Organocatalysis using novel axially chiral secondary amines

by

Nawaf Ibrahim Alsenani

A Doctoral Thesis

Submitted in partial fulfilment of the requirements of the degree of Doctor of Philosophy at the University of East Anglia, department of Chemistry

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DECLARATION

This thesis is submitted to the University of East Anglia for the Degree of Doctor of Philosophy and has not been previously submitted at this or any university for assessment. This work is original and has been carried out by the author alone.

Nawaf Ibrahim Alsenani
Abstract

Organocatalysis using novel axially chiral secondary amines

Keywords: Organocatalyst, Axial chirality, Aldol reaction, Mannich reaction, amino acid.

The field of organocatalysis has grown rapidly in the last 20 years. Moreover it is a big challenge in modern chemistry due to the rewards that can be gained from its efficiency, low cost and low toxicity. In addition, organocatalysis has many advantages in industrial chemistry it can save time and money by avoiding the use of large amounts of solvents and thus minimizing waste.

This Thesis is broken down into three chapters, the first one presents a review of organocatalysis including recent updates and developments, and introduces the different organocatalyst classes, their modes of activation, and a number of examples which show the selectivity improvements obtained.

The second chapter is divided into two parts. The first part describes the synthesis of certain binaphthyl organocatalysts and a description of the key steps of their synthesis: a diastereoselective Reformatsky addition and asymmetric lithiation and chloroformate/carboxylation addition steps. The second part focuses on the applications and the results obtained when these catalysts were used in aldol and Mannich reactions.

The third chapter contains the experimental data for the products that are discussed in chapter two.
Acknowledgements

First I would like to thank Professor Philip Bulman Page for giving me this opportunity to work within and under his supervision and laboratory for my Master and PhD.

Secondly, I would like to thank Dr. Yohan Chan for his help and guidance during these periods and I would like to thank Dr. Francesca Kinsey for all the support that she gave me during my project, and I would like to thank past Page group members.

Lastly, I would like to thank all the Page group, Dr. Saud Almutairi, Yannick Gama, Ross Goodyear and Gregory Hughes for making the time in lab more enjoyable and a big thank you for all the third floor specially Abdulaziz Almohyawi.

Special thanks to the ministry of education for the scholarship.

Special thanks to Dr. Yaser Alqurashi

Special thanks to my lovely wife Shahad and my daughter Kadi for making the PhD easier for me.

Special thanks to my Father Ibrahim, my mother Kadijah, my brothers, my sisters and all the family members for their support during my study in the UK.

Special thanks to all my friends in Norwich, UK and Saudi Arabia.
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Å</td>
<td>Ångström</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxy carbonyl</td>
</tr>
<tr>
<td>Boc2O</td>
<td>Di-tert-butyl dicarbonate</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carboxybenzyl</td>
</tr>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>Wavenumber</td>
</tr>
<tr>
<td>d</td>
<td>Days</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-3,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAc</td>
<td>Dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-Bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>DppONH2</td>
<td>O-(Diphenylphosphinyl)-hydroxylamine</td>
</tr>
<tr>
<td>e.e</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>E⁺</td>
<td>Electrophile</td>
</tr>
<tr>
<td>EDAC</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>equiv.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>g</td>
<td>Grams</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HOBT</td>
<td>Hydroxybenzotriazole</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution liquid chromatography</td>
</tr>
<tr>
<td>iPr</td>
<td>Iso-propyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>IPA</td>
<td>Iso-propyl alcohol</td>
</tr>
<tr>
<td>K</td>
<td>Kelvin scale</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>MHz</td>
<td>MegaHertz</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Resonance Spectroscopy</td>
</tr>
<tr>
<td>Nu⁻</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>OTf</td>
<td>Trifluromethanesulfonate</td>
</tr>
<tr>
<td>Oxone</td>
<td>Tetrabutylammonium hydrogen monopersulfate</td>
</tr>
<tr>
<td>p-TsCl</td>
<td>para-Toluenesulfonyl chloride</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-Toluenesulfonic acid</td>
</tr>
<tr>
<td>Pd/C</td>
<td>Palladium on carbon</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PhCF₃</td>
<td>Trifluorotoluene</td>
</tr>
<tr>
<td>PhCO₂H</td>
<td>Benzoic acid</td>
</tr>
<tr>
<td>PMB</td>
<td>Paramethoxybenzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-Butylhydroperoxide</td>
</tr>
<tr>
<td>Tf₂O</td>
<td>Trifluoromethanesulfonic anhydride</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPPP</td>
<td>Tetraphenylphosphonium monoperoxy sulfate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>Δ</td>
<td>Heat</td>
</tr>
</tbody>
</table>
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Chapter one: Introduction

1.0 Asymmetric catalysis
As the biological activities of many pharmaceutical compounds are related to their absolute configurations, the need to make chiral drugs in an enantiomerically pure form is growing rapidly. Before the 1980’s, drug synthesis generally provided racemic mixtures, which led to having two enantiomers, one was beneficial to use as a drug, while the second enantiomer could be inactive or even harmful. Because of the possibility of harmful effects coming from one enantiomer, worldwide governments developed roles and regulations for drug companies which synthesise chiral drugs, such as, the Committee for Proprietary Medical Products (EU) demanding them to separate any chiral drug and evaluate their individual activity and toxicity. Asymmetric catalysts could help to lower the pharmaceutical companies risk in terms of wasting money and time in synthesis and purification by affording a single enantiomer.

1.1 Classes of asymmetric catalysis
The classic methods for purifying and isolating a single pure enantiomer are: chiral auxiliary, kinetic resolution, resolution of the racemic mixture and chiral pool approach. However, these methods cannot be compared with asymmetric catalysis as it is considered the least wasteful. There are three main areas that asymmetric catalysis includes: organometallic catalysis, biocatalysis and organocatalysis.

1.1.1 Organometallic catalysis
Since the Nobel prize was awarded to Karl Ziegler, Giulio Natta, Geoffrey Wilkinson, and E. O. Fischer for their contributions in the area of science and technology specifically in organometallic chemistry, organometallic catalysis has become a powerful tool to increase production, such as high octane gasoline obtained by "cracking" of petroleum with organometallic catalysts, which was used during World War II by the Allied forces. On the other hand, Germany used diesel fuel which was synthesised using a metallic catalyst. In addition, the high demand for more highly pure chemicals led Ziegler and his co-workers to develop a catalyst to use in the synthesis of polyolefins. Furthermore, in 1968, Knowles had used and developed [Rh(R,R)-DiPAMP)COD]BF₄ as catalyst for the first industrial asymmetric catalytic reaction to synthesise a rare amino acid (S)-DOPA which is a chiral
drug used in the treatment of Parkinson’s disease, the catalyst was used in the synthesis of the drug for a hydrogenation step which afforded 1 in excellent e.e. (95%) and quantitative yield (Scheme 1).

![Scheme 1: The hydrogenation step for synthesis of (S)-DOPA 2 using metal rhodium catalyst.](image)

In addition, Noyori has used Ru-BINAP 3 in drug synthesis, such as, the synthesis of Naproxen, an anti-inflammatory drug. The result was 92% yield and 97% enantiomeric excess. Moreover, Noyori has also applied his Ru-BINAP in the synthesis of an antibiotic called Levofloxacin (Scheme 2).

![Scheme 2: Ru-BINAP catalyst 3 step in the synthesis of Naproxen.](image)

In 2001, Noyori, Knowles and Sharpless were awarded the Nobel Prize in chemistry. Sharpless won his share for his work on asymmetric oxidations. Sharpless focused his work on the formation of chiral epoxides and diols from carbon–carbon bonds. For example, by using a titanium (IV) catalyst with tert-butylhydroperoxide, allylic alcohols were converted into the respective epoxyalcohols. Sharpless selective methods have inspired Industry in the synthesis of stabilised enantio-enriched glycidol derivatives. Indeed, glycidyl 3-nitrobenzenesulfonate will generally be the substrate of choice for reactions requiring direct displacement of an
arenesulfonate moiety. Moreover, the Sharpless methodology has also been used to synthesise the key intermediate of several antibiotics, such as Methymycin, Erythromycin, and Leukotriene C-1 (Scheme 3).

![Scheme 3: The key intermediate 4 in the synthesis of antibiotic methycin.](image)

However, despite its huge success, organometallic catalysis has some disadvantages, for example, most of the reactions that involve metallic catalysts require exacting reaction conditions such as the exclusion of air and moisture. Furthermore, the cost of the catalysts is very high and commonly they are toxic.

### 1.1.2 Biocatalysis

The use of enzymes or macromolecules such as proteins in asymmetric catalysis to produce a chemical transformation is called biocatalysis. In contrast to organometallic catalysis, biocatalysis is generally cleaner and safer because the solvent is often water. In addition, the use of biocatalysts in organic reactions can afford the product in high yield and high enantioselectivity. For more than 50 years, biocatalysts have been used in industrial production of enantiomerically pure amino acids and their derivatives that are used in the preparation of pharmaceuticals, cosmetics, agricultural products and food industries. For instance, the synthesis of the artificial sweetener L-aspartyl L-phenylalanyl methyl ester (Aspartame) starts from L-aspartic acid. L-aspartic acid is synthesised from fumaric acid by aspartase-catalysed addition of ammonia. When using immobilised aspartate β-decarboxylase with L-aspartic acid, the amino acid L-alanine can be formed (Scheme 4).
However, despite the advantages of using biocatalysis, biocatalysts have limitations, for example, stability issues at high or low temperature and pH. In addition, they can only be used in a limited number of transformations, moreover, biocatalysts can be very sensitive, precluding the use of many solvents.

1.1.3 Organocatalysis

Organocatalysts are small chiral organic molecules mainly containing C, H, O, N, S and P atoms. Over the last 20 years, organocatalyses have had large successes and improved rapidly, due to their easy syntheses, low cost, low toxicity and their potential in several reactions. Moreover, another advantage is to reduce the high cost of drug production by synthesising different types of compounds and functional groups.

Cinchona alkaloids are a type of natural product that were used in the first asymmetric organocatalytic reaction reported. The quinuclidine ring can act as a Lewis base, a nucleophilic catalyst, and it can act as phase transfer catalyst after it has been alkylated. In addition, these alkaloids have a hydroxyl group that can act as hydrogen bond donor or acid, or it can be converted to an amine group that can also act as hydrogen bond donor or as an aminocatalyst (Figure 1).
In 1912, Bredig and Friske used quinine and quinidine as chiral catalysts in the first asymmetric organocatalysed reaction,\textsuperscript{13} used to synthesise mandelonitrile, by addition of HCN to benzaldehyde. The enantiomeric excess of the reaction was about 8%.\textsuperscript{14} Quinine was used again as a catalyst in 1960 by Pracejus, who used O-acetyl-quinine 11 with methanol and phenylmethylketene 12, to give product 13 in a quite remarkable 74\% ee (Scheme 5).\textsuperscript{15,16}

\textbf{Scheme 5}: Addition of O-acetyl quinine 11 (catalyst) to form phenylmethylketene 12.
1.2 Types of organocatalysts

Due to the large number of organocatalysts that have different functional groups and are used in various synthetic transformations, their classification is difficult. However, organocatalysts can be classified depending on their mode of activation of the substrate, and that could be further divided into two parts, covalent and non-covalent.

1.2.1 Examples of non-covalent organocatalysts

A non-covalent catalyst does not involve sharing of electrons and instead involves electrostatic, hydrophobic and Van der Waals interactions. An example of non-covalent catalysts are phase transfer catalysts: the asymmetric induction occurs due to the chiral environment provided by the chiral ion and the ion also allows a reactant to migrate between the organic and aqueous phases. That can be done, for example, by generating an onium-carbanion species: in 1997, Corey used chiral ammonium salt 15 as catalyst to alkylate glycine-benzophenone Schiff base 14, giving a yield of 71% and very huge ee of 97% (Scheme 6).

![Scheme 6: Alkylation of glycine Schiff base 14 using chiral quaternary ammonium salt phase transfer catalyst 15.](image)

In the example shown in scheme 6, at the interface, glycine Schiff base 14 reacts with CsOH·H$_2$O, an inorganic base, to give the corresponding metal enolate. The metal exchanges with the ammonium cation catalyst creating a chiral environment, and finally alkylation gives the product and regenerates the catalyst.  

In 2000, Jacobsen used thiourea-based organocatalysts in the Strecker reaction through hydrogen bonding to activate HCN to add to the N-benzyl imine. The catalyst 16 provides
hydrogen bonding from the urea moiety, and the asymmetric induction is directed by the α-amino acid and trans-1,2-diamino cyclohexane moieties (Scheme 7).\textsuperscript{18}

\begin{equation}
\begin{array}{c}
\text{Ph-N}^+\text{Ph} \\
\text{Me}
\end{array}
\rightleftharpoons
\begin{array}{c}
\text{HNN\text{tBu}} \\
\text{O}
\end{array}
\rightleftharpoons
\begin{array}{c}
\text{HO} \\
\text{N=\text{tBu}}
\end{array}
\rightleftharpoons
\begin{array}{c}
\text{Me_NHBn} \\
\text{CN}
\end{array}

\text{HCN, 2 mol \% of 16}
\text{toluene, -78 °C, 24h.}
\text{Yield: 97%}
\text{ee: 90%}

\textbf{Scheme 7:} Strecker reaction using thiourea-based organocatalyst 16.

\subsection*{1.2.2 Examples of covalent organocatalysts}

Electron-sharing between catalysts and reactants during the reaction is called covalent bonding and is used, for example, during atom transfer in epoxidation and aziridination reactions, Lewis base catalysis and aminocatalysis.

In 2002, the Fu group synthesised planar chiral DMAP derivatives which act as Lewis base organocatalysts due to the presence of a pyridine moiety.

The C-acylation reaction of silyl ketene acetals 18 using acetic anhydride catalysed by DMAP derivative 17 occurs following these mechanistic steps: the acylpyridinium ion is generated by reaction between the DMAP catalyst and acetic anhydride, the resulting acetate ion affords a reactive enolate when reacting with the silyl ketene acetal substrate, and finally, a coupling step between the enolate and the acylpyridinium gives 19 in high ee and reasonable yield (Scheme 8).\textsuperscript{19}
In the field of aziridination and epoxidation reactions, the Page group has obtained impressive results.\textsuperscript{20,21,22} Moreover, Page reported reasonable to excellent enantioselectivities for the oxidation of dialkyl sulfides using hydrogen peroxide in the presence of oxocamphorsulfonylimine catalyst \textsuperscript{20,23,24} The reaction between imine catalyst \textsuperscript{20} and hydrogen peroxide gives a very reactive oxidative intermediate which can transfer the oxygen atom to the sulfide enantioselectively (Scheme 9).\textsuperscript{25}

\begin{align*}
\text{MeO} & \overset{\text{5 \% of 17}}{\longrightarrow} \text{PhO} \\
\text{Me} & \overset{\text{Et}_2\text{O/DCM, rt, 24h}}{\longrightarrow} \text{Ph} \\
\text{Me} & \overset{}{\longrightarrow} \text{Me}
\end{align*}

**Scheme 8:** C-acylation of silyl ketene acetal catalyzed by DMAP derivative 17.

Denmark applied chiral phosphoramidate catalyst \textsuperscript{22} to an asymmetric intermolecular aldol reaction for the first time in 1999. Denmark achieved excellent results in terms of yield and ee: at low temperatures, several \(\alpha-\beta\) unsaturated, branched aliphatic and aromatic aldehydes were used as substrates with a reactive silyl enol ether as nucleophile (Scheme 10).\textsuperscript{26}
One year later, Denmark proposed a mechanism for the reaction and its transition state. The trichlorosilyl enolether would undergo ionisation in the presence of the phosphoramidate catalyst allowing the formation of a hexa-coordinated silicon centre from the cationic dichlorosilyl enolether, the aldehyde and the catalyst giving the anti-product.\(^{27}\)

In 2002, the MacMillan group reported Friedel-Crafts type alkylations of pyrroles and indoles with enals using secondary amine 23 as the catalyst. Co-catalysts, such as trifluoroacetic acid, improved the reaction rate and allowed the reaction to take place at low temperatures giving high selectivity.\(^{28}\) (Scheme 11). This type of catalysis, which can be classified as activation of carbonyls, is called aminocatalysis.

Scheme 10: The first asymmetric aldol reaction using chiral phosphoramidate catalyst 22.

Scheme 11: Indole alkylation using a secondary amine catalyst.
2.0 Mechanisms of aminocatalysis

Iminium species 25, can be formed by condensation of a primary or secondary amine 24 with an aldehyde or ketone, and the resulting iminium can equilibrate into its enamine 26 tautomer. Both these intermediates are very reactive and can easily combine with reaction partners (Scheme 12).

\[
\begin{align*}
&\text{24} & \text{25} & \text{26} \\
&\begin{array}{c}
\text{H} \\
\text{R}_1 \cdots R_1 \\
\text{N} \\
\text{R}_2 \\
\text{O} \\
\text{R}_2 \cdots R_3 \\
\end{array} & \text{H}^+ & \begin{array}{c}
\text{R} \cdots R_1 \\
\text{N} \\
\text{R}_2 \\
\text{O} \\
\text{R}_2 \cdots R_3 \\
\end{array} & \text{H}^+ & \begin{array}{c}
\text{R} \cdots R_1 \\
\text{N} \\
\text{R}_2 \\
\text{O} \\
\text{R}_2 \cdots R_3 \\
\end{array}
\end{align*}
\]

Scheme 12: Condensation of amines and carbonyls.

The iminium or enamine moiety is hydrolysed to free the amine catalyst after completion of the catalytic cycle.

2.1 Iminium activation

An iminium species is considered as an electrophile. Indeed, polarisation of π-electrons toward the positively charged nitrogen centre lowers the energy of the lowest unoccupied molecular orbital (LUMO) which increases the potential for combination with the highest occupied molecular orbital (HOMO) of the nucleophile.

2.2 Enamine activation

In contrast, enamine moieties are considered as nucleophiles, and their activity results from a higher energy of their highest occupied molecular orbital (HOMO), when compared with the parent carbonyl (Scheme 13).
Keto-enol tautomerisation is similar to the conversion of an iminium to the corresponding enamine species. Nevertheless, in the case of keto-enol tautomerism, the ketone is favoured, in contrast, in the iminium-enamine system, the enamine is favoured. 29

2.3 Non-selective aminocatalysis
In 1896, Knoevenagel reported the first non-selective aminocatalysis using primary and secondary amines and their salts, applying them to the aldol condensation of β-keto esters and malonates with aldehydes and ketones (Scheme 14). 30

Scheme 13: Iminum/enamine and keto-enol tautomerizations.

Scheme 14: Knoevenagel condensation using piperidine as the catalyst.
C-C bond-forming is highly important in organic synthesis, in particular for industry; as a result, the development and study of aminocatalysts was targeted. For example, in the case of the Knoevenagel condensation, the primary amino acids catalysts used, and the secondary amines used to catalyse self- and cross-aldol condensations of aldehydes, were extensively studied.\textsuperscript{31,32}

2.4 First asymmetric organocatalytic reactions

L-Proline 27 was used in an intramolecular aldol reaction with triketone 28 by Hajos and Parrish in 1971,\textsuperscript{33} and that reaction was named the Hajos–Parrish–Eder–Sauer–Wiechert reaction.\textsuperscript{34} In 1950, Miescher and Wieland synthesised and used achiral piperidinium and pyrrolidinium salts to give the racemic dione 29,\textsuperscript{35} 15 years later, the formation of enamine and iminium ion intermediates was suggested by Spencer \textit{et al.} as the reason for the accelerating reaction rates.\textsuperscript{36} In 1984, Agami \textit{et al.} shared the same idea, and they discovered that the attack of the nucleophilic carbon atom, in the case of a chiral enamine, differentiates between the two enantiotopic carbonyl groups (Scheme 15).\textsuperscript{37}

\begin{scheme}
\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme15}
\end{center}
\caption{Diketone 29 racemic product by Miescher and the Proline-catalysed asymmetric version.}
\end{scheme}
According to Hajos and Parrish, the role of L-proline was similar to that of an enzyme, and could be considered a simplified model of a biological system. They suggested an intermediate with amino and carbinol groups (Figure 3).

![Amino-carbinol intermediate proposed by Hajos.](image)

**Figure 3**: Amino-carbinol intermediate proposed by Hajos.

However, after further studies and investigation were carried out, Rutter proposed an aldolase class 1 mechanism, where the formation of enamine and how it reacts in the aldol reaction with the carbonyl group is described. In addition, in 1974, the amino acid sequence of the rabbit muscle aldolase was reported by Chang et al. Moreover, they mechanistically showed the lysine active site position prefers enamine and iminium ion catalysis.

Barbas and Lerner et al. worked on aldol reactions using antibodies, and they suggested that the antibody mechanism cycle is the same as the natural class 1 aldolase enzymes. Using the 38C2 antibody, the Hajos–Wiechert Robinson annelation produced, amongst several other examples, the Wieland-Miescher ketone 30 in 94% yield and 96% ee. In contrast, when (S)-proline was used, the product was obtained in 83% yield and 71% ee (Scheme 16).

![Scheme 16: Enantioselective Synthesis of the Wieland-Miescher ketone 30.](image)

**Scheme 16**: Enantioselective Synthesis of the Wieland-Miescher ketone 30.

In addition, the mechanism of the Hajos–Parrish–Eder–Sauer–Wiechert reaction was proved using 18O-enriched water, following the reaction by GC-MS.
Under completely air- and moisture-free conditions, during the running of the reaction, the product mixture was analysed and shown to contain aldol addition product 31, aldol condensation product 32 and dienamine 33. There was a single $^{18}$O atom incorporated in 31 and 32 as their molecular ions were two mass units higher than the corresponding $^{16}$O products; furthermore, the dienamine did not incorporate $^{18}$O, showing that the carbonyl group is where the addition occurs, as is proposed in the enamine mechanism, and after hydrolysis of the iminium ion using $^{18}$OH$_2$, the carbonyl group is regenerated (Scheme 17).

