Novel axially chiral amines as organocatalysts

by

Francesca Seraphina Kinsey

A Doctoral Thesis

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

2016

Francesca Kinsey

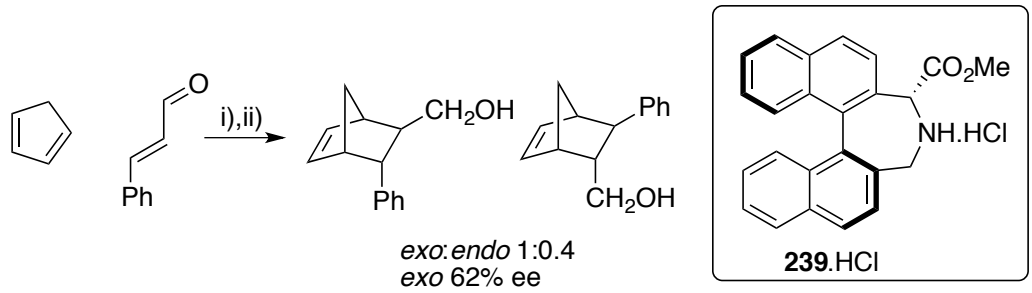
Abstract

Novel axially chiral amines as organocatalysts

Keywords: Axial chirality, asymmetric organocatalysis, Reformatsky reaction, Diels-Alder reaction, amino acid.

This body of research describes the recent developments our group has contributed towards the synthesis of novel axially chiral α- and β-functionalized amino acids and their application in asymmetric catalysis. This thesis is divided into three sections. The first chapter contains a review of the discovery and development of organocatalysis and includes key examples of its progression in terms of widening applications and improving selectivities.

The second chapter consists of the results and discussion section of this thesis and it is divided into two parts. Part one contains works relating to the synthesis of a series of binaphthyl and biphenyl organocatalysts and describes key selective synthetic steps: a diastereoselective Reformatsky addition and asymmetric lithiation and chloroformate/carboxylation addition steps. Part two focuses on the observed enantio- and diastereoselectivity of these catalysts in the aldol, Michael and Diels-Alder reactions.



Key steps: i) 10 mol% **239**.HCl, MeOH:H_2O, 0 °C ii) $LiAlH_4$ reduction

Section three contains the experimental data for the compounds described in chapter two.

Dedication

I would like to dedicate this thesis in memory of Sarah Rosanne Delf. Sarah was a fellow Ph.D student at UEA and was working on a total synthesis of hippeastrine. Sarah was a wonderful friend and an exceptionally kind-hearted person. She made working in the department fun and enjoyable simply by being her happy and smiling self everyday. She is dearly missed and will always be at the very heart of my happiest memories here.

Acknowledgements

Firstly I would like to unreservedly thank Professor Philip Bulman Page for the opportunity to join his research group, first for a Masters project and then for his encouragement to pursue a Ph.D. I feel very fortunate to have worked under his great supervision and guidance over these past five years.

Secondly I would like to thank Dr Yohan Chan. Without his continued input and advice this project wouldn't have come half as far as it has. For his support over the years I am very grateful.

I would like to thank Dr Ian Strutt, whose work I continued and who taught me (and put up with) so much over the first few years of my studies and Nawaf Alsenani who now takes over the mantle of asymmetric aminocatalysis in the Page group.

I would also like to thank all the members of the Page group, past and present. They, and other departmental chemists, have been a wonderfully welcoming and friendly bunch and it was a pleasure to work with them. A special thank you must go to Edmond Poon, Thu Pham Hoai, Jamie Martin, James Buttress, Amanda Chang, Cristina Macarov, Paulina Glowacka, Johanna Helary, Ketan Panchal and Ross Arthurs, and many other people that I have met here, for all the laughter and fun over the years.

I am also very grateful to the EU-funded AI:CHEM Interreg project for financing my Ph.D.

I'd like to thank my oldest and most wonderful friends: Annie Skidmore and Julia Wan, without their craziness, kindness and encouragement and I would be completely lost. And Rachael Gathercole, my dearest friend, whom I owe so much. I am eternally grateful to her for all her support and for a cat and gin refuge when I needed it the most.

And finally I'd like to thank my family; Katherine, Christopher and Liz (and Mort) for the unwavering support, love and patience they have shown me over the past few years.

Abbreviations

°C	Degrees Celsius
Å	Ångström
Ac	Acetyl
Ac_2O	Acetic anhydride
acac	Acetylacetone
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
aq	Aqueous
Ar	Aryl/Aromatic
Ar.	Argon
B	Base
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-Butyloxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
Bu	Butyl
BuLi	*n*-Butyllithium
CAN	Ammonium cerium IV nitrate
Cbz	Carboxybenzyl
cm^{-1}	Wavenumber
COD	1,5-Cyclooctadiene
Conc.	Concentrated
d	Days
d.r.	Diastereomeric ratio
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
DIPEA	*N*,*N*-Diisopropylethylamine
DMAc	Dimethylacetamide
DMAP	Dimethylaminopyridine
DMF	*N*,*N*-dimethylforamide
DMSO	Dimethylsulfoxide
DMT	Dimethyltartarate
dppe	1,2-Bis(diphenylphosphino)ethane
$DppONH_2$	*O*-(diphenylphosphinyl)-hydroxylamine
e.e.	Enantiomeric excess
E^+	Electrophile
EDAC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
equi.	Equivalents
Et	Ethyl
ETSA	Ethyl trimethylsilylacetate
g	Grams
h	Hour
HOBT	Hydroxybenzotriazole

HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
*i*Pr	*iso*-Propyl
IR	Infrared
IPA	*Iso*-propyl alcohol
K	Kelvin scale
LDA	Lithium diisopropylamide
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
PhCN	Benzonitrile
$PhCO_2H$	Benzoic acid
PhSH	Thiophenol
PMB	Paramethoxybenzyl
Ppm.	Parts per million
Quant.	Quantitative
r.t.	Room temperature
Ra-Ni	Raney-Nickel
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBHP	Tetrabutylhydrogen peroxide
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPPP	Tetraphenylphosphonium monoperoxysulfate
UV	Ultraviolet
Δ	Chemical shift
Δ	Heat

Table of Contents

Chapter one: Introduction

1.0 Asymmetric catalysis

Stereochemistry is now an essential part of the design and synthesis of new drug targets. Prior to the 1980's, the pharmaceutical industry was centred on the synthesis of drugs as racemic mixtures, until it was observed that the specificity of a drug increases with its structural and molecular complexity. Stereoisomers were shown to have strikingly different pharmacological and toxicological effects. In some cases while one enantiomer may yield the desired therapeutic response, the other can be inactive or even be antagonistic or damaging.[1] In addition, authorities introduced procedures on the regulation of chiral drugs such as *Policy Statement for the Development of New Stereoisomeric Drugs* (FDA) and the *Committee for Proprietary Medical Products* (EU) stipulating that stereoisomers of chiral drugs should be separated and both stereoisomers' activity and toxicology should be assessed.[2] Therefore, production of racemic drugs became a higher risk, wasteful and costly route for pharmaceutical companies. This, along with the advent of new technologies, led to the industry's growing preference for the synthesis of active compounds as single enantiomers.

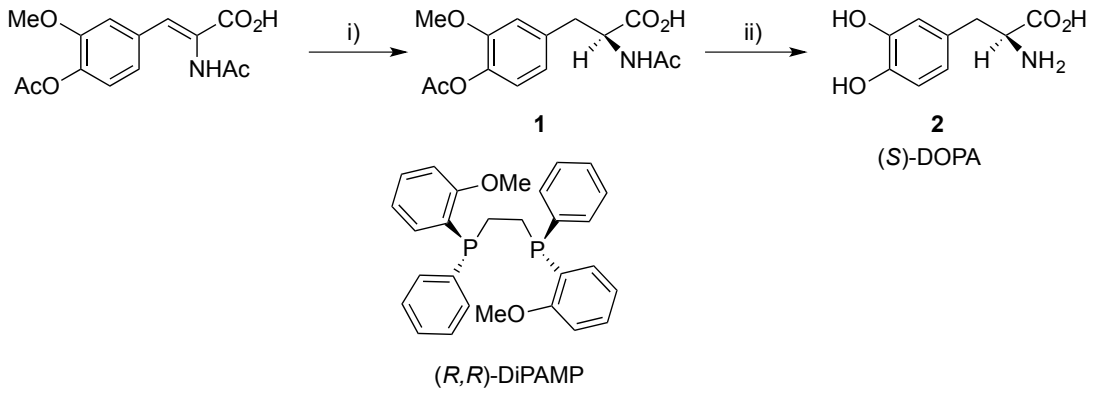
1.1 Classes of asymmetric catalysis

The demand for more sophisticated drug precursors possessing multiple chiral centres has led to huge advances in stereoselective synthesis. Whilst the isolation of pure enantiomers can be achieved by different methods, i.e. resolution of racemic mixtures, kinetic resolutions, chiral auxiliaries, extraction of pure enantiomers from natural products (chiral pool approach), asymmetric catalysis is considered the least wasteful. Asymmetric catalysis can be separated in three main areas; organometallic catalysis, biocatalysis and organocatalysis.

1.1.1 Organometallic catalysis

Organometallic catalysis has enjoyed tremendous success over the past century in industrial procedures ranging from olefin polymerization to the catalytic cracking of hydrocarbons for petroleum refining. These processes were developed following the work of Ziegler and Natta for their titanium- and chromium-based catalysts and the work of Wilkinson for his eponymous rhodium-based catalyst.[3] The success of these

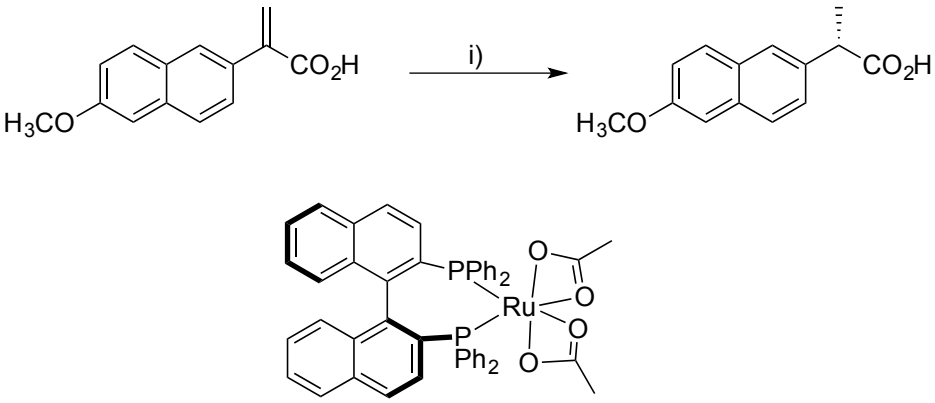
systems naturally led to the use of metal catalysts being extended to the synthesis of chiral drugs. Indeed, Knowles developed the first industrial asymmetric catalytic process: the synthesis of the rare amino acid (*S*)-DOPA, **2**, used in the treatment of Parkinson's disease. The key enantioselective step was a hydrogenation in the presence of a catalytic amount of [Rh(*R*,*R*)-DiPAMP)COD]BF_4 affording **1** in 95% e.e. and quantitative yield.[4]



Reagents and conditions: i) H_2, [Rh((R,R)-DiPAMP)COD]$^+BF_4^-$, *quant.,* 95% ee; ii) H_3O^+

Scheme 1: First industrial asymmetric catalytic hydrogenation in the synthesis of (*S*)-DOPA **2**.

