Investigation of Aminonitriles as Organocatalysts

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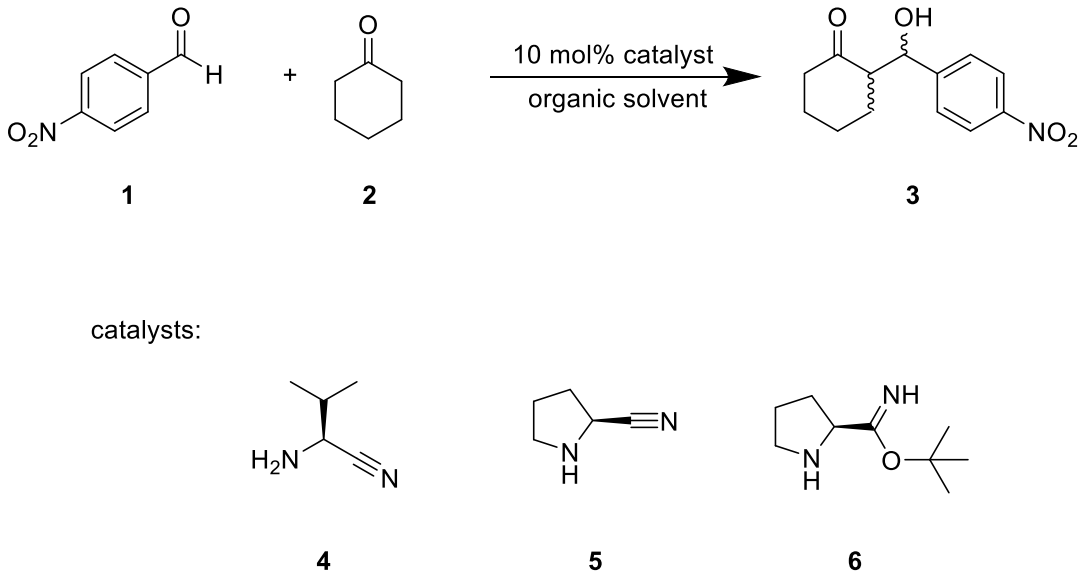
1. Abstract

This project built upon previous work with amino acid derivatives in the Clarke group. Originally, L-valine nitrile **4** and L-proline nitrile **5** were investigated for the first time as catalysts for the aldol reaction of 4-nitrobenzaldehyde **1** and cyclohexanone **2** in an array of organic solvents. Interestingly, a new proline derivative **6** was synthesised and also investigated for the first time (Scheme 1).



Scheme 1. Investigation of organocatalysed aldol reaction.

Aminonitrile **4** afforded the aldol adducts with an interesting major *syn* diastereomer but the results in terms of conversion and enantioselectivity were discouraging. Aminonitrile **5** showed a better catalytic efficiency than **4** in terms of conversion, however, the enantioselectivity was moderate. Proline imidate **6** was investigated as an organocatalyst for the first time and promising results were gained. L-Proline imidate **6** was trialled in an array of organic solvents and different aldehydes and **6** afforded the *anti* (major) aldol diastereomer in a good enantiomeric excess with up to 94% ee.

2. Contents

3. List of Figures

4. List of Schemes

5. List of Tables

6. Acknowledgments

First and foremost, I would like to thank my supervisor Dr Paul Clarke for giving me the opportunity to work on his group and on this exciting project. Throughout this year, his guidance and advice was invaluable to me. He constantly tried to get the best out of me. I would also like to thank him for proofreading my thesis several times, for being patient with my mistakes and for always pushing me towards perfection. It was a very demanding year; however, the group (PAC ladsssssssss) made it extremely fun and exciting.

I would like to thank my IPM Dr Martin Fascione, for giving timely feedback and guidance with the project during my TAP meetings, for pointing out my weaknesses and strengths, and for making me feel comfortable that I could reach him at any point during the year.

I would also like to thank Heather Fish, for her assistance with acquiring NMR and for patiently reminding me that there is a time limit per person in the NMR. I would also like to thank Karl Heaton for all the help in acquiring mass spectrometry data, and for his eagerness to find alternative methods to help me (without me asking) when some of the mass spectrometry methods failed to provide results.

This project would not have been possible without the warmth and camaraderie of the Clarke group who have made me, look forward to come back to the lab every day. I begin by thanking my mentor Giacomo Lodovici for being really patient with me over my first month, and for showing me around the department. A special and huge thank you to Dr (!!)Sam Griggs. Sammie was always there to help me since my first day in the lab. His advice and assistance cannot be overstated. He was always kind, helpful and put my work before his many times. He was always keen to answer any question I had. Sam helped me grow as a chemist and was a real role model to me. Furthermore, he proofread this thesis thoroughly and provided valuable feedback. I would also like to thank Dr Ian George. Even though I spent only 3 months in the same lab as Ian, he made me feel really comfortable since my first day. I thank Chris for helping me every time I needed help during my studies, for proofreading this thesis and for making the lab and the office such an enjoyable place to be. I sincerely do not think this year would have been the same without his presence. I thank Pavan, for always trying to help me when he saw me struggling and I hope he has an amazing time doing his PhD at the United States of America (hopefully we'll meet there at some point mate). I thank Haonan for repeatedly enquiring about the progress of my project and my life outside the lab (much appreciated mate). I thank Phil, (Br)Anna, Kirsten and Jack from Professor Dave Smith's

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Finally, I would like to thank my parents for their financial support, without which this year would simply not be possible (really thank you!) and for always believing in me, my amazing girlfriend, Maggie, for unconditionally supporting me over this year, for putting my needs before hers without hesitation and for always trying to take the pressure off me, my brother and cousin for helping me not feel nostalgic about home and their continuous moral support, and my godmother and godfather for always encouraging me to achieve my goals. They all helped me in their way, gave me the needed strength to complete this challenging year and for that I am truly grateful.

7. DECLARATION

I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text as references.

8. INTRODUCTION

8.1 Organocatalysis

Catalysis is an extremely useful area of organic chemistry and in particular, organic synthesis. The principle of catalysis is to increase the rate of a chemical reaction by the addition of a small quantity of a reagent - the catalyst – without being consumed itself. The catalyst works by forming a key intermediate between itself and one or more reactants, giving a lower activation barrier for reaction than the uncatalysed reaction, and consequently provides the reaction products faster.

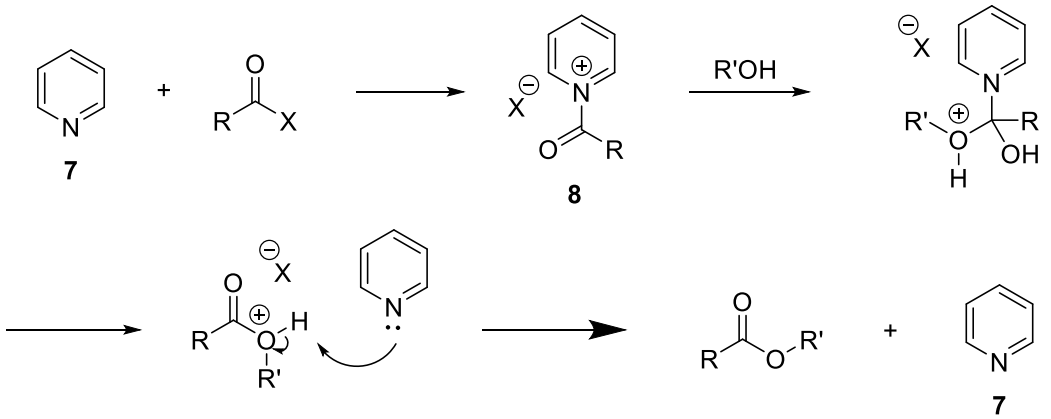
Organocatalysis is a significant and a highly dynamic area of organic chemistry. Impressively though, despite the importance and the recent research in the area, until recently the concept was not recognised.[1,2] The term refers to a form of catalysis, whereby a chemical reaction is accelerated by the addition of an organic compound which is called the organocatalyst. However, increasing the rate of a chemical reaction is not the only desired outcome. When a total synthesis of a natural product or a synthetic route towards the synthesis of a potent pharmaceutical agent is attempted, there is an imperative need for selectivity and this is one of the most important factors that chemists need to control.[3] The selectivity includes the diastereoselectivity, regioselectivity, chemoselectivity and most importantly enantioselectivity. Enantioselective synthesis or asymmetric synthesis is, as defined by the IUPAC, "the type of chemical reaction in which one or more stereogenic centres are being formed in a substrate molecule and which produces the enantiomeric or diastereoisomeric products in unequal amounts".[4] In the majority of the total synthesis of natural products projects, the asymmetric synthesis is the key and most challenging stage of the synthetic route, as it is the step which will provide the enantiopure product. It was not until the late 1990s, that organocatalysis started to be acknowledged as an individual area, as many different groups demonstrated the ability of enantiomerically pure organic molecules to catalyse enantioselective reactions.[5–10] It is now widely accepted that organocatalysis is one of the main branches of asymmetric synthesis, along with enzymatic catalysis and organometallic catalysis.[11]

Organocatalysis offers fundamental advantages compared to organometallic catalysis, namely in the cost and ease of carrying out a reaction in the laboratory.[11] First, a variety of organic compounds, such as amino acids, are naturally available from biological sources in enantiopure form. Therefore simple organocatalysts are easy to synthesise and can be accessed easily. Second, organic molecules are generally not air sensitive and in most cases no inert atmospheres or dry

solvents are required. Third, small organic molecules are typically non-toxic and environmentally friendly, compared to transition metal catalysts.[11] When an organocatalyst is chiral, an avenue is opened towards asymmetric synthesis. This is an exciting and promising field in organic synthesis. There is a need for new and effective chiral catalysts; catalysts that can undergo direct asymmetric reactions and control the formation of multiple stereogenic centres. Thus, the synthesis of enantiopure products or synthesis of complicated motifs is enabled and leads to the formation of synthetically and pharmacologically useful compounds.

8.2 History of Organocatalysis

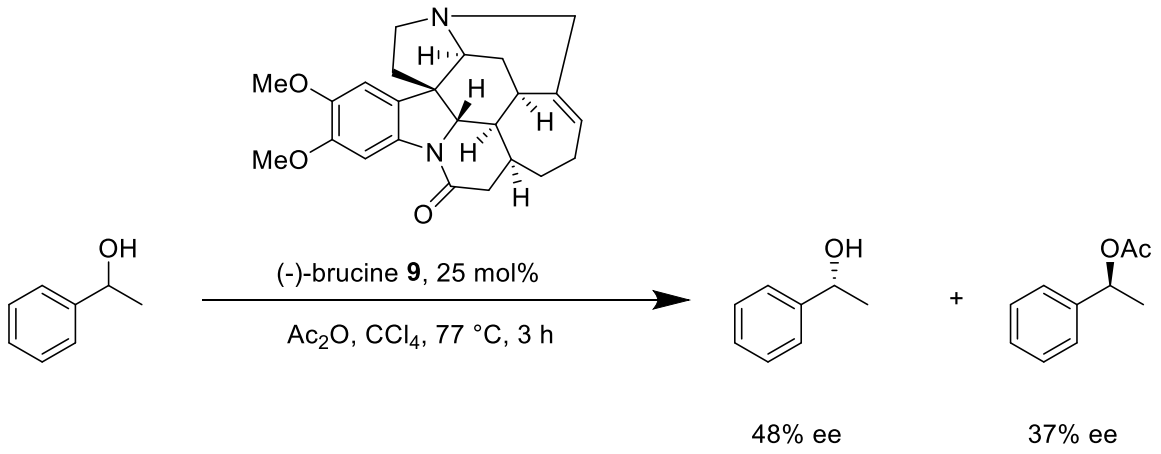
The first use of an amine as an organocatalyst can be traced back to 1898 when Einhorn and co-workers reported the use of pyridine **7** in acylation reactions.[12] Einhorn reported that the acylation of alcohols can be catalysed by pyridine in acetic anhydride, a reaction that is known as the Einhorn acylation or Einhorn reaction.[13] However, due to lack of evidence the underlying mechanism behind this reaction could not be established. It was not until the 1950's that kinetic studies were made on this reaction which tried to explain the precise role of pyridine **7** in this reaction.[14] Detailed research in this particular example over the following 10-20 years was finally able to provide a definitive answer for the role of the pyridine in the reaction (Scheme 2).[15,16] The key acylpyridinium intermediate **8** was detected spectroscopically and this encouraged more people into researching amines as organocatalysts.



Scheme 2. Proposed mechanism for the acylation of alcohols catalysed by pyridine.

It actually needed more than 50 years to prove, through mechanistic studies and spectroscopic data, the exact mechanism and how amines catalyse the reaction. Regardless though, it did not

stop pioneers to attempt and use organocatalysts for asymmetric reactions. Vavon and Peignier in 1929[17] were able to demonstrate the ability of the natural occurring amine, brucine **9** to introduce a chiral environment in the kinetic resolution of secondary alcohols (Scheme 3).

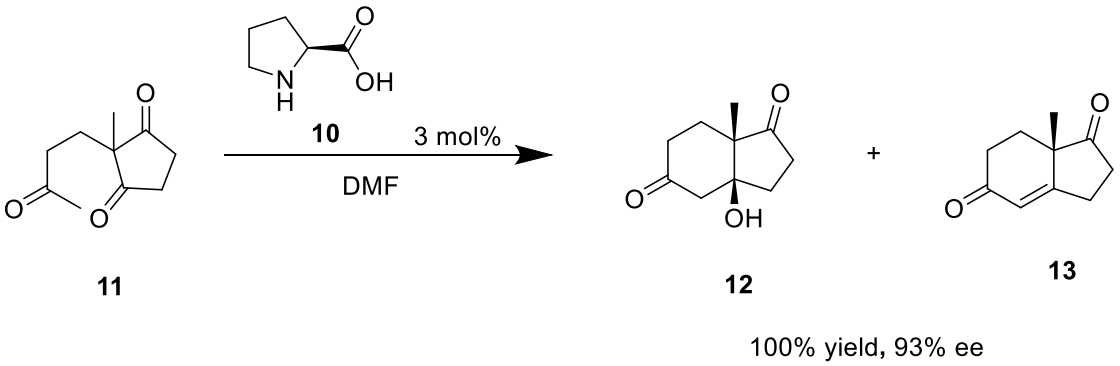


Scheme 3. Brucine **9** as an organocatalyst in the kinetic resolution of secondary alcohols.

Simultaneously, Wegler in 1930[18] used another natural occurring plant alkaloid, strychnine to induce enantioenrichement in the esterification of *meso*-dicarboxylic acids. These reactions were ground-breaking as it was the first demonstration of an asymmetric organocatalytic reaction. Moreover, they were a further indication that amines can in fact catalyse asymmetric reactions and they opened a new route for chemists.

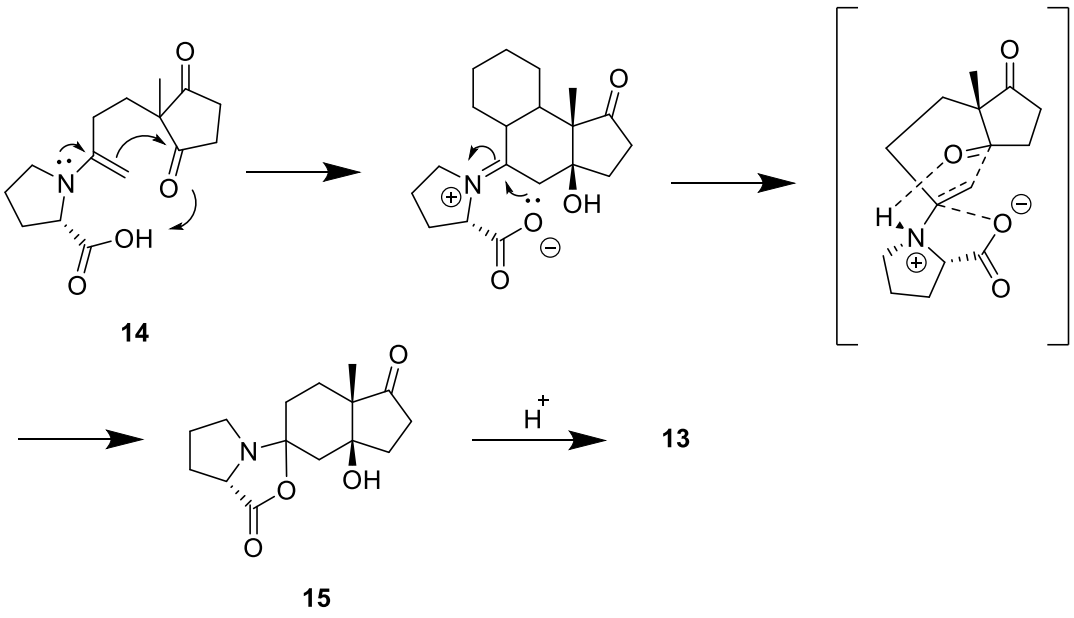
A note should be made for Wolfgang Langenbeck who in 1928 reported that amino acids or oligopeptides could catalyse organic reactions.[19] His contribution to the field is considerable as he used amino acids or small peptides to promote reactions that emulate the catalytic action of enzymes. Langenbeck also coined the term "Organic Catalysts".[20] While at the time, there was no suggested evidence that these reactions occur via an enamine mechanism, it can be deduced that this work directed future synthetic chemists in the investigation of other amino acids or amino acid derivatives.

Despite the interesting and promising results, organocatalysis did not really advance for another 40 years. The next crucial breakthrough happened in 1971 when the groups of Eder, Sauer and Weichert and Hajos and Parrish independently reported that proline **10** could catalyse the direct asymmetric aldol reaction of the triketone **11** to form the ketol **12** and the enone **13** (Scheme 4).[21,22] This reaction is now known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction, an enantioselective intramolecular aldol reaction.



Scheme 4. The Hajos-Parrish-Eder-Sauer-Weichert reaction.

In this example, the utility of the naturally occurring amino acid, L-proline **10** was demonstrated to promote the intramolecular aldol reaction to afford the ketol **12** in an excellent 100% yield and an excellent 93% enantiomeric excess. Dehydration of **12** provided the enone **13** in a 99% yield and an 88% optical purity. Moreover, this was the first reported example of proline being used in asymmetric synthesis, at ambient temperature and in catalytic quantities (3 mol%). At the time the underlying mechanism for this reaction was not yet established so Hajos and Parrish tried to provide a rational explanation on the mechanism. Initially, it was thought that the reaction was proceeding through an enamine intermediate, which would be expected based on previous suggested evidence (Scheme 5).[23]



Scheme 5. Proposed enamine based mechanism for the Hajos-Parrish-Eder-Sauer-Weichert reaction.

It was postulated that the nucleophilic L-proline **10** attacks the carbonyl on the side chain in the triketone **11** to form the active enamine intermediate **14**. Considering this possible reaction pathway, supporting data was sought to justify this theory using labelled ^{18}O water and mass spectroscopic analyses. This mechanism was discounted as it was not possible to detect the ^{18}O labelled installed in the optically active product **13**, which was a pre-requisite of this mechanism due to the hydrolysis of the oxazolidinone ring **15**. Being unsatisfied by this explanation, an alternative possible mechanism was proposed, in which proline attacks, in its zwitterionic form, one of the two carbonyls in the cyclopentanedione ring (Figure 1).

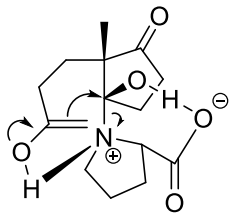
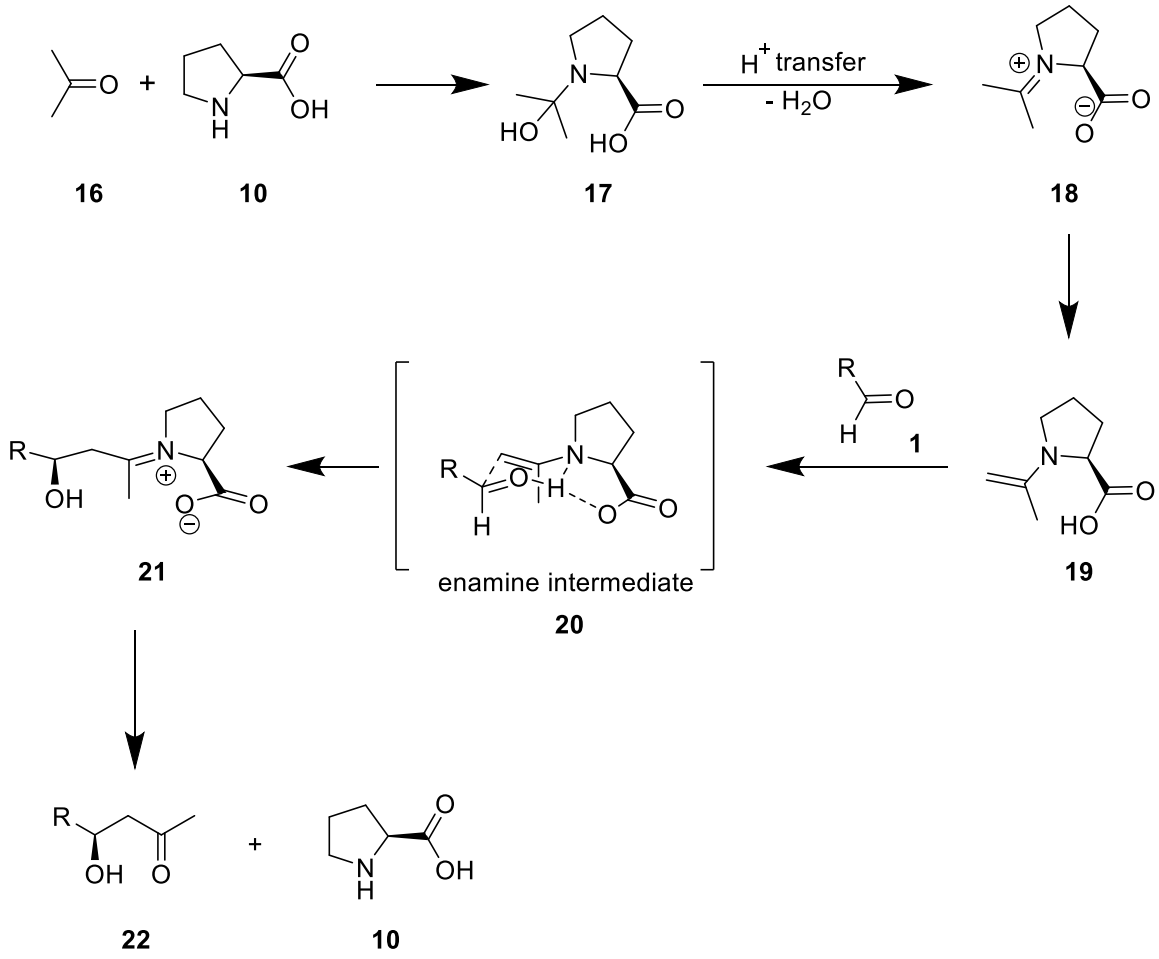


Figure 1. Second proposed intermediate for the Hajos-Parrish-Eder-Sauer-Weichert reaction.

It was illustrated that the second mechanism provides a satisfactory explanation for the excellent enantiomeric excess. In the proposed intermediate in the second reaction, the chiral centre of the catalyst is 3 bonds away from the methyl group and only 2 bonds away from the new stereocentre that is being formed in the product. Whereas, in the enamine intermediate these bond distances are 5 and 4 respectively. Furthermore, the oxygen in the side chain of the triketone **11** and the proton of the proline **10** provide the necessary hydrogen bonding in the intermediate to favour the correct conformation. Thus, the observed stereochemistry of the product is being justified.

In doing this research and reporting this example Hajos and Parrish managed to provide a better understanding of the underlying chemistry in this relatively new area. Many different chiral auxiliaries were examined in the aldol reaction and the conclusion was that secondary amines or compounds with another functional group provide better results. The ability of compounds to facilitate the aldol reaction was attributed to the protons in their structure. It was understood that by involving a proton in the structure, the catalyst enables hydrogen bonding between itself and the substrate thus directing the addition selectively.

In spite of these intriguing results and the clear advantages of using small organic molecules as catalysts, the field of organocatalysis did not have a significant breakthrough until 2000. This saw two truly elegant and innovative publications that paved the way for the exponential growth of this field. The two papers were published almost simultaneously, one by Barbas III, Lerner and List in the field of enamine catalysis,[24,25] and the other one from MacMillan's group, in iminium catalysis.[26] Barbas, Lerner and List are considered to be true pioneers in organocatalysis as their work was crucial in the enlightenment of the enamine mechanism for organocatalytic aldol reactions. The research highlights the reaction of acetone **16** with 4-nitrobenzaldehyde **1** using 30 mol% of L-proline **10** in DMSO with a good 66% yield and a good 76% enantiomeric excess for the *anti* product. The reaction was proposed to proceed through the enamine intermediate **15** (Scheme 6).

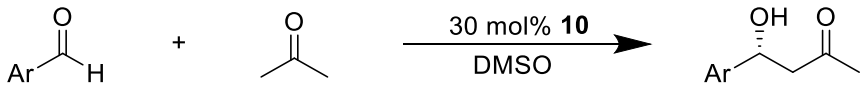


Scheme 6. Enamine mechanism for the direct asymmetric aldol reaction catalysed by L-proline.

In this example, the dual functionality of proline is exemplified. It was presumed that the carboxylate group initiates each individual step of the mechanism. Initially, the nucleophilic nitrogen of the proline **10** attacks the ketone **16** to form the intermediate **17** and then the carboxylate group dehydrates the intermediate **17** to form the imine **18**, a step which is followed

by enamine tautomerisation **19.** The next step is the critical part of the mechanism as it is the step which directs the addition and provides the enantioselectivity. The nucleophilic enamine bond attacks the aldehyde **1**, which is hydrogen bonded to the carboxylate group of **19** and leads to the carbon-carbon bond formation step **20**. The enantioselectivity is being achieved by the tricyclic hydrogen bonded framework in the intermediate **20**. Finally, the carboxylate group hydrolyses the iminium intermediate **21**, to provide the aldol adduct **22** and the free catalyst **10** which can undergo the same catalytic cycle again.

Table 1. Representative examples of the aldehydes used in the aldol reaction catalysed by **10**.

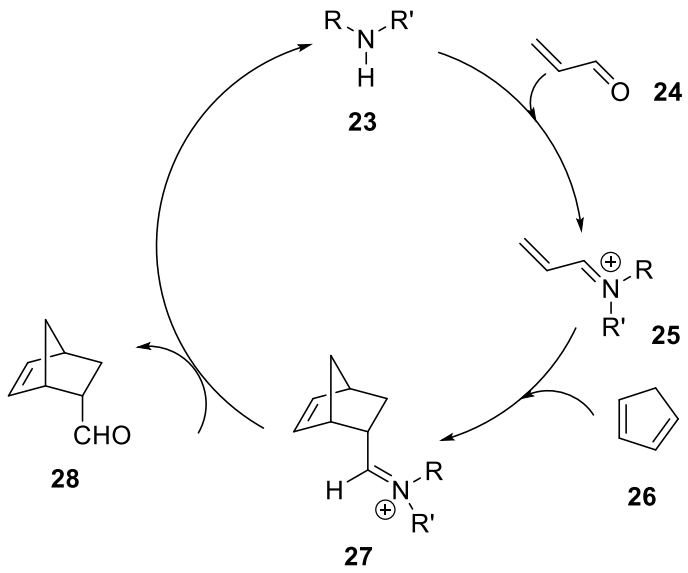


Aldehyde	Yield	Product ee
4-nitrobenzaldehyde	68%	76%
benzaldehyde	62%	60%
2-chlorobenzaldehyde	94%	69%

Reaction conditions: Proline (0.03-0.04 mmol) was stirred in 1 mL of DMSO/ acetone (4:1) for 15 minutes. The aldehyde (0.1 mmol) was added and the mixture was stirred for 4-24 hours.

The similar results obtained demonstrated the utility of the proline catalyst in the direct asymmetric aldol reaction. The importance of this paper is that it was the first example of a small organic molecule being used as a general catalyst. Proline is inexpensive and readily available in either enantiomeric form; therefore, it can be easily employed by synthetic chemists. The reaction required mild conditions: run at room temperature, without an inert atmosphere, and proline is non-toxic. Moreover, proline is water soluble and therefore can be easily removed with aqueous extractions. The authors envisaged that this enantioselective asymmetric aldol reaction using proline as organocatalyst was a novel reaction and could be further investigated by possibly employing new, modified organocatalysts.

Contemporaneously, MacMillan was the first to report an enantioselective Diels-Alder reaction using chiral organocatalysts. It was thought that the reaction was more likely to be occurring via an iminium ion intermediate (Scheme 7).

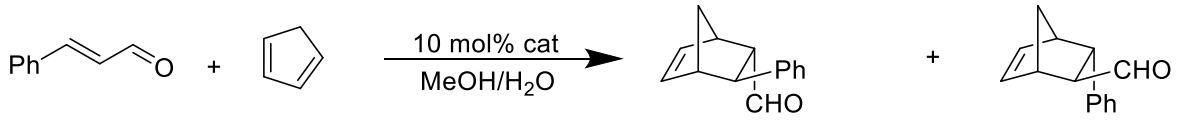


Scheme 7. Diels-Alder cycloaddition catalysed by chiral secondary amines.

It was hypothesised that the nucleophilic nitrogen of the enantiopure amine **23** would react with the carbonyl of the aldehyde (dienophile substrate) **24** and form the iminium **25**. Iminium **25** would then be able to participate in a Diels-Alder cycloaddition with the appropriate diene **26** and form the cycloadduct iminium ion **27**. Finally, upon hydrolysis, the enantiopure Diels-Alder product **28** would be liberated and accordingly the catalyst **23** would engage again in the cycle.

To test the hypothesis, MacMillan and co-workers tested various secondary amines as catalysts, primarily in the reaction of cyclopentadiene **26** with (*E*)-cinnamaldehyde **29** (Table 2). Using enantiopure *S*-proline ester (Table 2, Entry 1) *endo* **30** and *exo* **30** were obtained in a good 81% yield, with a 2.7:1 *exo*:*endo* diastereoselectivity and a moderate 48% enantiomeric excess for the *exo* product. *S*-abrine-methyl ester (Table 2, Entry 2), provided the Diels-Alder adducts in an 80% yield, with a 2.3:1 *exo*:*endo* diastereoselectivity and a moderate 59% enantiomeric excess for the *exo* product.

Table 2. Organocatalysed Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene.

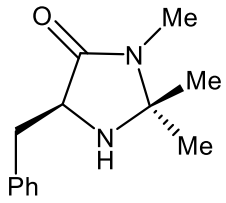


29 **26** **endo 30** **exo 30**

Entry	Catalyst	Time (h)	Yield	*exo*/*endo*	*exo* ee[a]
1	S-proline ester	27	81%	2.7:1	48%
2	S-abrine-methyl-ester	10	80%	2.3:1	59%
3	**26**	8	99%	1.3:1	93%

a) Product ratios determined by GLC analysis

Importantly, it was observed that when the catalyst was modified with the introduction of steric constraints (Table 2, Entry 3), the results exceeded expectations. Specifically, catalyst **31** (Figure 2) afforded the Diels-Alder cycloadduct in an excellent 99% yield and a medium 1.3:1 *exo*:*endo* diastereoselectivity. Crucially, it flourished the product in an excellent 93% ee for the *exo* isomer.

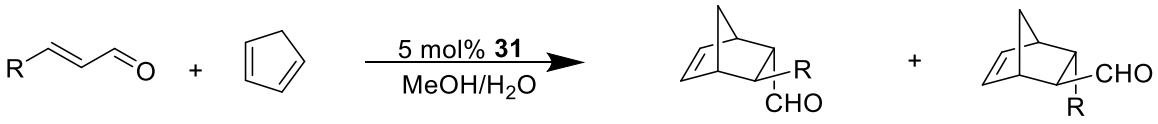


31

Figure 2. The chiral imidazolidinone catalyst **31** that provided the highest enantioenrichement.