![Scheme 17: Using $^{18}$O incorporation to prove enamine intermediate involvement.](image)

In 2001, to explain the selectivity when proline is used, Houk used density functional theory (DFT) mechanistic studies (using B3LYP and 6-31G basis set in Gaussian 98). Houk studied the intramolecular aldol reaction of 4-methyl-heptane-2,6-dione 34. He suggested that four diastereoisomeric aldol products can be formed, and the favoured product was the $(R,R)$-cyclization product 38, which was synthesised by hydrolysis of $(R,S)$-iminium species 37. In addition, he proposed that the rate-determining step of the reaction is the enamine attack on the ketone (Scheme 18).
The formation of the \((R,R)\)-diastereoisomer is due to favourable electrostatic interactions between the positively charged proline iminium moiety and the alkoxide ion in the \((R,S)\)-transition state \(37\). The electrostatic interactions were calculated for the \((R,S)\)-transition state and the \(\delta^+\text{NCH}--\text{O}\delta^-\) distance is 2.5 Å. In contrast, the \((S,R)\) transition state \(41\) has a calculated \(\delta^+\text{NCH}--\text{O}\delta^-\) distance of 3.2 Å: the 1 kcal/mol difference in energy would afford a 42% ee. The energy of transition state \((R,S)\) \(37\) is lower due to hydrogen bonding, which allows the iminium bond to be mostly planar. Indeed, the formation of the hydrogen bond is important in the reaction as it affords enhanced charge stability for the alkoxide ion, resulting in the enantioselectivity observed (Figure 4).
Wieland-Miescher ketone analogues, such as octahydronaphthalene dione 43, are very valuable intermediates in organic synthesis and have been used in the total synthesis of steroids cortisone, norethindrone and progesterone 44 (Scheme 19).45,46,47

Scheme 19: installation of stereogenic centers on bioactive protostereiols 44 by Corey.48
3.0 Examples of asymmetric aminocatalysis

List, Lerner and Barbas in 2000 reported using L-proline in direct asymmetric aldol reactions, drawing attention to asymmetric aminocatalysed reactions, and suggestion that the enantioselectivities would enormously increase in the further considering the chiral pool available for these aminocatalysts.

3.1 Asymmetric aminocatalytic aldol reaction

The aldol reaction is a very important reaction due to its ability to form a new carbon-carbon bond. Furthermore, the possibility of selectively forming one or two new stereogenic centres in the resulting β-hydroxy carbonyl compound is extremely attractive.

\[ \text{Scheme 20: The first intermolecular aldol reaction catalysed by proline.} \]

L-Proline 27 was used in asymmetric aminocatalytic intermolecular aldol reactions by List et al. for the first time in 2000 (Scheme 20 and 21). Proline, as a chiral pool catalyst, exhibited similar features to aldolase antibody 38C2, an efficient catalyst for many reactions, such as the Wieland-Miescher ketone synthesis. Indeed, proline reacts via an enamine intermediate.

\[ \text{Scheme 21: Transition state for aldol reaction between acetone and 4-nitrobenzaldehyde catalysed by proline proposed by Zimmerman-Traxler.} \]
High yields and enantioselectivities were obtained and a large number of aldehydes were tested using acetone as the only nucleophile (Table 1).

Table 1: Asymmetric aldol reaction using proline.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>62%</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>74%</td>
<td>65%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

After a comprehensive solvent screening, they found that the best solvent, considering reaction times and enantioselectivity, was anhydrous DMSO at room temperature. The highest ee was obtained when isobutyraldehyde 45 was used as the substrate, although a longer reaction time was required when compared with other aldehyde examples (48h vs 2-8h). In addition, the selectivities observed were much lower when aromatic aldehydes were used (Entries 2 and 3). However, unbranched aldehydes such as pentanal did not give the aldol product. To avoid the formation of self-aldolisation products azomethine-ylide 47, oxazole 48 or oxazolidinones 49-50, acetone were used in high concentration.
In 2010, Gschwind *et al.* reported the proline-catalysed self-aldolisation of propionaldehyde as a model, trying to isolate the ‘elusive’ enamine intermediate and the by-product from the reaction.\textsuperscript{51} As a result, the enamine intermediate and two diastereoisomeric oxazolidinones 49 and 50 were identified (Scheme 22).

![Scheme 22: Proline catalysed self-aldolisation and possible intermediates and products.](image-url)

In more detail, the formation of an oxazolidinone comes from the condensation of proline with a ketone or aldehyde substrate followed by a ring-closing step, and that step is called ‘a parasitic equilibrium’.\textsuperscript{54} The iminium intermediate 46 is key to the interconversions between aldehydes, oxazolidinones and enamine formations.\textsuperscript{52} Moreover, the *E*-enamine intermediate was not obtained directly from the iminium intermediate, but was formed via oxazolidinones 50 through an E2 mechanism as observed using NOESY NMR exchange spectroscopy.\textsuperscript{51,53} Furthermore, the studies tested the effect of water presence on the reaction, and a reduction of the quantity of oxazolidinone was observed as the iminium ion 46 was hydrolysed to proline.
List *et al.* attempted a similar study using 1,3-dicarbonyl compounds as substrates. In this case, thermodynamic effects disfavour the formation of the corresponding oxazolidinones. Indeed, the extended conjugation favours enaminone isomer 51 (*Scheme 23*).

In more detail, the enaminone 51 intermediate has the same electronic properties as an enamine when reacting with an electrophile. The electron density of both is removed away from the electron rich enamine-π-system. A study of crystal structures showed that the conformation for the enamine double bond is always (E) and relatively the position of the carboxylate is *anti* or *syn* to the enamine double bond.\(^{54}\)

Proline also gives very interesting results in many reactions, such as, carbon-carbon bond forming reactions (Michael reaction,\(^{55}\) aldol-modified dihydroxylation,\(^{56}\) cross aldolisation of non-equivalent aldehydes\(^ {57}\)) and heteroatom introduction reactions (\(\alpha\)-oxygenation of aldehydes with nitrosobenzene,\(^ {58}\) and \(\alpha\)-amination of aldehydes with diazodicarboxylates\(^ {59,60}\)).
3.2 Asymmetric aminocatalytic Mannich reaction

The Mannich reaction is another example of a carbon-carbon bond-forming reaction, giving β-amino-carbonyl compounds, which are very useful intermediate in natural product syntheses, such as alkaloids. The imine (or iminium) derived from a primary (or secondary) amine and an aldehyde (usually) acts as an acceptor, while the enolate issued from a carbonyl-containing compound acts as the donor.

After the huge success of L-proline in the asymmetric aldol reaction, List decided to apply L-proline to a direct catalytic asymmetric three-component Mannich reaction based on a report by Kobayashi (Table 2).61,62

Table 2: Asymmetric Mannich reaction using proline.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Aldehyde" /></td>
<td>35%</td>
<td>94%</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image2" alt="Aldehyde" /></td>
<td>90%</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Aldehyde" /></td>
<td>50%</td>
<td>94%</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image4" alt="Aldehyde" /></td>
<td>74%</td>
<td>73%</td>
</tr>
</tbody>
</table>

a: p-methoxyphenyl. b: reaction in pure acetone.

List examined reactions of several aldehydes with p-anisidine and acetone; the highest ee (94%) was observed when 2-naphthaldehyde 52 was used but the yield was a modest 35%. In addition, when a β-substituted aldehyde was used, such as isovaleraldehyde 53, high ee and
yield (93% and 90%, respectively) were obtained. The mechanism of the asymmetric Mannich reaction starts with the proline reacting with the ketone to give the corresponding enamine species, while anisidine reacts with the aldehyde to form the corresponding imine intermediate. Condensation of the two species followed by hydrolysis gives the Mannich product (Scheme 24).

Scheme 24: Mechanism of direct asymmetric Mannich reaction catalysed by proline.

In 2001, List proposed a transition state corresponding to the C-C bond formation step of the Mannich reaction. They assumed that the proline-derived enamine and the anisidine-imine have the (E)-configuration and due to steric repulsion of the PMP group and the pyrrolidine moiety of the enamine, the enamine selectively attacks the $\text{si}$-face of the imine (Figure 5). 63

Figure 5: Mannich reaction transition state.
### 4.0 Proline-derived catalysts

Proline proved to be a very versatile catalyst as well as a very successful one in terms of both enantio- and diastereoselectivity; in addition, proline can be cheaply bought in both enantiomeric forms. Nevertheless, there are some limitations using proline, such as solubility issues with all solvents except very polar solvent (methanol, dimethyl sulfoxide and water), which minimise its applications. Moreover, a high loading of proline is needed to achieve reaction completion in reasonable time.

List screened some examples of commercially available amino acid derivatives in the aldol reaction of acetone with 4-nitrobenzaldehyde 54 with the purpose of understanding the structure-activity of the secondary amine catalysts (Table 3).

**Table 3:** Examples of amino acid catalyst derivatives used in asymmetric aldol reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino acid catalyst</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>&lt;10%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>&lt;10%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>&lt;10%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>55%</td>
<td>40%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>68%</td>
<td>76%</td>
</tr>
</tbody>
</table>

As a result, the pyrrolidine ring, acting as a Lewis base, was found to be essential for selectivity and activity. In addition, in order to provide the asymmetric induction, the carboxylic acid...
group was also found to be essential. The carboxylic acid group acts as a Brønsted acid co-catalyst, promoting the formation of the iminium ion, and improves selectivity through the hydrogen bonding between the enamine and imine species enabling enantiofacial discrimination. Proline has bifunctional properties, allowing both Brønsted acid and nucleophilic Lewis base catalysis via enamines and iminium ions.49

In 2004, and due to proline solubility issues in classic solvents, Ley synthesised tetrazole 58 and acyl sulfonamide 60 in an attempt to keep a similar pKa to that of proline (Scheme 25).64,65 In more detail, beginning with N-benzyl oxycarbonyl-L-proline, a coupling reaction using ammonia, EDAC and HOBt provided amide 55 in quantitative yield, followed by a dehydration step in the presence of p-TsCl to give the nitrile compound 56.66 Addition of sodium azide afforded the tetrazole product 57 and deprotection of Cbz group gave the catalyst 58 in 89% yield.

Scheme 25: Synthesis of catalysts 58 and 60.
The acyl sulfonamide catalyst 60 was prepared from the same starting material, which reacted with EDAC and methanesulfonamide in the presence of DMAP, followed by a protecting group removal to give the catalyst. Both catalysts were applied to the Mannich reaction between cyclohexanone and imine 61 (Table 4).

Table 4: Mannich reaction catalysed by proline-derived catalysts between cyclohexanone and imine 61.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield %</th>
<th>d.r. syn:anti</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>2</td>
<td>65</td>
<td>&gt;19:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>24</td>
<td>65</td>
<td>&gt;19:1</td>
<td>83</td>
</tr>
</tbody>
</table>

When catalyst 58 is compared with proline, the reaction is significantly faster as well as more selective (when the loading is 5 mol% for both) (entry 2). A longer reaction time is required (16 h) if the catalyst loading is lowered to 1 mol% and the same ee is obtained. However, in the case of catalyst 60, after a 25h reaction time a 1% and 5% catalyst loading afforded the product in 53% yield and 40% ee, and, 65% yield and, 83% ee, respectively. The diastereoselectivity in both cases is similar. Ley also confirmed Houk’s suggestion that the hydrogen bonding is providing a rigid chiral environment; in addition, the imine protecting
group $p$-methoxyphenyl is axial to avoid any gauche interaction with the tetrazole ring, giving syn-product 62 (Scheme 26).

Ley also applied the tetrazole catalyst 58 in nitro-Michael, aldol and N-nitroso aldol reactions.67,68

In 2004, Jørgensen reported the first direct organocatalyzed enantioselective sulfenylation of aldehydes. Isovaleraldehyde was used as the model. He started his examination with L-proline, which gave a racemic mixture and low yield (16%). He then synthesised several proline derivatives, such as 63. The results suggested that the presence of different groups such as aryl and silyl would provide high selectivity (Table 5).
Diarylmethylpyrrolidine 66 afforded the desired product in 56% yield and 25% ee (Entry 2). However, diarylprolinol 67 did not provide the desired product (Entry 3), and Jørgensen realised that the catalyst was fully converted into oxazolidine 69 (Scheme 27). To improve the results, catalysts with increasingly bulky groups, such as catalyst 63 and 68 were synthesised.
After the successes observed using Jørgensen catalyst 63, it has been used in many reactions: benzylation of α,β-unsaturated aldehydes, cycloaddition reactions, aziridinations of 2,4-dienals, epoxidations of α-β unsaturated aldehydes, α-aminations of aldehydes and α-fluorinations of aldehydes.

As aminocatalysts have two modes of action, in 2006, Enders reported the use of diarylprolinol catalyst 68 in Michael/Michael/aldol condensation cascades in order to produce tetrasubstituted cyclohexene carbaldehydes with multiple stereogenic centres (Scheme 28). In more detail, enamine formation occurs by condensation of aliphatic aldehyde 70 and catalyst 68, a chemoselective step, followed by a Michael-type addition reaction with β-nitrostyrene 71, a Michael acceptor more reactive than cinnamaldehyde, the other acceptor present. Hydrolysis of the product affords γ-nitroaldehyde product 73 and liberates the catalyst 68, which condenses with cinnamaldehyde to form the corresponding iminium ion. The newly formed iminium species reacts with γ-nitroaldehyde 73 to form enamine 74. Finally, an intramolecular aldol condensation step affords polyfunctional cyclohexene derivative 75, which is too sterically hindered to undergo further transformations, stopping the catalytic cycle. During this reaction cascade, four stereogenic centres are generated, therefore, up to 16 different stereoisomers could possibly be obtained. However, only two easily separated diastereoisomers are formed. The high stereoselectivity in the Michael addition leads to
increased selectivity during the second step through sterically favourable interactions between the iminium ion and γ-nitroaldehyde 73 (Scheme 29).

![Scheme 29: The catalytic cycle of Enders cascade reaction.](image)

5.0 Axial chirality

Chirality in a compound can also form from planes, helices or axes, bringing the possibility of a new design for asymmetric catalysis. Axial chirality is encountered in compounds such as allenes, 2,2-disubstituted binaphthyls and tetra-ortho-substituted biphenyl compounds (where the rotation is prevented due to the steric effect of the substituent groups).

In the biaryl system, stereoisomers resulting from the hindered rotation are called atropoisomers; indeed, the steric strain barrier to rotation is very high, allowing the isolation of conformers,\textsuperscript{79,80} which can be specifically targeted and used in asymmetric catalysis.\textsuperscript{81} In addition, the stability of configuration and the stereochemical environment made these type of catalysts popular worldwide, including for mechanistic studies.\textsuperscript{82} Atropoisomerism can also be found in several drugs, natural products, chiral auxiliaries, and lately organocatalysts.
One of the most famous axial chiral compounds is probably BINAP 76, due to its huge success as a selective ligand resulting from its high stability towards axis rotation and the potential for coordination with a variety of metals. A good example of an axially chiral natural product is (−)-steganone 77, an anticancer agent (Figure 6).

![Figure 6: Axially chiral catalysts examples](image)

5.1 Axially chiral aminocatalysts

Due to the success of L-proline and its derivatives, it has been studied extensively. However, proline has a major drawback as it can decompose through decarboxylation. Therefore, modifications of the proline structure were targeted, particularly introducing more functional groups, and led to increased solubility and reactivity.

Shi’s prolinamide catalysts (S)-78 and Maruoka’s amino acid catalyst 79 were excellent examples of axially chiral amino acid catalysts for the aldol reaction. Prolinamide (S)-78 was applied for acetone addition to aryl aldehydes. For a 10 mol% catalyst loading and after optimisation, the best results were obtained using 10 mol% of acetic acid as an additive in toluene at −40 °C giving up to 98% ee, high dr (>98:2) and up to 90% yield. Comparing catalysts 78 and 80 (synthesised by Tang and his group), the selectivity obtained using 78 was higher, but a longer reaction time was needed. The higher selectivity can be explained by the presence of an extra aminocatalytic centre and the binaphthyl backbone, which increased the steric bulk and the chiral influence (Table 6).
In addition, Maruoka compared his catalyst to L-proline in DMSO, with acetone and 4-nitrobenzaldehyde as the substrates using a 5mol% catalyst loading. The kinetic study showed that although the initial rate of the reaction is high in the beginning when using proline, formation of oxazolidine (48%) caused a consumption of proline leading to a poor 18% yield.

In the case of catalyst 79, no by-product is obtained, and the aldol product is obtained in higher yield (Table 7).

**Table 6: Catalyst comparison in Aldol reaction.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst loading (mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>10</td>
<td>Acetone</td>
<td>72</td>
<td>58</td>
<td>65 (R)</td>
</tr>
<tr>
<td>2</td>
<td>CONH₂</td>
<td>10</td>
<td>Acetone</td>
<td>48</td>
<td>80</td>
<td>30 (R)</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>5</td>
<td>DMSO</td>
<td>24</td>
<td>70</td>
<td>93 (R)</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>5</td>
<td>DMSO</td>
<td>24</td>
<td>18</td>
<td>71 (R)</td>
</tr>
</tbody>
</table>
The use of amide-based solvents such as 1-methyl-2-pyrrolidone and N,N-dimethylformamide helped to improve the yield to 78% and 82%, respectively. Moreover, most aldehyde substrates gave ee above 90%. However, aromatic aldehydes gave low yields, whereas heteroaromatic, electron-deficient aromatic and olefinic aldehydes gave acceptable to very good yields.

Maruoka used catalyst 79 (10 mol %) with cyclohexanone and a range of aldehydes in dimethyl sulfoxide to obtain most of the aldol products in excellent enantioselectivities, diastereoselectivities and yields. In contrast, benzaldehyde and β-naphthylaldehyde gave low yields. The anti-aldol 81 was the major product, determined by chiral HPLC to be the (2S,1R)-diastereoisomer, which could be explained by a transition state in which the re face of the anti-enamine approaches the re face of aldehyde (Table 8), (Figure 6). 89

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{HCOAc})</td>
<td>80</td>
<td>95 (R)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{HCl})</td>
<td>91</td>
<td>95 (R)</td>
</tr>
<tr>
<td>3⁴</td>
<td>(\text{HCl})</td>
<td>35</td>
<td>96 (R)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{HOCl})</td>
<td>73</td>
<td>90ᵇ</td>
</tr>
</tbody>
</table>

a) 108 equivalents of acetone, the rest 27 equivalents used. b) absolute configuration not determined
Table 8: Catalyst 79 in aldol reaction between cyclohexanone and several aldehydes.

\[
\begin{align*}
&\text{Entry} & \text{Aldehyde} & \text{Yield (anti:syn) %} & \text{e.e (anti:syn) %} \\
&1 & \text{H} & \text{O} & \text{NO}_2 & 98 (95:5) & 98:5 \\
&2^a & \text{H} & \text{O} & \text{C} & 38 (91:9) & 98:16 \\
&3 & \text{H} & \text{O} & \text{TF} & 97 (>95:5) & 99:23 \\
&4 & \text{H} & \text{O} & \text{Cl} & 87 (95:5) & 97:30 \\
\end{align*}
\]

a) Reaction preformed for 126 h.

Figure 6: E-s-trans transition state of 79 enamine.
5.2 Maruoka’s organocatalysts

A number of successful axial chiral organocatalysts were synthesised by Maruoka and they can be classified according to their mode of action as enamine (82, 84, 85), iminium (83), or phase transfer (86) catalysts (Figure 7).

Maruoka relied on biaryl chiral backbones, based on their high chemical stability as well as allowing easy derivatisation. Furthermore, the design of the catalyst includes different aryl pendant functionalities, which provide different electronic properties tailored for different reaction types and conditions.

Figure 7: Biphenyl and binaphthyl catalysts synthesised by Maruoka.
5.2.1 Aldol reaction

Maruoka realised that catalyst 79 could be improved as the low nucleophilicity of the benzylic amine moiety slowed down the reaction rate, requiring a 10 mol% catalyst loading to achieve high yields. As a result, he synthesised catalyst 82, introducing electron-donating methoxy groups to increase the nucleophilicity of the amine moiety (Scheme 30).

The synthesis start with a reduction of the dicarboxylic acid compound 87 by borane-dimethyl sulfide (BMS) to make the corresponding diol product, followed by a bromination step using bromine and pyridine at −20 °C to give the product 88 in 95% yield over 2 steps. The diol product 88 was converted to the dibromide 89 in 75% yield using phosphorus tribromide at room temperature. A double nucleophilic substitution with allylamine to introduce the amine
moiety afforded the product 90 in 99% yield. The ethyl ester moiety was introduced using \( n\)-BuLi and ethyl carbonate to give product 91 in a moderate 48% yield. Deprotection of the allyl group using palladium followed by hydrolysis of the ethyl ester gave catalyst 82 in high yield (Scheme 30).

Maruoka suggested that having the methoxy groups in the biphenyl backbone catalyst 82 should increase the nucleophilicity of the catalyst, making it more reactive. A loading study confirmed the hypothesis: using catalyst loadings as low as 0.1 mol\%, ee and yields remained excellent at the expense of a longer reaction time (Table 9). 93

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol %)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>24</td>
<td>90</td>
<td>95 (R)</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>44</td>
<td>90</td>
<td>96 (R)</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>96</td>
<td>91</td>
<td>96 (R)</td>
</tr>
</tbody>
</table>

**Table 9: Loading study on catalyst (S)-82.**

5.2.2 Diels-Alder reaction

Using diamine catalyst 83 in an \( \text{exo} \)-selective Diels-Alder reaction gave a high selectivity with co-catalysts such as \( p \)-toluenesulfonic acid. The Diels-Alder reaction, between \( \alpha,\beta \)-unsaturated aldehydes and cyclopentadiene, gave high diastereo- (up to 20:1) and enantioselectivities (up to 95\% ee). However, when other dienes, such as 1,3-cyclohexadiene and 1,3-pentadiene, were used, only trace amounts of the Diels-Alder adduct were observed (Table 10). 94
Different electron-donating and –withdrawing groups were introduced and tested, and catalyst 83 allowed a fast iminium salt formation and hydrolysis. Diphenyl groups were introduced at positions 3- and 3’, which increased the exo selectivity and enantioselectivity. Introduction of tert-butyl groups at the same positions led to further increase of the exo selectivity and enantioselectivity as well as shorter reaction times. The presence of a larger group blocks one face of the iminium species allowing the other face to be easily approached by cyclopentadiene. Furthermore, the presence of two methylamino groups in the catalyst accelerated the reaction rate according to NMR studies.95

**Table 10:** Diels-Alder reaction with several aldehydes using catalyst 83.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield (%) (exo:endo)</th>
<th>e.e (%) (exo:endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCHO</td>
<td>93 (1.9:1)</td>
<td>86:68</td>
</tr>
<tr>
<td>2</td>
<td>HCOCH₃</td>
<td>72 (&gt;20:1)</td>
<td>88 (S): --</td>
</tr>
<tr>
<td>3</td>
<td>HCONC₆H₄Cl</td>
<td>99 (7.8:1)</td>
<td>92:96</td>
</tr>
<tr>
<td>4</td>
<td>HCONC₆H₄NO₂</td>
<td>99 (7.4:1)</td>
<td>95:98</td>
</tr>
</tbody>
</table>

a) Two more equivalents added after 48 h.
5.2.3 Mannich reaction

An *anti*-Mannich reaction between activated ketamine 92 and several aldehydes substrates using amino sulphonamide catalyst 84 was reported to give excellent results (Scheme 31).96

Because the *anti*-Mannich product was the only product obtained, Maruoka proposed a different transition state model whereby only the *s-cis* enamine is reacting, probably due to the longer distance between the amine species and the carboxylic acid than in the case of L-proline. Indeed, the L-proline catalysed reaction, via a *s-trans* enamine transition state, predominantly gave the *syn* product (Figure 8).97

![Scheme 31: Anti-Mannich reaction using amino sulphonamide catalyst 84.](image)

![Figure 8: S-trans transition state to form the syn-isomer using (L)-proline.](image)
5.2.4 Hydroxyamination of aldehydes
Catalyst 85 based on Jørgensen’s catalyst 67 was synthesised and tested and led to the $\alpha$-aminoxylation reactions between aldehydes and nitrosobenzene in very high diastereo- and enantioselectivities (Figure 9).  

