Organocatalysis using novel axially chiral secondary amines

by

Nawaf Ibrahim Alsenani

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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

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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 descries 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.

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Abbreviations

Å	Ångström
AIBN	Azobisisobutyronitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-Butyloxycarbonyl
Boc2O	Di-*tert*-butyl dicarbonate
Bu	Butyl
BuLi	*n*-Butyllithium
Cbz	Carboxybenzyl
°C	Degrees Celsius
cm^{-1}	Wavenumber
d	Days
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-dichloro-3,6-dicyano-1,4-benzoquinone
DIBAL	Diisobutylaluminium hydride
DMAc	Dimethylacetamide
DMAP	Dimethylaminopyridine
DMF	*N*,*N*-Dimethylforamide
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
DppONH2	*O*-(Diphenylphosphinyl)-hydroxylamine
e.e	Enantiomeric excess
E^+	Electrophile
EDAC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	Equivalents
Et	Ethyl
g	Grams
h	Hour
HOBT	Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution liquid chromatography
iPr	*Iso*-propyl
IR	Infrared
IPA	*Iso*-propyl alcohol
K	Kelvin scale
LUMO	Lowest unoccupied molecular orbital
M	Molar
m.p.	Melting point
Me	Methyl

MHz	MegaHertz
min	Minute
mL	Millilitre
mmol	Millimole
NBS	*N*-Bromosuccinimide
NMR	Nuclear Resonance Spectroscopy
Nu^-	Nucleophile
OTf	Trifluromethanesulfonate
Oxone	Tetrabutylammonium hydrogen monopersulfate
p-TsCl	*para*-Toluenesulfonyl chloride
p-TsOH	*para*-Toluenesulfonic acid
Pd/C	Palladium on carbon
Ph	Phenyl
$PhCF_3$	Trifluorotoluene
$PhCO_2H$	Benzoic acid
PMB	Paramethoxybenzyl
ppm	Parts per million
r.t.	Room temperature
TBHP	*tert*-Butylhydroperoxide
Tf2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPPP	Tetraphenylphosphonium monoperoxysulfate
UV	Ultraviolet
δ	Chemical shift
Δ	Heat

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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. [1] 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.[2] 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.

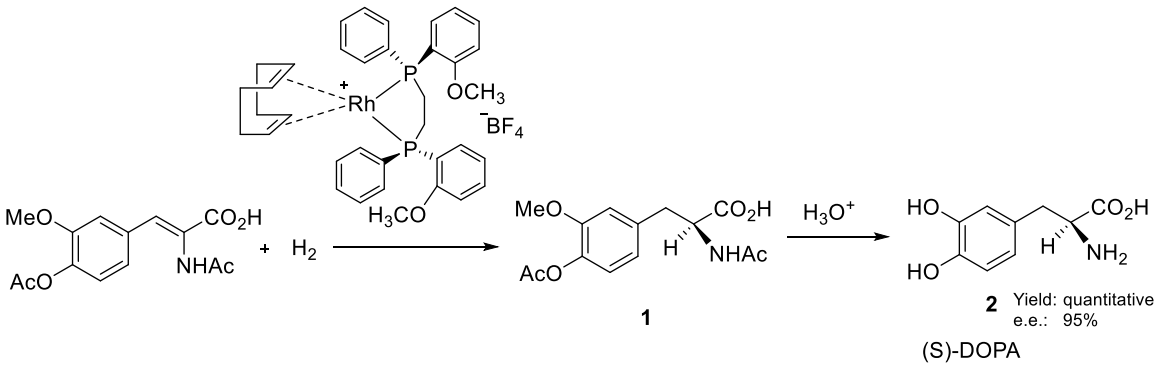
1.1 Classes of asymmetric catalysis

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

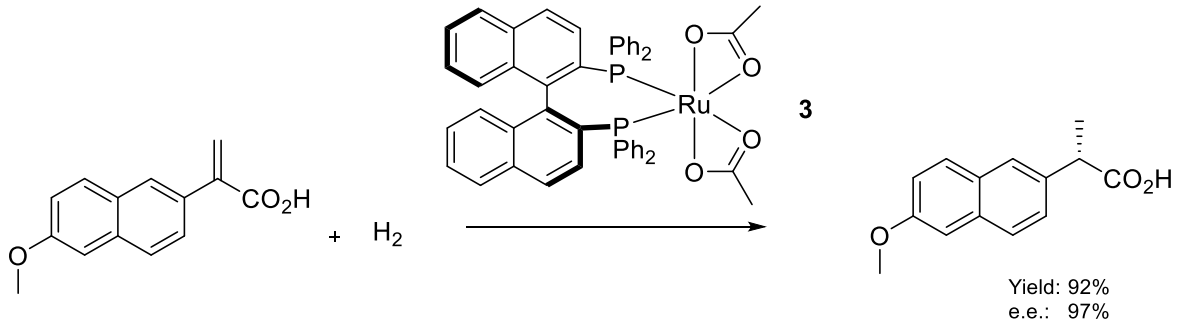
Since the Nobel prize was awarded to Karl Ziegler, Giulio Natta, Geoffrey Wilkinson, and E. O. Fischer for their contributions in the area of science and technology specifically in organometallic chemistry, organometallic catalysis has become a powerful tool to increase production, such as high octane 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.[3] Furthermore, in 1968, Knowles had used and developed [Rh(*R,R*)-DiPAMP)COD]BF_4 as catalyst for the first industrial asymmetric catalytic reaction to synthesise a rare amino acid (*S*)-DOPA **2** 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**).[4]



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

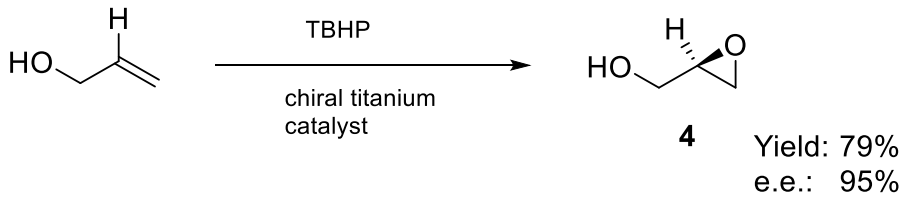
In addition, Noyori has used Ru-BINAP **3** in drug synthesis, such as, the synthesis of Naproxen, an anti-inflammatory drug. The result was 92% yield and 97% enantiomeric excess. Moreover, Noyori has also applied his Ru-BINAP in the synthesis of an antibiotic called Levofloxacin (**Scheme 2**).[5]



Scheme 2: Ru-BINAP catalyst **3** step in the synthesis of Naproxen.

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.[6] 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.[7] 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**).[8]

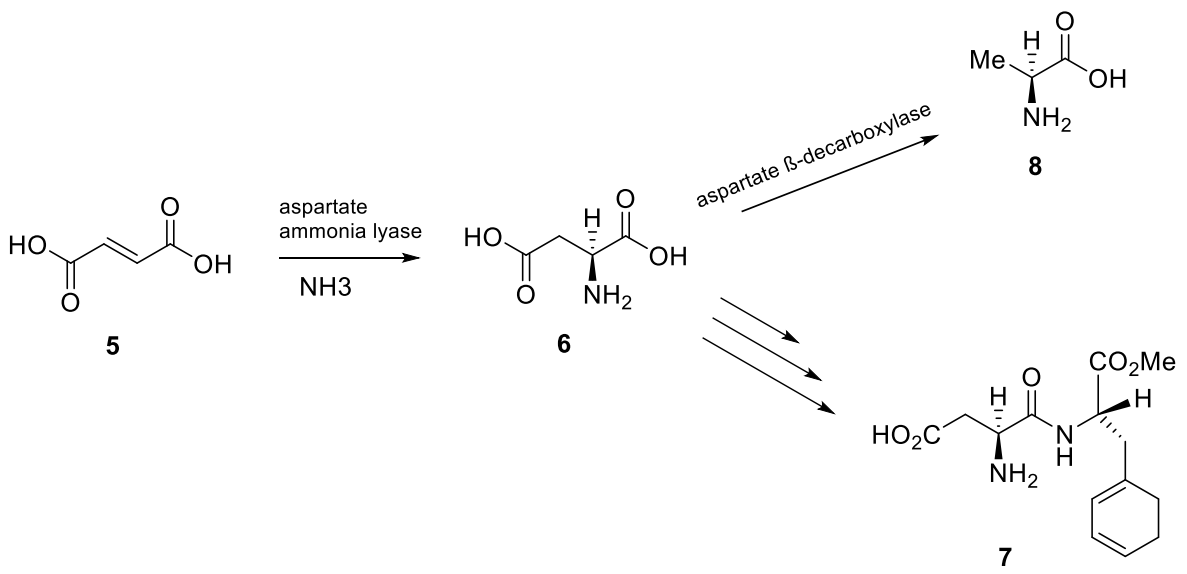


Scheme 3: The key intermediate **4** in the synthesis of antibiotic methycin.

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) **7** starts from L-aspartic acid **6**. L-aspartic acid is synthesised from fumaric acid **5** by aspartase-catalysed addition of ammonia. When using immobilised aspartate β-decarboxylase with L-aspartic acid **6**, the amino acid L-alanine **8** can be formed (**Scheme 4**).[9]



Scheme 4: Synthesis of (L)-aspartic acid **6** and (L)-alanine **8** using an enzyme catalyst.

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,[10] a nucleophilic catalyst,[11] and it can act as phase transfer catalyst after it has been alkylated.[12] 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**).[13]

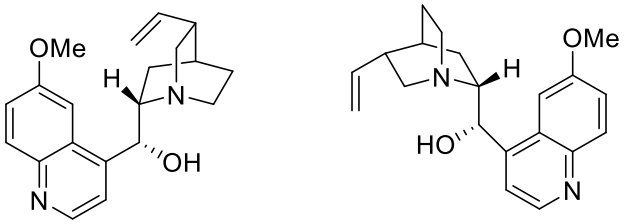
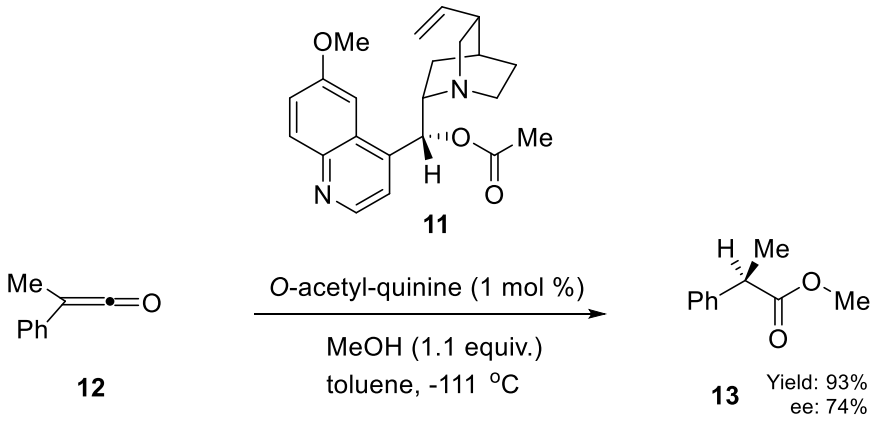


Figure 1: Quinine **9** and quinidine **10** natural product-derived diastereoisomeric cinchona alkaloids.

In 1912, Bredig and Friske used quinine and quinidine as chiral catalysts in the first asymmetric organocatalysed reaction,[13] used to synthesise mandelonitrile, by addition of HCN to benzaldehyde. The enantiomeric excess of the reaction was about 8%.[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**).[15,16]



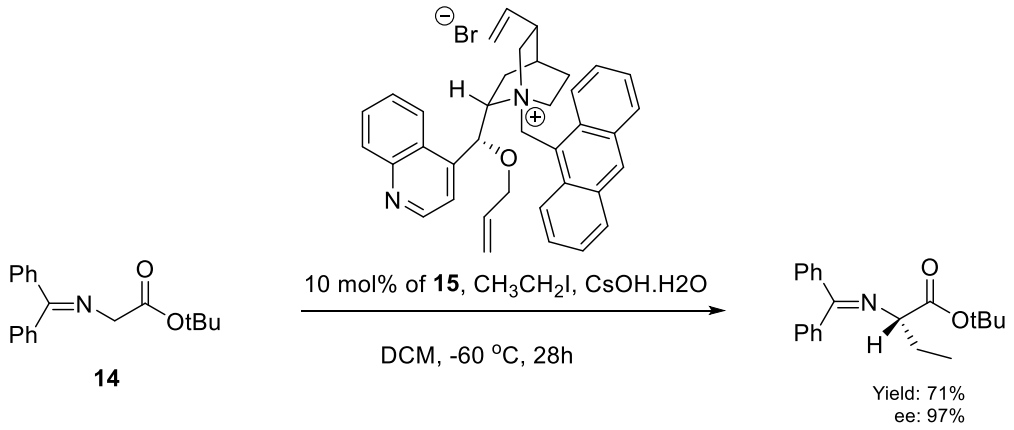
Scheme 5: Addition of O-acetyl quinine **11** (catalyst) to form phenylmethylketene **12**.

1.2 Types of organocatalysts

Due to the larg 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**).

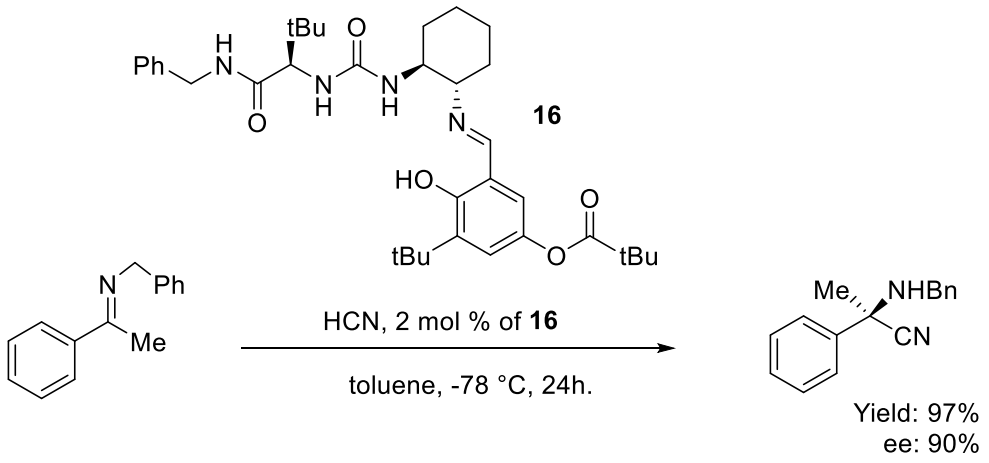


Scheme 6: Alkylation of glycine Schiff base **14** using chiral quaternary ammonium salt phase transfer catalyst **15**.

In the example shown in scheme 6, at the interface, glycine Schiff base **14** reacts with $CsOH.H_2O$, 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. [17]

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**).[18]



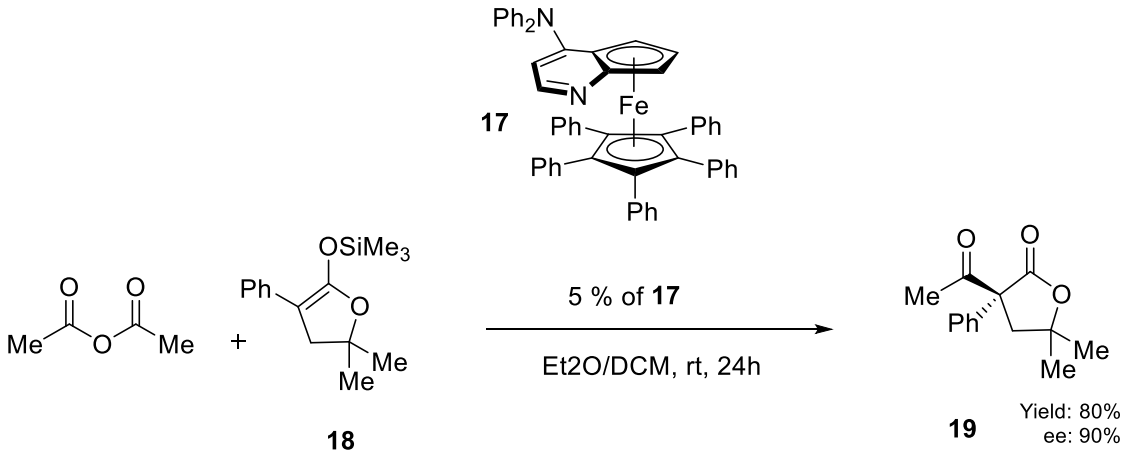
Scheme 7: Strecker reaction using thiourea-based organocatalyst **16**.

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.

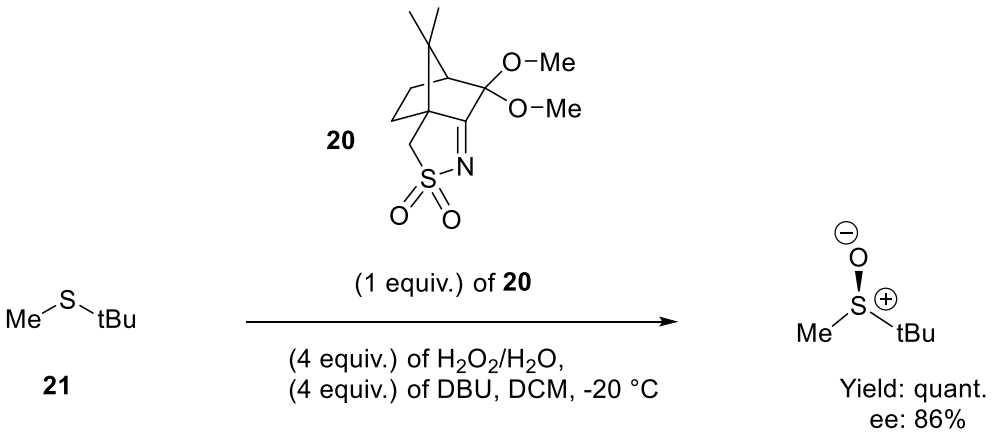
In 2002, the Fu group synthesised planar chiral DMAP derivatives which act as Lewis base organocatalysts due to the presence of a pyridine moiety.

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 acypyridinium gives **19** in high ee and reasonable yield (**Scheme 8**).[19]



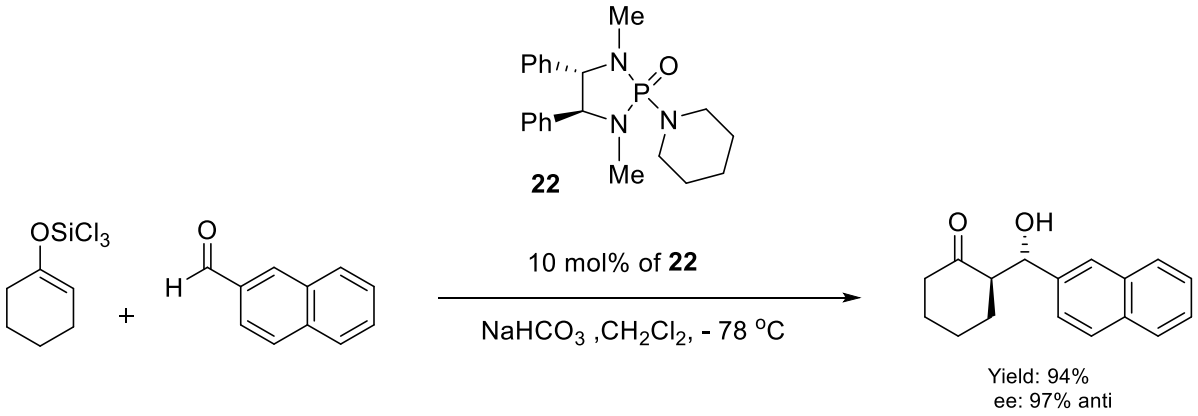
Scheme 8: C-acylation of silyl ketene acetals catalysed by DMAP derivative **17**.

In the field of aziridination and epoxidation reactions, the Page group has obtained impressive results.[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 **20**.[23,24] The reaction between imine catalyst **20** and hydrogen peroxide gives a very reactive oxidative intermediate which can transfer the oxygen atom to the sulfide enantioselectively (**Scheme 9**).[25]



Scheme 9: Oxidation reaction of sulphide **21** using hydrogen peroxide and oxocamphorsulfonylimine catalyst **20**.

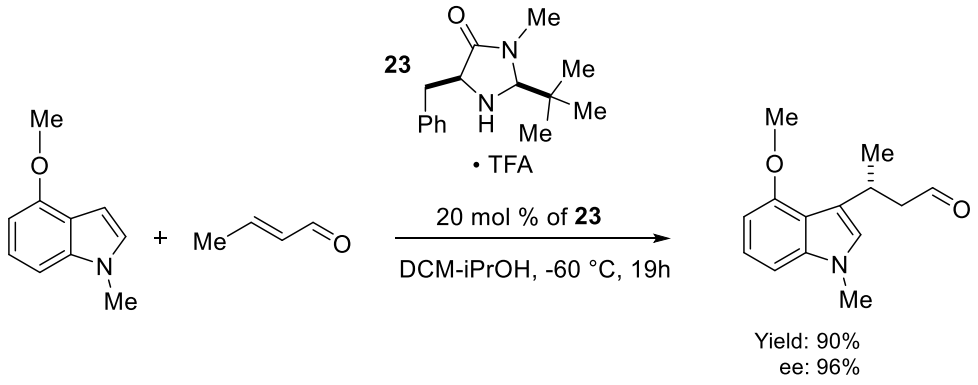
Denmark applied chiral phosphoramide catalyst **22** to an asymmetric intermolecular aldol reaction for the first time in 1999. Denmark achieved excellent results in terms of yield and ee: at low temperatures, several α-β unsaturated, branched aliphatic and aromatic aldehydes were used as substrates with a reactive silyl enol ether as nucleophile (**Scheme 10**).[26]



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

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 phosphoramide 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]

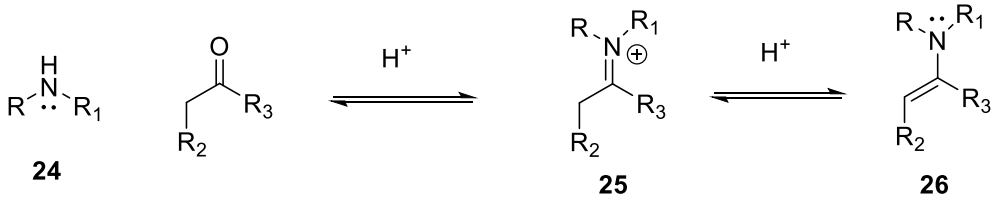
In 2002, the MacMillan group reported Friedel-Crafts type alkylations of pyrroles and indoles with enals using secondary amine **23** as the catalyst. Co-catalysts, such as trifluoroacetic acid, improved the reaction rate and allowed the reaction to take place at low temperatures giving high selectivity.[28]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



Scheme 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**).



Scheme 12: Condensation of amines and carbonyls .

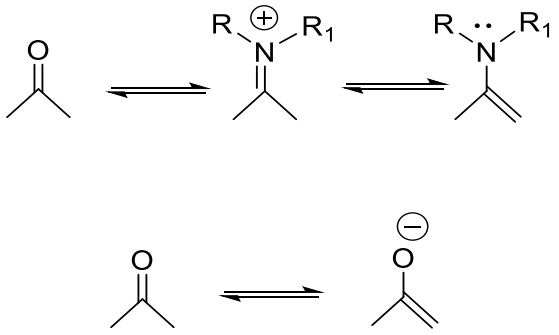
The iminium or enamine moiety is hydrolysed to free the amine catalyst after completion of the catalytic cycle.

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**).

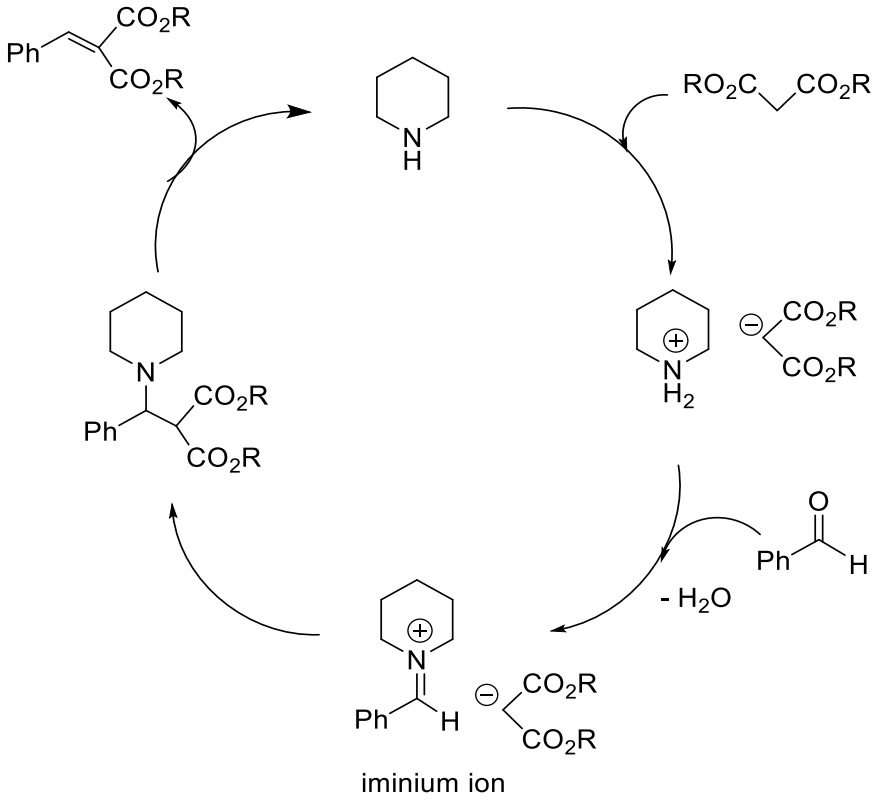


Scheme 13: Iminum/enamine and keto-enol tautomerizations.

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]

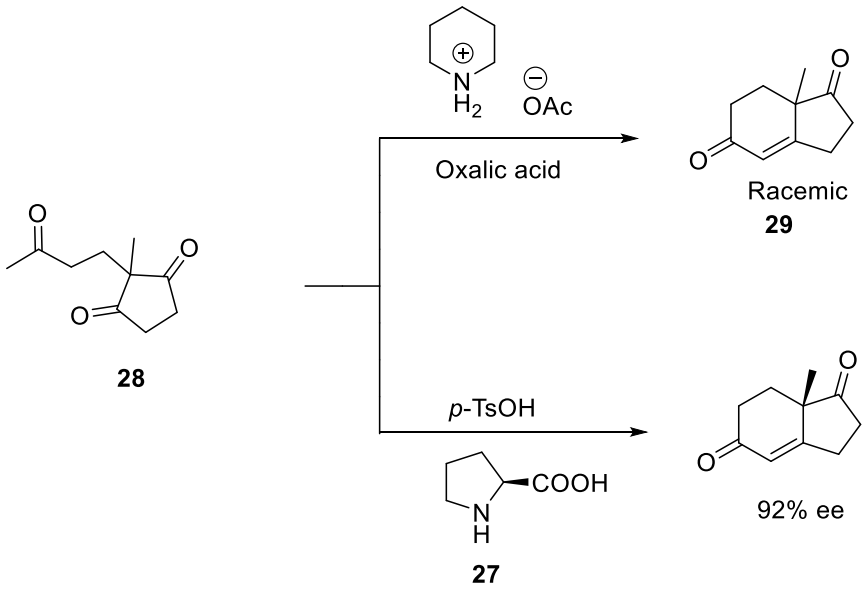


Scheme 14: Knoevenagel condensation using piperidine as the catalyst.

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.[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, [33] and that reaction was named the Hajos–Parrish–Eder–Sauer–Wiechert reaction.[34] In 1950, Miescher and Wieland synthesised and used achiral piperidinium and pyrrolidinium salts to give the racemic dione **29**,[35] 15 years later, the formation of enamine and iminium ion intermediates was suggested by Spencer *et al.* as the reason for the accelerating reaction rates.[36] In 1984, Agami *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**).[37]



Scheme 15: Diketone **29** racemic product by Miescher and the Proline-catalysed asymmetric version.

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**).

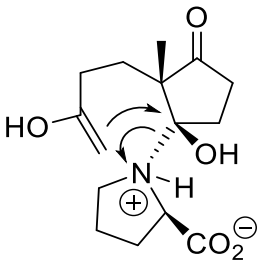
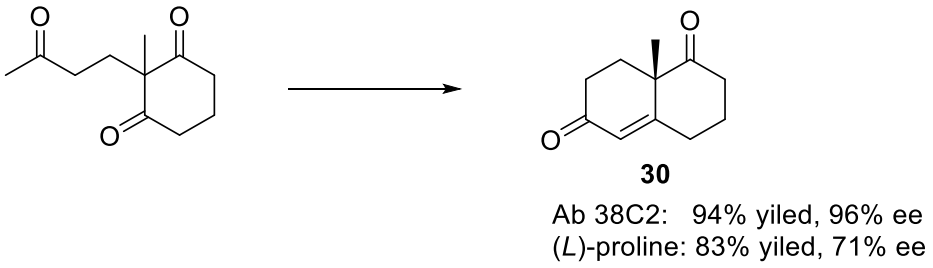


Figure 3: Amino-carbinol intermediate proposed by Hajos.