Building upon this result, the catalytic ability of the MacMillan's catalyst **31** with other substrates was examined. The variation of the dienophile with more sterically demanding substituents or aromatic rings did not affect the enantioselectivity of the reaction (Table 3). Furthermore, the reaction was scaled to 50 mmol of starting material and afforded 12 g of the enantiopure product.

Table 3. Diels-Alder reaction between cyclopentadiene and representative dienophiles.

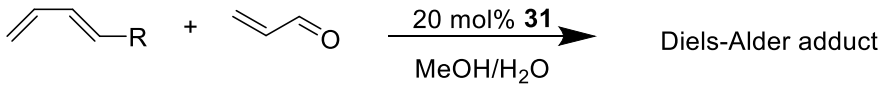


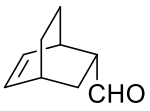
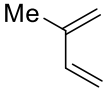
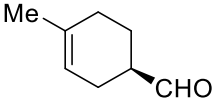
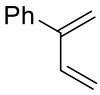
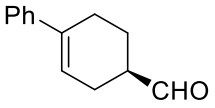
Entry	R	Time (h)	Yield	*exo*/*endo*	*exo* ee[a]	*endo* ee
1	Me	16	75%	1:1	86%	90%
2	*i*-Pr	14	92%	1:1	86%	90%
3	Ph	21	99%	1.3:1	93%	93%

a) Product ratios determined by GLC analysis

Following the successful screening of various dienophiles, it was decided to test how different dienes would affect the reaction. It was shown that the reaction was tolerant of the dienes used (Table 4).

Table 4. Diels-Alder reaction between acrolein and representative dienes.



Entry	Diene	Product	Yield	*exo/endo*	*exo* ee[a]
1			82%	1:14	94%
2			84%	-	89%
3			90%	-	83%

a) Product ratios determined by GLC analysis

It is important to note that in this case, similarly to the report of proline as an organocatalyst, the reactions were carried out without an inert atmosphere and using wet solvents. This highlighted one of the main advantages of organocatalysts.

It is not a hyperbole to say that the two publications revolutionised the discipline of organic synthesis and practically established the field of organocatalysis. In 1995 there were no reports of an organocatalyst and before 2000, there were just a few publications using organocatalysts. This number increased exponentially since the publication of the examples of proline and MacMillan's catalyst **26.** In 2011 there were more than 1200 publications of organocatalysis, and in parallel, the number of citations increased to 40,000.[27]

Compelled by those fascinating results, in 2002 MacMillan and co-workers reported the first enantioselective cross-aldol reaction of aldehydes using L-proline **10** as the promoter.[28] This was a pivotal report as for the first time; ketones were not used as an aldol donor. In doing so, MacMillan and co-workers demonstrated that two aldehydes with different substituents could participate in the cross-aldol reaction in the presence of proline by effectively avoiding homodimerisation.

The low price and the enantiopure availability of proline combined with the effectiveness it shown in the aldol reaction rendered it one of the most attractive molecules to study. In the 2000's, many groups around the world turned their attention to proline and attempted to modify the compound in order to search for new potent chiral promoters. Although the use of the naturally occurring amino acids in the asymmetric synthesis was easier and preferable, sometimes their use can be restricted by factors like the formation of undesired side products or moderate selectivity.[29] Such side products are covalent intermediates between the amino acid and the ketone substrate. In 2004 List and co-workers were able to detect and characterise oxazolidinones that were formed in reversible equilibrium between simple ketones and *S*-proline.[30] Therefore, to overcome such obstacles, synthetic chemists were trying to install simple and efficient modifications to amino acids in search for new and improved organocatalysts, based mainly on the principles of the enamine and iminium catalysis.[11]

8.3 Amino Acid Derived Enamine Catalysis

In 2001 Barbas and co-workers published a second report on the investigation of chiral amino acids as potent organocatalysts in the direct asymmetric aldol reaction.[31] The publication was focused on the development of the organocatalysis. It was tried to see whether amino acids with distinctively different moieties could show a similar reactivity, by copying the exact same reaction conditions as before (Scheme 8).

1 **16** <10% yield **22**

catalysts:

32 **33**

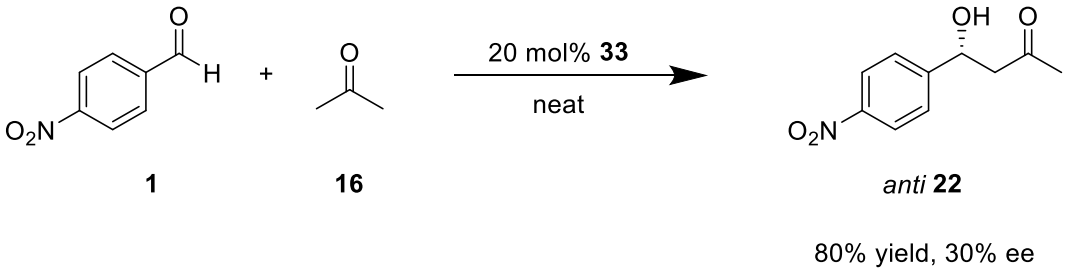
Scheme 8. Investigation of other amino acid derivatives in the asymmetric aldol reaction.

It was discovered that *N*-methyl-L-valine **32** and L-prolinamide **33** afforded the aldol adducts in low yields (< 10% yield). Interpretation of these results brought a new light to the underlying enamine mechanism. It was concluded that in proline, the cyclic moiety was crucial to the reaction and the acidic proton of the carboxylate in the correct spatial proximity was essential for the reaction.

When Barbas and co-workers explored the catalytic ability of **32** and **33**, the standard aldol conditions were replicated i.e. 20 mol% of **32** or **33** in 4:1 DMSO/acetone (Table 1). It was shown that **32** and **33** could not effectively catalyse the reaction of acetone **16** with 4-nitrobenzaldehyde **1** in DMSO.

In 2004, Zhuo Tang *et al* investigated many modified proline derivatives in search for new novel organocatalysts.[32] The initial thought was to replace the carboxylate group of proline with another functional group able to provide the necessary hydrogen bonding framework in the enamine intermediate. Understanding the importance of the acidic proton in the carboxylate group in proline it was decided to transform L-proline **10** to L-prolinamide **33** (Scheme 8).

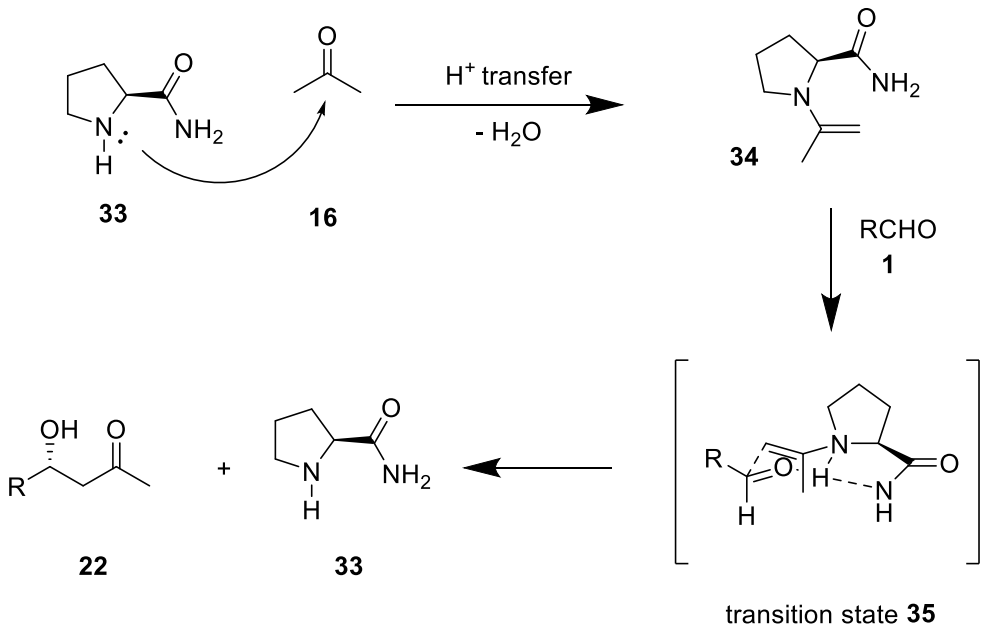
Bearing in mind Barbas's report in 2001, it was decided to replicate the reaction conditions in Scheme 8 without a solvent. It was postulated whether the absence of an organic solvent was an essential variable for the reaction. Initially the reaction of 4-nitrobenzaldehyde **1** and acetone **16** using 20 mol% of L-prolinamide **33** in no solvent was investigated (Scheme 9).



Scheme 9. Direct aldol reaction of 4-nitrobenzaldehyde with acetone using 20 mol% of L-prolinamide at RT.

The absence of an organic solvent was proved to be crucial for the reaction. The *anti* aldol adduct **22** was obtained in an 80% yield and a 30% ee.

The prolinamide catalyst **33** works in a similar way to proline (Scheme 10).



Scheme 10. Direct aldol reaction of 4-nitrobenzaldehyde with acetone catalysed by L-prolinamide via an enamine transition state.

The nucleophilic nitrogen of the pyrrolidine structure attacks the electrophilic carbonyl of the ketone **16** and forms the active enamine intermediate **34**. The transition state **35** explains the stereoselectivity as the proton of the amide group is directing the addition of the aldehyde from the top face. The formation of the hydrogen bonds between the proton of the amide, the nitrogen of the amine and the oxygen in the aldehyde provides the enantioenrichement in the reaction.

The enantioenrichement of this reaction was only 30% ee for the *anti* product; however, it was the first illustration of the L-prolinamide **33** as an organocatalyst in the direct aldol reaction. The successful outcome of the first aldol reaction prompted the researchers to try more modifications and test various secondary amides as catalysts. Initially, it was decided to install bulky substituents in the amide to try control the selectivity of the reaction. Some of the catalysts employed are shown below (Figure 3).

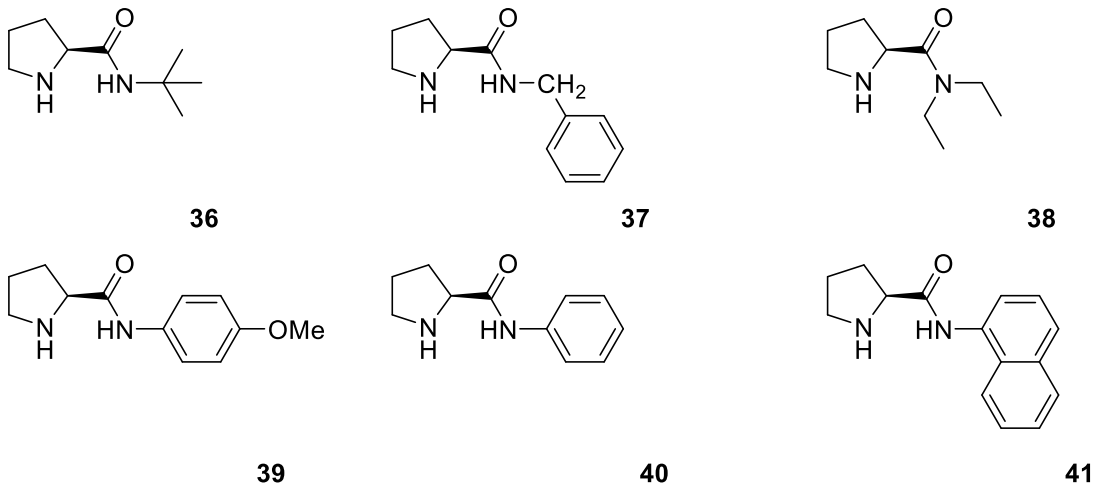
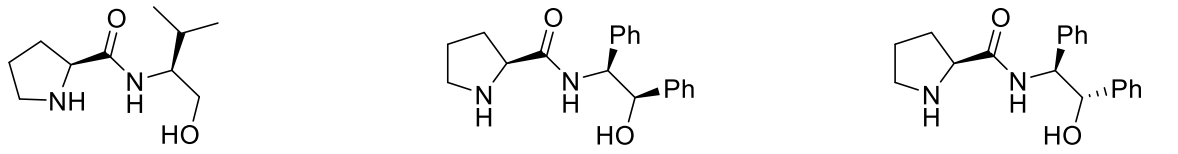


Figure 3. Secondary amides investigated in the aldol reaction of 4-nitrobenzaldehyde with acetone.

Catalysts in Figure 3 showed a strong catalytic efficiency. Catalyst **36** afforded the aldol adducts in the lowest 55% yield and catalyst **40** provided the product in the highest 88% yield**.** However, the enantioselectivity was consistently moderate. Catalyst **41** afforded the aldol products in a 46% ee for the *anti* product; the highest enantiomeric excess among the catalysts screened. Interestingly, catalyst **38** produced the aldol adduct in a poor 18% ee for the *anti* product. The low enantioselectivity of compound **38** was attributed to the absence of a proton in the amide. Due to the lack of proton, **38** was not able to form hydrogen bonds in the transition state. Thus the low enantiomeric excess obtained was explained and simultaneously, the importance of the proton in amides was highlighted.

Crucially, the importance of the acidic proton in the carboxylate group of the proline catalyst was further reinforced by this study. The authors attributed the poor enantioselectivity of the reactions to the very weak hydrogen bonding that is being formed between the proton of the amides and the aldehyde.

Based on the results, it was predicted that the installation of a terminal hydroxyl group in the amide could achieve a substantial increase in the selectivity of the reaction. The premise was that the terminal hydroxyl group could provide an extra source of hydrogen bonding thus improving the conversion and the enantioselectivity of the reaction. Representative examples of the catalysts employed are shown below in Figure 4.



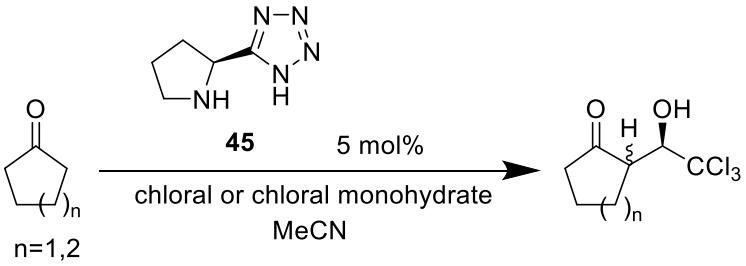
42 **43** **44**

Figure 4. Secondary amides with a terminal hydroxyl group as organocatalysts.

Satisfyingly, this hypothesis was proved correct. The hydroxyl prolinamide catalysts showed an increase in selectivity. Specifically, the yields were considerably higher ranging from 63-90% and concurrently an improved enantioenrichement was observed. The highest enantioselectivity was achieved using catalyst **44** and was 69% ee for the *anti* product. This promising result drew further attention on amide **44**. Initially, the reaction was repeated at a lower temperature in an attempt to achieve greater enantioselectivity. Gratifyingly, the assumption was correct as when the reaction was carried out at -25 °C an excellent 93% ee for the *anti* product was observed albeit in a lower 66% yield. Different aldehydes were trialled with the prolinamide catalyst **44** and consistently similar results were observed. This elegant work suggested further evidence on the importance of the carboxylate group of proline and the level of acidity in the proton of the hydroxyl group in the catalyst.

The modification of proline became an interesting and challenging research area after 2000. Many groups around the world started introducing different R groups in the carboxylate of proline, always having the principle of the acidic proton in mind. In 2004 Torii *et al* reported an outstanding example of tetrazole **45** (Scheme 11), another proline derivative.

Tetrazole **45** was used in catalytic quantities (5 mol%) as an organocatalyst to promote the direct aldol reaction of various ketones in a solution of chloral or chloral monohydrate in MeCN (Scheme 11).[33]



Scheme 11. Direct aldol reaction of chloral or chloral monohydrate with various ketones in the presence of catalyst **45**.

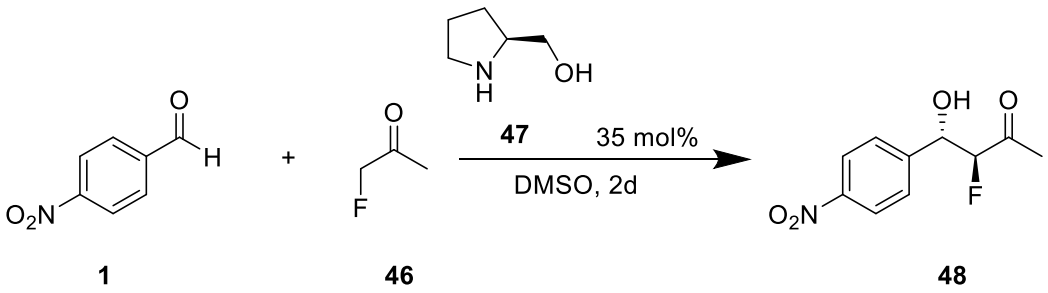
Initially, the reaction was performed in the presence of chloral in MeCN and without an inert atmosphere. However, preliminary results were considerably poor (less than 1% conversion after 60 hours of stirring). In contrast, upon the addition of water, the reaction rate was accelerated significantly with an 85% yield, an 80% de and an 84% ee after 50 h of stirring. Unexpectedly the major product of this reaction was the *syn* isomer. It was noticed that the increase in the amount of water in the reaction led to considerably improved results. When the amount of water was increased to 200 mol% and 500 mol% the enantioselectivity of the reaction was increased to 92% *syn* ee and 94% *syn* ee respectively albeit the diastereoselectivity was decreased to 67% and 52%. Similarly, when chloral was replaced with chloral monohydrate the reaction proceeded in the same efficiency affording the aldol product in an 83% yield and a 76% de and an 82% *syn* ee.

In order to understand the mechanism of the reaction kinetic studies were performed. Kinetic studies suggested that water was crucial for the initiation and acceleration of the reaction. Initially, it was believed that water would affect the reaction by shifting the aldehyde-iminium ion equilibrium towards the aldehyde. Surprisingly, no imine peaks were detected in the ^{1}H NMR spectrum during the reaction. Therefore, it was concluded that water, and the chloral monohydrate were critical for this catalysis.

Further evidence for this hypothesis was that in presence of simple chloral and **45** no reaction took place. However, the *syn* selectivity of the catalyst could not be justified. Catalyst **45** was later studied extensively and showed extraordinary reactivity with similar results in the Mannich and Michael reaction, proving the broad scope of the organocatalysts.[34]

In 2004 Barbas and co-workers reported the first example of an amino alcohol (Scheme 12) being used as an organocatalyst in the catalytic asymmetric aldol reaction.[35] The reaction between 4-

nitrobenzaldehyde **1** and fluoroacetone **46** mediated by prolinol **47** in DMSO was cited in this report.



Scheme 12. Aldol reaction of 4-nitrobenzaldehyde and fluoroacetone catalysed by L-prolinol.

The reason behind the choice of fluorine substituted ketone was the pharmacological activity of fluorine which was at the time being exploited by replacing hydroxy groups with fluorine atoms in drug molecules.[35] Originally, the reaction was performed using L-proline **10**, the amino acid with the most promising results based on previous studies. Surprisingly, the reactions were not effective, as the yields and enantioselectivities were considerably lower. Due to the unpredictable result of proline, attention was turned to other easily accessible molecules. Amino alcohol **47** was the catalyst with the best results. After employing the catalyst in a solution of 4-nitrobenzaldehyde **1** and fluoroacetone **46** in DMSO at RT for two days, the fluoroaldol adduct **48** was obtained in a good 82% yield. More importantly, the product was obtained in a 7:3 *anti*/*syn* diastereoselectivity and an excellent 94% regioselectivity. Moreover, the enantioselectivity for the major product (*anti*) was determined to be 84% ee. Gratifyingly, the results were reproduced with different aldehydes. The observed enantioselectivity can be justified with the enamine intermediate state which adopts the pseudo-chair conformation thus blocking the top face of the aldol addition (Figure 5).

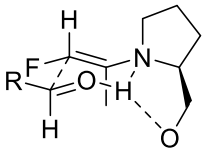
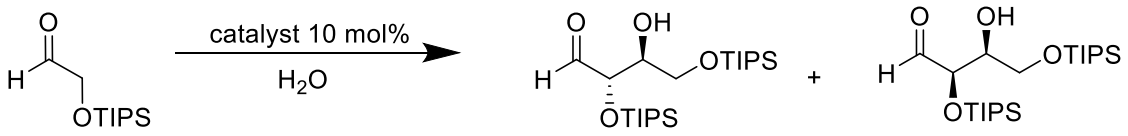


Figure 5. Proposed transition state of the L-prolinol catalysed aldol reaction.

In the next few years reports of organocatalytic asymmetric synthesis were multiplied. A field that was being overlooked for decades was now accepted and embraced collectively by all groups around the world. The community of synthetic chemists is unambiguously now recognizing the importance of organocatalysis and organocatalysts are now part of every synthetic chemist's toolbox, as the field is currently experiencing its "golden age".[36] Comprehensive research has been made since 2000 on the ability of small organic molecules to catalyse other reactions than the aldol reaction. This proved to be another vital advantage of organocatalysts. Proline, proline's derivatives or other simple and easily accessed organocatalysts have been reported to catalyse a scope of different reactions, including Mannich and Michael reaction and oxygenations.[37]

8.4 Aim of the project

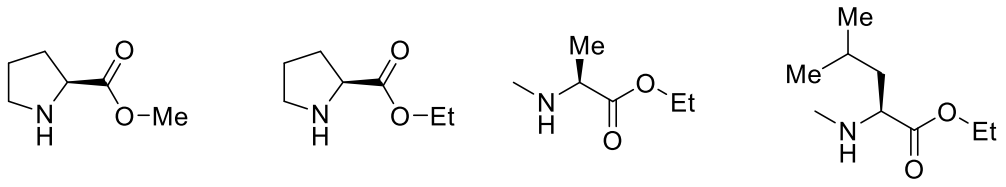
The Clarke group has an interest in the investigation of the Origins of Life. It is believed that life begun on Earth approximately 3.5 million years ago. This statement argues that the essential chemical molecules that define life must have been present and able to react at that time. The group attempts to apply synthetic techniques to form compounds that are known to be the essential building blocks of life. In principle, the group is interested in investigating amino acid derivatives as organocatalysts, ideally, in the absence of organic solvents, thus reinforcing the plausible prebiotic conditions. In 2010 Clarke and co-workers reported that amino esters, derivatives of naturally occurring (L)-amino acids can catalyse the formation of erythrose **50** and threose **51** from TIPS-glycolaldehyde **49** under aqueous media in an impressive 80% yield and 79% ee (Scheme 13).[38,39]



49 **50** **51**

up to 80% yield and up to 79% ee

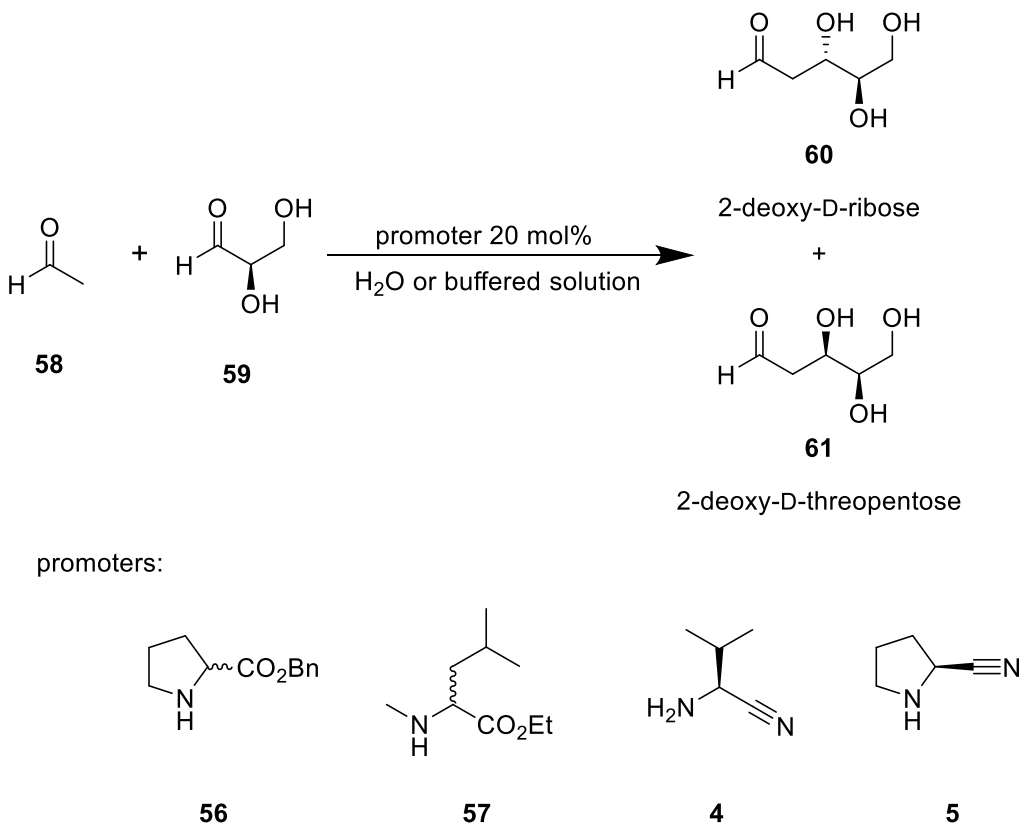
catalysts:



52 **53** **54** **55**

Scheme 13. Enantioselective formation of erythrose and threose.

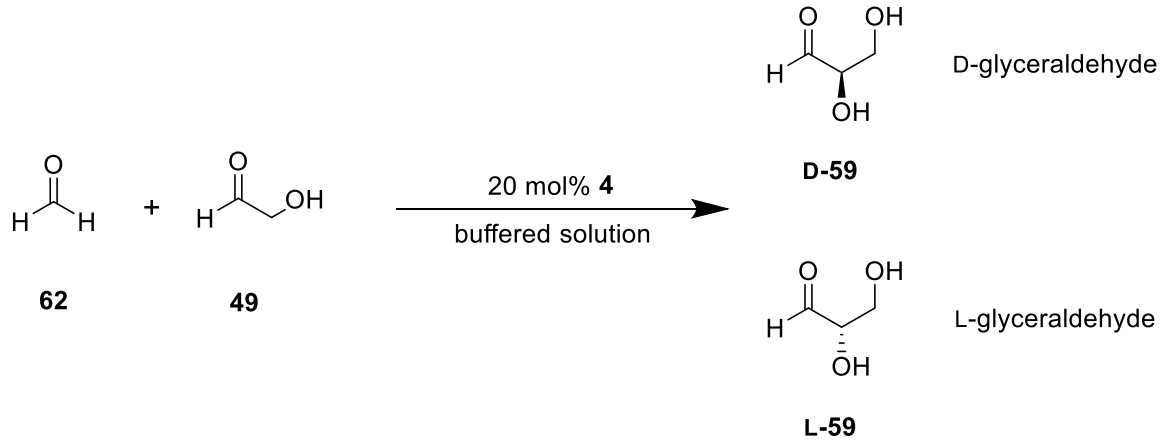
Since the report of Clarke in 2010, the group has continued to investigate amino esters to utilise them as catalysts in the synthesis of more complex carbohydrates. In 2017, Clarke and co-workers reported the stereoselective synthesis of 2-deoxy-D-ribose **60** over its diastereoisomer 2-deoxy-D-threopentose **61** by employing amino esters or aminonitriles as catalysts.[40] In this paper, the ability of amino esters and aminonitriles to catalyse the reaction of acetaldehyde **58** and D-glyceraldehyde **59** was highlighted. The product, 2-deoxy-D-ribose, was diastereoselectively formed under the reaction conditions (Scheme 14).



Scheme 14. Prebiotic formation of 2-deoxy-D-ribose using L-amino esters and L-amino nitriles as catalysts.

The reasoning behind the choice of aminonitriles was two-fold. There is still debate about the prebiotic nature of amino esters. In order to address this argument, it was postulated to broaden the research into including more feasible promoters. To do so, the attention was turned from amino esters to aminonitriles, precursors of amino acids as demonstrated in 2015 by the elegant work of Sutherland and co-workers.[41] In this report Sutherland described a network, starting from HCN and ultimately leading to RNA. Concurrently, it was shown that aminonitriles, along with acetaldehyde **58**, glycolaldehyde **49** and glyceraldehyde **59**, are formed under prebiotic conditions.

It was shown that aminonitriles can promote the enantioselective reaction of formaldehyde **62** and glycolaldehyde **49** to afford D-glyceraldehyde **59** with up to 6% ee (Scheme 15) and its subsequent conversion to 2-deoxy-D-ribose **60** under potentially prebiotic conditions.

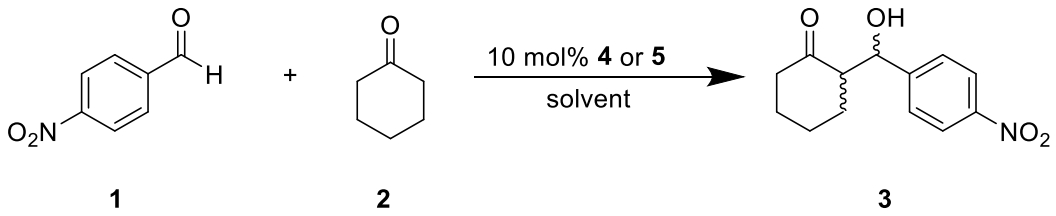


Scheme 15. *In situ* formation of glyceraldehyde with 6% ee using L-valine nitrile as catalyst.

The importance of this report was that aminonitriles are plausible prebiotic promoters and they were able to catalyse the aldol reaction to afford the 2-deoxy-D-ribose in a simple two-step synthesis. The reactions were performed in water or buffered solution thus mimicking the conditions proposed for the early Earth. Most importantly this was the first report in the literature of aminonitriles being used as organocatalysts. However, since the aim of this project was to investigate the formation of 2-deoxy-D-ribose under potentially prebiotic conditions, no reactions were carried out in an organic solvent. Therefore, the general catalytic ability of aminonitriles was still unknown.

The aminonitriles that were examined in this project are two amino acid derivatives. More specifically, L-valine nitrile **4** and L-proline nitrile **5** were investigated.

Initially, it was decided to investigate a reaction that was known to proceed under mild conditions and was extensively examined in the past. Therefore, it was agreed to investigate the aldol reaction of 4-nitrobenzaldehyde **1** and cyclohexanone **2** using 10 mol% of catalyst and screen various organic solvents (Scheme 16).

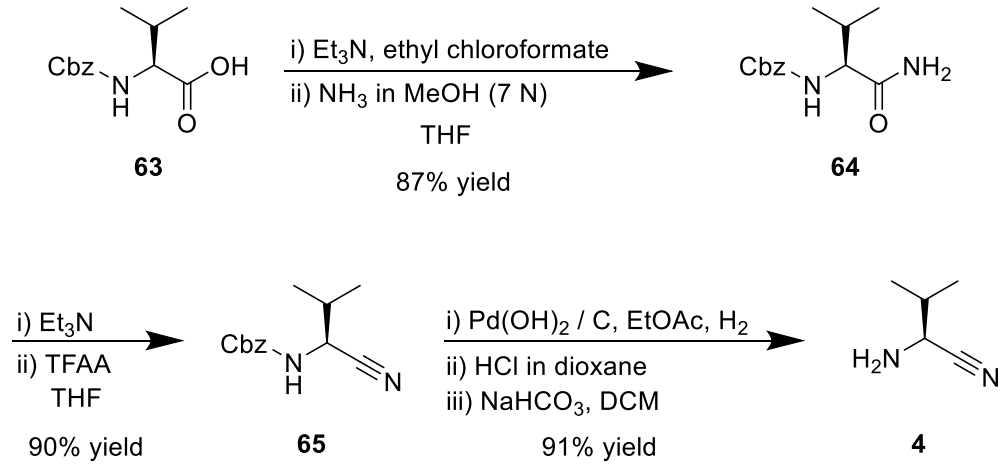


Scheme 16. Use of aminonitriles in aldol reaction in organic solvents.