Similarly, Noyori developed asymmetric olefin hydrogenations, employing ruthenium and C_2 symmetric bidentate BINAP ligands such as **3**. Industrial applications for this process have been widely demonstrated; for example, the synthesis of Naproxen®, an anti-inflammatory drug, was achieved in 97% enantiomeric excess. Other examples include highly selective syntheses of carbapenem antibiotics.[5]



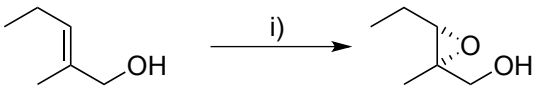
3

Ru(*S*)-2,2'-bis(diarylphosphino)
-1,1'binaphthyl catalyst

Reagents and conditions: i) H_2, Ru(II)(*S*)-BINAP, 92%, 97% e.e

Scheme 2: Noyori's ruthenium-BINAP catalyst **3** in the synthesis of Naproxen®

Noyori and Knowles were awarded the 2001 Nobel Prize in chemistry sharing the prize with Sharpless. Sharpless was rewarded for his work on asymmetric oxidations, most famously his epoxidation reactions. In this catalytic system, allylic alcohols are transformed into their respective epoxyalcohols using titanium (IV) catalyst, the oxidant t-butylhydroperoxide and an enantiopure dialkyltartrate ligand.[6] Industry has adopted this highly predictable and selective methodology in the synthesis of stabilized enantio-enriched glycidol derivatives.[7] In addition, key intermediates in the synthesis of antibiotics methymycin, erythromycin and leukotriene C-1 have been prepared using this process.[8]



4

Reagents and conditions: i) $Ti(OiPr)_4$, (+)-(DMT), TBHP, 79 %, >95% e.e

Scheme 3: Sharpless epoxidation used in the synthesis of a key intermediate **4** in antibiotic methycin

The Sharpless epoxidation is high yielding and very enantioselective as well as being applicable to a wide range of allylic alcohols. Conveniently, both stereoisomers of the desired epoxyalcohol product can be synthesised by changing the enantiomer of

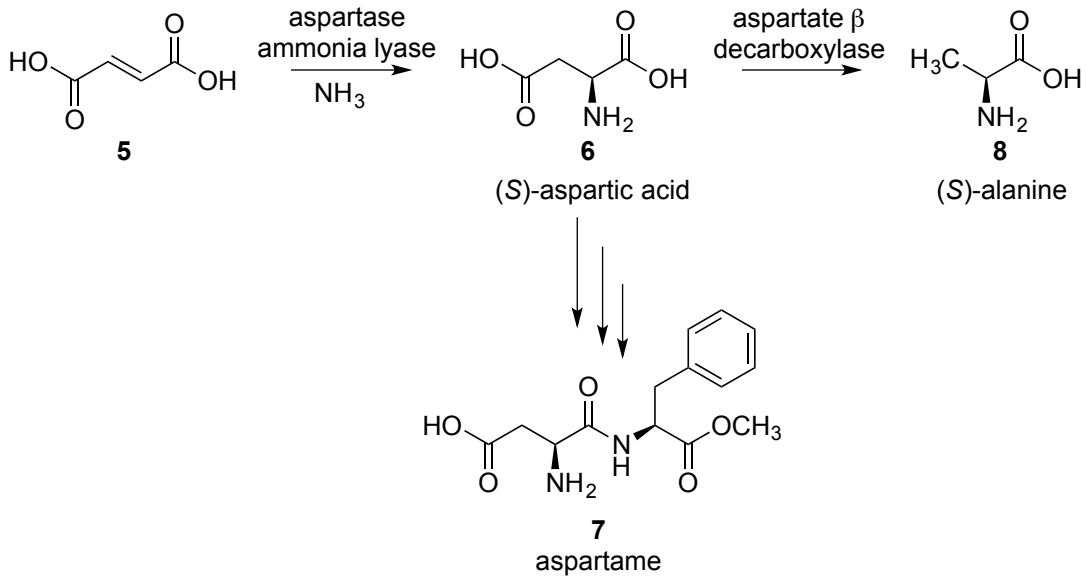
the dialkyltartrate ligand.

Despite its obvious successes, transition metal-mediated catalysis is inherently wasteful; the metal itself only plays an organizational role, while the organic ligands surrounding it create the chiral environment. Indeed, although metal-ligand catalysts are very tuneable, due to their molecular and structural diversity, they are generally expensive, frequently toxic, and require exacting reaction conditions such as the exclusion of air and moisture.

1.1.2 Biocatalysis

Biocatalysis, the use of enzymes or macromolecules such as proteins to perform chemical transformations on organic compounds is another area within asymmetric catalysis. Enzymatic catalysis is clean, safe, highly selective and can be as tuneable as metal catalysis as the performance of enzymes can often be optimized by mutation.

Enzymatic catalysis has proven useful in the production of enantiomerically pure amino acids and their derivatives for application in pharmaceutical, cosmetic, agricultural and food industries. For example, (*S*)-aspartic acid **6** is a starting material in the synthesis of the artificial sweetener (*S*)-aspartyl (*S*)-phenylalanine methyl ester, **7** (Aspartame). (*S*)-Aspartic acid is produced from the aspartase-catalysed addition of ammonia to fumaric acid **5**. The amino acid (*S*)-alanine **8** can also be enzymatically synthesized from (*S*)-aspartic acid using immobilized aspartate β-decarboxylase.[9]



Scheme 4: Enzyme-catalysed production of enantiomerically pure (*S*)-aspartic acid **6** and (*S*)-alanine **8**

However, enzymatic transformations can be highly substrate specific and sensitive to the reaction conditions. In general, they tolerate only a small number of solvents, such as H_2O, ethanol and DMSO. In addition, reaction conditions are limited as most enzymes are unstable at high temperatures.

In the drive to provide environmentally friendly, economical and reliable batch scale production of enantiopure drug precursors for the pharmaceutical industry, an obvious gap between biocatalysis and organometallic catalysis exists: the use of small chiral organic compounds as catalysts.

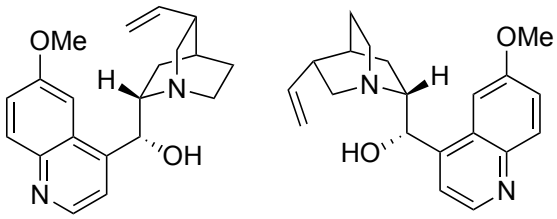
1.1.3 Organocatalysis

Asymmetric organocatalysis is the use of chiral organic molecules in sub-stoichiometric amounts to catalyse asymmetric transformations. Asymmetric organocatalysis has become a hugely successful and rapidly evolving field over the past two decades, and has demonstrated impressive stereoselectivity in hundreds of different reaction types. The potential application of organocatalysis in the synthesis of various types of compounds and functional groups provides a solution to the increasing demand for cheap and sustainable drug production. Indeed, organocatalysis may overtake both metal and enzymes as the most popular method

of asymmetric catalysis.

A large number of organocatalysts are either directly sourced from or related to the 'chiral pool' and are readily available and inexpensive to produce in large quantities as single enantiomers. Several rationally designed synthetic organocatalysts are now commercially available; furthermore, ligands previously used for organometallic chemistry have been shown to function independently as asymmetric catalysts themselves.

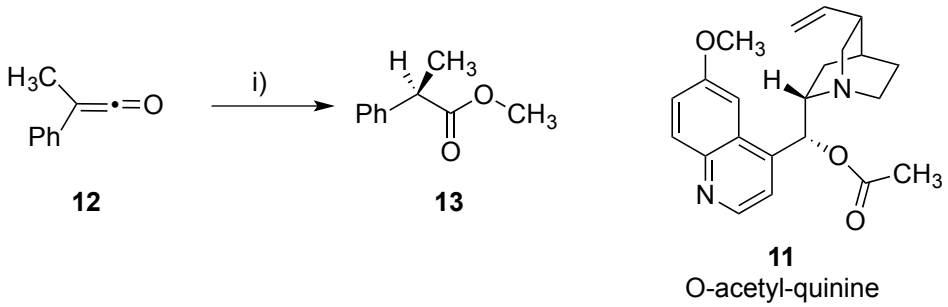
The first asymmetric organocatalytic reactions reported used cinchona alkaloids, a class of natural products. Cinchona alkaloids possess very useful moieties for organocatalysis. They contain a quinuclidine ring, which can act as a Lewis base,[10] a nucleophilic catalyst,[11] and, when alkylated, allows the compound to behave as a phase transfer catalyst.[12] The hydroxyl group can function as a hydrogen bond donor or can be converted into an amine moiety, which can act as a hydrogen bond donor or an aminocatalyst centre.[13]



(*R*,*S*)–**9** (*S*,*R*)–**10**

Figure 1: Natural product-derived diastereoisomeric cinchona alkaloids quinine (*R*,*S*)-**9** and quinidine (*S*,*R*)-**10**

Bredig and Friske reported the first asymmetric organocatalysed reaction in 1912:[14] the presence of cinchona alkaloids accelerated the rate of addition of HCN to benzaldehyde and gave optically active cyanohydrins. The enantiomeric excess was less than 10% and the opposite rotation was recorded when quinine and quinidine were used.[13] In 1940, Pracejus used *O*-acetyl-quinine **11** to catalyse the asymmetric addition of methanol to phenylmethylketene **12**, giving the product **13** in 74% ee.[15,16]



12 **13** **11**
O-acetyl-quinine

Reagents and conditions: i) *O*-acetyl-quinine **11** (1 mol %), MeOH (1.1 equiv.), toluene, 93%, 74% ee

Scheme 5: Pracejus' *O*-acetyl quinine **11** catalysed addition to phenylmethylketene **12**

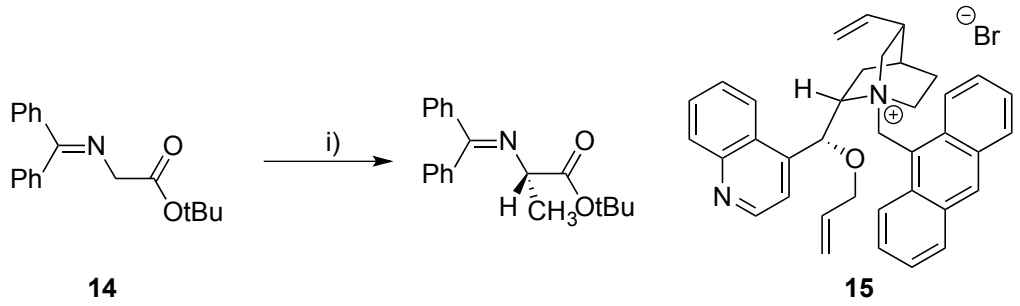
1.2 Types of organocatalysts

A large number of organic compounds with different functional groups have been shown to catalyse synthetic transformations, and, as a result, classification is difficult. However, organocatalysts can be generally classified according to how they activate substrates. This activation can be either active/dynamic (covalent) or passive (non-covalent).

1.2.1 Examples of non-covalent organocatalysts

Non-covalent catalysts include hydrophobic, electrostatic or Van der Waals type interactions such as Brønsted acid and base and hydrogen bonding catalysts. Phase transfer catalysts also operate through non-covalent catalysis as asymmetric inductions occur through a chiral ion pairing mechanism, which also transports reactants between organic and aqueous media.

Phase transfer catalysts facilitate reactions between substrates in different phases by generating an onium-carbanion species that can travel between immiscible phases. Scheme **6** shows a base-promoted alkylation of glycine Schiff base **14** where structurally rigid chiral ammonium salt **15** is responsible for the increased rate and asymmetric induction.



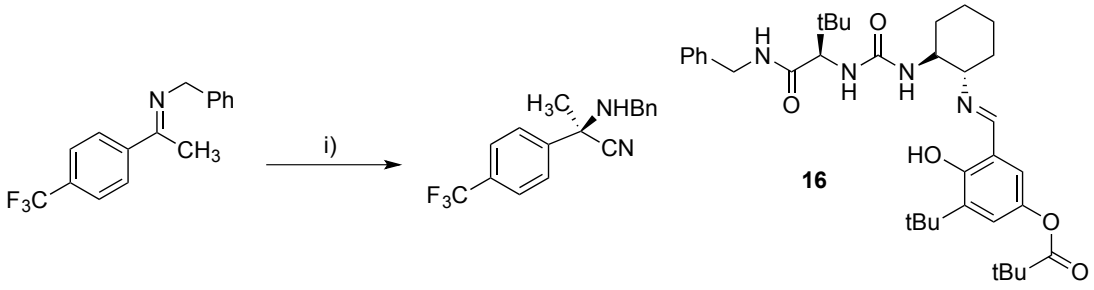
14 **15**

Reagents and conditions: i) 10 mol% **15**, CH_3I, $CsOH.H_2O$, CH_2Cl_2, −60 °C, 71%, 97% ee

Scheme 6: Corey's (1997) chiral quaternary ammonium salt phase transfer catalyst **15** for alkylation of derivatised glycine imines[17]

In this example, the Schiff base **14** reacts with the inorganic base, at the interface, to generate a caesium enolate. This metal enolate then exchanges with the cationic ammonium catalyst providing a chiral environment and increased lipophilicity, thus enabling it to pass into the organic phase of the reaction mixture and be alkylated, giving the product in 97% enantiomeric excess and regenerating the active catalyst **15**.

Hydrogen bonding provided by urea and thiourea-based organocatalysts allow for activation of both the HCN and the *N*-benzyl imine partners in the Strecker reaction (**Scheme 7**).



