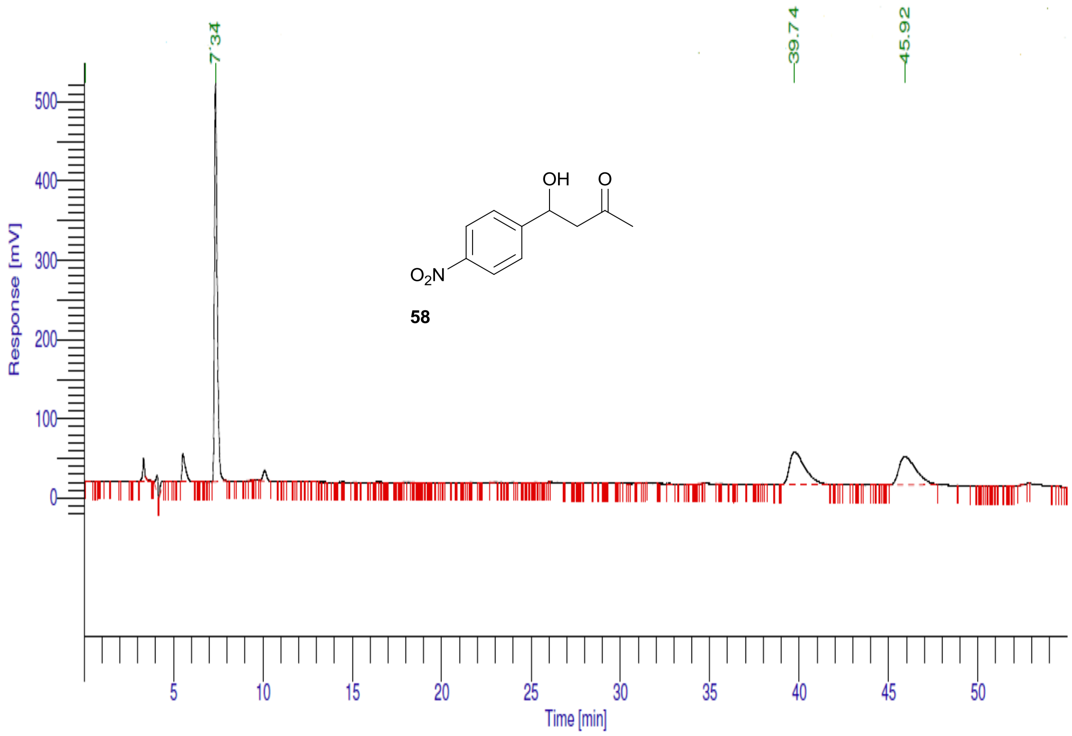

Figure 5.5 Example of HPLC spectrum of (*R*)- and (*S*)-aldol condensation product (t_R = 39.74 and 45.92 min respectively) used for the calibration curve outlined in Figure 5.2.