9. Results and Discussion

9.1 Synthesis of L-valine nitrile

One of the advantages of organocatalysts is their ready availability and easy accessibility from the chiral pool. The Clarke group has previously developed a concise and efficient 3-step synthetic route to access the desired aminonitriles from amino acids.[40] The first task of the project was to synthesise the two potential catalysts for the investigation of their catalytic ability. The Cbz-protected valine **63** was commercially available in an enantiopure form. The synthesis of the catalyst required the transformation of the protected amino acid **63** to the amide **64** (Scheme 17).



Scheme 17. Concise 3-step synthesis of L-valine nitrile.

Cbz-protected valine **63** was treated with Et_3N and ethyl chloroformate to form the mixed anhydride. To this was added NH_3 in MeOH to give the desired protected amide **64** in a good 87% yield, which did not require purification. The second step was the dehydration of the Cbz-L-valine amide **64** to the protected aminonitrile **65**. This was achieved by treatment of the amide with trifluoroacetic anhydride (TFAA) which formed the Cbz-protected aminonitrile in a good 90% yield after purification by column chromatography. Finally, the aminonitrile was revealed by a hydrogenation of the Cbz-protecting group using Pearlman's catalyst ($Pd(OH)_2$ on carbon) under a hydrogen atmosphere. Due to the observed high volatility of the catalyst[42] the aminonitrile could not be obtained through evaporation of the solvent. Alternatively, a solution of HCl in dioxane (4 M) was added in order to form the HCl salt of the valine nitrile. The free amine was liberated by dissolving the salt in DCM and stirring over sodium bicarbonate before filtering. This generated the

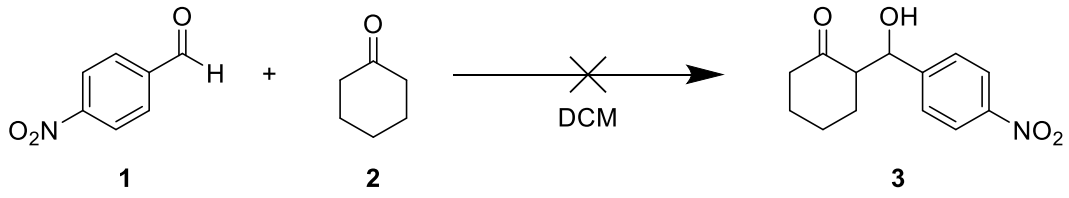
target aminonitrile **4** in a high 91% yield. Throughout each step, the optical purities of the compounds were regularly measured and compared to the literature values to confirm that racemisation had not occurred (Table 5). The preparation of the catalyst was carried out on a gram scale.

Table 5. Optical rotation values of compounds **64**, **65** and **4**, compared to literature values.

Compound	**$[\alpha]_D^{20}$ (deg cm^{-3} g^{-1} dm^{-1})**	**Literature $[\alpha]_D^{25}$ (deg cm^{-3} g^{-1} dm^{-1})**[40]	**Concentration**	**Literature Concentration**
64	+24.7	+25	1.0 g cm^{-3} in DMF	1.0 g cm^{-3} in DMF
65	-43.07	-37.3	1.0 g cm^{-3} in MeOH	0.97 g cm^{-3} in MeOH
4	-6.37	-8.3	1.0 g cm^{-3} in DCM	0.83 g cm^{-3} in DCM

Having the first catalyst ready, the screening of the first aldol reaction was ready to be attempted.

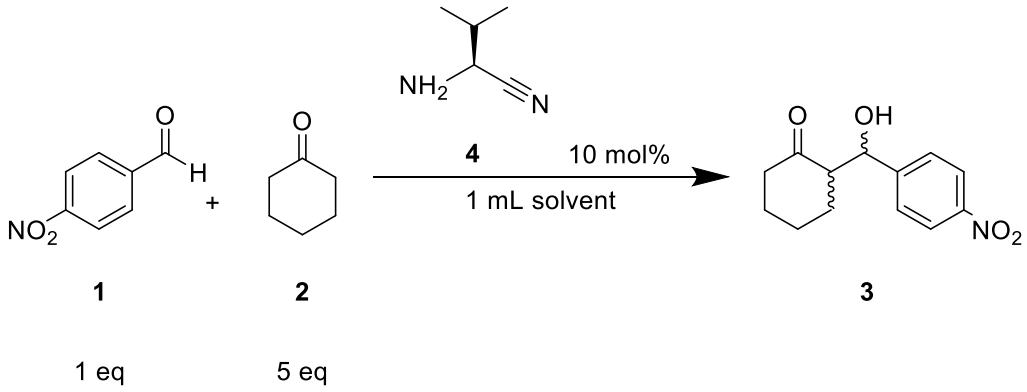
Prior to the first catalysed aldol reaction, a control reaction was needed to be performed. An uncatalysed reaction between 4-nitrobenzaldehyde **1** and cyclohexanone **2**, in DCM was carried out to ensure that no reaction took place without a catalyst. The control reaction was stirred for 24 hours at room temperature with 1 equivalent of 4-nitrobenzaldehyde **1** (0.25 mmol), 5 equivalents of cyclohexanone **2** (1.25 mmol) in 1 mL of DCM (Scheme 18). Unsurprisingly, no product was formed.



Scheme 18. Control reaction of 4-nitrobenzaldehyde and cyclohexanone in DCM.

9.2 Aldol reaction catalysed by L-valine nitrile

The aldol reaction between 4-nitrobenzaldehyde **1** and cyclohexanone **2** in the presence of L-valine nitrile **4** in a range of organic solvents was investigated. The reactions were carried out using 1 equivalent of 4-nitrobenzaldehyde (0.25 mmol), 5 equivalents of cyclohexanone (1.25 mmol) and 0.1 equivalent of L-valine nitrile at a 0.25 M concentration, at room temperature (Scheme 19). Prior to every reaction, the HCl salt of the L-valine nitrile was cracked and the optical purity of the free amine **4** was measured to ensure the enantiopurity of the catalyst. The optical rotation values confirmed that no racemisation had occurred as they were consistent with the initial value.



Scheme 19. Aldol reaction of 4-nitrobenzaldehyde with cyclohexanone using 10 mol% of L-valine nitrile in 1 mL of solvent in RT.

The free enantiopure amine (10 mol%) was added to a stirring solution of the aldehyde and the ketone in the organic solvent. The reaction continued to be stirred at room temperature for 24 hours. At 24 hours, the reaction was quenched with ammonium chloride and the organic solvent was removed *in vacuo*. The results are presented in Table 6.

Table 6. Screening of different solvents in the aldol reaction of 4-nitrobenzaldehyde and cyclohexanone using 10 mol% L-valine nitrile **4**.

Entry	Solvent	Conversion[a]	dr (*syn*/*anti*)[b]
1	DCM	11%	4.5:1
2	DMF	6.5%	2.3:1
3	Dioxane	8.5%	1.3:1
4	DMSO	N/A	N/A
5	THF	18%	3.8:1
6	EtOAc	14%	25>1
7	Toluene	13%	5.3:1
8	Cyclohexane	5%	3.0:1
9	Neat	16%	5.3:1

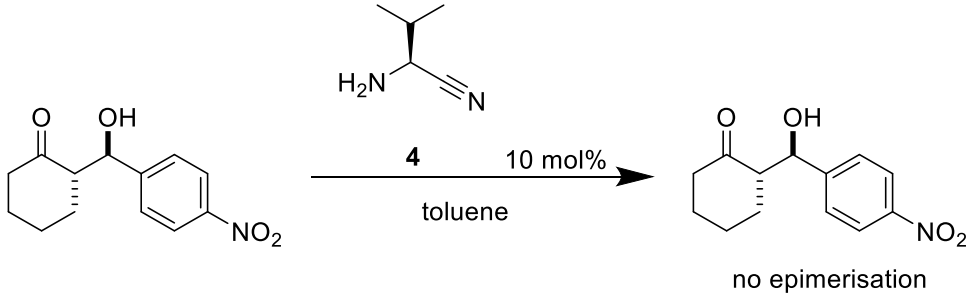
Reaction conditions: 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of L-valine nitrile in 1 mL of solvent at room temperature, for 24 hours, **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR spectrum of the crude reaction, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture

The conversion after 24 hours was found to be low in all cases. The reaction where DCM was screened (Table 6: Entry 1) afforded the aldol adducts in an 11% yield and moderate diastereoselectivity: *syn/anti* 4.5:1. Dioxane (Table 6: Entry 3) provided the aldol product with only 8.5% conversion and with the least diastereoselectivity: *syn/anti* 1.3:1. The least favoured solvent for this catalyst was proved to be DMSO (Table 6: Entry 4), as after 24 hours of stirring no product was detected. Tetrahydrofuran, EtOAc, toluene and no solvent (Table 6: Entries 5, 6, 7 and 9) provided comparable yields: 18%, 14%, 13% and 16% respectively and the diastereoselectivity was at: *syn/anti* 3.8:1, 25>1, 5.3:1 and 5.3:1 respectively. It was concluded that since the conversion after one day was less than 20% in every case, it was not relevant to see what the enantiomeric excess of these reactions were.

Despite the very low conversions, it was encouraging that in all the cases, the catalyst seemed to be *syn* selective. This result is uncommon amongst organocatalysts where *anti* is usually the major product.[43–47] However, it was accepted that regardless the diastereoselectivity, the reaction was still not valuable as a conversion below 20% after 24 hours of stirring makes the catalyst inefficient when compared to other commercially available organocatalysts.

The *syn* selectivity of the catalyst was unexpected and we tried to elucidate why this was the case. Originally, it was considered that the reaction provides the *anti* diastereoisomer as the major product, then L-valine nitrile **4** acts as a base and deprotonates the hydroxyl group, initiating a retro aldol reaction which promotes the conversion of the major *anti* product into the *syn* product over time.

To test this hypothesis the *syn* and *anti* diastereomers were isolated by flash column chromatography. The pure *anti* product was then submitted to a control reaction with 10 mol% of the L-valine nitrile in 1 mL of toluene. The solution was stirred for 24 hours. At 24 hours, a direct sample was taken from the reaction and was submitted for ^{1}H NMR spectroscopy. The spectrum proved that no epimerisation had occurred after 24 hours of stirring (Scheme 20). Therefore, the hypothesis was discounted.



Scheme 20. Control reaction with pure *anti* **3** and 10 mol% **4**.

This control experiment provided evidence that L-valine nitrile was forming the *syn* diastereoisomer as the major product of the reaction. Unfortunately, a satisfying explanation about the *syn* selectivity cannot be provided. An energy difference between the transition states of the two enamines could address the reason of the selectivity. However the diastereoselectivity was low in most cases and accordingly the energy difference between the transition states would be minimal. In order to provide a definitive answer computational studies need to be performed.

Driven by the *syn* selectivity, it was decided to search for ways to optimise the results. The primary goal was to increase the conversion whilst maintaining the diastereoselectivity. There were two possible options to achieve the desired increase of conversion. One was to increase the catalyst loading and the other was to increase the temperature of the reaction. As a consequence of time constraints, it was not possible to try both options. Therefore, it was decided to try the reaction at increased temperatures.

Three reactions were run at a higher temperature in toluene. The first reaction was run at 40 °C, the second at 80 °C and the last under reflux. These reactions were carried out on an identical scale as the previous reactions, with all the variables being the same with the exception of the increased temperature. The free enantiopure amine (10 mol%) was added to a stirring solution of 1 equivalent of 4-nitrobenzaldehyde and 5 equivalents of cyclohexanone and the reaction was stirred for 24 hours.

The results of this approach are summarised in Table 7.

Table 7. Aldol reaction of 4-nitrobenzaldehyde and cyclohexanone using 10 mol% of L-valine nitrile in 1 mL of toluene.

Entry	Temperature	Conversion[a]	dr (*syn/anti*)[b]	ee (*syn*)[c]	ee (*anti*)
1	40 °C	25%	2.9:1	31%	13%
2	80 °C	43%	2.3:1	19%	13%
3	reflux	93%	1.2:1	racemic	racemic

Reaction conditions: 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of L-valine nitrile in 1 mL of toluene, for 24 hours, **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR spectrum crude reaction, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, **c:** enantiomeric excess determined from HPLC using a chiralpak IB column

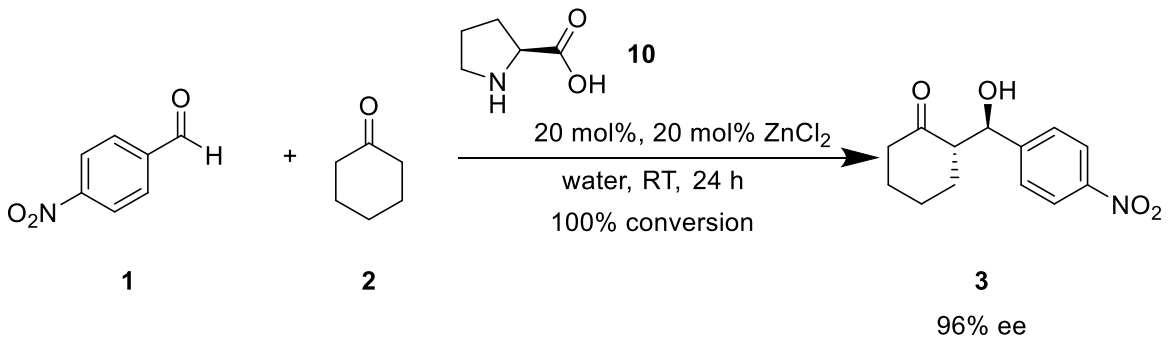
The results showed a clear improvement on the conversion of the reaction. As the temperature increased, so did the conversion. However, the selectivity significantly decreased. The first reaction at 40 °C (Table 7: Entry 1), afforded the aldol products in a slightly improved 25% conversion, while the diastereoselectivity was sustained: *syn*/*anti* 2.9:1. The enantioselectivity was moderate for the major diastereoisomer: 31% *syn* ee. The reaction at 80 °C (Table 7: Entry 2), provided the aldol adducts in an improved 43% yield. However, it demonstrated a significant decrease in the selectivity of the reaction. The diastereoselectivity was diminished to 2.3:1 s*yn*/*anti* and the enantiomeric excess was decreased to 19% for the *syn* diastereoisomer. The reaction run under reflux (Table 7: Entry 3) progressed to a near full conversion but essentially provided a 1:1 mixture of the two diastereoisomers, with no enantioenrichement at all.

Table 7 showed that the main disadvantage of the increased temperature was the very low enantioenrichement. The reaction at 40 °C (Table 7: Entry 1), afforded the aldol product in a 31% *syn* ee, which was the highest achieved enantioselectivity. It was clear that the rise in the reaction

temperature did not maintain the enantioselectivity of the catalyst as when the reaction was run under reflux (Table 7: Entry 3) it provided a racemic product of the *syn* and *anti* diastereosomers. The decrease of the enantioselectivity was not unexpected. Enantiomeric excess decreases at elevated temperatures as the energy differences between transition states gets lower.

The aldol reaction in Scheme 18 affords *syn* enantiomeric and *anti* enantiomeric aldol products. Therefore, determination of the enantiomeric excess required the use of chiral HPLC analyses. Chiral HPLC is a useful instrument which allows the separation of different stereoisomers and has wide application in analytical and synthetic chemistry.

Determination of the enantiomeric excess was achieved with HPLC analyses by following a report from Rolando and co-workers in 2011.[48] In this report the ability of L-proline **10** to catalyse the aldol reaction of 4-nitrobenzaldehyde **1** and cyclohexanone **2** in water in presence of $ZnCl_2$ with up to 96% ee for the *anti* product was demonstrated (Scheme 21).



Scheme 21. Direct asymmetric aldol reaction of 4-nitrobenzaldehyde and cyclohexanone co-catalysed by L-proline and $ZnCl_2$.

Rolando and co-workers postulated that the L-proline/ $ZnCl_2$ complex was facilitating the aldol reaction via an enamine transition state (Figure 6). Zinc is forming the necessary hydrogen bonding in the transition state to provide the *anti* aldol adduct enantioselectively.

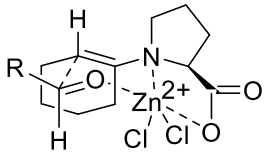
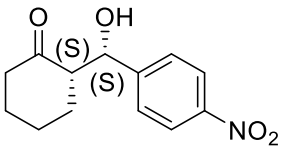
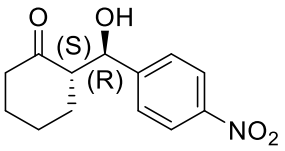


Figure 6. L-Proline/ $ZnCl_2$ transition state.

In the published paper the separation of the 4 stereoisomers, as a mixture of *syn* and *anti*, was reported using an HPLC with an IB chiral column in Hexane:IPA 97:3 and a 1 mL/min flow rate. The absolute configuration for the major *syn* and *anti* enantiomers was determined after the HPLC analysis of the crude reaction mixture (Figure 7).



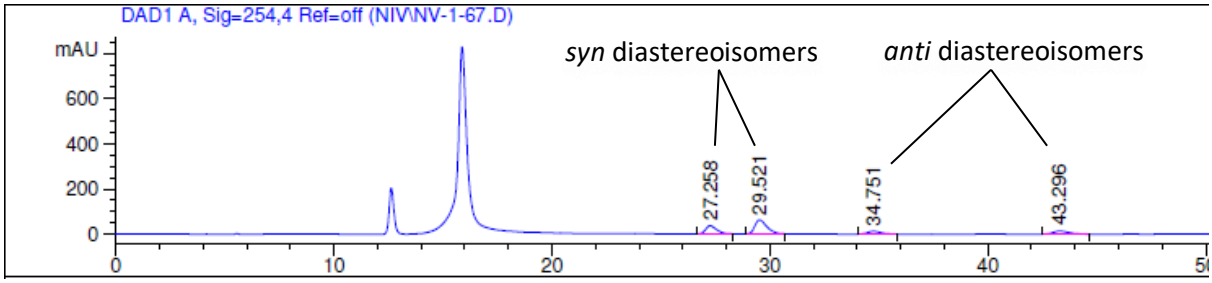
major *syn* enantiomer



major *anti* enantiomer

Figure 7. Absolute configuration for the major *syn* and *anti* enantiomers.

The reported retention times by Rolando and co-workers in the literature for the *syn* and *anti* diastereomers are: *syn* diastereomers: minor t_R= 23.6 min, major t_R= 26.7 min; *anti* diastereomers: major t_R= 28.8 min, minor t_R= 34.8.[48] Gratifyingly, following the same HPLC conditions i.e. 3% IPA in hexane with a 1 mL/min flow rate and using an IB chiral column, separation of the 4 aldol stereoisomers was achieved (Figure 8).



	syn (minor)	***syn*** (major)	***anti*** (minor)	***anti*** (major)
Retention times	27.258 min	29.521 min	34.751 min	43.296
Area %	25.9318	47.8728	10.9580	14.2374

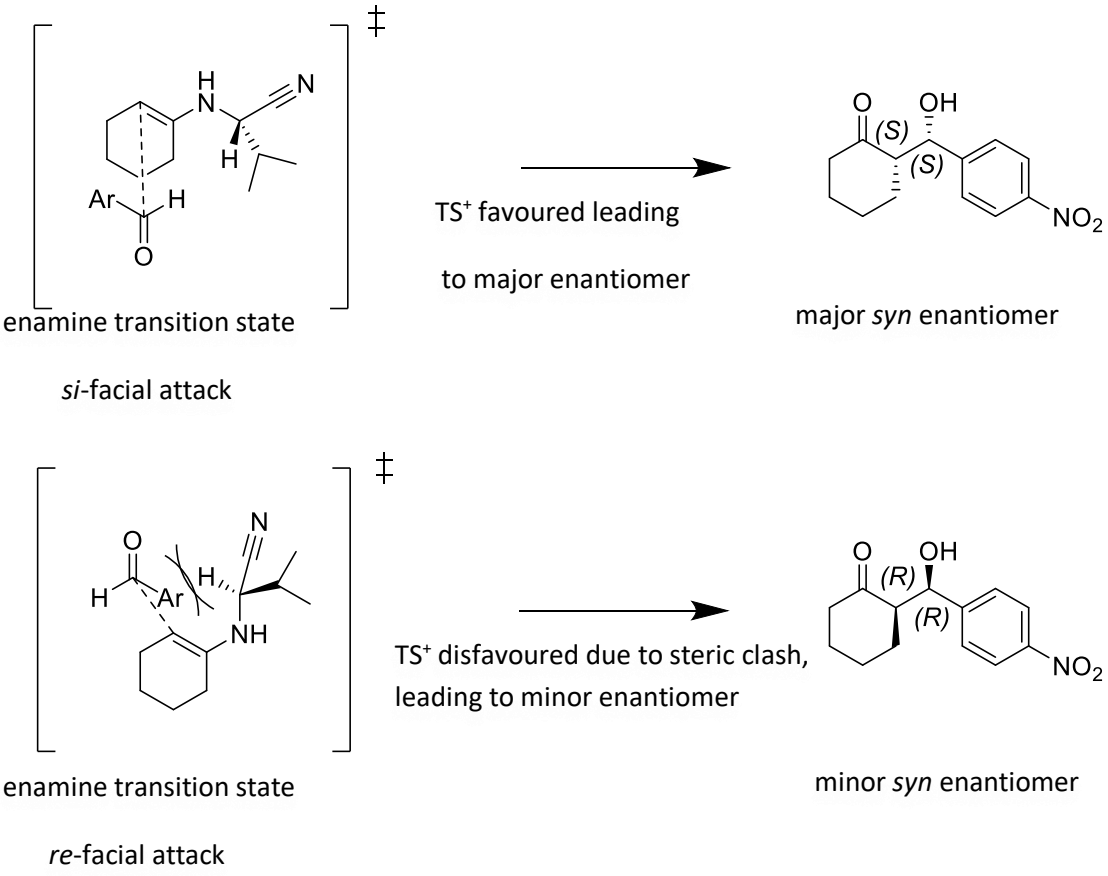
Figure 8. Representative HPLC trace of the aldol reaction catalysed by 10 mol% L-valine nitrile **4.**

The conditions provided a clean separation of the 4 aldol stereoisomers. A shift between our retention times and the retention times reported in the literature[48] was observed, possibly due to column properties or the difference in the temperature of the HPLC instrument, however, the relative times were consistent.

After the calculation of the enantiomeric excess (see Table 7) we wanted to determine if L-valine nitrile **4** was producing the same major stereoisomers as the literature report by Rolando and co-workers.

Interstingly, comparison of the retention times reported by Rolando and co-workers with the HPLC we obtained (Figure 8) showed that **4** was producing the same major *syn* enantiomer and a different major *anti* enantiomer than the L-proline/$ZnCl_2$ complex.

Based on the absolute configuration for the major *syn* and *anti* enantiomers produced by **4**, a reaction mechanism was suggested. The reaction is believed to occur via an enamine transition state. Scheme 22 shows the possible transition state for the two *syn* enantiomers of the reaction.

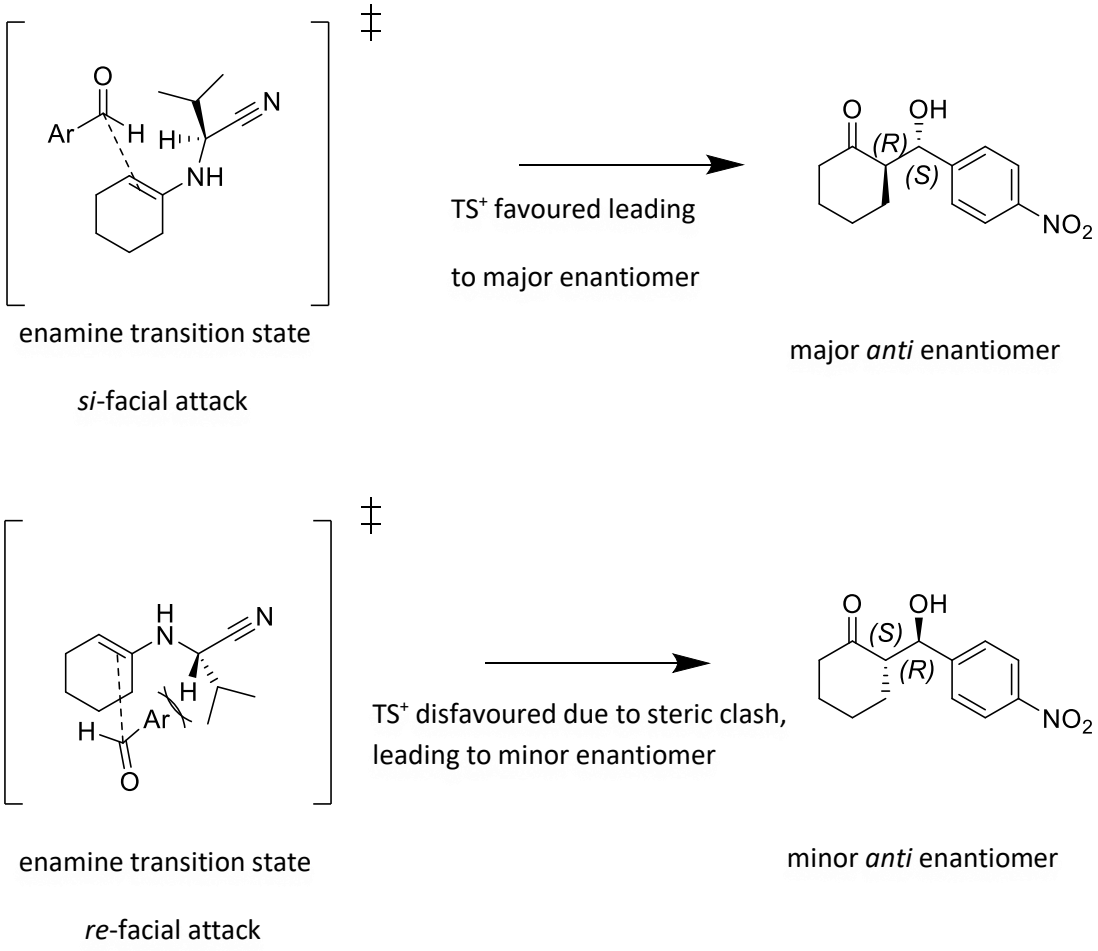


Scheme 22. Possible enamine transition state for the formation of the *syn* enantiomers.

Initially, L-valine nitrile **4** reacts with the cyclohexanone and forms the enamine intermediate. The bond rotation around the enamine leads to the enamine adding to the *si*-face of the aldehyde. The aldehyde approaches the enamine over the smaller group of the catalyst, the proton. In doing so

the steric restrictions are lower as the H-H interaction is minimal. The *si*-facial attack of the enamine provides an explanation for absolute configuration of the major *syn* enantiomer. The proposed enamine transition state also justifies the low enantiomeric excess obtained. The bond rotation around the enamine is quick as there are no restrictions to lock one conformation over the other and the enamine attacks *re*-facial the aldehyde to provide the minor *syn* enantiomer.

The diastereoselectivity was relatively low in most reactions (See Table 6). The proposed enamine transition state for the 2 *anti* enantiomers is given on Scheme 23.



Scheme 23. Possible enamine transition state for the formation of the *anti* enantiomers.

Scheme 23 provides a possible explanation for the absolute configuration of the major *anti* enantiomer produced. The aldehyde primarily approaches the enamine on *si*-face. In doing so there are no steric restrictions as the H-H interactions are minimal. The low enantioselectivity observed

for the *anti* diastereomers can be justified by the bond rotation of the enamine. The bond rotation of the enamine leads also to a *re*-facial attack to the aldehyde. The bond of the enamine is rotating quickly and accordingly there is not a favoured conformation in the transition state.

Study of the ^{1}H NMR spectra of reactions in Table 6 and Table 7, suggested that a side reaction was also taking place (Figure 9).

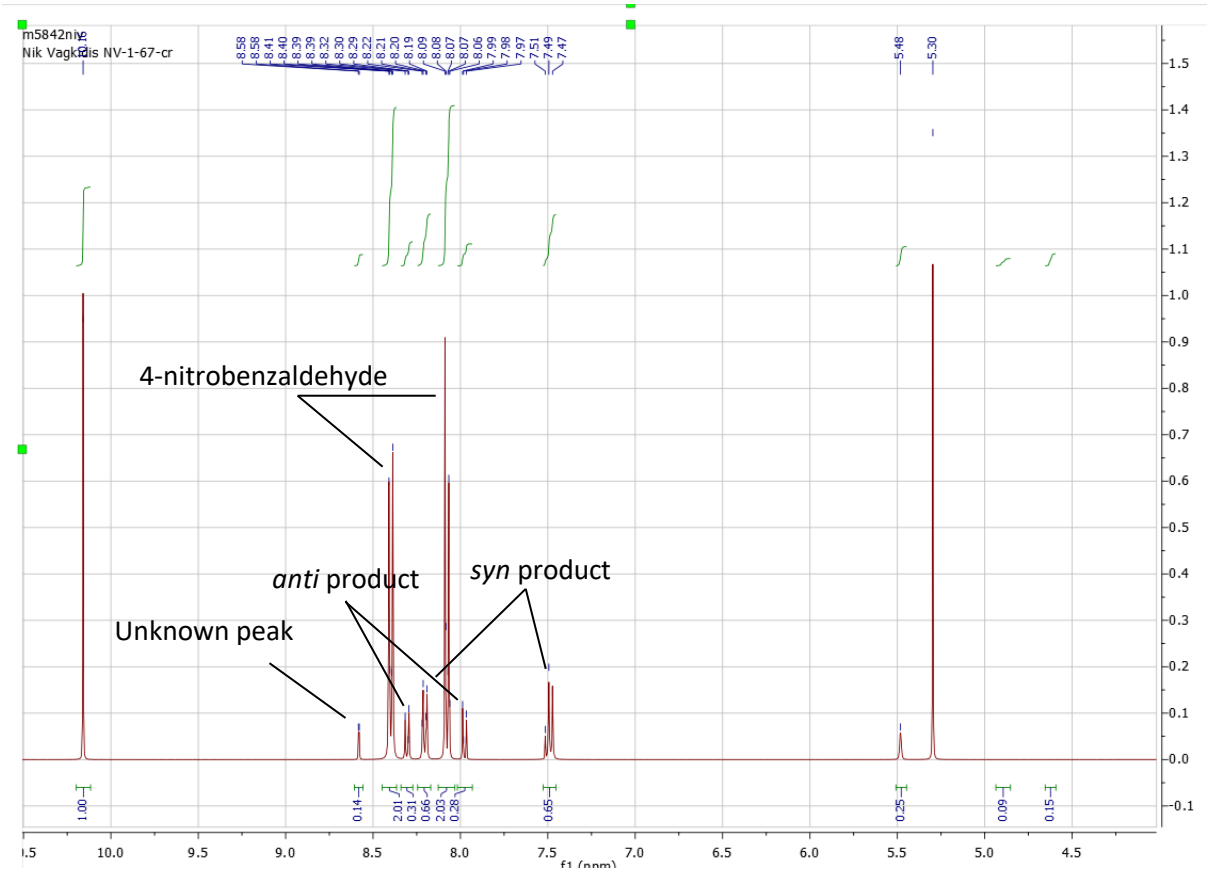
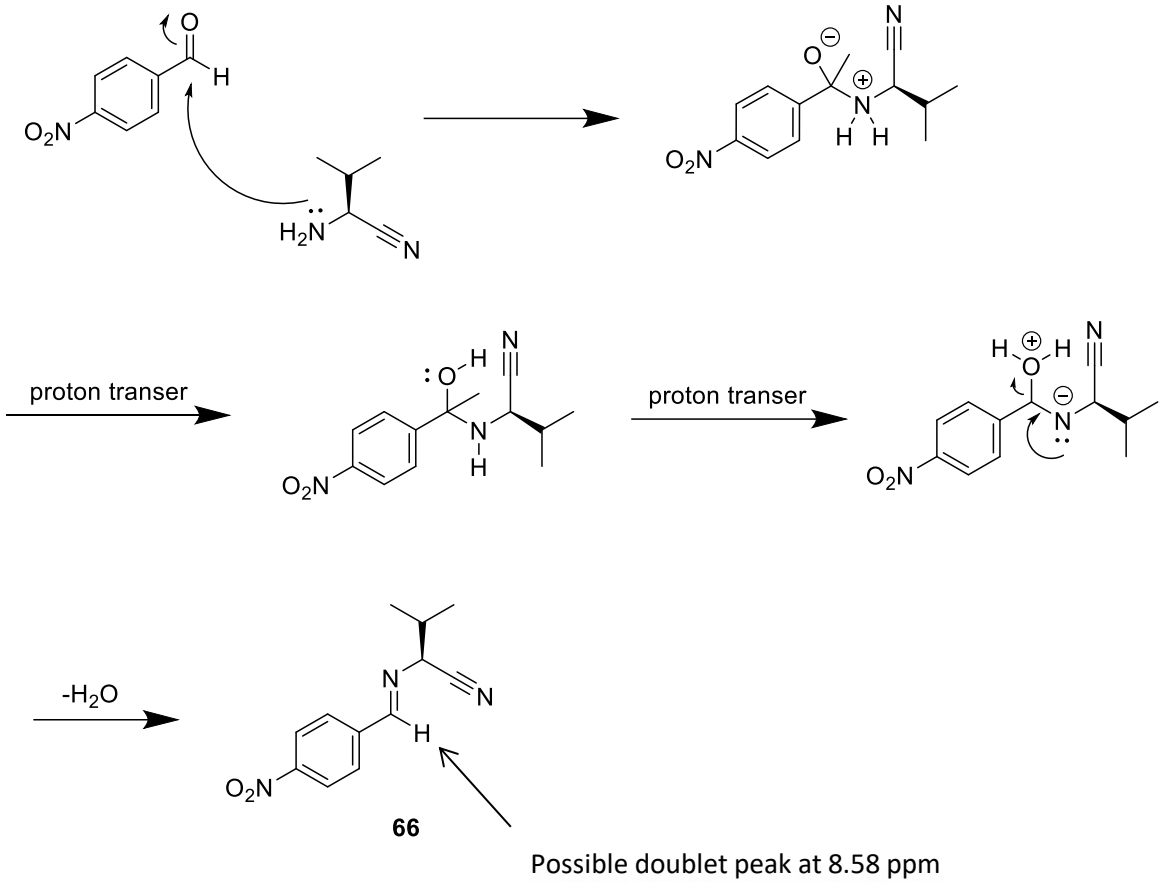


Figure 9. Representative ^{1}H NMR of the aldol reaction catalysed by L-valine nitrile **4**.