16

Reagents and conditions: i) HCN, 2 mol % **16**, toluene, −78 °C, *quant.,* 95% ee

Scheme 7: Jacobsen's (2000) Strecker HCN addition to ketoimines using hydrogen bonding urea catalyst **16**[18]

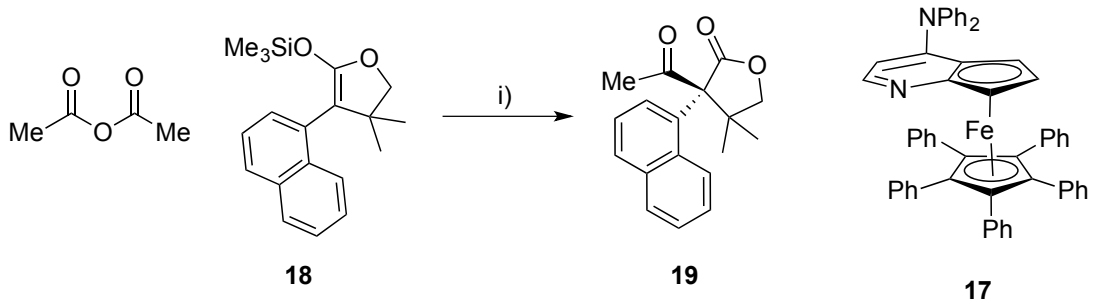
Catalyst **16** is composed of two important parts: the urea functionality is capable of hydrogen bonding to activate the substrate, and the α-amino acid and trans-1,2-

diamino cyclohexane unit are the parts responsible for the asymmetric induction.

1.2.2 Examples of covalent organocatalysts

Covalent catalysis refers to interactions between catalysts and substrates at the reaction centre and includes atom transfer catalysts for epoxidation and aziridination reactions, Lewis base and aminocatalysts (specifically amines catalysing reactions *via* enamine and iminium ion intermediates).

The Fu group designed planar chiral DMAP derivatives as Lewis basic (nucleophilic) organocatalysts. These catalysts can be classed as organocatalysts despite a ferrocenyl framework because the active centre is the 4-(dimethylamino)pyridine unit and not the iron centre (**Scheme 8**).



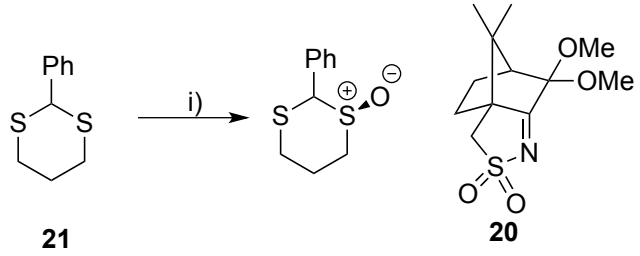
Reagents and conditions: i) 5 % **17**, Et_2O/CH_2Cl_2, r.t., 82%, 99% ee

Scheme 8: Fu's (1999) DMAP derivative **17** for nucleophilic catalysis in *C*-acylations of silyl ketene acetals[19]

DMAP derivative **17** was shown to catalyse the *C*-alkylation of silyl ketene acetals, such as **18**, with dimethyl anhydride. Mechanistically, it is hypothesized that the pyridine sp^2 nitrogen cleaves the anhydride to generate an acetate anion, which promotes the desilylation of compound **18** to generate a reactive enolate. The enolate then reacts with the chiral acylated pyridinium species to generate the product **19** in high enantioselectivity.

The Page group has achieved great success using atom transfer catalysts in aziridination and epoxidation reactions.[20,21,22] Similarly, Page reported moderate to excellent selectivities using oxocamphorsulfonylimine **20** in oxidations of dialkyl

sulfides using hydrogen peroxide (**Scheme 9**).



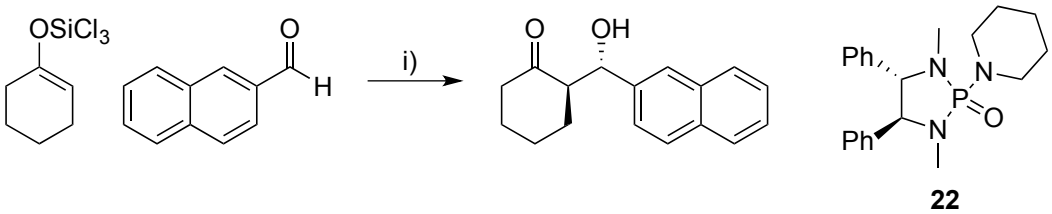
21 **20**

Reagents and conditions: i) **20** (1 equiv.), H_2O_2/H_2O, DBU, CH_2Cl_2, −20 °C, *quant.,* 98% ee

Scheme 9: Page's (1995) catalytic oxidation of sulphide **21** using hydrogen peroxide[23,24]

Sulfonylimine **20** reacts with hydrogen peroxide to produce highly reactive oxaziridine intermediates which transfer oxygen to the sulfides asymmetrically.[25] Four equivalents of DBU are used to suppress the direct oxidation of the substrates.

Denmark published the first example of an asymmetric intermolecular aldol reaction catalysed by an organic base: phosphoramide catalyst **22**.



22

Reagents and conditions: i) 10 mol% **22**, CH_2Cl_2, −78 °C, $NaHCO_3$, 94%, anti/syn >99:1, 97% ee anti

Scheme 10: Denmark's (1999) neutral Lewis base catalysed aldol reaction using phosphoramide catalyst **22**[26]

This indirect aldol reaction uses highly reactive silyl enol ether nucleophiles and affords the aldol products in high conversions and excellent enantioselectivites using aromatic, α-β unsaturated and branched aliphatic aldehydes at low temperatures.

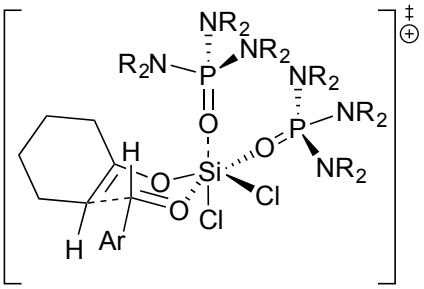
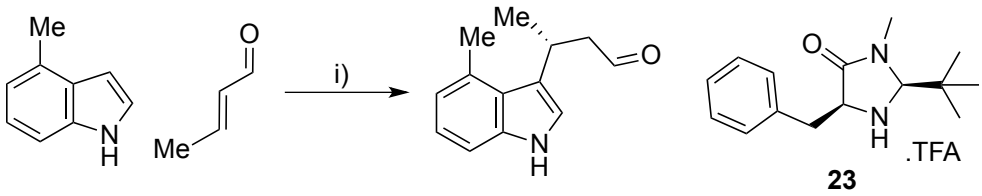


Figure 2: Denmark's proposed chair-like transition state structure

Denmark postulates an associative (closed) structure that assembles the reagents in such a way as to allow chirality to be transferred. A labile cationic hexa-coordinate silicon complex, which organizes the aldehyde, enol ether and two catalyst molecules around its centre, would account for the observed stereochemical control and predominant formation of the anti-product.[27]

Friedel-Crafts type alkylations of pyrroles and indoles with enals were reported by the MacMillan group using secondary amine catalyst **23.**



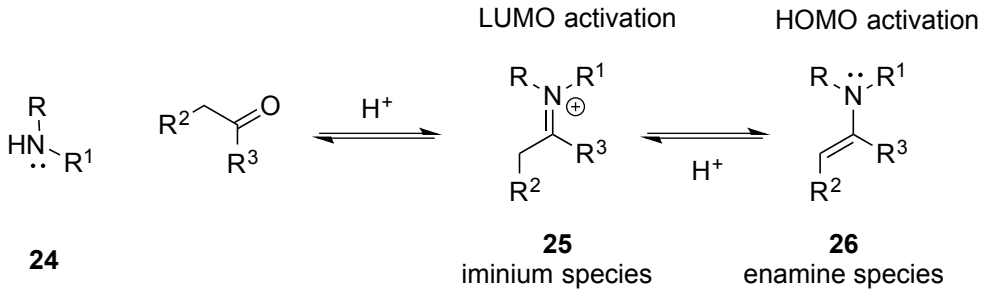
Reagents and conditions: i) 20 mol % **23,** CH_2Cl_2-*i*PrOH, −60 °C, 94%, 94% ee

Scheme 11: MacMillan's (2002) imidazolidinone catalysed indole alkylations[28]

Higher activity and selectivity were observed at low temperatures whilst using one equivalent of trifluoroacetic acid as a co-catalyst. This type of Lewis basic catalysis, which concerns the activation of carbonyls by primary or secondary amines, can be classified as *aminocatalysis*.

2.0 Mechanisms of aminocatalysis

Condensation of primary or secondary amine **24** with an aldehyde or a ketone results in the formation of an iminium species **25** and possible tautomerization to an enamine **26**. These intermediates are highly reactive and undergo facile combination with reaction partners.



Scheme 12: Condensation of amines and carbonyls

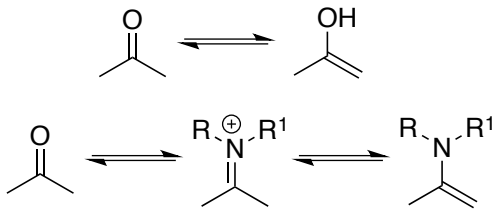
When the reaction cycle is completed, the iminium and enamine moieties can be hydrolysed to release the labile amine catalyst and allow for substrate turnover. These types of activation have been described in similar terms to Lewis acid activation in catalysis.

2.1 Iminium activation

An iminium species is highly susceptible to nucleophilic attack. As the amine reversibly binds to the carbonyl substrate it results in a redistribution of π-electrons toward the electropositive nitrogen centre, making the π-system electron-deficient. This electronic redistribution lowers the energetic potential of the lowest unoccupied molecular orbital (LUMO), resulting in an increased susceptibility toward combination with the highest occupied molecular orbital (HOMO) of the reaction partner.

2.2 Enamine activation

Enamine catalysis involves the generation of a carbon nucleophile from an carbonyl and an amine through an iminium intermediate.

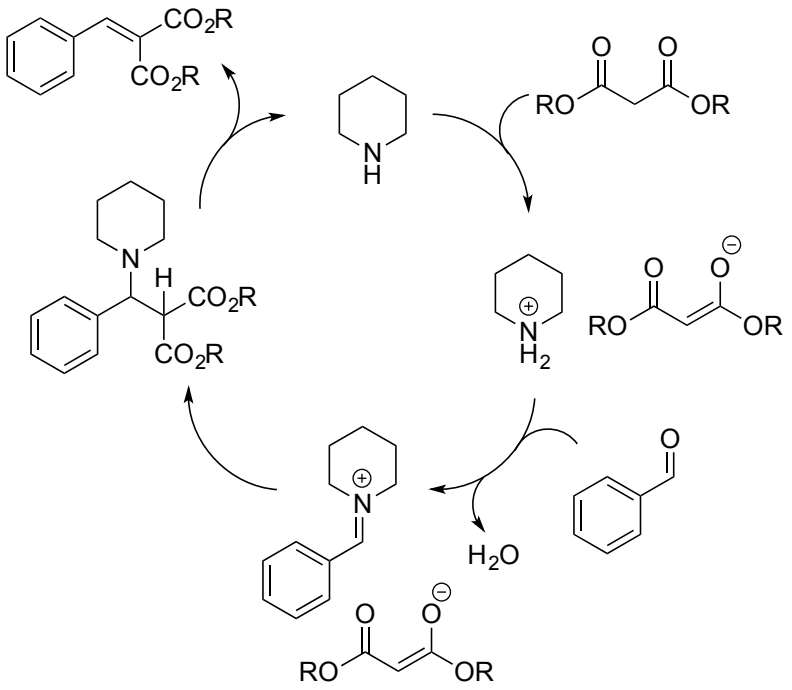


Scheme 13: Keto-enol and iminum/enamine tautomerizations

The conversion of an iminium species to the corresponding enamine is comparable to keto-enol tautomerism. However, whereas the ketone form is favoured in keto-enol systems, in iminium/enamine systems, the formation of the enamine moiety is favoured. Enamines are more nucleophilic than enols due to the increased energy of the highest occupied molecular orbital (HOMO).[29]

2.3 Non-selective aminocatalysis

The first example of non-selective aminocatalysis was reported in 1896, when Knoevenagel described achiral primary and secondary amines, and their salts, catalysing the condensation of β-keto esters, and malonates, with aldehydes and ketones.[30]