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.[38,39] 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.[40]

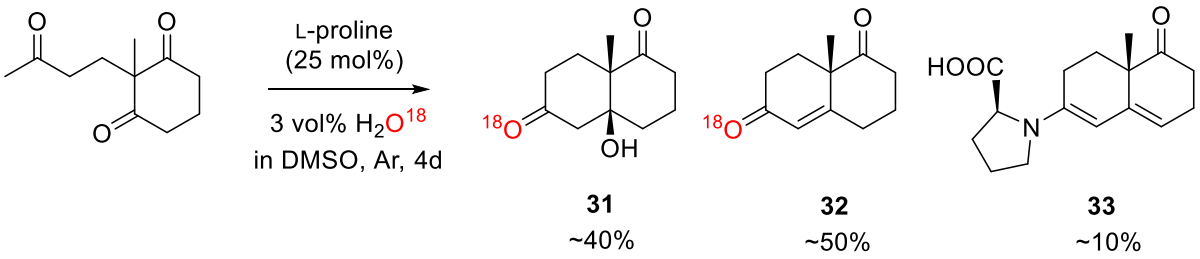
Barbas and Lerner *et al.* worked on aldol reactions using antibodies, and they suggested that the antibody mechanism cycle is the same as the natural class 1 aldolase enzymes.[41] Using the 38C2 antibody, the Hajos–Wiechert Robinson annelation produced, amongst several other examples, the Wieland-Miescher 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.**

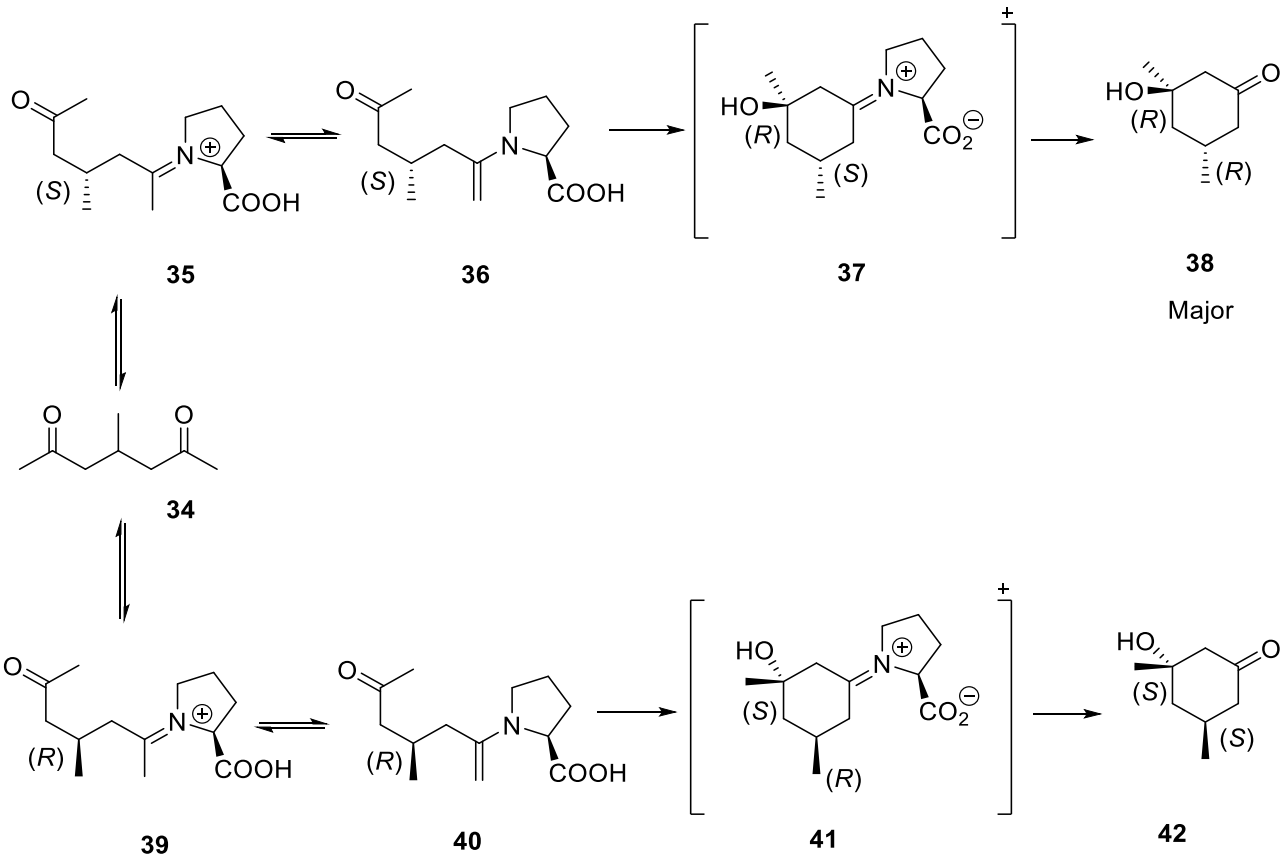
In addition, the mechanism of the Hajos– Parrish–Eder–Sauer–Wiechert reaction was proved using ^{18}O-enriched water, following the reaction by GC-MS.[42]

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.

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**.[43] 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**).



Scheme 18: DFT mechanistic studies by Houk.

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 $^{\delta+}$NCH--O$^{\delta-}$ distance is 2.5 Å. In contrast, the (*S*,*R*) transition state **41** has a calculated $^{\delta+}$NCH--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**).[44]

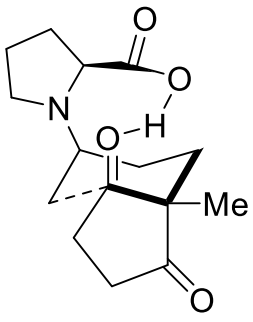
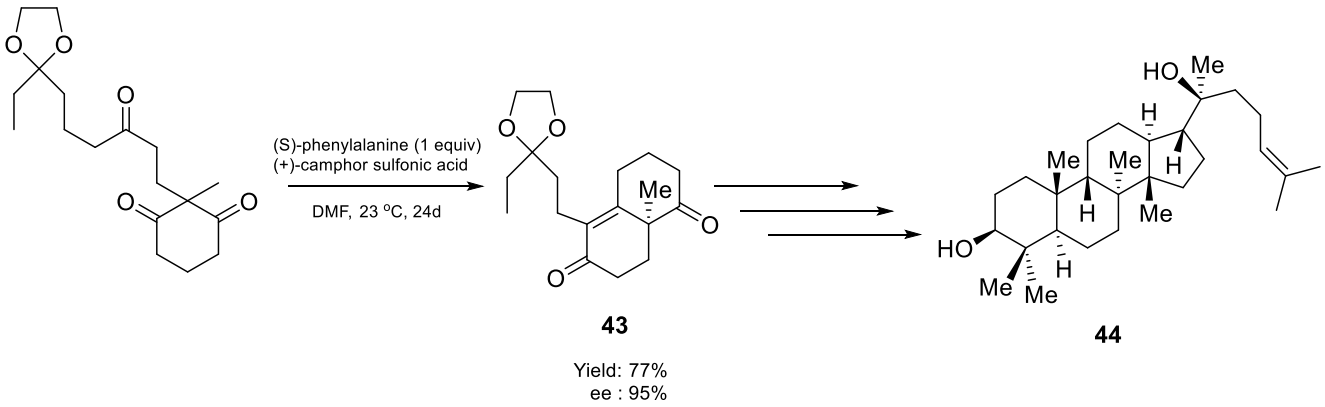


Figure 4: Chair transition state proposed by Houk.

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]



43

Yield: 77%
ee : 95%

44

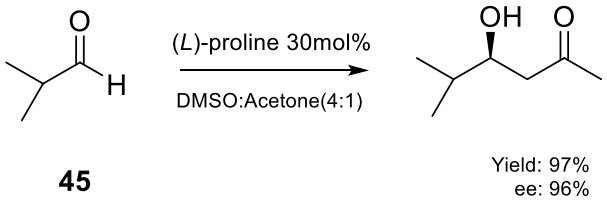
Scheme 19: installation of stereogenic centers on bioactive protosteneiols **44** by Corey.[48]

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.

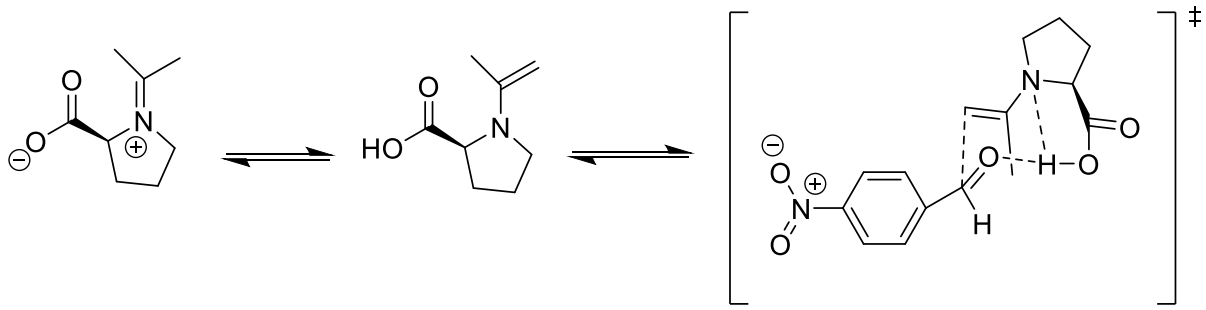
3.1 Asymmetric aminocatalytic aldol reaction

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.



Scheme 20: The first intermolecular aldol reaction catalaysed by proline.

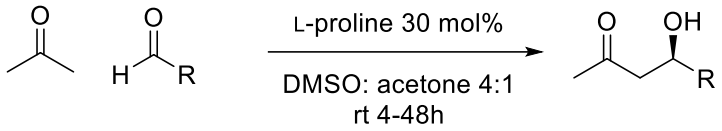
L-Proline **27** was used in asymmetric aminocatalytic intermolecular aldol reactions by List *et al.* for the first time in 2000 (**Scheme 20** and **21**).[49] Proline, as a chiral pool catalyst, exhibited similar features to aldolase antibody 38C2, an efficient catalyst for many reactions, such as the Wieland-Miescher ketone synthesis. Indeed, proline reacts via an enamine intermediate.[50]

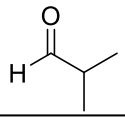
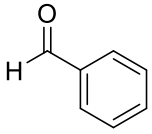
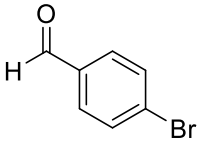
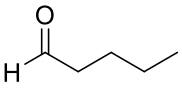


Scheme 21: Transition state for aldol reaction between acetone and 4-nitrobenzaldehyde catalysed by proline proposed by Zimmerman-Traxler.

High yields and enantioselectivities were obtained and a large number of aldehydes were tested using acetone as the only nucleophile (**Table 1**).

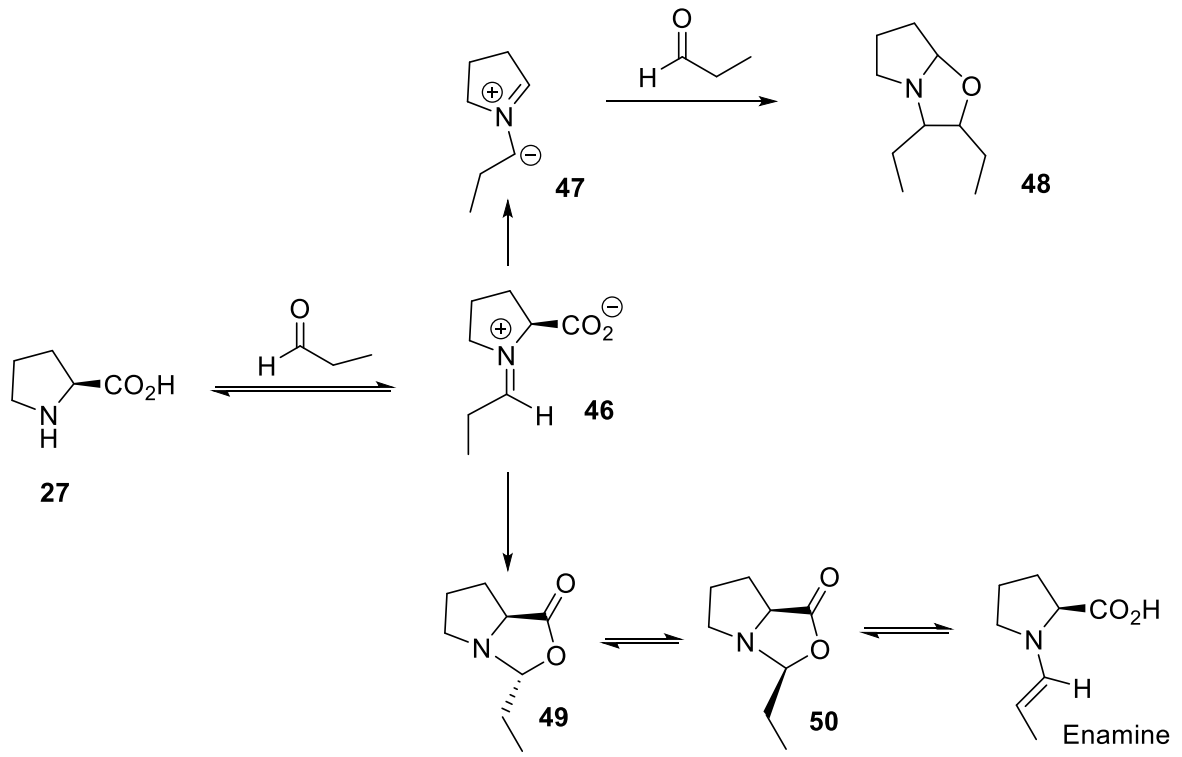
Table 1: Asymmetric aldol reaction using proline.



Entry	Aldehyde	Yield %	ee %
1		97%	96%
2		62%	60%
3		74%	65%
4		–	–

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.

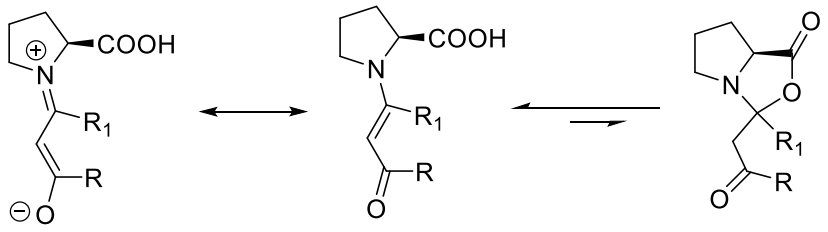
In 2010, Gschwind *et al.* reported the proline-catalysed self-aldolisation of propionaldehyde as a model, trying to isolate the 'elusive' enamine intermediate and the by-product from the reaction.[51] As a result, the enamine intermediate and two diastereoisomeric oxazolidinones **49** and **50** were identified (**Scheme 22**).



Scheme 22: Proline catalysed self-aldolisation and possible intermediates and products.

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'.[54] The iminium intermediate **46** is key to the interconversions between aldehydes, oxazolidinones and enamine formations.[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.[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**).



51

Scheme 23: Formation of enaminone.

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]

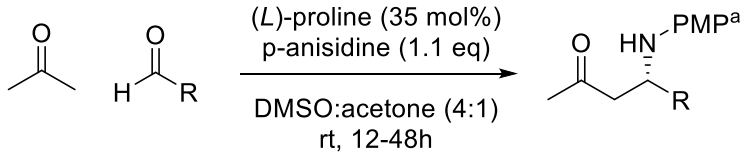
Proline also gives very interesting results in many reactions, such as, carbon-carbon bond forming reactions (Michael reaction,[55] aldol-modified dihydroxylation,[56] cross aldolisation of non-equivalent aldehydes[57]) and heteroatom introduction reactions (α-oxygenation of aldehydes with nitrosobenzene,[58] and α-amination of aldehydes with diazodicarboxylates[59,60]).

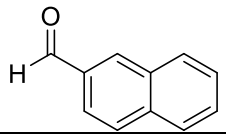
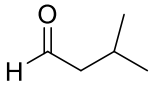
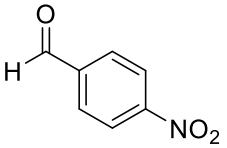
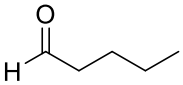
3.2 Asymmetric aminocatalytic Mannich reaction

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.

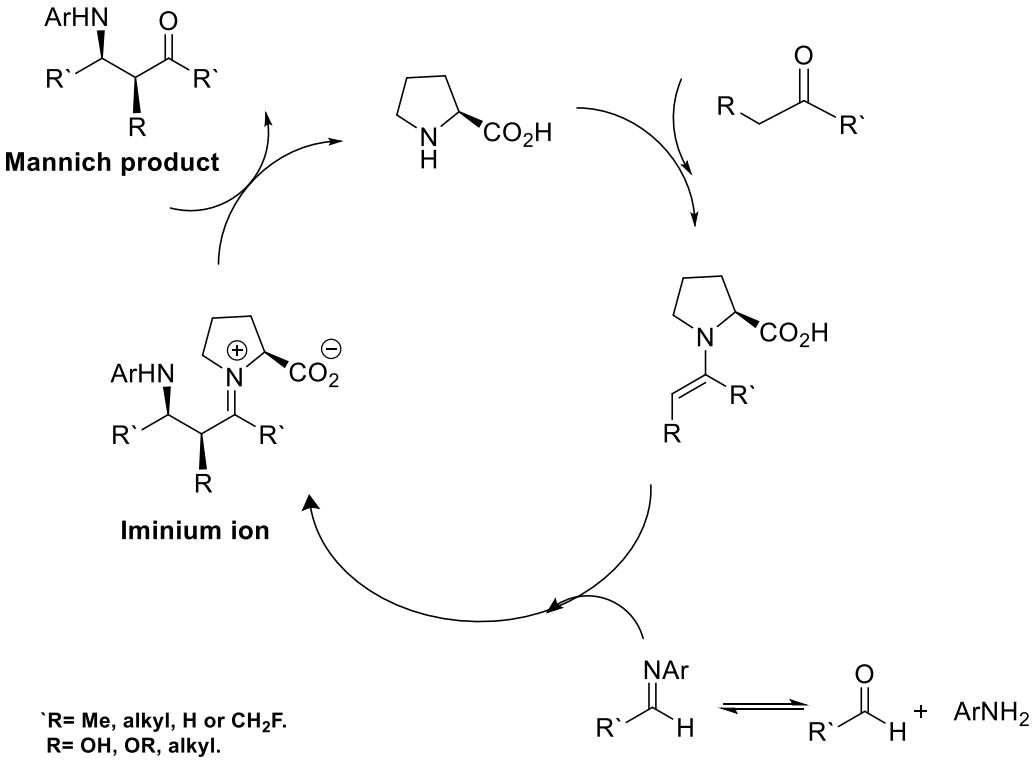


Entry	Aldehyde	Yield %	ee %
1		35%	94%
2[b]		90%	93%
3		50%	94%
4[b]		74%	73%

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 *si*-face of the imine (**Figure 5**). [63]

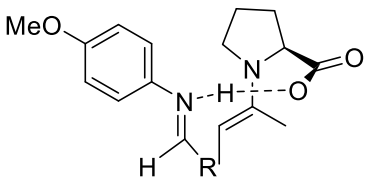


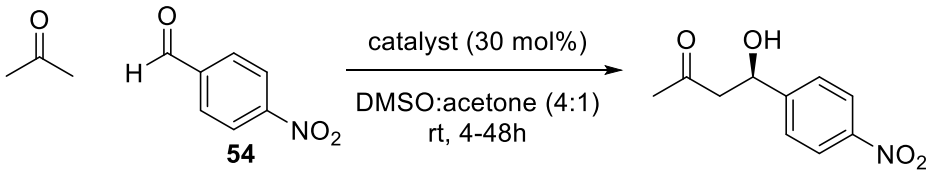
Figure 5: Mannich reaction transition state.

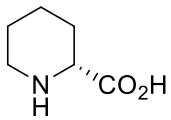
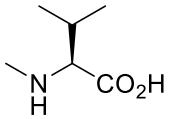
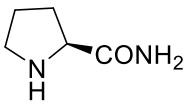
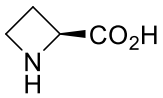
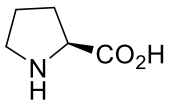
4.0 Proline-derived catalysts

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.

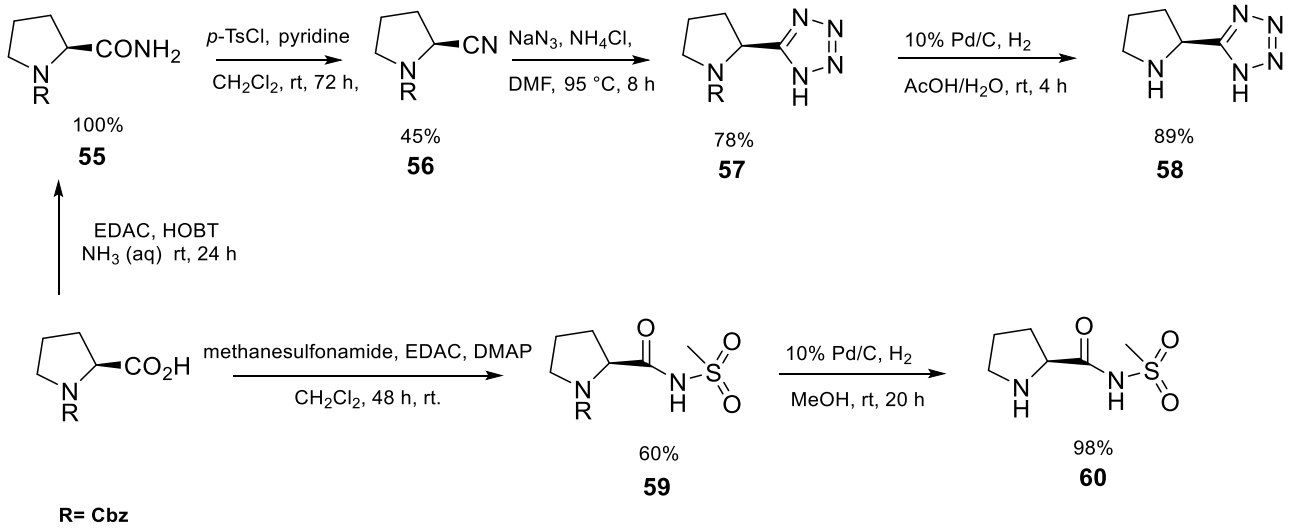


Entry	Amino acid catalyst	Yield %	ee %
1		<10%	-
2		<10%	-
3		<10%	-
4		55%	40%
5		68%	76%

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]

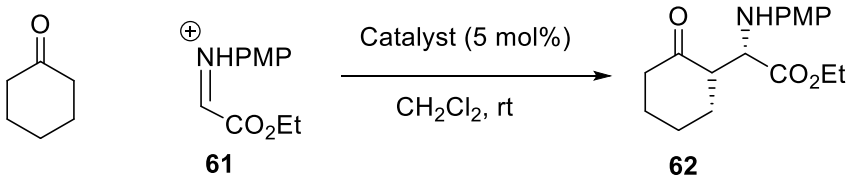
In 2004, and due to proline solubility issues in classic solvents, Ley synthesised tetrazole **58** and acyl sulfonamide **60** in an attempt to keep a similar pKa to that of proline (**Scheme 25**).[64,65] In more detail, beginning with *N*-benzyloxycarbonyl-L-proline, a coupling reaction using ammonia, 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.



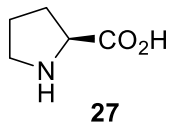
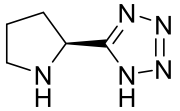
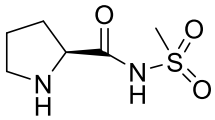
Scheme 25: Synthesis of catalysts **58** and **60**.

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**.

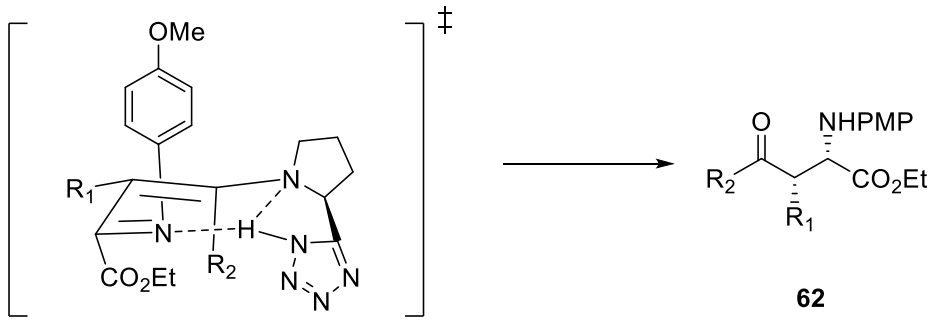


61 **62**

Entry	Catalyst	Time (h)	Yield %	d.r. syn:anti	ee %
1	 **27**	2	-	-	-
2	 **58**	2	65	>19:1	>99
3	 **60**	24	65	>19:1	83

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**).

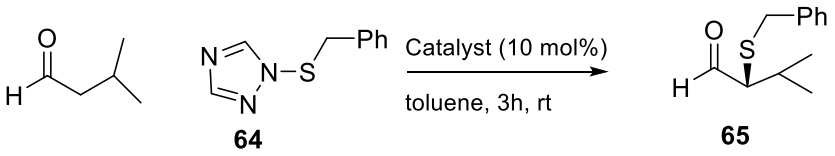


Scheme 26: Formation of *syn*-product **62** caused by the axial PMP group of imine 61.

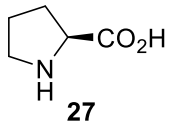
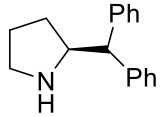
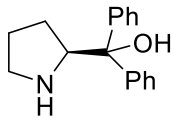
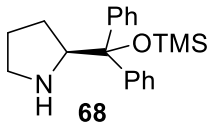
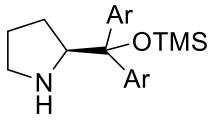
Ley also applied the tetrazole catalyst **58** in nitro-Michael, aldol and N-nitroso aldol reactions.[67,68]

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**).

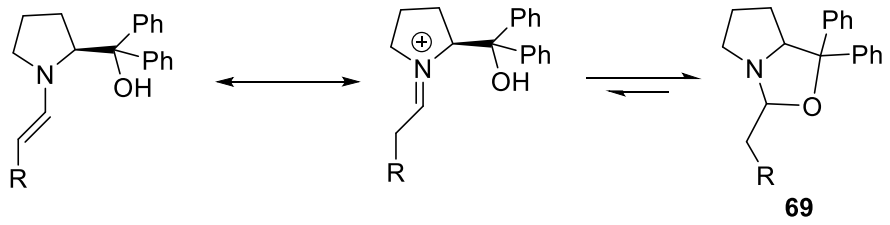
Table 5: α-sulfenylation of isovaleraldehyde by proline-derived catalysts.



64 **65**

Entry	Catalyst	Yield (%)	ee (%)
1	 **27**	16%	Racemic
2	 **66**	56%	25%
3	 **67**	-	-
4	 **68**	99%	77%
5	 Ar= 3,5-(CF_3)-C_6H_3 **63**	90%	98%

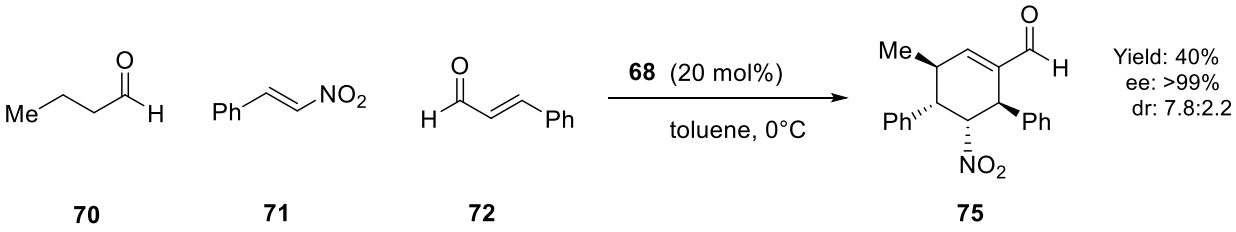
Diarylmethylpyrrolidine **66** afforded the desired product in 56% yield and 25% ee (**Entry 2**). However, diarylprolinol **67** did not provide the desired product (**Entry 3**), and Jørgensen realised that the catalyst was fully converted into oxazolidine **69** (**Scheme 27**). To improve the results, catalysts with increasingly bulky groups, such as catalyst **63** and **68** were synthesised.
69



Scheme 27: Deactivation of catalyst **67** through oxazolidine formation.

After the successes observed using Jørgensen catalyst **63**, it has been used in many reactions: benzylation of α,β-unsaturated aldehydes,[70] cycloaddition reactions,[71,72] aziridinations of 2,4-dienals,[73] epoxidations of α-β unsaturated aldehydes,[74] α-aminations of aldehydes[75] and α-fluorinations of aldehydes.[76]

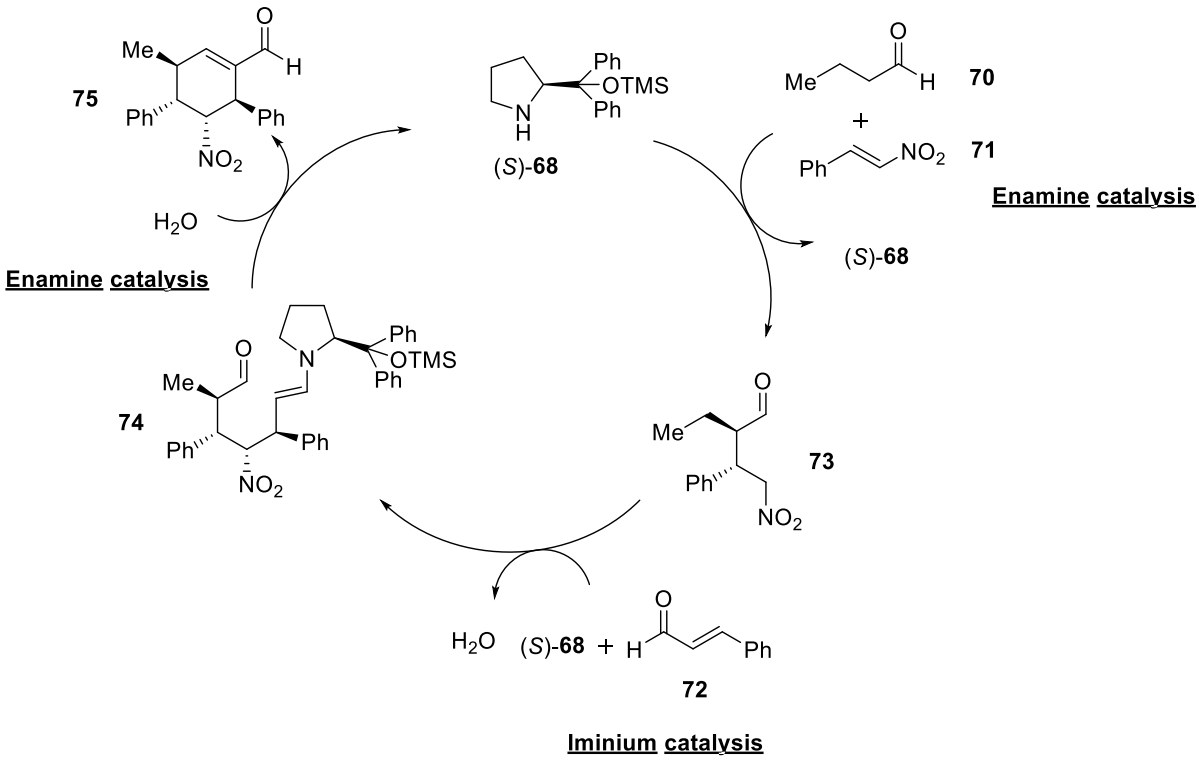
As aminocatalysts have two modes of action, in 2006, Enders reported the use of diarylprolinol catalyst **68** in Michael/Michael/aldol condensation cascades in order to produce tetra-substituted cyclohexene carbaldehydes with multiple stereogenic centres (**Scheme 28**).[77]



Scheme 28: Condensation 'domino' of Michael/Michael/aldol reaction.