The ^{1}H NMR of the crude reaction mixture showed 7 different doublet peaks in the aromatic region. Two doublets were assigned to the remaining limiting reagent of the reaction (4-nitrobenzaldehyde), two were assigned to the *syn* diastereoisomers and two to the *anti* diastereoisomers. However, there was one more doublet peak, at 8.58 ppm which was not product related. This peak was consistent in all reactions of tables 6 and 7. That prompted the consideration that a side reaction was occurring in the reaction. A peak at 8.58 ppm is a strong indication of an imine. It was hypothesised that L-valine nitrile was reacting with 4-nitrobenzaldehyde and was getting trapped as a catalytically unreactive imine (Scheme 24).



Scheme 24. Possible side reaction between L-valine nitrile **4** and 4-nitrobenzaldehyde to provide an imine adduct.

Furthermore, the ^{1}H NMR spectra showed a double doublet peak at 4.66 ppm, which was consistent in all cases of Tables 6 and 7 (Figure 10). This peak was tentatively assigned as the vinyl proton of the cyclohexyl enamine.

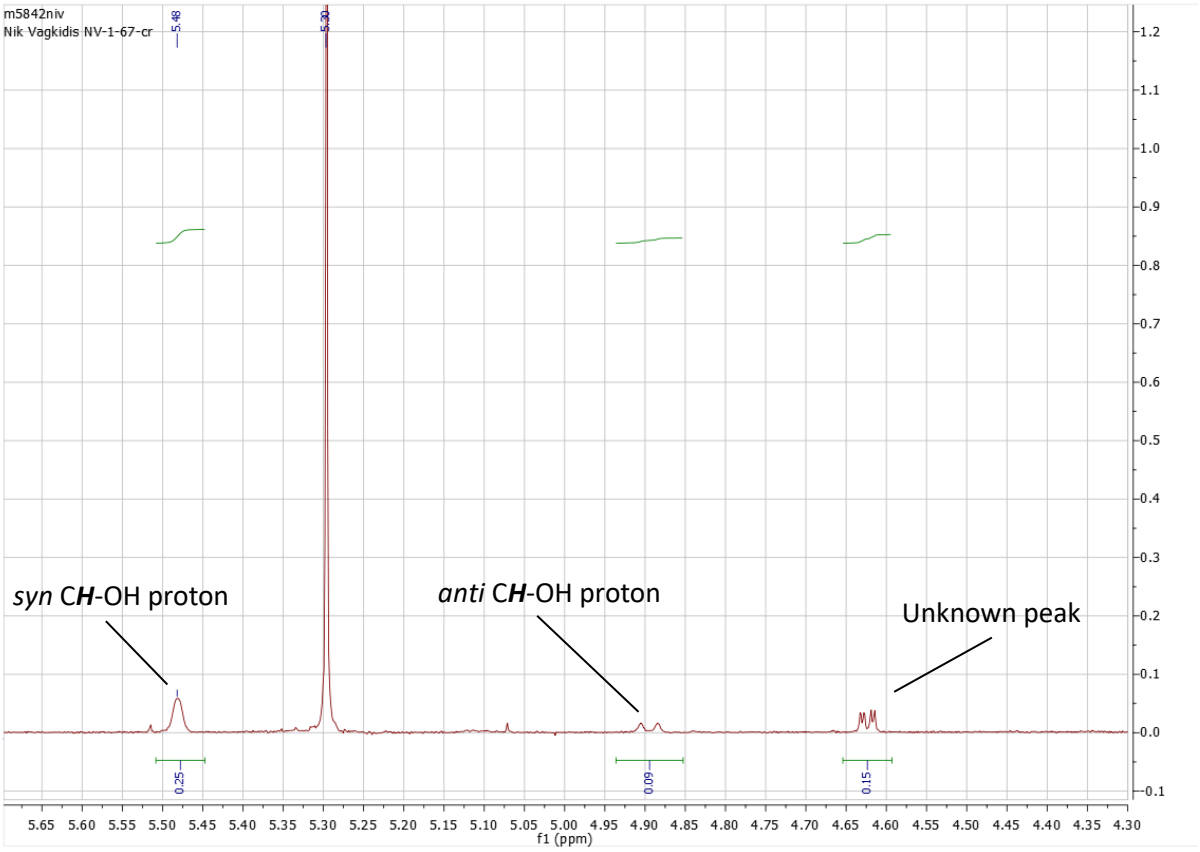
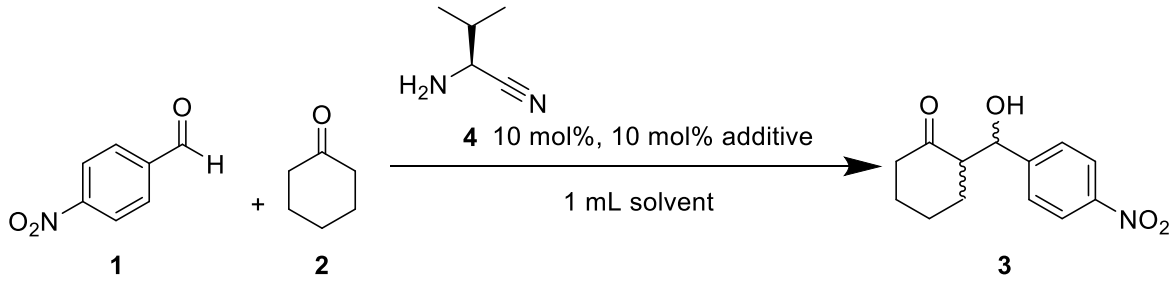


Figure 10. Expanded ^{1}H NMR of the aldol reaction catalysed by L-valine nitrile **4**.

However, neither the imine **66** nor the cyclohexyl enamine were isolated therefore it cannot be confirmed that the protons at 8.58 and 4.66 ppm are due to the presence of them.

Believing the formation of the imine **66** was retarding the process of the aldol reaction, it was decided to try and reverse the formation of the imine. For this purpose, the next reactions were carried with an additive to try and hydrolyse the imine back to the aldehyde. All other variables remained the same i.e. 4-nitrobenzaldehyde (0.25 mmol), cyclohexanone (1.25 mmol), L-valine nitrile (0.025 mmol) and toluene (1 mL) at room temperature. Three new reactions were performed, each one with a different acid as the additive. The results are summarised in Table 8.

Table 8. Aldol reaction of 4-nitrobenzaldehyde with cyclohexanone using 10 mol% of L-valine nitrile **4** and 10 mol % of additive in 1 mL of toluene at RT.



Entry	Additive	Conversion[a]	dr (*syn/anti*)[b]	ee (*syn*)[c]	ee (*anti*)
1	TFA	33%	2.9:1	20%	10%
2	BZA	13%	1.4:1	23%	50%
3	p-TsOH	5%	25>1	34%	N/A

Reaction conditions: 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of L-valine nitrile, 0.025 mmol of additive in 1 mL of toluene at room temperature for 24 hours, **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum of the crude mixture, **c:** enantiomeric excess determined by HPLC analysis with a chiralpak IB column

The addition of acid appeared to have altered the outcome of the aldol reaction. The addition of TFA (Table 8: Entry 1) improved the conversion of the reaction to 33% whilst the diastereoselectivity *syn*/*anti* was sustained to 3:1. Yet, the enantiomeric excess was still low: 20% ee for the *syn product* and 10% ee for the *anti product*. Benzoic acid (Table 8: Entry 2) afforded the *anti* product in an increased 50% ee. However, it did not provide any improvement in the conversion as it remained at the same levels as the non-acidic reactions: 13% and the diastereoselectivity dramatically decreased to *syn*/*anti* 1.4:1. Finally, when p-TsOH (Table 8: Entry 3) was used, the reaction proceeded poorly, with a 5% conversion after one day. However, only the *syn* product was detected by ^{1}H NMR spectroscopy. Moreover, it afforded the *syn* diastereoisomer in a 34% ee, the best enantioselectivity achieved for the major product of the reaction. In addition, there was also the absence of the doublet peak at 8.58 ppm in the ^{1}H NMR spectrum.

It was assumed that the addition of water could shift the equilibrium between the imine and the amine thereby enabling the L-valine nitrile to act catalytically in the reaction. Therefore, water was

added to the reaction where p-TsOH was used as an additive and the reaction was run at 40 °C. The results of this approach are shown in Table 9.

Table 9. Aldol reaction of 4-nitrobenzaldehyde with cyclohexanone using 10 mol% of L-valine nitrile **4** in 1 mL of toluene.

Entry	H_2O	Conversion[a]	dr (*syn/anti*)[b]	Temperature	Additive[c]
1	0.25 mmol	6.5%	25>1	40 °C	-
2	1.25 mmol	4%	25>1	40 °C	-
3	0.25 mmol	4%	25>1	RT	TsOH
4	1.25 mmol	10%	25>1	RT	TsOH

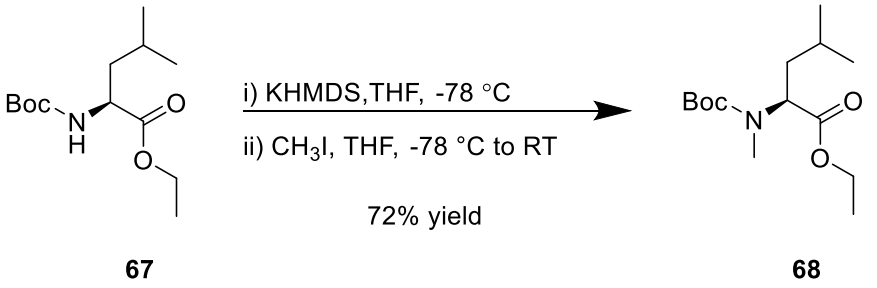
Reaction conditions: 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of L-valine nitrile, in 1 mL of toluene at room temperature for 24 hours **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum of the reaction mixture, **c:** 0.025 mmol of TsOH was used

It was disappointing to see that the addition of water did not increase the conversion of the reactions. However, the *syn* selectivity of the L-valine nitrile was intriguing. Thus, it was decided to try and modify the aminonitrile in an attempt to synthesise a more effective catalyst.

9.3 Synthesis and investigation of *N*-methyl-L-valine nitrile

The initial idea was to replace one of the amine's protons with another R group. The simplest R group that could be induced into the molecule was a methyl group. It was envisaged that by transforming **4** into a secondary amine the formation of the imine would be less favoured.

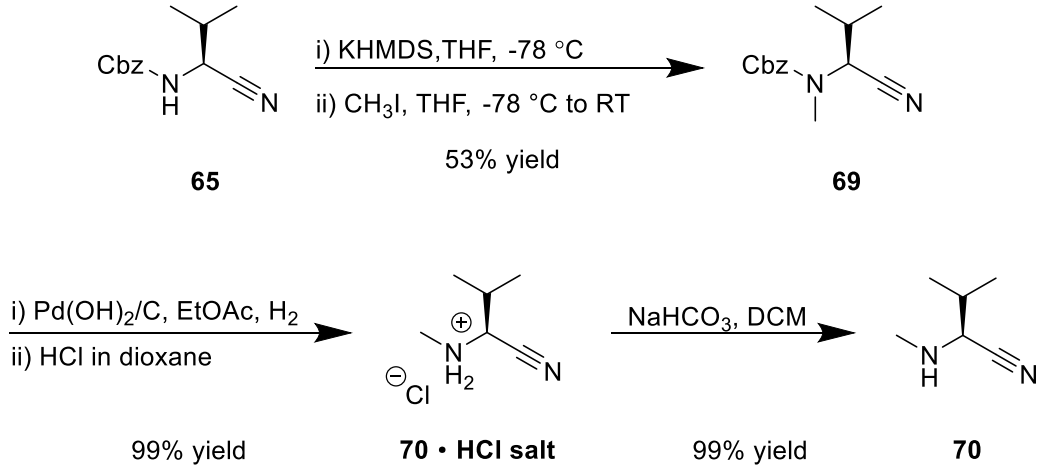
Laurence Burroughs, a previous PhD student in the Clarke group, worked with amino esters and had achieved the *N*-methylation of *N*-Boc-L-leucine ethyl ester **67** using KHMDS at -78 °C and iodomethane in a 72% yield (Scheme 25).[49]



67 **68**

Scheme 25. Methylation of *N*-Boc-L-leucine ethyl ester.

The synthesis of the new compound, *N*-methyl-L-valine nitrile **70** was achieved following Laurence Burroughs's conditions (Scheme 26).



65 **69**

99% yield **70 • HCl salt** 99% yield **70**

Scheme 26. Synthesis of *N*-methyl-L-valine nitrile **70**.

Cbz-protected aminonitrile **65** was alkylated with iodomethane to give Cbz-*N*-methyl-L-valine nitrile **69**, which was isolated in a moderate 53% yield after flash column chromatography. The free amine could be obtained through a similar procedure to the Cbz deprotection of the L-valine nitrile **4**. Pearlman's catalyst was employed in EtOAc under a H_2 atmosphere to remove the Cbz-protecting group from **69**. After the successful removal of the Cbz-group, as judged by TLC, HCl in dioxane (4 M) was added to form the salt of the amine. The HCl salt of the amine **70** was obtained in an excellent 99% yield. The free amine **70** was liberated by dissolving the HCl salt in DCM and stirring over sodium bicarbonate before filtering and concentrating in *vacuo* in an excellent 99% yield.

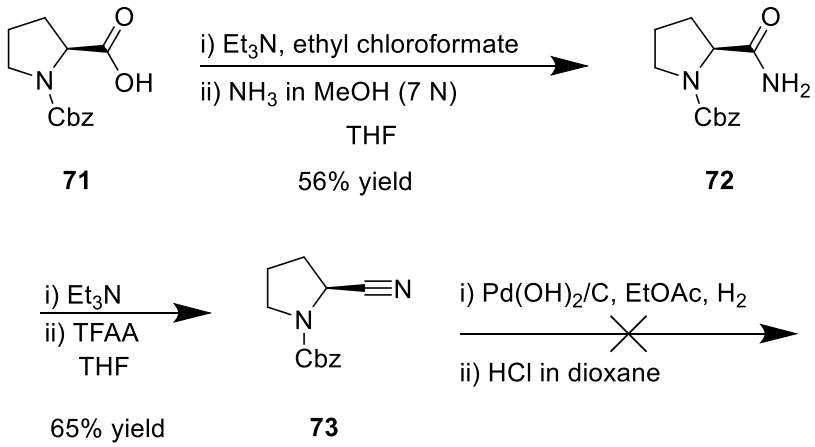
Having installed the methyl group and having successfully removed the Cbz-protection group the catalytic efficiency of the aminonitrile catalyst **70** could be probed. The catalyst's activity was

examined under the standard aldol conditions and in an array of solvents that were trialled with the previous catalyst. The free amine **70** (10 mol%), was dissolved in an organic solvent and was added to a stirring solution of 4-nitrobenzaldehyde (0.25 mmol) and cyclohexanone (1.25 mmol). The solution was continued to be stirred for a further 24 hours at room temperature. Contrary to expectations, no product was detected in any of the reactions trialled.

Due to time constraints, the in-depth investigation of the compound's inability to catalyse the aldol reaction was not possible.

9.4 Synthesis of L-proline nitrile

With our disappointing results with L-valine nitrile, we decided to investigate L-proline nitrile. The initial strategy for the synthesis of the L-proline nitrile **5** was to replicate the synthetic route described for the L-valine nitrile **4** (Scheme 27).



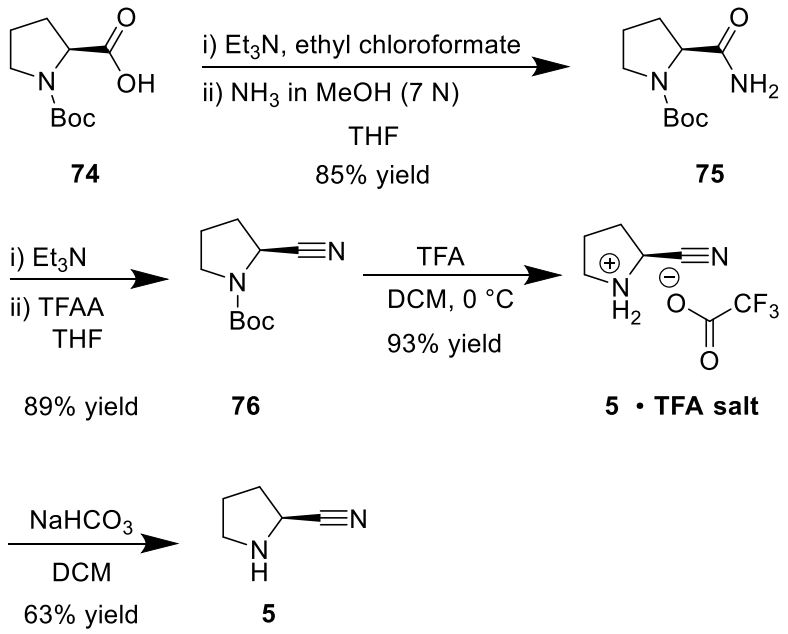
Scheme 27. First attempt to synthesise L-proline nitrile **5.**

Cbz-protected proline **71** was commercially available in an enantiopure form and the synthesis began by converting the protected amino acid **71** to the amide **72**. The transformation was achieved by addition of Et_3N and ethyl chloroformate to form the mixed anhydride which was treated with NH_3 in MeOH. The Cbz-protected amide **72** was obtained in a moderate 56% yield without purification. The next step was the dehydration of the Cbz-amide **72** to the Cbz-aminonitrile **73** which was achieved by addition of TFAA and provided the Cbz-aminonitrile **73** in a 65% yield after purification with flash column chromatography. The final deprotection of the Cbz-group was

challenging. Originally, the hydrogenation was attempted by reproducing the conditions for the deprotection of the L-valine nitrile **4**. The Pearlman's catalyst in EtOAc was not able to remove the Cbz-group as after two days of stirring the Cbz group was still intact. Next, hydrogenation of the protected aminonitrile **73** was tried in a variety of different solvents (MeOH, acetone, AcOH, EtOH) but either the deprotection did not occur or the Cbz-group was removed but the product decomposed. The hydrogenation catalyst was then changed to palladium on carbon in EtOAc, but this still did not provide the free amine, as the Cbz-group was not removed. Palladium on carbon was used with all the previous solvents but once again the deprotected aminonitrile was not formed.

Alternative methods for Cbz-removal were then investigated. Catalytic transfer hydrogenolysis was attempted using formic acid and palladium on carbon, a procedure previously reported to remove the Cbz-protection group from various amino acids and peptides.[50] The reaction was monitored by TLC and was deemed complete after 4 hours. However, in the crude ^{1}H NMR spectrum, only starting material could be detected with no removal of the Cbz-protection group.

Due to the inability to remove the Cbz-group, an alternative route was investigated. It was decided to proceed through the commercially available Boc-L-proline **74** (Scheme 28)



Scheme 28. Synthetic route for the access of L-proline nitrile **5**.

The synthetic route was reminiscent to the strategy followed for the synthesis of the valine catalyst. Enantiopure Boc-L-proline **74** was subjected to the amidation reaction using Et_3N and ethyl chloroformate to form the mixed anhydride, followed by addition of NH_3 in MeOH. Boc-L-Prolinamide **75** was obtained in a high 85% yield and without further purification. The conversion of the Boc-protected amide **75** to the protected aminonitrile **76** was possible using TFAA, which afforded the Boc-L-proline nitrile **76** in a high 89% yield after purification by column chromatography. It should be noted that dry ampules of TFAA were required to achieve high yields of reaction. Older bottles of TFAA contain TFA, which arises from TFAA decomposition, and consequently lowers the reaction yield. The valine catalyst was less sensitive to the condition of the TFAA as this problem did not occur in the synthesis of L-valine nitrile **4**. The final deprotection of the Boc-L-proline nitrile **76** was again challenging.

Initially, 25 equivalents of TFA at 0 °C were added to a solution of the Boc-L-proline nitrile **76** in dry DCM, a common deprotection method for the Boc group.[51] Unexpectedly though, the reaction was not clean as the ^1H NMR of the crude material showed extra peaks and the mass spectrometry analysis found another compound with a different mono isotopic mass.

Seeing this unexpected outcome, the reaction was carefully monitored by TLC. Upon consumption of the starting material, TFA was concentrated in *vacuo*. This provided the catalyst as the pure TFA salt of the aminonitrile **5** in an excellent 93% yield after further purification with trituration using Et_2O. The TFA salt was washed with aqueous saturated sodium bicarbonate and was extracted with DCM in an effort to gain the free aminonitrile. However, no product was obtained following this technique, probably due to the compound's solubility in water. Ultimately, aminonitrile **5** was obtained by dissolving in DCM and stirring over sodium bicarbonate, before filtering and concentrating in *vacuo* in a 63% yield. As with the valine catalyst, the optical rotation values of the compounds were repeatedly measured upon obtaining and before using in the next step (Table 10).

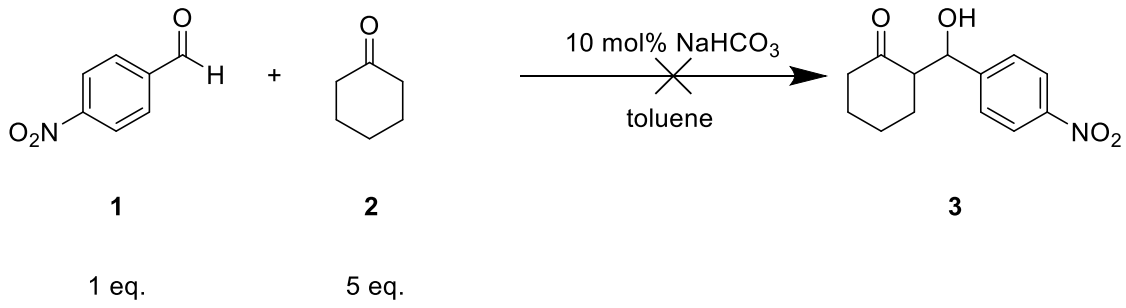
Table 10. Optical rotation values of compounds **75**, **76** and **5** compared to literature values.

Compound	$[\alpha]_D^{20}$ (deg cm^{-3} g^{-1} dm^{-1})	Literature $[\alpha]_D^{25}$ (deg cm^{-3} g^{-1} dm^{-1})	Concentration	Literature Concentration
75	-44.7	-42.4[52]	1.0 g cm^{-3} in MeOH	1.0 g cm^{-3} in MeOH
76	-91.15	-95.5[52]	1.3 g cm^{-3} in MeOH	1.3 g cm^{-3} in MeOH
5	-11.6	-16.7[40]	1.0 g cm^{-3} in MeOH	0.83 g cm^{-3} in MeOH

9.5 Aldol reaction catalysed by L-proline nitrile

With L-proline nitrile **5** in hand, the catalytic ability was then probed in the aldol reaction. The TFA salt of the L-proline nitrile was cracked and DCM was evaporated to gain the free amine. However, due to compound's high volatility, a substantial amount of the catalyst was lost upon concertation in *vacuo*. To avoid this, it was considered employing the catalyst as the TFA salt of the amine **5** and cracking it *in situ* with solid sodium bicarbonate.

Prior to performing the aldol reaction catalysed by the TFA salt of L-proline nitrile **5**, a control reaction with 4-nitrobenzaldehyde and cyclohexanone in an organic solvent and in the presence of solid sodium bicarbonate needed to be run (Scheme 29).

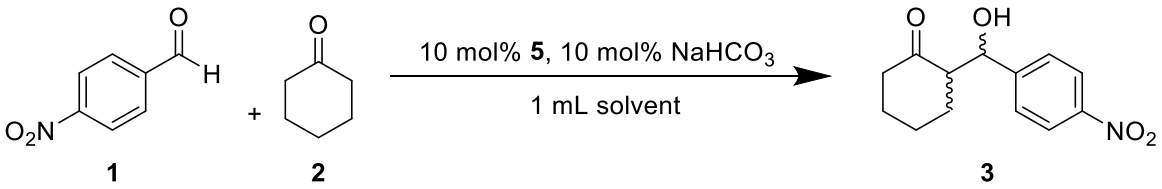


Scheme 29. Control reaction of 4-nitrobenzaldehyde and cyclohexanone in presence of solid sodium bicarbonate.

The control reaction proved that no reaction takes place in absence of the catalyst. Having showed that sodium bicarbonate does not affect the reaction progress, the catalytic ability of **5** was ready to be investigated. The scale of the reaction was maintained the same; 0.025 mmol of L-proline nitrile TFA salt dissolved in 1 mL of organic solvent were added to 1.25 mmol of cyclohexanone,

0.25 mmol of 4-nitrobenzaldehyde and 0.025 mmol of solid sodium bicarbonate were added to the solution and it was stirred for 24 hours at room temperature. The results are shown in Table 11.

Table 11. Aldol reaction of 4-nitrobenzaldehyde with cyclohexanone using 10 mol% of L-proline nitrile TFA salt **5** and 0.025 mmol of solid sodium bicarbonate in 1 mL of solvent at RT.



Entry	Solvent	Conversion[a]	dr (*anti/syn*)[b]	ee (*anti*)[c]	ee (*syn*)
1	DCM	43%	4.0:1	13%	11%
2	DMF	6.5%	2.5:1	20%	18%
3	Dioxane	55%	4.8:1	11%	11%
4	MeCN	11%	2.9:1	20%	20%
5	DMSO	3%	1.7:1	N/A	N/A
6	THF	39%	3.9:1	40%	12%
7	EtOAc	51%	3.9:1	23%	15%
8	Toluene	75%	4.8:1	20%	6%
9	Cyclohexane	75%	4.0:1	13%	racemic

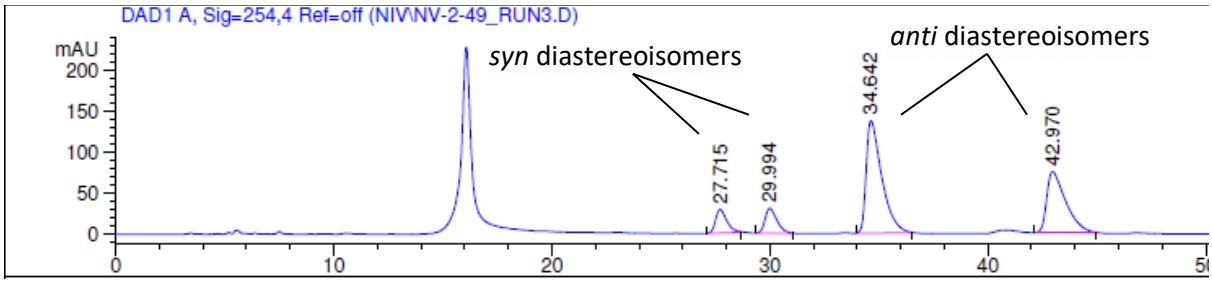
Reaction conditions: 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of L-proline nitrile, 0.025 mmol of solid sodium bicarbonate in 1 mL of solvent, at room temperature for 24 hours, **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR of the crude reaction mixture, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR at the crude, **c:** enantiomeric excess determined by HPLC using chiralpak IB column

Table 11 shows that in general, L-proline nitrile **5** is a more effective catalyst than L-valine nitrile **4** in the aldol reaction. The yields were significantly higher with the highest reported with toluene and cyclohexane (Table 11: Entry 8 and Entry 9), 75% respectively. Dichloromethane, dioxane, THF and EtOAc (Table 11: Entry 1, Entry 3, Entry 6 and Entry 7) afforded the aldol adduct in similar yields ranging from 39-55% while DMF, MeCN and DMSO (Table 11: Entry 2, Entry 3 and Entry 5) provided less than 11% conversion. The diastereoselectivity was consistently moderate amongst the solvents that favoured the reaction i.e. DCM: *anti/syn* 4.0:1, dioxane: *anti/syn* 4.8:1, THF: *anti/syn* 3.9:1,

EtOAc: *anti/syn* 3.9:1, toluene: *anti/syn* 4.8:1 and cyclohexane: *anti/syn* 4.0:1. In contrast to the valine catalyst, this time *anti* was consistently the major product.

The enantiomeric excess was determined by HPLC using a chiralpak IB column. The eluent was 3% IPA in hexane with a 1 mL/min flow rate. The enantioselectivity of the reactions however was still low averaging at 20% ee for the *anti product* (DMF, MeCN, EtOAc and toluene). The highest ee for the *anti* product was obtained when THF was screened (40% ee).

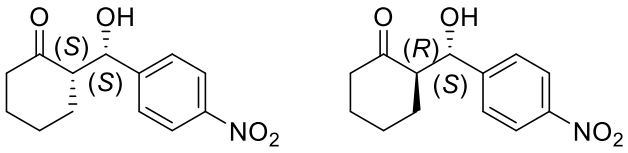
A representative HPLC trace is shown in Figure 11.