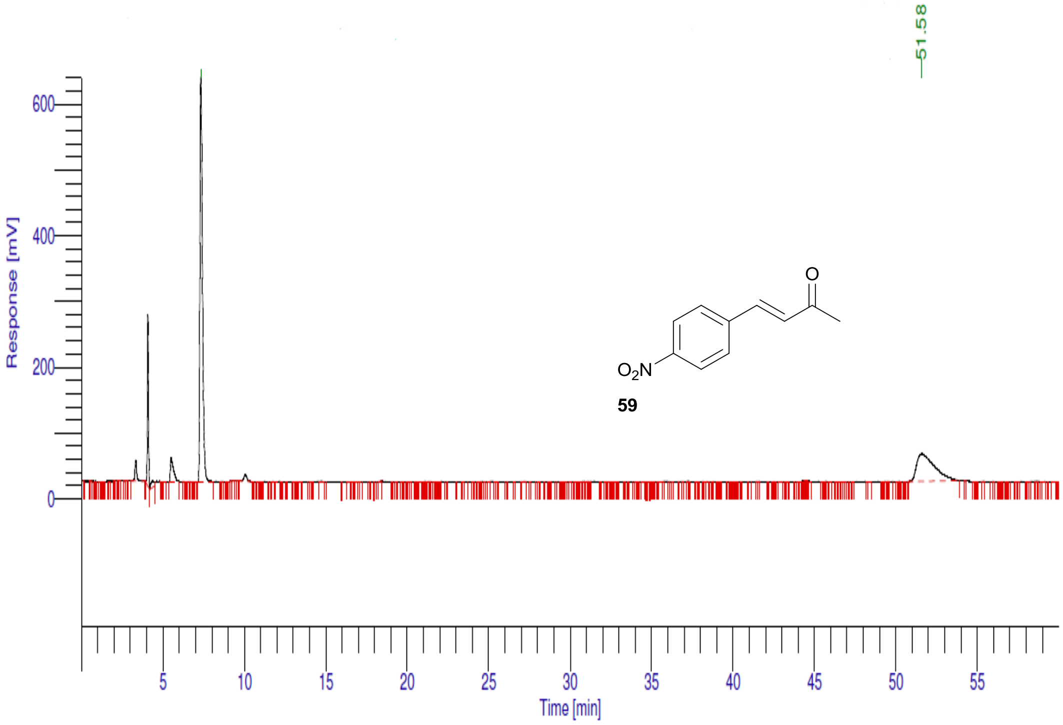

Figure 5.6 Example of HPLC spectrum of aldol elimination product (t_R = 51.58 min) used for the calibration curve outlined in Figure 5.3.

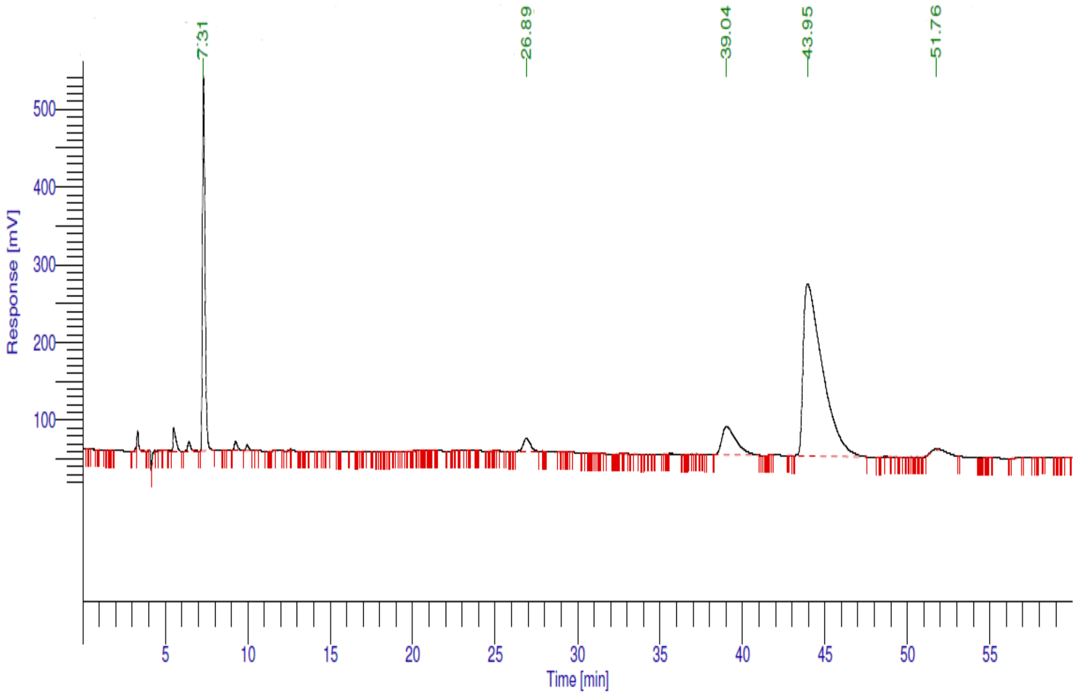

Figure 5.7 Example of HPLC spectrum for the aldol reaction outlined in eqn. 2.12 .