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.[78] 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**).



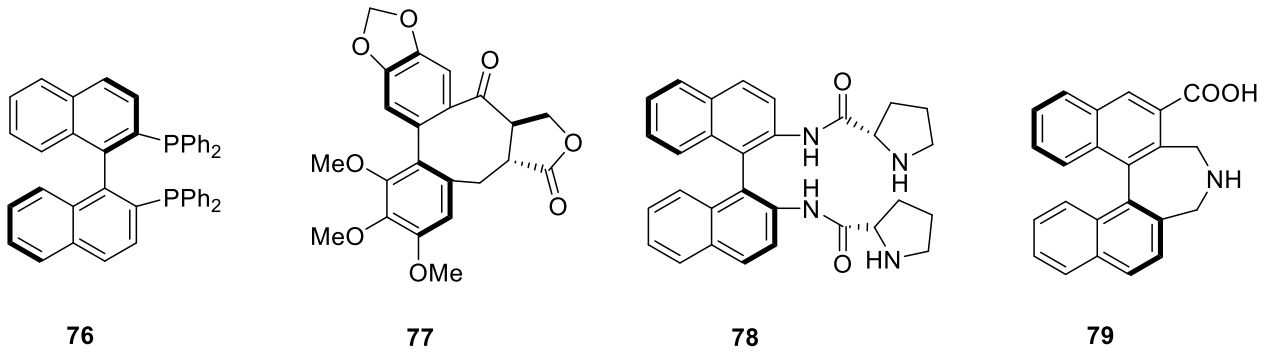
Scheme 29: The catalytic cycle of Enders cascade reaction.

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,[79,80] which can be specifically targeted and used in asymmetric catalysis.[81] In addition, the stability of configuration and the stereochemical environment made these type of catalysts popular worldwide, including for mechanistic studies.[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.[83] A good example of an axially chiral natural product is (–)-steganone **77**, an anticancer agent (**Figure 6**). [84]



76 **77** **78** **79**

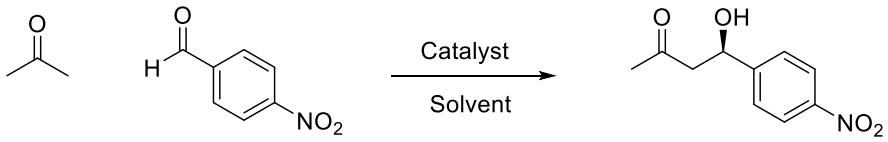
Figure 6: Axially chiral catalysts examples

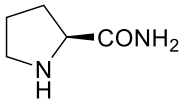
5.1 Axially chiral aminocatalysts

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.[85] 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.[86, 87] 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[88]), 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**).

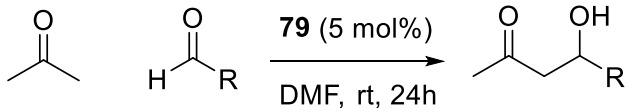
Table 6: Catalyst comparison in Aldol reaction.

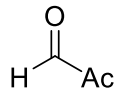
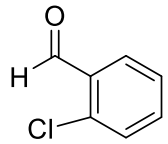
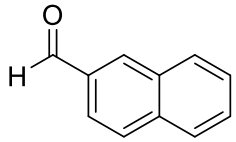
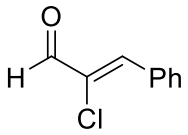


Entry	Catalyst	Catalyst loading (mol%)	Solvent	Time (h)	Yield (%)	Ee (%)
1	**78**	10	Acetone	72	58	65 (*R*)
2	 **80**	10	Acetone	48	80	30 (*R*)
3	**79**	5	DMSO	24	70	93 (*R*)
4	**27**	5	DMSO	24	18	71 (*R*)

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 7: Catalyst **79** in Aldol reaction between acetone and several aldehydes.



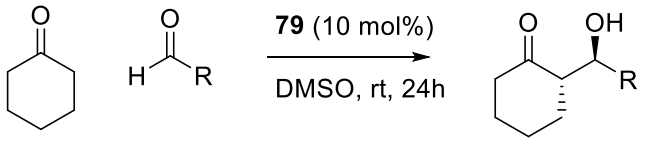
Entry	Aldehyde	Yield (%)	Ee (%)
1		80	95 (*R*)
2		91	95 (*R*)
3[a]		35	96 (*R*)
4		73	90[b]

a)108 equivalents of acetone, the rest 27 equivalents used. b) absolute configuration not determined

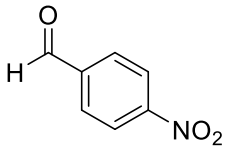
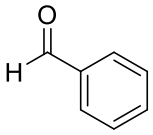
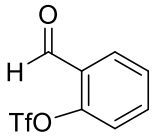
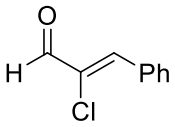
The use of amide-based solvents such as 1-methyl-2-pyrrolidone and *N*,*N*-dimethylformamide helped to improve the yield to 78% and 82%, respectively. Moreover, most aldehyde substrates gave ee above 90%. However, aromatic aldehydes gave low yields, whereas heteroaromatic, electron-deficient aromatic 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 (2*S*,1*R*)-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 8: Catalyst **79** in aldol reaction between cyclohexanone and several aldehydes.



81
(2*S*,1*R*)

Entry	Aldehyde	Yield (anti:syn) %	e.e (anti:syn) %
1		98 (95:5)	98:5
2[a]		38 (91:9)	98:16
3		97 (>95:5)	99:23
4		87 (95:5)	97:30

a) Reaction preformed for 126 h.

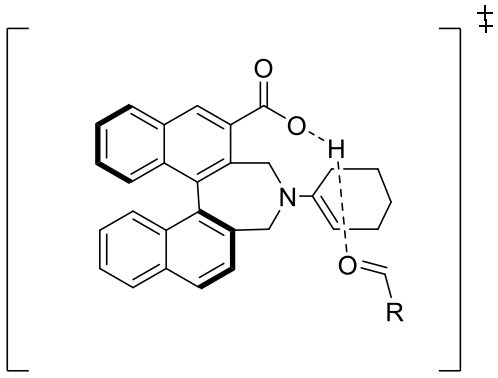
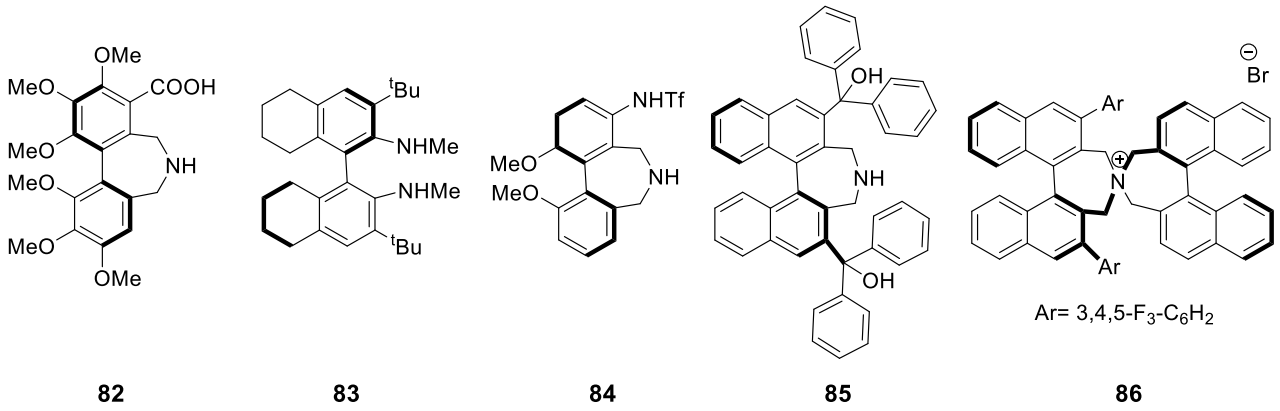


Figure 6: *E-s-trans* transition state of **79** enamine.

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**),[90] iminium (**83**),[91] or phase transfer (**86**)[92] catalysts (**Figure 7**).



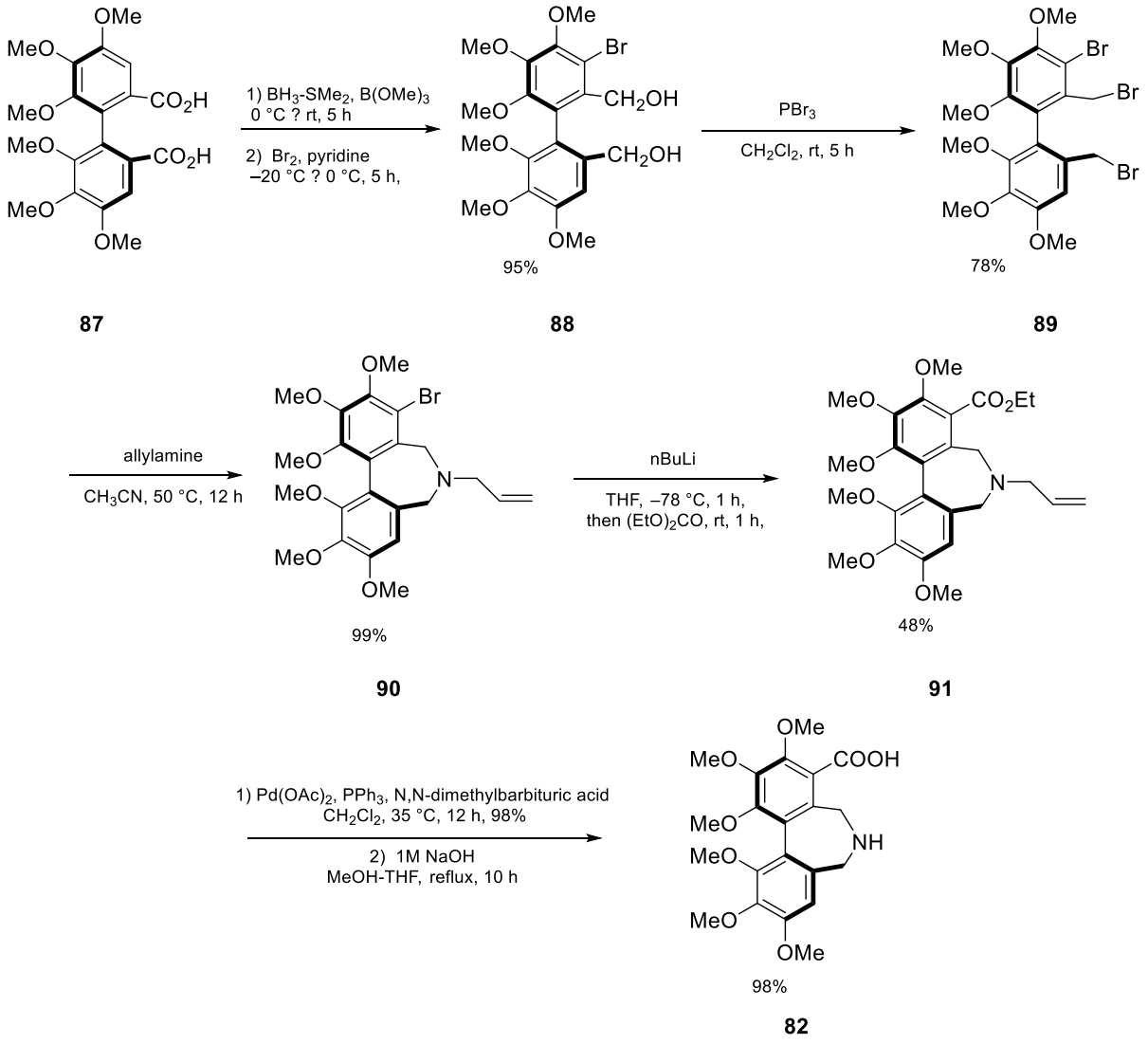
82 **83** **84** **85** **86**

Figure 7: Biphenyl and binaphthyl catalysts synthesised by Maruoka.

Maruoka relied on biaryl chiral backbones, based on their high chemical stability as well as allowing easy derivatisation.[95] Furthermore, the design of the catalyst includes different aryl pendant functionalities, which provide different electronic properties tailored for different reaction types and conditions.

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**).



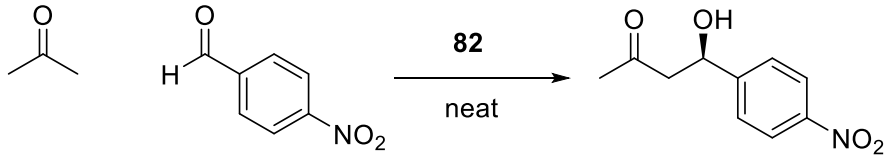
Scheme 30: Catalyst (*S*)-**82** synthesis.

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

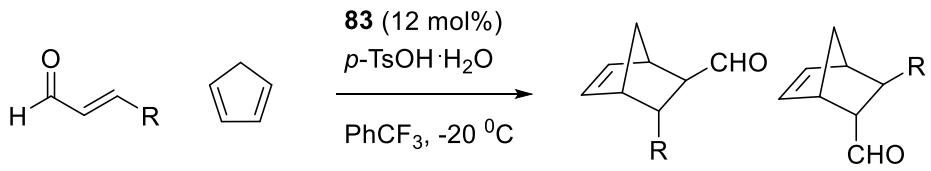


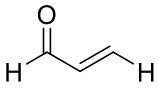
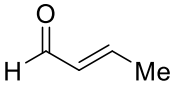
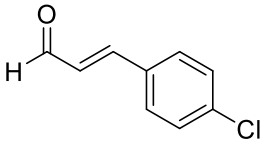
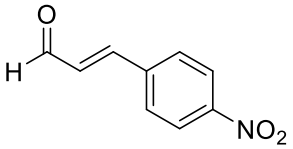
Entry	Catalyst loading (mol %)	Time (h)	Yield (%)	e.e (%)
1	1	24	90	95 (*R*)
2	0.5	44	90	96 (*R*)
3	0.1	96	91	96 (*R*)

5.2.2 Diels-Alder reaction

Using diamine catalyst **83** in an *exo*-selective Diels-Alder reaction gave a high selectivity with co-catalysts such as *p*-toluenesufonic acid. The Diels-Alder reaction, between α,β-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]

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



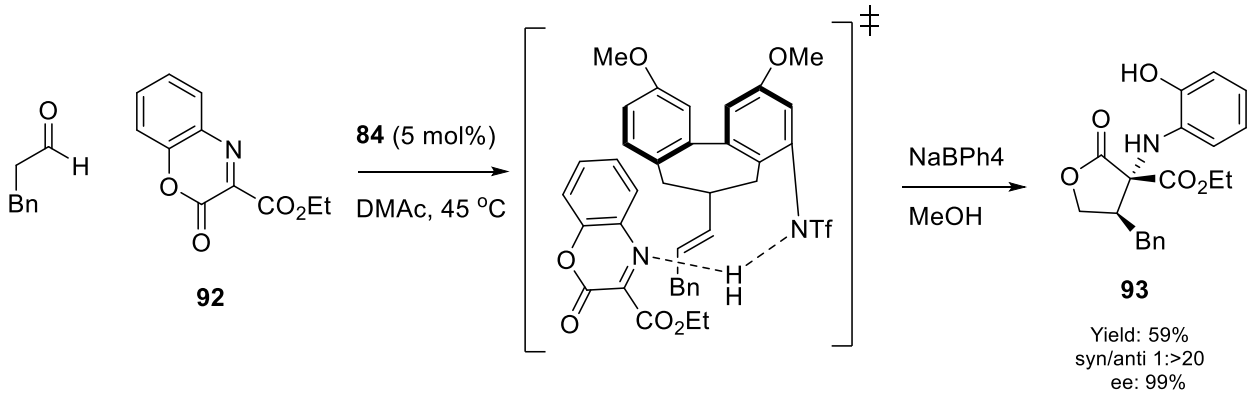
Entry	Aldehyde	Yield (%) (exo:endo)	e.e (%) (exo:endo)
1		93 (1.9:1)	86:68
2		72 (>20:1)	88 (*S*): --
3[a]		99 (7.8:1)	92:96
4		99 (7.4:1)	95:98

a) Two more equivalents added after 48 h.

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]

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]



Scheme 31: Anti-Mannich reaction using amino sulfonamide catalyst **84**.

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]

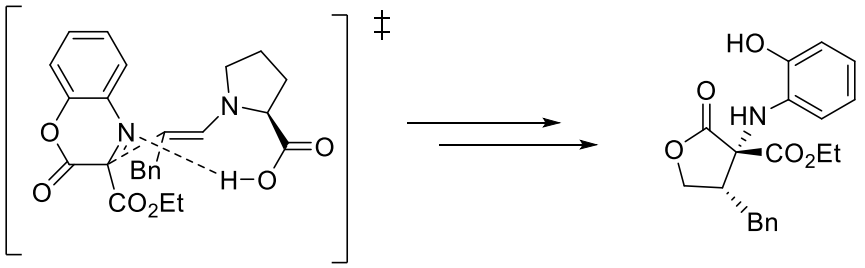
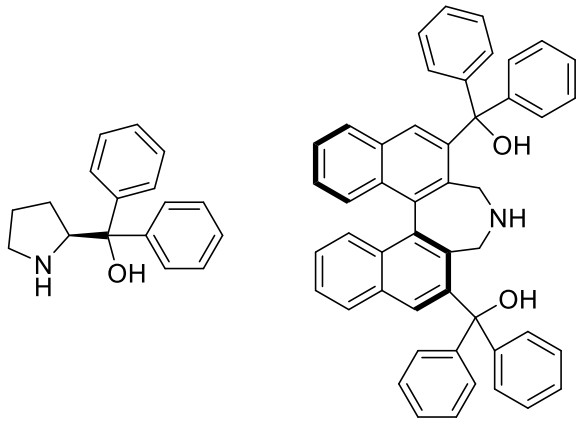


Figure 8: *S-trans* transition state to form the syn-isomer using (*L*)-prloine.

5.2.4 Hydroxyamination of aldehydes

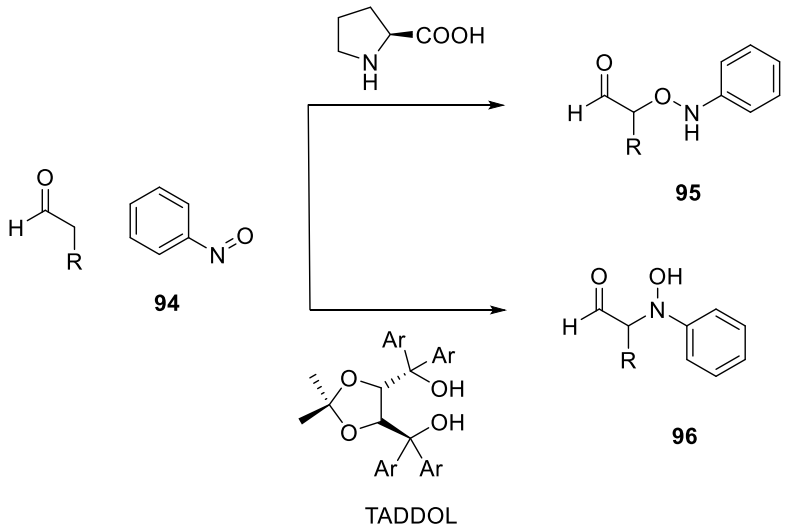
Catalyst **85** based on Jørgensen's catalyst **67** was synthesised and tested and led to the *α*-aminoxylation reactions between aldehydes and nitrosobenzene in very high diastereo- and enantioselectivities (**Figure 9**).[98]



67 **85**

Figure 9: Maruoka's version of diaryl prolinol catalyst.

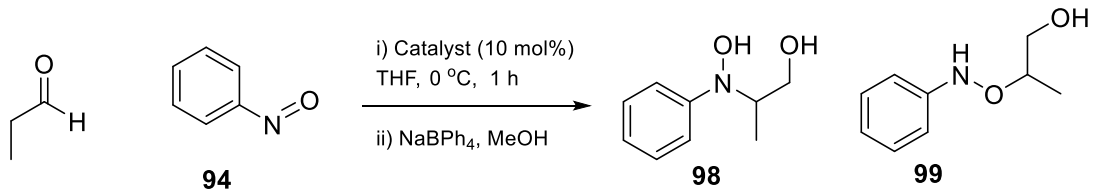
The reaction between aldehydes and nitrosobenzene **94** can produce one of two products depending on the catalyst used. An *O*-nitroso aldol product **95** can be formed using tetrazole **58**, proline and glycolic acid.[99, 100, 101] The presence of the acid enables hydrogen bonding and causes the nitrosobenzene **94** to act as an oxy-electrophile resulting in the formation of α-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**).



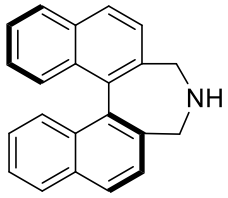
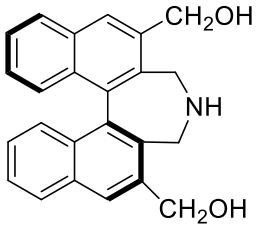
Scheme 32: *O*-nitroso **95** and *N*-nitroso **96** products.

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.



94 **98** **99**

Entry	Catalyst	Ratio 98/99	Yield (%)	e.e (%)
1	 **97**	>99/1	22	29 (*S*)
2	 **100**	>99/1	55	77 (*S*)
3	**85**	>99/1	90	99 (*S*)
4	**67**	>99/1	9	23 (*R*)

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**).

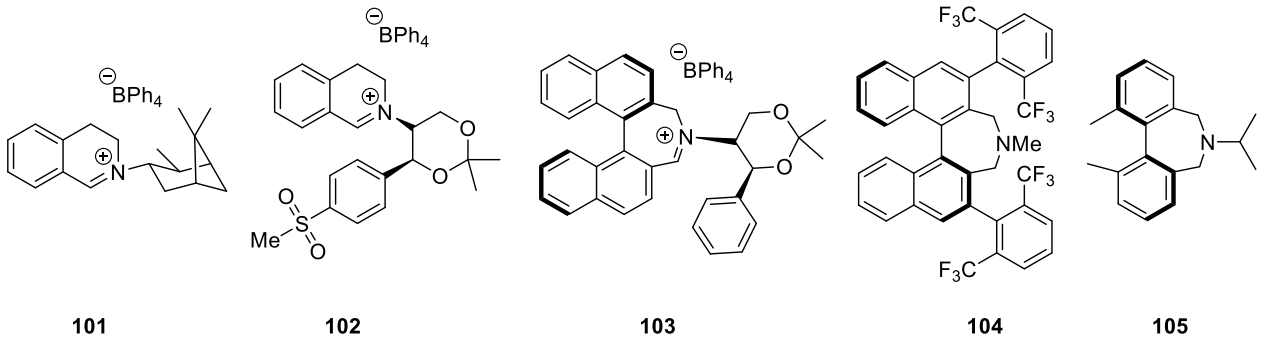
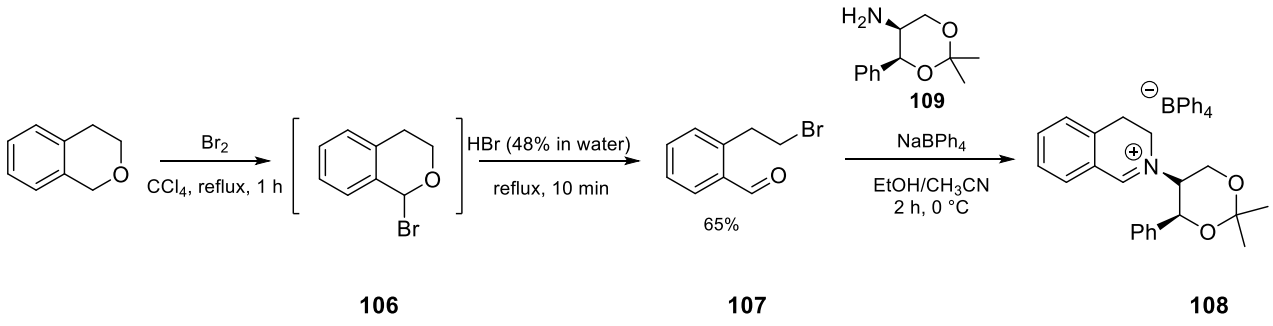


Figure 10: Epoxidation and aziridination catalysts synthesised by Page.

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.[102] 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**).

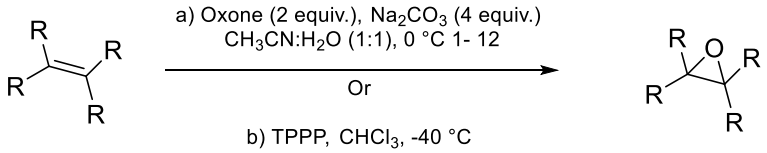


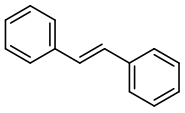
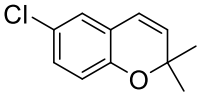
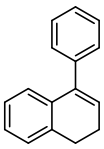
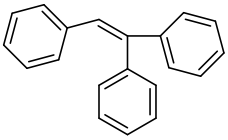
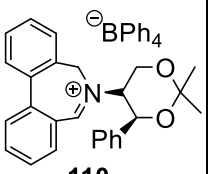
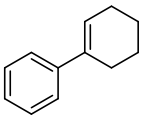
Scheme 33: Synthesis of Catalyst **108**.

In the presence of an oxidising agent such as oxone or TPPP, 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 **109** based chiral features using axially chiral biphenyl and binaphthyl backbones.[103,104,105]

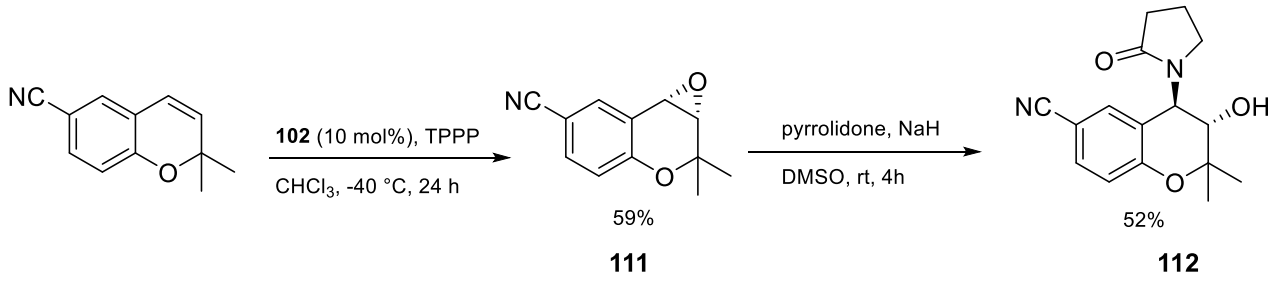
Catalyst **101**, derived from isopinocampheyl amine, gave good ee (73%) when tested with *trans*-stilbene. However, the most successful catalysts having an acetonamine moiety, such as **102**, **103**, **108** and **110**, showing increased enantioselectivity when compared with other chiral amines. Catalyst **102** afforded the highest enantioselectivities (up to 97%) when used in the oxidation of cyclic *cis*-alkenes in the presence of TPPP at low temperatures (**Table 12**).[106]

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



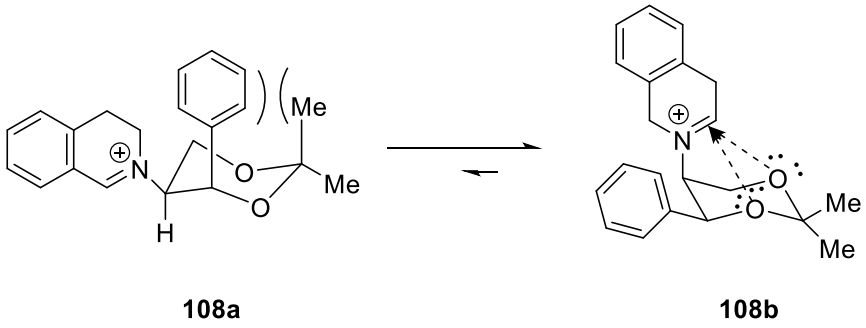
Entry	Catalyst (mol%)	Alkene	Yield (%)	e.e (%)	Major Epoxide
1[a]	**101** (10 mol%)		78	73	(+)-(1*R*,2*R*)
2[b]	**102** (10 mol%)		76	93	(-)-(1*S*,2*S*)
3[a]	**103** (5 mol%)		66	95	(+)-(1*S*,2*R*)
4[a]	**108** (5 mol%)		54	59	(-)-(*S*)
5[a]	 **110** (5 mol%)		100	60	(-)-(1*S*,2*S*)

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**).[107]



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

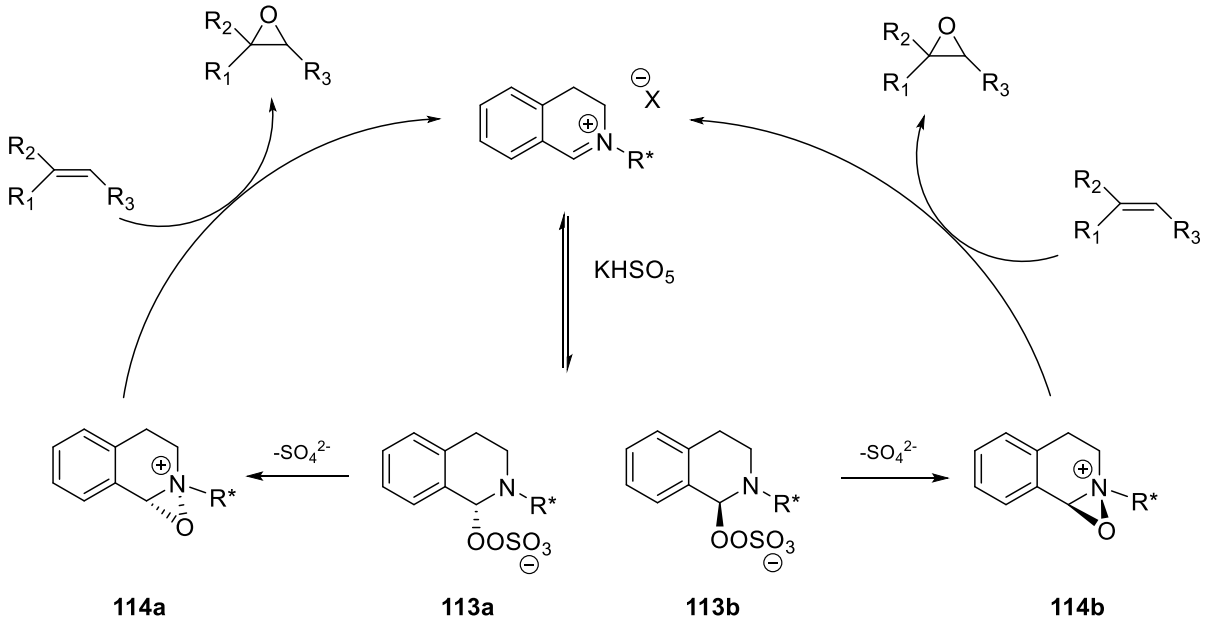
In the case of catalyst **108**, epoxidation of triphenylethylene was achieved in moderate selectivity (59%). The selectivity could be due to the chair conformation of the dioxane substituent, as observed in the solid state by using single crystal X-ray crystallography, implying that the dihydroisoquinoline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



108a **108b**

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**).