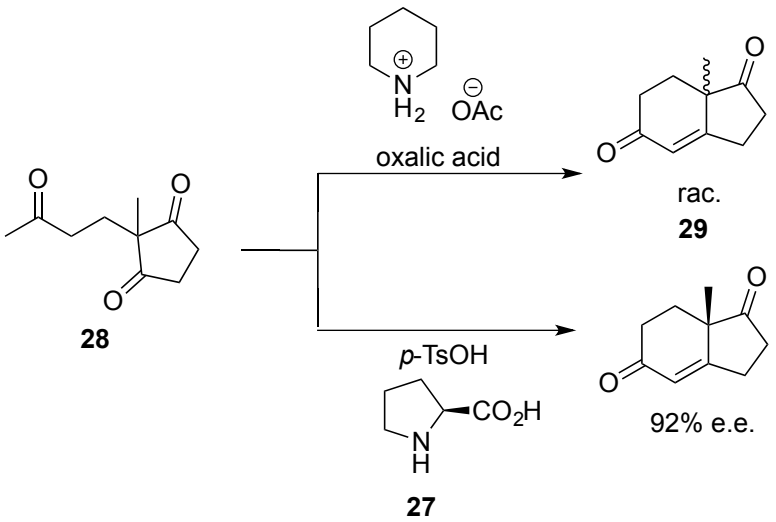


Scheme 14: Piperidine-catalysed Knoevenagel condensation[30,31]

This powerful C-C bond forming reaction, used widely in industry, provided an early foundation for the study of aminocatalysts. Indeed, based on this seminal reaction, primary amino acids were shown to catalyse the Knoevenagel condensation, and secondary amines were used as catalysts in the self- and cross-aldol condensations of aldehydes.[31,32]

2.4 First asymmetric organocatalytic reactions

In 1971, Hajos and Parrish reported that (*S*)-proline **27** could be used in the intramolecular aldol reaction of triketone **28**.[33] It was named the Hajos–Parrish–Eder–Sauer–Wiechert reaction.[34] In the years following, the role of proline was disputed despite the studies undertaken previously. Indeed, Miescher and Wieland (1950) synthesized the racemic dione **29** using achiral piperidinium acetate salts,[35] and Spencer *et al.* (1965) suggested that enamine and iminium ion intermediates were responsible for the accelerated reaction rates.[36] Agami *et al.* also supported the intermediate enamine, and determined that the carbon nucleophile must discriminate between two enantiotopic carbonyl groups.[37]



Scheme 15: Miescher's racemic diketone **29** synthesis and the proline-catalysed asymmetric version

Initially Hajos and Parrish proposed a 'simplified model of a biological system in which (*S*)-proline plays the role of enzyme' nevertheless, despite the literature precedents, the enamine intermediate was dismissed and an 'amino-carbinol' intermediate was suggested.

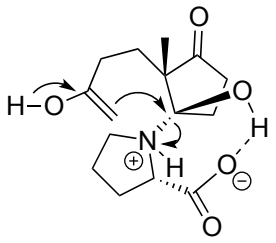
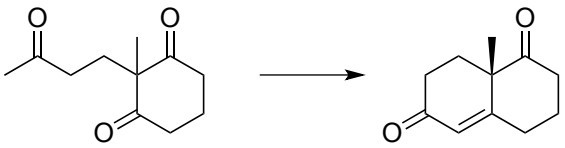


Figure 3: Hajos' proposed amino-carbinol intermediate[38]

However the suggestion was quickly abandoned, and the role of proline was investigated further, leading to the deduction that proline's catalytic action mimics that of the aldolase enzymes.[39] Indeed, the aldolase class 1 mechanism proposed by Rutter clearly describes enamine formation and subsequent aldol-type reaction at a partner carbonyl group.[40] Chang *et al.* reported the amino acid sequence of the rabbit muscle aldolase, and showed that the position of the lysine active site residues were integral to the function of successive enamine and iminium ion catalysis.[41]

Barbas and Lerner *et al.* worked extensively on recreating the action of class 1

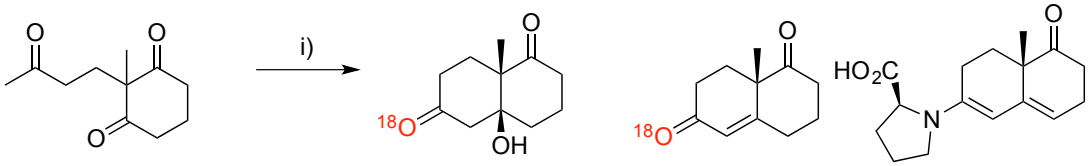
aldolase enzymes in antibodies.[42] The Hajos–Wiechert Robinson annelation was performed using antibody 38C2 giving a variant of the Wieland-Miescher ketone **30** in 94% yield and 96% ee (when (*S*)-proline is used, the product is obtained in 83% yield and 71% ee).



30
AB 38C2: 94 %, 96 % ee
(*S*)-proline: 83 %, 71 % ee

Scheme 16: Synthesis of the Wieland-Miescher ketone **30** by antibody 38C2

Evidence for the mechanism of these reactions was provided when the Hajos–Parrish–Eder–Sauer–Wiechert reaction was conducted in the presence of ^{18}O-enriched water, and the reaction mixtures were analysed using GC-MS detector.[43]



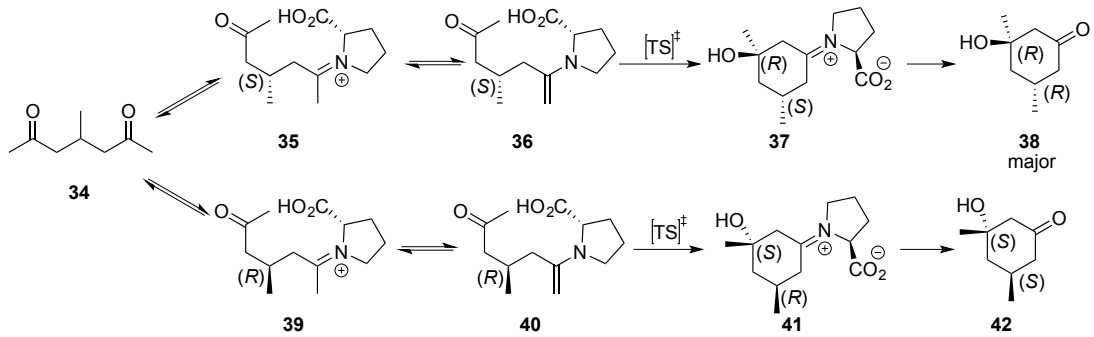
31 40% **32** 50% **33** 10%

Reagents and conditions: i) (*S*)-Proline (25 mol %), 3 vol% H_2O^{18}, d-$_6$ DMSO, Ar, 4 d

Scheme 17: Proof of enamine mechanism by ^{18}O incorporation

The product mixture was composed of aldol addition product **31**, aldol condensation product **32** and dienamine **33**. The aldol addition and the aldol condensation products incorporated a single ^{18}O atom as their molecular ions were two mass units higher than the corresponding ^{16}O products. Dienamine **33** did not incorporate the labelled oxygen indicating that the carbonyl group is where the addition occurs. ^{18}O incorporation supports the enamine intermediate theory, as the final step in the catalytic cycle is the hydrolysis of the iminium ion to furnish the carbonyl group.

Houk attempted DFT mechanistic studies (using B3LYP and 6-31G basis set in Gaussian 98) to explain the selectivity observed when proline was used. The intramolecular aldol reaction of 4-methyl-heptane-2,6-dione **34** was chosen as the model.[44] The transition state energies leading to each of the four possible diastereoisomers were calculated, and the formation of (*R,R*)-cyclization product **38** was found to be favoured: the hydrolysis of (*R,S*)-iminium species **37** gives the (*R,R*)-ketol product. The enamine attack on the ketone, hypothesized to be the rate-determining step, was studied in detail. Although both chair and boat transition state conformers were analysed, only the products from the favoured chair transition state are shown below.



Scheme 18: Houk's DFT mechanistic studies

The preference for (*R,R*)-diastereoisomer **38** is attributed to the transition state leading to (*R,S*)-**37** having favourable electrostatic interactions between the positively charged iminium ion and the alkoxide ion. This interaction means that the transition state $^{\delta+}$NCH--O$^{\delta-}$ distance was calculated as 2.5 Å, whereas the transition state leading to (*S,R*)-**41** had a calculated $^{\delta+}$NCH--O$^{\delta-}$ distance of 3.2 Å. This 1 kcal/mol difference in energy accounts for the experimentally detected 42% ee. Hydrogen bonding in transition state leading to (*R,S*)-**37** also allows for a more planar iminium bond formation compared to the corresponding (*S,R*)-TS, where the forming iminium double bond is somewhat distorted. Hydrogen bonding has been shown to be essential in this reaction, providing charge stabilization in the formation of the alkoxide ion and being responsible for the observed enantioselectivity.[45]

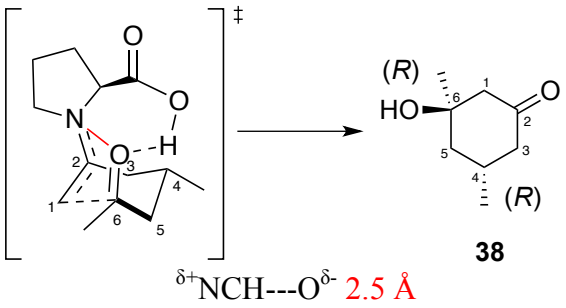
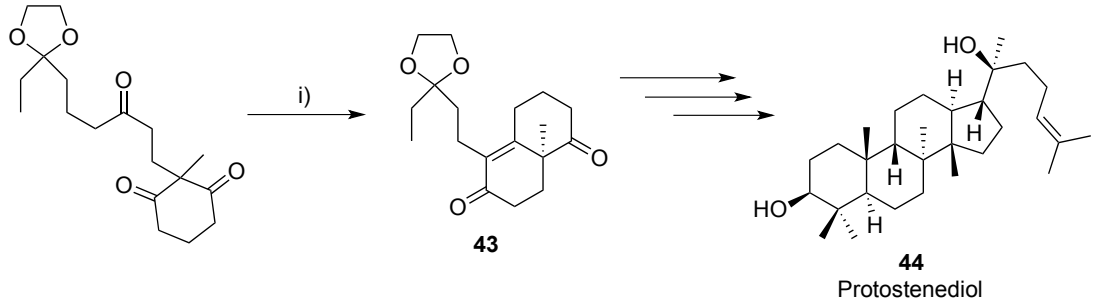


Figure 4: Houk's chair transition state model

Variants of the Wieland-Miescher ketone are synthetically very useful, as octahydronaphtalene dione **43** can be used in the total synthesis of steroids cortisone, norethindrone and progesterone **44**.[46,47,48]



Reagents and conditions: i) (*S*)-phenylalanine (1 equiv.), (+)-camphor sulfonic acid, DMF, 23 °C, 24 d, 77%, 95% ee

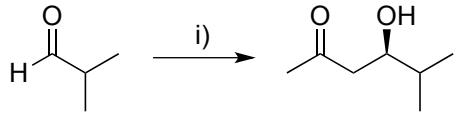
Scheme 19: Hajos-Parrish-Eder-Sauer-Wiechert reaction used to install chiral centres in the framework of bioactive protostenediols in a total synthesis by Corey[49]

3.0 Recent examples of asymmetric aminocatalysis

In the late twentieth century examples of asymmetric amine-catalysed reactions had been sporadically reported with little attention or understanding about their mechanistic similarities. These reactions employed catalysts obtained directly from the chiral pool and gave increasingly impressive enantioselectivities. However, the early exciting results were largely ignored and it was not until a publication by List, Lerner and Barbas in 2000 that the use of (*S*)-proline was explored further.

3.1 Asymmetric aminocatalytic aldol

The aldol reaction is an essential reaction in the formation of new C-C bonds. It relies on the formation of an enol from a carbonyl group which then reacts with an acceptor, usually a less readily enolisable carbonyl group, resulting in the formation of one or two new stereogenic centres.