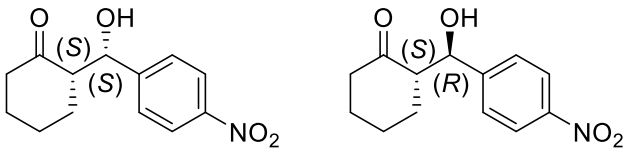
	syn (minor)	***syn*** (major)	***anti*** (major)	***anti*** (minor)
Retention Times	27.715 min	29.994 min	34.642 min	42.970 min
Area %	7.5680	8.4527	50.4377	33.5417

Figure 11. Representative HPLC analysis of the aldol reaction catalysed by L-proline TFA salt **5**.

Comparison of Figures 8 and 11 showed that that L-proline nitrile **5** TFA salt produced the same major *syn* enantiomer but a different *anti* major enantiomer in comparison to L-valine nitrile **4** (Figure 12).



major *syn* and *anti* enantiomer obtained with L-valine nitrile **4**

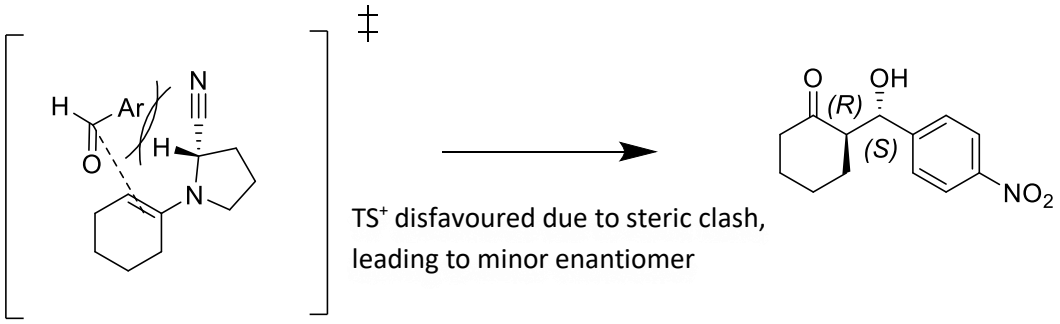


major *syn* and *anti* enantiomer obtained with L-proline nitrile **5 ● TFA salt**

Figure 12. Major enantiomers in the aldol reaction catalysed by **4** and **5**.

At this moment, a satisfying explanation for this observation cannot be rationalised. This is an interesting outcome and further investigation needs to be executed to determine the reason for this selectivity.

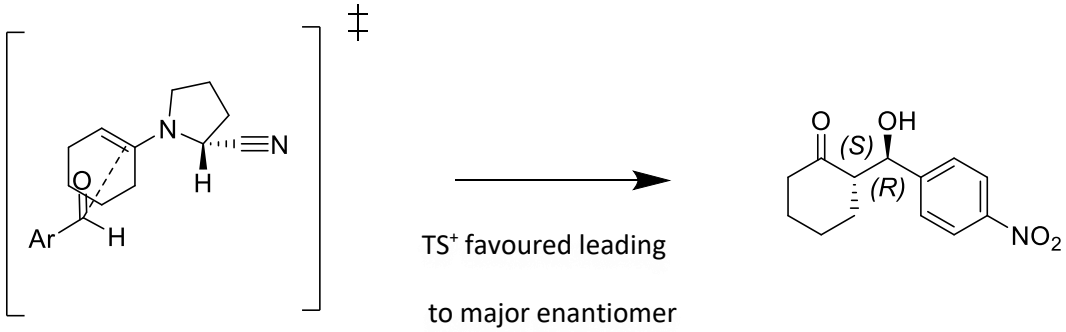
Based on the absolute configuration of the major *syn* and *anti* enantiomer, the following enamine transition state was proposed as the most feasible reaction mechanism (Scheme 30). The absolute configuration for the major *anti* enantiomer in Scheme 30 was determined by the HPLC trace in Figure 11. The aldehyde approaches the enamine over the smallest substituent of the catalyst, the proton, as the H-H steric restrictions are minimal. The enamine attacks the aldehyde *re*-facial leading to the major *anti* enantiomer. The bond rotation around the enamine leads to low enantioselectivity. The enamine still attacks the aldehyde *si*-facial to provide the minor *anti* enantiomer. The conformation of the enamine transition state is tighter than the L-valine nitrile enamine (Scheme 22 and 23) and so an increase in the ee is observed.



enamine transition state

si-facial attack

minor *anti* enantiomer



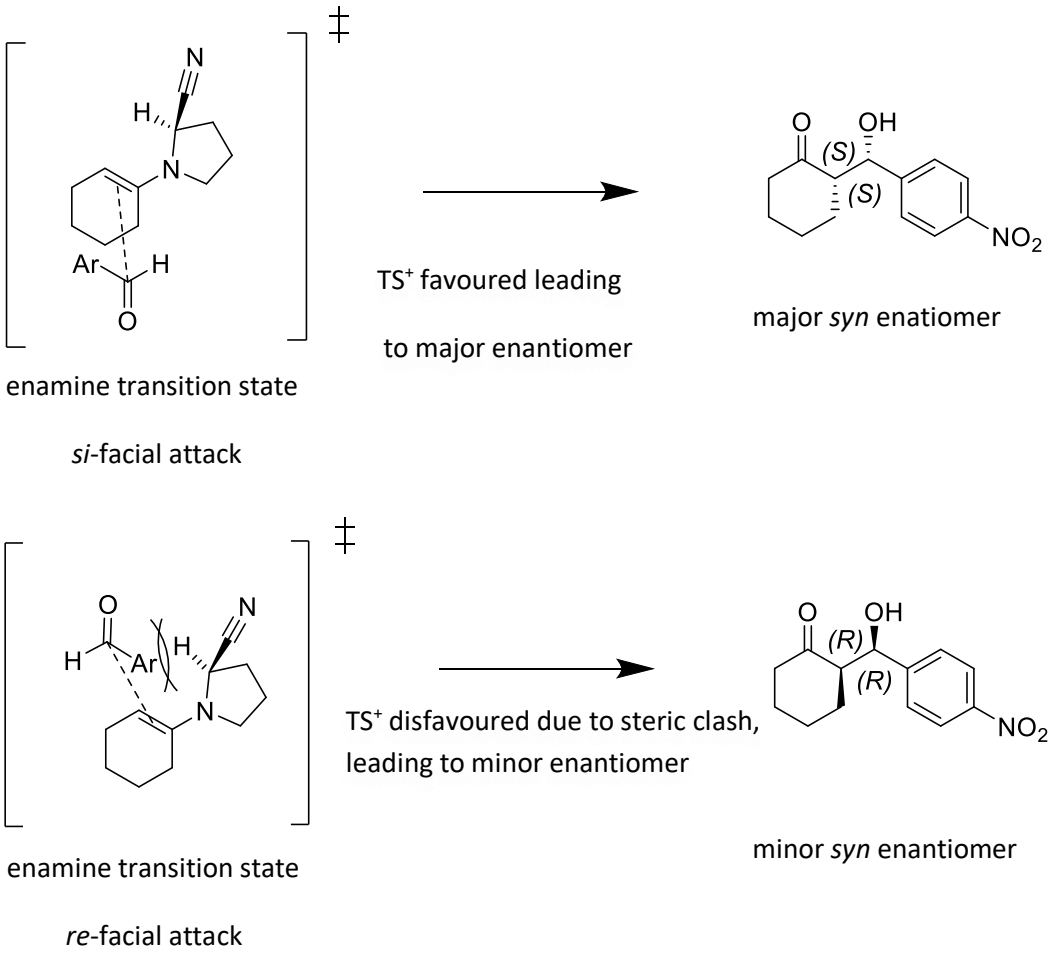
enamine transition state

re-facial attack

major *anti* enantiomer

Scheme 30. Proposed enamine transition state for the formation of the *anti* diastereomers catalysed by L-proline nitrile **5**.

The major *syn* enantiomer was consistently the same as when the reaction was catalysed by L-valine nitrile **4**. The enamine transition state for this selectivity is presumably the same as the L-valine nitrile transition state (see Scheme 22). Scheme 31 provides a possible transition state for the L-proline nitrile **5** enamine transition state. The aldehyde again approaches the enamine over the smallest substituent of the catalyst. In doing so the H-H interaction is minimal, leading to a *si*-facial attack of the enamine and the absolute configuration for the major *syn* enantiomer is explained.



Scheme 31. Proposed enamine transition state for the formation of the *syn* diastereomers catalysed by L-proline nitrile **5**.

Interestingly, when it was attempted to synthesise fresh catalyst for further investigation, the removal of the Boc-protecting group could not be repeated. The reaction was attempted following the same procedure as before. Boc-L-Proline nitrile **76** was dissolved under a nitrogen atmosphere in dry DCM. To the solution, 25 equivalents of TFA were added. Upon consumption of the starting material, as monitored by TLC, TFA was removed and the product was submitted for ^{1}H NMR analysis. However, the crude ^{1}H NMR spectrum was showing peaks unrelated to the proline nitrile. The removal of the Boc-protecting group was capricious and a side product was formed to varying degrees. The following Figure 13 is a representative ^{1}H NMR of this reaction.

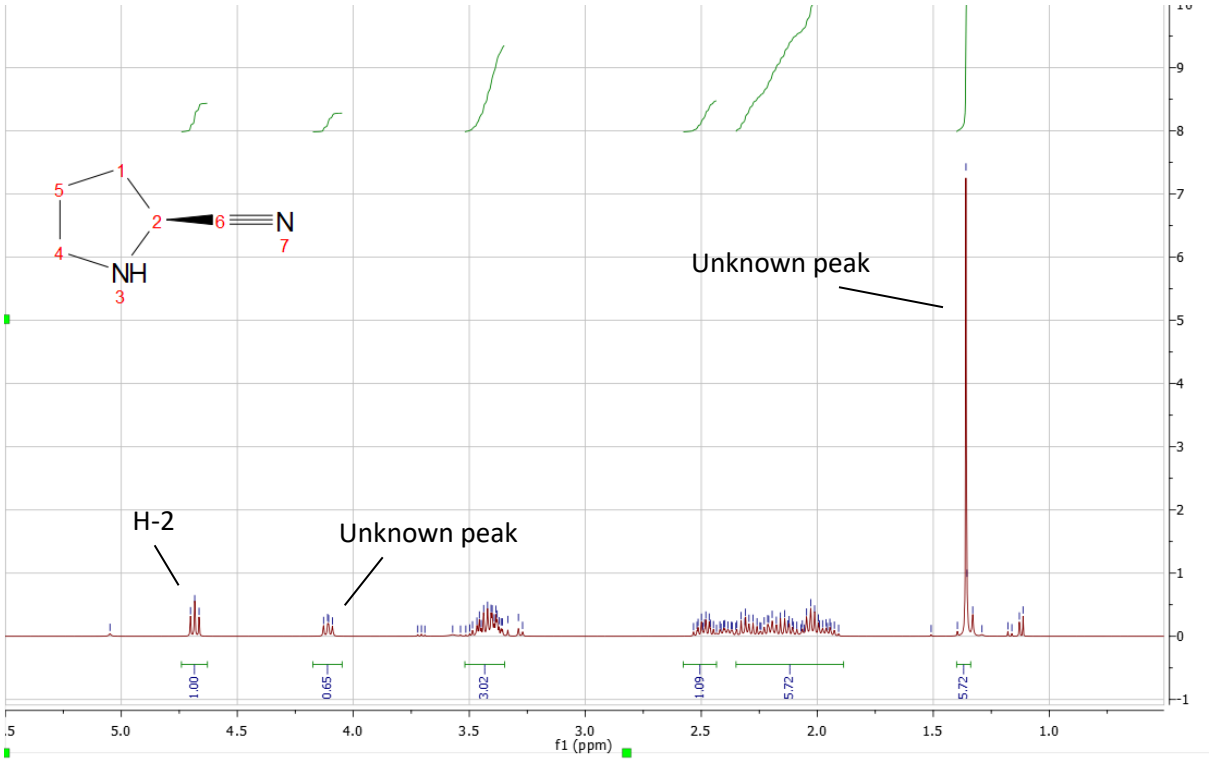


Figure 13. A representative ^{1}H NMR of the deprotection of Boc-L-proline nitrile using TFA in DCM at 0 °C.

The triplet peak at 4.66 ppm is the proton of carbon-2 of L-proline nitrile. However there is an extra double doublet peak at 4.11 ppm which integrates as 0.65 and is not a signal that can be assigned to the L-proline nitrile. Furthermore, there is a singlet peak at 1.36 ppm that integrates as 5.72. The singlet at 1.35 ppm was originally theorised to be *t*-BuOH as this is the reported chemical shift for this in the literature.[53] Despite prolonged periods on the rotatory evaporator the peak at 1.36 did not decrease. To understand these two peaks, further data was acquired. The mass spectroscopy spectrum of the reaction is shown below (Figure 14).

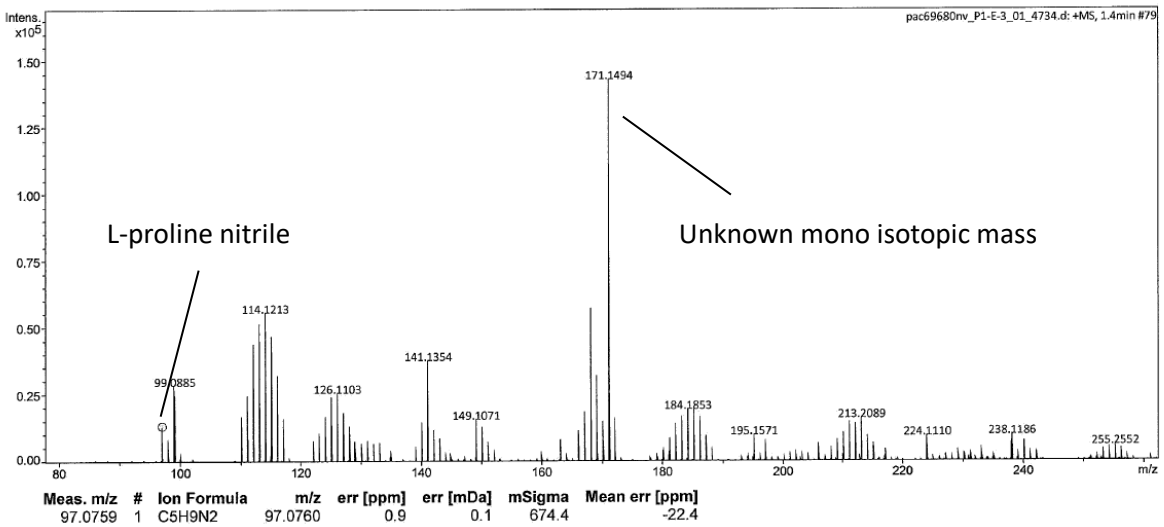
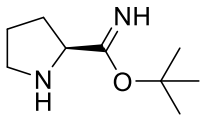


Figure 14. Mass spectrometry analysis of the deprotection of Boc-L-proline nitrile using TFA in DCM at 0 °C.

The mass spectrometry analysis suggested that L-proline nitrile had been formed in the reaction, however, there was unquestionably another side product formed with a mono isotopic mass of 170.1494. This number matches the mono isotopic mass of proline imidate **6** (Figure 15).

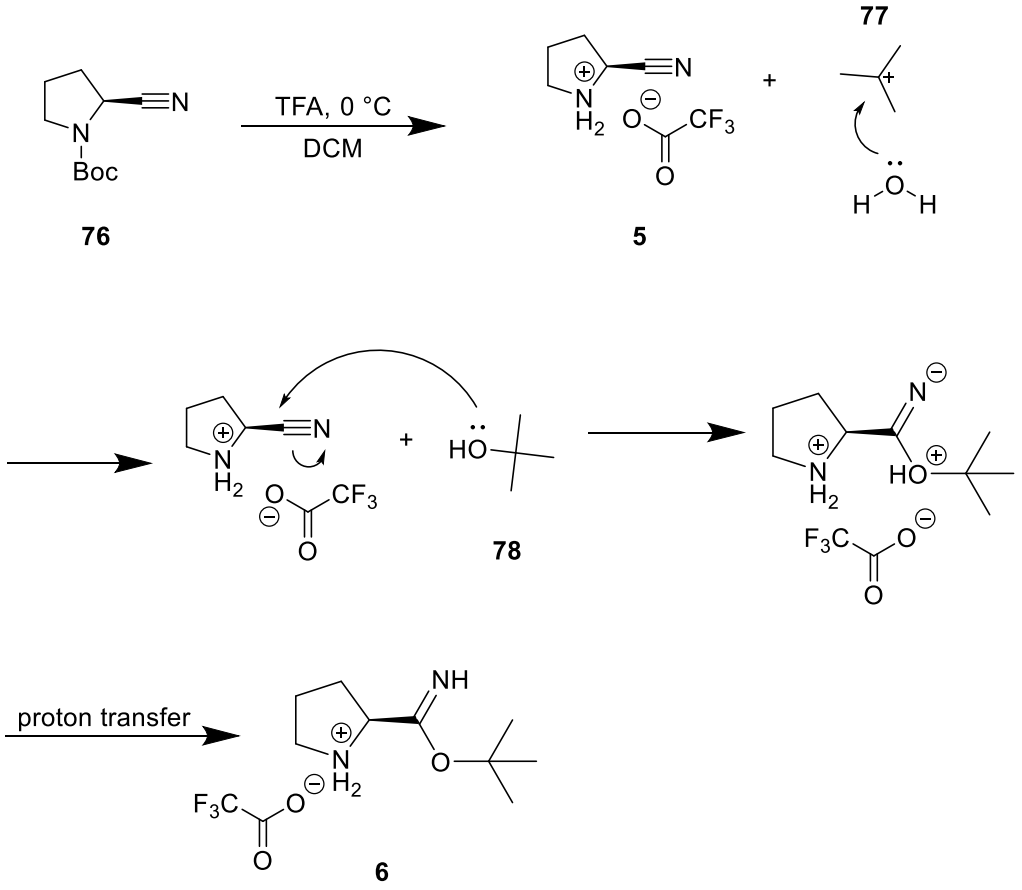


6

Figure 15. Proline imidate with a 170.1419 mono isotopic mass.

9.6 Synthesis of the L-proline imidate

It was hypothesised that the formation of the L-proline imidate **6** was subject to the condition of the TFA solution employed. A potential mechanism for the side formation of L-proline imidate **6** is given in Scheme 32.

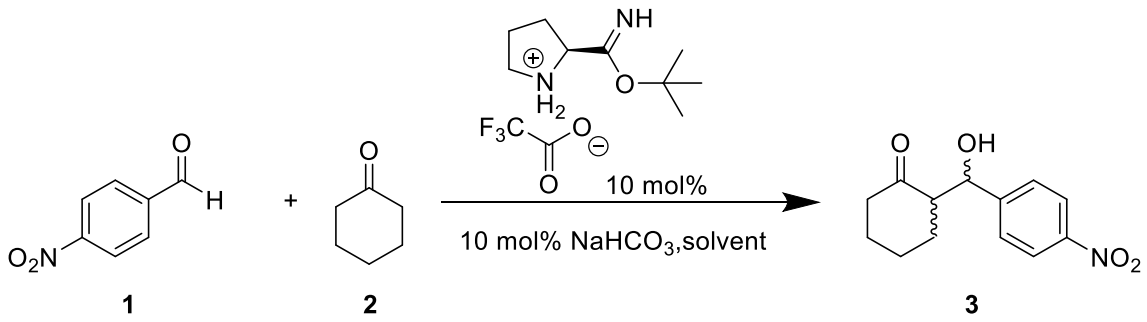


Scheme 32. Proposed mechanism for the *in situ* formation of *t*-butanol and its subsequent reaction with L-proline nitrile TFA salt.

If TFA was wet, water could initiate a further reaction after the removal of the Boc-protecting group and the formation of the TFA salt of proline nitrile. One of the by-products of the TFA deprotection is the *t*-butyl cation **77**. Supposing water is present in the reaction, the oxygen of the water can attack the *t*-butyl cation to form *in situ t*-BuOH **78**. The nucleophilic oxygen of the *t*-BuOH **78** can subsequently attack the carbon of the nitrile and form the C=N bond that ultimately leads to the TFA salt of proline imidate **6**.

It was observed that leaving the reaction for an extended period of time favoured the formation of the proline imidate **6** over the aminonitrile **5**. Stirring the reaction under the same conditions for 48 hours provided the proline imidate **6** as the only product of the reaction. The product was obtained clean, in a moderate 56% yield as the TFA salt of proline imidate, after trituration with hot isopropyl ether. Having formed a new potentially catalytic compound, it was decided to test it as a catalyst in the aldol reaction of 4-nitrobenzaldehyde **1** with cyclohexanone **2**. The reactions were carried out following the same procedure: 0.025 mmol of the TFA salt of proline imidate **6** were dissolved in the organic solvent and were added to 1.25 mmol of cyclohexanone. To the solution, 0.25 mmol 4-nitrobenzaldehyde and 0.025 mmol of solid sodium bicarbonate were added and the reaction was stirred for 24 hours at room temperature. Initially, the compound's catalytic ability was tested in toluene and DCM. Table 12 shows these results.

Table 12. Summarised results of aldol reaction using L-proline imidate TFA salt **6**.



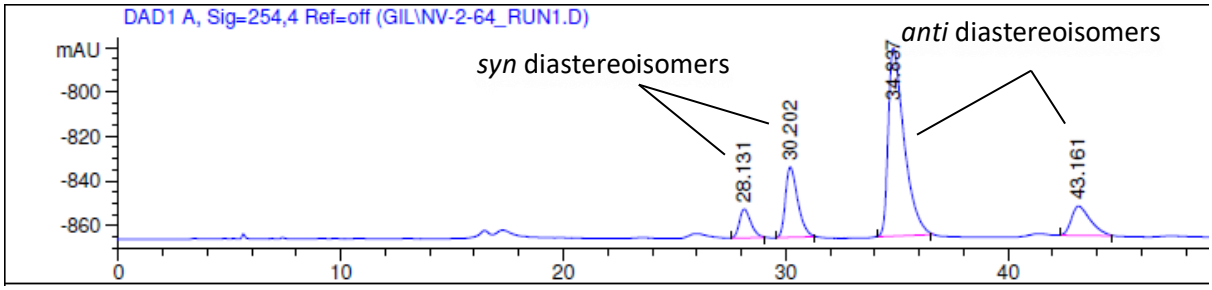
Entry	Solvent	Conversion[a]	dr (*anti/syn*)[b]	ee (*anti*)[c]	ee (*syn*)
1	Toluene	85%	4.6:1	58%	27%
2	DCM	61%	5.6:1	69%	45%

Reaction conditions: 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of proline imidate, 0.025 mmol of solid sodium bicarbonate in 1 mL of solvent, at room temperature, for 24 hours **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum at the crude, **c:** enantiomeric excess determined by HPLC using chiralpak IB column

Preliminary results with proline imidate **6** exceeded expectations. The diastereoselectivity was slightly higher than when L-proline nitrile was used. Toluene (Table 15: Entry 1) afforded the aldol adducts effectively with the same diastereoselectivity: *anti/syn* 4.6:1 and DCM (Table 15: entry 2) provided the aldol adducts in the best selectivity: *anti/syn* 5.7:1. Impressively though, the conversions of these two reactions were significantly higher with toluene reaching 85% yield after

24 hours of stirring. Similarly, the enantioenrichement was the highest yet achieved and crucially for the major product. Toluene provided the *anti* product in a 58% ee while DCM afforded the *anti* aldol adduct in a 69% ee.

Figure 16 is the HPLC trace of entry 2 (Table 12).



	syn (minor)	***syn*** (major)	***anti*** (major)	***anti*** (minor)
Retention times	28.131	30.202	34.837	43.161
Area %	6.9081	18.2689	63.2065	11.6165

Figure 16. Representative HPLC analysis of the aldol reaction catalysed by L-proline imidate TFA salt **6**.

The HPLC trace in Figure 16 shows that L-proline imidate **6** produces the same major enantiomers as L-proline nitrile **5**.

The catalyst was presumed to facilitate the reaction via an enamine mechanism (Figure 17).

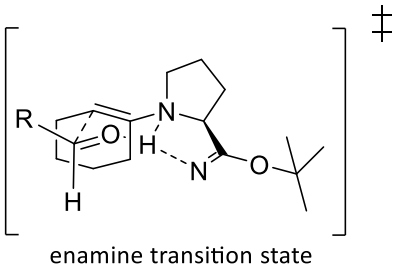
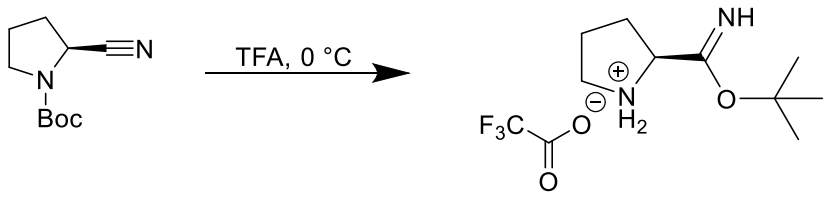


Figure 17. Proposed enamine transition state for the aldol reaction catalysed by L-proline imidate**.**

A plausible mechanism is the adoption of the pseudo-chair transition state similarly to examples of proline organocatalysis.[24,54] The increased enantioselectivity obtained with proline imidate **6**

compared to the aminonitriles can be attributed to the possible hydrogen bonding framework that is being formed between the oxygen of the aldehyde and the hydrogen of the proline imidate.

A literature search was carried out to see how proline imidate **6** was synthesised. There was only one report of this molecule where it was obtained by treating Boc-L-proline nitrile **76** with neat TFA (Scheme 33).[55]



76 **6**

Scheme 33. Literature report for the synthesis of proline imidate.

However, this report exclusively formed the proline imidate for further use in another reaction, therefore the molecule was not purified and characterised. Attempts to reproduce the reported procedure failed as they provided a mixture of L-proline nitrile **5** and L-proline imidate **6**. Thus, it was concluded that a novel, robust procedure for the synthesis of proline imidate **6** was required.

A series of control experiment were conducted, and the results are shown in Table 13:

Table 13. Control experiments to determine a procedure for the formation of the proline imidate **6**.

Entry	Solvent	TFA equivalents	Time (h)	Temperature	Product (ratio)
1	DCM	25	24	0 °C to RT	**6**
2	DCM	25	1.5	0 °C	**5**
3	DCM	40	24	0 °C to RT	**5:6** (1.50:1)
4	DCM	40	1.5	0 °C	**5**
5	Neat	25	24	0 °C to RT	**5:6** (1:3.50)
6	Neat	25	1.5	0 °C	**5**
7	Neat	40	24	0 °C to RT	**6**
8	Neat	40	1.5	0 °C	**5:6** (6.80:1)

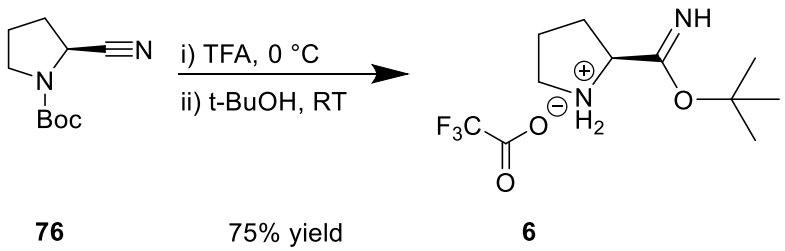
The amount of TFA was being switched between 25 and 40 equivalents. The premise for this shift was that a higher amount of TFA could potentially accelerate the removal of the Boc-group and in doing so could favour the formation of the L-proline nitrile over the L-proline imidate in shorter reaction periods. Reactions were run for 1.5 hours and 24 hours to determine the difference of time in the reaction. The time of 1.5 hours was opted as this was the time 25 equivalents of TFA needed to successfully remove the Boc-protecting group from the Boc-L-proline nitrile **76**. The literature precedent for the formation of the proline imidate reported the reaction in absence of organic solvent. Therefore, every reaction was carried out in dry DCM and in neat TFA to determine whether the solvent or the concentration of the reaction would favour the formation of one product over the other. The reactions that were run for 1.5 hours were carried out at 0 °C. The reactions that were left stirring for 24 hours, were initially run at 0 °C and allowed to warm at room temperature after 1.5 hours.

Table 13 shows that the formation of the product was not affected by the solvent as entries 1 and 5, 2 and 6, 4 and 8 afforded essentially the same product. The absence or not of solvent and the equivalents of TFA used, did not affect crucially the product of the reaction.

The dominating factor for the outcome of the reaction proved to be the duration of the reaction. Reactions that were left for 1.5 hours (entries 2, 4, 6, 8) provided either pure L-proline nitrile **5** or a

mixture where L-proline nitrile **5** vastly predominated. Conversely, reactions that were run for 24 hours (entries 1 and 7) afforded the L-proline imidate **6** as the only product, and entry 5 provided a mixture of the two compounds in favour of the L-proline imidate **6**. For unspecified reasons, entry 3 provided a mixture with a ratio of 1.50:1 in favour of the L-proline nitrile **5**.

It was thus suggested, that prolonged reaction times favour the formation of the L-proline imidate **6** over the L-proline nitrile **5**. Therefore, it was required to find a procedure which would consistently afford the proline imidate **6** and not a mixture of products. Originally, it was considered allowing the reaction to stir for 48 hours. However, it was believed that a more direct approach was feasible. Considering water was facilitating the *in situ* formation of *t*-BuOH, it was hypothesised that either addition of water or *t*-BuOH in the reaction mixture would assist the formation of the proline imidate **6**. Accordingly, a reaction with the addition of 2 equivalents of *t*-BuOH was conducted (Scheme 34).



76 75% yield **6**

Scheme 34. Attempt to synthesise the proline imidate **6** by addition of *t*-BuOH.

Boc-L-proline nitrile **76** was stirred in TFA (40 equivalents) at 0 °C. Upon consumption of the starting material, as monitored by TLC, 2 equivalents of *t*-BuOH were added, and the reaction was allowed to warm at room temperature. The reaction was continued to be stirred over night at room temperature. Gratifyingly, this method afforded the pure TFA salt of the proline imidate **6** in a good 75% yield after trituration of the salt with hot isopropyl ether.

9.7 Aldol reaction catalysed by L-proline imidate

Once the procedure for the synthesis of the proline imidate TFA salt was established, it was time to examine the new potential catalyst in the aldol reaction. In continuation of the previous work, the compound's ability to catalyse the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone in an array of solvents was investigated. The catalyst was used as the TFA salt and the reaction's conditions were maintained i.e. 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of catalyst and 0.025 mmol of solid sodium bicarbonate. The reactions were stirred for 24 hours at room temperature.

Due to time constraints, it was not possible to examine all the solvents that were screened initially with the two aminonitriles. Consequently, cyclohexane and THF were selected as solvents. Cyclohexane was opted as it provided the highest yield in the aldol reaction catalysed by L-proline nitrile **5** (Table 13: Entry 9) while THF afforded the *anti* aldol adduct in the highest ee (Table 13: entry 6). The optical rotation value of the catalyst was measured prior to every reaction and was compared to our initial value. The values were consistently close (i.e. -41.2 to -47.23, C=1.0 g cm^{-3} in DCM), proving that no racemisation had occurred. Table 14 summarises the results of the aldol reaction catalysed by the L-proline imidate **6**.

Table 14. Results of the aldol reaction catalysed by the TFA salt of proline imidate **6**.