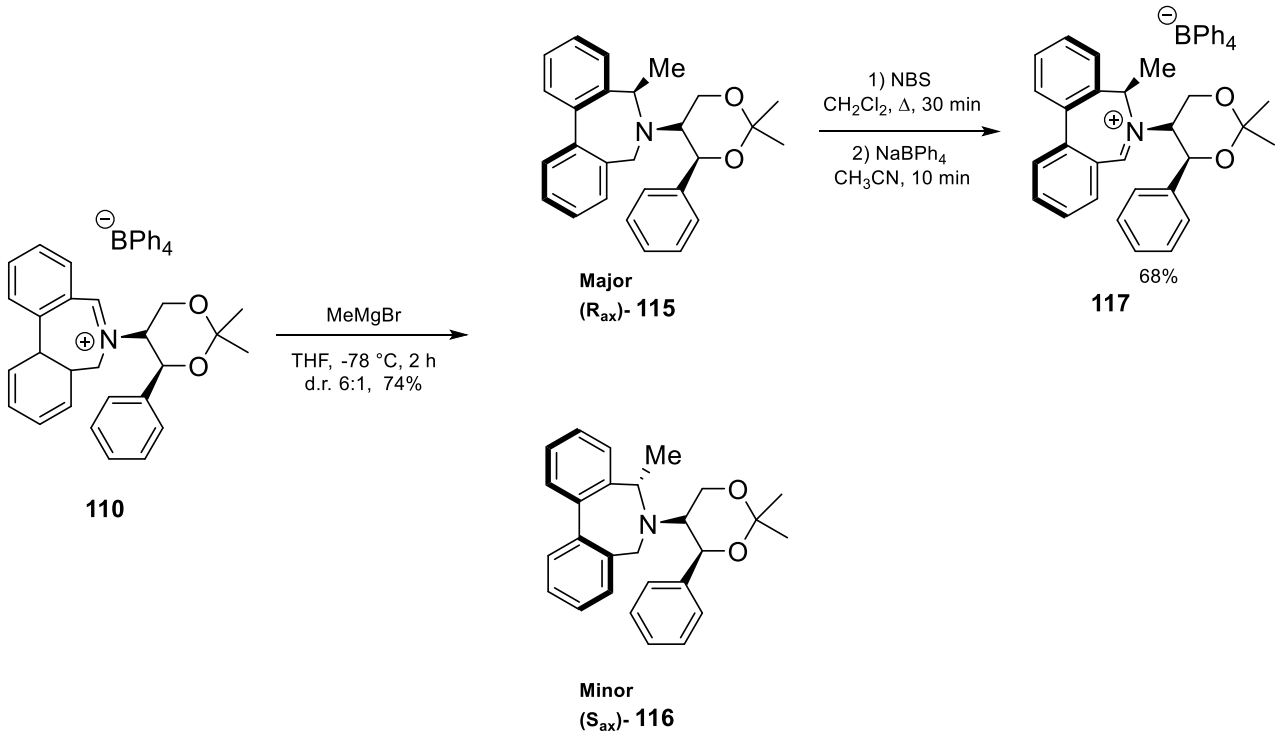
Scheme 36: Catalytic cycle using Oxone proposed by Page in 2001.

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 ^{1}H 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}

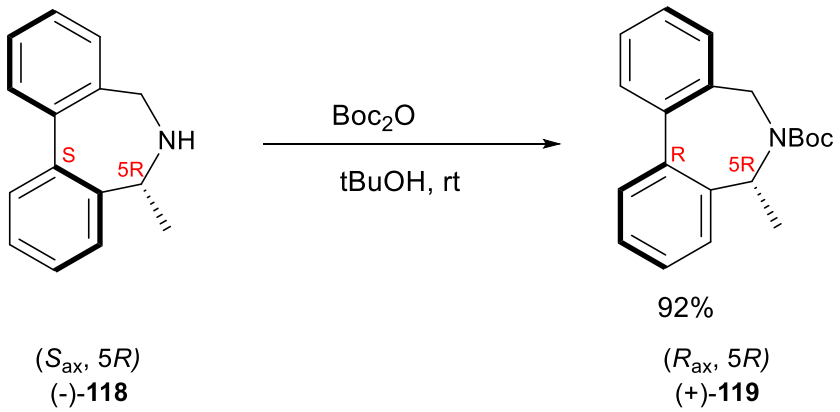
conformation (89:11) was favoured for the biphenyl species due to reduction of the interaction with the nitrogen substituent. Mixtures of two diastereoisomers were formed when Grignard reagents (methyl, isopropyl, phenyl, and benzyl) were added to iminium species **110** at −78 °C. For example, when 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**.

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 δ_{Me} 0.68 ppm and **116** at δ_{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})

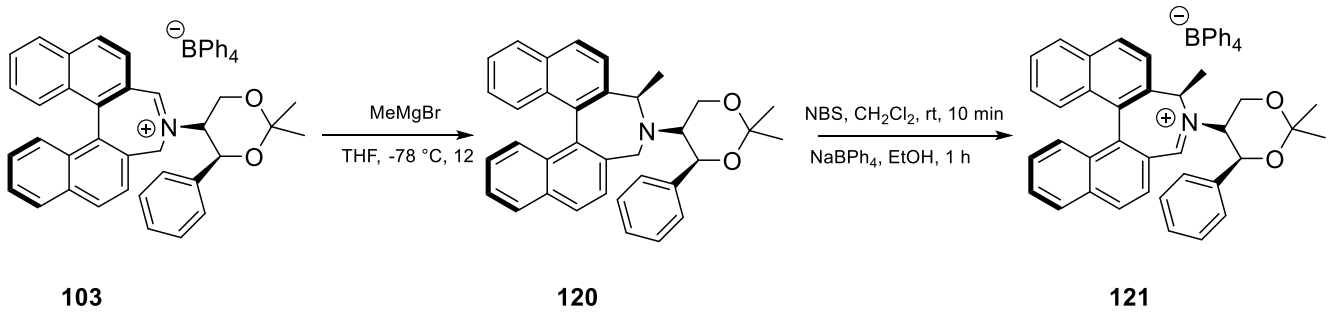
biaryl backbone and the methyl group in position **5** is pseudo-equatorial. However, when azepine **118** is converted into *N*-Boc-azepine **119**, the addition of a bulky *N*-Boc group forces a switch in the axial chirality of the backbone, and the α-substituent orientation switches to a pseudo-axial orientation (**Scheme 38**).[110]



Scheme 38: Addition of the Boc group causes a swich to the biphenyl backbone chirality.

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*).

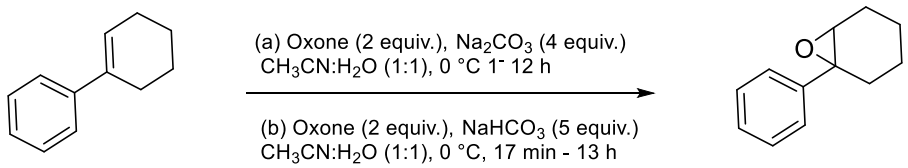
In the case of the binaphthyl compound **103**, the Grignard reagents were introduced completely diastereoselectively (**Scheme 39**).



Scheme 39: Diastereoselective addition of Grignard reagent diastereoselective onto iminium salt **103**.

In order to prepare the catalysts, (R_{ax},*R*,*S*,*S*)-**115** and (*Rax*,*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 13: Binaphthyl and biphenyl-based catalyst screening.



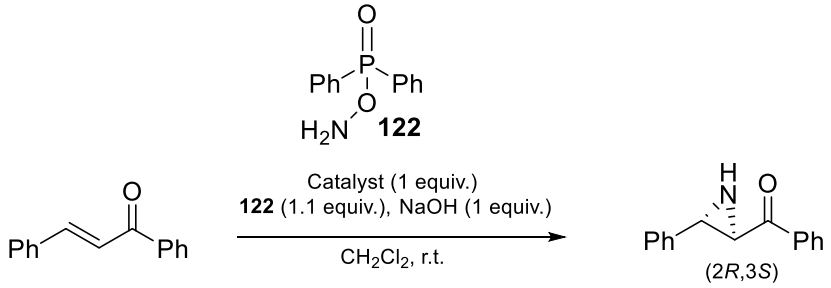
Entry	Catalyst	Conversion (%)	e.e (%)	Major Epoxide
1[a]	**110**	100	60	(-)-(1S,2S)
2[a]	**117**	100	82	(-)-(1S,2S)
3[b]	**103**	99	91	(-)-(1S,2S)
4[b]	**121**	99	94	(-)-(1S,2S)

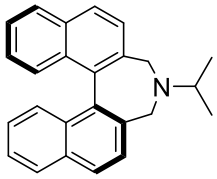
5.3.2 Aziridination catalysts

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.

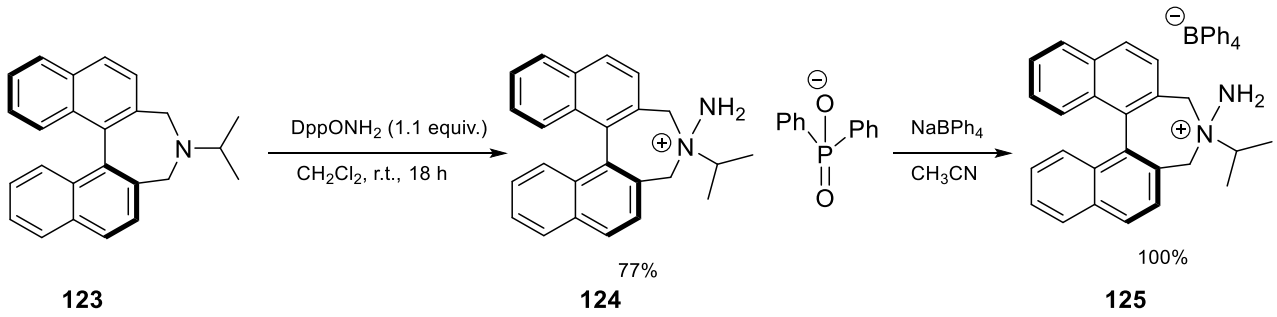
Using *O*-(diphenylphosphinyl)-hydroxylamine ($DppONH_2$) **122** as the nitrogen transferring reagent and NaOH as the base in dichloromethane was found to be the optimal conditions. Using 3,3'-disubstituted catalyst **104**, a moderate 43% ee with a very low 10% conversion was observed, maybe due to steric hindrance. In addition, *N*-isopropyl azepine **105** gave higher conversion (70%) and a lower 35% ee (**Table 14**).

Table 14: Aziridination conditions used by Page.



Entry	Catalyst	Time (h)	Conversion (%)	e.e (%)
1	**105**	48	70	35
2	**104**	48	10	43
3	 **123**	24	38	34

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**).



Scheme 40: Synthesis of hydrazinium salts **124** and **125**.

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**).

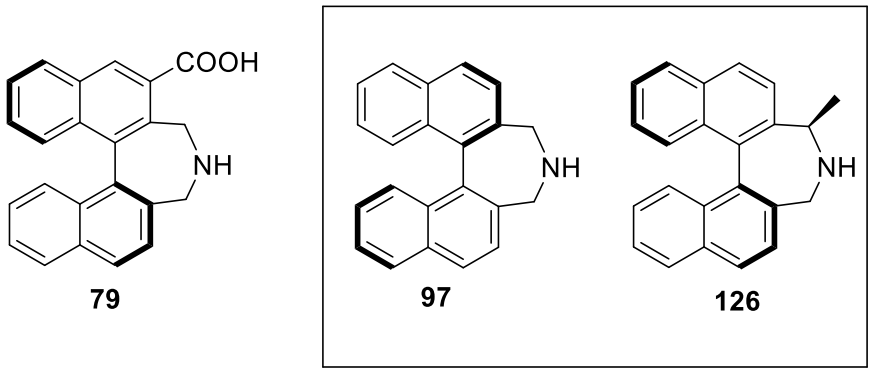
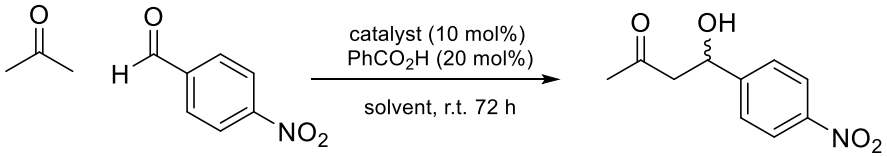


Figure 11: Page's group aminocatalysts **97** and **126**.

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 ^{o}C, the (*S*)-enantiomer was obtained in 30% ee (**Table 15**).

Table 15: Catalyst **97** and **126** screening on aldol reaction.



Entry	Catalyst	Temperature	Solvent	conv. (%)	e.e (%)
1	**97**	r.t.	H_2O	50	16 (*R*)
2	**97**	r.t.	neat	100	-
3	**97**	r.t.	THF	100	3 (*S*)
4	**97**	r.t.	DMF	<5	-
5	**97**	r.t.	CH_3CN	100	2 (*S*)
6	**97**	r.t.	DMSO	<5	3 (*S*)
7	**97**	r.t.	Et_2O	100	4 (*S*)
8	**97**	r.t.	MeOH	30	2 (*S*)
9	**97**	r.t.	EtOH	50	3 (*S*)
10	**97**	r.t.	iPrOH	40	3 (*S*)
11	**126**	r.t.	H_2O	10	16 (*R*)
12	**126**	r.t.	CH_3CN	65	6 (*S*)
13	**126**	0 ^oC	CH_3CN	25	30 (*S*)
14	**126**	r.t.	THF	70	7 (*S*)
15	**126**	0 ^oC	THF	15	5 (*S*)
16	**126**	r.t.	Et_2O	50	6 (*S*)
17	**126**	0 ^oC	Et_2O	15	11 (*S*)
18	**126**	r.t.	Toluene	75	5 (*S*)
19	**126**	0 ^oC	Toluene	15	5 (*S*)

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**,[111] diarylprolinol silyl ether **68**,[112] 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**).

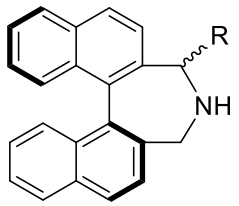


Figure 12: The project catalysts design

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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 mannich 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**).

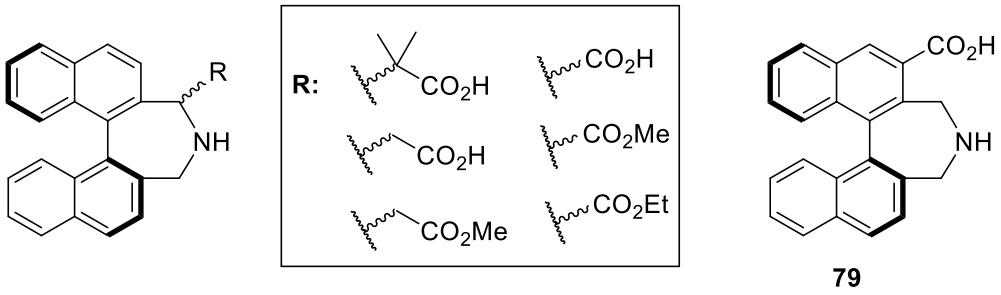
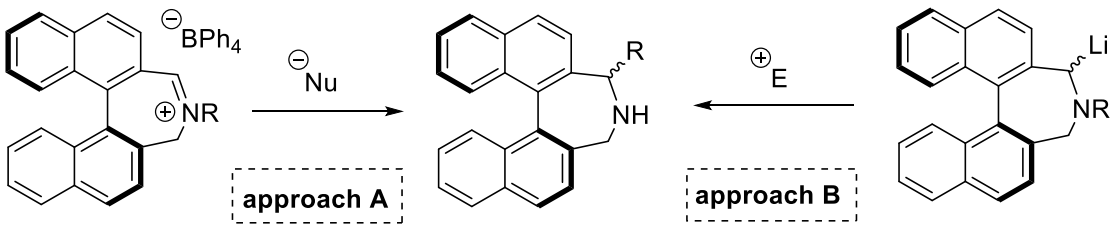


Figure 13: The targeted catalysts.

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] Wallace[6] and Superchi[1].

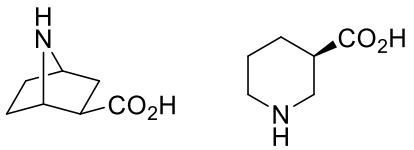


Scheme 41: Approaches to α-functionalized catalysts.

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 α is been activated to be deprotonated (**Scheme 41**).

2.0 Synthesis of the β-amino acid catalyst

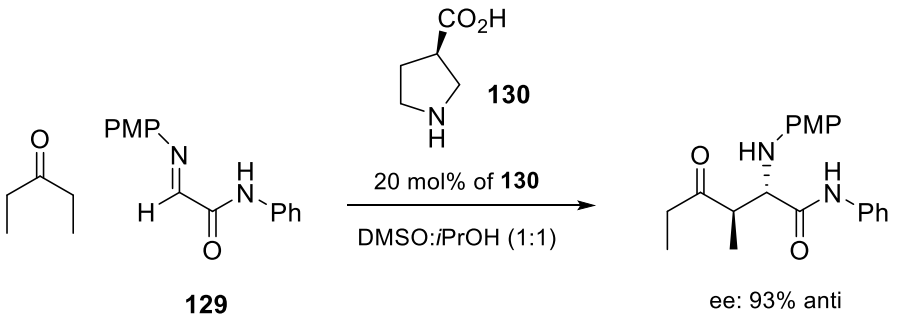
Our first aim was to synthesise a catalyst analogous to proline. In addition, introduction of a carboxylic acid group was also considered. A number of β-amino acid proline analogues have been studied and their application tested in aldol reaction such as **127**[7] and Mannich reaction such as **128**[8]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



127 **128**

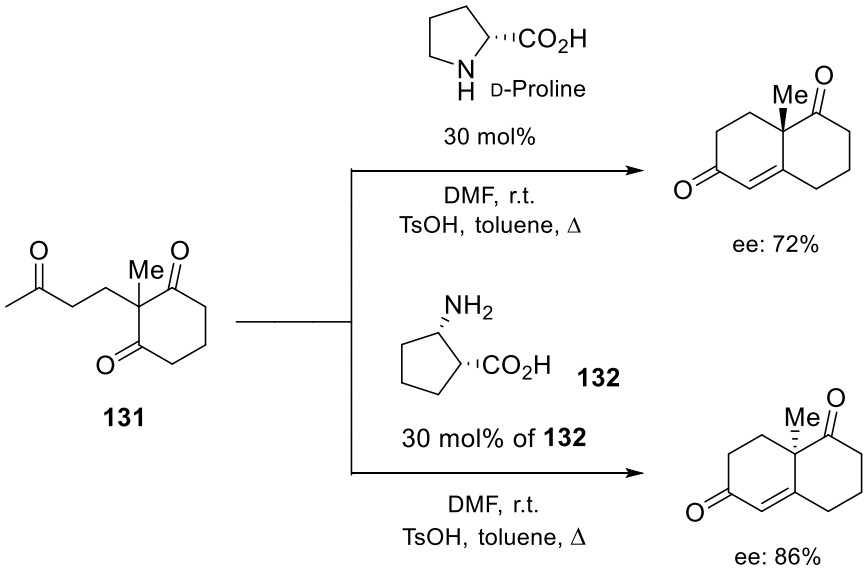
Figure 14: Example of catalysts tested in aldol and mannich reactions.

In more detail, comparing L-proline with these catalysts in the Mannich reaction between 3-pentanone and α-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].



Scheme 42: *anti*-Mannich reaction catalysed by **130**.

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**)[8].

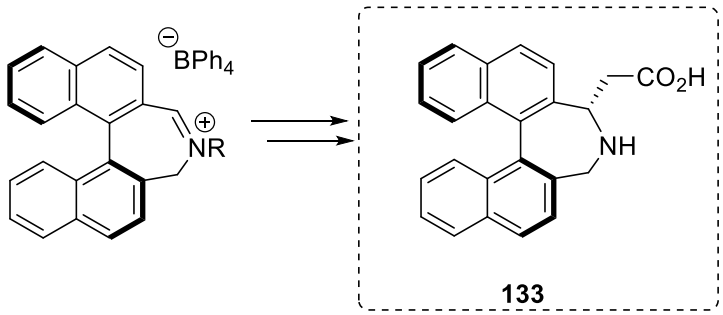


Scheme 43: Hajos-Parrish-Eder-Sauer-Wiechert reaction.

Therefore, chiral β-amino acids seems very interesting as a catalytic design.

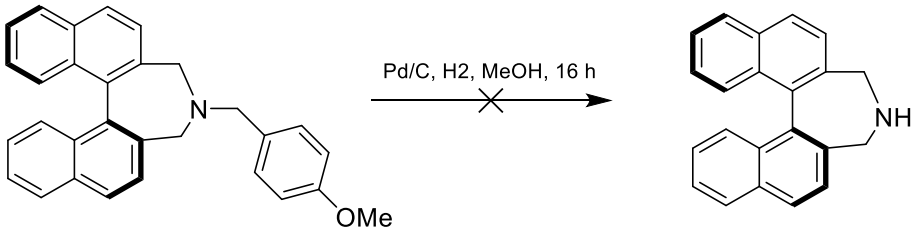
2.1 Initial retrosynthetic approaches to the β-amino acid catalyst

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 introduced suitable nucleophilic reagents selectively following by conversion into the corresponding carboxylic acid **133** (**Scheme 44**).



Scheme 44: The targeted β-amino acid catalyst.

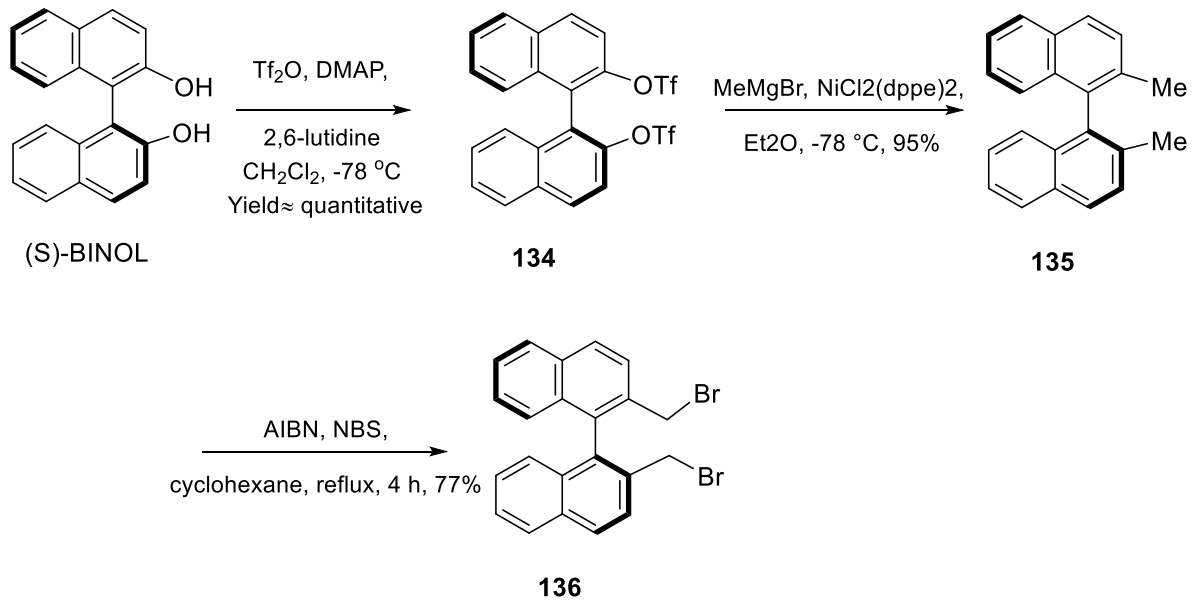
To allow iminium salt formation, a nitrogen protectiong group is essential, and in addition it is a fundamental synthetic step for the catalyst that can be removed easily. Furthermore, basic and nucleophilic conditions are important as is tolerance of oxidation. Previously in the group the *p*-methoxybenzyl 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 of Deprotection of the *p*-methoxybenzyl group.

3.0 Azepine synthesis

We Started from enantipure *(S)*-BINOL to synthesise a range of binaphthyl catalysts.[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) ($Ni(dppe)_2Cl_2$) 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**).[2]

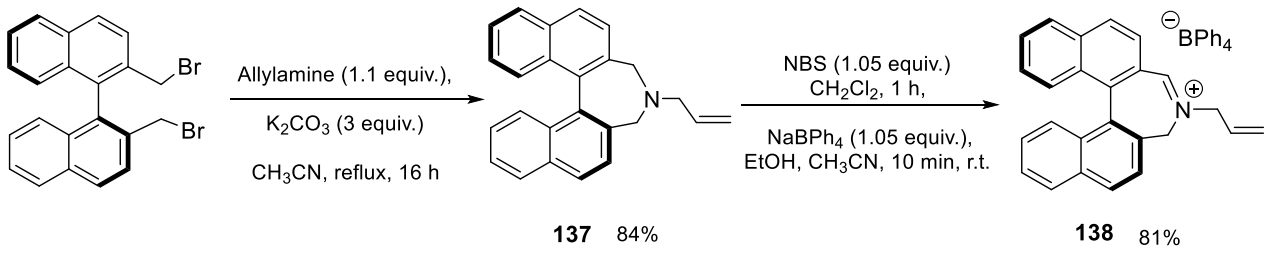


Scheme 46: Dibromobinaphthyl **136** synthesis.

The first three steps did not required 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.[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**).

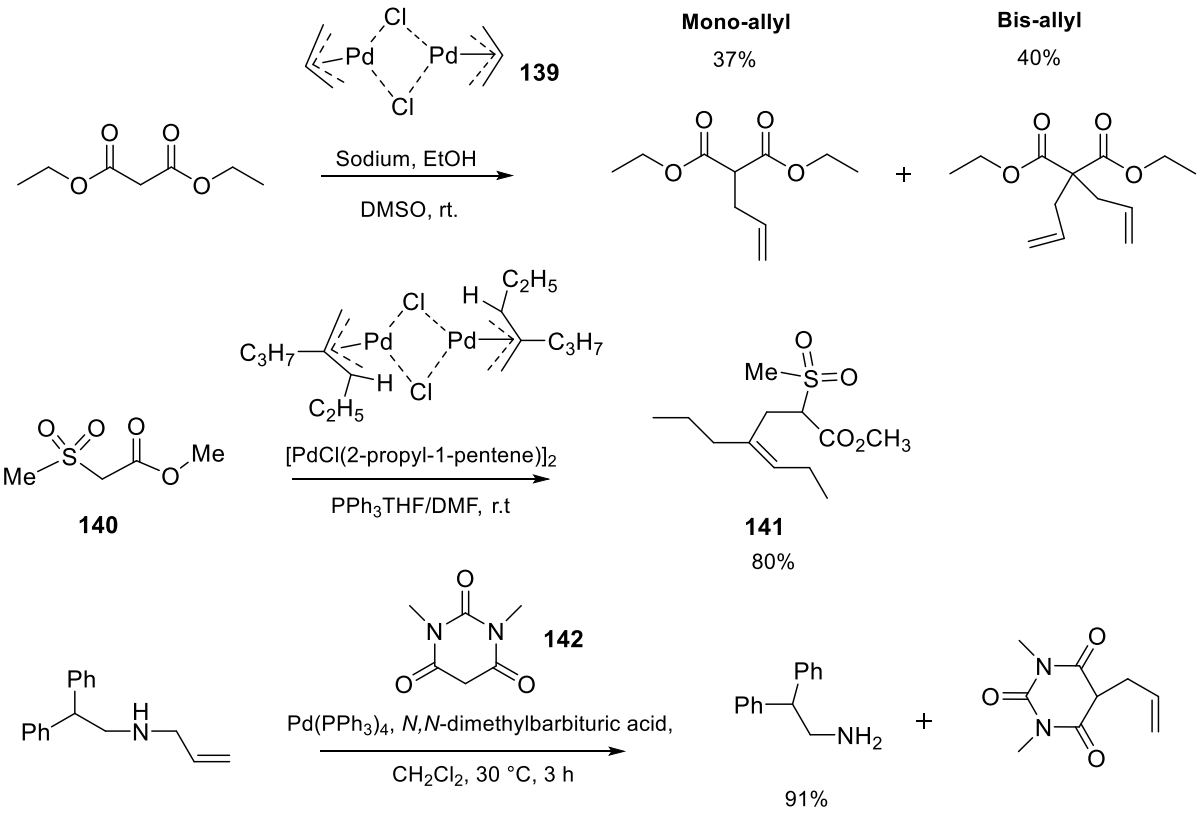


137 84% **138** 81%

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

4. Allyl protecting group

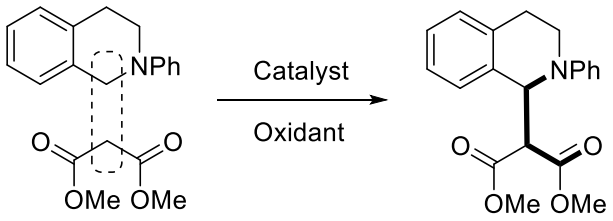
Knowing the Page's group previous difficulty in removing the PMB group, we focused on the allyl group, which is used widely to protect amine and alcohol moieties, and was also used by Maruoka.[11] Tsuji's original procedure used a palladium mediated allylation reaction by adding diethyl malonate to the ŋ3-diallyl dichlorodipalladium complex **139**. This resulted in two products, mono- and bis-allyl.[13] 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 ŋ3 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.[14] To remove the allyl protection group, *N,N*-Dimethylbarbituric acid **142** was used as a nucleophilic allyl scavenger (**Scheme 48**).[15]



Scheme 48: Addition and removal of the allyl froup based on the Tsuji-Trost reaction.