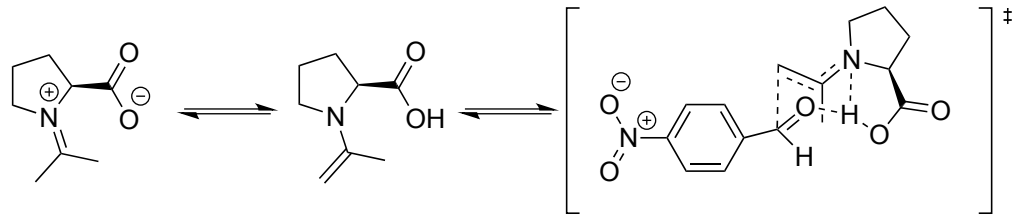


45

Reagents and conditions: i) 30 mol % (*S*)-proline **27,** DMSO: acetone (4:1), r.t., 48 h, 97%, 96% ee

Scheme 20: First proline-catalysed asymmetric organocatalytic intermolecular aldol

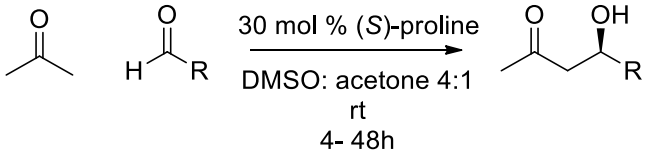
In 2000, List *et al.* reported the first asymmetric aminocatalytic intermolecular aldol reaction using (*S*)-proline **27** as a catalyst (**Scheme 20** and **21**).[50] List describes proline as a unique chiral pool catalyst and attributes the discovery of the proline-catalysed direct intermolecular aldol to an examination of the action of a biocatalyst: the aldolase antibody 38C2.[51] The similarities between the 38C2 antibody and proline's 'micro-aldolase' activity were examined in an asymmetric Hajos–Parrish–Eder–Sauer–Wiechert reaction (**Scheme 16**).[48]

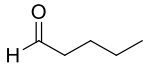
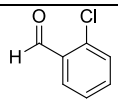
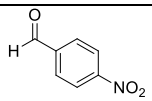


Scheme 21: Proposed Zimmerman-Traxler type transition state for the proline-catalysed aldol reaction between acetone and 4-nitrobenzaldehyde

High yields and enantioselectivities were observed when using 30-40 mol% of proline in aldol reactions with acetone and different aldehydes (**Table 1**).

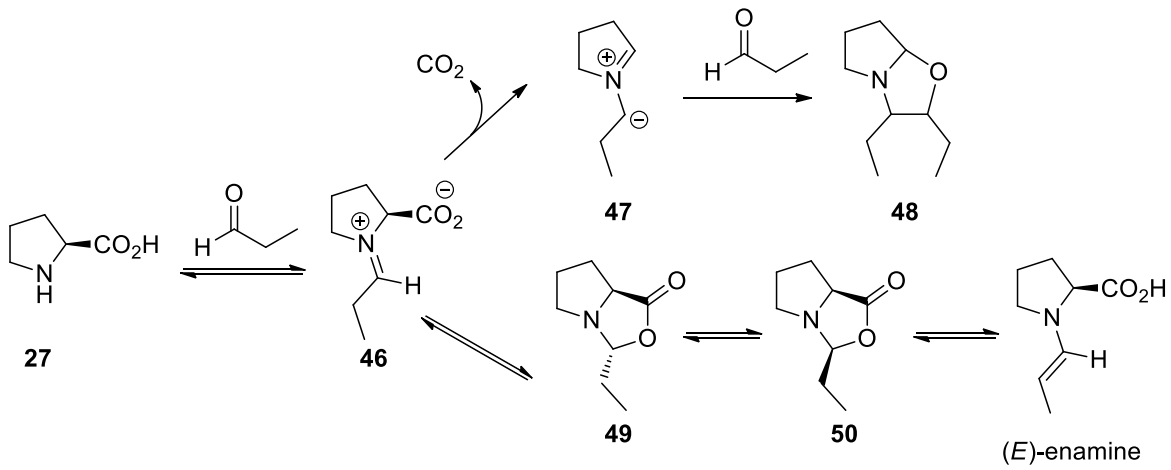
Table 1: Proline-catalysed asymmetric aldol reaction



Entry	Aldehyde	Yield (%)	ee (%)
1		-	-
2		94	69
3		68	76
4		97	96

No conversion was observed when linear aldehydes, such as pentanal, were used; however, branched aldehyde isobutyraldehyde **45** gave the best result (96% ee), though a much longer reaction time of 48 h was required. Lower selectivities were reported when aromatic aldehydes were employed (**Entries 2** and **3**). Acetone was used in large excess to suppress self-aldolisation products, such as azomethine-ylide **47** and subsequent irreversible formation of oxazole **48** or oxazolidinones **49-50** (**Scheme 22**).

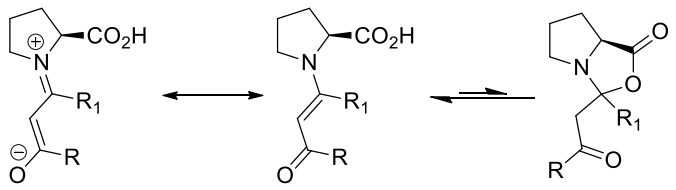
The proline catalysed self-aldolisation of propionaldehyde was investigated by Gschwind *et al.* in an attempt to detect the 'elusive' enamine intermediate, as well as the unwanted species.[52] Two diastereoisomeric oxazolidinones **49** and **50** in thermodynamic equilibrium and the enamine intermediate were identified (**Scheme 22**).



Scheme 22: Possible products and intermediates from a proline catalysed self-aldolisation

The condensation of proline with a ketone or aldehyde substrate can lead to the formation of an oxazolidinone (**49** and **50**, **Scheme 22**), which is said to be in 'a parasitic equilibrium' with the catalytically active enamine intermediate.[54] It has long been assumed that the iminium intermediate is crucial and responsible for rapid interconversions between aldehydes, oxazolidinones and enamine formation.[53] Interestingly, studies using NOESY NMR exchange spectroscopy found that *E*-enamine intermediate was not formed directly from the condensation of proline and the aldehyde but *via* the oxazolidinones, suggested as a concerted E2 mechanism.[52,54] The presence of water was investigated and found to suppress the oxazolidinone formation by shifting the equilibrium from iminium ion **46** to the free proline and aldehyde, which is expected for a reversible condensation reaction.

List *et al.* attempted to isolate enamine intermediates to confirm their structure; however, due to the thermodynamic preference for the formation of oxazolidinones, enamines are difficult to isolate. When 1,3-dicarbonyls are used as substrates, the equilibrium is shifted and the enaminone constitutional isomer **51** is preferred due to the extended conjugation (**Scheme 23**).



51

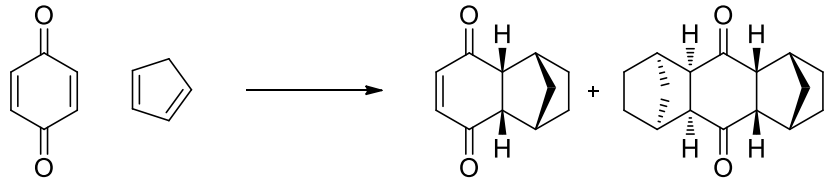
Scheme 23: Enaminone formation

The transition state model of an enamine reacting with an electrophile exhibits similar electronic properties to the enaminone model: in both cases, the electron density is directed away from the electron rich enamine π-system. Crystal structure determination showed that the enamine double bond configuration is always (*E*) and that the position of the carboxylate is *anti* (or trans) relative to the enamine double bond.[55] The same reasoning was applied to catalytic enamines, and this orientation leaves *re* and *si* faces exposed to allow for the adjacent carboxylic acid group to organise the substrates through enantio-discriminating hydrogen bonds, as well as providing stabilization of the transition state structures.

Proline, **27**, has also been applied successfully to intra and intermolecular nucleophilic C-C bond forming reactions (Mannich reaction,[56] Michael reaction,[57] aldol-modified dihydroxylation,[58] cross aldolization of non-equivalent aldehydes[59]) and the introduction of heteroatoms (α-oxygenation of aldehydes with nitrosobenzene,[60] and α-amination of aldehydes with diazodicarboxylates[61,62]).

3.2 Asymmetric aminocatalytic Diels-Alder

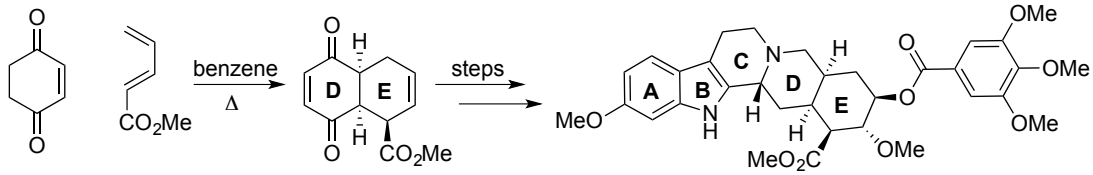
The Diels-Alder reaction is a very useful pericyclic reaction between conjugated *s-cis*-1, 3-diene and dienophile starting materials. The reaction is a [4+2] concerted cycloaddition where two new σ bonds and one new π bond are generated from three π bonds. Otto Paul Hermann Diels and Kurt Alder reported the first example in a landmark 1928 article whilst studying the reaction of benzoquinone **52** with cyclopentadiene where both the monadduct **53** and the diadduct **54** were isolated.[63]



52 **53** **54**

Scheme 24: First reported Diels-Alder reaction

The Diels-Alder reaction was a breakthrough in organic synthesis as it allows for the facile formation of six membered rings with the installation of up to four contiguous new chiral centres. The importance of the Diels-Alder reaction was realised immediately: '*the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps even alkaloids, has been moved near prospect'*.[62] The reaction has indeed been proven a vital tool in the total syntheses of many complex multicyclic compounds including steroids (cortisone,[63] cholesterol,[64] gibberellic acid[65]), alkaloids (reserpine **55**,[66] norsecurinine,[67] strychnine,[68] gelsemine[69]), antifungals (ambruticin[70]) and antibiotics (myrocin C[71]).



52 **55**

Scheme 25: Diels-Alder reaction in the total synthesis of alkaloid (−)-reserpine **55**[72]

The Diels-Alder reaction is stereospecific and the stereochemistry of the dienophile is retained in the product. Attempts to explain the Diels-Alder reaction's observed regio, stereo and diastereo-selectivity have provided organic chemists with the *Alder-endo* and *Frontier Molecular Orbital* theories. The Frontier Molecular Orbital theory, especially, has provided increased understanding of complex pericyclic reactions and has helped to explain the patterns of reactivity that all pericyclic reactions show, thus allowing for far more predictability in synthesis.

In the 1950s, Kenichi Fukui postulated that an approximation of the reactivity of two aromatic hydrocarbons could be predicted by looking at the 'frontier orbitals': the

Highest Occupied Molecular Orbital (abbreviated to HOMO) of one component and Lowest Unoccupied Molecular Orbitals (LUMO) of another.[73] The assumption was that the reactivity of the two electrons (frontier electrons) occupying the HOMO in the ground state are distinct from the other π-electrons. Fukui's theory is described as the Frontier Molecular Orbital Theory and its selection rules are equivalent to those obtained from the principle called "*the conservation of orbital symmetry*" by Woodward and Hoffmann.[74] These two theories state that the ease by which two components react depends on the degree of overlap of orbitals and how close these orbitals are in energy. If the symmetries of the HOMO and LUMO of the diene and those of the LUMO and HOMO of the dienophile, respectively, are found to be of matching symmetry (i.e. in-phase with each other) then concerted cyclic interaction is favourable.[75]

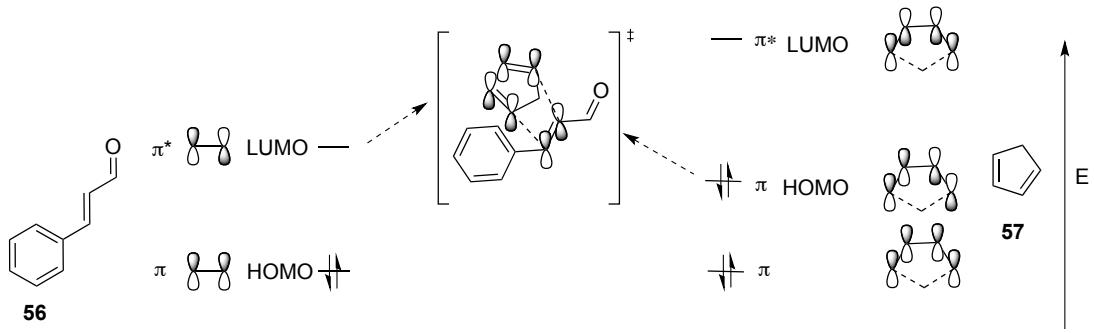


Figure 5: Frontier molecular orbitals of *trans*-cinnamaldehyde **56** and cyclopentadiene **57**

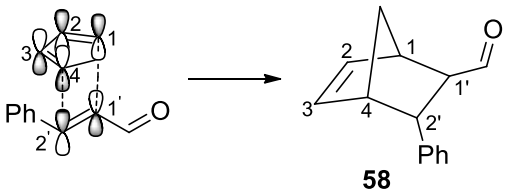
Essentially, the conservation of orbital symmetry requires that during the course of a reaction pathway, the symmetry of the molecular orbitals of the reactants remains identical to the symmetry of those of the resulting products. The Woodward-Hoffmann rules govern all pericyclic reactions both thermal and photochemical:

1) For thermal reactions: 'A ground state pericyclic change is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components are odd.'