![Diagram of catalysts 67 and 85](image)

**Figure 9:** Maruoka’s version of diaryl prolinol catalyst.

The reaction between aldehydes and nitrosobenzene 94 can produce one of two products depending on the catalyst used. An $O$-nitroso aldol product 95 can be formed using tetrazole 58, proline and glycolic acid. 99, 100, 101 The presence of the acid enables hydrogen bonding and causes the nitrosobenzene 94 to act as an oxy-electrophile resulting in the formation of $\alpha$-nitroso-aldehydes. The $N$-nitroso product or hydroxyamination product 96 can be formed using tertiary alcohols such as TADDOL, with a pre-formed enamine (Scheme 32).

![Scheme 32: O-nitroso 95 and N-nitroso 96 products](image)
Maruoka wanted to find a pathway to achieve hydroxyamination products: using propanal and nitrosobenzene. Amine 97 was tested first to provide a reference free of hydrogen-bond donor. The ratio between the hydroxyamination and O-nitroso aldol products was very high (>99/1), but, the yield and ee obtained were low (22% and 29% (S), respectively). Alcoholic solvents were also examined, such as methanol and tert-butanol, increasing the yield slightly. In an attempt to improve the catalyst by targeting in-situ enamine formation and hydrogen bonding, two hydroxymethyl groups were introduced to form amine 100, resulting in a large increase in the yield and the enantioselectivity. Finally, catalyst 85 was found to be the best catalyst using the same conditions, providing high yields and excellent regio- and enantioselectivity (Table 11).

Table 11: Screening of several catalysts for the hydroxyamination of propanal.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ratio 98/99</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Catalyst 97" /></td>
<td>&gt;99/1</td>
<td>22</td>
<td>29 (S)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Catalyst 100" /></td>
<td>&gt;99/1</td>
<td>55</td>
<td>77 (S)</td>
</tr>
<tr>
<td>3</td>
<td>85</td>
<td>&gt;99/1</td>
<td>90</td>
<td>99 (S)</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>&gt;99/1</td>
<td>9</td>
<td>23 (R)</td>
</tr>
</tbody>
</table>
5.3 Page’s axially chiral atom transfer catalysts

The Page group has been involved in the synthesis of several electrophilic atom-transfer organocatalysts, beginning from dihydroisoquinoline-based (101 and 102) evolving to more complex chirally axial backbones for epoxidation (103) and aziridination (104 and 105) reactions (Figure 10).

![Figure 10: Epoxidation and aziridination catalysts synthesised by Page.](image)

5.3.1 Epoxidation catalysts

Using a dihydroisoquinoline backbone and several primary amines, Page synthesised a range of catalysts which had a chiral exocyclic groups on the iminium nitrogen. Page introduced the chiral element close to the reaction centre hoping to improve the enantioselectivity.

The synthesis of dihydroisoquinoline catalyst 108 started with bromination of isochroman to give 1-bromo-isochroman 106, and in the presence of hydrobromic acid, compound 106 was converted to 2-(2-bromoethyl)benzaldehyde 107 in a good 65% yield. A condensation step with acetonamine 109 afforded the iminium species followed by anion exchange with sodium tetraphenylborate to form catalyst 108 (Scheme 33).

![Scheme 33: Synthesis of Catalyst 108.](image)
In the presence of an oxidising agent such as oxone or TPP, the iminium catalyst is converted into the corresponding oxaziridinium ion, followed by the oxygen atom transfer to the alkene substrates. Page also synthesised catalysts that have acetonamine based chiral features using axially chiral biphenyl and binaphthyl backbones. Catalyst 101, derived from isopinocampheyl amine, gave good ee (73%) when tested with trans-stilbene. However, the most successful catalysts having an acetonamine moiety, such as 102, 103, 108 and 110, showing increased enantioselectivity when compared with other chiral amines. Catalyst 102 afforded the highest enantioselectivities (up to 97%) when used in the oxidation of cyclic cis-alkenes in the presence of TPP at low temperatures (Table 12).

Table 12: Epoxidation reactions screening using Page’s iminium salts catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Alkene</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
<th>Major Epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>101 (10 mol%)</td>
<td></td>
<td>78</td>
<td>73</td>
<td>(+)-(1R,2R)</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>102 (10 mol%)</td>
<td></td>
<td>76</td>
<td>93</td>
<td>(-)-(1S,2S)</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>103 (5 mol%)</td>
<td></td>
<td>66</td>
<td>95</td>
<td>(+)-(1S,2R)</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>108 (5 mol%)</td>
<td></td>
<td>54</td>
<td>59</td>
<td>(-)-(S)</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>110 (5 mol%)</td>
<td></td>
<td>100</td>
<td>60</td>
<td>(-)-(1S,2S)</td>
</tr>
</tbody>
</table>
Page applied catalyst **102** to the synthesis of antihypertensive (−)-cromakalim **112** by forming epoxide product **111** followed by an epoxide ring-opening reaction using 2-pyrrolidinone to give the (−)-cromakalim (**Scheme 34**).\(^\text{107}\)

\[
\begin{align*}
\text{NC} & \quad \text{102 (10 mol%), TPPP} \\
\text{CHCl}_3, -40 ^\circ \text{C}, 24 \text{ h} & \quad \text{pyrrolidone, NaH} \\
\text{59%} & \quad \text{DMSO, rt, 4 h} \\
\text{111} & \quad \text{52%} \\
\text{NC} & \quad \text{112}
\end{align*}
\]

**Scheme 34:** Synthesis of (−)-cromakalim **112**.

In the case of catalyst **108**, epoxidation of triphenylethylene was achieved in moderate selectivity (59%). The selectivity could be due to the chair conformation of the dioxane substituent, as observed in the solid state by using single crystal X-ray crystallography, implying that the dihydroisoquinoline moiety is axial.\(^\text{108}\)

\[
\begin{align*}
\text{108a} & \quad \text{108b}
\end{align*}
\]

**Scheme 35:** Possible conformations of **108**.

To avoid the 1,3-diaxial interaction present in conformer **108a**, the thermodynamically favoured conformation becomes **108b**, in addition, the oxygen atoms lone pairs could increase the stability of the iminium moiety further favouring **108b**. The phenyl group probably shields one side of the iminium bond, therefore making attack on one face favoured (**Scheme 35**).
The catalytic cycle starts with the nucleophilic oxidant attacking the iminium species on its *si* or *re* face, potentially forming two diastereoisomers: 113a and 113b. As the phenyl group hinders the oxidant’s approach towards one face of the iminium species, the formation rate of the diastereoisomers will be different. Therefore, one of the ring closed oxaziridinium species 114a or 114b will be formed preferentially. As a result, oxygen atom transfer to a prochiral alkene substrate will occur selectively (Scheme 36).

Catalyst (S)-binaphthyl azepinium salt 103 gave phenyl-1,2-dihydronaphthalene oxide in high ee (95%) due to the axially chiral binaphthyl backbone. Furthermore, the Page group improved the biaryl iminium catalyst series by introducing a substituent at the α-position to the azepinium nitrogen atom thus increasing the steric constraint around the iminium species to improve the selectivity. In the case of biphenyl catalyst 110, where there is no barrier to interconversion between atropoisomers at room temperature, addition of the substituent locks the conformation, preventing the interconversion, and the formation of two separable atropoisomers is observed.

In more detail, low-temperature 1H NMR experiments were carried out on catalyst 110 to observe the preferred lowest energy conformation. The rotation around the biphenyl C-C and N-C bonds allowed the detection of four conformers which were identified. The $R_{ax}$
conformation (89:11) was favoured for the biphenyl species due to reduction of the interaction with the nitrogen substituent. Mixtures of two diastereoisomers were formed when Grignard reagents (methyl, isopropyl, phenyl, and benzyl) were added to iminium species 110 at −78 °C. For example, when methylmagnesium bromide was used, the major diastereoisomer was $(R_{ax}, R,S,S)-115$ and was isolated alongside the minor diastereoisomer $(S_{ax}, S,S,S)-116$ (Scheme 37).

![Scheme 37: Methyl Grignard reagent addition onto iminium salt 110.](image)

As the rotation around the biaryl axis was prevented, the substituent adopted a pseudo-axial orientation to minimise its steric interaction with the acetonamine moiety. Using $^1$H NMR spectroscopic analysis, the chemical shift for 115 at $\delta_{Me}$ 0.68 ppm and 116 at $\delta_{Me}$ 0.41 ppm allowed the group to identify the configuration of the two atropoisomers; the chemical shift for the protons on the pseudo-axial methyl group is affected by the ring current effect causing deshielding. Single crystal X-ray crystallography confirmed the absolute configuration of 117 to be $(R_{ax}, R,S,S)$. Through a double stereochemical relay, the two atropoisomers were produced selectively: the chiral group attached to the nitrogen favoured product 115 and in addition controlled the selectivity of the Grignard reagent addition.$^{109}$ Such a stereochemical relay was observed by Wallace when conducting dynamic axial chirality studies. Azepine 118 has a $(S_{ax})$
biaryl backbone and the methyl group in position 5 is pseudo-equatorial. However, when azepine 118 is converted into N-Boc-azepine 119, the addition of a bulky N-Boc group forces a switch in the axial chirality of the backbone, and the α-substituent orientation switches to a pseudo-axial orientation (Scheme 38). \(^{110}\)

![Scheme 38: Addition of the Boc group causes a switch to the biphenyl backbone chirality.](image)

Steric interactions between the methyl group and the N-substituent force this switch: the methyl group adopts a pseudo-axial orientation to minimise the steric interaction with the Boc groups, which leads to a change of the biphenyl backbone chirality from \((S)\) to \((R)\).

In the case of the binaphthyl compound 103, the Grignard reagents were introduced completely diastereoselectively (Scheme 39).

![Scheme 39: Diastereoselective addition of Grignard reagent diastereoselective onto iminium salt 103.](image)
In order to prepare the catalysts, \((R_{ax},R,S,S)-115\) and \((R_{ax},R,S,S)-120\) were oxidised using NBS giving the corresponding iminium salts. The presence of the methyl group at the C5 position was shown to improve the selectivity of the epoxidation reaction of 1-phenyl-1-cyclohexene (Scheme 39), (Table 13).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion (%)</th>
<th>e.e (%)</th>
<th>Major Epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>110</td>
<td>100</td>
<td>60</td>
<td>((-)-(1S,2S))</td>
</tr>
<tr>
<td>2(^a)</td>
<td>117</td>
<td>100</td>
<td>82</td>
<td>((-)-(1S,2S))</td>
</tr>
<tr>
<td>3(^b)</td>
<td>103</td>
<td>99</td>
<td>91</td>
<td>((-)-(1S,2S))</td>
</tr>
<tr>
<td>4(^b)</td>
<td>121</td>
<td>99</td>
<td>94</td>
<td>((-)-(1S,2S))</td>
</tr>
</tbody>
</table>

5.3.2 Aziridination catalysts

In 2013, Page adapted the binaphthyl and biphenyl catalyst structures in order to probe their activity and selectivity in the aziridination reaction of chalcones. The modification introduced substituents at the 3- or 3,3’ positions as well as the introduction of different groups on the azepine nitrogen atom.

Using \(O\)-(diphenylphosphinyl)-hydroxylamine (DppONH\(_2\)) \(122\) as the nitrogen transferring reagent and NaOH as the base in dichloromethane was found to be the optimal conditions. Using 3,3’-disubstituted catalyst \(104\), a moderate 43% ee with a very low 10% conversion was observed, maybe due to steric hindrance. In addition, \(N\)-isopropyl azepine \(105\) gave higher conversion (70%) and a lower 35% ee (Table 14).
Moreover, azepine 123 enabled the preparation and isolation of hydrazinium salt 124 in good yield (77%). Tetraphenylborate counter ion exchange gave product 125 in quantitative yield, which was found to be bench-stable for a long period of time (two years) (Scheme 40).

Under the same condition, 124 and 125 were both used as aziridination reagents giving the same ee and yield as 123 which probably shows that hydrazinium salts are an intermediate in the catalytic cycle.
5.3.3 Page’s axially chiral aminocatalysts

After the good results obtained using the axially chiral atom transfer organocatalysts, Page attempted to adapt the structures of his azepine compounds to be suitable as aminocatalysts. Starting with 97 and 126, binaphthyl aminocatalysts were prepared and compared with Maruoka’s successful amino-acid catalyst (S)-79 using the aldol reaction of 4-nitrobenzaldehyde and acetone (Figure 11).

Using Maruoka’s preferred solvents (dimethylsulfoxide or N,N-dimethylformamide), catalyst 97 gave very poor conversions and racemic products. On the other hand, complete conversion to the aldol product in a low ee was observed when aprotic solvents, such as acetonitrile, acetone and tetrahydrofuran, were used. In addition, the major isolated enantiomer was the (S)-enantiomer with all solvents apart from water, which gave the (R)-enantiomer in 16% ee. In the case of catalyst 126, generally, similar results in terms of ee and conversion were observed. Using acetonitrile at 0 °C, the (S)-enantiomer was obtained in 30% ee (Table 15).
**Table 15:** Catalyst 97 and 126 screening on aldol reaction.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temperature</th>
<th>Solvent</th>
<th>conv. (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97</td>
<td>r.t.</td>
<td>H₂O</td>
<td>50</td>
<td>16 (R)</td>
</tr>
<tr>
<td>2</td>
<td>97</td>
<td>r.t.</td>
<td>neat</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>97</td>
<td>r.t.</td>
<td>THF</td>
<td>100</td>
<td>3 (S)</td>
</tr>
<tr>
<td>4</td>
<td>97</td>
<td>r.t.</td>
<td>DMF</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>r.t.</td>
<td>CH₃CN</td>
<td>100</td>
<td>2 (S)</td>
</tr>
<tr>
<td>6</td>
<td>97</td>
<td>r.t.</td>
<td>DMSO</td>
<td>&lt;5</td>
<td>3 (S)</td>
</tr>
<tr>
<td>7</td>
<td>97</td>
<td>r.t.</td>
<td>Et₂O</td>
<td>100</td>
<td>4 (S)</td>
</tr>
<tr>
<td>8</td>
<td>97</td>
<td>r.t.</td>
<td>MeOH</td>
<td>30</td>
<td>2 (S)</td>
</tr>
<tr>
<td>9</td>
<td>97</td>
<td>r.t.</td>
<td>EtOH</td>
<td>50</td>
<td>3 (S)</td>
</tr>
<tr>
<td>10</td>
<td>97</td>
<td>r.t.</td>
<td>iPrOH</td>
<td>40</td>
<td>3 (S)</td>
</tr>
<tr>
<td>11</td>
<td>126</td>
<td>r.t.</td>
<td>H₂O</td>
<td>10</td>
<td>16 (R)</td>
</tr>
<tr>
<td>12</td>
<td>126</td>
<td>r.t.</td>
<td>CH₃CN</td>
<td>65</td>
<td>6 (S)</td>
</tr>
<tr>
<td>13</td>
<td>126</td>
<td>0 °C</td>
<td>CH₃CN</td>
<td>25</td>
<td>30 (S)</td>
</tr>
<tr>
<td>14</td>
<td>126</td>
<td>r.t.</td>
<td>THF</td>
<td>70</td>
<td>7 (S)</td>
</tr>
<tr>
<td>15</td>
<td>126</td>
<td>0 °C</td>
<td>THF</td>
<td>15</td>
<td>5 (S)</td>
</tr>
<tr>
<td>16</td>
<td>126</td>
<td>r.t.</td>
<td>Et₂O</td>
<td>50</td>
<td>6 (S)</td>
</tr>
<tr>
<td>17</td>
<td>126</td>
<td>0 °C</td>
<td>Et₂O</td>
<td>15</td>
<td>11 (S)</td>
</tr>
<tr>
<td>18</td>
<td>126</td>
<td>r.t.</td>
<td>Toluene</td>
<td>75</td>
<td>5 (S)</td>
</tr>
<tr>
<td>19</td>
<td>126</td>
<td>0 °C</td>
<td>Toluene</td>
<td>15</td>
<td>5 (S)</td>
</tr>
</tbody>
</table>
6.0 The project

The aim of the project is to synthesise and design organocatalysts that share a similarity with catalysts reported before, such as proline $27$, tetrazole $58$, diaerylprolinol silyl ether $68$, and Maruoka’s amino acid $79$. The novel targeted catalysts may have a stereogenic centre on the azepine ring and the structures will be axially chiral. Introducing different R substituents next to the nitrogen atom should lead to interaction with the in situ generated iminium or enamine species (depending on the reaction type) by hydrogen bonding, ionic or/and steric interactions to encourage increased enantiofacial selectivity, therefore, leading to highly enantioselective reactions (Figure 12).

![Figure 12: The project catalysts design](image-url)
Introduction references

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3413-3426.
773-775.
Asymmetry, 1995, 6, 2911.
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Chapter two: Results and Discussion

1.0 Project Aim

The project aim is to synthesise novel axial chiral aminocatalysts, and test their efficiency on two asymmetric reactions, aldol and manich reactions (Michael and Diels-Alder reactions have been evaluated previously in the Page group). Our design is similar to Maruoka’s aryl bifunctionalized organocatalyst 79, which showed excellent selectivity, but on the other hand, the addition of groups that are closer to the aminocatalytic centre has not been investigated on the BINAP system. Our catalyst would have conformational stability due to the fixed chiral backbone. In addition, as was proved successful with Page’s epoxidation catalysts, the stereogenic centre would be sited at an α-position with respect to the azepine nitrogen atom (Figure 13).

The synthetic approaches until producing the binaphthyl azepines have been reported before.1,2,3 At the 2-position of the azepine ring, the introduction of a substituent is rarely reported, except for a few reports of asymmetric additions of alkyl groups. However, there have been two successful approaches reported: The diastereoselective Grignard reagent addition on an iminium salt by Page,4 and base-mediated alkylation method as used by Meyers,5 Wallace6 and Superchi1.

Figure 13: The targeted catalysts.
Using the **approach A** is preferred when the protection group of the azepines is electron-donating due to the stability of the iminium species. Where is **approach B** is preferred is when an electron-withdrawing group is protecting the azepines, as position $\alpha$ is been activated to be deprotonated (Scheme 41).

### 2.0 Synthesis of the $\beta$-amino acid catalyst

Our first aim was to synthesise a catalyst analogous to proline. In addition, introduction of a carboxylic acid group was also considered. A number of $\beta$-amino acid proline analogues have been studied and their application tested in aldol reaction such as 127$^7$ and Mannich reaction such as 128$^8$ (Figure 14).

![Diagram](image)

**Figure 14**: Example of catalysts tested in aldol and manich reactions.

In more detail, comparing L-proline with these catalysts in the Mannich reaction between 3-pentanone and $\alpha$-imino amide 129 for example, resulted in a 73% yield when 130 used as catalyst after 3 days.$^9$ In contrast, using L-proline gave <10% conversion after 3 days, proving that these catalysts have a higher reactivity than L-proline in this reaction. (Scheme 42)$^7$. 

58
In addition, the Hajos-Parrish-Eder-Sauer-Wiechert reaction of 131 catalysed by D-proline gave 72% ee while using 132 gave a higher selectivity of 86% ee (Scheme 43). Therefore, chiral β-amino acids seems very interesting as a catalytic design.
2.1 Initial retrosynthetic approaches to the β-amino acid catalyst

**Approach A** was used in the synthesis of catalyst 133 starting from iminium salt as the Page group had developed this method. As the addition of Grignard reagents onto the azepinum species is totally diastereoselective, we aimed to introduce suitable nucleophilic reagents selectively following by conversion into the corresponding carboxylic acid 133 (Scheme 44).

![Scheme 44: The targeted β-amino acid catalyst.](image)

To allow iminium salt formation, a nitrogen protection group is essential, and in addition it is a fundamental synthetic step for the catalyst that can be removed easily. Furthermore, basic and nucleophilic conditions are important as is tolerance of oxidation. Previously in the group the *p*-methoxybenzyl group was introduced, which added more stability to the iminium moiety, but unfortunately decomposition accrued when its removal was attempted (Scheme 45). As a result, the allyl amine group was targeted which was also applied in the Maruoka binaphthyl catalysts successfully.10

![Scheme 45: Attempted deprotection of the *p*-methoxybenzyl group.](image)
3.0 Azepine synthesis

We started from enantipure (S)-BINOL to synthesise a range of binaphthyl catalysts.\textsuperscript{11} At low temperature a conversion of bis-alcohol to bis-triflate using triflic anhydride and 2,6-lutidine gave 134 in quantitative yield. A methylation step by a Kumada cross-coupling reaction by using 1,2-bis-(diphenylphosphino)ethane dichloronickel(II) (Ni(dppe)Cl\textsubscript{2}) with methyl magnesium bromide gave 135. Formation of product 136 by a radical bromination reaction using N-bromosuccinimide and azobisisobutyronitrile as an initiator gave modest yields of 135 (between 47% to 77%) (Scheme 46).\textsuperscript{2}

![Scheme 46: Dibromobinaphthyl 136 synthesis.](image)

The first three steps did not require using column chromatography as the products can be purified by recrystallization or precipitation, giving the products in high purity with complete retention of absolute configuration.

Having a dibromo product will provide variety of tertiary azepines for future derivatization by a double nucleophilic substitution reaction which was a general reaction procedure as previously reported by Page to synthesise several highly substituted biphenyl azepines giving biphenyl products in moderate to high yield.\textsuperscript{12} The reaction could be carried out by treatment of the dibromo product 136 with small excess of a primary amine and heating under reflux in
the presence of anhydrous potassium carbonate in acetonitrile. By oxidation using NBS followed by anion exchange using sodium tetraphenylborate the corresponding iminium salt formed in a good yield of 81%. Our attention after having the iminium species, turned to the diastereoselective addition of nucleophiles (Scheme 47).

Scheme 47: Introduction of the allyl protection group and its iminium salt.