4.1 Oxidative cross coupling reactions

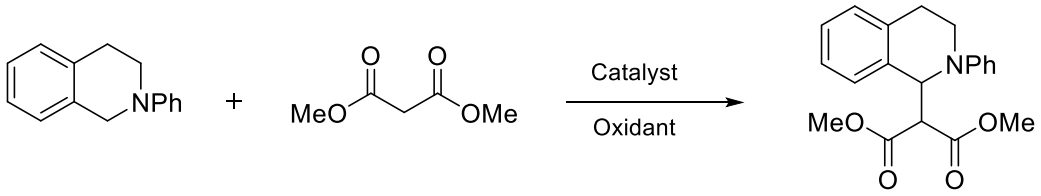
Cross dehydrogenative coupling (CDC) reactions can take place by conversion of one reaction partner into an electrophile through *in situ* oxidization as an electron-rich coupling partner attacks. In this type of reaction, a high tolerance of function groups is involved. The reaction is capable of functionalizing sp3 C-H bonds with sp, sp2 and sp3 hybridized starting materials by using catalysts based on copper or iron salts (**Scheme 49**).[16]



Scheme 49: Oxidative CDC coupling.[20]

There are many reports of oxidations of C-H bonds close to nitrogen atoms in tertiary amines.[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**).[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**).[19]

Table 16: CDC reaction of tetrahydroisoquinoline **143** and dimethyl malonate.

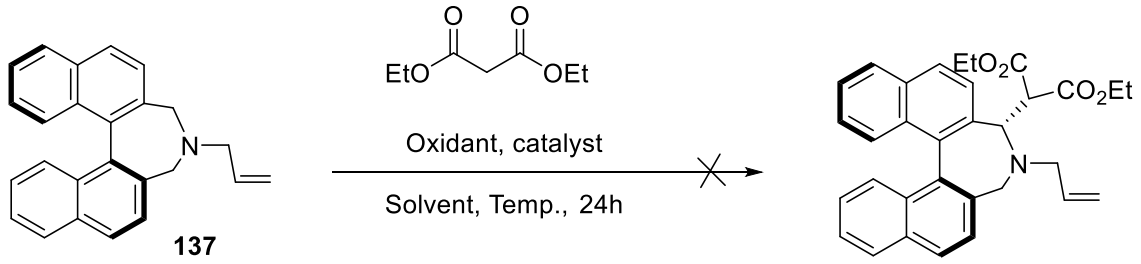


143 **144**

Entry	Catalyst	Oxidant	Temp (°C)	Time (h)	Yield (%)
1	5 mol% CuBr	TBHP (1 equiv.)	r.t.	16	90
2	10 mol% I_2	H_2O_2 (2 equiv.)	50	12	73

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**).

Table 17: Allyl azepine **137** oxidative coupling reaction with diethyl malonate.

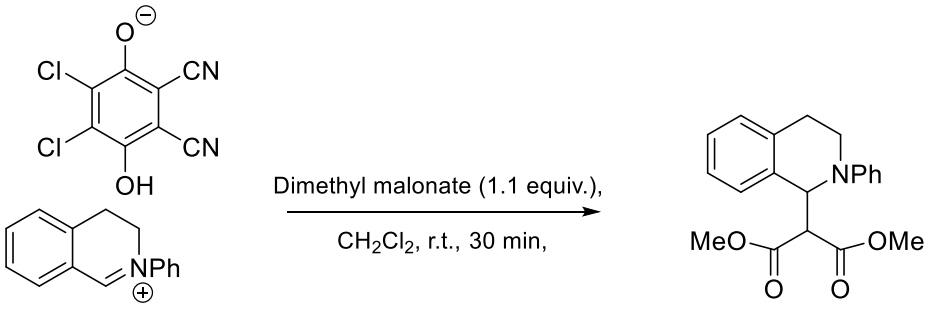


Entry	Oxidant	Catalyst	Solvent	Temp. (°C)	Yield (%)
1 [a]	TBHP	CuBr	-	r.t.	S.M.
2 [a]	TBHP	CuBr	CH_2Cl_2	r.t.	S.M.
3 [b]	H_2O_2	I_2	-	50	S.M.
4 [b]	H_2O_2	I_2	CH_2Cl_2	50	S.M.
5 [b]	H_2O_2	I_2	CH_2Cl_2	r.t.	S.M.

[a] Diethyl malonate (except when used in excess; 3 equiv.), TBHP (1 equiv.), CuBr (5 mol%);
[b] Diethyl malonate (except when used in excess; 2 equiv.), H2O2 (2 equiv.), I2 (10 mol%)

From a mechanistic view, generation of an electrophilic iminium ion is essential inder 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 α-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]



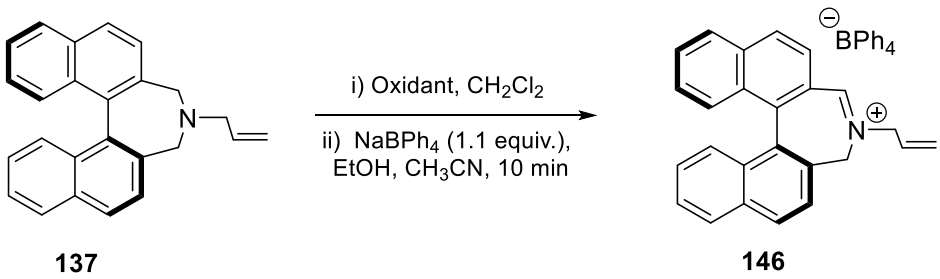
145 **144** 73%

Scheme 50: DDQ iminium salt **145** after isolation and continuo the coupling reaction.

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 ^{o}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.**

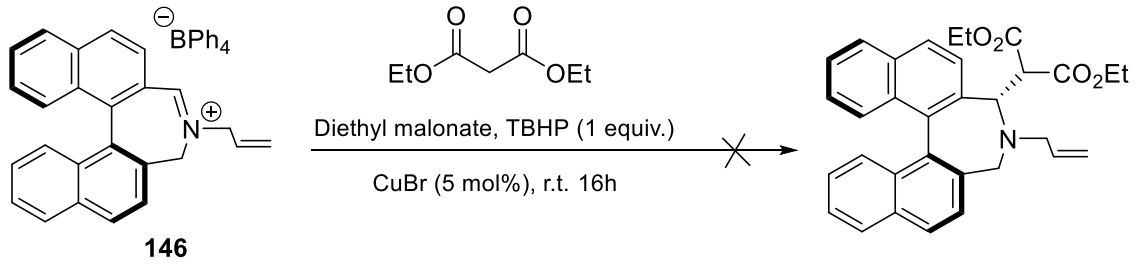


137 **146**

Entry	Reagent	Temp (^{o}C)	Time (h)	Yield (%)
1	NBS (1.05 equiv.)	r.t.	1	51
2	NBS (1.05 equiv.)	0	2	79
3	DDQ (2 equiv.)	r.t.	1	43

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.

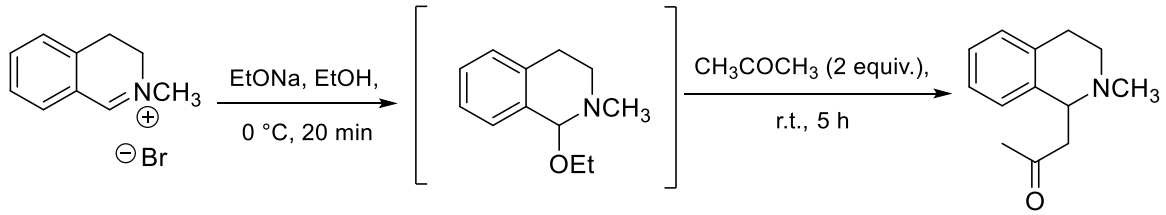


146

Entry	Reagent	Additive	Solvent	Yield (%)
1	CuBr	TBHP	Diethyl malonate	-
2	CuBr	-	Diethyl malonate	-
3	CuBr	-	Ch_2Cl_2	-

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]

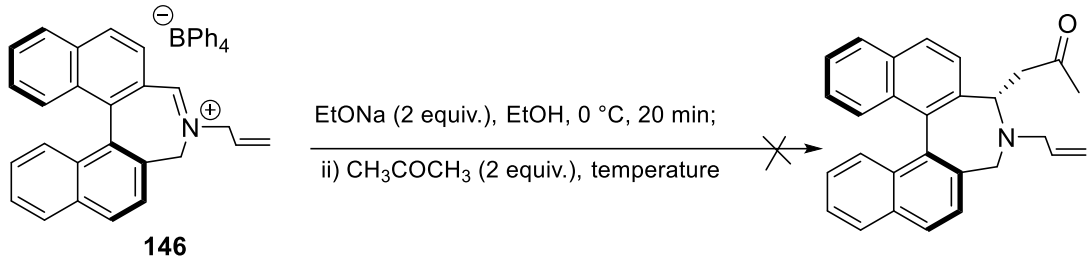


147 **148** **149** 97%

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.

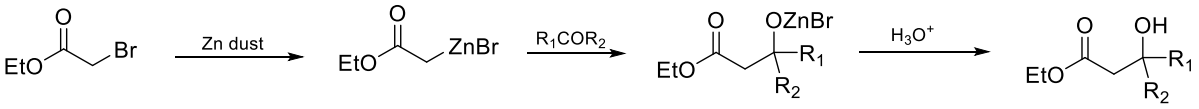


146

Entry	Reagent	Temp (°C)	Time (h)	Yield (%)
1	Acetone	0	16	-
2	Acetone	0 to r.t.	16	-
3	Acetone	0 to 40	5	-

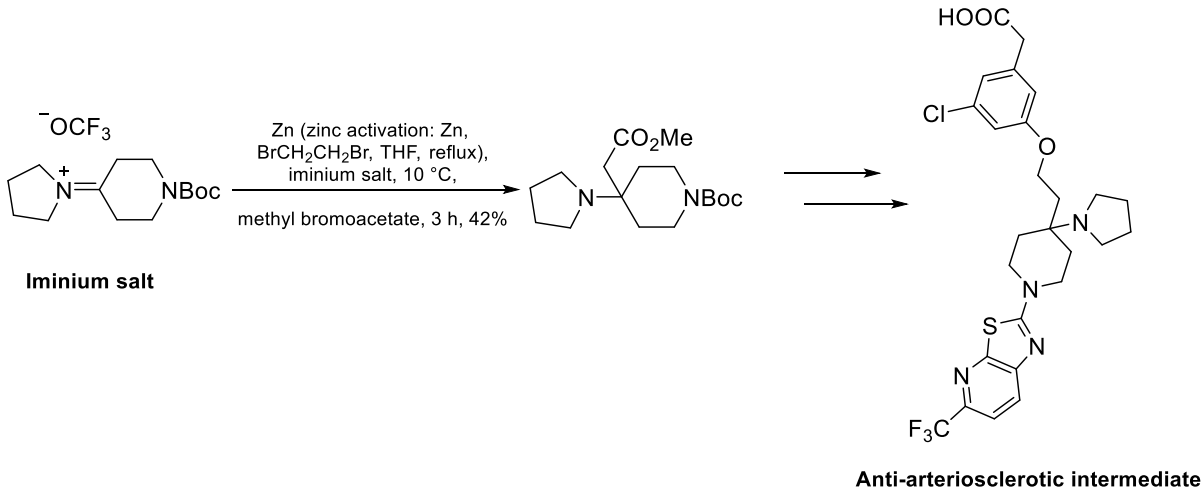
4.2 Reformatsky reaction

The Reformatsky reaction uses organo-zinc reagents which can be formed from oxidative addition of zinc into carbon-halide bonds of α-halogen esters, [22] which when added to carbonyl containing compounds result in β-hydroxyester compounds (**Scheme 52**).



Scheme 52: Traditional Reformatsky reaction.

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.[23] In addition, addition of α-haloesters to iminium salts were reported in alarge-scale in synthesis of an anti-arteriosclerotic intermediate (**Scheme 53**).[24]



Iminium salt

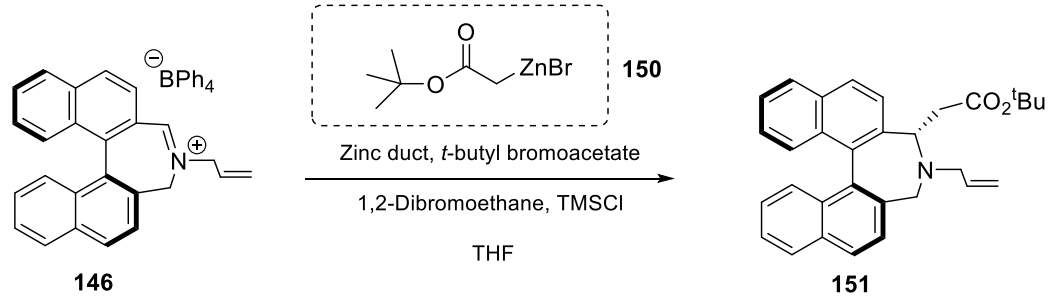
Anti-arteriosclerotic intermediate

Scheme 53: Synthesis of **Anti-arteriosclerotic intermediate involving Reformatsky reaction.**

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 ^{o}C for 12 h, but unfortunately, due to instability of the Reformtsky reagent **150** or iminium salt **146** in higher temperatures, product **151 was** not obtained (**Entry 4**), (**Table 21**).

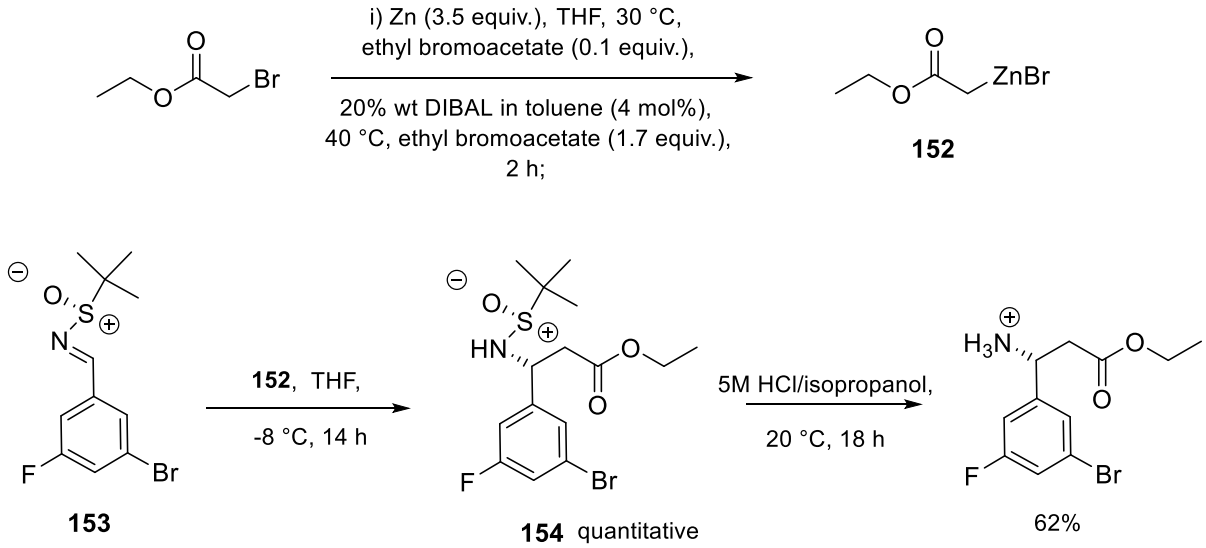
Table 21: Reformatsky reaction with allyl iminium salt **146**.



146 **151**

Entry	*t*-butyl bromoacetate	Zinc Dust	1,2-Dibromoethane	TMSCl	Temp (°C)	Time (h)	Yield (%)
1	5 equiv	6 equiv	5 mol%	4 mol%	25 to 30	12	trace
2	10 equiv	10 equiv	10 mol%	10 mol%	25 to 30	24	17
3	10 equiv	10 equiv	1 equiv	1 equiv	25 to 30	48	24
4	5 equiv	6 equiv	10 mol%	10 mol%	65	12	-

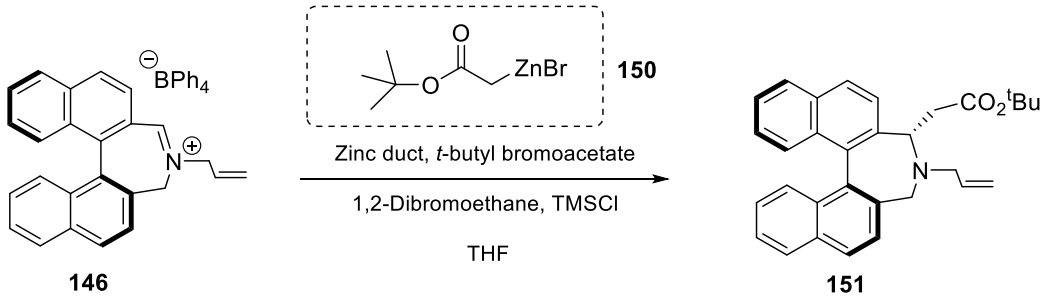
The iminium salt **146** was instable and therefore, a procedure using chiral *N*-sulfinyl imine **153** which undergoes Reformatsky reactions at low temperature, was investigated. The corresponding ester **154** was formed in quantitative yield using a novel zinc activation method using DIBAL, which 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 ^{o}C, which gave a higher yield of 43% (**Entry 2**). In addition, the iminium salt **146** was added to the activated zinc at -78 ^{o}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**).

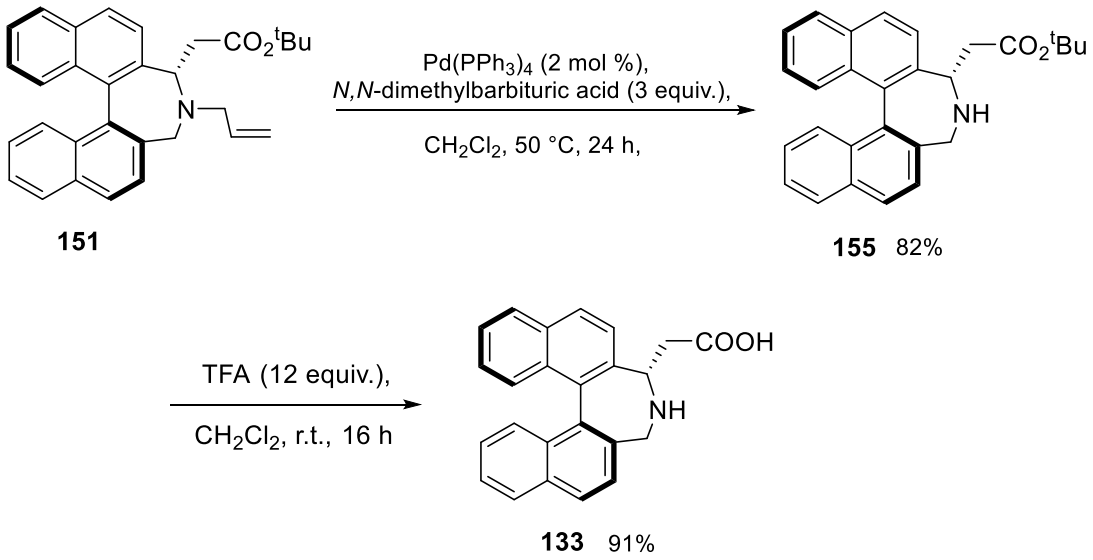
Table 22: Low temperature addition of **150**.



146 **151**

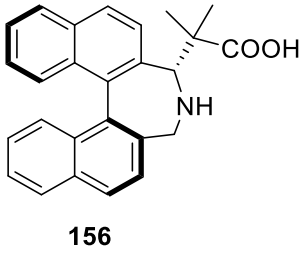
Entry	*t*-butyl bromoacetate	Zinc Dust	Additive	Additive Temp.	Temp (°C)	Time (h)	Yield (%)
1	1.7 equiv.	3.5 equiv.	DIBAL (4 mol%)	40	-78 to r.t.	12	25
2	10 equiv	10 equiv	TMSCl (1 equiv.)	65	0 to r.t.	48	43
3	10 equiv	10 equiv	TMSCl (1 equiv.)	65	-78 to r.t.	48	68

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.

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**).

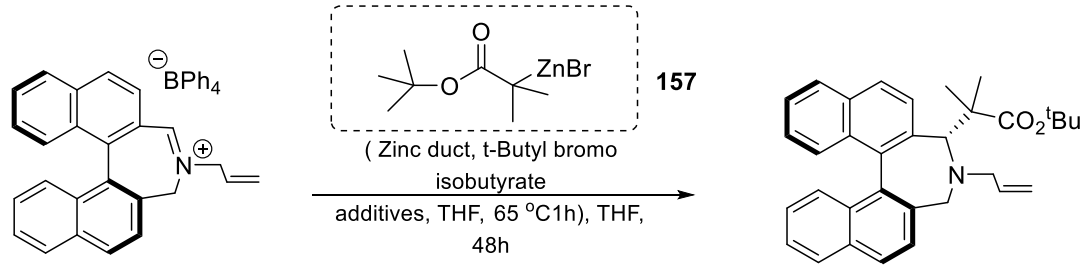


156

Figure 14: Congested sterically ß-amino acid **156**.

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 ^{o}C gave better yields of product **158,** isolated in 52% and 74% respectively (**Entry 2 and 3**), (**Table 23**).

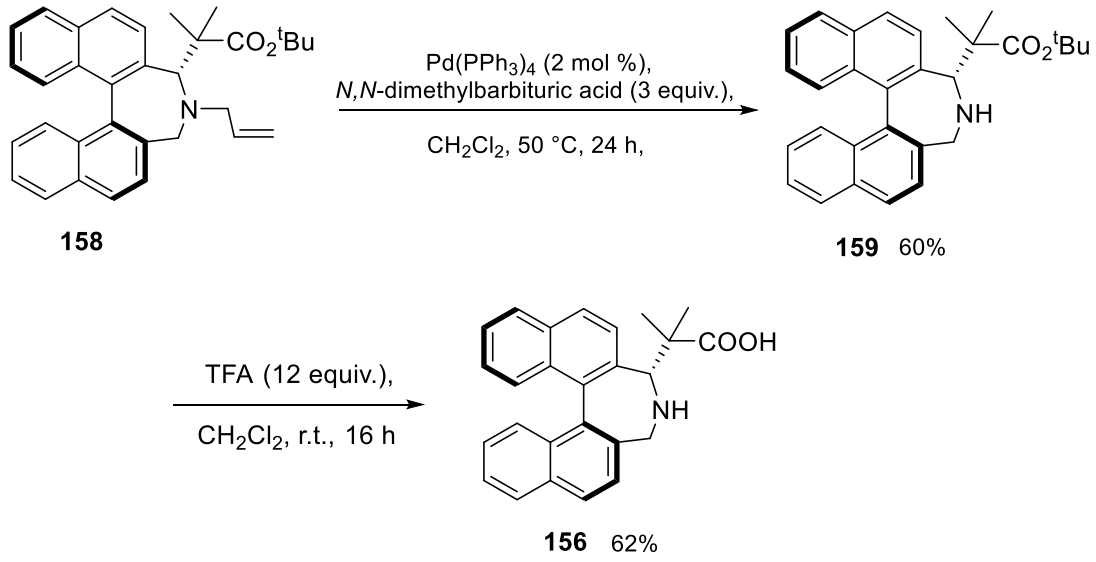
Table 23: Reformatsky reaction with ***t*-butyl bromo isobutyrate.**



146 **158**

Entry	*t-Butyl bromo isobutyrate*	Zinc Dust	1,2-Dibromoethane	TMSCl	Temp (°C)	Yield (%)
1	5 equiv	10 equiv	1 equiv.	1 equiv.	25 to 30	47
2	15 equiv	15 equiv	-	1 equiv	0 to r.t.	52
3	10 equiv	10 equiv	-	1 equiv	-78 to r.t.	74

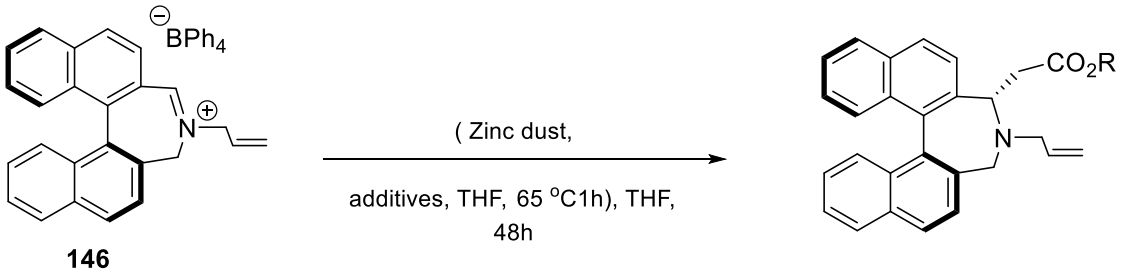
After we had **158** in hand, deallylation under palladium-catalysed conditions gave product **159** in 60% yield, and after the saponification step using TFA, product **156** was obtained in a moderate yield of 62% (**Scheme 56**).



Scheme 56: Tert-butyl and allyl group removal.

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**).

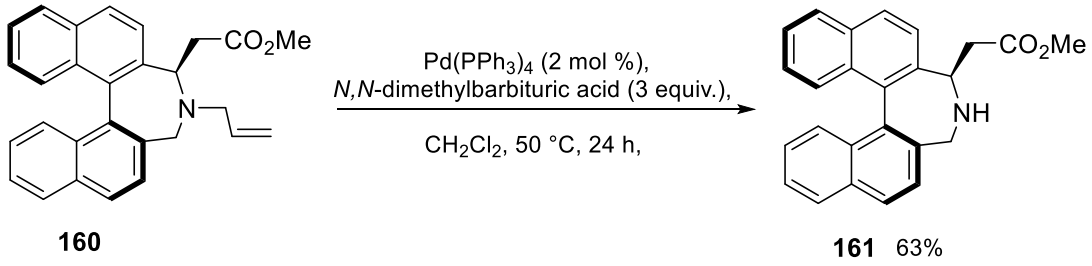
Table 24: Reformatsky reaction to form β–esters.



Entry	Reagent (10 equiv.) (R)	Zinc Dust	TMSCl	Temp (°C)	Yield (%)
1	Methyl chloroacetate	10 equiv	1 equiv	-78 to r.t.	79%
2	Ethyl chloroacetate	10 equiv	1 equiv	-78 to r.t.	S.T.

To remove the allyl group, **160** was treated with palladium catalyst to give the β-methyl ester catalyst **161** in 63% yield (**Scheme 57**).

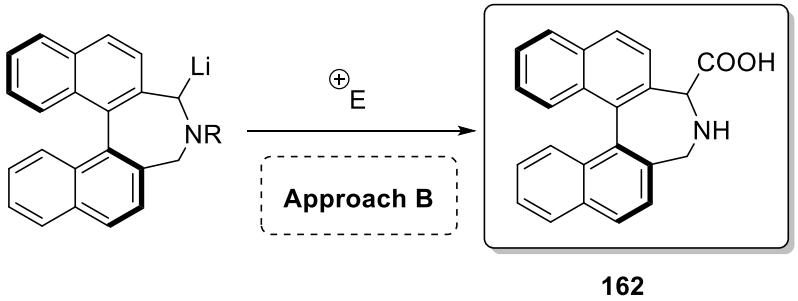
Scheme 57: Removal of allyl group.



160 **161** 63%

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**).



162

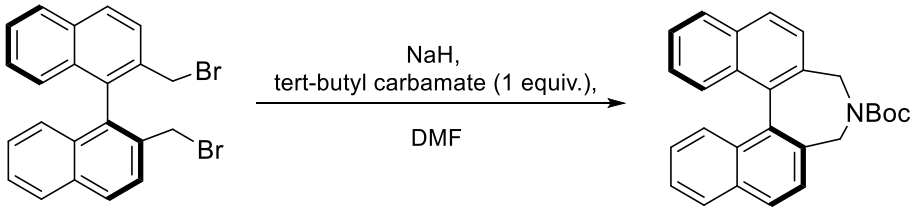
Scheme 58 : Approach B to the synthesis of the α-amino acid catalyst.

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.[26] 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**).[27] 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 ^{o}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

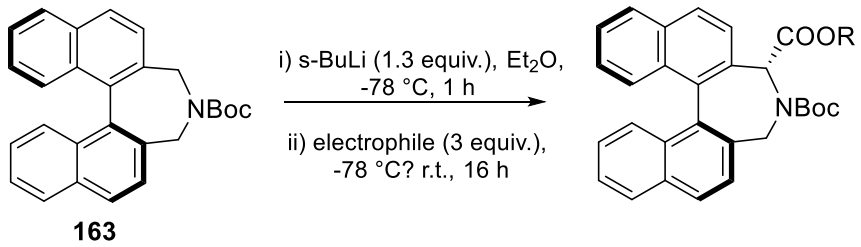


136 **163**

Entry	NaH (equiv.)	Time (d)	Temp (^{o}C)	Yield (%)
1	2.1	4	0 to r.t.	54
2	3	4	0 to r.t.	65
3	4	4	0 to r.t.	87
4	4	1	0 to 50	31

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 ^{o}C with *sec*-BuLi followed by alkyl chloroformate addition which was carried out under Blakemore's conditions gave good results.[28] 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**).