2) For photochemical reactions: 'A pericyclic change in the first electronically excited state is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components are even.'

These equations relate to the number of electrons in the participating π bonds of the

two components in the reaction: the diene and the dienophile. The letters $_s$ and $_a$ are refer to *suprafacial* or *antarafacial* character in bond formation and the letters r and q are integer values. For example, the dienophile component, cinnamaldehyde **56**, has a contributing π-bond containing two electrons and therefore counts as a (4q+2) component where q is an integer (and is equal to zero). The diene, **57**, has two π-bonds containing four electrons therefore is the (4r) component where r is equal to one. However, as in all Diels-Alder reactions, the new bonds are forming from the same face; and consequently, the geometry of approach is described as being *suprafacial.* The suprafacial character of the formation of these bonds is shown (**Scheme 26**).

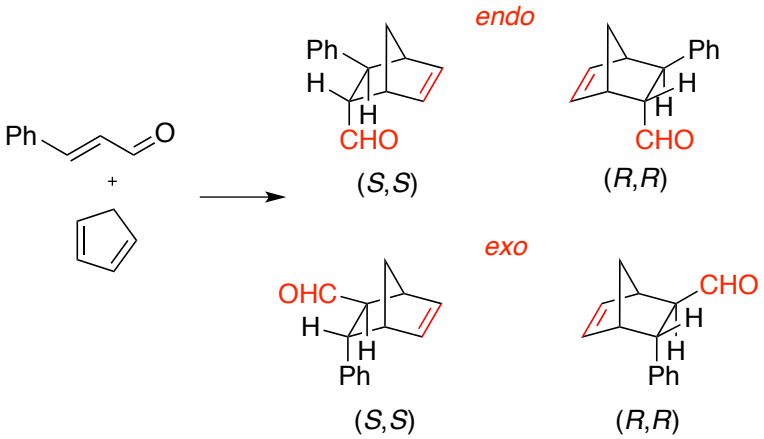


58

Scheme 26: Suprafacial bond formation

Indeed, the formation of the new C1-C1' and C4-C2' bonds occurs on the same face the cyclopentadiene π-bond, and similarly from the same face of the dienophiles, therefore both components are labelled suprafacial or *s*. Consequently we can discount $(4r)_a$ as neither the diene or the dienophile will have bonds forming antarafacially. Only the $(4q+2)_s$ component is counted, as the dienophile satisfies the (4q+2) rule. Accordingly the number of total components is odd and the reaction of cinnamaldehyde and cyclopentadiene is therefore a symmetry-allowed thermal [π4S+π2S] pericyclic reaction (**Figure 5**).

Alder's Endo rule relates to the effect of the orientation of the substituents in the transition state on the resulting products. Indeed, two diastereoisomers can be formed in the Diels-Alder reaction: they have been termed *exo* and *endo* adducts with their names referring to the position of the substituents relative to that of the newly created double bond (**Scheme 27**).

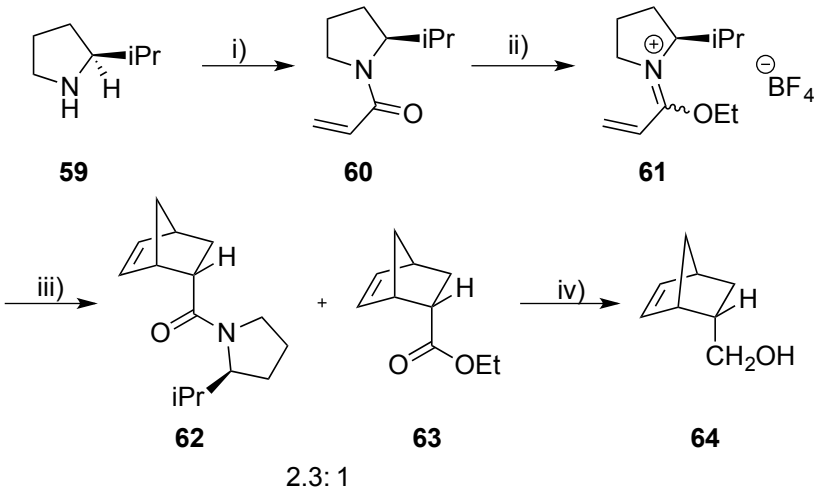


Scheme 27: Diastereoisomeric products from the *trans*-cinnamaldehyde and cyclopentadiene Diels-Alder reaction

The *exo* product is a result of the substituents pointing away from the conjugated system in the transition state. The *endo* has the substituent pointing towards the conjugated system. Alder's *endo* rule describes that when permitting, non-bonding interactions between orbitals of the diene π bond and the group on the dienophile provide stabilization of the transition state resulting in a lower energy profile for the formation of the *endo* isomer. **Scheme 26** shows that between C2 and C3 on the diene and the carbonyl group of the dienophile, the orbitals allow for an additional *secondary orbital overlap* leading to the preferential formation of the *endo* isomer. As a result, although the *endo* transition state experiences more steric repulsion, it is the favoured product under kinetic control, and, conversely, the more stable, less sterically crowded *exo* product is the thermodynamic product.

3.2.1 Studies towards an asymmetric Diels-Alder reaction

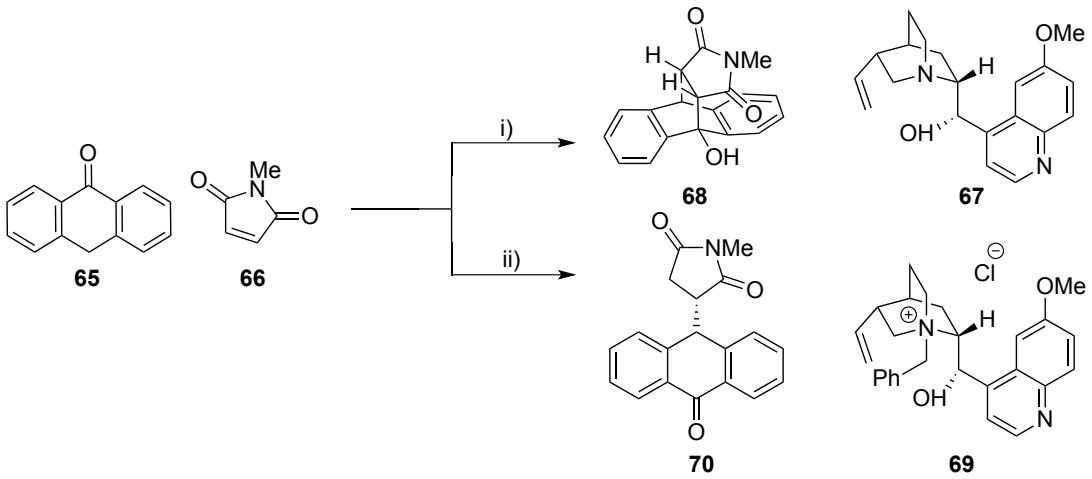
In 1976, Baum reported the use of iminium-activated acetylene tetrafluoroborate salts as substrates for a facile, high yielding cycloaddition reaction with cyclopentadiene.[76] Later, Jung *et al.* reported the first asymmetric Diels-Alder reactions using cyclic amines, such as **59**, as chiral auxiliaries: alkoxy-heterocyclic iminium salts, similar to **61**, were shown to promote the reaction with enantioselectivities as high as 96% ee (**Scheme 28**).[77]



Reagents and conditions: i) $CH_2CHCOCl$, *i*Pr_2NEt, Et_2O, −78 °C; ii) Et_2OBF_4, CH_2Cl_2, 25 °C; iii) C_5H_6, 12 h, 0 °C, H_2O, 2 h; iv) $LiAlH_4$ Et_2O, 85% ee

Scheme 28: Jung's enantioselective Diels-Alder reaction using chiral auxiliaries

Later, Riant and Kagan demonstrated that cinchona alkaloids were capable of catalysing the Diels-Alder reaction. Riant screened a range of alkaloids and β-amino alcohols, and obtained the best results when quinidine **67** was used in chloroform; the reaction between the masked diene anthrone **65** and N-methylsuccinimide **66** at –50 °C afforded the Diels-Alder cycloadduct **68** in 61% ee (**Schemes 29** and **30**).

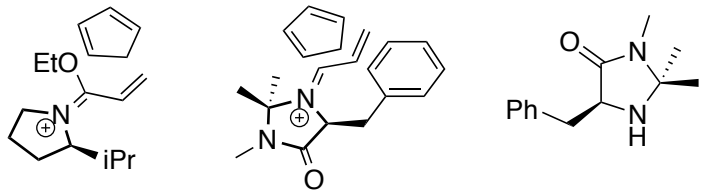


Reagents and conditions: i) **67** (10 mol%), $CHCl_3$, −50 °C 97%, 61% ee;
ii) **69** (20 mol %), KF (1 equiv.), toluene, 80%, 16% ee

Scheme 29 and **30**: Products **68,** from the quinidine-catalysed Diels-Alder reaction, and **70** from phase transfer catalysis Michael reaction

This base-catalysed Diels-Alder reaction was thought to occur by the quinuclidine base abstracting a proton from anthrone to create an oxyanion diene. Hydrogen bonding from the free hydroxyl group on the catalyst and the ion pairing association of the enolate anthrone to the chiral amine counter-ion seem essential for asymmetric induction. Indeed, the transfer of chirality requires as much association between ionic species in the organic phase as possible as a racemic product was obtained when methanol was used as the solvent. When phase transfer catalysis conditions were employed, the Michael addition product **70** was obtained in 16% ee.[78]

In 2000, MacMillan reported the first highly selective asymmetric organocatalytic Diels-Alder reaction.[79] The work by Baume and Jung *et al.* using activated dienophiles containing electron-withdrawing groups inspired MacMillan's research; indeed, he hypothesized that catalysis that typically employed Lewis acids and could be made enantioselective using chiral amine catalysts, such as **71** to generate activated iminium ion intermediates (**Figure 6**).

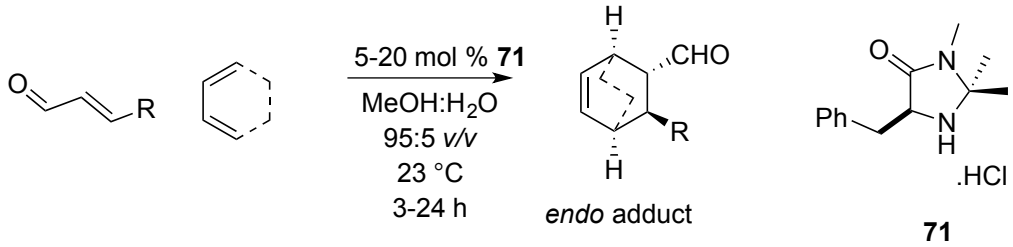


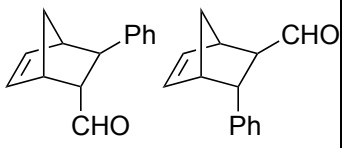
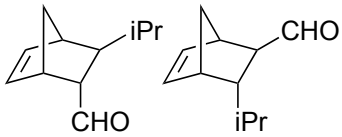
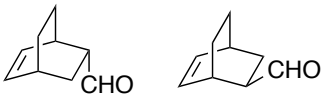
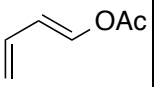
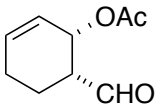
Jung *et al*, **1989** MacMillan *et al*, **2000** **71**

Figure 6: Proposed reaction intermediates using Jung's chiral auxiliary **61** and MacMillan's catalyst **71**[79]

α,β-Unsaturated dienophiles were activated with chiral secondary amine catalyst **71** and then subjected to cyclization reactions with a range of dienes (**Table 2**). MacMillan reported very high enantioselectivities and diastereoselectivities using 5-20 mol% of catalyst **71**. Cyclohexadiene gave the best results in terms of diastereoselectivity, 1:14 *exo*:*endo* isomers (**Entry 3**), whereas changing substituents on the dienophiles did not greatly affect the enantioselectivity.