Entry	Solvent	Conversion[a]	dr (*anti*/*syn*)[b]	ee (*anti*)[c]	ee *(syn*)
1	Toluene	85%	4.6:1	58%	27%
2	DCM	61%	5.6:1	69%	45%
3	Cyclohexane	100%	5.3:1	76%	51%
4	THF	57%	5.8:1	46%	36%

Reaction conditions: 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of proline imidate, 0.025 mmol of solid sodium bicarbonate in 1 mL of solvent, at room temperature for 24 hours, **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum at the crude, **c:** enantiomeric excess determined by HPLC using chiralpak IB column

The data acquired from these reactions were very encouraging as when cyclohexane was screened as solvent (Table 14: Entry 3) the reaction proceeded to 100% conversion and simultaneously

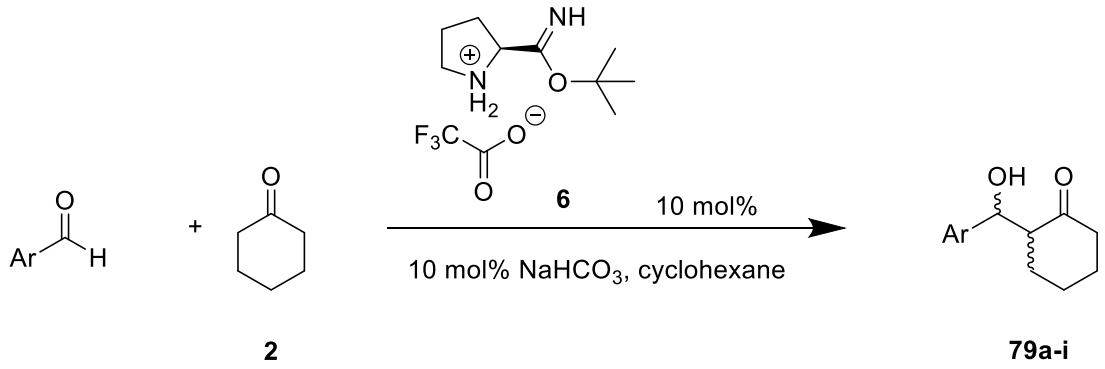
afforded the aldol adducts in a good *anti*/*syn* diastereoselectivity: 5.3:1. Crucially, it afforded the *anti* product in a 76% ee, our highest reported enantiomeric excess for the reaction.

The results in Table 14 warranted a further investigation of the new catalyst. It was decided to try two reactions using cyclohexane and toluene at 0 °C. In parallel it was decided to start screening different substrates and examine what the compound's scope of catalytic activity is. Considering this was a compound never before studied there was no information about the general catalytic ability of **6**.

The screening of different aldehydes was started. Cyclohexane was opted as the solvent since it was the solvent that afforded the aldol adducts in 100% yield after 24 hours of stirring. Cyclohexanone was preserved as the ketone of the reaction. The conditions of the reactions maintained the same i.e. 0.025 mmol of the L-proline imidate TFA salt were dissolved in 1 mL of cyclohexane and were added to a solution of 1.25 mmol of cyclohexanone, 0.025 mmol of solid sodium bicarbonate and 0.25 mmol of aldehyde and the reaction was stirred for 24 hours at room temperature.

Table 15 shows the results of the aldehydes screening.

Table 15. Summarised results of the aldol reaction between cyclohexanone and various aromatic aldehydes catalysed by L-proline imidate TFA salt **6**.



2 **79a-i**

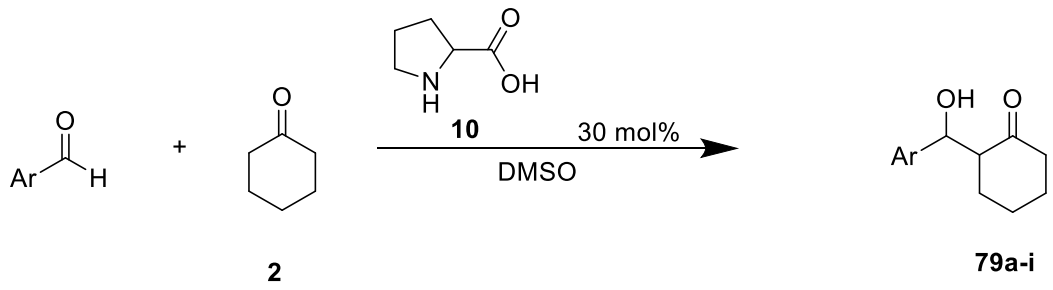
Entry	Aldehyde	Conversion[a]	Product	dr (*anti/syn*)[b]	ee (*anti*)[c]
1	2-nitrobenzaldehyde	100%	**79a**	4.7:1	75%
2	3-nitrobenzaldehyde	100%	**79b**	3.0:1	63%
3	2-chlorobenzaldehyde	98%	**79c**	5.0:1	76%
4	3-chlorobenzaldehyde	96%	**79d**	3.0:1	67%
5	4-chlorobenzaldehyde	94%	**79e**	2.7:1	57%
6	2-bromobenzaldehyde	100%	**79f**	7.0:1	69%
7	3-bromobenzaldehyde	99%	**79g**	2.5:1	71%
8	4-bromobenzaldehyde	90%	**79h**	3.0:1	61%
9	benzaldehyde	69%	**79i**	3.5:1	67%

Reaction conditions: 0.25 mmol of aldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of proline imidate, 0.025 mmol of solid sodium bicarbonate in 1 mL of cyclohexane, at room temperature for 24 hours, **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR of the crude reaction mixture, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR at the crude, **c:** enantiomeric excess determined by HPLC using chiralpak IB and AD-H column.

The results of the substrate screening proved that **6** was an effective catalyst irrespective of the aldehyde used. All the entries showed a satisfying conversion above 90% with the exception of benzaldehyde (Table 15, Entry 9) where the reaction proceeded to a moderate 69% conversion. The *anti* product consistently predominated over its diastereoisomer. The diastereoselectivity was consistently moderate. The lowest *anti*/*syn* ratio was reported in entries 5 and 7 when 4-chlorobenzaldehyde and 3-bromobenzaldehyde were screened 2.7:1 and 2.5:1 respectively and the highest *anti*/*syn* diastereoselectivity was obtained in entry 6: 7.0:1.

Determination of the enantiomeric excess for these reactions was time consuming. The current HPLC method i.e. 3% IPA in hexane in a chiral IB column could not be followed. There was no literature precedent for the separation of the 4 stereoisomers of the aldol products, as the previously followed paper did not screen the aldehydes of Table 15. A literature search revealed that the separation of the stereoisomers was achieved using HPLC with either a chiral AD-H or a chiral OD-H column.[56,57] In house unavailability of AD-H and OD-H columns required the discovery of new HPLC conditions for all the reactions run with an IB column.

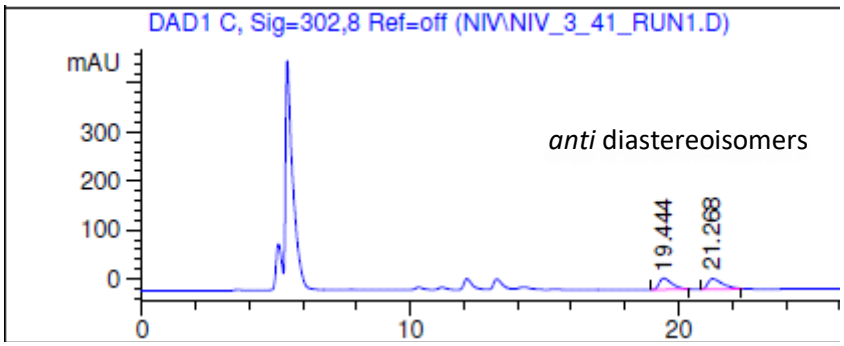
To achieve that, racemic samples of all the reactions were necessary. Therefore, all entries in Table 19 were repeated using racemic proline as the catalyst. The procedure followed for the racemic samples was replicated from Barbas's III and co-workers paper in 2000 (Scheme 35).[24]



Scheme 35. Procedure for the synthesis of the racemic samples.

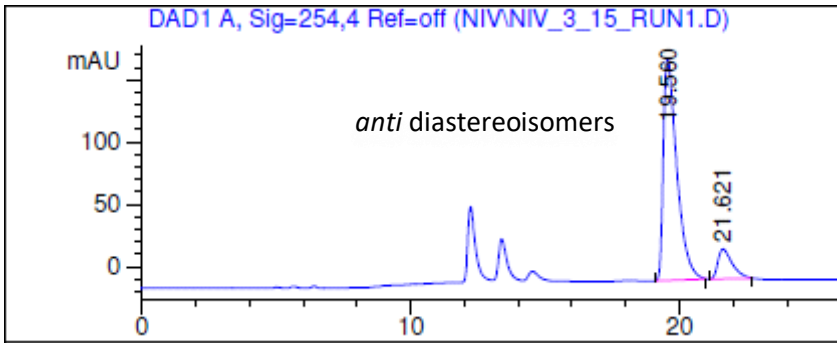
In doing so, a racemic mixture of all four stereoisomers was formed. With the racemates in hand, a general method was needed to separate the stereoisomers in HPLC. It was theorised that the method already used for the aldol adducts of the reaction between 4-nitrobenzaldehyde and cyclohexanone, could likely provide a clean separation. The premise was proved correct for most of the cases. Separation of the stereoisomers was achieved following the same HPLC conditions. For the cases where separation was not possible using the IB chiralpak column, the four stereoisomers were separated using an AD-H chiralpak column and following previous literature precedent. Representative examples of the HPLC traces (racemic and catalysed) are listed in Figures 18-21.

Figure 18. HPLC trace of racemic **79a**.



Hexane:IPA	Flow rate	*anti* (min)	*anti* (min)
97:3	1 mL/min	19.4	21.2

Figure 19. HPLC trace of enantioenriched **79a**.



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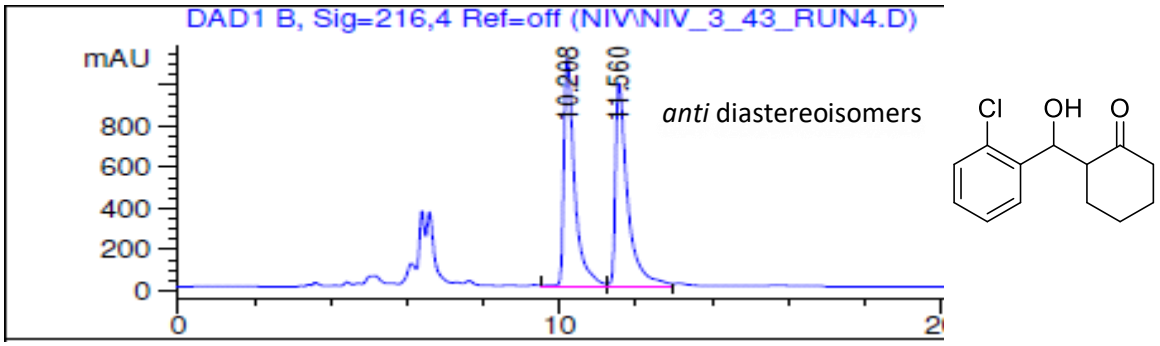
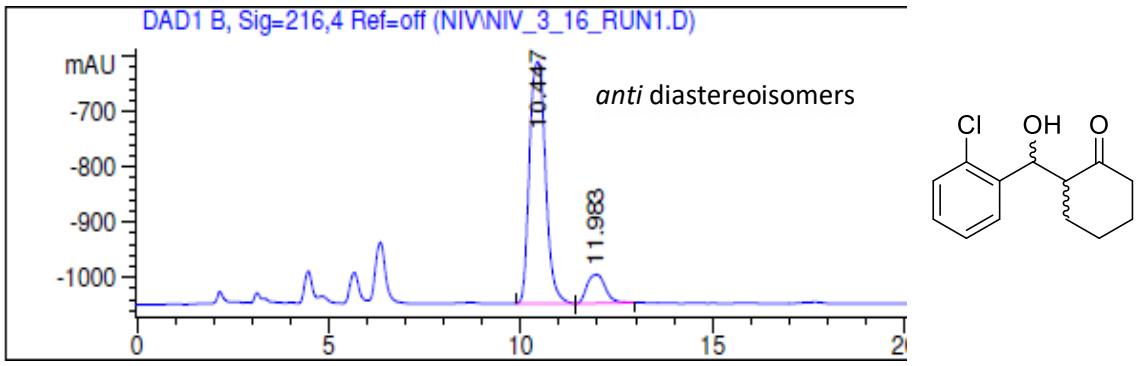
Hexane:IPA	Flow rate	*anti* (major) (min)	*anti* (minor) (min)
97:3	1 mL/min	19.5	21.6

Figure 20. HPLC trace of racemic **79c**.



Hexane:IPA	Flow rate	*anti* (min)	*anti* (min)
97:3	1 mL/min	10.2	11.5

Figure 21. HPLC trace of enantioenriched **79c**.



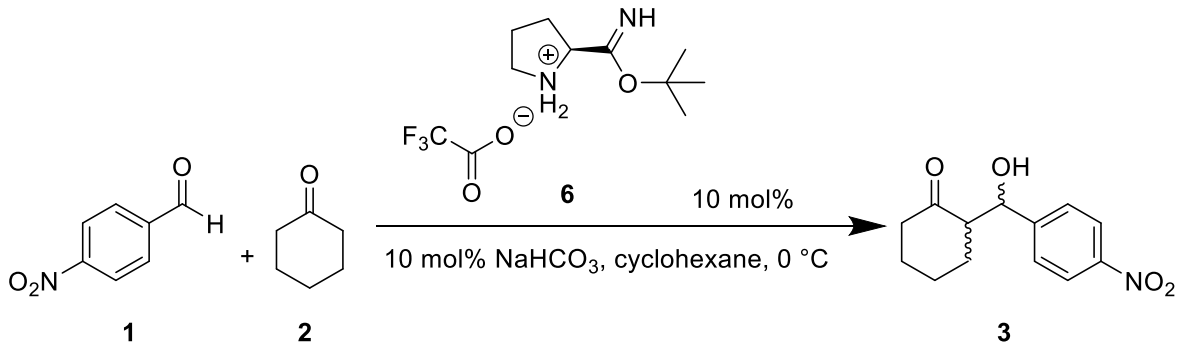
Hexane:IPA	Flow rate	*anti* (major) (min)	*anti* (minor) (min)
97:3	1 mL/min	10.4	11.9

The screening of different substrates was successful. It decisively illustrated that the catalytic scope of **6** extends to more substrates. Results were consistently moderate. 4-Chlorobenzaldehyde (Table 15, Entry 5) afforded the *anti* diastereoisomer in a 57% ee, which was the lowest reported enantiomeric excess. For entries 1, 3, 4, 6, 7 and 9 the enantiomeric excess for the major diastereoisomer *anti* was ranging between 67-76%.

Comparison of the enantiomeric excess in entries with the same substituent in a different position of the aromatic ring showed that the 3-position was not preferable when the substituent was NO_2. 3-Nitrobenzaldehyde (Table 15, Entry 2) afforded the major aldol product in a 63% *anti* ee while 2-nitrobenzaldehyde (Table 15, Entry 1) and 4-nitrobenzaldehyde (Table 15, Entry 3) produced the *anti* stereoisomer in a 75% and a 76% *anti* ee respectively. On the contrary, entries where the substituent was a Br or a Cl the 4 position seemed to be the least favoured for the reaction. 4-Chlorobenzaldehyde and 4-bromobenzaldehyde (Table 15: Entries 5 and 8) produced the *anti* product in a 57% and 61% ee respectively. The 2-chlorobenzaldehyde and 3-chlorobenzaldehyde (Table 15: Entries 4 and 5) afforded the *anti* stereoisomers in an improved 76% and 67% ee respectively. Similarly, when 2-bromobenzaldehyde and 3-bromobenzaldehyde (Table 15: Entry 6 and 7) were screened the *anti* adduct was obtained in a 69% and 71% ee.

Simultaneously, it was decided to run two reactions at a lower temperature. It was considered that running reactions at 0 °C would most likely decrease the conversion of the reaction. However, it could potentially affect the enantioselectivity, providing more enantiopure products. Toluene and cyclohexane were opted as solvents as they afforded the aldol adducts in the highest yields (85% and 100% respectively). These reactions were run using 4-nitrobenzaldehyde as the aldehyde substrate. The purpose of using this aldehyde was that it was easy to collect all the data needed since the HPLC conditions were known for this reaction. The scale and conditions of the reaction were maintained the same; 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexane, 0.025 mmol of the proline imidate TFA salt **6** and 0.025 mmol of solid sodium bicarbonate in 1 mL of solvent. The reactions were stirred for 7 hours at 0 °C and were then quenched with ammonium chloride. Table 16 shows the results.

Table 16. Aldol reactions at 0 °C catalysed by the L-proline imidate TFA salt **6**.



Entry	Solvent	Time (h)	Conversion[a]	dr (*anti/syn*)[b]	ee (*anti*)[c]	ee *(syn*)
1	Toluene	7	50%	6.2:1	71%	67%
2	Cyclohexane	7	40%	5.7:1	94%	40%

Reaction conditions: 0.25 mmol of 4-nitrobenzaldehyde, 1.25 mmol of cyclohexanone, 0.025 mmol of proline imidate, 0.025 mmol of solid sodium bicarbonate in 1 mL of cyclohexane, at 0 °C for 7 hours, **a**: The conversion of the reaction was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, **b:** diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum at the crude, **c:** enantiomeric excess determined by HPLC using chiralpak IB column

In conformity with the original hypothesis the lower temperature provided interesting results. The conversion in both cases decreased to 50% from 85% in toluene and to 40% from 100% in cyclohexane. Decisively though, the selectivity was increased. The *anti* product was predominant in both cases and at increased selectivity. Toluene afforded the aldol products in a good 6.2:1 *anti*/*syn* diastereoselectivity and cyclohexane in a good *anti*/*syn* 5.7:1. Furthermore, the enantioselectivity was improved. The reaction in toluene afforded the aldol adducts in a 71% *anti* ee and a 67% *syn* ee. Remarkably, when the reaction was run in cyclohexane the *anti* product was obtained in an excellent 94% ee.

Due to time constraints, it was not possible to screen more solvents or carry out more reactions with different substrates at 0 °C.

9.8 Conclusions and Future Work

In conclusion, the first study of aminonitriles as organocatalysts was displayed. Two compounds with distinctive differences were investigated; L-valine nitrile **4**, an aliphatic primary amine and L-proline nitrile **5**, a cyclic secondary amine. When L-valine nitrile was employed the results were disappointing in terms of conversion and enantioselectivity, however, the aldol products were formed with interesting *syn* diastereoselectivity. Future work in this area should be focused on computational studies to provide a satisfying answer on the *syn* selectivity of the catalyst and simultaneously attempt to optimise the conversion of the reaction.

L-proline nitrile **5** provided significantly better results in the aldol reaction. The conversions of the reactions were moderate to good in all cases of Table 13. Unfortunately, the enantioenrichement of the reactions was low, and the investigation of other substrates was halted. Screening of an array of solvents showed that cyclohexane and toluene were the optimal solvents for the reaction conditions. Future work should be focused on trying aldol reactions using L-proline nitrile as catalyst, at 0 °C, as recent results with an alternative catalyst demonstrated an increase in enantioselectivity.

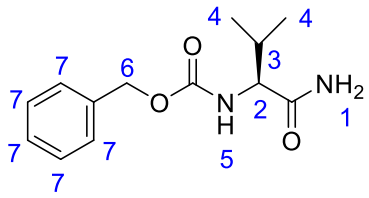
Gratifyingly, a new organocatalyst was discovered. The L-proline imidate **6** was synthesised and fully characterised. Moreover, it was examined for the first time as an organocatalyst. Results in the aldol reaction catalysed by L-proline imidate TFA salt **6** were encouraging and consistent. The catalyst afforded the aldol adducts in excellent yields. The *anti* stereoisomer was regularly predominant and the enantiomeric excess for the major product was, for the majority of the entries, above the region of 70% (Table 18). Importantly, the scope of the catalyst was demonstrated. L-proline imidate **6** was an effective catalyst irrespective of the solvent used (Table 18) or the aromatic aldehyde examined (Table 19). Further research on this catalyst should be focused in two directions. Firstly, the scope of the ketones that can undergo the aldol reaction catalysed by **6** and secondly, optimizing the results, possibly by repeating the reaction at lower temperatures.

The switch in the diastereoselectivity and enantioselectivity between L-valine nitrile **4** and L-proline nitrile **5**/ L-proline imidate **6** is interesting and worth further investigation.

10. Experimental

10.1 Experimental Procedures

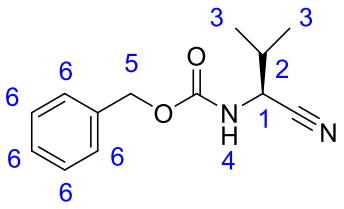
Cbz-L-valine-amide (64)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cbz-L-valine (2.0 g, 7.96 mmol) was added to the flask. To this flask EtN_3 (1.2 mL, 1.1 eq.) and dry THF (40 mL) was added. The solution was cooled at 0 °C and was stirred. After 10 minutes, ethyl chloroformate (0.8 mL, 1 eq.) was added and the reaction was continued to be stirred at 0 °C. After 1 h NH_3 in MeOH (7 N) was added (1.66 mL, 1.5 eq.) and the reaction was continued to be stirred at 0 °C for another 1 h. After 1 h, the reaction was allowed to warm at room temperature and was continued to be stirred. After a further 17 hours, the reaction was deemed complete by TLC (90:10 DCM:MeOH) and the stirring stopped. The solvent was removed *in vacuo* and the white precipitate was filtered and washed with ice cold water to give the pure Cbz-protected amide **64** as a white solid in 87% yield (1.73 g, 6.92 mmol). Data identical to that reported in the literature.[40]

Melting Point: 206-209 °C, literature 205-208 °C.[58] **IR** (ATR): 3374, 3315 (N-H), 3201, 3030, 2972, 2958, 2895, 2872 (C-H), 1681, 1654 (C=O), 1243 (C-O) cm^{-1}. **[α]**$_D^{20}$ (deg cm^{-3} g^{-1} dm^{-1}) +24.7 (c=1.0 g cm^{-3} in DMF), **[α]**$_D^{25}$ (deg cm^{-3} g^{-1} dm^{-1}) literature +25.0 (c=1.0 g cm^{-3} in DMF).[40] **^{1}H NMR** (400 MHz, *DMSO-d_6*) δ ppm: 7.38 - 7.28 (6 H, m, H-7, H-1), 7.16 (1 H, d, *J*=8.9 Hz, H-5), 7.03 (1 H, br. s, H-1), 5.03 (2 H, s, H-6), 3.80 (1 H, dd, *J*=8.9, 6.6 Hz, H-2), 1.99 - 1.28 (1 H, apparent oct, J=6.6 Hz, H-3), 0.86 (3 H, d, *J*=6.6 Hz, H-4), 0.83 (3 H, d, *J*=6.6 Hz, H-4). **^{13}C NMR** (400 MHz, *DMSO-d_6*) δ ppm: 173.2 (C=O amide), 156.2 (C=O carbamate), 137.2 (Ar), 128.4 (7), 127.8 (7), 127.3 (7), 65.4 (6), 60.1 (2), 30.2 (3), 19.4 (4), 18.0 (4). **HRMS** (ESI): $[M+Na]^+$ HRMS found 107.0407, C_2D_6NaOS required 107.0408. $[M+Na]^+$ HRMS found 273.1210, $C_{13}H_{18}N_2O_3$ required 273.1210.

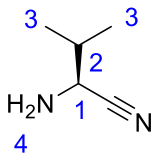
Cbz-L-Valine nitrile (65)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cbz-L-valine amide **64** (1.75 g, 7.00 mmol), dissolved in dry THF (30 mL), and was added to the flask. The flask was cooled at 0 °C, and EtN_3 (2.18 mL, 2.2 eq.) was added and the solution was stirred. After 30 minutes, TFAA (1.50 mL, 10.5 eq.) was added and the reaction was continued to be stirred at 0 °C for 1 hour and a further 17 hours at room temperature. The reaction was deemed complete by TLC (90:10 DCM:MeOH) and the stirring stopped. The solvent was removed in *vacuo* and the crude oil was re-dissolved in EtOAc. The crude mixture was washed with 2 M HCl and extracted with EtOAc (3 x 10 mL), organic layers combined and washed with saturated $NaHCO_3$ (3 x 10 mL), then washed with brine and extracted (1 x 10 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and the solution was concentrated *in vacuo* to give the crude product as red translucent oil. The crude product was then, further purified by column chromatography (90:10 hexane: EtOAc) and gave the pure Cbz-protected aminonitrile **65** as a red solid in a 90 % yield (1.47 g, 6.30 mmol). Data identical to that reported in the literature.[40]

Melting Point: 49-51 °C, literature 53 °C.[59] **IR** (ATR): 3298 (N-H),3064, 3032, 2970, 2930, 2877 (C-H), 2459 (CN), 1686 (C=O), 1213 (C-N), 1176 (C-O) cm^{-1}, $[\alpha]_D^{20}$ (deg cm^3 g^{-1} dm^{-1}) -43.07 (c = 1.0 g cm^{-3} in MeOH) , $[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) literature -37.3 (c = 0.97 g cm^{-3} in MeOH)[40] **^{1}H NMR** (400 MHz *DMSO* d^6): δ ppm 8.22 (1H, br. d, J= 8.0 Hz, H-4), 7.39-7.31 (5H, m, H-6), 5.09 (2H, s, H-5), 4.40 (1H, apparent t, J= 8.0, H-1), 1.98, (1H, m, H-2), 1.00 (3H, d, J= 6.8 Hz, H-3), 0.94 (3H, d, J= 6.8 Hz, H-3). **^{13}C NMR** (400 MHz, *DMSO-d_6*) δ ppm: 155.5 (C=O carbamate), 135.7 (Ar), 128.8 (6), 128.6 (6), 128.4 (6), 117.8 (CN), 67.9 (5), 49.1 (1), 31.9 (2), 18.7 (3), 18.0 (3). **HRMS** (ESI): $[M+Na]^+$ HRMS found 107.0406, $C_{13}D_6NaOS$ required 107.0408 $[M+Na]^+$ HRMS found 255.1105,$C_{13}H_{16}N_2O_2Na$ required 255.1104.

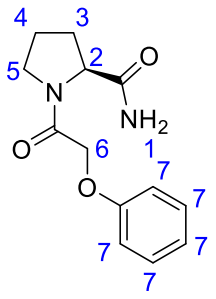
L-Valine nitrile (4)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cbz-L-valine nitrile **65** (200 mg, 0.86 mmol) in EtOAc (7.5 mL) and Pearlman's reagent (20% b.w., 60 mg, 0.1 eq.) were placed in the flask and the flask was evacuated. Then the flask was placed under a hydrogen atmosphere (60 psi) and was stirred. After 1.5 h of stirring the reaction was deemed complete by TLC (95:5 DCM:MeOH) and the stirring stopped. The mixture was filtered through a pad of celite and the celite was washed thoroughly with EtOAc (50 mL). 4 M HCl in dioxane (1.0 mL) was added and the reaction was stirred for 30 minutes turning the solution cloudy. Upon evaporation the salt of the amine was isolated as a white-yellow solid. The free amine **4** was liberated by dissolving the salt in DCM and stirring over sodium bicarbonate for 30 mins before filtering and concentrating in *vacuo***,** as yellow oil in a 91% yield (76 mg, 0.78 mmol). Data identical to that reported in the literature. [40]

IR (ATR): 3384 (N-H), 2228 (CN), 1098 (C-N) cm^{-1}, **$[\alpha]_D^{20}$** (deg cm^3 g^{-1} dm^{-1}) -6.37 (c = 1.0 g cm^{-3} in DCM) **$[\alpha]_D^{25}$** (deg cm^3 g^{-1} dm^{-1}) literature -8.3 (c = 0.83 g cm^{-3} in DCM)[40] **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 3.52 (1 H, d, J=5.6 Hz, H-1), 1.93 (1 H, dspt, J=6.8, 5.6 Hz, H-2), 1.64 (2 H, br. s, H-4), 1.07 (3 H, d, J=6.8 Hz, H-3), 1.06 (3 H, d, J=6.8 Hz, H-3) **^{13}C NMR** (400 MHz, $CDCl_3$): δ 121.1 (CN), 49.7 (1), 32.8 (2), 18.8 (3), 17.5 (3); **HRMS** (ESI): $[M+H]^+$ HRMS found 99.0919, $C_5H_{11}N_2$ required 99.0917.

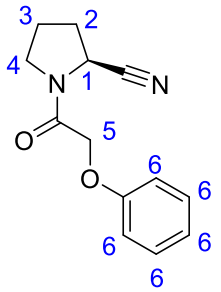
Cbz-L-Proline Amide (72)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cbz-L-proline (3.0 g, 12.0 mmol) was added to the flask. The flask was cooled at 0 °C, Et_3N (1.82 mL, 1.1 eq.) and dry THF (40 mL) were added and the reaction was stirred. After 15 minutes of stirring, ethyl chloroformate (1.14 mL, 1 eq.) was added and the reaction was continued to be stirred at 0 °C. After 1 h NH_3 in MeOH (7 N) was added (2.5 mL, 1.5 eq.) and the reaction was continued to be stirred at 0 °C, for 1 hour. After that, the reaction was allowed to warm at room temperature and was continued to be stirrer. After a further 14 h the reaction was deemed complete by TLC (90:10 DCM:MeOH) and the stirring stopped.. The solvent was removed *in vacuo*. The solution was then washed with water (10 mL) and extracted with EtOAc (3 x 10 mL). Organic layers combined, washed with $NaHCO_3$ and extracted (3 x 10 mL). Organic layers once again combined, dried over magnesium sulfate, filtered and the solution was concentrated in *vacuo*, to give the title product **72** as a white solid in a 56% yield (1.72 g, 6.7 mmol). Data identical to that reported in the literature.[60]

Melting Point: 88-90 ˚C, literature 91-93 ˚C.[60] **IR** (ATR): 3386 (N-H), 1677 (C=O), 1120 (C-N) cm^{-1}, **$[\alpha]_D^{25}$** (deg cm^3 g^{-1} dm^{-1}) -34.4 (c= 1.0 g cm^{-3} in MeOH), **$[\alpha]_D^{20}$** (deg cm^3 g^{-1} dm^{-1}) literature -36.0 (c= 1.0 g cm^{-3}, MeOH).[61] **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 7.36 (5 H, br. s. H-7), 6.71 (1H, s. H-1), 5.58 (1 H, br. s. H-1), 5.18 - 5.13 (2 H, m, H-6), 4.41 - 4.26 (1 H, m, H-2), 3.62-3.45 (2 H, m. H-5), 2.35-1.87 (4 H, m. H-3, H-4). **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 174.4 (C=O amide), 156.2 (C=O carbamate), 136.4 (Ar), 128.6 (7), 128.3 (7), 128.1 (7), 67.5 (C-O), 47.2 (2), 31.2 (CH_2), 28.3 (CH_2), 24.7 (CH_2) **HRMS** (ESI): $[M+H]^+$ HRMS found 249.1235, $C_{13}H_{17}N_2O_3$ required 249.1234. $[M+Na]^+$ HRMS found 271.1053, $C_{13}H_{16}N_2NaO_3$ required 271.1053.