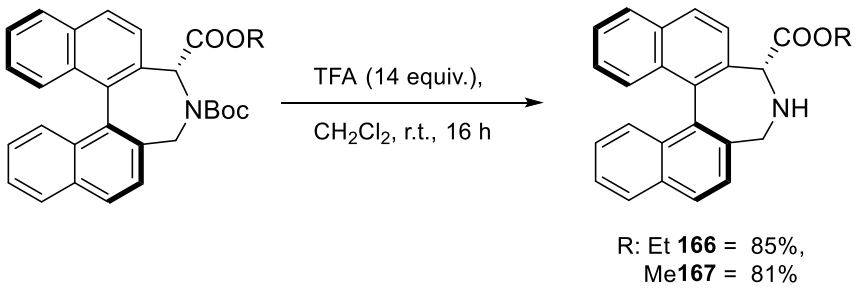
Table 26: Deprotonation of **163** and electrophile addition.



163

Entry	Electrophile	Yield (%)	Product
1	Ethyl chloroformate	70	**164**
2	Methyl chloroformate	80	**165**
3	di-*tert*-butyl carbonate	-	-

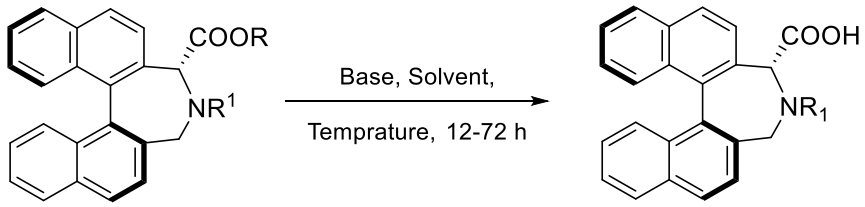
Only starting material was obtained upon trying to remove the Boc group using mild microwave heating in water.[29] However, successful deprotection of the Boc group for both ethyl and methyl azepines using an excess of trifluoroacetic acid in dichloromethane gave **166** and **167** in 85% and 81% yield 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**).[30] 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**).[31]

Table 27: Saponification attempts on ethyl and methyl esters.

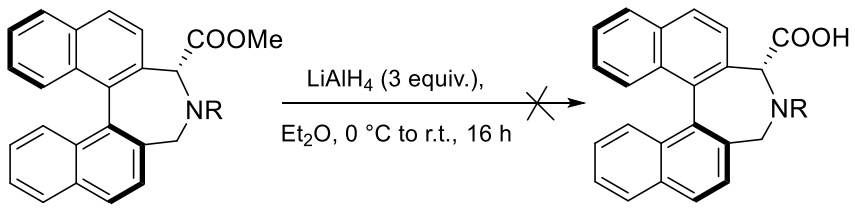


Entry	R	R^1	Reagent	Slovent	Temp (°C)	Yield (%)
1	Et	H	LiOH (1 equiv.)	$MeOH:H_2O$	r.t.	S.M.
2	Et	H	LiOH (6 equiv.)	$CH_3CN:H_2O$	r.t.*	S.M.
3	Et	H	NaOH (3 equiv.)	$MeOH:H_2O$	r.t.	S.M.
4	Et	Boc	HCl (6 M)	-	70	**166**
5	Me	H	TMSCl and NaI	CH_3CN	r.t.	S.M.
6	Me	Boc	TMSCl and NaI	CH_3CN		**167**
7	Me	Boc	NaOH (1 equiv.)	$MeOH:H_2O$	r.t.*	S.M.
8	Me	Boc	KOH 18-crown-6	$MeOH:H_2O$	r.t.	S.M.
9	Me	Boc	NH_2NH_2 (80%)	H_2O	r.t.	Complex mixture.

* Reaction also performed at reflux

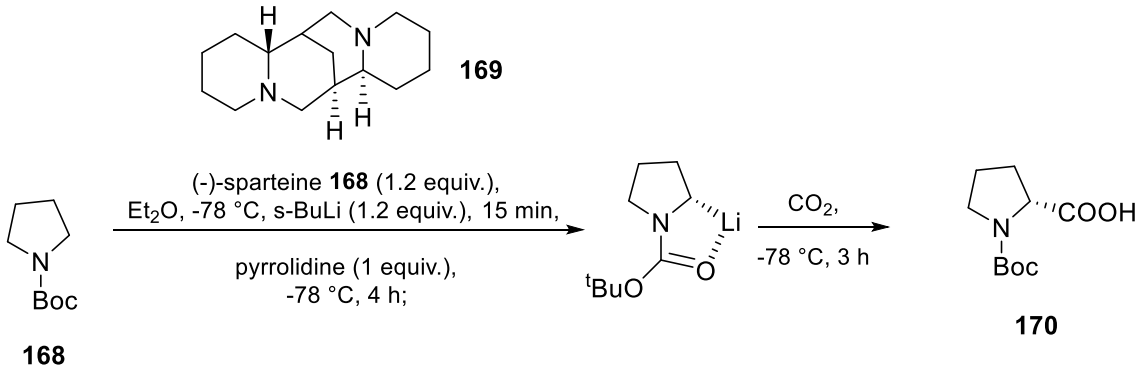
Another approach was tested, by reduction of the ester group using lithium aluminium hydride. Unfortunately, only starting material was isolated when three equivalents of the reduction reagent was used with methyl ester **165 (Entry 2)**. Furthermore, we thought that the bulky *tert*-butyl group was the reason for the reduction not occuring. 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



Entry	R	Yield (%)
1	H (167)	S.M.
2	Boc (165)	S.M.

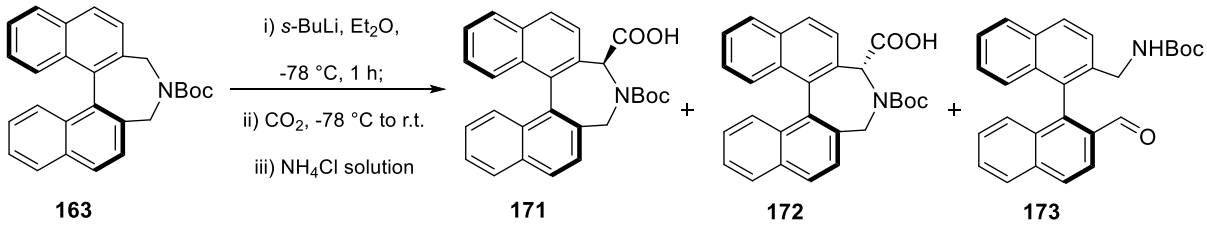
After the failure of saponification of both esters **164** and **165**, we found another approach to synthesise carboxylic acid **162** from a paper by Beak published in 1991.[32] Beak attempted to introduce a carboxylic acid at the α-position of Boc-pyrrolidine **168** using sec-butyllithium with the 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**).



Scheme 60: Asymmetric lithiation.

Following the same method and conditions, Boc-azepine **163** was dissolved in diethyl ether at -78 ^{o}C and *sec*-BuLi added to the solution for 1 h and CO_2 gas was bubbled through the reaction mixture through $CaCl_3$ 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 CO_2 affected the yield for both distereoisomeric acids causing a minor decrease in yields (**Entry 4 and 5**) (**Table 29**).

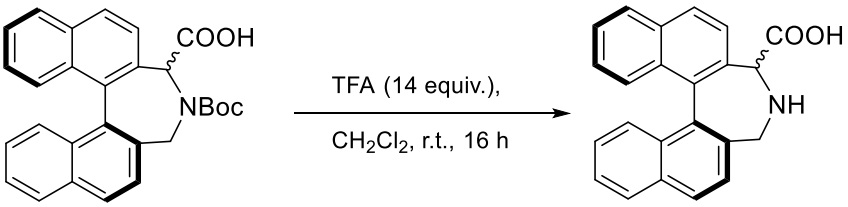
Table 29: CO_2 addition.



Entry	*S*-BuLi (equiv.)	CO_2	Time (h)	169 (Yield %)	170 (Yield %)	171 (Yield %)
1	1.3	Gas	2	30	34	12
2	1.3	Gas	16	33	31	16
3	2	Gas	24	11	10	13
4	1.3	Solid	2	30	25	5
5	2	Solid	16	23	25	11

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**).[33]

Table 30: Removal of Boc group.

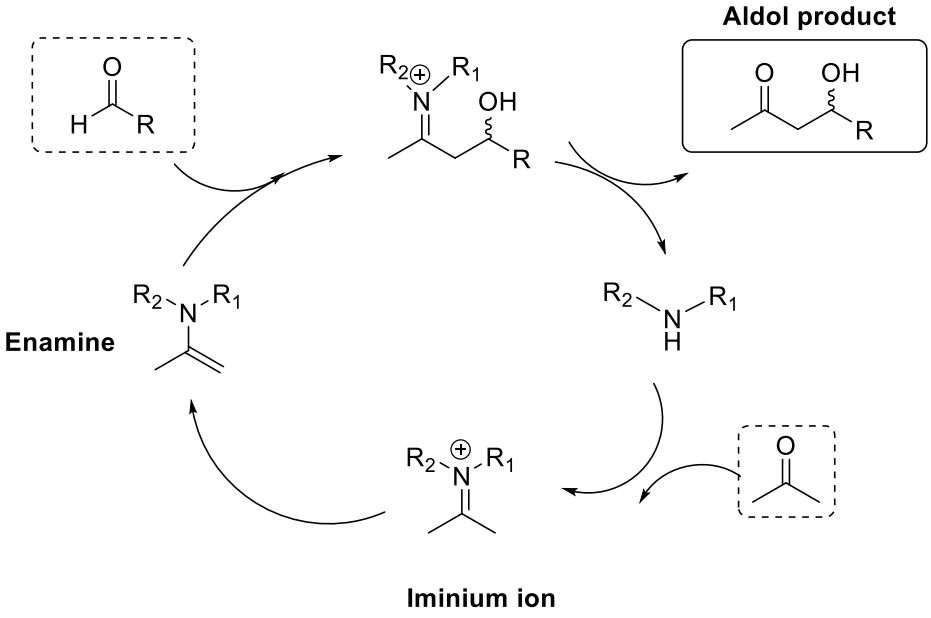


Entry	Product	Yield (%)	Product
1	**171**	71	**174**
2	**172**	80	**175**

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**).



Scheme 61: Organocatalysed aldol reaction general catalytic cycle.

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]

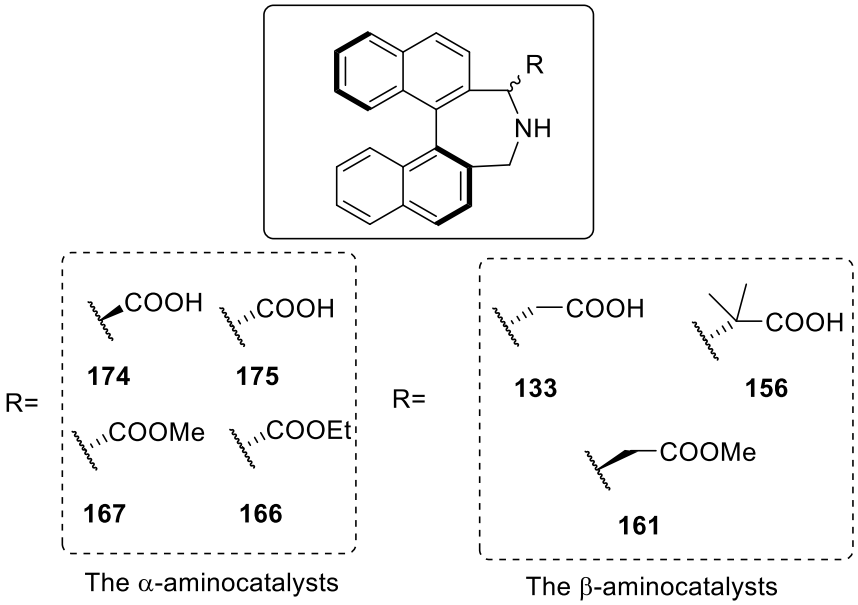
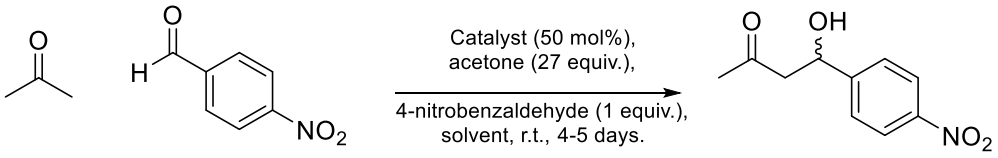


Figure 15: catalysts for screening.

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**.



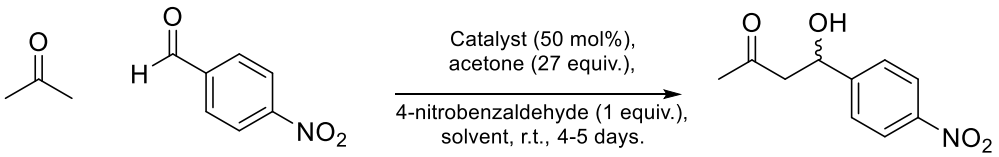
Entry	Catalyst	Solvent	Conversion (%)[a]	e.e (%)[b,c]
1	(L)-proline[d]	DMSO	68	74%
2	174	DMSO	S.M	--
	175		S.M	--
3	174	DMF	S.M	--
	175		S.M	--
4	174	EtOAc	S.M	--
	175		30	8 (R)
5	174	THF	S.M	--
	175		28	9 (R)
6	174	Acetone	S.M	--
	175		17	Racemic
7	174	CH_3CN	S.M	--
	175		S.M	--
8	174	MeOH	S.M	--
	175		15	11 (R)

[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 ^{o}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)**.

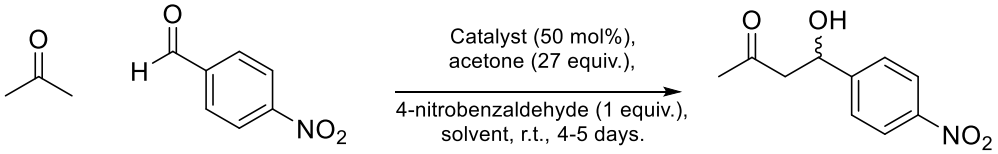
Table 32: Aldol reaction catalysed by **166** and **167**.



Entry	Catalyst	Solvent	Conversion (%)	e.e (%)
1	166	DMSO	28	17 (R)
	167		15	Racemic
2	166	Acetone	44	4 (R)
	167		25	12 (R)
3	166	CH_3CN	30	Racemic
	167		12	Racemic
4	166	MeOH	46	17 (S)
	167		51	5 (S)
5	166	EtOH	S.M	--
	167		S.M	--

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**).

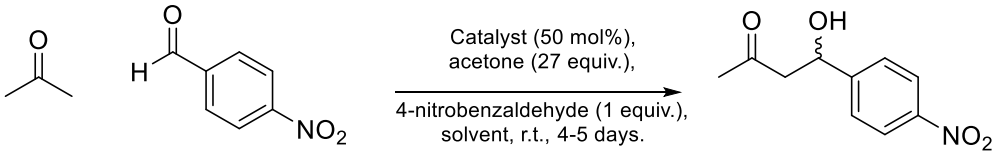
Table 33: Aldol reaction catalysed by **133**and **156**.



Entry	Catalyst	Solvent	Conversion (%)	e.e (%)
1	133	DMSO	57	19 (S)
	156		S.M.	--
2	133	Acetone	71	10 (S)
	156		S.M.	--
3	133	EtOAc	15	8 (S)
	156		S.M.	--
4	133	CH_3CN	S.M.	--
	156		S.M.	--
5	133	MeOH	S.M	--
	156		S.M	--

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.**

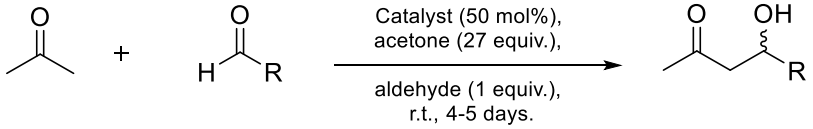


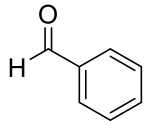
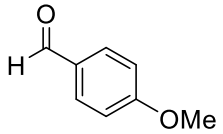
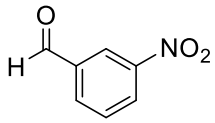
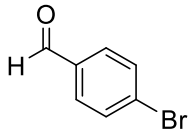
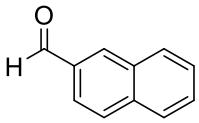
Entry	Catalyst	Solvent	Conversion (%)	e.e (%)
1	161	DMSO	5	11 (S)
2	161	Acetone	24	8 (S)
3	161	EtOAc	37	9 (S)
4	161	CH_3CN	50	Racemic
5	161	MeOH	S.M.	--

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 **133** or **166** except that catalyst **133** gave a poor conversion of 27% and 21% e.e when 3-nitrobenzaldehyde was used (**Entry 3**) (**Table 35**).

Table 35: Aldol reaction of acetone with several aldehydes.



Entry	Catalyst	Aldehyde	Conversion (%)	e.e (%)
1[a]	133		S.M.	--
	166		S.M.	--
2[b]	133		S.M.	--
	166		S.M.	--
3[c]	133		27	21 (R)
	166		S.M.	--
4[d]	133		S.M.	--
	166		S.M.	--
5[e]	133		S.M.	--
	166		S.M.	--

Conditions of the HPLC **a**) Chiralcel® AD_H column: (hexane/iPrOH= 92:8, λ=210 nm), 0.8 mL, r.t. ^{o}C; major enantiomer 14.1 min, minor enantiomer 15.4 min. **b**) Chiralcel® AD_H column: (hexane/iPrOH= 92:8, λ=220 nm), 0.8 mL, r.t. ^{o}C; major enantiomer 19.3 min, minor enantiomer 22.0 min. **c**) Chiralcel® AD_H column: (hexane/iPrOH= 92:8, λ=220 nm), 0.8 mL, r.t. ^{o}C; major enantiomer 23.3 min, minor enantiomer 25.0 min. **d**) Chiralcel® AD_H column: (hexane/iPrOH= 98:2, λ=221 nm), 0.8 mL, r.t. ^{o}C; major enantiomer 50.7 min, minor enantiomer 56.3 min. **e**) Chiralcel® AD_H column: (hexane/iPrOH= 85:15, λ=254 nm), 1 mL, r.t. ^{o}C; major enantiomer 11.9 min, minor enantiomer 14.1 min.

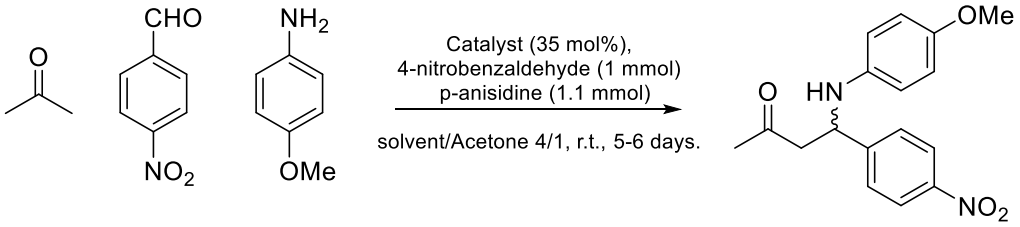
Unfortunately the results in the aldol reaction were not promising, and we therefore decided to test the ability of our catalysts in another reaction.

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**.



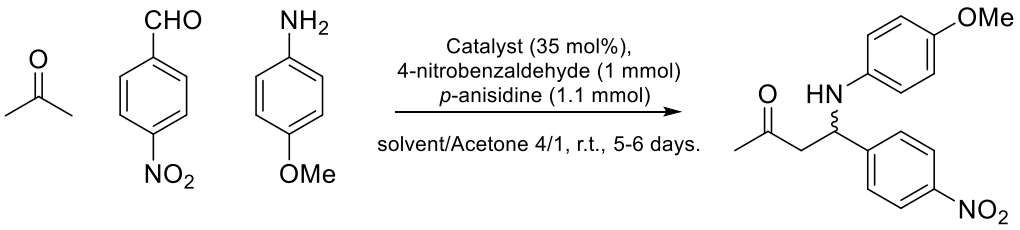
Entry	Catalyst	Solvent	Yield (%)	e.e (%)[a,b]
1	(L)-proline	DMSO	43%	90 (S)
2	174 175	DMSO	S.M 32	-- Racemic
3	174 175	Acetone	32 18	7 (R) Racemic
4	174 175	DCM	12 27	Racemic 3 (S)
5	174 175	EtOAc	9 S.M.	5 (R) --
6	174 175	$CHCl_3$	16 S.M	3 (R) --

a) Enantiomeric excess was determined using HPLC with Chiralcel® AD_H column: (hexane/iPrOH=80:20, λ=254 nm), 1 mL, r.t. ^{o}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**.

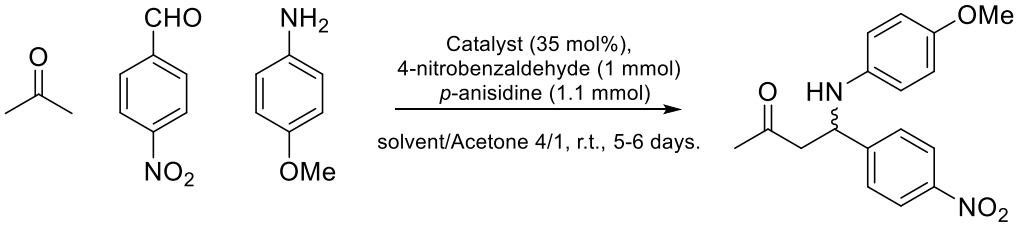


Entry	Catalyst	Solvent	Yield (%)	e.e (%)
1	166 167	DMSO	S.M 13	-- 3 (R)
2	166 167	Acetone	34 76	20 (R) 28 (R)
3	166 167	DCM	3 9	16 (R) 5 (R)
4	166 167	$CHCl_3$	15 28	43 (R) 25 (R)

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**).

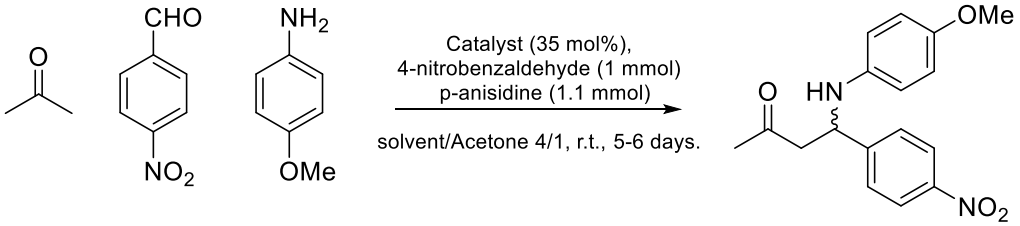
Table 38: Mannich reaction catalysed by **133** and **156**.



Entry	Catalyst	Solvent	Yield (%)	e.e (%)
1	133	DMSO	S.M	--
	156		S.M	--
2	133	Acetone	S.M	--
	156		S.M	--
3	133	DCM	S.M	--
	156		S.M	--
4	133	$CHCl_3$	S.M	--
	156		S.M	--

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**.

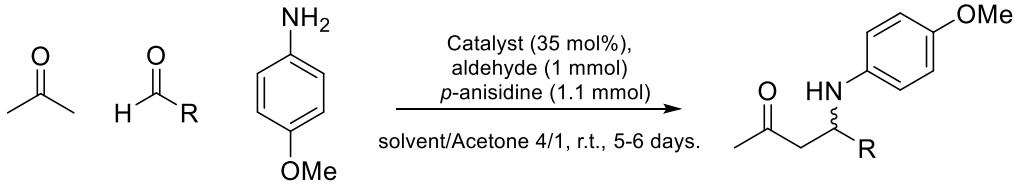


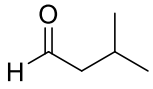
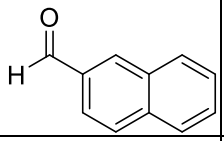
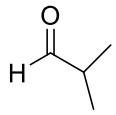
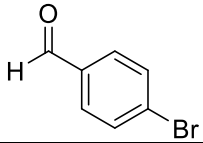
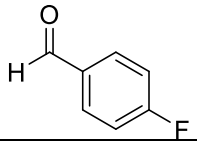
Entry	Catalyst	Solvent	Yield (%)	e.e (%)
1	161	DMSO	S.M	--
2	161	Acetone	39	22 (R)
3	161	DCM	27	3 (R)
4	161	$CHCl_3$	13	11 (R)

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.



Entry	Catalyst	Aldehyde	Yield (%)	e.e (%)
1[a]	166		11	7
	167		43	6
2[b]	166		S.M.	--
	167		S.M.	--
3[c]	166		--	--
	167		26	45
4[d]	166		S.M.	--
	167		S.M.	--
5[e]	166		S.M.	--
	167		S.M.	--

Conditions of the HPLC **a**) Chiralcel® AD_H column: (hexane/iPrOH=90:10, λ=256 nm), 1 mL, r.t. ^{o}C; major enantiomer 11.5 min, minor enantiomer 17.7 min. **b**) Knauer-Eurocel 01, 5 µm. XD_6 column: (hexane/iPrOH=90:10, λ=311 nm), 0.6 mL, r.t. ^{o}C; major enantiomer 18.6 min, minor enantiomer 13.9 min.
c) Chiralcel® AD_H column: (hexane/iPrOH=90:10, λ=254 nm), 0.6 mL, r.t. ^{o}C; major enantiomer 11.6 min, minor enantiomer 14.7 min.d) Knauer-Eurocel 01, 5 µm. XD_6 column: (hexane/iPrOH=90:10, λ=211 nm), 0.6 mL, r.t. ^{o}C; major enantiomer 14.0 min, minor enantiomer 11.8 min.
e) Knauer-Eurocel 01, 5 µm. XD_6 column: (hexane/iPrOH=90:10, λ=211 nm), 0.6 mL, r.t. ^{o}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**).

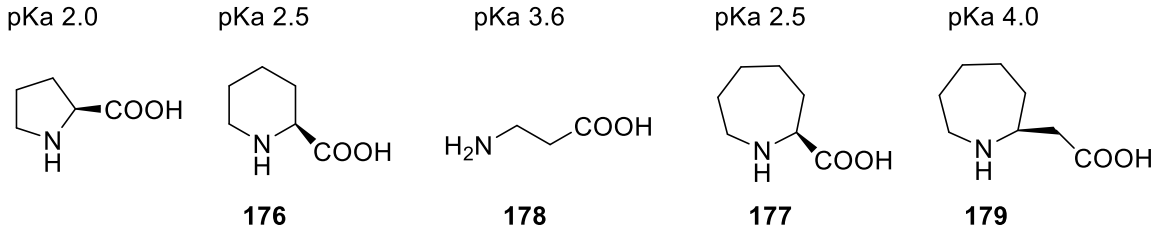
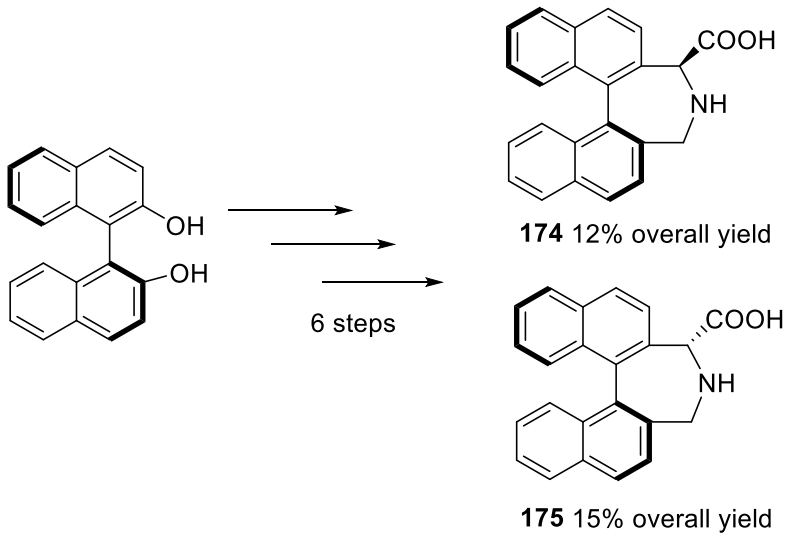


Figure 16: pKa values of α– and β–amino acid derivatives.

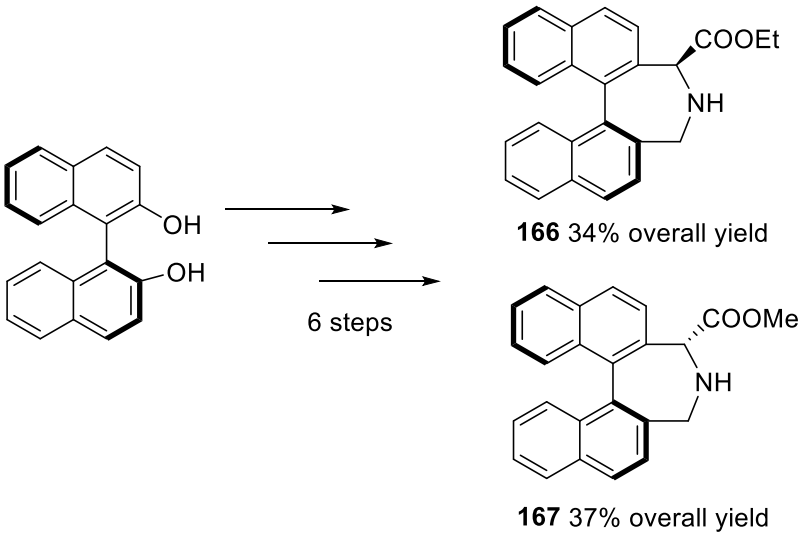
7.0 Conclusion

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**).