4. Allyl protecting group

Knowing the Page’s group previous difficulty in removing the PMB group, we focused on the allyl group, which is used widely to protect amine and alcohol moieties, and was also used by Maruoka. Tsuji’s original procedure used a palladium mediated allylation reaction by adding diethyl malonate to the η3-diallyl dichlorodipalladium complex 139. This resulted in two products, mono- and bis-allyl. In addition, Trost’s is work in allyl protection resulted in short time reaction by addition of triphenylphosphine, and controlled use of the nucleophile in the addition to the η3 complex by steric and electronic properties of the nucleophile. As an example reaction of methylsulfonyl acetate 140, the product 141 was the only one isolated. To remove the allyl protection group, N,N-Dimethylbarbituric acid 142 was used as a nucleophilic allyl scavenger (Scheme 48).
Cross dehydrogenative coupling (CDC) reactions can take place by conversion of one reaction partner into an electrophile through in situ oxidization as an electron-rich coupling partner attacks. In this type of reaction, a high tolerance of function groups is involved. The reaction is capable of functionalizing sp3 C-H bonds with sp, sp2 and sp3 hybridized starting materials by using catalysts based on copper or iron salts (Scheme 49).\(^{16}\)

## 4.1 Oxidative cross coupling reactions

Cross dehydrogenative coupling (CDC) reactions can take place by conversion of one reaction partner into an electrophile through \textit{in situ} oxidization as an electron-rich coupling partner attacks. In this type of reaction, a high tolerance of function groups is involved. The reaction is capable of functionalizing sp3 C-H bonds with sp, sp2 and sp3 hybridized starting materials by using catalysts based on copper or iron salts (Scheme 49).\(^{16}\)
There are many reports of oxidations of C-H bonds close to nitrogen atoms in tertiary amines.\textsuperscript{17} A coupling reaction reported by Li et al. between tetrahydroisoquinoline 143 and dimethyl malonate (used as a solvent) in the presence of t-BuOOH (TBHP) and copper bromide catalyst (5 mol%), which was in mild conditions resulted in β-diester tetrahydroisoquinoline analogue 144 at room temperature in high yield of 90\% (Entry 1).\textsuperscript{18} In addition, Itoh reported the first use of iodine as a metal-free oxidative catalyst in CDC reactions of tertiary amines which was in the presence of hydrogen peroxide giving 144 in a good yield of 73\% (Entry 2), (Table 16).\textsuperscript{19}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mol% CuBr</td>
<td>TBHP (1 equiv.)</td>
<td>r.t.</td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>10 mol% I\textsubscript{2}</td>
<td>H\textsubscript{2}O\textsubscript{2} (2 equiv.)</td>
<td>50</td>
<td>12</td>
<td>73</td>
</tr>
</tbody>
</table>

By applying the Li conditions to our protected allyl azepine 137, using the copper catalyst, nothing appeared except starting material in the reaction mixture after 24 h. It was assumed that this was due to the poor solubility of the azepine 137 in the solvent diethyl malonate. Furthermore, when dichloromethane was used as the solvent, unfortunately only starting material was observed. Use of Itoh conditions using the iodine with the oxidant hydrogen peroxide, afforded only of starting material, even when a higher temperature of 50 °C was applied (Table 17).
From a mechanistic view, generation of an electrophilic iminium ion is essential under the Li and Itoh CDC reactions. Itoh suggested that by reaction between iodine and hydrogen peroxide, the hypoiodous acid (HOI) is formed, which is the active oxidant in the conversion of 143 into the iminium species.

Li proposed that copper can activate the dimethyl malonate and also coordinate to 143 to form an iminium intermediate by hydrogen abstraction at the $\alpha$-position of tetrahydroisoquinoline. Excitingly, in a CDC reaction between tetrahydroisoquinoline 143 and dimethyl malonate with DDQ as an oxidant by Todd, the reaction could not progress if the iminium ion 145 was not isolated and then added to the dimethyl malonate solution, resulting 144 after 30 min in 73% yield (Scheme 50).20
This could explain the failure of our CDC reactions with the azepine 137, so we decided to isolate the iminium salt first and then test the copper-catalysed coupling conditions.

Azepine 137 was oxidized with NBS or DDQ followed by ion-exchange with sodium tetraphenylborate, resulting in the iminium salt 146 as an orange solid. Moreover, using NBS at room temperature gave a moderate yield of 51\% (Entry 1), and, by lowering the temperature at 0 °C the yield increased to 79\% (Entry 2). Using the DDQ at room temperature gave a lower yield of 43\% (Entry 3), (Table 18).

**Table 18: Oxidation of 137.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS (1.05 equiv.)</td>
<td>r.t.</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>NBS (1.05 equiv.)</td>
<td>0</td>
<td>2</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>DDQ (2 equiv.)</td>
<td>r.t.</td>
<td>1</td>
<td>43</td>
</tr>
</tbody>
</table>
After we had synthesised 146 in a good yield, the Li coupling conditions were examined, in the presence of additive TBHP and without (Table 19).

**Table 19: Iminium salt 146 coupling reaction attempted.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr</td>
<td>TBHP</td>
<td>Diethyl malonate</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CuBr</td>
<td>-</td>
<td>Diethyl malonate</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>CuBr</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
</tbody>
</table>

After 16 h, only decomposition of the starting material, the iminium salt 146 was observed. No formation of the desired product was observed.

Another method was tried for the CDC reaction by generating a reactive ethoxy intermediate 148, which was prepared from isoquinolinium bromide 147 with sodium ethoxide. The ethoxide group was replaced by several ketones, use of acetone giving the highest yield (Scheme 51). ²¹

**Scheme 51: Preparation of 149.**
Unfortunately when tested on 146, no formation of the desired product was observed after 16 h, both low and high temperature conditions giving only starting material (Table 20).

**Table 20: Iminium salt 146 nucleophilic addition attempts.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone</td>
<td>0</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Acetone</td>
<td>0 to r.t.</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Acetone</td>
<td>0 to 40</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>
4.2 Reformatsky reaction

The Reformatsky reaction uses organo-zinc reagents which can be formed from oxidative addition of zinc into carbon-halide bonds of α-halogen esters, which when added to carbonyl containing compounds result in β-hydroxyester compounds (Scheme 52).

![Scheme 52: Traditional Reformatsky reaction.](image)

The Reformatsky reactions has been used to introduce functionality onto several substrates, and has been most studied on aldehydes and ketones. However, addition to imine and iminium moieties has been only rarely reported. In addition, addition of α-haloesters to iminium salts were reported in alarge-scale in synthesis of an anti-arteriosclerotic intermediate (Scheme 53).

![Scheme 53: Synthesis of Anti-arteriosclerotic intermediate involving Reformatsky reaction.](image)

We decided to try the Reformatsky reaction with the iminium salt 146 as a Reformatsky reagent acceptor. As we predicted that the saponification step would involve mild conditions, t-butyl bromoacetate was used.
In more detail, a zinc suspension in tetrahydrofuran was heated under reflux in the presence of chlorotrimethylsilane and 1,2-dibromoethane for 1 h. Unfortunately, only trace amounts of the desired product 151 were obtained (Entry 1). By increasing the reagent amount, the desired product was isolated in 17% yield as a single diastereoisomer (Entry 2). In addition, leaving the reaction for a longer time of up to 48 h and increasing the Reformatsky reagent equivalents, a slight improvement in the yield was found at 24% (Entry 3). Trying to increase the yield the temperature was raised to 65 °C for 12 h, but unfortunately, due to instability of the Reformatsky reagent 150 or iminium salt 146 in higher temperatures, product 151 was not obtained (Entry 4) (Table 21).

\[ \text{Table 21: Reformatsky reaction with allyl iminium salt 146.} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>t-butyl bromoacetate</th>
<th>Zinc Dust</th>
<th>1,2-Dibromoethane</th>
<th>TMSCl</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 equiv</td>
<td>6 equiv</td>
<td>5 mol%</td>
<td>4 mol%</td>
<td>25 to 30</td>
<td>12</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>10 equiv</td>
<td>10 equiv</td>
<td>10 mol%</td>
<td>10 mol%</td>
<td>25 to 30</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>10 equiv</td>
<td>10 equiv</td>
<td>1 equiv</td>
<td>1 equiv</td>
<td>25 to 30</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>5 equiv</td>
<td>6 equiv</td>
<td>10 mol%</td>
<td>10 mol%</td>
<td>65</td>
<td>12</td>
<td>-</td>
</tr>
</tbody>
</table>
The iminium salt 146 was instable and therefore, a procedure using chiral $N$-sulfinyl imine 153 which undergoes Reformatsky reactions at low temperature, was investigated. The corresponding ester 154 was formed in quantitative yield using a novel zinc activation method using DIBAL, which has also been reported for large scale synthesis (Scheme 54).$^{25}$

Scheme 54: Imine 153 Reformatsky reaction with DIBAL zinc activation at low temperature.
At low temperature, the substrate 146 using DIBAL zinc activation gave ester 151 in 25% yield (Entry 1). We tried to improve the yield by activating the zinc with a stoichiometric amount of TMSCl, and adding the iminium salt 146 to the activated zinc slurry at 0 °C, which gave a higher yield of 43% (Entry 2). In addition, the iminium salt 146 was added to the activated zinc at -78 °C yielding the desired product 151 in 68% yield. A crystal structure of 151 has been obtained in the Page group previously (Entry 3), (Table 22).

Table 22: Low temperature addition of 150.

<table>
<thead>
<tr>
<th>Entry</th>
<th>t-butyl bromoacetate</th>
<th>Zinc Dust</th>
<th>Additive</th>
<th>Additive Temp.</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7 equiv.</td>
<td>3.5 equiv.</td>
<td>DIBAL (4 mol%)</td>
<td>40</td>
<td>-78 to r.t.</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>10 equiv</td>
<td>10 equiv</td>
<td>TMSCl (1 equiv.)</td>
<td>65</td>
<td>0 to r.t.</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>10 equiv</td>
<td>10 equiv</td>
<td>TMSCl (1 equiv.)</td>
<td>65</td>
<td>-78 to r.t.</td>
<td>48</td>
<td>68</td>
</tr>
</tbody>
</table>
The next step was removal of both the allyl and t-butyl protecting groups. Deallylation of 151 led to the azepine product 155 in 82% yield, followed by removal of the t-butyl group using TFA to afford the β-amino acid catalyst 133 in a high yield of 91% (Scheme 55).

![Scheme 55: Tert-butyl and allyl groups removal.](image)

Furthermore, we estimated that a more steric congested analogue of β-amino acid catalyst 133 would gave more selectivity by increasing crowding near to the amine centre, and that led us to synthesise β-amino acid 156 (Figure 14).

![Figure 14: Congested sterically β-amino acid 156.](image)
The Reformatsky substrate was t-butyl bromoisobutyrate. A higher temperature was used, which gave a moderate yield of 47% (Entry 1). Moreover, decreasing the temperature to 0 and -78 °C gave better yields of product 158, isolated in 52% and 74% respectively (Entry 2 and 3), (Table 23).

Table 23: Reformatsky reaction with t-butyl bromo isobutyrate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>t-Butyl bromo isobutyrate</th>
<th>Zinc Dust</th>
<th>1,2-Dibromoethane</th>
<th>TMSCl</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 equiv</td>
<td>10 equiv</td>
<td>1 equiv.</td>
<td>1 equiv.</td>
<td>25 to 30</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>15 equiv</td>
<td>15 equiv</td>
<td>-</td>
<td>1 equiv</td>
<td>0 to r.t.</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>10 equiv</td>
<td>10 equiv</td>
<td>-</td>
<td>1 equiv</td>
<td>-78 to r.t.</td>
<td>74</td>
</tr>
</tbody>
</table>
After we had 158 in hand, deallylation under palladium-catalysed conditions gave product 159 in 60% yield, and after the saponification step using TFA, product 156 was obtained in a moderate yield of 62% (Scheme 56).

![Scheme 56: Tert-butyl and allyl group removal.](image)

Further, we applied the same conditions to add methyl and ethyl esters, but we were only able to produce the β-methyl ester 160 (Entry 1), (Table 24).

**Table 24: Reformatsky reaction to form β–esters.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (10 equiv.) (R)</th>
<th>Zinc Dust</th>
<th>TMSCI</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methyl chloroacetate</td>
<td>10 equiv</td>
<td>1 equiv</td>
<td>-78 to r.t.</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td>Ethyl chloroacetate</td>
<td>10 equiv</td>
<td>1 equiv</td>
<td>-78 to r.t.</td>
<td>S.T.</td>
</tr>
</tbody>
</table>
To remove the allyl group, 160 was treated with palladium catalyst to give the β-methyl ester catalyst 161 in 63% yield (Scheme 57).

Scheme 57: Removal of allyl group.

5.0 Initial retrosynthetic approaches to the α-amino acid catalyst

After we had successfully synthesised β-amino acids 133 and 156, and to evaluate the groups’ effect depending upon their distance from the catalytic centre. Therefore, the α-amino acid 162 route was evaluated, 162 being which could synthesised through a lithiation and electrophilic trapping route (Scheme 58).

Scheme 58: Approach B to the synthesis of the α-amino acid catalyst.

The deprotonation step in approach B would require a metaleation of the binaphthyl azepine, which could be done using a metal hydride base or an organo-lithium. Use of electron-withdrawing N-protecting groups was thought to be essential to deprotonate the proton at α-position, because the protecting group would increase the acidity at α-position by stabilization of the anion intermediate. and that followed by addition of the electrophilic reagent which will quench the anion giving the α-functionalized catalyst.
5.1 Boc protecting group

Starting from dibromo product 136 using tert-butyl carbamate in DMF with sodium hydride (2.1 equivalent) as base for 4 days, gave the Boc-protected product 163 in 54% yield (Entry 1). Increasing the number of the equivalents of base to 3 and 4 showed improvement of 65% and 87% yield respectively (Entry 2 and 3). Increasing the temperature to 50 °C and reducing the reaction time led to poor yield of 31% and inseparable side products (Entry 4), (Table 25).

Table 25: Optimization attempts on N-Boc azepine 163 synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>NaH (equiv.)</th>
<th>Time (d)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1</td>
<td>4</td>
<td>0 to r.t.</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
<td>0 to r.t.</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4</td>
<td>0 to r.t.</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1</td>
<td>0 to 50</td>
<td>31</td>
</tr>
</tbody>
</table>
Having the Boc-azepine 163 in hand, we investigated its deprotonation and alkylation with functional groups that could be converted into a carboxylic acid, for example by a saponification reaction. Therefore, deprotonation of Boc-azepine 163 at -78 °C with sec-BuLi followed by alkyl chloroformate addition which was carried out under Blakemore’s conditions gave good results. Addition of ethyl and methyl chloroformate gave good yields of 70% and 80% respectively (Entry 1 and 2). However, the addition of di-tert-butyl carbonate was unsuccessful (Entry 3), (Table 26).

**Table 26: Deprotonation of 163 and electrophile addition.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Yield (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl chloroformate</td>
<td>70</td>
<td>164</td>
</tr>
<tr>
<td>2</td>
<td>Methyl chloroformate</td>
<td>80</td>
<td>165</td>
</tr>
<tr>
<td>3</td>
<td>di-tert-butyl carbonate</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Only starting material was obtained upon trying to remove the Boc group using mild microwave heating in water. However, successful deprotection of the Boc group for both ethyl and methyl azepines using an excess of trifluoroacetic acid in dichloromethane gave 166 and 167 in 85% and 81% yield respectively (Scheme 59).

**Scheme 59: Removal of Boc protecting group.**
Unfortunately, all saponification reactions that were examined for both the methyl and the ethyl esters failed. Further, basic and acidic conditions and higher temperatures were examined for both methyl and ethyl esters. However, only starting material was obtained. Use of TMSCl combined with NaI was tested, but surprisingly, instead of saponifying the methyl ester, the Boc group was removed (Entry 6). In addition, using hydrochloric acid under reflux also caused removal of the Boc group with the ethyl ester (Entry 4). Lastly, a complex mixture was found when hydrazine was used (Entry 9), (Table 27).

**Table 27: Saponification attempts on ethyl and methyl esters.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>H</td>
<td>LiOH (1 equiv.)</td>
<td>MeOH:H₂O</td>
<td>r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>H</td>
<td>LiOH (6 equiv.)</td>
<td>CH₃CN:H₂O</td>
<td>r.t.*</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>H</td>
<td>NaOH (3 equiv.)</td>
<td>MeOH:H₂O</td>
<td>r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>Boc</td>
<td>HCl (6 M)</td>
<td>-</td>
<td>70</td>
<td>166</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>H</td>
<td>TMSCl and NaI</td>
<td>CH₃CN</td>
<td>r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Boc</td>
<td>TMSCl and NaI</td>
<td>CH₃CN</td>
<td></td>
<td>167</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>Boc</td>
<td>NaOH (1 equiv.)</td>
<td>MeOH:H₂O</td>
<td>r.t.*</td>
<td>S.M.</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>Boc</td>
<td>KOH 18-crown-6</td>
<td>MeOH:H₂O</td>
<td>r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>Boc</td>
<td>NH₂NH₂ (80%)</td>
<td>H₂O</td>
<td>r.t.</td>
<td>Complex mixture.</td>
</tr>
</tbody>
</table>

* Reaction also performed at reflux
Another approach was tested, by reduction of the ester group using lithium aluminium hydride. Unfortunately, only starting material was isolated when three equivalents of the reduction reagent was used with methyl ester 165 (Entry 2). Furthermore, we thought that the bulky tert-butyl group was the reason for the reduction not occurring. The free amine 167 was therefore tested under the same conditions, but only starting material was obtained (Entry 1), (Table 28).

**Table 28: Reduction attempts**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>Boc</td>
<td>S.M.</td>
</tr>
</tbody>
</table>

After the failure of saponification of both esters 164 and 165, we found another approach to synthesise carboxylic acid 162 from a paper by Beak published in 1991.[32] Beak attempted to introduce a carboxylic acid at the α-position of Boc-pyrrolidine 168 using sec-butyllithium with the chiral additive (-)-sparteine 167, which results in enantioselective deprotonation of the Boc-pyrrolidine 168, giving one enantiomer. To form product L-proline 170, carbon dioxide gas was bubbled into the reaction mixture of the deprotonated Boc-pyrrolidine 168, giving the desired compound 170 in 88% ee and modest yield of 55% (Scheme 60).
Following the same method and conditions, Boc-azepine 163 was dissolved in diethyl ether at -78 °C and sec-BuLi added to the solution for 1 h and CO₂ gas was bubbled through the reaction mixture through CaCl₂ drying tube. Two hours later, the reaction was quenched using saturated aqueous ammonium chloride. Both distereoisomeric acids 171 and 172 were obtained and isolated in 30% and 34% yield, respectively. In addition 12% yield of side product 173 was formed (Entry 1). There was little rise in the yield when the reaction was left longer. Increasing the number of equivalents of sec-BuLi and the reaction time resulted in a reduction in yield (Entry 3). Using the dry ice pellets as a source of the CO₂ affected the yield for both distereoisomeric acids causing a minor decrease in yields (Entry 4 and 5) (Table 29).

### Table 29: CO₂ addition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>S-BuLi (equiv.)</th>
<th>CO₂</th>
<th>Time (h)</th>
<th>169 (Yield %)</th>
<th>170 (Yield %)</th>
<th>171 (Yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3</td>
<td>Gas</td>
<td>2</td>
<td>30</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>Gas</td>
<td>16</td>
<td>33</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Gas</td>
<td>24</td>
<td>11</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>1.3</td>
<td>Solid</td>
<td>2</td>
<td>30</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Solid</td>
<td>16</td>
<td>23</td>
<td>25</td>
<td>11</td>
</tr>
</tbody>
</table>
Finally, deprotection of the Boc group using trifluoroacetic acid afforded the free amines 174 and 175 in high yield (Entry 1 and 2), (Table 30).\textsuperscript{33}

**Table 30: Removal of Boc group.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>171</td>
<td>71</td>
<td>174</td>
</tr>
<tr>
<td>2</td>
<td>172</td>
<td>80</td>
<td>175</td>
</tr>
</tbody>
</table>
6 Catalyst testing

6.1 Aldol reaction

The aldol reaction between nitrobenzaldehyde 54 and acetone employing the catalysts was the first reaction used in our evaluation. With an aminocatalyst, the activation of the enamine from the ketone substrate can be achieved (Scheme 61).

Our α 166, 167, 174, 175 and β 133, 156, 161 amino catalysts (Figure 15) share structural and function group similarities with Maruoka’s amino acid catalyst 79; his catalyst showed in the aldol reaction high e.e up to 99% (Table 7 and 8); we hoped that our catalysts would provide similar results.34
Following the Maruoka and List conditions, using DMSO as a solvent with acetone and 4-nitrobenzaldehyde 54, we first examined the α-carboxylic acids 174 and 175 as catalysts in DMSO and several solvents.
In the case of 174, unfortunately only starting material was obtained in all different solvents. On the other hand, catalyst 175 shows a poor conversion of 15% with 11% ee, and 17% conversion and a racemic mixture with solvents methanol and acetone, respectively (Entry 8 and 6). However, an increase in conversion was observed when THF and ethyl acetate were used, although with poor ees of 9% and 8% respectively (Entry 4 and 5) (Table 31).

**Table 31**: Aldol reaction catalysed by 174 and 175.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(L)-proline(^d)</td>
<td>DMSO</td>
<td>68</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>174</td>
<td>DMSO</td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>174</td>
<td>DMF</td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>174</td>
<td>EtOAc</td>
<td>S.M 30</td>
<td>8 (R)</td>
</tr>
<tr>
<td>5</td>
<td>174</td>
<td>THF</td>
<td>S.M 28</td>
<td>9 (R)</td>
</tr>
<tr>
<td>6</td>
<td>174</td>
<td>Acetone</td>
<td>S.M 17</td>
<td>Racemic</td>
</tr>
<tr>
<td>7</td>
<td>174</td>
<td>CH(_3)CN</td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>174</td>
<td>MeOH</td>
<td>S.M 15</td>
<td>11 (R)</td>
</tr>
</tbody>
</table>

[a] Conversion determined from \(^1\)H NMR spectra analysis of the reaction mixture [b] Enantiomeric excess was determined using HPLC with Chiralcel® AD-H column: (hexane/iPrOH=92:8, λ=220 nm), 0.8 mL, 15 °C; major enantiomer 34.9 min, minor enantiomer 33.3 min. [c] absolute configuration was determined by comparison with known HPLC retention times [d] 30 mol%.
Due to the poor results we obtained from the α-carboxylic acid catalysts 174 and 175, we tested the α-ethyl and methyl ester catalysts 166 and 167 to check their efficiency in the same reaction screening with several solvents.

In general the results were better compared with the carboxylic group. In the case of the ethyl ester catalyst 166, using DMSO gave 28% conversion with 17% ee (Entry 1). Whereas, using acetone gave an increase in the conversion of 44% but a lower ee was obtained of 4% (Entry 2). A racemic mixture with a slight decrease in conversion of 30% was observed when acetonitrile was used (Entry 3). Using methanol gave the highest result of 46% conversion and 17% ee (Entry 4). Starting material was obtained when ethanol was used (Entry 5). The methyl ester catalyst 167 gave a racemic mixture when DMSO and acetonitrile were used and gave 15% and 12% conversion respectively (Entry 1 and 3). A slightly improved conversion of 25% and 12% ee was seen when acetone was used (Entry 2). A higher conversion was obtained using methanol of 51% but with low ee of 5% (Entry 4). Lastly, only starting material was obtained when ethanol was used (Entry 5) (Table 32).