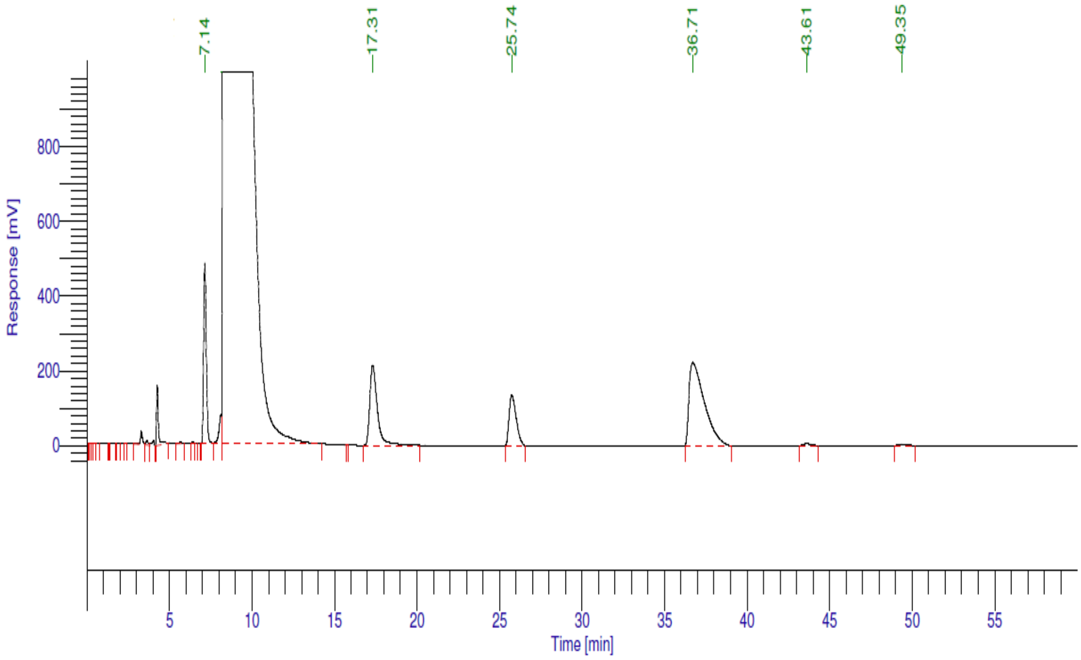

Figure 5.8 Example of HPLC spectrum for the aldol reaction outlined in eqn. 2.16 .

5.5 X-Ray Crystallography Data

*5.5.1 Crystallography Data for compound **64***

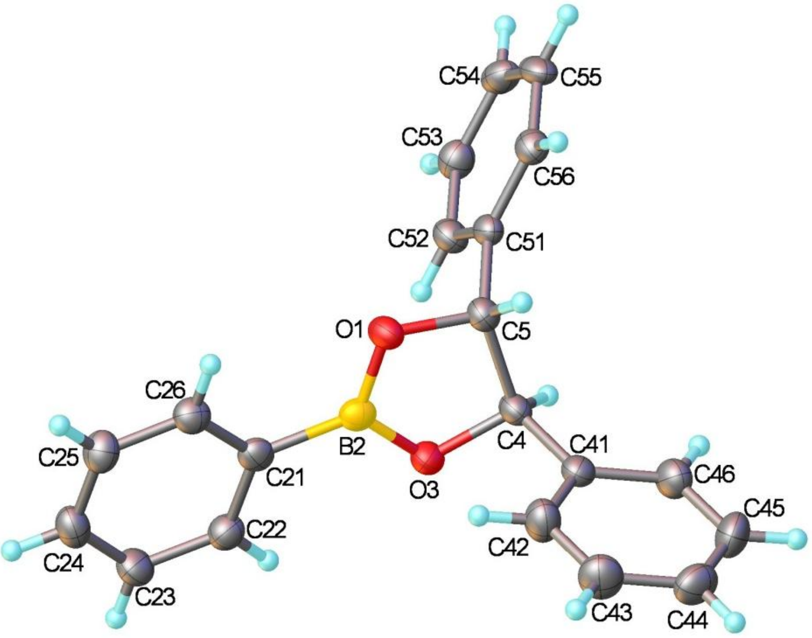

Table 5.1 Crystal data and structure refinement

Empirical formula	$C_{20}H_{17}BO_2$
Formula weight	300.15
Temperature/K	120
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	5.41785 (12)
b/Å	17.0100 (1)
c/Å	17.2637 (3)
α/Å	90.00
β/Å	90.00
γ/Å	90.00
Volume/$Å^3$	1590.98 (14)
Z	4
P_{calc} mg/mm^3	1.253
m/mm^{-1}	0.618
F(000)	632.0
Crystal size/mm^3	0.36 × 0.17 × 0.07
2Θ range for data collection	7.3 to 120.76°
Index ranges	$-5\leq h \leq 6, -19\leq k \leq 19, -19\leq 1 \leq 19$
Reflections collected	19157
Independent reflections	2362[R(int) = 0.0345]
Data/restraints/parameters	2362/0/208
Goodness-of-fit on F^2	1.057
Final R indexes [I>2σ (I)]	$R_1 = 0.0248$, $wR_2 = 0.0625$
Final R indexes [all data]	$R_1 = 0.0257$, $wR_2 = 0.0632$
Largest diff. peak/hole/ e $Å^{-3}$	0.09/-0.14
Flack parameter	-0.11 (18)