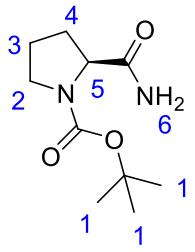
Cbz-L-Proline Nitrile (73)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cbz-L-proline amide **72** (1.5 g, 6.3 mmol) was dissolved in dry THF (30 mL) and was added to the flask and the flask was cooled at 0 °C. To this flask was added EtN_3 (1.9 mL, 2.2 eq.) and the solution was stirred. After 30 minutes TFAA was added (2.0 g, 1.5 eq.) dropwise and the reaction was continued to be stirred at 0 °C. After 45 minutes, the reaction was allowed to warm at room temperature. After a further 16 h, the reaction was deemed complete by TLC (90:10 DCM:MeOH) and the stirring stopped. The solvent was removed in *vacuo* and the red oil was re-dissolved in EtOAc. The solution was washed with 2 M HCl and extracted with EtOAc (3 x 10 mL). Organic layers were combined and washed with $NaHCO_3$ and extracted (3 x 10 mL). Organic layers were once again combined, washed with brine and extracted (3 x 10 mL). Then the combined organic layers dried over magnesium sulfate and filtered. The solution was concentrated *in vacuo* to give the crude mixture as red oil. The mixture was further purified by column chromatography (80:20 hexane:EtOAc) to give the title compound **73** as a colourless oil in 65% yield (950 mg, 4.13 mmol). Data identical to that reported in the literature.[34]

IR (ATR): 2239 (CN), 1704 (C=O), 1119 (C-N) $cm^{-1,}$, $\mathbf{[\alpha]_D^{25}}$ (deg cm^3 g^{-1} dm^{-1}) -88.0 (c= 1.0 g cm^{-3} in $CHCl_3$), $\mathbf{[\alpha]_D^{25}}$ (deg cm^3 g^{-1} dm^{-1}) literature -89.0 (c= 1.0 g cm^{-3}, $CHCl_3$).[34] **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 7.44 - 7.30 (5 H, m, H-6), 5.25 - 5.12 (2 H, m, H-5), 4.66 - 4.52 (1 H, m, H-1), 3.65 - 3.51 (2 H, m, H-4), 2.32 - 2.03 (4 H, m, H-3, H-2). **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 153.7 (C=O), 136.1 (Ar), 128.7 (6), 128.4 (6), 128.3 (6), 119.1 (CN), 67.9 (5), 47.1 (5), **HRMS** (ESI): $[M+Na]^+$ HRMS found 253.0946, $C_{13}H_{14}N_2NaO_3$ required 253.0947.

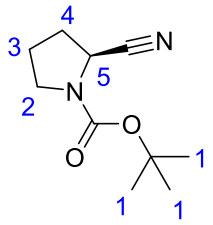
Boc-L-Proline Amide (75)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Boc-L-proline (2.0 g, 9.2 mmol) and dry THF (30 mL) were added to the flask. To this flask, EtN_3 (1.43 mL, 1.1 eq.) was added and the solution was stirred, at room temperature. After 15 minutes, ethyl chloroformate (0.86 mL, 1 eq.) was added and the reaction was continued to be stirred at room temperature. After 1 h, NH_3 in MeOH (7 N) (2 mL), was added and the reaction was continued to be stirred for a further 14 hours. After that, the reaction was deemed complete by TLC (70:30 hexane:EtOAc) and the stirring stopped. The solvent was removed *in vacuo* and the solution was washed with water (10 mL) and extracted with DCM (5 x 10 mL). The combined organic layers dried over magnesium sulfate and the solution was concentrated in vacuo to give the title compound **75** as a white solid in an 85% yield (1.67 g, 7.8 mmol). Spectroscopic data are in agreement with the literature.[40]

IR (ATR): 3344 (N-H stretch), 1676 (C=O, stretch), 1164 (C-O stretch) cm^{-1}, $\mathbf{[\alpha]_D^{25}}$ (deg cm^3 g^{-1} dm^{-1}) -44.7 (c= 1.0 g cm^{-3} in MeOH), $\mathbf{[\alpha]_D^{25}}$ (deg cm^3 g^{-1} dm^{-1}) literature -42.4 (c=1.0 g cm^{-3} in MeOH).[52] **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 6.85 (1H, s, H-6), 5.40-6.10 (1H, m, H-6), 4.35-4.15 (1H, m, H-5), 3.55-3.25 (2H, m, H-2), 2.40-1.80 (4H, m, H-2, H-4), 1.45 (9H, s, H-1), **HRMS** (ESI): $[M+Na]^+$ HRMS found 237.1209, $C_{10}H_{18}N_2O_3Na$ required 237.1210.

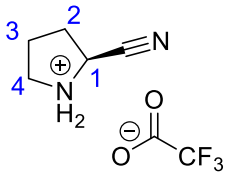
Boc-L-Proline Nitrile (76)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Boc-L-proline amide **75** (625 mg, 2.92 mmol) in dry THF (20 mL) and Et_3N (0.9 mL, 2.2 eq.) were added to the flask. The flask was cooled at 0 °C and stirred. After 30 minutes of stirring, TFAA in a dry ampule (1.0 g, 1.5 eq.) was added and the reaction was continued to be stirred at 0 °C. After 2 hours the reaction was warmed at room temperature and was continued to be stirred. After a further 16 hours the reaction was deemed complete by TLC (90:10 DCM:MeOH) and the stirring stopped. The solvent was removed in *vacuo*. The crude yellow oil was re-dissolved in EtOAc and was washed with 2 M HCl and extracted with EtOAc (3 x 10 mL). Organic layers were combined, washed with saturated $NaHCO_3$ and extracted (3 x 10 mL). Organic layers again, were combined, washed with brine and extracted (3 x 10 mL). Organic layers were combined, dried over magnesium sulfate and filtered. The solution was concentrated *in vacuo* to give the crude product as an orange oil. The crude oil was further purified by column chromatography (20:80 EtOAc:hexane) to give the title compound **76** as a pale yellow oil in a 89% yield (508 mg, 2.60 mmol). Data identical to that reported in the literature.[40]

IR (ATR): 2976, 2239 (CN), 1797, 1692 (C=O stretch) cm^{-1}; $[\alpha]_D^{20}$ (deg cm^3 g^{-1} dm^{-1}) -91.15 (c= 1.3 g cm^{-3} in MeOH), $[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) literature -95.5 (c= 1.3 g cm^{-3} in MeOH).[52] **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 4.60 - 4.40 (1 H, m, H-5), 3.58-3.25 (2 H, m, H-2,) 2.30 – 1.95 (4 H, m, H-3, H-4), 1.50 - 1.45 (9 H, m, H-1), **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 153.1 (C=O), 119.3 (CN), 81.6 (*t*-Bu), 47.3 (5), 45.8 (CH2), 31.8 (CH2), 28.4 (1), 23.9 (CH2); **HRMS** (ESI) $[M+Na]^+$ HRMS found 219.1105, $C_{10}H_{16}N_2O_2Na$ required 219.1104

L-proline nitrile salt (5)



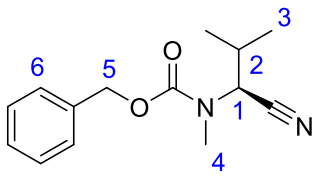
A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Boc-L- proline nitrile **78** (364 mg, 1.7 mmol) and TFA (3.6 mL, 25 eq.) in dry DCM (5 mL) were added to the flask and the flask was cooled at 0 °C. The solution was stirred until the reaction was deemed complete by TLC (90:10 DCM:MeOH). The stirring was stopped and solvent was removed *in vacuo*. Trituration with Et_2O provided the pure TFA salt of L-proline nitrile **5** in a 93% yield (318 mg, 1.58 mmol)**.** Spectroscopic data are in agreement with the literature.[40]

IR (ATR): 3323 (N-H stretch), 2943, 2831, 2269 (CN), 1665 (C=O); **Melting Point** 90-92 °C; literature 92-94 °C.[62] **$[\alpha]_D^{20}$** (deg cm^3 g^{-1} dm^{-1}) -11.6 (c=1.0 g cm^{-3} in MeOH), **$[\alpha]_D^{25}$** (deg cm^3 g^{-1} dm^{-1}) literature -16.7 (c= 1.0 g cm^{-3} in MeOH),[40] **^{1}H NMR** (400 MHz, *MeOD* d^4) δ ppm: 4.60 (1 H, t, *J*=7.4 Hz, H-1), 3.62 - 3.43 (2 H, m, H-4), 2.58 - 2.47 (1 H, m, H-2), 2.27 – 1.97 (3 H, m, H-2, H-3), **^{13}C NMR** (400 MHz, *MeOD* d^4) δ ppm: 161.8 (q, J=34.7 Hz, C-F_3), 115.2 (CN), 46.8 (1), 45.8 (4), 29.9 (2) , 23.2 (3). **HRMS** (ESI) $[M+H]^+$ HRMS found 97.0759 $C_5H_9N_2$ required 97.0760.

The free amine was liberated by dissolving the salt in DCM and stirring over sodium bicarbonate for 30 mins before filtering and concentrating in *vacuo* in a 63% yield (90 mg, 1.07 mmol).

^{1}H NMR (400 MHz, *MeOD* d^4) δ ppm: 4.07 (1 H, dd, J = 7.9, 4.7 Hz, H-1), 3.10 – 2.85 (2 H, m, H-4), 2.15 (1 H, m, H-2), 2.07 – 1.74 (3 H, m, H-3, H-2).

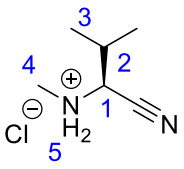
Cbz-*N*-methyl-L-valine nitrile (69)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cbz-L-valine nitrile **65** (400 mg, 1.72 mmol) was dissolved in dry THF (10 mL) and was added to the flask. Potassium bis (trimethyl silyl) amide 0.5 M in toluene (343.10 mg, 1.72 mmol) was then added to this flask at -78° C. After 0.5 hours, iodomethane (0.11 mL, 1.90 mmol) was added to the solution. The reaction mixture was then allowed to warm at room temperature overnight. After a further 18 h, the solution was washed with saturated aqueous potassium carbonate solution (30 mL), then brine (30 mL) followed by 1 mol dm^{-3} aqueous sodium hydroxide solution (30 mL). The aqueous washes were each extracted with EtOAc (3 × 10 mL). The organic fractions were then combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to give the crude title compound as a yellow oil which was then further purified by column chromatography (10:90 EtOAc:hexane) to give the pure title compound **69** in 53% yield (1.07 g, 4.13 mmol) as a colourless oil. Data identical to the reported in the literature.[63]

IR (ATR): 2968, 2253 (CN), 1699 (C=O), 1453, 1397 $cm^{-1,}$; $\mathbf{[\alpha]_D^{25}}$ (deg cm^3 g^{-1} dm^{-1}) -52.5 (c= 1.15 g cm^{-3} in $CHCl_3$), $\mathbf{[\alpha]_D^{25}}$ (deg cm^3 g^{-1} dm^{-1}) literature -53.64 (c=2.0 g cm^{-3} in $CHCl_3$),[63] **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 7.42 – 7.30 (5 H, m, H-6), 5.17 (2 H, d, J = 3.1 Hz, H-5), 4.87 (1 H, d, J = 10.6 Hz, H-1), 2.98 (3 H, s, H-4), 2.11 (1 H, dhept, J = 10.6, 7.1 Hz, H-2), 1.16 (3 H, d, J = 7.1 Hz, H-3), 0.92 (3 H, d, J = 7.1 Hz, H-3), **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 156.3 (C=O), 136.1 (Ar), 128.7 (6), 128.4 (6), 128.1 (6), 117.4 (CN), 68.2 (5), 54.8 (1), 30.3 (4), 30.1 (2), 19.4 (3), 18.3 (3), **HRMS** (ESI): $[M+H]^+$ HRMS found 247.1441, $C_{14}H_{19}N_2O_2$ required 247.1441, $[M+Na]^+$ HRMS found 269.1260, $C_{14}H_{18}N_2NaO_2$ required 269.1260.

N-methyl-L-valine nitrile salt (70)



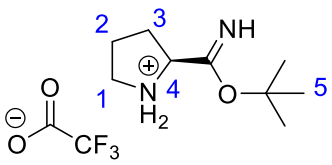
A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cbz-N-methyl-L-valine nitrile **69** (50 mg, 0.20 mmol) dissolved in EtOAc (1.8 mL) and Pearlman's reagent (20% b.w., 14 mg, 0.1 eq.) were added to this flask and the flask was evacuated. Then the flask was placed under a hydrogen atmosphere (60 psi) and was stirred. After a further 1.5 h the reaction was deemed complete by TLC (95:5 DCM:MeOH) and the stirring stopped. The mixture was filtered through a pad of celite and the celite was washed thoroughly with EtOAc (20 mL). 4 M HCl in dioxane (1.0 mL) was added and the solution was stirred for 30 minutes became cloudy. Upon evaporation the salt of the amine **70** was isolated as a white-yellow gum in a 99% yield (30mg, 0.20mmol).

IR (ATR): 2925, 2254 (CN) cm^{-1}; **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 10.36 (2 H, br. s. H-5), 4.04 (1 H, br. s. H-1), 2.90 (3 H, br. s, H-4), 2.61 (1 H, br. s. H-2), 1.32 (3 H, d, J = 6.0 Hz, H-3), 1.23 (3 H, d, J = 6.0 Hz, H-3). **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 113.1 (CN), 56.8 (1), 32.9 (4), 29.8 (2) 19.7 (3), 18.0 (3); **HRMS** (ESI) $[M+H]^+$ HRMS found 113.1071, $C_6H_{13}N_2$ required 113.1073

The free amine was isolated by neutralisation with saturated sodium bicarbonate and subsequent extraction with DCM**,** as a yellow oil in a 99% yield (22 mg, 0.20 mmol).

IR (ATR): 2925, 2254 (CN) cm^{-1}; **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 3.26 (1 H, d, J= 6.8 Hz, H-1), 2.56 (3 H, s, H-4), 2.00 (1 H, dq., J=13.3 Hz, 6.8 Hz, H-2), 1.09 - 1.07 (6 H, dd, J = 6.8 Hz, 2.4 Hz, H-3). **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 119.3 (CN), 59.4 (1), 34.4 (4), 29.9 (2) 19.2 (3), 18.1 (3); **HRMS** (ESI) $[M+H]^+$ HRMS found 113.1071, $C_6H_{13}N_2$ required 113.1073

L-proline imidate salt (6)



A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Boc-L- proline nitrile **76** (200 mg, 1.02 mmol) dissolved in TFA (3.55 mL, 45 eq.) were added to this flask and the flask was cooled at 0 °C. Upon consumption of the starting material (TLC check) *t*-BuOH (0.2 mL, 2 eq.) was added and the reaction was allowed to warm at room temperature. The reaction was left stirring overnight. Stirring was stopped and the solvent was removed *in vacuo*. Trituration with hot isopropyl ether provided the TFA salt of the L-proline imidate **6** in a 75% yield (217.5 mg, 0.77 mmol).

Melting Point 88-90 °C, **IR** (ATR): 3300 (N-H), 2967, 2872, 1658 (C=N) cm^{-1}; **$[\alpha]_D^{25}$** (deg cm^3 g^{-1} dm^{-1}) -47.23 (c= 1.0 g cm^{-3} in DCM), **^{1}H NMR** (400 MHz, *MeOD*) δ ppm: 8.00 (1 H, br. s, N-H), 4.15 (1 H, dd, J = 8.4, 6.8 Hz, H-4), 3.44 – 3.32 (2 H, m, H-1), 2.48 – 2.34 (1 H, m, H-3), 2.09 – 1.89 (3 H, m, H-2, H-3), 1.36 (9-H, s, H-5). **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 167.2 (C=N), 59.9 (4), 51.4 (*t*-Bu), 51.2 (3), 46.1 (1), 30.1 (2), 29.7 (5), **HRMS** (ESI) $[M+H]^+$ HRMS found 171.1491, $C_9H_{19}N_2O$ required 171.1492

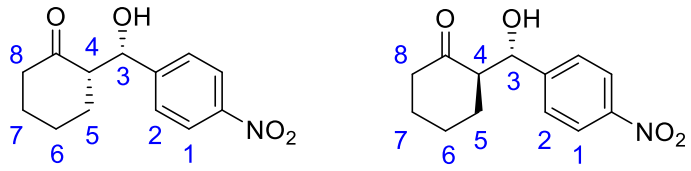
The free L-proline imidate was liberated by dissolving the salt in DCM and stirring over sodium bicarbonate for 30 mins before filtering and concentrating *in vacuo* in a 55% yield (31 mg, 0.18 mmol).

IR (ATR): 3300 (N-H), 2967, 2872, 1658 cm^{-1}; **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm: 7.44 (1 H, br. s, N-H), 3.69 (1 H, dd, J = 8.8, 5.6 Hz,H-4), 3.10 – 2.86 (3 H, m, H-1, H-3) 2.18 – 2.05 (1 H, ddt, J= 12.6, 8.8, 7.1 Hz, H-3), 1.92 – 1.81 (1 H, m, H-2), 1.78-1.64 (1 H, m, H-2), 1.33 (9 H, s, H-5). **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 173.5 (C=N), 61.1 (4), 50.4 (*t*-Bu), 47.2 (1), 30.8 (3), 28.8 (5), 26.1 (2), **HRMS** (ESI) $[M+H]^+$ HRMS found 171.1491, $C_9H_{19}N_2O$ required 171.1492

10.2 General Procedure for the Aldol Reaction catalysed by L-valine nitrile

A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cyclohexanone (0.13 mL, 1.25 eq.) was added to this flask. Catalyst (0.025 mmol, 0.1 eq.) was dissolved in 1 mL of solvent and was added to the flask and the flask was stirred. After 5 minutes, 4-nitrobenzaldehyde (37.78 mg, 0.25 mmol) was added and the reaction was continued to be stirred for a further 24 h. The stirring stopped after 24 h and the reaction was quenched with NH_4Cl and the solvent was removed *in vacuo* at room temperature. The crude product was re-dissolved in DCM and washed with water (5 mL) and extracted with DCM (3 x 10 mL). Organic layer was dried over sodium sulfate and filtered. The solution was then concentrated *in vacuo*. The conversion of the reaction was determined by integrating the ^{1}H NMR of the crude reaction mixture using the aldehyde peak as a reference. *Syn/anti* ratio was determined by integrating the ^{1}H NMR of the crude reaction mixture and by comparing the two C***H***-OH peaks. The enantiomeric excess of the crude product was analysed, via HPLC using a chiralpak IB column.

2-(hydroxy((4-nitrophenyl)methyl)cyclohexanone (3)



The two *syn* and *anti* diastereoisomers were isolated after column chromatography (5:95 EtOAc:hexane).

Retention times for the *syn* and *anti* stereoisomers catalyzed by L-valine nitrile **4**: *syn* diastereomer: minor enantiomer t_R = 27.9 min, major enantiomer t_R = 29.5 min; *anti* diastereomer: minor enantiomer t_R = 34.7 min, major enantiomer t_R = 43.3 min.

Spectroscopic data of **3** catalysed by L-valine nitrile **4:**

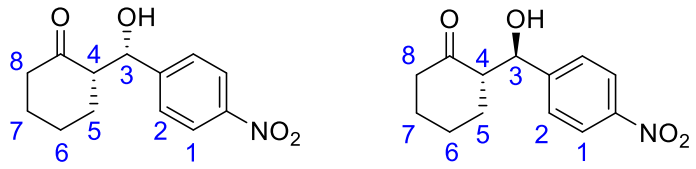
syn diastereomer: **IR** (ATR): 3517, 2940, 1700, 1516, 1346 cm^{-1}, **^{1}H NMR** (400 MHz, *$CDCl_3$)* δ ppm: 8.21 (2 H, m, H-1), 7.49 (2 H, m, H-2), 5.49 (1 H, br. s, H-3), 3.18 (1 H, br. s, O*H*), 2.66-2.59 (1 H, m, H-4), 2.52-2.46 (1 H, m, H-8), 2.45 - 2.35 (1 H, m, H-8), 2.15-2.08 (1 H, m, H-7), 1.89-1.82 (1H, m, H-6), 1.76-1.65 (2 H, m, H-5, H-7), 1.63-1.47 (2 H, m, H-5, H-6), **^{13}C NMR** (400 MHz, *$CDCl_3$*) δ ppm: 214.0 (C=O), 149.1 (Ar), 147.1 (C-N), 126.7 (2), 123.8 (1), 70.2 (3), 56.9 (4), 42.7 (8), 28.0 (7), 26.0 (5), 25.0 (6), **HRMS** (ESI) HRMS found 272.0875, $C_{13}H_{15}NNaO_4$ required 272.0893

anti diastereoisomer: **IR** (ATR): 3510, 2939, 1693, 1520, 1346 cm^{-1}, **^{1}H NMR** (400 MHz, *$CDCl_3$)* δ ppm: 8.21 (2 H, m, H-1), 7.51 (2 H, m, H-2), 4.89 (1H, dd, J=3.2 Hz, 8.35 Hz, H-3), 4.08 (1 H, d, J=3.2 Hz, O*H*), 2.64-2.54 (1 H, m, H-4), 2.53-2.46 (1 H, m, H-8), 2.42 - 2.31 (1 H, m, H-8), 2.15-2.08 (1 H, m, H-7), 1.89-1.79(1 H, m, H-6), 1.74-1.64 (1 H, m, H-5,), 1.63-1.47 (2 H, m, H-5, H-6), 1.45-1.34 (1 H, m, H-7), **HRMS** (ESI) HRMS found 272.0879, $C_{13}H_{15}NNaO_4$ required 272.0893. Spectroscopic data are in agreement with the literature.[56]

10.3 General Procedure for the Aldol Reaction catalysed by L-proline nitrile and L-proline imidate

A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cyclohexanone (0.13 mL, 1.25 eq.) was added to this flask. The TFA salt of the catalyst (0.025 mmol, 0.1 eq.) was dissolved in 1 mL of solvent and was added to the flask. Solid sodium bicarbonate (0.025 eq.) was then added to the flask and the flask was stirred. After 5 minutes, 4-nitrobenzaldehyde (37.78 mg, 0.25 mmol) was added and the reaction was continued to be stirred for a further 24 h. The stirring stopped after 24 h and the reaction was quenched with NH_4Cl and the solvent was removed *in vacuo* at room temperature. The crude product was re-dissolved in DCM and washed with water (5 mL) and extracted with DCM (3 x 10 mL). Organic layer was dried over sodium sulfate and filtered. The solution was then concentrated *in vacuo*. The conversion of the reaction was determined by integrating the ^{1}H NMR of the crude reaction mixture using the aldehyde peak as a reference. *Syn/anti* ratio was determined by integrating the ^{1}H NMR of the crude reaction mixture and by comparing the two C***H***-OH peaks. The enantiomeric excess of the crude product was analysed, via HPLC using a chiralpak IB/AD-H column.

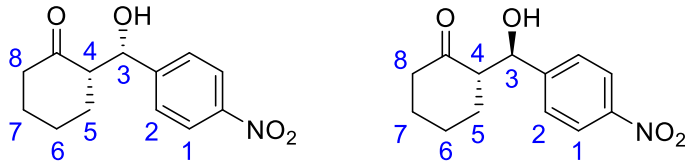
2-(hydroxy((4-nitrophenyl)methyl)cyclohexanone (3)



Retention times for the *syn* and *anti* stereoisomers catalyzed by L-proline nitrile **5**: *syn* diastereomer: minor enantiomer t_R = 27.7 min, major enantiomer t_R = 30.0 min; *anti* diastereomer: major enantiomer t_R = 34.6 min, minor enantiomer t_R = 43.0 min.

Spectroscopic data for **3** catalysed by L-proline nitrile **5** were identical as when the reaction was catalysed by L-valine nitrile **4**.

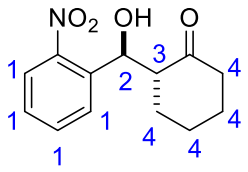
2-(hydroxy((4-nitrophenyl)methyl)cyclohexanone (3)



Retention times for the *syn* and *anti* stereoisomers catalyzed by L-proline imidate **6**: *syn* diastereomer: minor enantiomer t_R = 28.1 min, major enantiomer t_R = 30.2 min; *anti* diastereomer: major enantiomer t_R = 34.8 min, minor enantiomer t_R = 43.1 min.

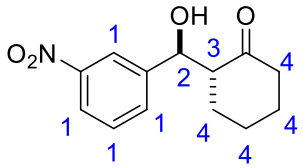
Spectroscopic data for **3** catalysed by L-proline imidate **6** were identical as when the reaction was catalysed by L-valine nitrile **4**.

2-(hydroxy((2-nitrophenyl)methyl)cyclohexanone (79a)



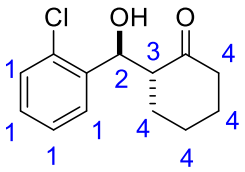
Diastereomeric ratio *anti*/*syn*=4.7/1.0, 75% *anti* ee; **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ(ppm) (as a mixture of *anti*/*syn* diastereomers): 8.03-7.98 (1 H, m, *syn* H-1), 7.88-7.81 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 7.79-7.75 (1 H, m, *anti* H-1), 7.67-7.60 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 7.46-7.40 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 5.96 (1 H, d, J=2.2 Hz, *syn* H-2), 5.45 (1 H, d, J=5.1 Hz, *anti* H-2), 4.18 (1 H, br. s., *anti* CH-O***H***), 2.93-2.85 (1 H, m, *syn* H-3), 2.80-2.71 (1 H, m, *anti* H-3), 2.50-2.28 (4 H, m, 2 *syn* H-4, 2 *anti* H-4), 2.15-2.04 (2 H, m, 1 *syn* H-4, 1 *anti* H-4), 1.90-1.45 (10 H, m, 5 *syn* H-4, 5 *anti* H-4). Spectroscopic data are in agreement with the literature.[64]

2-(hydroxy((3-nitrophenyl)methyl)cyclohexanone (79b)



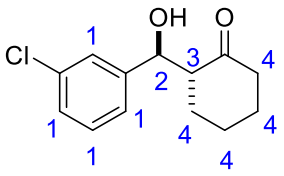
Diastereomeric ratio *anti*/*syn*=3.0/1.0, 63% *anti* ee; **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) (as a mixture of *anti*/*syn* diastereomers): 8.22-8.09 (4 H, m, 2 *syn* H-1, 2 *anti* H-1), 7.70-7.63 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 7.56-7.48 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 5.48 (1 H, d, J=2.6 Hz, *syn* H-2), 4.89 (1 H, d, J=8.4 Hz, *anti* H-2), 4.12 (1 H, br. s., *anti* CH-O***H***), 3.18 (1 H, br. s., *syn* CH-O***H***), 2.69-2.57 (2 H, m, *syn* H-3, *anti* H-3) 2.54-2.45 (2 H, m, 1 *syn* H-4, 1 *anti* H-4), 2.16-2.06 (2 H, m, 1 *syn* H-4, 1 *anti* H-4), 1.91-1.50 (12 H, 6 *syn* H-4, 6 *anti* H-4). Spectroscopic data are in agreement with the literature.[64]

2-(hydroxy((2-chlorophenyl)methyl)cyclohexanone (79c)



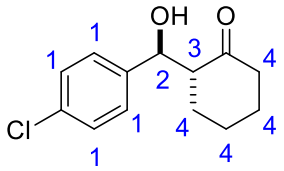
Diastereomeric ratio *anti*/*syn*=5.0/1.0, 76% *anti* ee; **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) (as a mixture of *anti*/*syn* diastereomers): 7.58-7.51 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 7.35-7.28 (4 H, m, 2 *syn* H-1, 2 *anti* H-1), 7.24-7.18 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 5.71 (1 H, br. s., *syn* H-2), 5.35 (1 H, d, J=8.1 Hz, *anti* H-2), 4.02 (1 H, br. s., *anti* CH-O***H***), 3.14 (1 H, br. s., *syn* CH-O***H***), 2.86-2.77 (1 H, m, *syn* H-3), 2.74-2.60 (1 H, m, *anti* H-3), 2.40-2.28 (4 H, m, 2 *syn* H-4, 2 *anti* H-4), 2.16-2.02 (2 H, 1 *syn* H-4, 1 *anti* H-4), 1.80-1.49 (10 H, 5 *syn* H-4, 5 *anti* H-4). Spectroscopic data are in agreement with the literature. [64]

2-(hydroxy((3-chlorophenyl)methyl)cyclohexanone (79d)



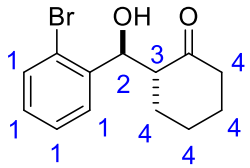
Diastereomeric ratio *anti*/*syn*= 3.0/1.0, 67% *anti* ee; **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ(ppm) (as a mixture of *anti*/*syn* diastereomers): 7.35-7.29 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 7.26-7.23 (2 H, m, 1 *syn* H-1, 1 *anti* H-1), 7.22-7.13 (4 H, 2 *syn* H-1, 2 *anti* H-1), 5.35 (1 H, br. s., *syn* H-2), 4.74 (1 H, d, J=8.6 Hz, *anti* H-2), 4.01 (1 H, br. s., *anti* CH-O***H***), 3.08 (1 H, br. s., *syn* CH-O***H***), 2.62-2.53 (2 H, m, *syn* H-3, *anti* H-3), 2.50-2.37 (4 H, m, 2 *syn* H-4, 2 *anti* H-4), 2.13-2.05 (2 H, m, 1 *syn* H-4 and 1 *anti* H-4), 1.81-1.76 (2 H, m, 1 *syn* H-4 and 1 *anti* H-4), 1.67-1.48 (8 H, m, 4 *syn* H-4, 4 *anti* H-4). Spectroscopic data are in agreement with the literature.[65]

2-(hydroxy((4-chlorophenyl)methyl)cyclohexanone (79e)



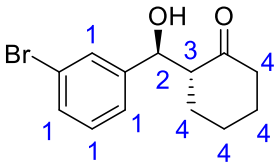
Diastereomeric ratio *anti*/*syn*= 2.7/1.0, 57% *anti* ee; **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ(ppm) (as a mixture of *anti*/*syn* diastereomers): 7.34-7.28 (4 H, m, 2 *syn* H-1, 2 *anti* H-1), 7.25-7.20 (4 H, m, 2 *syn* H-1, 2 *anti* H-1), 5.36 (1 H, d, J=2.5 Hz, *syn* H-2), 4.76 (1 H, d, J=8.7 Hz, *anti* H-2), 2.60-2.30 (6 H, m, *syn* H-3, *anti* H-3, 2 *syn* H-4, 2 *anti* H-4), 2.15-2.03 (2 H, m, 1 *syn* H-4, 1 *anti* H-4), 1.91-1.48 (10 H, m, 5 *syn* H-4, 5 *anti* H-4). Spectroscopic data are in agreement with the literature. [66]

2-(hydroxy((2-bromophenyl)methyl)cyclohexanone (79f)



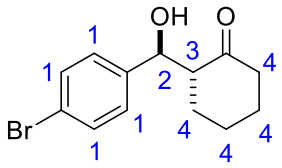
Diastereomeric ratio *anti*/*syn*= 7.0/1.0, 69% *anti* ee; **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) (*anti*): 7.56-7.48 (2 H, m, H-1), 7.39-7.30 (1 H, m, H-1), 7.17-7.09 (1 H, m, H-1), 5.33 (1 H, dd, J=8.5 Hz, 4.0 Hz, H-2), 4.05 (1 H, br. s., CH-O***H***), 2.73-2.63 (1 H, m, H-3), 2.50-2.44 (1 H, m, H-4), 2.39-2.35 (1 H, m, H-4), 2.14-2.06 (1 H, m, H-4), 1.81-1.75 (1 H, m, H-4), 1.69-1.50 (4 H, m, H-4). Spectroscopic data are in agreement with the literature.[67]

2-(hydroxy((3-bromophenyl)methyl)cyclohexanone (79g)



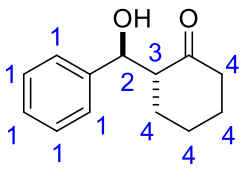
Diastereomeric ratio *anti*/*syn*= 2.5/1.0, 71% *anti* ee; **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) (as a mixture of *anti*/*syn* diastereomers): 7.55-7.32 (4 H, m, 2 *syn* H-1, 2 *anti* H-1), 7.24-7.16 (4 H, m, 2 *syn* H-1, 2 *anti* H-1), 5.36 (1 H, d, J=2.3 Hz, *syn* H-2), 4.74 (1 H, d, J=8.7 Hz, *anti* H-2), 4.01 (1 H, br. s., *anti* CH-O***H***), 2.62-2.38 (6 H, m, *syn* H-3, *anti* H-3, 2 *syn* H-4, 2 *anti* H-4), 2.15-2.04 (2 H, m, 1 *syn* H-4, 1 *anti* H-4), 1.90-1.50 (10 H, m, 5 *syn* H-4, 5 *anti* H-4). Spectroscopic data are in agreement with the literature.[68]

2-(hydroxy((4-bromophenyl)methyl)cyclohexanone (79h)



Diastereomeric ratio *anti*/*syn*= 3.0/1.0, 61% *anti* ee; **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) (as a mixture of *anti*/*syn* diastereomers): 7.50-7.41 (4 H, m, 2 *syn* H-1, 2 *anti* H-1), 7.23-7.14 (4 H, m, 2 *syn* H-1, 2 *anti* H-1), 5.34 (1 H, d, J=2.5 Hz, *syn* H-2), 4.75 (1 H, d, J=8.7 Hz, *anti* H-2), 2.61-2.27 (6 H, m, *syn* H-3, *anti* H-3, 2 *syn* H-4, 2 *anti* H-4), 2.15-2.01 (2 H, m, 1 *syn* H-4, 1 *anti* H-4), 1.92-1.40 (10 H, m, 5 *syn* H-4, 5 *anti* H-4). Spectroscopic data are in agreement with the literature.[66]

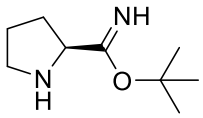
2-hydroxy((phenyl)methyl)cyclohexanone (79i)



Diastereomeric ratio *anti*/syn: 3.5/1.0, 67% *anti* ee; **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) (as a mixture of *anti*/*syn* diastereomers): 7.38-7.28 (10 H, m, 5 *syn* H-1, 5 *anti* H-1), 5.39 (1 H, d, J=2.4 Hz, *syn* H-2), 4.79 (1 H, d, J=8.9 Hz, *anti* H-2), 2.67-2.56 (2 H, m, *syn* H-3, anti H-3), 2.52-2.38 (4 H, m, 2 *syn* H-4, 2 *anti* H-4), 2.14-2.03 (2 H, m, 1 *syn* H-4, 1 *anti* H-4), 1.81-1.45 (10 H, m, 5 *syn* H-4, 5 *anti* H-4). Spectroscopic data are in agreement with the literature.[66]

10.4 Appendix

Figure 22. ^{1}H NMR spectrum of L-proline imidate **6**.