Table 32: Aldol reaction catalysed by 166 and 167.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>166 167</td>
<td>DMSO</td>
<td>28 15</td>
<td>17 (R)</td>
</tr>
<tr>
<td>2</td>
<td>166 167</td>
<td>Acetone</td>
<td>44 25</td>
<td>4 (R) 12 (R)</td>
</tr>
<tr>
<td>3</td>
<td>166 167</td>
<td>CH₃CN</td>
<td>30 12</td>
<td>Racemic</td>
</tr>
<tr>
<td>4</td>
<td>166 167</td>
<td>MeOH</td>
<td>46 51</td>
<td>17 (S) 5 (S)</td>
</tr>
<tr>
<td>5</td>
<td>166 167</td>
<td>EtOH</td>
<td>S.M S.M</td>
<td>-- --</td>
</tr>
</tbody>
</table>

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We also tested the β-amino catalysts starting with the carboxylic acids 133 and 156 screening with several solvents. Catalyst 133 gave 57% conversion and 19% e.e when the standard solvent DMSO was used (Entry 1). Acetone gave a higher conversion of 71% but with a lower ee of 10% (Entry 2), EtOAc gave the lowest conversion and e.e of 15% and 8% respectively (Entry 3), unfortunately no product obtained when acetonitrile and methanol were used (Entry 4 and 5). On the other hand, unfortunately, catalyst 156 did not give any product with any of the solvents, perhaps because of steric effects of both the methyl groups (Table 33).

**Table 33: Aldol reaction catalysed by 133 and 156.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>133, 156</td>
<td>DMSO</td>
<td>57 S.M.</td>
<td>19 (S)</td>
</tr>
<tr>
<td>2</td>
<td>133, 156</td>
<td>Acetone</td>
<td>71 S.M.</td>
<td>10 (S)</td>
</tr>
<tr>
<td>3</td>
<td>133, 156</td>
<td>EtOAc</td>
<td>15 S.M.</td>
<td>8 (S)</td>
</tr>
<tr>
<td>4</td>
<td>133, 156</td>
<td>CH₃CN</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>133, 156</td>
<td>MeOH</td>
<td>S.M.</td>
<td>--</td>
</tr>
</tbody>
</table>
In addition the β-amino methyl ester catalyst was screened with several solvents. Starting with DMSO giving a poor conversion of 5% with 11% e.e (Entry 1), an increase in conversion to 24% with a lower e.e of 8% was seen when acetone was used (Entry 2), and a slight increase of the conversion when ethyl acetate was used to 37% with 9% e.e (Entry 3). A racemic mixture was obtained with 50% conversion using acetonitrile (Entry 4), and no product was obtained when methanol was used (Entry 5) (Table 34).

**Table 34: Aldol reaction catalysed by 161.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>161</td>
<td>DMSO</td>
<td>5</td>
<td>11 (S)</td>
</tr>
<tr>
<td>2</td>
<td>161</td>
<td>Acetone</td>
<td>24</td>
<td>8 (S)</td>
</tr>
<tr>
<td>3</td>
<td>161</td>
<td>EtOAc</td>
<td>37</td>
<td>9 (S)</td>
</tr>
<tr>
<td>4</td>
<td>161</td>
<td>CH₃CN</td>
<td>50</td>
<td>Racemic</td>
</tr>
<tr>
<td>5</td>
<td>161</td>
<td>MeOH</td>
<td>S.M.</td>
<td>--</td>
</tr>
</tbody>
</table>

After we tested all the α- and β-amino catalysts, we chose the best conditions that we had found which were the α-ethyl ester 166 with methanol (Entry 4, Table 32) and the β-carboxylic acid 133 with DMSO (Entry 1, Table 33), and tested them with several aldehydes.
Unfortunately, no aldol product was obtained for either catalyst \textbf{133} or \textbf{166} except that catalyst \textbf{133} gave a poor conversion of 27\% and 21\% e.e when 3-nitrobenzaldehyde was used (Entry 3) (Table 35).

\textbf{Table 35: Aldol reaction of acetone with several aldehydes.}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Aldehyde</th>
<th>Conversion (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textbf{1} \textsuperscript{a}</td>
<td>133</td>
<td>166</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td>\textbf{2} \textsuperscript{b}</td>
<td>133</td>
<td>166</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td>\textbf{3} \textsuperscript{c}</td>
<td>133</td>
<td>166</td>
<td>S.M.</td>
<td>27% 21% (R)</td>
</tr>
<tr>
<td>\textbf{4} \textsuperscript{d}</td>
<td>133</td>
<td>166</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td>\textbf{5} \textsuperscript{e}</td>
<td>133</td>
<td>166</td>
<td>S.M.</td>
<td>--</td>
</tr>
</tbody>
</table>

Conditions of the HPLC: a) Chiralcel® AD-H column: (hexane/IPrOH=92:8, \( \lambda = 210 \) nm), 0.8 mL, r.t. 3°C; major enantiomer 14.1 min, minor enantiomer 15.4 min. b) Chiralcel® AD-H column: (hexane/IPrOH=92:8, \( \lambda = 220 \) nm), 0.8 mL, r.t. 3°C; major enantiomer 19.3 min, minor enantiomer 22.0 min. c) Chiralcel® AD-H column: (hexane/IPrOH=92:8, \( \lambda = 220 \) nm), 0.8 mL, r.t. 3°C; major enantiomer 23.3 min, minor enantiomer 25.0 min. d) Chiralcel® AD-H column: (hexane/IPrOH=98:2, \( \lambda = 221 \) nm), 0.8 mL, r.t. 3°C; major enantiomer 50.7 min, minor enantiomer 56.3 min. e) Chiralcel® AD-H column: (hexane/IPrOH=85:15, \( \lambda = 254 \) nm), 1 mL, r.t. 3°C; major enantiomer 11.9 min, minor enantiomer 14.1 min.

Unfortunately the results in the aldol reaction were not promising, and we therefore decided to test the ability of our catalysts in another reaction.
6.2 Mannich reaction

After the failure of our catalysts in the aldol reaction, we considered the Mannich reaction to test our catalysts. Following List’s conditions using 4-nitrobenzaldehyde and p-anisidine we employed acetone/DMSO (1:4), and also tried several other solvents.

We started with the α-amino carboxylic acids 174 and 175. Firstly, using catalyst 174, no product was observed using DMSO (Entry 2). Unfortunately the highest e.e we found was 7% and the highest yield 32% using acetone as only solvent (Entry 3). Racemic product was observed with DCM, with a poor yield of 12% (Entry 4). Using ethyl acetate and chloroform gave poor results of 9% yield, 5% e.e, and 16% yield, 3% e.e respectively (Entry 5 and 6) (Table 36).

Table 36: Mannich reaction catalysed by 174 and 175.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>e.e (%)a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(L)-proline</td>
<td>DMSO</td>
<td>43%</td>
<td>90 (S)</td>
</tr>
<tr>
<td>2</td>
<td>174 175</td>
<td>DMSO</td>
<td>S.M 32</td>
<td>-- Racemic</td>
</tr>
<tr>
<td>3</td>
<td>174 175</td>
<td>Acetone</td>
<td>32 18</td>
<td>7 (R) Racemic</td>
</tr>
<tr>
<td>4</td>
<td>174 175</td>
<td>DCM</td>
<td>12 27</td>
<td>Racemic 3 (S)</td>
</tr>
<tr>
<td>5</td>
<td>174 175</td>
<td>EtOAc</td>
<td>9 S.M. 5 (R)</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>174 175</td>
<td>CHCl₃</td>
<td>16 S.M. 3 (R)</td>
<td>--</td>
</tr>
</tbody>
</table>

a) Enantiomeric excess was determined using HPLC with Chiralcel® AD-H column: (hexane/iPrOH=80:20, λ=254 nm), 1 mL, r.t. 5°C; major enantiomer 23.8 min, minor enantiomer 18.6 min.

b) Absolute configuration was determined by comparison with known HPLC retention times.
Secondly, we tested the ethyl and the methyl ester catalysts 166 and 167 using the same conditions and solvents. Beginning with ethyl ester 166, only starting material was obtained when DMSO was used (Entry 1), while 34% yield and 20% e.e were found when acetone was used (Entry 2). A very poor yield of 3% and 16% e.e was obtained in DCM (Entry 3), and using chloroform the highest e.e of 43% was found but with a poor yield of 15% (Entry 4). On the other hand, for the methyl ester 167, the highest e.e that we had was 28% using acetone which also gave the highest yield of 76% (Entry 2). A very poor yield of 9% and 5% e.e were seen when DCM was used (Entry 3), while using chloroform gave 28% yield and 25% e.e (Entry 4) (Table 37).

Table 37: Mannich reaction catalysed by 166 and 167.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>166 167</td>
<td>DMSO</td>
<td>S.M 13</td>
<td>-- 3 (R)</td>
</tr>
<tr>
<td>2</td>
<td>166 167</td>
<td>Acetone</td>
<td>34 76</td>
<td>20 (R) 28 (R)</td>
</tr>
<tr>
<td>3</td>
<td>166 167</td>
<td>DCM</td>
<td>3 9</td>
<td>16 (R) 5 (R)</td>
</tr>
<tr>
<td>4</td>
<td>166 167</td>
<td>CHCl₃</td>
<td>15 28</td>
<td>43 (R) 25 (R)</td>
</tr>
</tbody>
</table>
After we had evaluated all our α-amino catalysts, we tested the β-amino catalysts in the Mannich reaction. We began with the β-carboxylic acids 133 and 156 using the same conditions and solvents.

Unfortunately all the attempts failed, with only starting materials obtained (Table 38).

**Table 38**: Mannich reaction catalysed by 133 and 156.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>133</td>
<td>DMSO</td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>1</td>
<td>156</td>
<td></td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>133</td>
<td>Acetone</td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>156</td>
<td></td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>133</td>
<td>DCM</td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>156</td>
<td></td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>133</td>
<td>CHCl₃</td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>156</td>
<td></td>
<td>S.M</td>
<td>--</td>
</tr>
</tbody>
</table>
After the failure of the β-carboxylic acids, we tested the methyl ester catalyst 161. Starting with DMSO, only starting material was obtained (Entry 1), but using acetone gave 39% yield with 22% e.e (Entry 2). A decrease of the yield using DCM of 27% yield was observed as well as a huge drop in the e.e to 3% (Entry 3). Lastly, a poor yield of 13% and 11% e.e were found when chloroform was used (Entry 4) (Table 39).

Table 39: Mannich reaction catalysed by 161.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>161</td>
<td>DMSO</td>
<td>S.M</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>161</td>
<td>Acetone</td>
<td>39</td>
<td>22 (R)</td>
</tr>
<tr>
<td>3</td>
<td>161</td>
<td>DCM</td>
<td>27</td>
<td>3 (R)</td>
</tr>
<tr>
<td>4</td>
<td>161</td>
<td>CHCl₃</td>
<td>13</td>
<td>11 (R)</td>
</tr>
</tbody>
</table>

After we had tested all the α-and β-amino catalysts, we chose the best conditions that we had found, which were the α-ethyl ester 166 with chloroform (Entry 4, Table 37) and the α-methyl ester 167 with acetone (Entry 2, Table 37), and tested them with several aldehydes.
The ethyl ester catalyst 166 gave a poor yield with isovaleraldehyde and a disappointing e.e of 7% (Entry 1). Only starting material was observed when isobutyraldehyde used (Entry 3). Unfortunately, only starting material was obtained when 2-napthaldehyde and both halogen benzaldehydes the bromo and the fluoro were used (Entry 2, 4 and 5). However, with the methyl ester catalyst 167, when isovaleraldehyde was used a moderate yield of 43% but a very poor e.e of 6% was obtained (Entry 1). Isobutyraldehyde gave a poor yield of 26% but the highest e.e of 45% (Entry 3). As with the ethyl ester catalyst, no Mannich product was obtained when 2-napthaldehyde and both halogen benzaldehydes the bromo and the fluoro were used (Entry 2, 4 and 5) (Table 40).

Table 40: Mannich reaction with several aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>166</td>
<td>OMe</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>OMe</td>
<td>43</td>
<td>6</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>166</td>
<td>OMe</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>OMe</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>166</td>
<td>OMe</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>OMe</td>
<td>26</td>
<td>45</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>166</td>
<td>OMe</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>OMe</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>166</td>
<td>OMe</td>
<td>S.M.</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>OMe</td>
<td>S.M.</td>
<td>--</td>
</tr>
</tbody>
</table>

Conditions of the HPLC a) Chiralcel® AD-H column: (hexane/IPrOH=90:10, λ=256 nm), 1 mL, r.t., 3°C; major enantiomer 11.6 min, minor enantiomer 17.7 min. b) Knauer-Raycerel 01, 5 μm. XD_6 column: (hexane/IPrOH=90:10, λ=311 nm), 0.6 mL, r.t., 3°C; major enantiomer 18.5 min, minor enantiomer 13.9 min. c) Chiralcel® AD-H column: (hexane/IPrOH=90:10, λ=254 nm), 0.6 mL, r.t., 3°C; major enantiomer 11.6 min, minor enantiomer 14.7 min. d) Knauer-Raycerel 01, 5 μm. XD_6 column: (hexane/IPrOH=90:10, λ=211 nm), 0.6 mL, r.t., 3°C; major enantiomer 14.0 min, minor enantiomer 11.8 min. e) Knauer-Raycerel 01, 5 μm. XD_6 column: (hexane/IPrOH=90:10, λ=211 nm), 0.6 mL, r.t., 3°C; major enantiomer 14.2 min, minor enantiomer 10.3 min.
Unfortunately, results for both aldol and Mannich reactions were poor, and after investigation we think that the low acidity of the carboxylic acid group could be the reason after a comparison with several amino acid catalysts. In the L-proline, 2-piperidinecarboxylic acid 176, and 177 the values of the carboxylic acid pKa were 2.0, 2.5 and 2.5 respectively. In addition, the less acidic pKa in β-alanine 178 and 179 of 3.6 and 4.0 respectively.³⁵,³⁶ Therefore, this may indicate that a more acidic group may be required for these reactions to be catalysed efficiently (Figure 16).

Figure 16: pKa values of α– and β–amino acid derivatives.
7.0 Conclusion

Synthesis of new axially chiral aminocatalysts was the target of our project, motivated from the excellent results that L-proline has delivered. Starting with synthesis of the α-carboxylic acids from BINOL in a six step procedure with a key of lithiation/carboxylation step gave both α-acid diastereomeric catalysts were obtained. Products 174 and 175 were obtained in 12% and 15% yields overall respectively (Scheme 62).

![Scheme 62: Compound 174 and 175 synthetic route.](image)

In addition, we have synthesised the corresponding binaphthyl α-ethyl 166 and the methyl 167 ester amino acids (Scheme 63).

![Scheme 63: Compound 166 and 167 synthetic route.](image)
Moreover, to assess the effect of adding a carbon atom between the amino and the carboxylic acid groups we successfully synthesised the β-binaphthyl carboxylic acids 133 and 156, in addition to the β-methyl ester 161, over an 8-step process for the acids and 7-steps for the methyl ester, including a Reformatsky addition. The overall yield of 133 was 22%, and, for the bulkier acid 156 was 12%. Lastly, the overall yield of the methyl ester 161 was 22% (Scheme 64).

Scheme 64: Compound 133, 156 and 161 synthetic route.
8.0 Future work

Further modification in our design of catalysts to be more complex in order to reach higher enantioselectivities, as in many successful catalysts, would be desirable (Figure 16).

Following Maruoka who tried to improve his catalyst to be more nucleophilic by introduction of electron-donating groups on the ring as in catalyst 82. Including of more acidic groups instead of the carboxylic acid such as the triflamide groups 180. Adding both electron-donating group and acidic groups (such trifamide) to provide more acidic groups (than the carboxylic groups) and more nucleophilic amines 181 (Figure 17).

Catalyst synthesis might be achieved using the same methods that we used before. Starting with 146, NBS oxidation and diastereoselective nucleophilic Grignard addition to provide 182, followed by allyl/Boc deprotection and protection step to give 183. Asymmetric lithiation and addition of chloroformate, and finally deprotection of the Boc group, to give the improved catalyst 185, which should be more nucleophilic caused by the effect of the donating group (iso-propane) (Scheme 65).
Scheme 65: Future catalyst design.
Results and discussion references


34. X. Chen, S. Duan, C. Tao, H. Zhai, F. G. Qiu, *Nature Communications*, 2015, 6, 7204, 1-7


Chapter three: Experimental section

IR spectres were recorded on a Perkin-Elmer 100 FT-IR spectrophotometer and samples were used as thin film DCM solutions on KBr plates, melting points were recorded using a Büchi B-545 Melting Point apparatus. NMR spectra were recorded on a Bruker 500 MHz Spectrometer. Chemical shifts were recorded in parts per million (ppm), J values are given in Hertz (Hz) and are referenced against tetramethylsilane (TMS) or the residual deuterated solvents peak. Optical rotations were obtained using a Bellingham and Stanley Ltd ADP440 polarimeter and the solvents used for these measurements were of HPLC-grade quality. High-resolution mass spectra were obtained from the EPSRC Mass Spectrometry Unit at the University of Swansea. Enantiomeric excesses were determined by chiral high performance liquid chromatography using a Hitachi Elite LaChrom HPLC system using an L-2200 autosampler, L-2130 pump and L-2400 UV detector. All HPLC samples were run against racemate as a standard and using a hexane-isopropanol mixture. Conditions varied and are provided in detail below.

Unless otherwise stated, all starting materials were sourced from commercial suppliers and were used without any purification. Reactions which required the use of anhydrous solvents were, in the case of THF and Et2O, dried and distilled over sodium and benzophenone. DCM and CH3CN were distilled over CaH2 and DMF was distilled over MgSO4. Needles and glassware were oven-dried were and allowed to cool under a positive pressure of nitrogen gas prior to use. Light petroleum ether was distilled at 40-60 °C to remove impurities.
1.0 Synthesis of azepines

(S)-[1,1’]-Binaphthalene-2,2’-diol bis-trifluoromethanesulfonate 134

(S)-[1,1]-2-2’-Binaphthalene diol (10.00 g, 35 mmol) and 4-dimethylaminopyridine (1.71 g, 14 mmol, 0.4 equiv.) were dissolved in dry dichloromethane (250 mL) and the reaction was cooled to -78°C. 2, 6-Lutidine (12.2 mL, 104 mmol, 3.0 equiv.) and trifluromethanesulfonic anhydride (18.0 mL, 104 mmol, 3.0 equiv.) were added to the reaction. The reaction mixture turned from yellow to pink and was allowed to reach room temperature overnight. The reaction mixture during this time turned from pale pink to dark brown. Silica gel was added (~10 g) and the solvent was evaporated under reduced pressure. The silica gel was washed with petroleum ether (around 2 L) in a sintered funnel. The petroleum ether fractions were mixed and the solvent removed under reduced pressure to yield the title compound as a colorless solid (18.6 g, 96%) without further purification.

M.p. 85-86 °C [Lit 86-88 °C] ; [α]D\textsuperscript{24.0} +146 (c=1.00, CHCl\textsubscript{3}), (Lit [α]D\textsuperscript{22.5} +144), (c 1.00, CHCl\textsubscript{3})\textsuperscript{1}; ν\textsubscript{max} (CH\textsubscript{2}Cl\textsubscript{2})/cm\textsuperscript{-1} 3065, 1592, 1509, 1423, 1216, 1139, 1066, 963, 940, 703, 768, 750, 656; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.18 (d, J = 9.0 Hz, 2H), 8.05 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 9.1 Hz, 2H), 7.63 (ddd, J = 8.1, 6.8, 1.1 Hz, 2H), 7.45 (ddd, J = 8.2, 6.8, 1.2 Hz, 2H), 7.33 – 7.28 (m, 2H). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 145.3, 133.1, 132.3, 131.9, 128.3, 127.9, 127.3, 126.7, 123.4, 119.3, 116.9.
(S)-2,2'-Dimethyl-[1,1']binaphthalene 135

(S)-[1,1’]-Binaphthalene-2,2'-dil-bis-trifluoromethanesulfonate (16.26 g, 29.5 mmol) and 1,3-bis(diphenylphosphino)propane nickel (II) chloride (1.11 g, 2.06 mmol, 0.07 equiv.) were dissolved in dry Et₂O (300ml). The reaction mixture was cooled to -78 °C and solution of methyl magnesium bromide (3M in Et₂O, 39.3 mL, 118.1 mmol, 4.0 equiv.) was added slowly and the reaction left to reach room temperature overnight. H₂O (around 50 mL) was added at 0 °C to quench the excess of Grignard reagent and the reaction was diluted with Et₂O (100 mL) and left for 30 min to stir. The mixture was filtered over a plug of Celite® and washed with Et₂O (around 50 mL) and the filtrate was transferred to separating funnel and the organic layer was washed with H₂O (4 x 50 mL) and a brine (2 x 30 mL), dried over anhydrous MgSO₄ and filtered. The solvents were evaporated under reduced pressure. The mixture was recrystallized with hot methanol to yield the title compound as colorless crystals (7.9 g, 94%).

m.p. 76–78 °C (Lit 75–77 °C) [1]; [α]D²⁴⁺⁺⁺³.₅ (c 1.00, CHCl₃), (Lit [α]D²¹⁺⁺⁺.₅ +36.5), (c 1.00, CHCl₃) [1]; νmax(CH₂Cl₂)/cm⁻¹ 3051, 3008, 2856, 1442, 1507, 1421, 1352, 1221 1027; ¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H) 7.51 (d, J = 8.4 Hz, 2H), 7.40 (ddd, J = 8.1, 6.8, 1.1 Hz, 2H), 7.21 (ddd, J = 8.2, 6.8, 1.2 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 2.04 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 135.1, 134.3, 132.7, 132.2, 128.7, 127.9, 127.4, 126.1, 125.6, 124.9, 20.0.
(S)-2,2’-Bis-bromomethyl-[1,1’]binaphthalene 136

(S)-2,2’-Dimethyl [1,1’] binaphthalene (2.50 g, 8.85 mmol), N-bromosuccinimide (3.93 g, 22.1 mmol, 2.5 equiv.) and azobisisobutyronitrile (0.14 g, 0.88 mmol, 0.1 equiv.) were dissolved in cyclohexane (14 mL, 14% w/v solution). The mixture was heated at reflux 4 h until completion was observed using TLC. The reaction was cooled to 0 °C and EtOAc (4 mL, 1/3 of the volume of cyclohexane) and distilled water (28 mL, double the volume of cyclohexane) were added. The reaction was stirred for 1 h to allow for precipitation and filtration to give the title compound as a yellow solid (2.84 g, 73%).