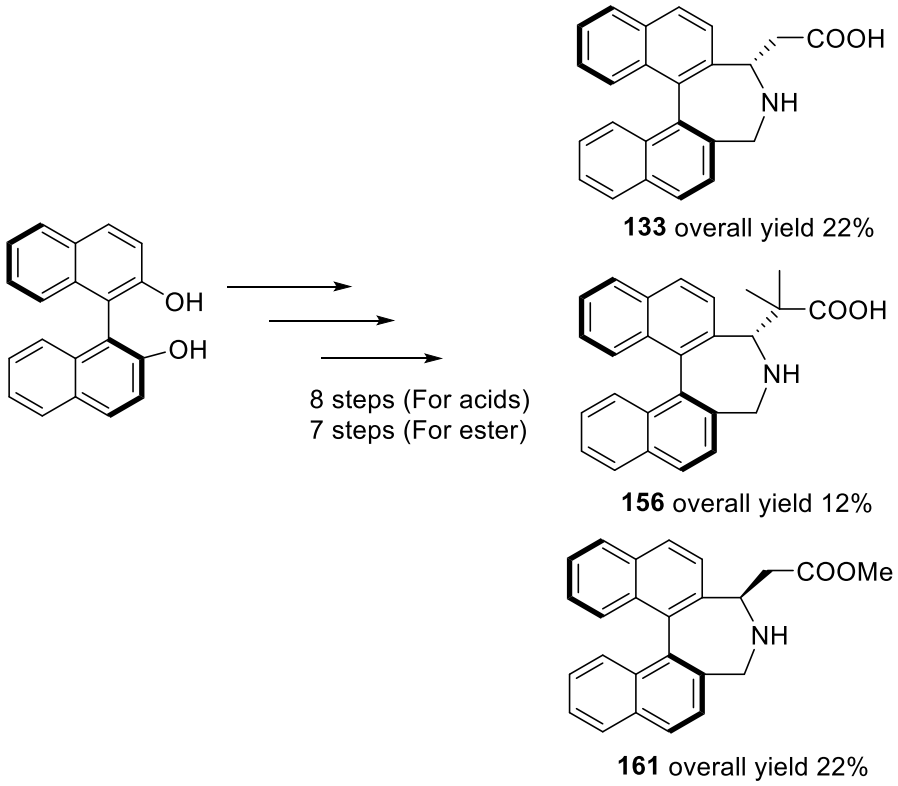
Scheme 62: Compound **174** and **175** synthetic route.

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.

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**).

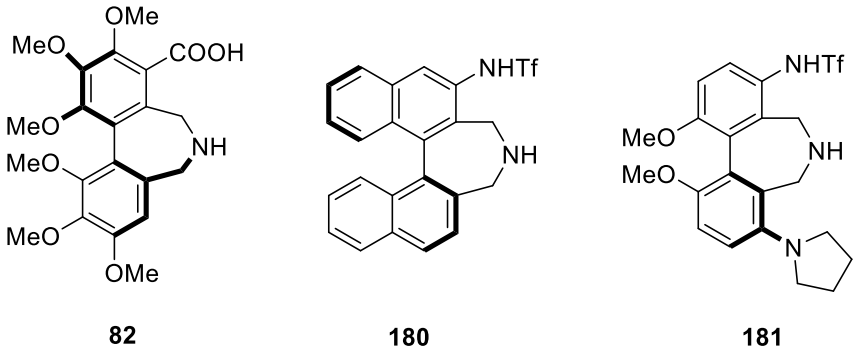


Scheme 64: Compound **133, 156** and **161** synthetic route.

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**).

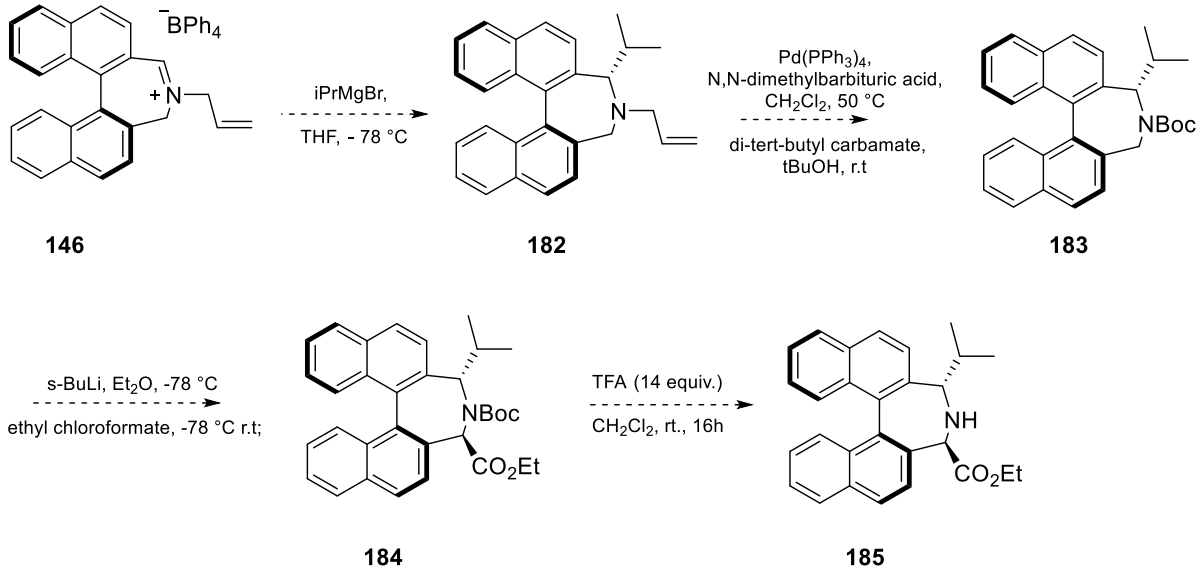
Following Maruoka who tried to improve his catalyst to be more nucleophilic by introduction of electron-donating groups on the ring as in catalyst **82**.[37] Including of more acidic groups instead of the carboxylic acid such as the triflamide groups **180**. Adding both electron-donating group and acidic groups (such trifamide) to provide more acidic groups (than the carboxylic groups) and more nucleophilic amines **181** (**Figure 17**).[38, 39, 40, 41]



82 **180** **181**

Figure 17: Catalysts with high selectivity.

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.

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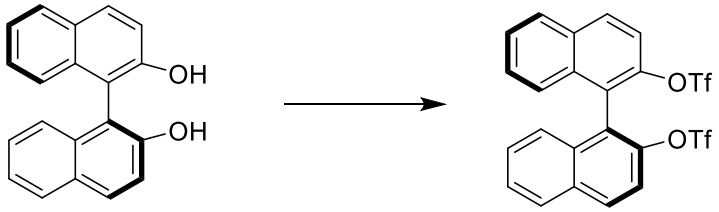
Chapter three: Experimental section

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 Et_2O, dried and distilled over sodium and benzophenone. DCM and CH_3CN were distilled over CaH_2 and DMF was distilled over $MgSO_4$. 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[1]

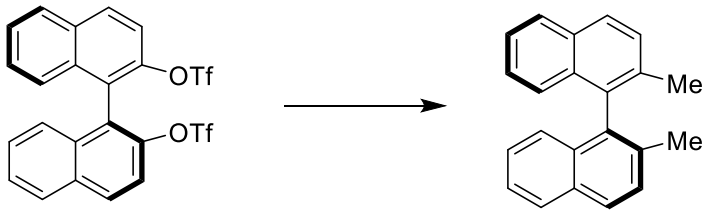


134

(*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][1]; $[\alpha]_D^{24.0}$ +146 (*c*=1.00, $CHCl_3$), (Lit $[\alpha]_D^{22.5}$ +144), (*c* 1.00, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm^{-1} 3065, 1592, 1509, 1423, 1216, 1139, 1066, 963, 940, 703, 768, 750, 656; ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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[1]

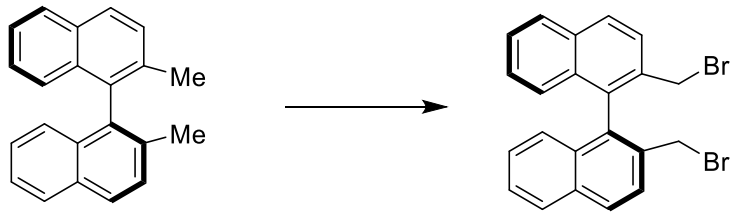


134 **135**

(S)-[1,1']-Binaphthalene-2,2'-diol-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 Et_2O (300ml). The reaction mixture was cooled to -78 °C and solution of methyl magnesium bromide (3M in Et_2O, 39.3 mL, 118.1 mmol, 4.0 equiv.) was added slowly and the reaction left to reach room temperature overnight. H_2O (around 50 mL) wa added at 0 °C to quench the excess of Grignard reagent and the reaction was diluted with Et_2O (100 mL) and left for 30 min to stir. The mixture was filtered over a plug of Celite® and washed with Et_2O (around 50 mL) and the filtrate was transferred to separating funnel and the organic layer was washed with H_2O (4 x 50 mL) and a brine (2 x 30 mL), dried over anhydrous $MgSO_4$ 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], $[\alpha]_D^{24.0}$ +35.5 (*c* 1.00, $CHCl_3$), (Lit $[\alpha]_D^{22.5}$ +36.5), (*c* 1.00, $CHCl_3$) [1]; ν_{max} (CH_2Cl_2)/cm-1 3051, 3008,2856, 1442, 1507, 1421, 1352, 1221 1027; ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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[2]

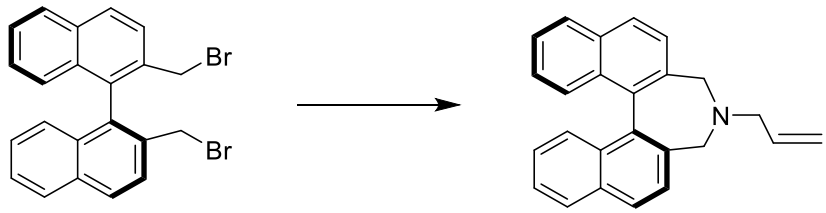


135 **136**

(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]; ν_{max} (CH_2Cl_2)/cm-1 3050, 2978, 2315, 1693, 1433, 1211, 851, 754, 725; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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[3]

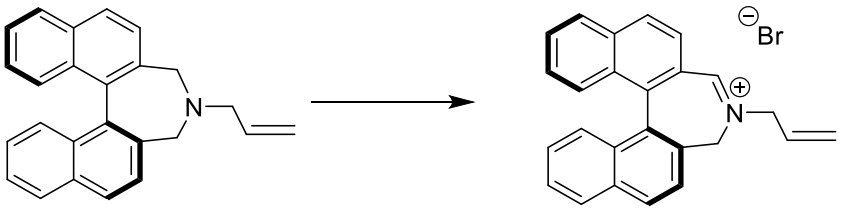


136 137

(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 H_2O (3 x 10 mL), a brine (2 x 20 mL) and dried over anhydrous $MgSO_4$ 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], $[\alpha]_D^{23.0}$ +399.1 (*c* 1.80, $CHCl_3$) (Lit $[\alpha]_D^{22.5}$ +396.2 (*c* 1.80, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm-1 3414, 3051, 2923, 2802, 263, 2492, 2296, 1508, 1423, 1163, 880, 822; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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[1]

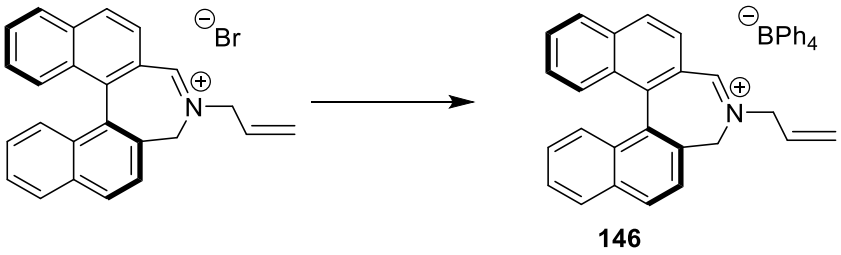


137

(*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*), $[\alpha]_D^{23.5}$ +317.4 (*c* 1.00, $CHCl_3$) (Lit. $[\alpha]_D^{22.5}$ +316.0 (*c* 1.00, $CHCl_3$)[1]; ν_{max}(CH_2Cl_2)/cm^{-1} 3657, 3469, 3053, 2891, 2386, 1772, 1708, 1650, 1508, 1428, 1350, 1179, 1062; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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-ium tetraphenylborate 146[1]



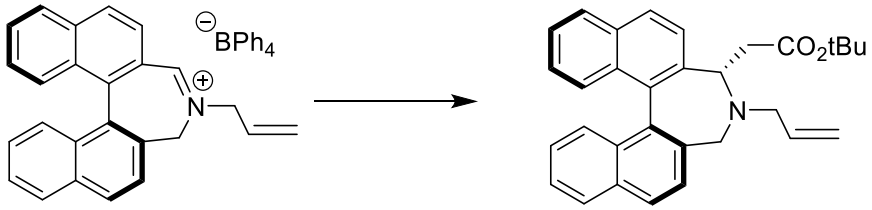
146

Crude *(S)*-4-allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium 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.*)[1], $[\alpha]_D^{23}$ +409.7 (*c* 1.00, MeCN), (Lit. $[\alpha]_D^{22.5}$ +410.5 (*c* 1.00, MeCN)[1]; ν_{max}(CH_2Cl_2)/cm^{-1} 3054, 2998, 2672, 2397, 2315, 1709, 1508, 1265, 1150, 817; ^{1}H 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); ^{13}C 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, 129.6, 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 of β-amino acids and derivatives

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

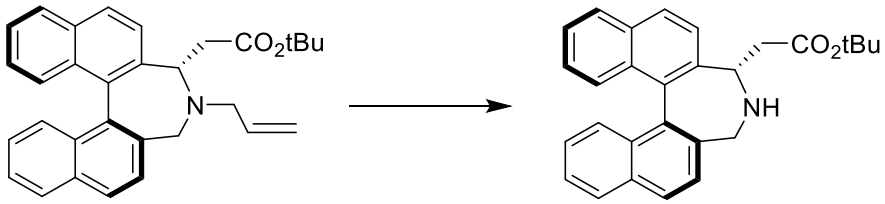


146 **151**

Zinc dust (2.29 g, 35.1 mmol, 10 equiv.) and TMSCl (0.44mL, 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), Et_2O (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 H_2O (3 x 20 mL), brine (3 x 20 mL), and dried over anhydrous $MgSO_4$ 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 petoleum 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], $[\alpha]_D^{23.5}$ +158.6 (c 1.00, $CHCl_3$) (Lit. $[\alpha]_D^{22.4}$ +158), (c 1.00, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm-1 3050, 2976, 1725, 1507, 1366, 1246, 1149, 819; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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-((3*S*,11c*S*)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl) acetate 155[1]**

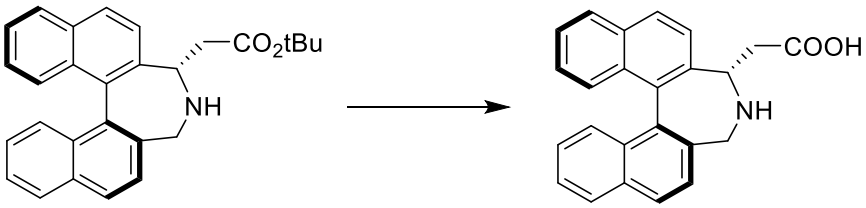


151 155

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(PPh3)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_2O (60 mL) and transferred to a separating funnel. The organic layer was washed with 1 M NaOH solution (2 x 20 mL), H_2O (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)[1]; $[\alpha]_D^{23.1}$ +205.1 (*c* 1.00, $CHCl_3$), (Lit $[\alpha]_D^{22.4}$ +206), (*c* 1.00, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm-1 3054, 2981, 1719, 1509, 1436, 1366, 1301, 1217, 1147, 1116, 819;^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, 125.6, 125.4, 80.1, 60.4, 59.1, 48.7, 42.9, 27.9.

2-((3*S*,11c*S*)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetic acid 133[1]

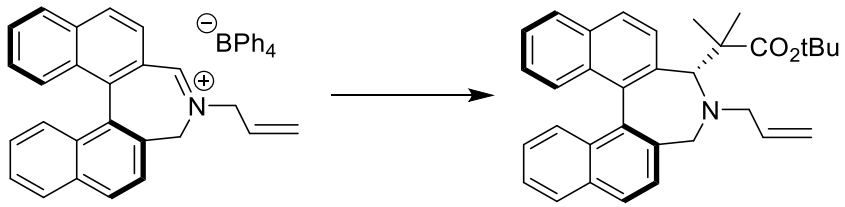


155 **133**

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 H_2O (10 mL), brine (2 x 10 mL) and dried over anhydrous $MgSO_4$ and filtered. After the filtration, the solvent was removed under reduced pressure and the residue recrystallized (CH_2Cl_2 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)[1]; $[\alpha]_D^{22.3}$ +261.8 (*c* 1.00, $CHCl_3$) (Lit. $[\alpha]_D^{22.4}$ +264 (*c* 1.00, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm-1 3390, 3053, 2968, 1682, 1595, 1392, 1200, 1121, 821; ^{1}H 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); ^{13}C 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, 126.8, 126.5, 126.3, 56.9, 46.4, 38.8.

***Tert*-Butyl-2-((3*R*,11c*S*)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3yl)-2-methylpropanoate 158**[1]

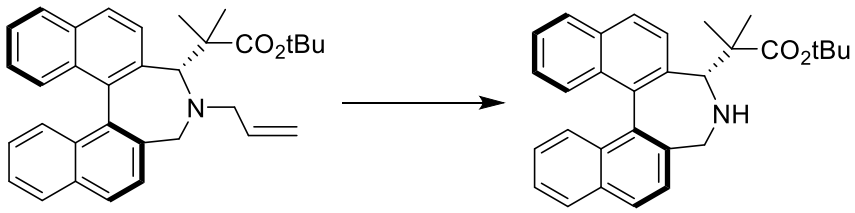


146 **158**

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), Et_2O (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 H_2O (3 x 20 mL), brine (3 x 20 mL), and dried over anhydrous $MgSO_4$ 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 petoleum 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); $[\alpha]_D^{21.8}$ +102.1 (c 1.0, $CHCl_3$) $[\alpha]_D^{18.9}$ +102.8 (c 1.3, $CHCl_3$); ν_{max} ($CHCl_3$)/cm-1 3051, 2977, 2934, 1713, 1458, 1469, 1367, 1253, 1168, 1035, 918, 753, 673; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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-((3*R*,11c*S*)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate 159[1]**

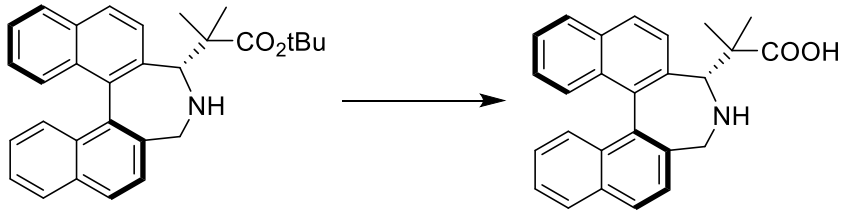


158 **159**

Tert-Butyl-2-((3*R*,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(PPh3)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_2O (70 mL) and transferred to a separating funnel. The organic layer was washed with 1 M NaOH solution (2 x 20 mL), H_2O (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]; $[\alpha]_D^{22.3}$ +316.7 (c 1.00, $CHCl_3$) (Lit. $[\alpha]_D^{20.1}$ +314.0 (c 1.00, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm-1 3057, 2974, 2929, 2414, 1725, 1609, 1507, 1464, 1388, 1366, 1249, 1139, 1113, 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, 132.8, 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-((3*S*,11c*S*)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoic acid 156[1]

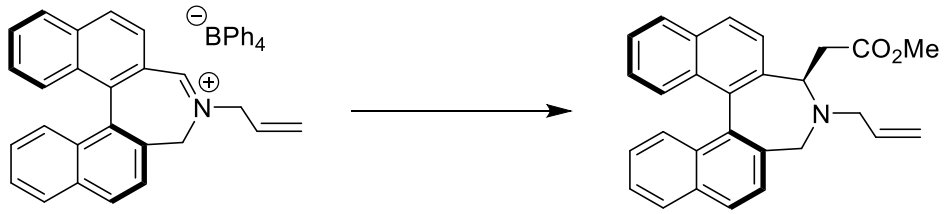


159 **156**

Tert-Butyl-2-((3*R*,11c*S*)-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 H_2O (20 mL), brine (2 x 10 mL), dried over anhydrous $MgSO_4$ filtered. After the filtration, the solvent was removed under reduced pressure and the residue recrystallized ($CHCl_3$ 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)[1]; $[\alpha]_D^{22.6}$ +140.4 (c 1.0, $CHCl_3$) $[\alpha]_D^{24.9}$ +138.1 (c 0.9, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm-1 3417, 3057, 2974, 2846, 1675, 1598, 1470, 1200, 1135, 821, 749; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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.

Methyl 2-((3*R*,11c*S*)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetate 160

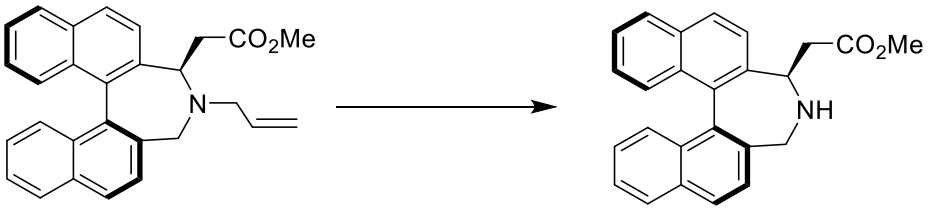


146 160

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-ium (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), Et_2O (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 H_2O (3 x 10 mL), brine (3 x 10 mL), and dried over anhydrous $MgSO_4$ 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 petoleum ether/ EtOAc) to yield the title compound as a colourless oil (0.746, 79%)

m.p. 127-128 °C $[\alpha]_D^{23.8}$+245.3 (*c* 1.00, CH_2Cl_2); ν_{max} (CH_2Cl_2)/cm^{-1} *3051, 2977, 2948, 1734, 1507, 1435, 1265, 1173, 820;* ^{1}H 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);^{13}C 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, 126.4, 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; $[C_{28}H_{25}NO_2]$+ requires 408.1958.

Methyl 2-((3*R*,11c*S*)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetate 161



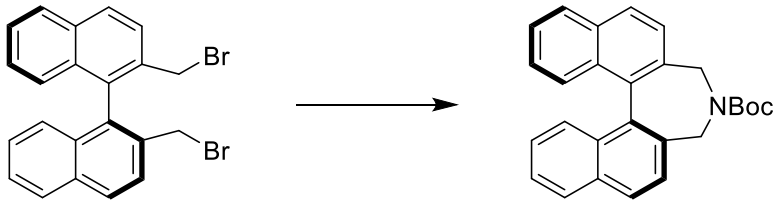
160 **161**

Methyl-2-((3*R*,11c*S*)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetate (0.320g, 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 redissolved in Et_2O (30 mL) and transferred to a separating funnel. The organic layer was washed with 1 M NaOH solution (2 x 10 mL), H_2O (2 x 10 mL), brine (10 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 (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; $[\alpha]_D^{23.8}$ +342.8 (*c* 1.00, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm^{-1} 3338, 3049, 2948, 2842, 1732, 1506, 1435, 1263, 821; ^{1}H 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); ^{13}C 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; $[C_{25}H_{21}NO_2]$+ 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[1]

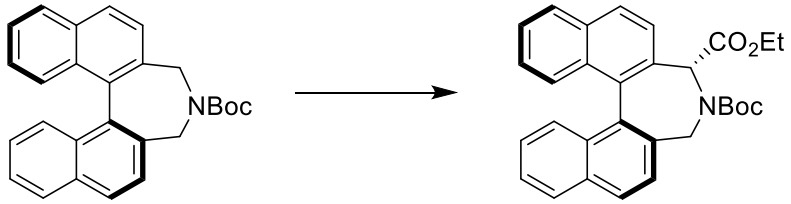


136 163

(*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. Et_2O (110 mL) was added to the mixture and the organic layer washed with H_2O (4 x 15 mL), brine (3 x 15 mL), dried over anhydrous $MgSO_4$ 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)[1]; $[\alpha]_D^{18.4}$ −11.0 (*c* 1.00, $CHCl_3$); (Lit. $[\alpha]_D^{22.5}$ −7.0 (*c* 1.00, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm^{-1} 3051, 2976, 2930, 2869, 1922, 1687, 1508, 1463, 1402, 1365, 1274, 1251, 1216, 1162, 1103, 906, 858, 818; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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

(3*R*,11c*S*)-4-*Tert*-Butyl 3-ethyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)dicarboxylate 164[1]

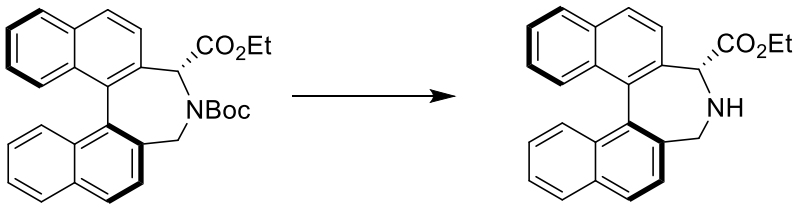


163 **164**

(*S*)-*Tert*-Butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate (0.965 g, 2.43 mmol) was dissolved in Et_2O (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 H_2O (3 x 40 mL), brine (3 x 40 mL), dried over anhydrous $MgSO_4$ 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)[1]; $[\alpha]_D^{21.7}$ −19.2 (*c* 1.00, $CHCl_3$) (Lit. $[\alpha]_D^{22.1}$ −17.6 (*c* 1.00, $CHCl_3$)[1]; ν_{max} (CH_2Cl_2)/cm^{-1} 3053, 2977, 2933, 1745, 1697, 1476, 1456, 1392, 1313, 1250, 1217, 1156, 916, 863; ^{1}H 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.05, 169.63, 154.26, 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.

(3*R*,11c*S*)-Ethyl 4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylate 166[1]

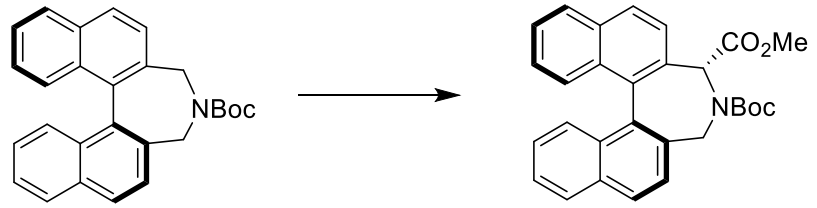


164 **166**

(3*R*,11c*S*)-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 H_2O (3 x 20 mL), brine (3 x 20 mL) and dried over anhydrous $MgSO_4$ 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; $[\alpha]_D^{21.4}$ +379.2 (*c* 1.00, $CHCl_3$), (Lit. $[\alpha]_D^{23.1}$ +386.0 (*c* 1.00, $CHCl_3$)[1] ; ν_{max}(CH_2Cl_2)/cm^{-1} 3316, 3050, 2979, 2869, 1724, 1463, 1222, 1205, 1110, 912, 813; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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.

(3*R*,11c*S*)-4-*Tert*-butyl 3-methyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)dicarboxylate 165[1]

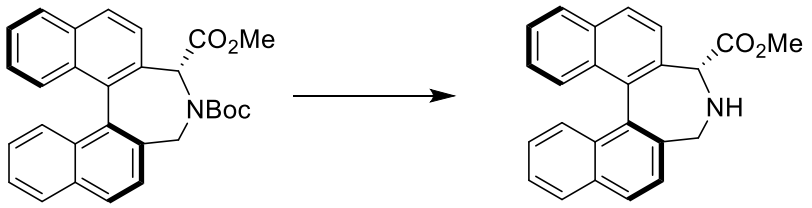


163 **165**

(*S*)-*Tert*-Butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate (1.60 g, 4.04 mmol) was dissolved in Et_2O (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 H_2O (3 x 30 mL), brine (3 x 30 mL), dried over anhydrous $MgSO_4$ 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]; $[\alpha]_D^{19.2}$ −17.3 (*c* 0.5, $CHCl_3$), (Lit. $[\alpha]_D^{22.6}$ −20.8 (*c* 0.5, $CHCl_3$))[1]; ν_{max} (CH_2Cl_2)/cm^{-1} 3052, 2975, 2947, 2880, 1751, 1695, 1508, 1456, 1391, 1366, 1296, 1155, 953, 822; ^{1}H 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); ^{13}C 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, 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.

(3*R*,11c*S*)-Methyl 4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylate 167[1]

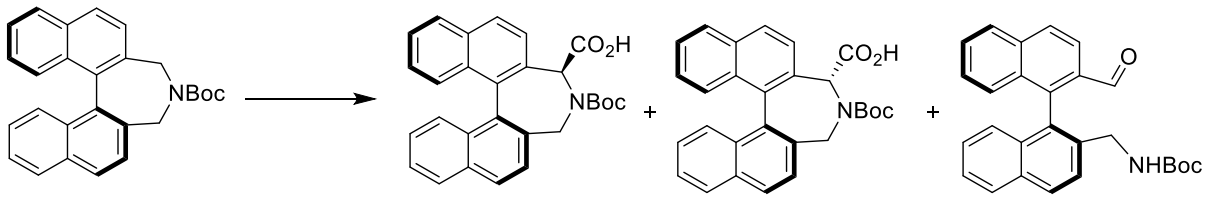


165 **167**

(3*R*,11c*S*)-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 H_2O (3 x 30 mL), brine (3 x 30 mL), dried over anhydrous $MgSO_4$ and filtered. After the filtration, the solvent removed under reduced pressure and recrystallized ($CHCl_3$ 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)[1] ; $[\alpha]_D^{22.1}$ +432.5 (*c* 1.0, $CHCl_3$), (Lit. $[\alpha]_D^{21.4}$ +420 (*c* 1.03, $CHCl_3$))[1]; ν_{max} (CH_2Cl_2)/cm^{-1} 3314, 3051, 2948, 2870, 1730, 1507, 1432, 1222, 1205, 1112, 991, 866, 821; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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.