Table 5.2 Fractional atomis coordinates and equivalent isotropic displacement parameters

Atom	*x*	*y*	*z*	U_{eq}
O1	7677.7 (17)	4577.0 (5)	2834.2 (5)	28.3 (2)
O3	4809.6 (18)	4781.8 (5)	1884.1 (5)	28.4 (2)

C4	4895 (3)	5512.2 (7)	2312. 1 (7)	26.5 (3)
C5	6458 (3)	5307.9 (8)	3044.7 (7)	27.2 (3)
C21	7336 (3)	3505.8 (7)	1796.0 (7)	26.7 (3)
C22	5982 (3)	3192.2 (8)	1177.8 (8)	30.1 (3)
C23	6651 (3)	2485.1 (8)	843.0 (8)	33.8 (3)
C24	8695 (3)	2085.3 (8)	1106.5 (8)	33.9 (3)
C25	10101 (3)	2391.6 (8)	1704.9 (8)	32.9 (3)
C26	9410 (3)	3094.3 (8)	2047.8 (7)	29.7 (3)
C41	5959 (3)	6159.1 (8)	1811.2 (7)	27.2 (3)
C42	8016 (3)	6033.0 (8)	1351.3 (8)	38.4 (4)
C43	8961 (3)	6627.9 (9)	892.9 (9)	44.1 (4)
C44	7858 (3)	7357.4 (9)	890.5 (9)	43.2 (4)
C45	5828 (3)	7494.7 (9)	1349.2 (9)	43.3 (4)
C46	4885 (3)	6896.8 (8)	1805.7 (8)	36.0 (3)
C51	4942 (3)	5192.0 (7)	3767.8 (7)	25.5 (3)
C52	2847 (3)	4719.1 (8)	3750.1 (8)	29.3 (3)
C53	1406 (3)	4622.1 (8)	4404.3 (8)	32.2 (3)
C54	2039 (3)	5003.8 (8)	5084.8 (8)	33.7 (3)
C55	4109 (3)	5473.4 (8)	5110.1 (7)	33.0 (3)
C56	5563 (3)	5568.2 (7)	4454.1 (7)	28.0 (3)
B2	6584 (3)	4295.5 (9)	2177.1 (8)	26.2 (3)

Table 5.3 Anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	29.4 (5)	31.5 (5)	23.9 (4)	-4.1 (4)	-1.7 (4)	6.0 (4)
O3	34.7 (5)	25.0 (4)	25.4 (4)	-2.3 (4)	-4.2 (4)	0.8 (4)
C4	30.4 (7)	26.0 (6)	23.2 (6)	-5.0 (5)	-2.0 (6)	3.7 (6)
C5	30.8 (7)	24.7 (6)	25.9 (7)	-3.1 (5)	-1.1 (6)	1.2 (6)
C21	28.7 (7)	27.4 (7)	24.1 (6)	2.7 (5)	4.8 (6)	-3.5 (6)
C22	31.4 (8)	29.5 (7)	29.3 (7)	2.5 (6)	-1.6 (6)	0.0 (6)
C23	40.0 (9)	29.7 (7)	31.5 (7)	-4.0 (6)	-4.1 (7)	-2.8 (7)
C24	37.3 (9)	27.2 (7)	37.4 (7)	-3.9 (6)	6.6 (7)	0.4 (7)
C25	27.5 (7)	30.2 (7)	40.9 (8)	1.3 (6)	0.1 (7)	2.3 (7)