m.p. 183-185 °C (Lit 188-190 °C)\(^1\), \([\alpha]_D^{23.5} -173.9\) (c 1.00, CHCl\(_3\)), (Lit \([\alpha]_D^{22.5} -174.4\), (c 1.00, CHCl\(_3\))\(^1\); \(\nu_{\max}\) (CH\(_2\))\(_2\)/cm\(^{-1}\) 3050, 2978, 2315, 1693, 1433, 1211, 851, 754, 725; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.02 (d, \(J = 8.6\) Hz, 2H), 7.93 (d, \(J = 8.2\) Hz, 2H), 7.75 (d, \(J = 8.6\) Hz, 2H), 7.49 (ddd, \(J = 8.1, 6.8, 1.1\) Hz, 2H), 7.30 – 7.26 (m, 2H), 7.08 (d, \(J = 7.9\) Hz, 2H), 4.26 (s, 4H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 134.21, 134.11, 133.29, 132.53, 129.39, 128.05, 127.77, 126.87, 126.84, 126.81, 32.6.
(S)-Allyl-4,5-dihydro-3H-4-aza-cyclohepta[2,1-a;3,4-a']dinaphthalene 137

(S)-2,2'-Bis-(bromomethyl)-[1-1']-binaphthalene (1.50 g, 3.40 mmol) and allylamine (0.27 mL, 3.74 mmol, 1.1 equiv.) were dissolved in acetonitrile (20 mL). Potassium carbonate anhydrous (1.40.98 g, 10.2 mmol, 3.0 equiv.) was added to the mixture and heated at reflux overnight or until completion was observed using TLC. The reaction mixture was cooled to room temperature and diluted with dichloromethane (30 mL) and filtered to remove potassium carbonate. The filtrate was transferred to a separating funnel and the organic layer washed with H2O (3 x 10 mL), a brine (2 x 20 mL) and dried over anhydrous MgSO4 and filtered. The solvent was removed under reduced pressure giving an orange solid. Recrystallization (hot acetone) yielding the title compound as a pale yellow solid (0.97 g, 85%).

m.p. 166-168 °C (Lit 167-169 °C)1, [α]D23.0 +399.1 (c 1.80, CHCl3) (Lit [α]D22.5 +396.2 (c 1.80, CHCl3)1; νmax (CH2Cl2)/cm-1 3414, 3051, 2923, 2802, 263, 2492, 2296, 1508, 1423, 1163, 880, 822; 1H NMR (500 MHz, CDCl3) δ 7.96 (d, J = 8.3 Hz, 4H), 7.56 (d, J = 8.2 Hz, 2H), 7.52 – 7.44 (m, 4H), 7.27 (ddd, J = 6.8, 4.9, 1.3 Hz, 2H), 6.07 – 5.97 (m, 1H), 5.28 (dd, J = 16.9, 1.8 Hz, 1H), 5.28 (dd, J = 10.5, 1.0 Hz, 1H), 3.76 (d, J = 12.4 Hz, 2H), 3.18 (d, J = 12.4 Hz, 2H), 3.16 – 3.09 (m, 2H); 13C NMR (126 MHz, CDCl3) δ 136.4, 135.2, 133.5, 133.3, 131.6, 128.5, 128.4, 127.9, 127.6, 125.9, 125.6, 118.1, 58.6, 55.0.
(S)-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium bromide

(S)-Allyl-4,5-dihydro-3H-4-aza-cyclohepta[2,1-a:3,4-a']dinaphthalene (1.40 g, 4.17 mmol) was dissolved in dichloromethane (70 mL). The flask was placed in an ice bath and N-bromosuccimide (0.77 g, 4.37 mmol, 1.05 equiv.) was added and the reaction was stirred for 1 h or until completion was observed using TLC. The solvent was removed under reduced pressure to yield the crude bromide salt as an orange foamy solid (4.21 g crude mass, not routinely isolated).

m.p. 105-107°C (Lit m.p. * 110 °C (decomp), [α]D +317.4 (c 1.00, CHCl3) (Lit. [α]D +316.0 (c 1.00, CHCl3)¹; υ max (CH2Cl2)/cm⁻¹ 3657, 3469, 3053, 2891, 2386, 1772, 1708, 1650, 1508, 1428, 1350, 1179, 1062; ¹H NMR (500 MHz, CDCl3) δ 10.84 (1H, s), 8.47 (1H, d, J = 8.5 Hz), 8.13 (1H, d, J = 8.6 Hz), 8.09 (1H, d, J = 8.3 Hz), 8.04 (1H, d, J = 8.4 Hz), 7.92 (1H, d, J = 8.3 Hz), 7.74 (1H, ddd, J = 8.2, 6.6, 1.0 Hz), 7.62 (1H, d, J = 8.4 Hz), 7.52–7.48 (2H, m.), 7.37 (1H, m), 7.25 (1H, ddd, J = 8.2, 6.7, 1.1 Hz), 7.07-7.06 (1H, d, J = 8.3 Hz), 5.95 (1H, m.), 5.70 (1H, d, J = 16.8 Hz), 5.53 (1H, d, J = 10.7 Hz), 5.34 (1H, dd, J = 14.5, 6.7 Hz), 5.20 (1H, dd, J = 14.0, 6.5 Hz), 5.01 (1H, d, J = 13.2 Hz), 4.51 (1H, d, J = 13.1 Hz); ¹³C NMR (126 MHz, CDCl3) δ 177.6, 170.0, 141.3, 135.6, 134.8, 133.8, 132.0, 131.5, 131.4, 130.4, 129.6, 129.5, 128.7, 128.5, 127.7, 127.4, 127.3, 127.3, 127.2, 127.0, 125.4, 125.1, 63.6, 56.4, 30.1
(S)-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-i um tetraphenylborate 146°

Crude (S)-4-allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-i um bromide (4.21 g) was dissolved in a minimum volume of ethanol. In another flask sodium tetraphenylborate (1.56 g, 4.58 mmol, 1.1 equiv.) was dissolved in minimum volume of acetonitrile and combined with the first solution. The solution was stirred for 10 min. A bright yellow precipitate formed immediately. The solid was filtered and washed with cold ethanol to yield the title compound as a yellow solid and dried at 70 °C overnight (5.29 g, 79%).

m.p.* 158 °C (Lit. m.p.* 160 °C (*decomp.)), [α]D23 +409.7 (c 1.00, MeCN), (Lit. [α]D22.5 +410.5 (c 1.00, MeCN)); νmax (CH2Cl2)/cm⁻¹ 3054, 2998, 2672, 2397, 2315, 1709, 1508, 1265, 1150, 817; 1H NMR (500 MHz, DMSO) δ 9.57 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.27 (t, J = 8.7 Hz, 2H), 8.10 (dd, J = 14.5, 8.3 Hz, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.19 (s, 8H), 7.00 (d, J = 8.6 Hz, 1H), 6.94 (t, J = 7.4 Hz, 8H), 6.80 (t, J = 7.2 Hz, 4H), 6.01 – 5.92 (m, 1H), 5.67 (d, J = 18.4 Hz, 1H), 5.55 (d, J = 10.1 Hz, 1H), 5.16 (d, J = 13.5 Hz, 1H), 4.86 (d, J = 4.7 Hz, 2H), 4.71 (d, J = 13.7 Hz, 1H); 13C NMR (126 MHz, DMSO) δ 180.0, 164.3, 164.1, 163.5, 163.1, 141.2, 136.9, 136.2, 135.1, 133.4, 131.8, 131.5, 131.3, 131.2, 130.8, 129.8, 129.6, 129.2, 128.5, 127.7, 127.3, 126.9, 126.7, 125.8, 125.8, 125.8, 125.7, 124.3, 123.2, 63.3
2.0 Synthesis of β-amino acids and derivatives

*tert*-Butyl-2-((35,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]-azepin-3yl) acetate 151

![Diagram](image)

Zinc dust (2.29 g, 35.1 mmol, 10 equiv.) and TMSCl (0.44 mL, 3.51 mmol, 1 equiv.) were added to anhydrous THF (50 mL) in a flame-dried nitrogen-purged round-bottom flask. The reaction was heated to reflux for 30 min. *Tert*-butyl bromoacetate (0.51 mL, 3.51 mmol, 1 equiv.) was added and the reaction was heated to reflux for a further 30 min. The reaction was cooled to –78 °C. (S)-4-allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium tetraphenylborate (2.30 g, 3.51 mmol) was dissolved in anhydrous THF (50 mL) in separate flame-dried round-bottom flask and then transferred into the zinc solution at –78 °C by using a cannula. The mixture was stirred at –78 °C for 1 h and *t*-butyl bromoacetate (5.18 mL, 35.1 mmol, 10 equiv.) was added in small portions over 15 to 20 min. Reaction was allowed to reach the room temperature and monitored by TLC. The reaction was quenched using a saturated ammonium chloride solution (10 mL), Et₂O (60 mL) was added and the mixture filtered through a pad of Celite®. The filtrate was transferred to a separating funnel and the organic layer washed with H₂O (3 x 20 mL), brine (3 x 20 mL), and dried over anhydrous MgSO₄ and filtered. The solvent was removed under reduced pressure to give a yellow oil. The product was purified using column chromatography on silica gel (12:1 light petroleum ether/EtOAc) to yield the title compound as a colourless oil (1.09 g, 68%)

m.p. 93-95 °C (Lit. m.p. 92-94)¹, [α]D² 23.5 +158.6 (c 1.00, CHCl₃) (Lit. [α]D² 22.4 +158), (c 1.00, CHCl₃)¹; νmax (CH₂Cl₂)/cm⁻¹ 3050, 2976, 1725, 1507, 1366, 1246, 1149, 819; ¹H NMR (500 MHz, CDCl₃) δ 7.97 – 7.91 (m, 4H), 7.63 (d, J = 8.3 Hz, 1H), 7.48 – 7.41 (m, 4H), 7.36 (d, J = 8.1 Hz, 1H), 7.27 – 7.22 (m, 2H), 6.01 – 5.92 (m, 1H), 5.25 (dd, J = 17.1, 1.6 Hz, 1H), 5.19 (d, J = 10.1 Hz, 1H), 4.41 (d, J = 11.1 Hz, 1H), 3.69 (d, J = 11.4 Hz, 1H), 3.33 – 3.22 (m, 2H), 3.08 (d, J = 10.9 Hz, 1H), 1.72 (dd, J = 15.1, 7.1 Hz, 1H), 1.50 (dd, J = 15.1, 8.4 Hz, 1H), 1.15 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 171.3, 136.1, 135.5, 135.2, 135.0, 133.5, 133.3, 133.0, 131.9, 131.8, 130.0, 129.0, 128.4, 128.3, 128.1, 128.0, 127.6, 127.4, 125.9, 125.7, 125.6, 125.6, 118.0, 79.9, 64.1, 61.4, 56.1, 42.6, 27.9
Tert-Butyl 2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepin-3-yl) acetate 155\(^1\)

![Diagram](image)

Tert-Butyl 2-((3S,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepin-3-yl)acetate (1.70 g, 3.78 mmol) was dissolved in anhydrous dichloromethane (70 mL). Pd(PPh\(_3\))\(_4\) (0.08 g, 0.07 mmol, 0.02 equiv.) and 1,3-dimethylbarbituric acid (1.77 g, 11.34 mmol, 3 equiv.) were added and the reaction slowly heated to reflux overnight or until full consumption of the starting material was observed by TLC. The reaction was allowed to reach room temperature and the solvent was removed under reduced pressure and the residue was redissolved in Et\(_2\)O (60 mL) and transferred to a separating funnel. The organic layer was washed with 1 M NaOH solution (2 x 20 mL), H\(_2\)O (2 x 20 mL), brine (20 mL), dried over anhydrous MgSO\(_4\) and filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified using column chromatography on silica gel (6:4 light petroleum ether/EtOAc) to yield the title compound as a pale yellow foam (1.27 g, 82%).

m.p. 75-77 °C (Lit. m.p. 78-79 °C); \([\alpha]\)_D\(^{23.1}\) +205.1 (c 1.00, CHCl\(_3\)), \([\alpha]\)_D\(^{22.4}\) +206) (c 1.00, CHCl\(_3\)); \(\nu\)\(_{\text{max}}\) (CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 3054, 2981, 1719, 1509, 1436, 1366, 1301, 1217, 1147, 1116, 819;\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.95 (dt, \(J = 14.6, 7.4\) Hz, 4H), 7.58 (d, \(J = 8.3\) Hz, 1H), 7.52 (d, \(J = 8.4\) Hz, 1H), 7.48 – 7.43 (m, 2H), 7.40 (d, \(J = 8.6\) Hz, 1H), 7.34 (d, \(J = 8.5\) Hz, 1H), 7.26 – 7.21 (m, 2H), 4.62 (t, \(J = 7.6\) Hz, 1H), 3.79 (d, \(J = 12.1\) Hz, 1H), 3.72 (d, \(J = 12.1\) Hz, 1H), 1.77 (dd, \(J = 15.0, 7.5\) Hz, 1H), 1.70 (dd, \(J = 15.0, 7.7\) Hz, 1H), 1.18 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 171.4, 137.4, 136.6, 134.9, 133.8, 133.1, 133.0, 132.0, 129.2, 129.0, 128.8, 128.3, 128.1, 127.4, 127.3, 126.9, 125.8, 125.6, 125.4, 80.1, 60.4, 59.1, 48.7, 42.9, 27.9.
2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetic acid 133

![Chemical structure](image)

Tert-Butyl 2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl) acetate (0.419 g, 1.02 mmol) was dissolved in dichloromethane (20 mL) and trifluoroacetic acid (0.93 mL, 12.24 mmol, 12 equiv.) was added. The mixture was stirred until consumption of the starting material was observed by TLC. A saturated sodium hydrogen carbonate solution was added until the pH of the solution was neutral. The mixture was transferred to a separating funnel and the organic layer washed with H₂O (10 mL), brine (2 x 10 mL) and dried over anhydrous MgSO₄ and filtered. After the filtration, the solvent was removed under reduced pressure and the residue recrystallized (CH₂Cl₂ and light petroleum ether) to yield the title compound as a white solid (0.332 g, 91%).

m.p. 224-226 °C (Lit. m.p. 228–230 °C); [α]D²².³ +261.8 (c 1.00, CHCl₃) (Lit. [α]D²².⁴ +264 (c 1.00, CHCl₃); νmax (CH₂Cl₂)/cm⁻¹ 3390, 3053, 2968, 1682, 1595, 1392, 1200, 1121, 821;

¹H NMR (500 MHz, DMSO) δ 8.08 (d, J = 8.3 Hz, 2H), 8.05 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.34 – 7.27 (m, 2H), 7.24 (d, J = 8.7 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 4.63 (dd, J = 10.1, 5.6 Hz, 1H), 3.93 (d, J = 11.9 Hz, 1H), 3.50 (d, J = 12.0 Hz, 1H), 1.70 (dd, J = 16.1, 5.5 Hz, 1H), 1.28 (dd, J = 15.8, 4.8 Hz, 1H);

¹³C NMR (126 MHz, DMSO) δ 175.8, 136.7, 135.1, 133.3, 133.2, 133.2, 131.9, 131.8, 131.7, 129.6, 129.4, 129.3, 129.0, 128.7, 127.9, 126.9, 126.8, 126.8, 126.5, 126.3, 56.9, 46.4, 38.8.
Zinc dust (1.19 g, 18.3 mmol, 10 equiv.) and TMSCl (0.23 mL, 1.83 mmol, 1 equiv.) added to anhydrous THF (30 mL) in a flame-dried nitrogen-purged round-bottom flask. The reaction was heated to reflux for 30 min. tert-Butyl α-bromoisobutyrate (0.34 mL, 1.83 mmol, 1 equiv.) was added and the reaction was refluxed for a further 30 min. The reaction was cooled to −78 °C. The (S)-4-allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium (1.2 g, 1.83 mmol) was dissolved in anhydrous THF (30 mL). In separate flame-dried round-bottom flask and then transferred into the zinc solution at −78 °C by using a cannula. The mixture was stirred at −78 °C for 1 h and tert-Butyl α-bromoisobutyrate (3.41 ml, 18.3 mmol, 10 equiv.) was added in small portions over 15 to 20 min. The reaction allowed to reach the room temperature and monitored by TLC. The reaction was quenched using a saturated ammonium chloride solution (5 mL), Et₂O (50 mL) was added and the mixture filtered through a pad of Celite®. The filtrate was transferred to a separating funnel and the organic layer washed with H₂O (3 x 20 mL), brine (3 x 20 mL), and dried over anhydrous MgSO₄ filtered. After the filtration, the solvent was removed under reduced pressure to give a yellow oil. The product was purified using column chromatography on silica gel (12:1 light petroleum ether/ EtOAc) to yield the title compound as a colourless oil (0.65 g, 74%) (NB: inseparable impurities)

m.p. 118-120 °C (Lit. m.p. 118-115 °C); [α]D21.8 +102.1 (c 1.0, CHCl₃) [α]D18.9 +102.8 (c 1.3, CHCl₃); νmax (CHCl₃)/cm⁻¹ 3051, 2977, 2934, 1713, 1458, 1469, 1367, 1253, 1168, 1035, 918, 753, 673; ¹H NMR (400 MHz, CDCl₃) δ 7.92 – 7.85 (m, 4H), 7.54 (d, J = 8.3 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.37 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.19 – 7.14 (m, 1H), 6.00 – 5.85 (m, 1H), 5.27 – 5.18 (m, 1H), 5.17 – 5.08 (m, 1H), 4.55 (s, 1H), 3.65 (d, J = 11.3 Hz, 1H), 3.51 – 3.45 (m, 2H), 3.41 (d, J = 11.3 Hz, 1H), 1.29 (s, 9H), 0.43 (s, 3H), 0.29 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 176.9, 136.4, 136.0, 135.9, 135.7, 134.1, 133.0, 132.9, 132.7, 132.2, 128.6, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 125.8, 125.6, 125.3, 125.1, 117.1, 81.7, 80.3, 79.7, 64.5, 55.1, 51.0, 27.9, 22.4, 22.3.
**Tert-Butyl-2-((3R,11c$S$)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate 159**

![Chemical Structure](image)

*Tert-Butyl-2-((3R,11c$S$)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate (1.3 g, 2.72 mmol) was dissolved in anhydrous dichloromethane (80 mL). Pd(PPh$_3$)$_4$ (0.05 g, 0.05 mmol, 0.02 equiv.) and 1,3-Dimethylbarbituric acid (1.27 g, 8.16 mmol, 3 equiv.) were added and the reaction slowly heated to reflux overnight or until full consumption of the starting material was observed by TLC. The reaction was allowed to reach room temperature and the solvent was removed under reduced pressure and the residue was redissolved in Et$_2$O (70 mL) and transferred to a separating funnel. The organic layer was washed with 1 M NaOH solution (2 x 20 mL), H$_2$O (2 x 20 mL), brine (2 x 20 mL), dried over anhydrous MgSO$_4$ filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified using column chromatography on silica gel (1:1 light petroleum ether/EtOAc) to yield the title compound as a pale yellow foam (0.71 g, 60%).

m.p. 91-93 °C (Lit. m.p. 87-89 °C)$^1$; [α]$^2$D$^22.3$ +316.7 (c 1.00, CHCl$_3$) (Lit. [α]$^2$D$^{20.1}$ +314.0 (c 1.00, CHCl$_3$)$^1$; \( \nu_{\text{max}} \) (CH$_2$Cl$_2$)/cm$^{-1}$ 3057, 2974, 2929, 2414, 1725, 1609, 1507, 1464, 1388, 1366, 1249, 1139, 1080, 849, 820; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (dd, J = 8.3, 4.5 Hz, 4H), 7.50 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.26 (d, J = 7.3 Hz, 2H), 7.20 (ddd, J = 9.4, 5.3, 2.0 Hz, 1H), 7.14 (ddd, J = 9.6, 5.4, 2.1 Hz, 1H), 4.89 (s, 1H), 3.95 (d, J = 12.6 Hz, 1H), 3.73 (d, J = 12.7 Hz, 1H), 1.38 (s, 9H), 0.73 (s, 3H), 0.23 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 176.7, 139.0, 136.1, 134.8, 134.6, 133.4, 132.8, 132.7, 132.4, 128.7, 128.3, 128.1, 127.8, 127.7, 127.4, 126.6, 125.8, 125.6, 125.3, 124.9, 80.0, 70.3, 50.7, 49.3, 28.0, 23.6, 19.5.
2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoic acid 156

*Tert*-Butyl-2-((3R,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate (0.230 g, 0.52 mmol) was dissolved in dichloromethane (20 mL) and trifluoroacetic acid (0.47 mL, 6.24 mmol, 12 equiv.) was added. The mixture was stirred until consumption of the starting material was observed by TLC. A saturated sodium hydrogen carbonate solution was added until pH of the solution was neutral. The mixture was transferred to a separating funnel and the organic layer washed with H2O (20 mL), brine (2 x 10 mL), dried over anhydrous MgSO4 filtered. After the filtration, the solvent was removed under reduced pressure and the residue recrystallized (CHCl3 and light petroleum ether) to yield the title compound as a white solid (0.124 g, 62%).

m.p. 189-191 °C (Lit. m.p. 192-194 °C); [α]D22.6 +140.4 (c 1.0, CHCl3) [α]D24.9 +138.1 (c 0.9, CHCl3); νmax (CH2Cl2)/cm-1 3417, 3057, 2974, 2846, 1675, 1598, 1470, 1200, 1135, 821, 749;