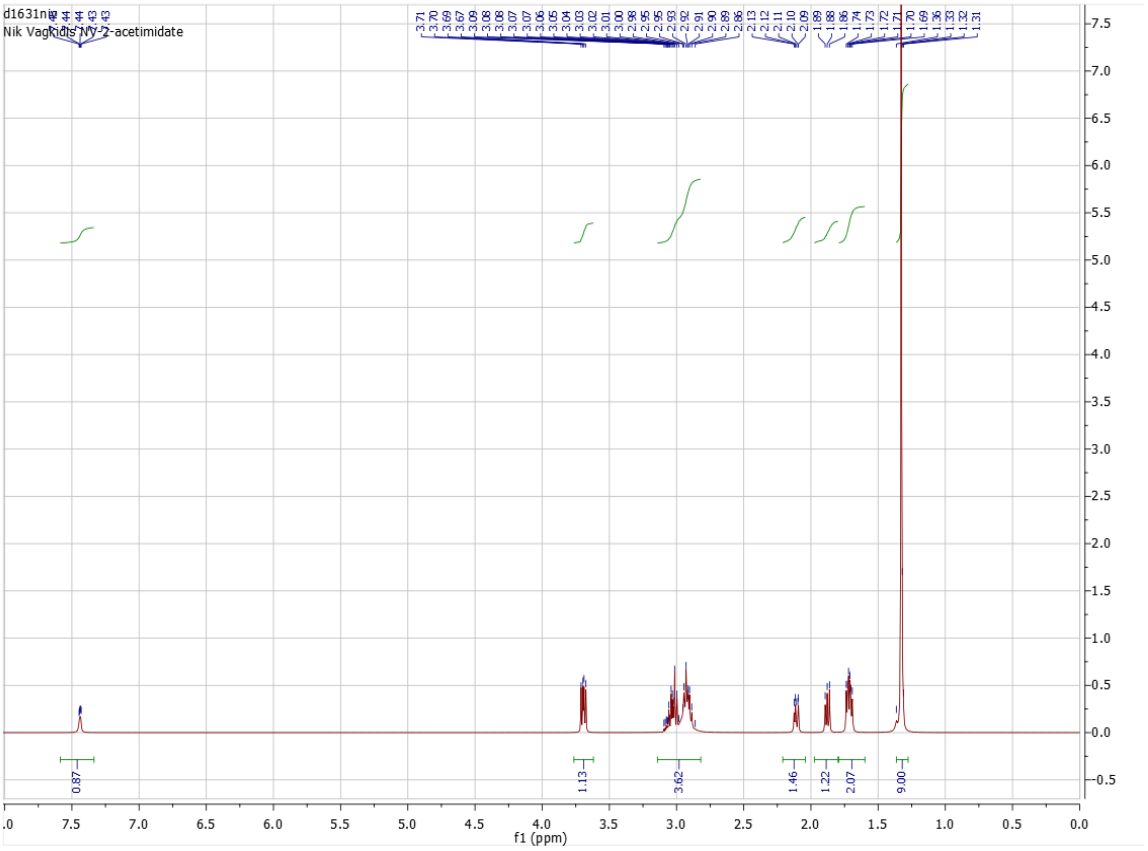
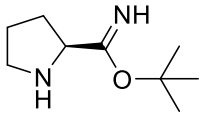


Figure 23. ^{13}C NMR spectrum of L-proline imidate **6**.



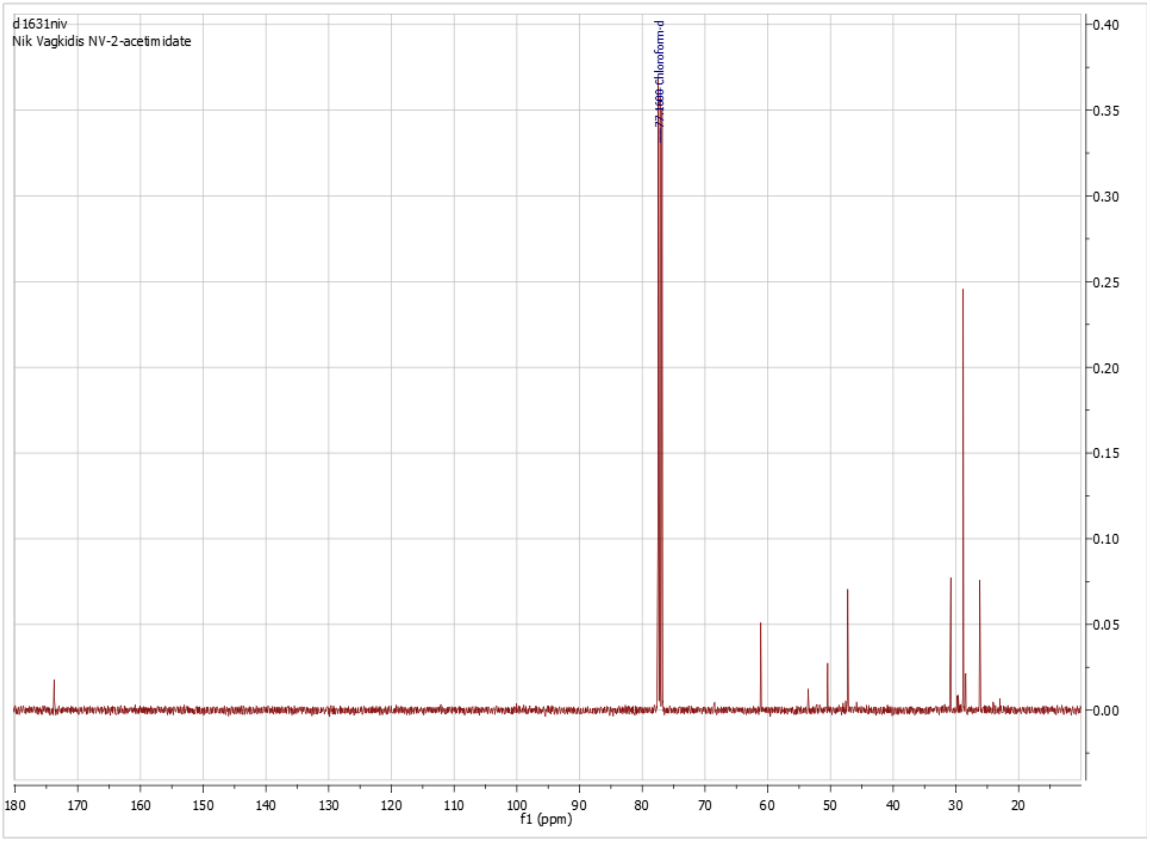
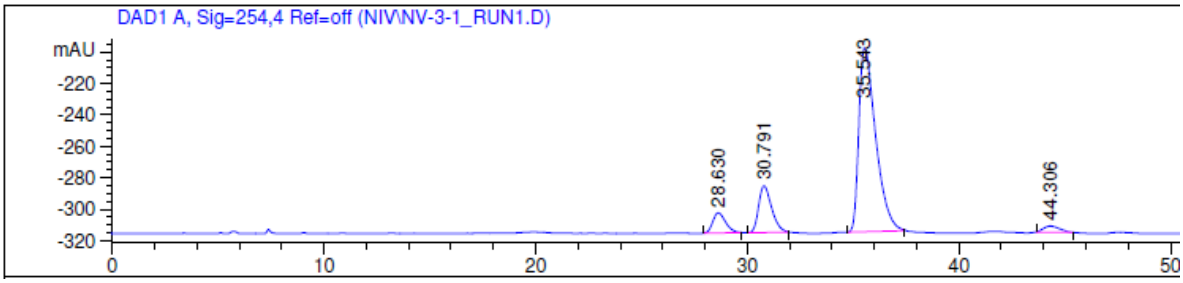
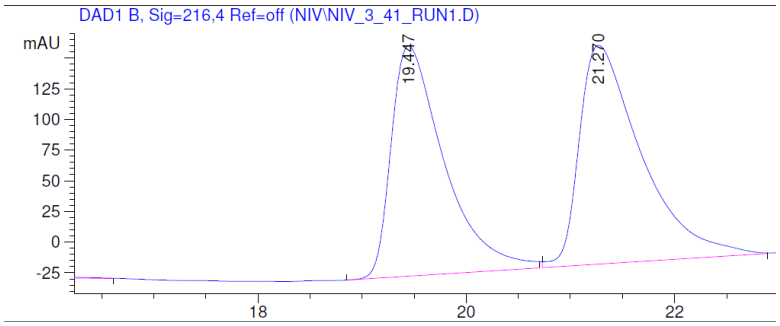


Figure 24. Representative HPLC trace of the aldol reaction between 4-nitrobenzaldehyde **1** and cyclohexanone **2** catalysed by L-proline imidate **6**.



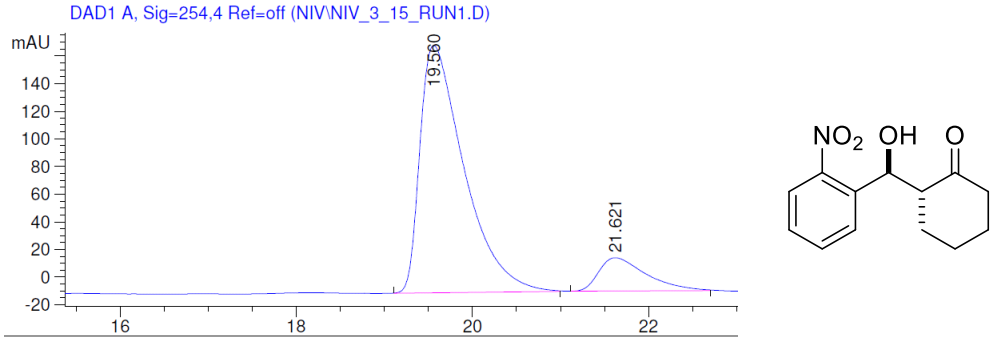
Peak	Retention time (min)	Area %
1	28.6	6.370
2	30.8	14.979
3	35.5	76.126
4	44.3	2.525

Retention times are in agreement with the literature.[48]



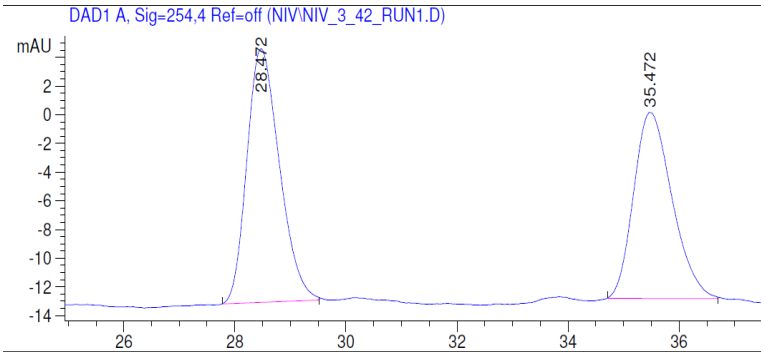
Peak	Retention time (min)	Area %
1	19.4	49.557
2	21.3	50.443

Figure 25. HPLC trace of racemic **79a**.



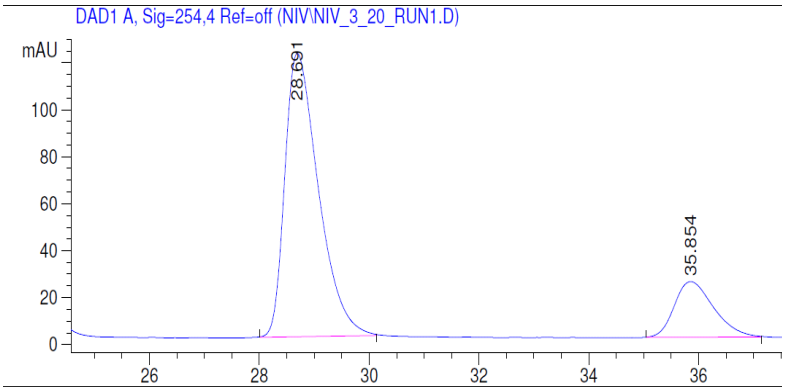
Peak	Retention time (min)	Area %
1	19.5	87.413
2	21.6	12.587

Figure 26. HPLC trace of enantioenriched **79a**.



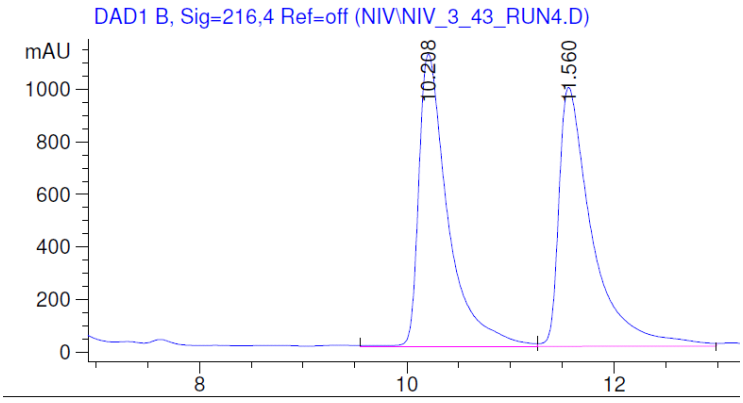
Peak	Retention time (min)	Area %
1	28.5	51.000
2	35.5	49.000

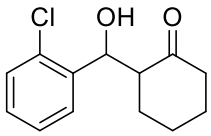
Figure 27. HPLC trace of racemic **79b**.



Peak	Retention time (min)	Area %
1	28.7	81.164
2	35.9	18.836

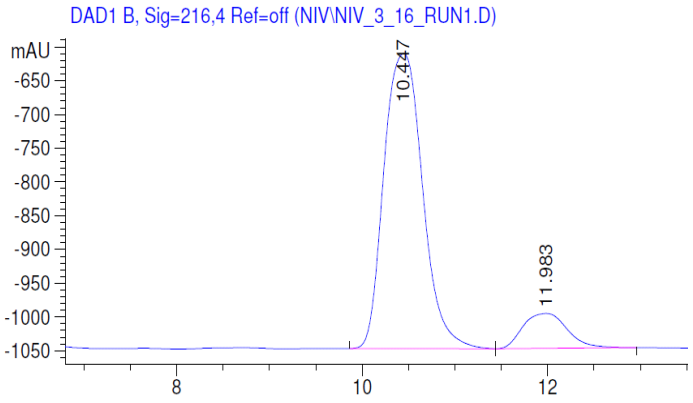
Figure 28. HPLC trace of enantioenriched **79b**.

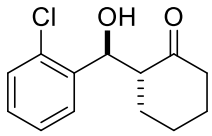




Peak	Retention time (min)	Area %
1	10.2	49.3933
2	11.6	50.6067

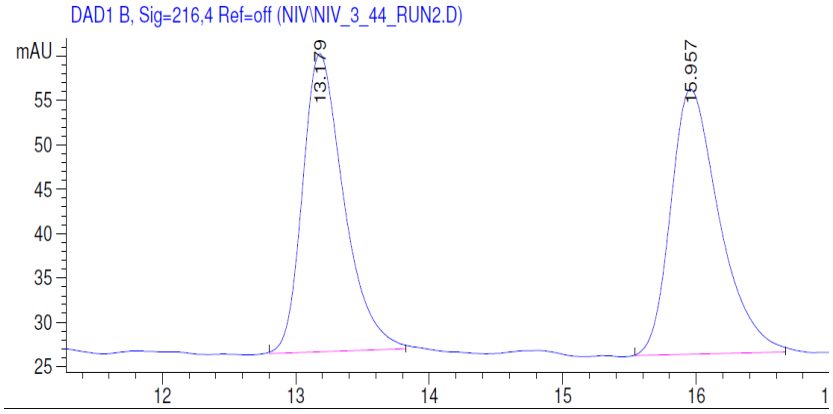
Figure 29. HPLC trace of racemic **79c**





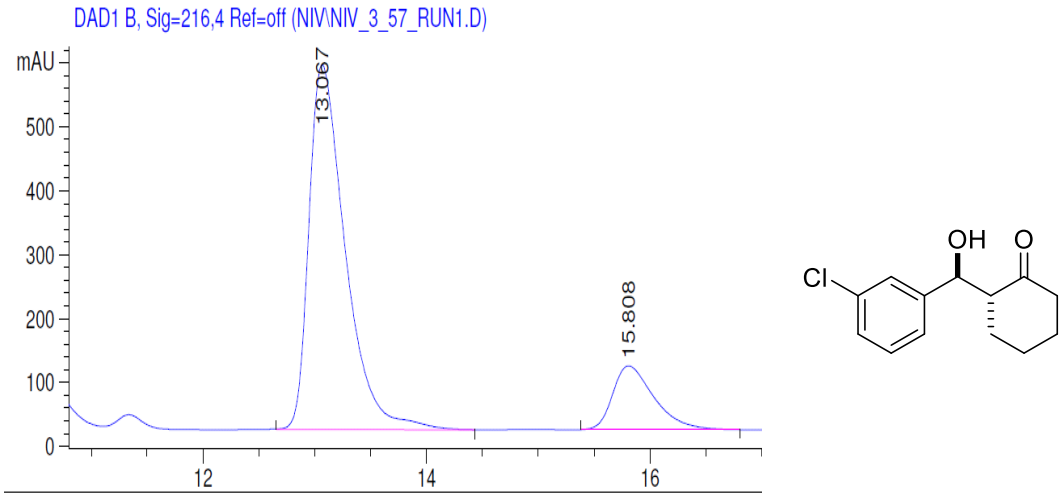
Peak	Retention time (min)	Area %
1	10.4	87.865
2	11.9	12.135

Figure 30. HPLC trace of enantioenriched **79c**.



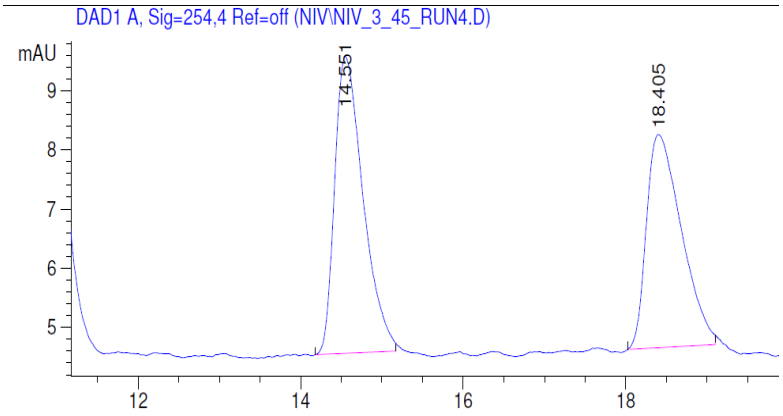
Peak	Retention time (min)	Area %
1	13.2	48.8651
2	16.0	51.1349

Figure 31. HPLC trace of racemic **79d**.



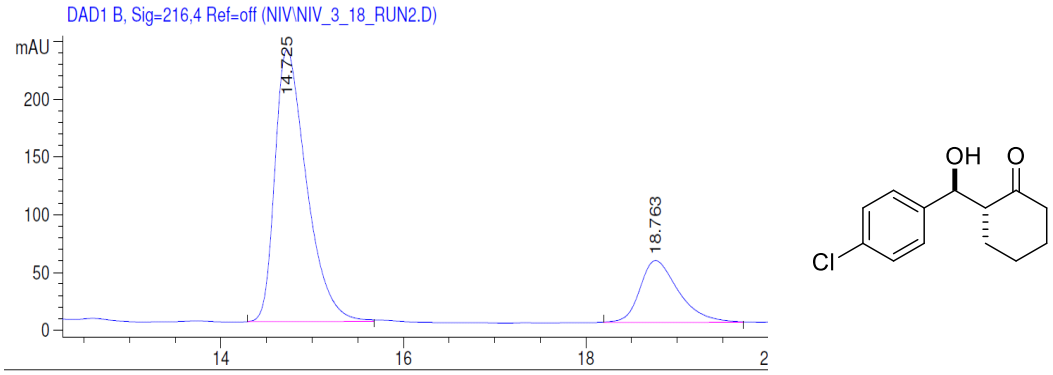
Peak	Retention time (min)	Area %
1	13.1	83.395
2	15.8	16.605

Figure 32. HPLC trace of enantioenriched **79d**.



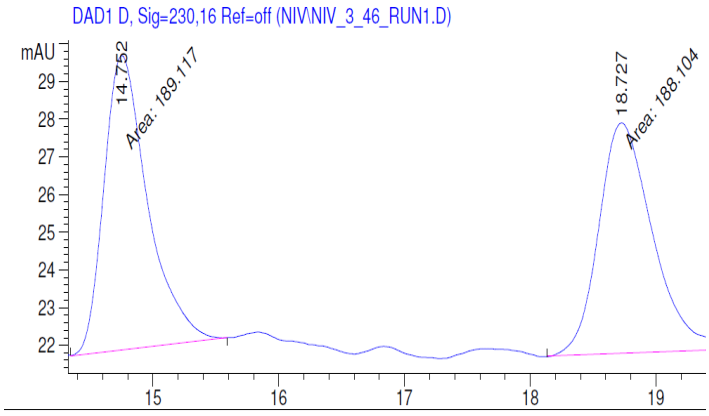
Peak	Retention time (min)	Area %
1	14.6	51.933
2	18.4	48.067

Figure 33. HPLC trace of racemic **79e**.



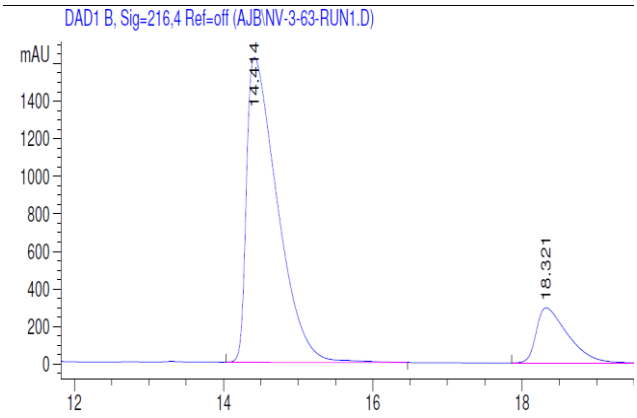
Peak	Retention time (min)	Area %
1	14.7	78.280
2	18.7	21.720

Figure 34. HPLC trace of enantioenriched **79e**.



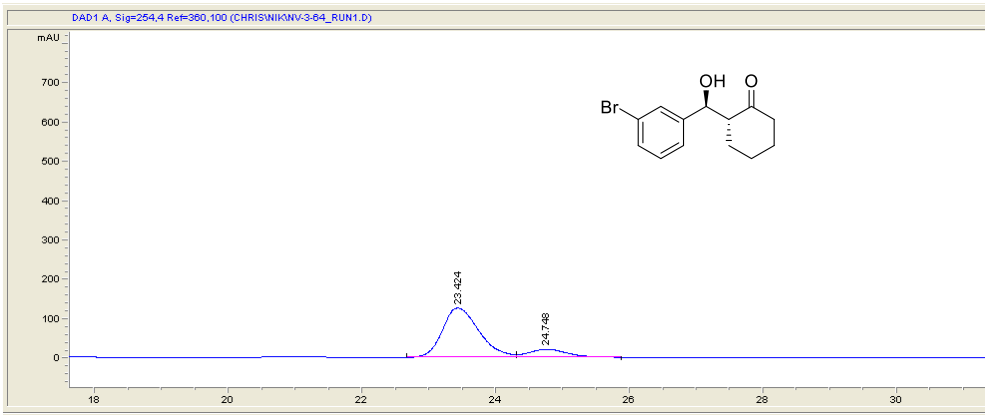
Peak	Retention time (min)	Area %
1	14.7	51.489
2	18.7	48.551

Figure 35. HPLC trace of racemic **79f**.



Peak	Retention time (min)	Area %
1	14.4	84.382
2	18.3	15.618

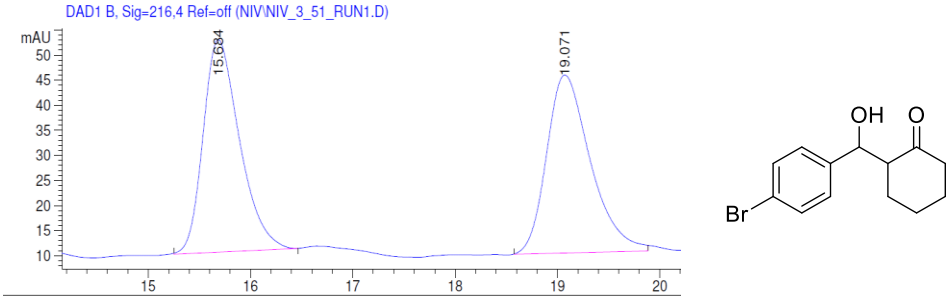
Figure 36. HPLC trace of enantioenriched **79f**.



Peak	Retention time (min)	Area %
1	23.4	85.179
2	24.7	14.821

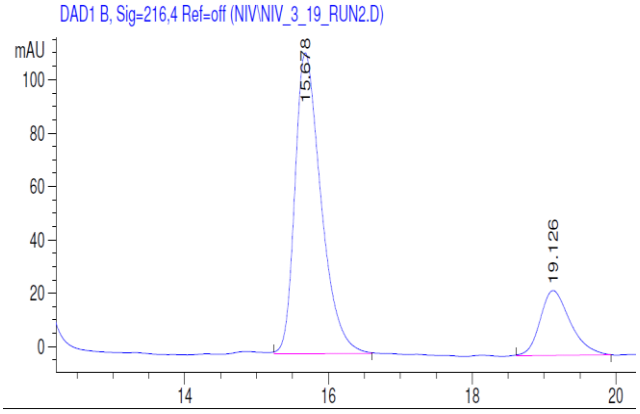
Figure 37. HPLC trace of enantioenriched **79g**.

Retention times are in agreement with the literature.[56]



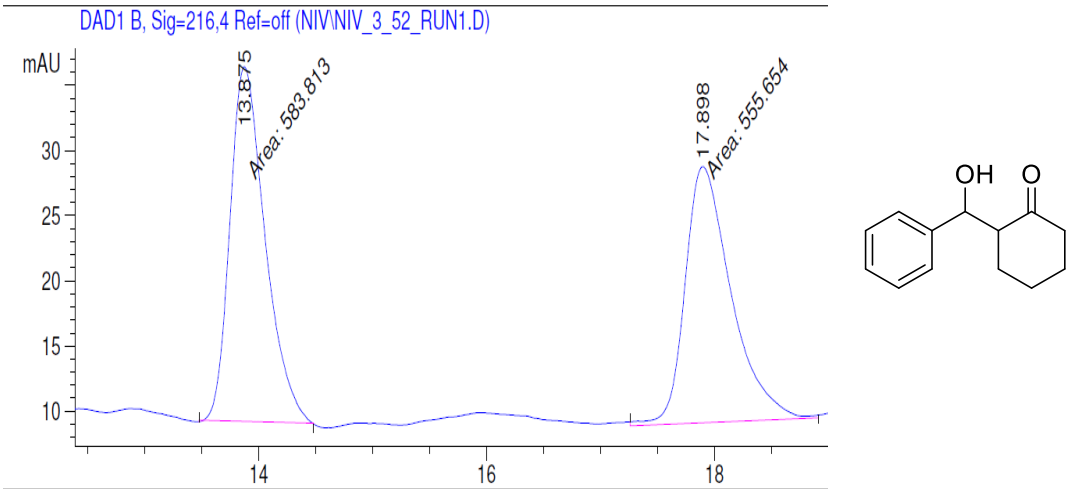
Peak	Retention time (min)	Area %
1	15.6	49.755
2	19.0	50.245

Figure 38. HPLC trace of racemic **79h**.



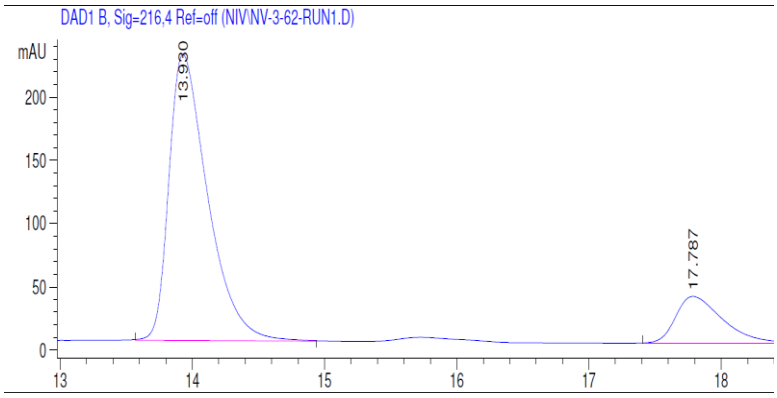
Peak	Retention time (min)	Area %
1	15.7	80.117
2	19.1	19.883

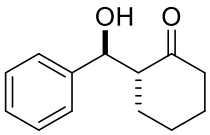
Figure 39. HPLC trace of enantioenriched **79h**.



Peak	Retention time (min)	Area %
1	13.9	51.245
2	17.9	48.755

Figure 40. HPLC trace of racemic **79i.**





Peak	Retention time (min)	Area %
1	13.9	83.350
2	17.8	16.650

Figure 41. HPLC trace of enantioenriched **79i**.

11. Abbreviations

Ac	acetyl
Ar	aryl
BZA	benzoic acid
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Cbz	carboxybenzyl
cat.	catalyst
de	diastereomeric excess
dr	diastereomeric ration
DCM	dichloromethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
ESI	electrospray ionisation
ee	enantiomeric excess
eq.	equivalent(s)
Et	ethyl
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IUPAC	International Union of Pure and Applied Chemistry
IPA	isopropanol
KHMDS	Potassium bis(trimethylsilyl)amide
Me	methyl
NMR	Nuclear Molecular Resonance
p-TsOH	para-toluensulfonic acid
Ph	phenyl
RT	room temperature
t	tert
$\mathbf{t_R}$	retention time
***t*-BuOH**	*tert*-butanol
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
Ts	transition state
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

12. References

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