Table 2: MacMillan's asymmetric organocatalytic Diels-Alder



Entry	Diene	R	Product (*endo*:*exo*)	Yield (%)	*Exo*: *Endo*	*Exo* ee (%)	*Endo* ee (%)
1		Ph		99	1.3:1	93	93
2		*i*Pr		81	1:1	84	93
3		H		82	1:14	-	94
4		H		72	1:11	-	85

In a standard electron demand Diels-Alder reaction, the HOMO of the diene overlaps with the LUMO of the dienophiles, and the reaction can be accelerated by changing the electronic properties of the reactants. Substituting the diene with electron-donating groups raises the energy of the HOMO, whereas the dienophile can be substituted with electron-withdrawing groups (or extended conjugation) to lower the energy of the LUMO. The Diels-Alder reaction can often be accelerated by the addition of Lewis acids such as $AlCl_3$ or BF_3. Lewis acids can coordinate at Lewis basic sites on the dienophile, withdrawing electron density and therefore making the

dienophile more reactive.[80] Similarly, when imidazolinone catalyst **71** reversibly condenses with an α,β-unsaturated aldehyde, the electron density flows toward the electropositive nitrogen centre, lowering the energy profile of the LUMO. The lowering in energy creates a smaller energy gap between the HOMO and LUMO of the reaction partners and allows the reaction to proceed more rapidly. The positively charged iminium species is activated toward nucleophilic attack at the terminal carbon of the conjugated π-system because of the low energy of the empty π* orbital created. Both nucleophilic attacks and cycloadditions can occur as a result.[78]

Catalyst **71** was designed with large enantio-discriminating groups to provide high levels of iminium geometry control, which is considered essential for asymmetric induction. Indeed, condensation of catalyst **71** with aldehyde substrates leads to the exclusive formation of the (*E*)-iminium isomer (**Figure 7**). This orientation avoids steric interactions between the geminal methyl groups on the catalyst and the olefinic substrate.[79] The *re* face of the (*E*)-iminium isomer is shielded by the benzyl group, leaving the *si* face exposed for the cycloaddition to occur.[81,82]

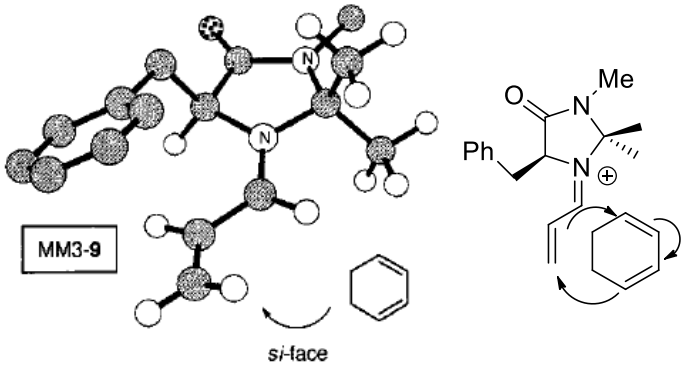
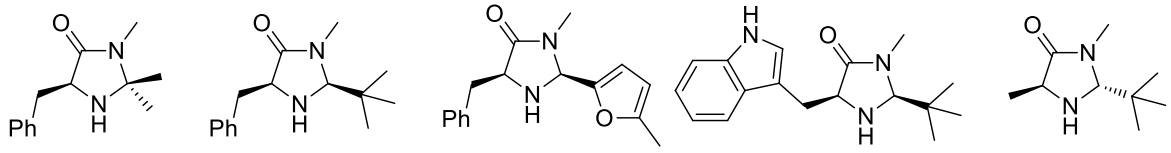


Figure 7: *Si* facial approach of the incoming diene[79]

MacMillan went on to apply catalyst **71** to 1,3-dipolar [4+2]-nitrone additions to α-β-unsaturated aldehydes,[83] α-chlorination of aldehydes,[84] and Friedel–Crafts alkylations of pyrrole systems.[85] The group has also altered the structure of the imidazolidinone catalyst for amine conjugate additions,[86] organocatalytic hydride reductions,[87] and aldehyde α-nitroalkylation using SOMO catalysis.[88]

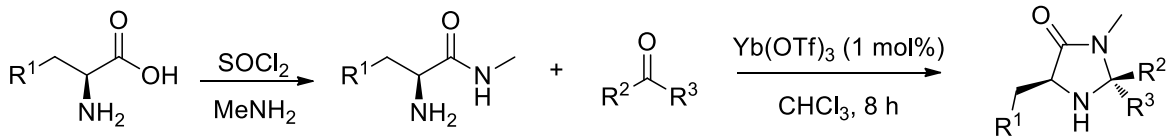


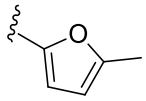
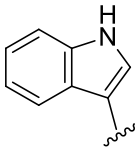
71 **72** **73** **74** **75**

Figure 8: MacMillan's catalysts

MacMillan's catalysts are now commercially available and are easily synthesized from enantiopure and readily available amino acid: *(S)*-tryptophan, (*S)*-phenylalanine, (*S)*-alanine and glycine derivatives, and their condensation with various ketones and aldehydes in the presence of catalytic quantities of Lewis acid.[89]

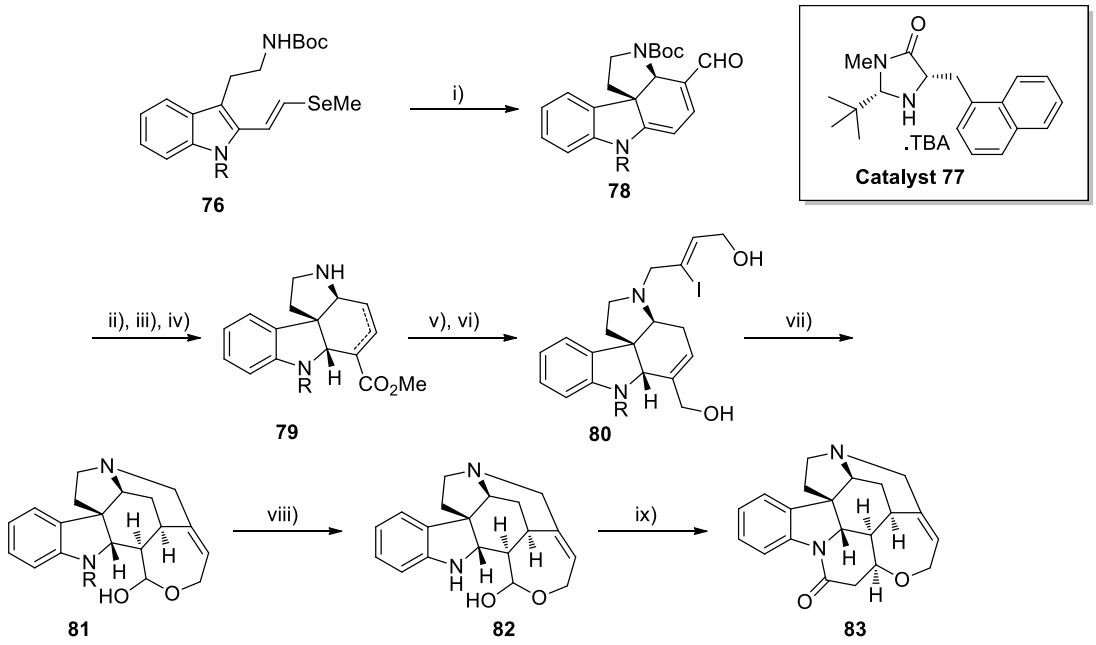
Table 3: Synthesis of MacMillan's catalysts[89]



Entry	R^1	R^2	R^3	Yield (%)	Ee (%)	Imidazolidinone
1	Ph	Me	Me	96	>99	**71**
2	Ph	^{t}Bu	H	22	>99	**72**
3	Ph		H	32	>99	**73**
4		^{t}Bu	H	26	>99	**74**
5	H	H	^{t}Bu	77	>99	**75**

Recently, MacMillan published a collective total synthesis of structurally diverse terpene alkaloids from the *Strychnos*, *Aspidospermine* and *Kopsia* families: (−)-strychnine, (−)-akuammiane, (−)-kopsinine, (−)-kopsanone, (+)-aspidospermidine, (+)-vincadifformine. These structures share a common tetracyclic spiroindoline

core **78** that can be accessed using an asymmetric organocatalytic Diels-Alder/elimination/conjugate addition organocascade sequence from a tryptamine-derived starting material (**Scheme 31**).[90]



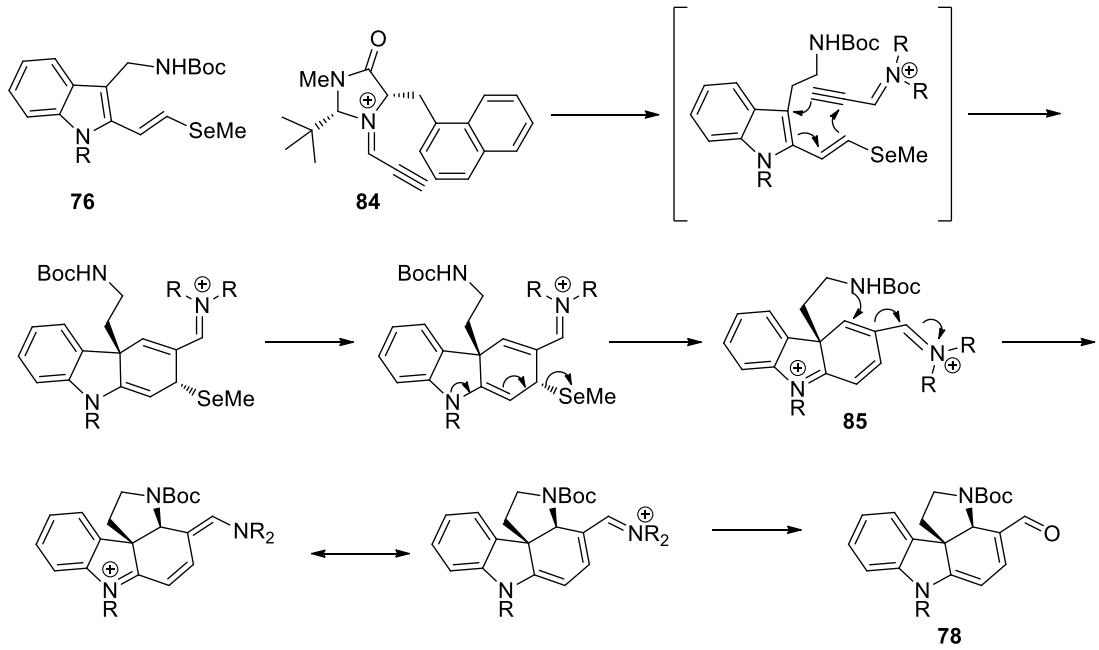
R=PMB, *Reagents and conditions*: i) propynal, 20 mol% **77**.TBA, toluene, 40 °C→ rt, 82%, 97% ee; ii) $(Ph_3P)_3RhCl$, toluene, PhCN, 120 °C; iii) $COCl_2$, Et_3N, toluene, –45 °C→ rt, then MeOH, –30 °C → rt; iv) DIBAL, CH_2Cl_2, –78 °C→ rt, then TFA, –78 °C→ rt, 61% over three steps; v) DBU, K_2CO_3, DMF, (*Z*)-4-bromo-3-iodobut-2-enyl acetate, rt; vi) DIBAL, CH_2Cl_2, –78 °C, 76% over two steps; vii) 25 mol% $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, EtOAc, rt, 58%; viii) PhSH, TFA, 45 °C, 66%; ix) NaOAc, Ac_2O, AcOH, malonic acid, 120 °C, 69%.

Scheme 30: MacMillan's total synthesis of (−)-strychnine **83**

The synthesis began with the organocatalytic *endo*-selective Diels-Alder reaction of 2-(vinyl-1-selenomethyl) tryptamine **76** and propynal in the presence of 20 mol% of imidazolidinone catalyst **77**, resulting in the isolation of the enantioenriched tetracyclic spiroindoline core **78** in 82% yield and 97% ee.[91] The synthesis continued over eight additional steps including a decarbonylation step using Wilkinson's rhodium catalyst, treatment with phosgene and methanol to install the methyl ester group, and DIBAL reduction of the cyclic enamine to introduce the ring junction stereocentre in **79** in 61% overall yield. The allylation reaction with (*Z*)-4-bromo-3-iodobut-2-enyl acetate and alkene isomerization followed by a DIBAL reduction of both ester functionalities gave **80** in 76% yield.