C26	29.9 (8)	29.7 (7)	29.5 (7)	0.0 (6)	-1.1 (6)	-3.9 (6)
C41	34.2 (8)	25.5 (7)	22.0 (6)	-2.8 (5)	-3.4 (6)	0.2 (6)
C42	43.8 (10)	30.7 (7)	40.8 (8)	0.3 (6)	7.3 (7)	5.1 (7)
C43	45.8 (10)	44.3 (9)	42.2 (8)	2.4 (7)	12.3 (8)	-1.3 (8)
C44	55.8 (11)	35.9 (8)	38.0 (8)	8.9 (7)	-1.4 (8)	-9.6 (8)
C45	55.7 (11)	27.4 (7)	46.7 (9)	6.1 (6)	-3.0 (8)	7.2 (7)
C46	39.8 (8)	33.7 (7)	34.5 (7)	-1.1 (6)	2.8 (7)	8.6 (7)
C51	30.4 (8)	24.0 (6)	22.2 (6)	-1.1 (5)	-1.8 (6)	6.9 (6)
C52	33.0 (8)	28.7 (6)	26.2 (7)	-5.1 (6)	-2.5 (6)	1.4 (6)
C53	31.7 (8)	30.1 (7)	34.6 (7)	2.7 (6)	2.3 (7)	1.0 (6)
C54	38.6 (10)	37.2 (7)	25.4 (7)	5.9 (6)	-5.3 (6)	9.6 (7)
C55	42.9 (9)	37.2 (8)	19.0 (6)	-4.1 (6)	-4.4 (6)	9.4 (7)
C56	27.6 (8)	27.4 (7)	28.9 (7)	-1.0 (5)	-4.4 (6)	3.3 (6)
B2	26.4 (8)	28.5 (8)	23.7 (7)	3.3 (6)	2.2 (6)	-4.0 (7)

Table 5.4 Bond lengths

Atoms	Length [Å]	Atoms	Length [Å]
O1-C5	1.4541 (16)	C25-C26	1.3854 (19)
O1-B2	1.3665 (18)	C41-C42	1.385 (2)
O3-C4	1.4464 (14)	C41-C46	1.3834 (19)
O3-B2	1.3654 (18)	C42-C43	1.383 (2)
C4-C5	1.5612 (18)	C43-C44	1.377 (2)
C4-C41	1.5135 (18)	C44-C45	1.375 (2)
C5-C51	1.5073 (18)	C45-C46	1.384 (2)
C21-C22	1.4004 (19)	C51-C52	1.391 (2)
C21-C26	1.394 (2)	C51-C56	1.3880 (18)
C21-B2	1.550 (2)	C52-C53	1.383 (2)
C22-C23	1.3828 (19)	C53-C54	1.385 (2)
C23-C24	1.377 (2)	C54-C55	1.378 (2)
C24-C25	1.385 (2)	C55-C56	1.3889 (19)

Table 5.5 Bond angles

Atoms	Angle [°]	Atoms	Angle [°]
B2-O1-C5	108.06 (10)	C46-C41-C42	118.36 (13)
B2-O3-C4	107.97 (10)	C43-C42-C41	120.83 (14)
O3-C4-C5	103.88 (9)	C44-C43-C42	120.05 (15)
O3-C4-C41	110.17 (10)	C45-C44-C43	119.86 (14)
C41-C4-C5	114.72 (12)	C44-C45-C46	119.89 (14)
O1-C5-C4	103.55 (9)	C41-C46-C45	121.00 (14)
O1-C5-C51	110.05 (10)	C52-C51-C5	120.13 (11)
C51-C5-C4	113.86 (12)	C56-C51-C5	120.96 (12)
C22-C21-B2	121.06 (13)	C56-C51-C52	118.89 (12)
C26-C21-C22	117.95 (12)	C53-C52-C51	120.77 (12)
C26-C21-B2	120.98 (12)	C52-C53-C54	119.80 (14)
C23-C22-C21	120.85 (13)	C55-C54-C53	120.01 (13)
C24-C23-C22	120.14 (14)	C54-C55-C56	120.22 (12)
C23-C24-C25	120.20 (13)	C51-C56-C55	120.32 (13)
C24-C25-C26	119.64 (14)	O1-B2-C21	122.82 (13)
C25-C26-C21	121.20 (13)	O3-B2-O1	113.62 (12)
C42-C41-C4	121.43 (12)	O3-B2-C21	123.55 (12)
C46-C41-C4	120.21(13)		

Table 5.6 Hydrogen atom coordinates and isotropic displacement parameters

Atom	*x*	*y*	*z*	U_{eq}
H4	3220	5657	2472	32
H5	7695	5719	3133	33
H22	4617	3463	990	36
H23	5718	2279	439	41
H24	9133	1608	882	41
H25	11501	2127	1876	39
H26	10348	3295	2453	36
H42	8771	5542	1351	46
H43	10343	6535	587	53
H44	8484	7756	579	52

H45	5091	7988	1353	52
H46	3508	6993	2113	43
H52	2412	4465	3293	35
H53	15	4302	4387	39
H54	1067	4943	5525	40
H55	4534	5728	5568	40
H56	6961	5885	4475	34