1H NMR (500 MHz, CDCl3) δ 7.95 (dd, J = 16.9, 9.3 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.60 – 7.43 (m, 4H), 7.26 – 7.20 (m, 4H), 7.18 (d, J = 7.7 Hz, 1H), 5.32 (s, 1H), 4.17 (d, J = 13.0 Hz, 1H), 3.96 (d, J = 12.7 Hz, 1H), 1.00 (s, 3H), -0.11 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 179.6, 136.1, 133.8, 133.8, 133.4, 132.8, 132.4, 131.7, 131.4, 129.5, 129.4, 129.2, 128.7, 128.1, 128.0, 127.6, 127.4, 126.8, 126.6, 126.3, 126.1, 77.0, 67.7, 47.2, 27.6, 26.2.
Zinc dust (1.49 g, 22.9 mmol, 10 equiv.) and TMSCl (0.29 mL, 2.29 mmol, 1 equiv.) were added to anhydrous THF (30 mL) in a flame-dried nitrogen-purged round-bottom flask. The reaction was heated to reflux for 30 min. Methyl chloroacetate (0.20 mL, 2.29 mmol, 1 equiv.) was added and the reaction was heated to reflux for a further 30 min. The reaction was cooled to −78 °C. The (S)-4-allyl-3H-dinaphtho[2,1-c:1′,2′-e]azepin-4-i um (1.50 g, 2.29 mmol) was dissolved in anhydrous THF (30 mL) in a separate flame-dried round-bottom flask and then transferred into the zinc solution at −78 °C using a cannula. The mixture was stirred at −78 °C for 1 h and methyl chloroacetate (2.0 ml, 22.9 mmol, 10 equiv.) was added in small portions over 15 to 20 min. The reaction allowed to reach the room temperature and monitored by TLC. The reaction was quenched using a saturated ammonium chloride solution (5 mL), Et₂O (40 mL) was added and the mixture filtered through a pad of Celite®. The filtrate was transferred to a separating funnel and the organic layer washed with H₂O (3 x 10 mL), brine (3 x 10 mL), and dried over anhydrous MgSO₄ and filtered. After the filtration, the solvent was removed under reduced pressure to give a yellow oil. The product was purified using column chromatography on silica gel (12:1 light petroleum ether/ EtOAc) to yield the title compound as a colourless oil (0.746, 79%)

m.p. 127-128 °C [α]D⁰ 23.8 +245.3 (c 1.00, CH₂Cl₂); ν max (CH₂Cl₂)/cm⁻¹ 3051, 2977, 2948, 1734, 1507, 1435, 1265, 1173, 820; ¹H NMR (500 MHz, DMSO) δ 8.09 – 8.03 (m, 4H), 7.68 (d, J = 8.3 Hz, 1H), 7.50 (ddd, J = 8.5, 5.7, 4.0 Hz, 3H), 7.33 – 7.30 (m, 1H), 7.30 – 7.27 (m, 2H), 7.19 (d, J = 8.5 Hz, 1H), 5.93 – 5.84 (m, 1H), 5.24 (dd, J = 17.2, 1.7 Hz, 1H), 5.16 (dd, J = 10.2, 1.8 Hz, 1H), 4.43 (dd, J = 8.6, 6.5 Hz, 1H), 3.70 (d, J = 10.9 Hz, 1H), 3.30 (s, 3H), 3.26 (dd, J = 13.9, 5.9 Hz, 1H), 3.19 (dd, J = 13.8, 7.1 Hz, 1H), 2.92 (d, J = 10.8 Hz, 1H), 1.61 (dd, J = 15.6, 6.4 Hz, 1H), 1.50 (dd, J = 15.7, 8.7 Hz, 1H); ¹³C NMR (126 MHz, DMSO) δ 171.7, 136.5, 135.4, 135.3, 135.1, 133.0, 131.5, 129.8, 129.4, 129.0, 128.9, 128.7, 128.4, 126.9, 126.8, 126.5, 126.2, 126.1, 118.1, 63.3, 61.2, 55.4, 51.3, 40.9; HRMS (NSI+) m/z found for [M+H]⁺: 408.1958; [C₂₈H₂₅NO₂]⁺ requires 408.1958.
Methyl 2-((3R,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1’,2’-e]azepin-3-yl)acetate 161

Methyl-2-((3R,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1’,2’-e]azepin-3-yl)acetate (0.320 g, 0.785 mmol) was dissolved in anhydrous dichloromethane (30 mL). Pd(PPh3)4 (0.017 g, 0.015 mmol, 0.02 equiv.) and 1,3-dimethylbarbituric acid (0.366 g, 2.35 mmol, 3 equiv.) were added and the reaction slowly heated to reflux overnight or until full consumption of the starting material was observed by TLC. The reaction was allowed to reach room temperature and the solvent was removed under reduced pressure and the residue was redisolved in Et2O (30 mL) and transferred to a separating funnel. The organic layer was washed with 1 M NaOH solution (2 x 10 mL), H2O (2 x 10 mL), brine (10 mL), dried over anhydrous MgSO4 and filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified using column chromatography on silica gel (1:1 light petroleum ether/EtOAc,) to yield the title compound as a pale yellow foam (0.182 g, 63%).

m.p. 86-88 °C; [α]D23.8 +342.8 (c 1.00, CHCl3); νmax (CH2Cl2)/cm⁻¹ 3338, 3049, 2948, 2842, 1732, 1506, 1435, 1263, 821; 1H NMR (500 MHz, DMSO) δ 8.08 – 8.01 (m, 4H), 7.65 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.32 – 7.25 (m, 2H), 7.23 (d, J = 8.2 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 4.58 (dd, J = 8.3, 6.7 Hz, 1H), 3.73 (d, J = 11.5 Hz, 1H), 3.41 (d, J = 11.5 Hz, 1H), 3.30 (s, 3H), 1.69 (dd, J = 15.5, 6.6 Hz, 1H), 1.59 (dd, J = 15.5, 8.5 Hz, 1H); 13C NMR (126 MHz, DMSO) δ 171.9, 137.0, 134.8, 133.2, 133.0, 131.8, 129.4, 129.3, 129.2, 128.8, 128.7, 127.9, 126.8, 126.4, 126.3, 126.0, 125.9, 58.1, 51.3, 48.2, 41.6; HRMS (NSI+) m/z found for [M+H]+: 368.1649; [C25H21NO2]+ requires 368.1645.
3.0 Synthesis of α-amino acid and derivatives

(S)-Tert-Butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate 163

(S)-2,2'-Bis-bromomethyl-[1,1']binaphthalene (600 mg, 1.36 mmol) was dissolved in anhydrous DMF (35 mL). The yellow solution was cooled to 0 °C, and NaH (130 mg, 5.45 mmol, 4 equiv.) was added in one portion. t-Butyl carbamate (160 mg, 1.36 mmol, 1 equiv.) was added slowly to the solution. The reaction mixture was stirred for 4 days or until full consumption of the starting material was seen by TLC and it was observed the colour of solution changed to a pale pink. The reaction was quenched by addition of ammonium chloride (15 mL) at 0 °C and the solvent was removed under reduced pressure. Et₂O (110 mL) was added to the mixture and the organic layer washed with H₂O (4 x 15 mL), brine (3 x 15 mL), dried over anhydrous MgSO₄ and filtered. After the filtration, recrystallization with hot acetone yielding the title compound as a colourless solid (469 mg, 87%).

m.p. 220-222 °C (Lit. m.p. 219-221 °C); [α]D⁰¹₈.₄ −11.0 (c 1.00, CHCl₃); (Lit. [α]D²².⁵ −7.0 (c 1.00, CHCl₃); νmax (CH₂Cl₂)/cm⁻¹ 3051, 2976, 2930, 2869, 1922, 1687, 1508, 1463, 1402, 1365, 1274, 1251, 1216, 1162, 1103, 906, 858, 818; H NMR (500 MHz, CDCl₃) δ 8.03 – 7.93 (m, 4H), 7.62 (d, J = 8.3 Hz, 2H), 7.48 (ddd, J = 8.1, 6.7, 1.1 Hz, 2H), 7.43 (dd, J = 8.5, 0.6 Hz, 2H), 7.30 – 7.25 (m, 2H), 4.93 (br s, 2H), 3.64 (d, J = 12.5 Hz, 2H), 1.51 (s, 9H); C NMR (126 MHz, CDCl₃) δ 154.4, 135.0, 133.3, 133.2, 131.5, 129.1, 128.3, 127.5, 127.4, 126.0, 125.7, 84.0, 79.9, 28.5, 27.3
(3R,11cS)-4-Tert-Butyl 3-ethyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)dicarboxylate

(S)-Tert-Butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate (0.965 g, 2.43 mmol) was dissolved in Et₂O (80 mL) at -78 °C. Sec-BuLi (2.42 mL, 3.15 mmol, 1.3 equiv., 1.3 M in cyclohexane) was added dropwise causing the pale yellow solution to turn black and left for 1 h. Ethyl chloroformate (0.69 mL, 7.29 mmol, 3 equiv.) was added in one portion, the solution turn from black to bright yellow. The reaction was allowed to reach room temperature overnight or until full consumption of the starting material was observed by TLC. The reaction was quenched with saturated ammonium chloride solution (20 mL) at 0 °C. The organic layer was washed with H₂O (3 x 40 mL), brine (3 x 40 mL), dried over anhydrous MgSO₄ and filtered. After the filtration, the solvent removed under reduced pressure. The crude product was purified using column chromatography on silica gel (7:3 light petroleum ether/EtOAc) yielding the title compound as a colourless solid (0.803 g, 70%)

m.p. 97-99 °C (Lit. m.p. 101-103 °C); [α]D²¹.⁷ -19.2 (c 1.00, CHCl₃) (Lit. [α]D²².¹ -17.6 (c 1.00, CHCl₃)); ν_max (CH₂Cl₂)/cm⁻¹ 3053, 2977, 2933, 1745, 1697, 1476, 1456, 1392, 1313, 1250, 1217, 1156, 916, 863; ¹H NMR (500 MHz, DMSO at 360 K) δ 8.02 (d, J = 8.2 Hz, 1H), 7.96 (m, 2H), 7.89 (d, J = 8.2 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.58 – 7.47 (m, 2H), 7.46 – 7.39 (m, 2H), 7.33 (dd, J = 8.5, 3.3 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.25 – 7.21 (m, 1H), 5.69 (s, 1H), 5.03 (d, J = 13.3 Hz, 1H), 3.64 (d, J = 13.4 Hz, 1H), 3.09 – 3.02 (m, 1H), 2.83 – 2.74 (m, 1H), 1.47 (s, 9H), 0.47 (t, J = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 170.05, 169.63, 154.26, 154.06, 154.06, 134.87, 134.46, 134.32, 134.0, 133.42, 133.4, 133.21, 133.17, 133.15, 131.78, 131.56, 131.35, 129.76, 129.38, 129.28, 128.83, 128.51, 128.25, 128.11, 127.86, 127.6, 127.3, 127.3, 127.12, 126.30, 126.25, 126.28, 126.07, 126.02, 125.8, 125.6, 80.6, 80.6, 62.3, 61.1, 60.8, 60.7, 47.8, 46.7, 28.4, 28.3, 13.5, 13.2.
(3R,11cS)-Ethyl 4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylate 166

![Chemical Structure](image)

(3R,11cS)-4-Tert-butyl 3-ethyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)-dicarboxylate (0.720 g, 1.53 mmol) was dissolved in dichloromethane (30 mL). Trifluoroacetic acid (1.63 mL, 21.42 mmol, 14 equiv.) was added and the reaction was stirred until consumption of the starting material was observed by TLC. Saturated sodium hydrogen carbonate solution was added until the pH of the solution was neutral. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (20 mL). The organic layer was washed with H₂O (3 x 20 mL), brine (3 x 20 mL) and dried over anhydrous MgSO₄ and filtered. After filtration, the solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (EtOAc), giving the title compound as a yellow solid (0.481 g, 85%).

m.p. 119-201 °C; [α]D^[21.4] +379.2 (c 1.00, CHCl₃), (Lit. [α]D[^23.1] +386.0 (c 1.00, CHCl₃)^1 ;

ν_max (CH₂Cl₂)/cm⁻¹ 3316, 3050, 2979, 2869, 1724, 1463, 1222, 1205, 1110, 912, 813; ^1H NMR (500 MHz, CDCl₃) δ 8.03 (d, J = 8.3 Hz, 1H), 7.96 (m, 2H), 7.90 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.45 – 7.36 (m, 3H), 7.29 – 7.23 (m, 2H), 4.68 (s, 1H), 3.91 (d, J = 13.7 Hz, 1H), 3.59 (d, J = 13.7 Hz, 1H), 3.29 – 3.19 (m, 1H), 2.64 – 2.55 (m, 1H), 0.50 (t, J = 7.1 Hz, 3H); ^13C NMR (126 MHz, CDCl₃) δ 173.2, 134.8, 133.5, 133.4, 133.0, 133.0, 131.5, 131.5, 129.7, 129.1, 129.1, 128.8, 128.3, 128.3, 127.3, 127.2, 126.9, 126.0, 125.9, 125.5, 125.5, 62.2, 61.2, 48.1, 13.2.
(3R,11cS)-4-Tert-butyl 3-methyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)dicarboxylate 165

(S)-Tert-Butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate (1.60 g, 4.04 mmol) was dissolved in Et₂O (80 mL) at -78 °C. sec-BuLi (4.03 mL, 5.25 mmol, 1.3 equiv., 1.3 M in cyclohexane) was added dropwise causing the pale yellow solution to turn black and the mixture was left for 1 h. Methyl chloroformate (0.938 mL, 12.12 mmol, 3equiv.) was added in one portion, the solution turned from black to bright yellow. The reaction was allowed to reach room temperature overnight or until full consumption of the starting material was observed by TLC. The reaction was quenched with saturated ammonium chloride solution (40 mL) at 0 °C. The organic layer was washed with H₂O (3 x 30 mL), brine (3 x 30 mL), dried over anhydrous MgSO₄ and filtered. After the filtration, the solvent removed under reduced pressure. The crude product was purified using column chromatography on silica gel (9:1 light petroleum ether/EtOAc) yielding the title compound as a colourless solid (1.471 g, 80%)
m.p. 121-123 °C (Lit. m.p. 124-126 °C)¹; [α]D¹⁹.² −17.3 (c 0.5, CHCl₃), (Lit. [α]D²².⁶ −20.8 (c 0.5, CHCl₃)¹); ν_max (CH₂Cl₂)/cm⁻¹ 3052, 2975, 2947, 2880, 1751, 1695, 1508, 1456, 1391, 1366, 1296, 1155, 953, 822; ¹H NMR (500 MHz, DMSO at 380 K) δ 8.14 (1H, d, J= 8.2 Hz), 8.08 (1H, d, J= 8.3 Hz), 8.05 (1H, d, J= 8.3 Hz), 8.01 (1H, d, J= 8.1 Hz), 7.82 (1H, d, J= 8.4 Hz), 7.63 (1H, d, J= 8.4 Hz), 7.58 (1H, ddd, J= 8.2, 6.7, 1.3 Hz), 7.53 (1H, ddd, J= 8.2, 6.7, 1.2 Hz), 7.39-7.34 (1H, m), 7.31–7.25 (2H, m), 7.11 (1H, d, J= 8.5 Hz), 5.67 (1H, s), 5.08 (1H, d, J= 12.9 Hz), 3.57 (1H, d, J= 13.1 Hz), 2.44 (3H, s), 1.48 (9H, s); ¹³C NMR (126 MHz, DMSO at 380 K) δ 168.9, 151.2, 136.8, 136.8, 134.6, 134.3, 134.3, 133.4, 133.2, 132.4, 130.7, 129.3, 128.9, 128.6, 128.3, 127.6, 127.4, 126.4, 126.2, 126.0, 125.9, 125.5, 83.7, 77.2, 77.0, 49.0, 28.1, 28.0.
(3R,11cS)-Methyl 4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepine-3-carboxylate 167

(3R,11cS)-4-Tert-butyl 3-methyl 3H-dinaphtho[2,1-c:1′,2′-e]azepine-3,4,(5H)-dicarboxylate (1.00 g, 2.20 mmol) was dissolved in dichloromethane (20 mL). Trifluoroacetic acid (2.35 mL, 30.8 mmol, 14 equiv.) was added and the reaction was stirred until consumption of the starting material was observed by TLC. Saturated sodium hydrogen carbonate solution was added until the pH of the solution was neutral. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (50 mL). The organic layer was washed with H₂O (3 x 30 mL), brine (3 x 30 mL), dried over anhydrous MgSO₄ and filtered. After the filtration, the solvent removed under reduced pressure and recrystallized (CHCl₃ and light petroleum ether) giving the title compound as a white solid (0.637 g, 81%).

m.p. 213-215 °C (Lit. m.p. 214-216 °C); [α]D⁺²¹,⁴ +432.5 (c 1.0, CHCl₃), (Lit. [α]D⁺²¹,⁴ +420 (c 1.03, CHCl₃))¹; νmax (CH₂Cl₂)/cm⁻¹ 3314, 3051, 2948, 2870, 1730, 1507, 1432, 1222, 1205, 1112, 991, 866, 821; ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, J = 8.2 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.91 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.44 – 7.41 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.25 – 7.23 (m, 1H), 4.64 (s, 1H), 3.86 (d, J = 13.7 Hz, 1H), 3.58 (d, J = 13.7 Hz, 1H), 2.49 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.0, 137.1, 133.5, 133.4, 133.4, 132.9, 131.5, 131.4, 129.7, 129.1, 128.4, 128.3, 128.3, 127.2, 127.0, 126.8, 126.1, 126.0, 126.0, 125.5, 62.1, 51.7, 48.3.
(11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine3-carboxylic acid synthesis

![Diagram]

(S)-Tert-Butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate (1.00 g, 2.52 mmol) was dissolved in anhydrous Et₂O (60 mL) at -78 °C. sec-Buli (2.51 mL, 3.27 mmol, 1.3 equiv., 1.3 M in cyclohexane) was added causing the solution turn from pale yellow to black and the reaction was stirred for 1 h. CO₂ gas was bubbled directly into the solution via a drying tube. The reaction was stirred until consumption of the starting material was observed by TLC. The reaction was quenched at 0 °C with ammonium chloride (15 mL) and EtOAc (30 mL) was added. The organic layer was washed with H₂O (2 x 20 mL), dried over anhydrous Na₂SO₄ and the solvent removed under reduced pressure.
The first diastereoisomer:

(3S,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'e]azepine-3-carboxylic acid 171

Purification by column chromatography on silica gel (EtOAc), isolated as a colourless solid (0.34 g, 30%)

m.p. 247-249 °C (Lit. m.p. 255-257 °C)\(^1\); \([\alpha]_D^{20.9} +56.7 \text{ (c 1.00, CHCl}_3\text{)} \) (Lit. \([\alpha]_D^{23.9} +58.4 \text{ (c 1.00, CHCl}_3\text{)}\)\(^1\); \(v_{\text{max}} \text{ (CHCl}_3\text{/cm}-1 = 3054, 3001, 2972, 1750, 1725, 1697, 1401, 1367, 1251, 1220, 1150, 820; \)

\(^1\)H NMR (500 MHz, DMSO, VT NMR at 353 K) \(\delta 8.11 – 7.78 \text{ (m, 4H), 7.66} \text{ (d, } J = 6.7 \text{ Hz, 1H), 7.62 – 7.36} \text{ (m, 4H), 7.35 – 7.26} \text{ (m, 2H), 7.23} \text{ (d, } J = 8.4 \text{ Hz, 1H), 5.00} \text{ (d, } J = 15.3 \text{ Hz, 1H), 4.69} \text{ (s, 1H), 3.73} \text{ (d, } J = 13.7 \text{ Hz, 1H), 1.46} \text{ (s, 9H).}

\(^{13}\)C NMR (126 MHz, DMSO, VT NMR at 353 K) \(\delta 171.2, 136.5, 133.4, 133.2, 131.7, 131.5, 130.5, 129.7, 129.4, 129.2, 128.9, 128.3, 128.2, 128.1, 127.5, 126.4, 126.3, 126.2, 125.9, 125.8, 125.3, 124.2, 79.9, 61.9, 45.9, 28.2.\)
The Second diastereoisomer:

\((3R,11cS)-4-(\text{Tert-butoxycarbonyl})-4,5\text{-dihydro-3H-dinaphtho}[2,1-c:1',2'e]azepine-3\text{-carboxylic acid} \) 172

Purification by column chromatography on silica gel (4:1 light petroleum ether/ EtOAc), isolated as a colourless solid (0.38 g, 34 %)

m.p. 174-176 °C (Lit. m.p. 164-167 °C); \([\alpha]D^{21.3} = -44.9 \ (c \ 1.00, \text{CHCl}_3)\) (Lit. \([\alpha]D^{23.9} = -47.2 \) (c 1.00, CHCl3)); \(v_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \) 3053, 2981, 1754, 1395, 1366, 1300, 1244, 1156, 913, 820; \(^1\)H NMR (500 MHz, DMSO, VT NMR at 363 K) \(\delta\) 8.01 (d, \(J = 8.3 \text{ Hz}, 1\text{H})\), 7.95 (d, \(J = 8.2 \text{ Hz}, 1\text{H})\), 7.92-7.90 (m, 2H), 7.61 (d, \(J = 8.3 \text{ Hz}, 1\text{H})\), 7.55 (d, \(J = 8.1 \text{ Hz}, 1\text{H})\), 7.49 (ddd, \(J = 10.4, 5.7, 2.4 \text{ Hz}, 1\text{H})\), 7.43 (ddd, \(J = 8.1, 6.7, 1.2 \text{ Hz}, 1\text{H})\), 7.37 (d, \(J = 8.5 \text{ Hz}, 1\text{H})\), 7.27 (dd, \(J = 7.5, 1.9 \text{ Hz}, 1\text{H})\), 7.25 (d, \(J = 3.2 \text{ Hz}, 1\text{H})\), 7.22-7.16 (m, 1H), 5.89 (s, 1H), 5.02 (d, \(J = 14.8 \text{ Hz}, 1\text{H})\), 3.67 (d, \(J = 14.3 \text{ Hz}, 1\text{H})\), 1.52 (s, 9H); \(^{13}\)C NMR (126 MHz, DMSO, VT at 363 K) \(\delta\) 170.6, 154.3, 134.7, 133.9, 131.7, 131.7, 129.4, 129.3, 128.6, 128.4, 127.7, 127.2, 126.4, 126.1, 126.1, 80.4, 62.7, 48.4, 28.5.
By product:

\((S)-\text{Tert-Butyl (2'-formyl-[1,1'-binaphthalen]-2-yl)methyl)carbamate}\ 173

\begin{center}
\includegraphics[width=0.2\textwidth]{173}
\end{center}

Eluted first in on silica gel (4:1 light petroleum ether/EtOAc) as colourless oil (0.13 g, 12%).

m.p. 123-125 °C; \([\alpha]_D^{22.4} +4.2\) (c 0.5, CHCl\(_3\)), (Lit. \([\alpha]_D^{23.7} +6.0\) (c 0.5, CHCl\(_3\)));

\(\nu_{\max}\) (CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 3351, 3060, 3000, 2979, 2932, 1763, 1695 1603, 1507, 1461, 1430, 1401, 1376, 1320, 1231, 1168, 1023, 855, 819; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.58 (s, 1H), 8.16 (d, \(J = 8.6\) Hz, 1H), 8.07 – 8.02 (m, 2H), 7.98 (d, \(J = 8.2\) Hz, 1H), 7.94 (d, \(J = 8.0\) Hz, 1H), 7.72 (d, \(J = 8.5\) Hz, 1H), 7.61 (t, \(J = 7.5\) Hz, 1H), 7.47 (t, \(J = 7.5\) Hz, 1H), 7.34 (ddd, \(J = 8.2, 6.8, 1.2\) Hz, 1H), 7.29 – 7.26 (m, 1H), 7.24 (d, \(J = 8.8\) Hz, 1H), 7.02 (d, \(J = 8.5\) Hz, 1H), 4.54 (s, 1H), 4.02 (d, \(J = 5.8\) Hz, 2H), 1.36 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 191.9, 155.6, 142.7, 136.3, 136.2, 133.7, 132.5, 132.6, 132.3, 129.4, 129.2, 129.0, 128.6, 128.1, 127.5, 127.0, 126.9, 126.2, 125.9, 122.3, 79.7, 42.8, 28.3, 28.1.
(3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid 174′