(11c*S*)-4-(*Tert*-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine3-carboxylic acid synthesis

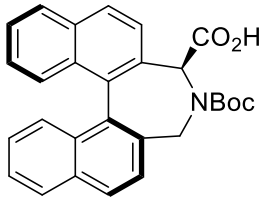


163 **171** **172** **173**

(*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 Et_2O (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. CO_2 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 H_2O (2 x 20 mL), dried over anhydrous Na_2SO_4 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[1]



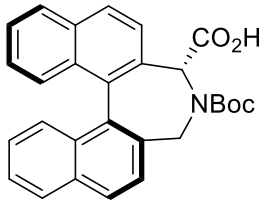
171

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 (*c* 1.00, $CHCl_3$) (Lit. $[\alpha]_D^{23.9}$ +58.4 (*c* 1.00, $CHCl_3$)[1]; ν_{max} (CHCl3)/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) δ 8.11 – 7.78 (m, 4H), 7.66 (d, *J* = 6.7 Hz, 1H), 7.62 – 7.36 (m, 4H), 7.35 – 7.26 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 5.00 (d, *J* = 15.3 Hz, 1H), 4.69 (s, 1H), 3.73 (d, *J* = 13.7 Hz, 1H), 1.46 (s, 9H).
^{13}C NMR (126 MHz, DMSO, VT NMR at 353 K) δ 171.2, 136.5, 133.4, 133.2, 131.7, 131.5, 130.5, 129.7, 129.4, 129.2, 128.9, 128.3, 128.3, 128.2, 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:

(3*R*,11c*S*)-4-(*Tert*-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'e]azepine-3-carboxylic acid 172[1]



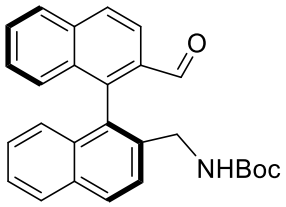
172

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)[1]; $[\alpha]_D^{21.3}$ −44.9 (*c* 1.00, $CHCl_3$) (Lit. $[\alpha]_D^{23.9}$ −47.2 (*c* 1.00, $CHCl_3$)[1]; ν_{max} ($CHCl_3$)/cm-1 3053, 2981, 1754, 1395, 1366, 1300, 1244, 1156, 913, 820; ^{1}H NMR (500 MHz, DMSO, VT NMR at 363 K) δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.92-7.90 (m, 2H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.49 (ddd, *J* = 10.4, 5.7, 2.4 Hz, 1H), 7.43 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.27 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.25 (d, *J* = 3.2 Hz, 1H), 7.22 – 7.16 (m, 1H), 5.89 (s, 1H), 5.02 (d, *J* = 14.8 Hz, 1H), 3.67 (d, *J* = 14.3 Hz, 1H), 1.52 (s, 9H); ^{13}C NMR (126 MHz, DMSO, VT at 363 K) δ 170.6, 154.3, 134.7, 133.9, 131.7, 131.7, 129.4, 129.3, 128.6, 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*)-*Tert*-Butyl ((2'-formyl-[1,1'-binaphthalen]-2-yl)methyl)carbamate 173

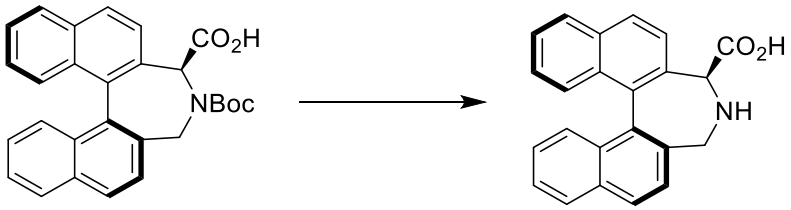


173

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, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm-1 3351, 3060, 3000, 2979, 2932, 1763, 1695 1603, 1507, 1461, 1430, 1401, 1367, 1320, 1231, 1168, 1023, 855, 819; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

(3*S*,11c*S*)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid 174[1]

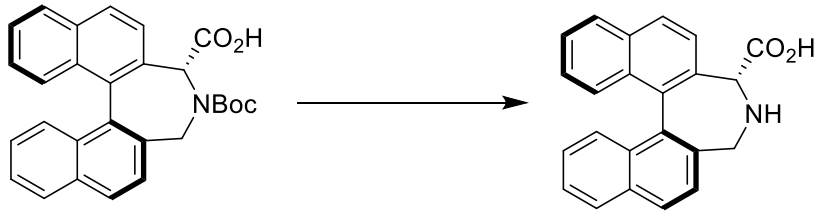


171 **174**

(3*S*,11c*S*)-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 H_2O (3 x 10 mL), brine (3 x 10 mL), dried over anhydrous $MgSO_4$ and filtered. After the filtration, the solvent removed under reduced pressure and the residue was recrystallized ($CHCl_3$ and light petroleum ether) giving the title compound (0.533 g, 71%).

m.p. 271-273 °C (Lit. m.p. 276-280 °C)[1]; $[\alpha]_D^{19.3}$ +191.7 (*c* 1.00, $CHCl_3$), $[\alpha]_D^{24.5}$ +196.0 (*c* 1.00, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm-1 3384, 3055, 2995, 2961, 2586, 1724, 1633, 1397, 1370 1344, 1194, 1139, 1036, 821, 749; ^{1}H 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); ^{13}C 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, 126.8, 126.7, 126.6, 60.2, 45.9.

(3*R*,11c*S*)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid 175 [1]



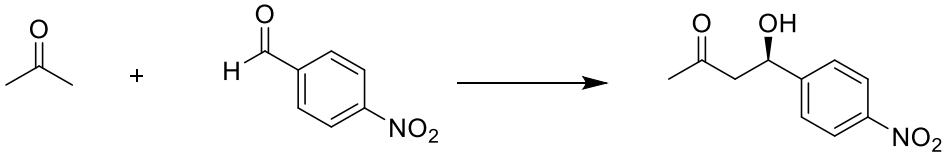
172 **175**

(3*R*,11c*S*)-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 H_2O (3 x 5 mL), brine (3 x 5 mL), dried over anhydrous $MgSO_4$ and filtered. After the filtration, the solvent removed under reduced pressure and the residue was recrystallized ($CHCl_3$ and light petroleum ether) giving the title compound (0.200 g, 80%).

m.p. 270-272 °C (Lit. m.p. 269-271 °C)[1]; $[\alpha]_D^{23.5}$ +274.1 (*c* 1.00, $CHCl_3$), (Lit. $[\alpha]_D^{24.5}$ +272.8 (*c* 1.00, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm-1 3394, 3053, 2593, 1719, 1636, 1370, 1201, 1134, 820, 750; ^{1}H 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).^{13}C 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[5]

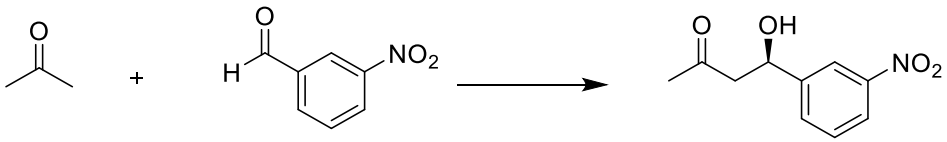
(4*R*)-(4-Nitrophenyl)-4-hydroxy-2-butanone



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. 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 H_2O (1 mL), brine (1 mL) and dried over $MgSO_4$ 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, $CHCl_3$)[6] ; ν_{max} (CH_2Cl_2)/cm^{-1} 3419, 2921, 2851, 1711, 1518, 1346, 1163, 1076, 856; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (126 MHz, $CDCl_3$) δ 208.5, 149.8, 126.4, 124.0, 123.8, 68.9, 51.5, 30.7.

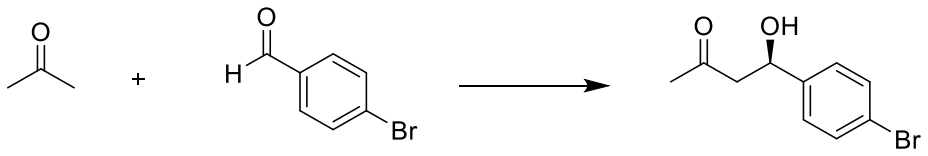
(4*R*)-(3-Nitrophenyl)-4-hydroxy-2-butanone



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 H_2O (1 mL), brine (1 mL) and dried over $MgSO_4$ 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%).

$[\alpha]_D^{25.5}$ +43.2 (*c* 1.00, $CHCl_3$)[7]; ν_{max} (CH_2Cl_2)/cm^{-1} 3423, 2923, 2851, 1709, 1528, 1350, 1164, 1068, 808; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.6, 131.8, 129.5, 122.6, 120.7, 68.8, 51.5, 30.7.

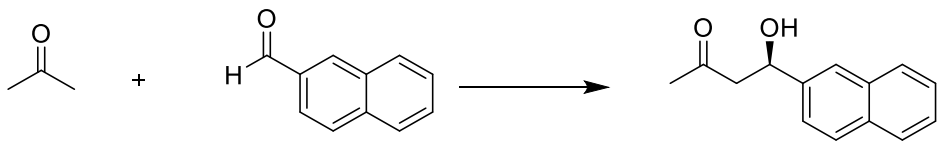
(4*R*)-(3-Bromophenyl)-4-hydroxy-2-butanone



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. 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 H_2O (1 mL), brine (1 mL) and dried over $MgSO_4$ 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%).

$[\alpha]_D^{25.5}$ +42.9 (*c* 1.00, $CHCl_3$)[8]; ν_{max} (CH_2Cl_2)/cm^{-1} 3417, 2920, 2851, 1712, 1487, 1361, 1162, 1070, 828, 538; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H), 7.26 – 7.22 (m, 2H), 5.12 (dd, *J* = 8.2, 4.0 Hz, 1H), 3.34 (s, 1H), 2.87 – 2.76 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9, 141.7, 131.6, 127.3, 121.4, 69.2, 51.7, 30.7.

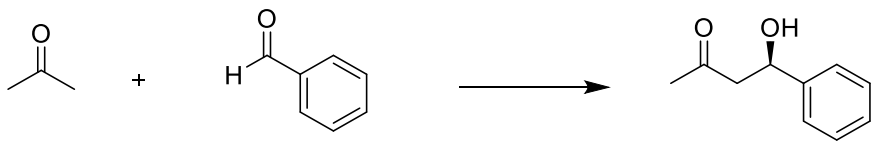
(4*R*)-(2-naphthyl)-4-hydroxy-2-butanone



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. 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 H_2O (1 mL), brine (1 mL) and dried over $MgSO_4$ 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 (*c* 1.00, $CHCl_3$);)[9]; ν_{max} (CH_2Cl_2)/cm^{-1} 3463, 2921, 2858, 1708, 1488, 1361, 1164, 1064, 820; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.80 (m, 4H), 7.51– 7.44 (m, 3H), 5.33 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.37 (s, 1H), 3.01 – 2.88 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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.

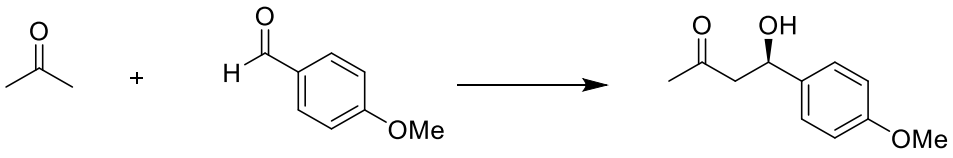
(4*R*)-(4-phenyl)-4-hydroxy-2-butanone



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 H_2O (1 mL), brine (1 mL) and dried over $MgSO_4$ 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 (0.010g, 62%).

$[\alpha]_D^{25.5}$ + 19.7 (*c* 1.00, $CHCl_3$)[10]; ν_{max} (CH_2Cl_2)/cm^{-1} 3431, 2920, 2850, 1712, 1515, 1361, 1163, 1061, 843; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 142.7, 128.5, 127.7, 125.6, 69.8, 51.9, 30.7.

(4*R*)-(4-methoxyphenyl)-4-hydroxy-2-butanone

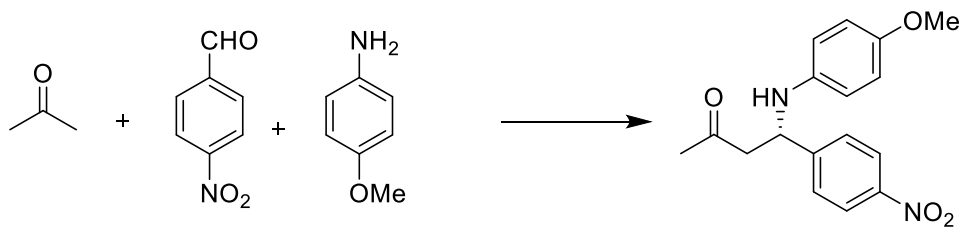


L-proline (0.0045 g, 0.035 mmol, 0.035 equiv.) was added to mixture of acetone (0.2 mL, 2.7 mmol, 27 equiv.) and dimethyl sulfoxide (0.8 mL) and the mixture stirred for 15 min. 4-Methoxybenzaldehyde (0.0121 mL, 0.1 mmol) was added and the reaction stirred overnight or until the starting material was 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 H_2O (1 mL), brine (1 mL) and dried over $MgSO_4$ 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%).

$[\alpha]_D^{23.1}$ +38.6 (*c* 1.00, $CHCl_3$)[8]; ν_{max} (CH_2Cl_2)/cm^{-1} 3444, 2957, 2837, 1710, 1514, 1361, 1248, 1031, 834; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 159.1, 134.9, 126.9, 113.9, 69.5, 55.3, 51.9, 30.7.

5.0 Mannich examples reaction.[11]

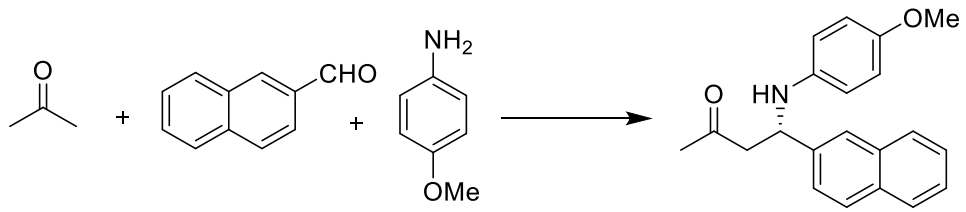
(4*S*)-4-[(4-Methoxyphenyl)amino]-4-(4-nitrophenyl)-2-butanone



L-proline (0.40 g, 0.35 mmol, 0.35 equiv.)), *p*-anisidine (0.135, 1.1 mmol, 1.1 equiv.) and 4-nitrobenzaldehyde (0.151 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 $MgSO_4$, 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%).

ν_{max} (CH_2Cl_2)/cm^{-1} 3418, 2923, 2851, 1645, 1510, 1244, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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.

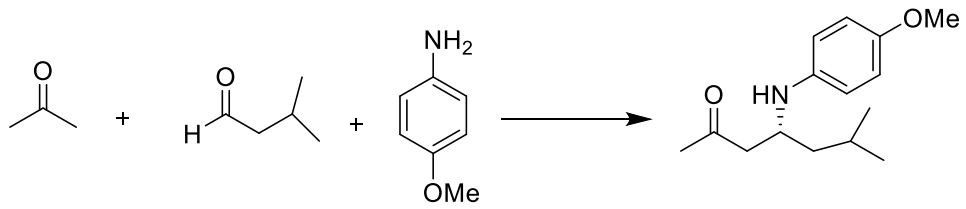
(4*S*)-4-[(4-Methoxyphenyl)amino]-4-(2-naphthyl)-2-butanone



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 $MgSO_4$, 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 white solid (0.097 g, 30%).

ν_{max} (CH_2Cl_2)/cm^{-1} 3409, 2919, 2832, 1708, 1510, 1238, 1035, 817; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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.

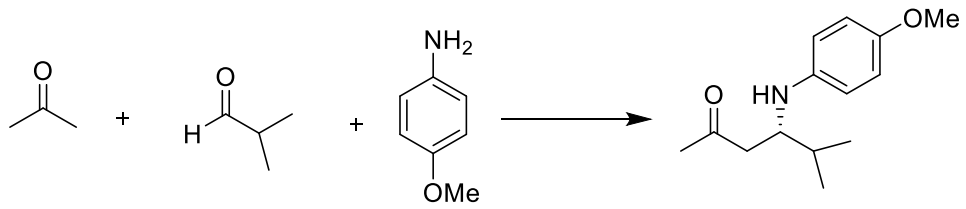
(*4R*)-4-[(4-Methoxyphenyl)amino]-6-methyl-2-heptanone



L-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 $MgSO_4$, 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 (0.217 g, 87%).

ν_{max} (CH_2Cl_2)/cm^{-1} 3378, 2955, 2927, 1709, 1510, 1464, 1243, 1035, 825; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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.

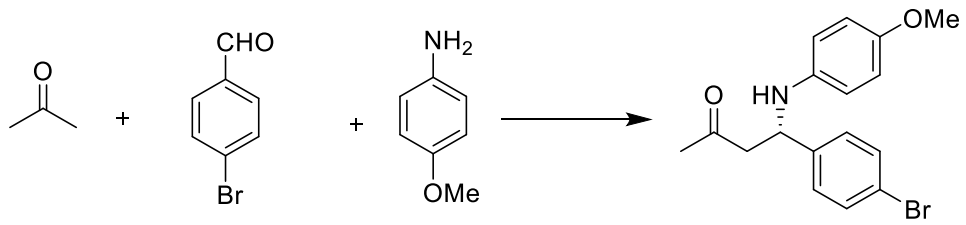
(4*S*)-4-[(4-Methoxyphenyl)amino]-5-methyl-2-hexanone



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 $MgSO_4$, 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 colourless oil (0.114 g, 48%).

ν_{max} (CH_2Cl_2)/cm^{-1} 3363, 2957, 2832, 1707, 1511, 1465, 1237, 1036, 822; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (126 MHz, $CDCl_3$) δ 208.4, 152.1, 141.6, 115.0, 56.2, 55.8, 45.2, 31.2, 30.6, 18.7, 18.4.

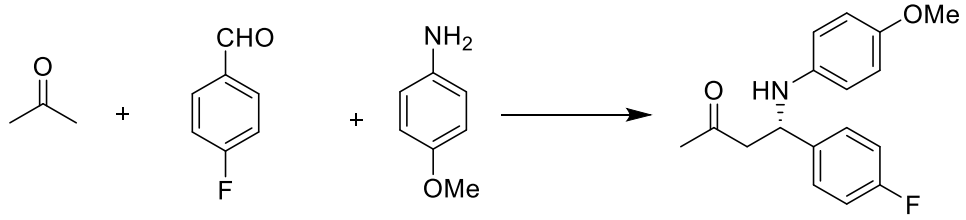
(4*S*)-4-(4-Bromophenyl)-4-[(4-methoxyphenyl)amino]-2-butanone



L-proline (0.40 g, 0.35 mmol, 0.35 equiv.)), *p*-anisidine (0.135, 1.1 mmol, 1.1 equiv.) and 4-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 $MgSO_4$, 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 colourless solid (0.254 g, 72%).

ν_{max} (CH_2Cl_2)/cm^{-1} 3373, 2955, 2833, 1710, 1510, 1402, 1238, 1034, 815, 527; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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.

(4*S*)-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 $MgSO_4$, 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 orange oil (0.071 g, 24%). ν_{max} (CH_2Cl_2)/cm^{-1} 3381, 2999, 2833, 1711, 1509, 1359, 1237, 1036, 820, 537; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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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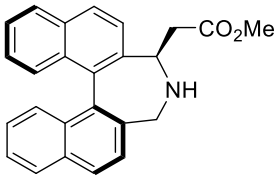
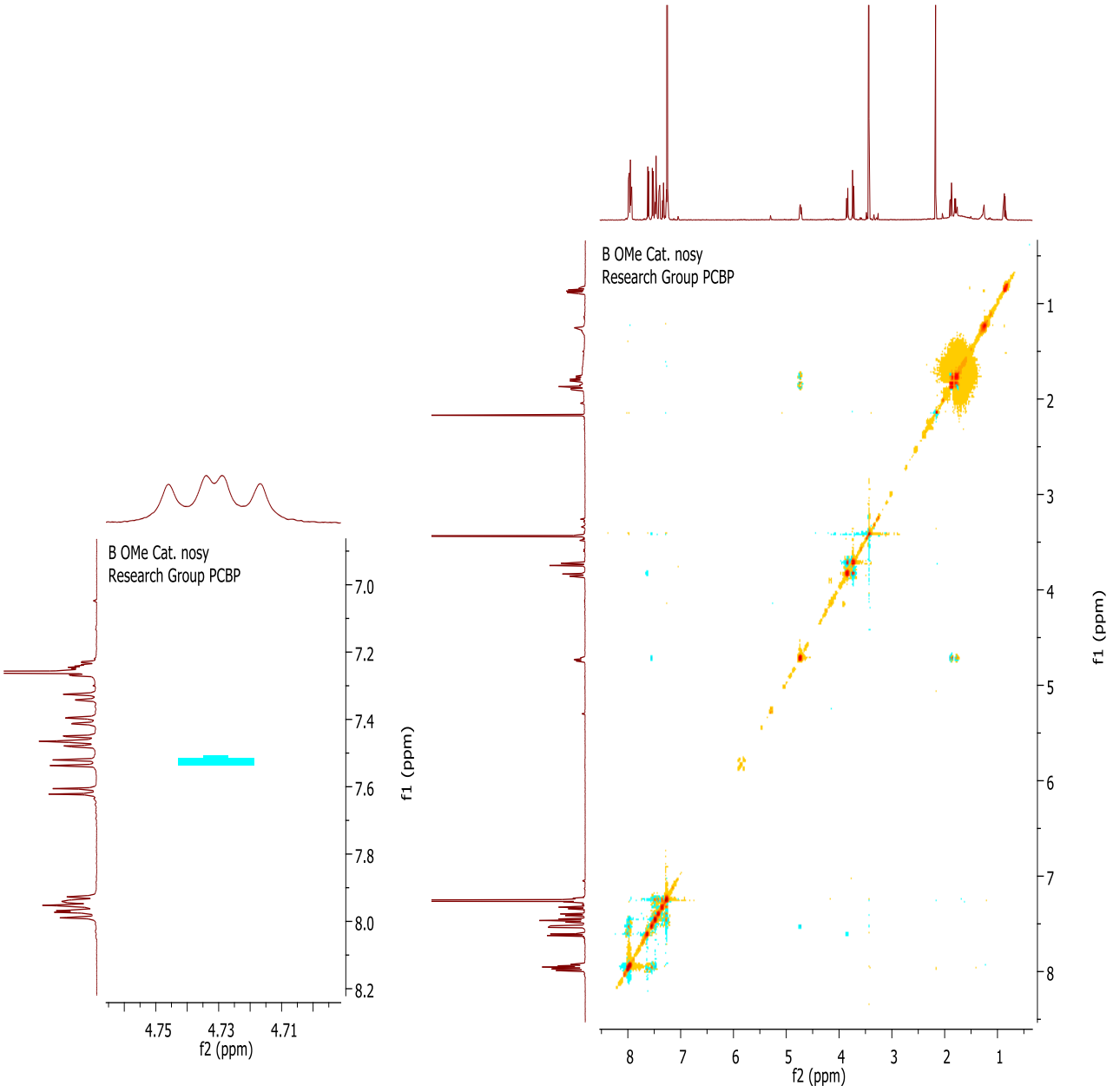
Appendix



161



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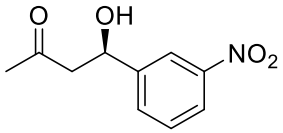

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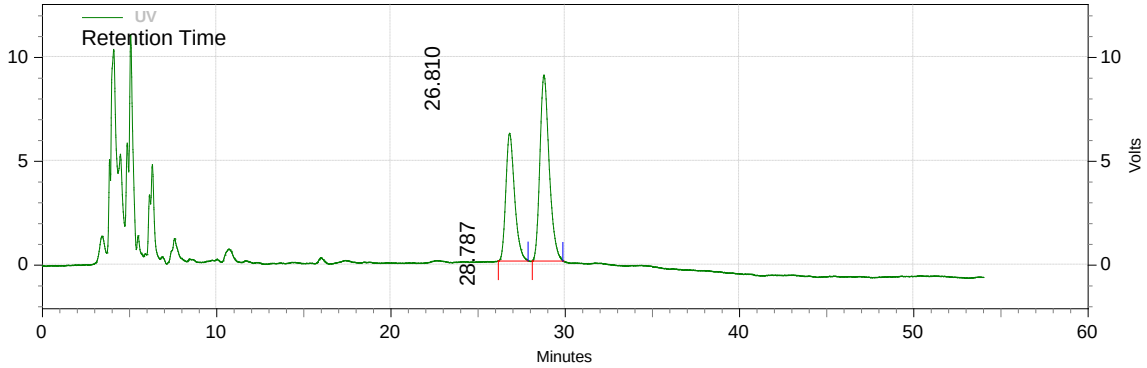

UV Results

Retention Time	Area	Area %	Height	Height %
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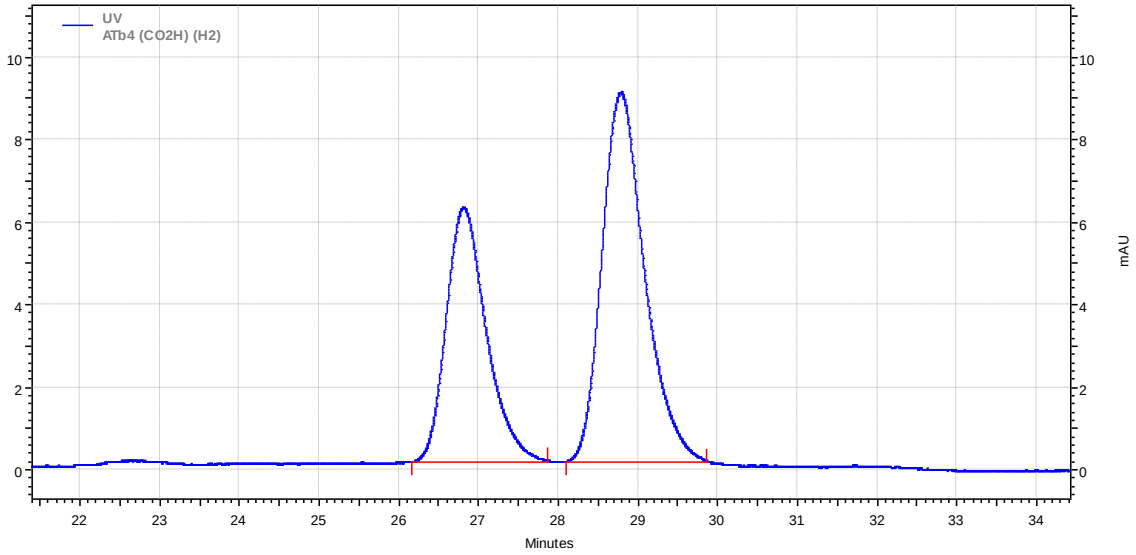
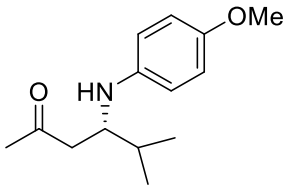
28.787	1330277	60.72	35814	59.28

Totals	2190871	100.00	60420	100.00



Area % Report



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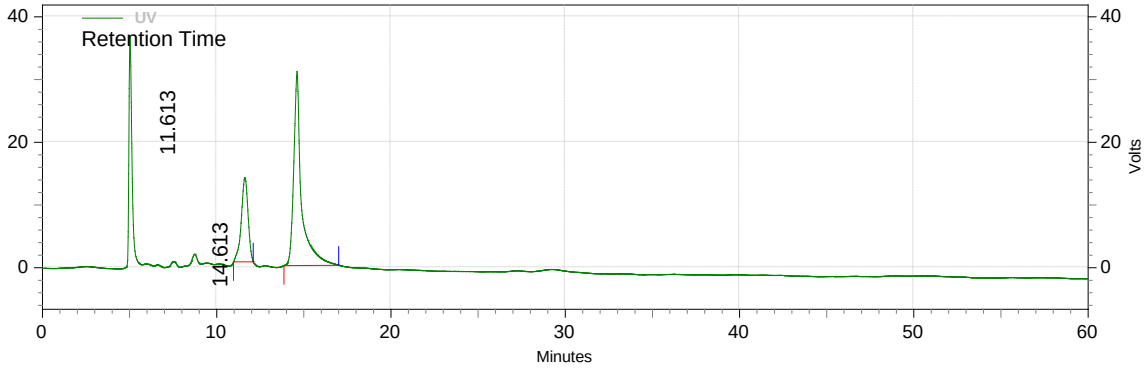

UV Results

Retention Time	Area	Area %	Height	Height %
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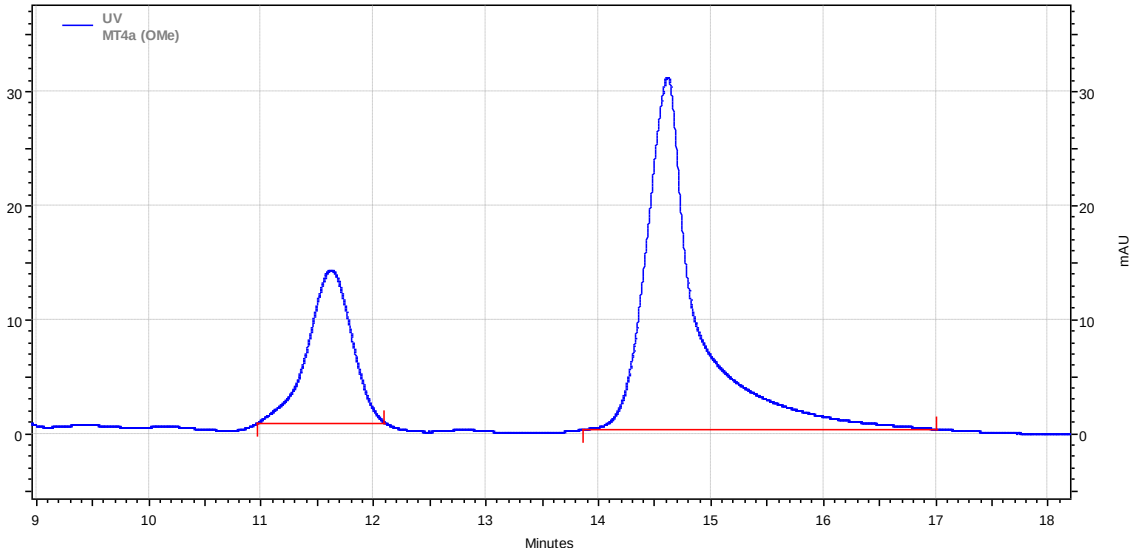
Totals	5272411	100.00	177375	100.00


UV
MT4a (OMe)
30
20
10
0
mAU
9
10
11
12
13
14
15
16
17
18
Minutes