(3S,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid (0.970 g, 2.20 mmol) was dissolved in dichloromethane (15 mL), trifluoroacetic acid (2.35 mL, 30.8 mmol, 14 equiv.) was added. The reaction was stirred for 30 min, a saturated solution of sodium hydrogen carbonate was added to neutralised the pH of the solution. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (15 mL). The organic layer was washed with H2O (3 x 10 mL), brine (3 x 10 mL), dried over anhydrous MgSO4 and filtered. After the filtration, the solvent removed under reduced pressure and the residue was recrystallized (CHCl3 and light petroleum ether) giving the title compound (0.533 g, 71%).

m.p. 271-273 °C (Lit. m.p. 276-280 °C)1; [α]D19.3 +191.7 (c 1.00, CHCl3), [α]D24.5 +196.0 (c 1.00, CHCl3); νmax (CH2Cl2)/cm⁻¹ 3384, 3055, 2995, 2961, 2586, 1724, 1633, 1397, 1370 1344, 1194, 1139, 1036, 821, 749; ¹H NMR (500 MHz, DMSO) δ 8.14 (ddd, J = 20.9, 10.5, 6.1 Hz, 4H), 7.72 (d, J = 8.3 Hz, 2H), 7.59 (dt, J = 9.2, 7.6 Hz, 2H), 7.44 – 7.39 (m, 1H), 7.38 – 7.34 (m, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 4.12 (d, J = 13.1 Hz, 1H), 3.83 (s, 1H), 3.37 (d, J = 13.0 Hz, 1H); ¹³C NMR (126 MHz, DMSO) δ 170.4, 135.2, 135.1, 133.7, 133.6, 131.2, 130.8, 129.5, 129.2, 129.1, 129.0, 128.9, 128.5, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6, 60.2, 45.9.
(3R,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid 175

(3R,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid (0.320 g, 0.72 mmol) was dissolved in dichloromethane (10 mL), Trifluoroacetic acid (0.77 mL, 10.08 mmol, 14 equiv.) was added. The reaction was stirred for 30 min and a saturated solution of sodium hydrogen carbonate was added to neutralise the pH of the solution. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (10 mL). The organic layer was washed with H2O (3 x 5 mL), brine (3 x 5 mL), dried over anhydrous MgSO4 and filtered. After the filtration, the solvent removed under reduced pressure and the residue was recrystallized (CHCl3 and light petroleum ether) giving the title compound (0.200 g, 80%).

m.p. 270-272 °C (Lit. m.p. 269-271 °C)1; [α]D23.5 +274.1 (c 1.00, CHCl3), (Lit. [α]D24.5 +272.8 (c 1.00, CHCl3); νmax (CH2Cl2)/cm-1 3394, 3053, 2593, 1719, 1636, 1370, 1201, 1134, 820, 750; 1H NMR (500 MHz, DMSO) δ 8.21 (d, J = 8.4 Hz, 1H), 8.13 (dd, J = 8.3, 2.9 Hz, 2H), 8.07 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.58 (dt, J = 17.9, 7.4 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.17 (dd, J = 8.4, 5.0 Hz, 2H), 5.47 (s, 1H), 4.29 (d, J = 13.1 Hz, 1H), 3.63 (d, J = 13.0 Hz, 1H).13C NMR (126 MHz, DMSO) δ 168.8, 134.7, 134.5, 133.9, 133.7, 131.4, 131.2, 131.2, 131.1, 130.7, 129.9, 129.9, 129.8, 128.9, 128.9, 128.5, 127.5, 127.2, 127.1, 126.8, 126.6, 60.7, 45.4
4.0 Aldol examples procedure®

(4R)-(4-Nitrophenyl)-4-hydroxy-2-butaneone

\[ \text{L-proline (0.0045 g, 0.035 mmol, 0.035 equiv.) was added to a mixture of acetone (0.2 mL, 2.7 mmol, 27 equiv.) and dimethyl sulfoxide (0.8 mL) and the mixture stirred for 15 min. 4-Nitrobenzaldehyde (0.015 g, 0.1 mmol) was added and the reaction stirred overnight or until the starting material was consumed as indicated by TLC. The mixture was treated with saturated aqueous ammonium chloride solution (1 mL) and the solvent removed under the reduced pressure and the residue was redissolved in EtOAc and washed with H₂O (1 mL), brine (1 mL) and dried over MgSO₄ and filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3:1 light petroleum ether/EtOAc) giving the title compound as a colourless solid (0.014 g, 68%).} \]

\[ \alpha_d^{25.5} +42.7 \ (c 1.00, \text{CHCl}_3)^6 \ ; \nu_{\max} (\text{CH}_2\text{Cl}_2)/\text{cm}^{-1} \ 3419, 2921, 2851, 1711, 1518, 1346, 1163, 1076, 856; ^1\text{H NMR} (400 MHz, \text{CDCl}_3) \delta 8.13 – 8.08 (m, 2H), 7.47 – 7.38 (m, 2H), 5.16 (dd, \ J = 8.2, 4.1 Hz, 1H), 3.44 (s, 1H), 2.77 – 2.68 (m, 2H), 2.11 (s, \ J = 4.4 Hz, 3H); ^{13}\text{C NMR} (126 MHz, \text{CDCl}_3) \delta 208.5, 149.8, 126.4, 124.0, 123.8, 68.9, 51.5, 30.7. \]
(4R)-(3-Nitrophenyl)-4-hydroxy-2-butanone

L-proline (0.0045 g, 0.035 mmol, 0.035 equiv.) was added to a mixture of acetone (0.2 mL, 2.7 mmol, 27 equiv.) and dimethyl sulfoxide (0.8 mL) and the mixture stirred for 15 min. 3-Nitrobenzaldehyde (0.015 g, 0.1 mmol) was added and the reaction stirred overnight or until the starting material was consumed as indicated by TLC. The mixture was treated with saturated aqueous ammonium chloride solution (1 mL) and the solvent removed under the reduced pressure and the residue was redissolved in EtOAc and washed with H₂O (1 mL), brine (1 mL) and dried over MgSO₄ and filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3:1 light petroleum ether/EtOAc) giving the title compound as a colourless solid (0.0109 g, 52%).

[α]D²⁵+43.2 (c 1.00, CHCl₃); νmax (CH₂Cl₂)/cm⁻¹: 3423, 2923, 2851, 1709, 1528, 1350, 1164, 1068, 808; ¹H NMR (500 MHz, CDCl₃) δ 8.24 (q, J = 1.8 Hz, 1H), 8.14 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.53 (t, J = 7.9 Hz, 1H), 5.26 (dd, J = 8.0, 4.1 Hz, 1H), 3.61 (s, 1H), 2.93 – 2.83 (m, 2H), 2.23 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 208.6, 131.8, 129.5, 122.6, 120.7, 68.8, 51.5, 30.7.
L-proline (0.0045 g, 0.035 mmol, 0.035 equiv.) was added to a mixture of acetone (0.2 mL, 2.7 mmol, 27 equiv.) and dimethyl sulfoxide (0.8 mL) and the mixture stirred for 15 min. 4-bromobenzaldehyde (0.0185 g, 0.1 mmol) was added and the reaction stirred overnight or until the starting material was consumed as indicated by TLC. The mixture was treated with saturated aqueous ammonium chloride solution (1 mL) and the solvent removed under the reduced pressure and the residue was redissolved in EtOAc and washed with H₂O (1 mL), brine (1 mL) and dried over MgSO₄ and filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3:1 light petroleum ether/EtOAc) giving the title compound as white solid (0.018 g, 74%).

\[ \alpha \]D \textsuperscript{25.5} \textsuperscript{20} +42.9 (c 1.00, CHCl₃); \nu \textsuperscript{max} (CH₂Cl₂)/\textsuperscript{cm} \textsuperscript{-1} 3417, 2920, 2851, 1712, 1487, 1361, 1162, 1070, 828, 538; \textsuperscript{1}H NMR (500 MHz, CDCl₃) \delta 7.51 – 7.43 (m, 2H), 7.26 – 7.22 (m, 2H), 5.12 (dd, \textit{J} = 8.2, 4.0 Hz, 1H), 3.34 (s, 1H), 2.87 – 2.76 (m, 2H), 2.20 (s, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl₃) \delta 208.9, 141.7, 131.6, 127.3, 121.4, 69.2, 51.7, 30.7.
L-proline (0.0045 g, 0.035 mmol, 0.035 equiv.) was added to a mixture of acetone (0.2 mL, 2.7 mmol, 27 equiv.) and dimethyl sulfoxide (0.8 mL) and the mixture stirred for 15 min. 2-naphthaldehyde (0.0156 g, 0.1 mmol) was added and the reaction stirred overnight or until the starting material was consumed as indicated by TLC. The mixture was treated with saturated aqueous ammonium chloride solution (1 mL) and the solvent removed under the reduced pressure and the residue was redissolved in EtOAc and washed with H2O (1 mL), brine (1 mL) and dried over MgSO4 and filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3:1 light petroleum ether/EtOAc) giving the title compound as a colourless solid (0.0114 g, 53%).

\[ [\alpha]_D^{25.5} = -34.6 \quad (c \ 1.00, \text{CHCl}_3) \];

\[ \nu_{\text{max}} (\text{CH}_2\text{Cl}_2)/\text{cm}^{-1} \]

3463, 2921, 2858, 1708, 1488, 1361, 1164, 1064, 820; 1H NMR (500 MHz, CDCl3) \( \delta \) 7.87 – 7.80 (m, 4H), 7.51 – 7.44 (m, 3H), 5.33 (dd, \( J = 8.9, \ 3.1 \text{ Hz}, \ 1\text{H} \)), 3.37 (s, 1H), 3.01 – 2.88 (m, 2H), 2.22 (s, 3H); 13C NMR (126 MHz, CDCl3) \( \delta \) 209.1, 140.0, 133.3, 132.9, 128.4, 128.0, 127.7, 126.2, 125.9, 124.3, 123.7, 70.0, 51.9, 30.8.
(4R)-(4-phenyl)-4-hydroxy-2-butanone

L-proline (0.0045 g, 0.035 mmol, 0.035 equiv.) was added to mixture of acetone (0.2 mL, 2.7 mmol, 27 equiv.) and dimethyl sulfoxide (0.8 mL) and the mixture stirred for 15 min. Benzaldehyde (0.010 mL, 0.1 mmol) was added and the reaction stirred overnight or until the starting material was consumed as indicated by TLC. The mixture was treated with saturated aqueous ammonium chloride solution (1 mL) and the solvent removed under the reduced pressure and the residue was redissolved in EtOAc and washed with H₂O (1 mL), brine (1 mL) and dried over MgSO₄ and filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3:1 light petroleum ether/EtOAc) giving the title compound as white solid (0.010 g, 62%).

\[ [\alpha]_{D}^{25.5} + 19.7 \ (c \ 1.00, \ CHCl_3)^{10}, \nu_{max} (CH_2Cl_2/cm^{-1}) 3431, 2920, 2850, 1712, 1515, 1361, 1163, 1061, 843; ^1H NMR (500 MHz, CDCl_3) \delta 7.37 (dd, J = 9.5, 2.4 Hz, 4H), 7.36 – 7.26 (m, 1H), 5.18 (d, J = 8.9 Hz, 1H), 3.38 (s, J = 8.6 Hz, 1H), 2.92 (dd, J = 17.5, 9.2 Hz, 1H), 2.83 (dd, J = 17.5, 3.2 Hz, 1H), 2.22 (s, J = 1.3 Hz, 3H); ^13C NMR (126 MHz, CDCl_3) \delta 209.1, 142.7, 128.5, 127.7, 125.6, 69.8, 51.9, 30.7. \]
(4R)-(4-methoxyphenyl)-4-hydroxy-2-butanone

L-proline (0.0045 g, 0.035 mmol, 0.035 equiv.) was added to mixture of acetone (0.2 mL, 2.7 mmol, 27 equiv.) and dimethyl sulfoxide (0.8 mL) and the mixture stirred for 15 min. 4-Methoxybenzaldehyde (0.0121 mL, 0.1 mmol) was added and the reaction stirred overnight or until the starting material was consumed as indicated by TLC. The mixture was treated with saturated aqueous ammonium chloride solution (1 mL) and the solvent removed under the reduced pressure and the residue was redissolved in EtOAc and washed with H₂O (1 mL), brine (1 mL) and dried over MgSO₄ and filtered. After the filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3:1 light petroleum ether/EtOAc) giving the title compound as a colourless oil (0.0129 g, 66%).

[α]D²³ 38.6 (c 1.00, CHCl₃); νmax (CH₂Cl₂)/cm⁻¹ 3444, 2957, 2837, 1710, 1514, 1361, 1248, 1031, 834; ¹H NMR (500 MHz, CDCl₃) δ 7.30 – 7.26 (m, 2H), 6.90 – 6.86 (m, 2H), 5.11 (dt, J = 9.3, 3.0 Hz, 1H), 3.80 (s, 3H), 3.17 (d, J = 3.1 Hz, 1H), 2.89 (dd, J = 17.5, 9.3 Hz, 1H), 2.79 (dd, J = 17.4, 3.2 Hz, 1H), 2.19 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 209.1, 159.1, 134.9, 126.9, 113.9, 69.5, 55.3, 51.9, 30.7.
5.0 Mannich examples reaction.\textsuperscript{11}

\textit{(4S)-4-[(4-Methoxyphenyl)amino]-4-(4-nitrophenyl)-2-butanone}

\[ \text{Acetyl} + \text{PhCHO} + \text{NH}_2 \rightarrow \text{HN-} + \text{MeO-}
\]

L-proline (0.40 g, 0.35 mmol, 0.35 equiv.), \textit{p}-anisidine (0.135, 1.1 mmol, 1.1 equiv.) and 4-nitrobenzaldehyde (0.151 g, 1 mmol) were dissolved in DMSO/acetone (4:1, 10 mL). The reaction was stirred at room temperature overnight or until the starting material was consumed as indicated by TLC. The mixture was extracted with phosphate-buffered saline (PBS) solution (pH 7.4) and ethyl acetate. The organic layer was dried with MgSO\textsubscript{4}, filtered, the solvent removed under reduced pressure and the residue purified by column chromatography with (2:1 light petroleum ether/ethyl acetate), giving the title compound as a yellow oil (0.136 g, 43%).

\[ \nu_{\max} (\text{CH}_2\text{Cl}_2)/\text{cm}^{-1} \] 3418, 2923, 2851, 1645, 1510, 1244, 1032; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 8.19 – 8.15 (m, 2H), 7.58 – 7.53 (m, 2H), 6.71 – 6.66 (m, 2H), 6.48 – 6.45 (m, 2H), 4.85 (t, \( J = 6.3 \) Hz, 1H), 3.69 (s, 3H), 2.95 (d, \( J = 6.2 \) Hz, 2H), 2.15 (s, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \( \delta \) 206.0, 153.7, 150.5, 147.2, 141.6, 127.4, 124.0, 115.5, 114.8, 114.8, 55.6, 54.7, 54.7, 50.6, 30.7.
(4S)-4-[(4-Methoxyphenyl)amino]-4-(2-naphthyl)-2-butanone

L-proline (0.40 g, 0.35 mmol, 0.35 equiv.), p-anisidine (0.135, 1.1 mmol, 1.1 equiv.) and 4-nitrobenzaldehyde (0.156 g, 1 mmol) were dissolved in DMSO/acetone (4:1, 10 mL). The reaction was stirred at room temperature overnight or until the starting material was consumed as indicated by TLC. The mixture was extracted with phosphate-buffered saline (PBS) solution (pH 7.4) and ethyl acetate. The organic layer was dried with MgSO₄, filtered, the solvent removed under reduced pressure and the residue purified by column chromatography with (2:1 light petroleum ether/ethyl acetate), giving the title compound as a white solid (0.097 g, 30%).

ν<sub>max</sub> (CH₂Cl₂)/cm<sup>-1</sup> 3409, 2919, 2832, 1708, 1510, 1238, 1035, 817; <sup>1</sup>H NMR (500 MHz, CDCl₃) δ 7.82 – 7.78 (m, 4H), 7.50 – 7.44 (m, 3H), 6.69 – 6.65 (m, 2H), 6.57 – 6.53 (m, 2H), 4.92 (t, J = 6.5 Hz, 1H), 3.67 (s, 3H), 3.00 – 2.96 (m, 2H), 2.12 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl₃) δ 207.1, 152.4, 149.7, 140.9, 140.2, 133.4, 128.7, 127.9, 127.6, 126.1, 125.8, 125.1, 124.4, 115.4, 114.7, 55.6, 55.5, 51.3, 30.7.
(4R)-4-[(4-Methoxyphenyl)amino]-6-methyl-2-heptanone

1-proline (0.40 g, 0.35 mmol, 0.35 equiv.), p-anisidine (0.135, 1.1 mmol, 1.1 equiv.) and Isovaleraldehyde (0.109 mL, 1 mmol) were dissolved in DMSO/acetone (4:1, 10 mL). The reaction was stirred at room temperature overnight or until the starting material was consumed as indicated by TLC. The mixture was extracted with phosphate-buffered saline (PBS) solution (pH 7.4) and ethyl acetate. The organic layer was dried with MgSO₄, filtered, the solvent removed under reduced pressure and the residue purified by column chromatography with (2:1 light petroleum ether/ethyl acetate), giving the title compound as a yellow oil (0.217 g, 87%).

ν<sub>max</sub> (CH₂Cl₂)/cm<sup>-1</sup> 3378, 2955, 2927, 1709, 1510, 1464, 1243, 1035, 825; <sup>1</sup>H NMR (500 MHz, CDCl₃) δ 6.78 – 6.75 (m, 2H), 6.60 – 6.56 (m, 2H), 3.79 (ddd, J = 13.0, 8.0, 4.9 Hz, 1H), 3.74 (s, 3H), 2.66 (dd, J = 16.4, 5.0 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.12 (s, 3H), 1.74 (qd, J = 13.1, 6.6 Hz, 1H), 1.47 (ddd, J = 14.2, 8.2, 6.2 Hz, 1H), 1.33 (ddd, J = 13.7, 8.0, 5.7 Hz, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl₃) δ 208.6, 152.4, 141.8, 115.1, 114.9, 55.9, 49.3, 48.2, 44.8, 31.1, 25.1, 23.1, 22.4.
(4S)-4-[(4-Methoxyphenyl)amino]-5-methyl-2-hexanone

L-proline (0.40 g, 0.35 mmol, 0.35 equiv.), \( p \)-anisidine (0.135, 1.1 mmol, 1.1 equiv.) and Isobutyraldehyde (0.091 mL, 1 mmol) were dissolved in DMSO/acetone (4:1, 10 mL). The reaction was stirred at room temperature overnight or until the starting material was consumed as indicated by TLC. The mixture was extracted with phosphate-buffered saline (PBS) solution (pH 7.4) and ethyl acetate. The organic layer was dried with MgSO₄, filtered, the solvent removed under reduced pressure and the residue purified by column chromatography with (2:1 light petroleum ether/ethyl acetate), giving the title compound as a colourless oil (0.114 g, 48%).

\[ \nu_{\text{max}} \text{(CH}_2\text{Cl}_2)/\text{cm}^{-1} = 3363, 2957, 2832, 1707, 1511, 1465, 1237, 1036, 822; \]
\[ ^1\text{H NMR (500 MHz, CDCl}_3) \delta 6.78 – 6.73 (m, 2H), 6.61 – 6.54 (m, 2H), 3.73 (s, 3H), 3.65 (dd, J = 12.3, 5.4 Hz, 1H), 2.55 (qd, J = 16.0, 6.2 Hz, 2H), 2.14 (s, 3H), 1.97 – 1.88 (m, 1H), 0.96 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); \]
\[ ^{13}\text{C NMR (126 MHz, CDCl}_3) \delta 208.4, 152.1, 141.6, 115.0, 56.2, 55.8, 45.2, 31.2, 30.6, 18.7, 18.4. \]
(4S)-4-(4-Bromophenyl)-4-[(4-methoxyphenyl)amino]-2-butane-1-one

**1-proline** (0.40 g, 0.35 mmol, 0.35 equiv.), *p*-anisidine (0.135, 1.1 mmol, 1.1 equiv.) and 4-Bromobenzaldehyde (0.185 g, 1 mmol) were dissolved in DMSO/acetone (4:1, 10 mL). The reaction was stirred at room temperature overnight or until the starting material was consumed as indicated by TLC. The mixture was extracted with phosphate-buffered saline (PBS) solution (pH 7.4) and ethyl acetate. The organic layer was dried with MgSO₄, filtered, the solvent removed under reduced pressure and the residue purified by column chromatography with (2:1 light petroleum ether/ethyl acetate), giving the title compound as a colourless solid (0.254 g, 72%).

\[
\nu_{\text{max}}^{-1} (\text{CH}_2\text{Cl}_2)/\text{cm}^{-1} \quad 3373, 2955, 2833, 1710, 1510, 1402, 1238, 1034, 815, 527; \quad ^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.45 – 7.40 (m, 2H), 7.25 – 7.20 (m, 2H), 6.71 – 6.66 (m, 2H), 6.47 (d, J = 8.3 Hz, 2H), 4.71 (t, J = 5.6 Hz, 1H), 3.69 (s, 3H), 2.88 (d, J = 6.5 Hz, 2H), 2.11 (s, 3H); \quad ^{13}\text{C} \text{NMR} (126 \text{ MHz, CDCl}_3) \delta 206.8, 131.8, 128.1, 121.0, 115.4, 114.7, 60.4, 55.6, 54.7, 51.1, 30.7, 21.0, 14.2.
(4S)-4-(4-Fluorophenyl)-4-[(4-methoxyphenyl)amino]-2-butanone

L-proline (0.40 g, 0.35 mmol, 0.35 equiv.), p-anisidine (0.135, 1.1 mmol, 1.1 equiv.) and 4-fluorobenzaldehyde (0.124 g, 1 mmol) were dissolved in DMSO/acetone (4:1, 10 mL). The reaction was stirred at room temperature overnight or until the starting material was consumed as indicated by TLC. The mixture was extracted with phosphate-buffered saline (PBS) solution (pH 7.4) and ethyl acetate. The organic layer was dried with MgSO₄, filtered, the solvent removed under reduced pressure and the residue purified by column chromatography with (2:1 light petroleum ether/ethyl acetate), giving the title compound as an orange oil (0.071 g, 24%).

ν_max (CH₂Cl₂)/cm⁻¹ 3381, 2999, 2833, 1711, 1509, 1359, 1237, 1036, 820, 537; ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.29 (m, 2H), 7.03 – 6.98 (m, 2H), 6.71 – 6.67 (m, 2H), 6.52 – 6.46 (m, 2H), 4.74 (t, J = 6.5 Hz, 1H), 3.69 (s, 3H), 2.89 (d, J = 6.1 Hz, 2H), 2.11 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 207.0, 130.1, 127.9, 122.1, 116.4, 115.4, 114.8, 114.7, 55.6, 55.5, 54.6, 52.5, 30.9, 30.7, 15.9.
Experimental section reference


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