A palladium-catalysed cascade Jeffery-Heck cyclization/lactol formation gave the protected Wieland-Gumlich aldehyde **81** in 58% yield. Natural product strychnine **83** was isolated following a TFA-mediated protecting group removal and subsequent lactam formation by heating in the presence of malonic acid, acetic anhydride and acetic acid (**Scheme 30**).[89]

The asymmetric organocatalytic Diels-Alder/elimination/conjugate addition organocascade sequence started with the formation of iminium **84** from propynal and **77 (Scheme 31**).



Scheme 31: Organocatalytic Diels-Alder/elimination/conjugate addition organocascade sequence to common spiroindoline core intermediate **78**

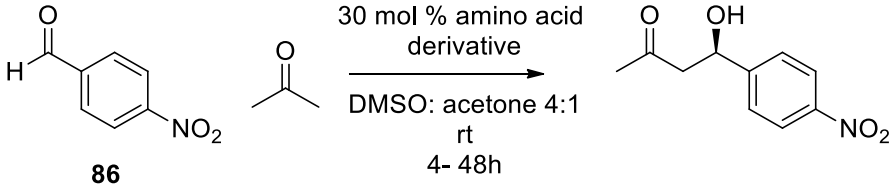
The acetylenic functionality of iminium **84** is orientated as far from the bulky *tert*-butyl group as possible, allowing the naphthyl group to shield the bottom face of the reacting alkyne to impart maximum enantiotopic discrimination. The organocatalytic Diels-Alder step generated solely the *endo* isomer. The *in situ* β-elimination of methyl selenide yielded unsaturated iminium **85** which then underwent a second iminium-catalysed step: the Michael addition of the pendant *N*-carbamate to form the pyrrolidine ring. Hydrolysis yielded the enantioenriched tetracyclic spiroindoline core **78** in 82% yield and 97% ee.[89]

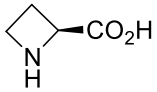
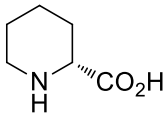
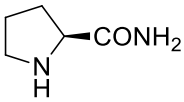
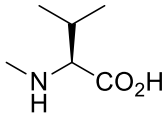
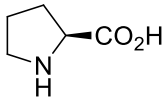
4.0 Proline-derived catalysts

Proline has proven to be a very versatile catalyst, affording high enantio- and diastereoselectivities as well as being cheap and available in both enantiomeric forms. However, proline has limitations: its limited solubility in all but very polar solvents such as dimethyl sulphoxide, methanol and water restricts potential applications. It also requires high catalyst loadings in order to complete reactions in a tolerable timescale.

In order to understand the structure-activity relationship of the secondary amine catalysts, proline-type catalysts were assessed in organocatalytic reactions. List screened commercially available amino acid derivatives in the aldol reaction of acetone and 4-nitrobenzaldehyde **86** (**Table 4**).

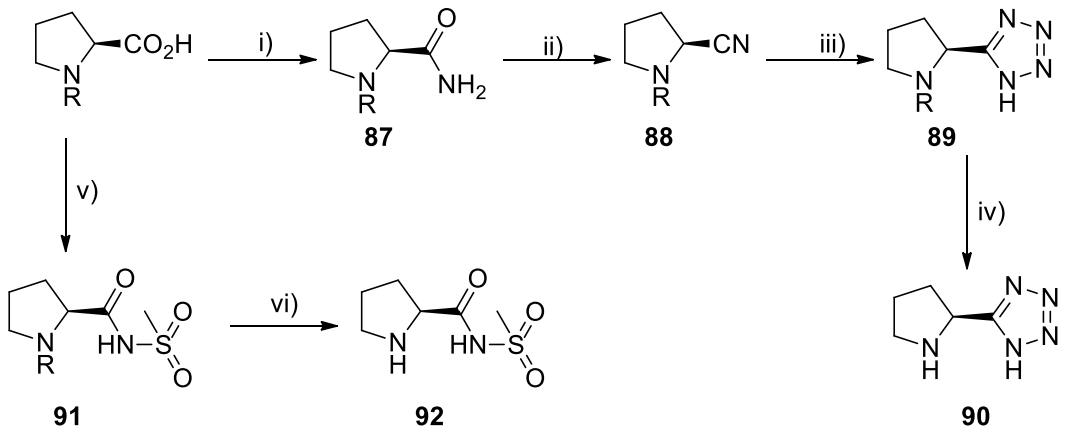
Table 4: Amino acid derivative screening in asymmetric aldol



Entry	Amino acid derivative	Yield (%)	Ee (%)
1		55	40
2		<10	-
3		<10	-
4		<10	-
5		68	76

Both the pyrrolidine ring and carboxylic acid group were found to be necessary to catalyse the reaction and to impart chirality. The carboxylic acid functionality acts as a Brønsted acid co-catalyst, aiding the formation of the iminium ion; and the enamine species facilitates enantiofacial discrimination by hydrogen bonding. The bifunctional nature of proline allows for both Brønsted acid and nucleophilic Lewis base catalysis *via* enamines and iminium ions.[50]

Ley synthesized tetrazole **90** and acyl sulphonamide **92** in order to improve solubility, whilst retaining the pKa profile of proline (**Scheme 32**).[92]

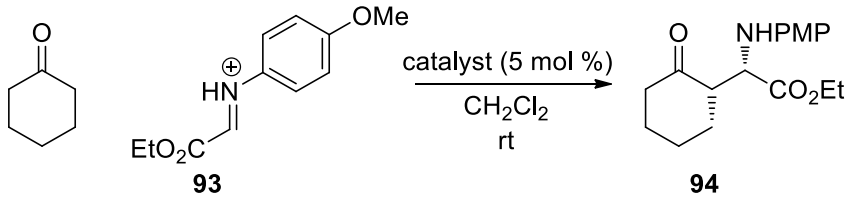


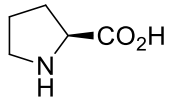
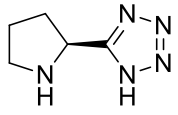
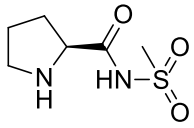
R= Cbz, *Reagents and conditions*: i) EDAC, HOBT, NH_3 (aq), rt, 24 h, 100%; ii) *p*-TsCl, pyridine, CH_2Cl_2, rt, 72 h, 45%; iii) NaN_3, NH_4Cl, DMF, 95 °C, 8 h, 78%; iv) 10% Pd/C, H_2, AcOH/H_2O, rt, 4 h, 89%; v) methanesulfonamide, EDAC, DMAP, CH_2Cl_2, 48 h, rt, 60%; vi) 10% Pd/C, H_2, MeOH, rt, 20 h, 98%.

Scheme 32: Synthesis of catalysts **90** and **92**[91]

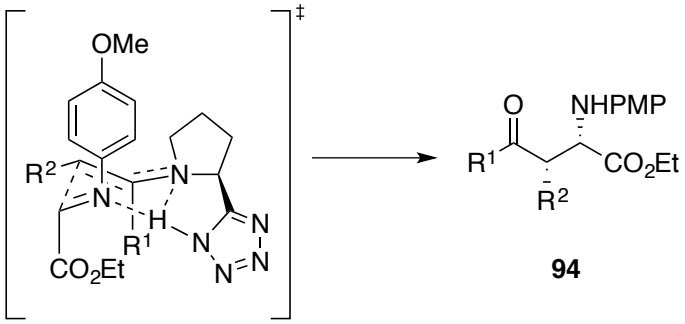
The synthesis of tetrazole **90** was adapted from the reported synthesis of a pentapeptide; an EDAC and HOBt mediated coupling reaction quantitatively furnish amide **87**, which is then converted to the corresponding nitrile by dehydration in the presence of *p*-TsCl.[93] Addition of sodium azide and gentle heating resulted in tetrazole formation and the Cbz protecting group was removed by hydrogenation with Pd/C to give catalyst **90** in high yield. From the same commercially available *N*-benzyloxycarbonyl-(*S*)-proline, acyl sulphonamide **92** was synthesised using another EDAC mediated coupling with methanesulphonamide facilitated by DMAP. The catalysts were assessed using the Mannich reaction between cyclohexanone and imine **93** (**Table 5**).

Table 5: Mannich reaction between imine **93** and cyclohexanone catalysed by proline-derived catalysts



Entry	Catalyst	Time (h)	Yield (%)	d.r. syn:anti	ee (%)
1	 **27**	2	0	-	-
2	 **90**	2	65	19:1	>99
3	 **92**	24	65	19:1	83

The use of catalysts **90** and **92** improved on the yields and selectivities observed when proline was used as the catalyst where, in the example shown (**Table 5**), no conversion was observed. Lower catalyst loadings (as low as 1 mol% in the case of catalyst **90**) still provided fast reaction times and no detrimental effect on enantioselectivity was observed. Again, the diastereo- and enantioselectivity were thought to be induced by hydrogen bonding which provides a rigid chiral environment, as suggested by Houk.[94] The tetrazole group causes the *p*-methoxyphenyl group on the imine to sit axially to avoid gauche interactions, resulting in *syn*-product **94**.

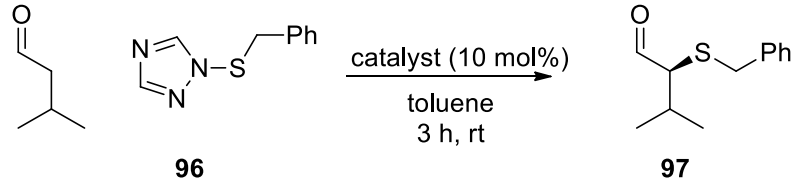


Scheme 33: The PMP group of imine **93** sits axially, resulting in preferential formation of *syn*-product **94**[92]

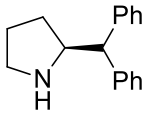
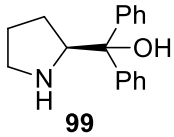
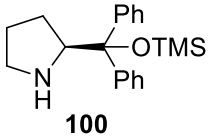
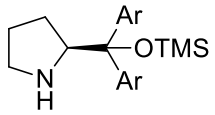
Tetrazole **90** was also used as a catalyst for nitro-Michael and aldol reactions[95] as well as the *N*-nitroso aldol reaction of aldehydes and nitrosocarbonyl compounds generated *in-situ*.[96]

Jørgensen was the first to describe organocatalyst **95**, which was realised after a series of optimisation steps on prolinol derived catalysts for the α-sulfenylation reaction of isovaleraldehyde.[97] Screening of catalysts began with (*S*)-proline **27** which was shown to give racemic product in poor yield. The diaryl proline-derived systems were explored because they were thought to provide effective enantiofacial shielding and therefore provide increased stereoselectivities.

Table 6: Proline-derived catalysts screened in α-sulfenylation of isovaleraldehyde

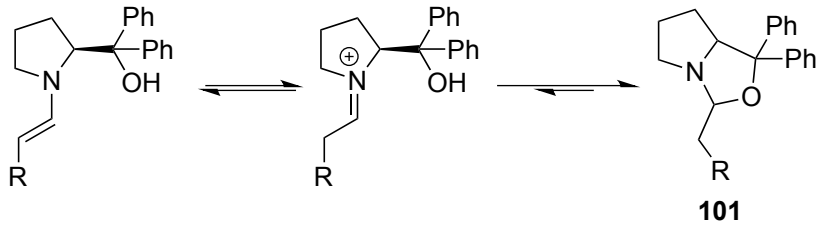


96 **97**

Entry	Catalyst	Yield (%)	Ee (%)
1	**27**	16	0
2	 **98**	56	25
3	 **99**	-	-
4	 **100**	99	77
5	 Ar= 3,5-(CF_3)-C_6H_3 **95**	90	98

While diarylmethylpyrrolidine **98** gave a low yield and disappointing enantioselectivity, diarylprolinol **99** gave no substrate turnover whatsoever. The potential formation of oxazolidine **101**, a parasitic species similar to the oxazolidinones observed when using proline as a catalyst, was thought to be responsible.[96] Various silyl protecting and aryl groups were tested and a combination of trimethylsilyl and bis(trifluoromethyl)phenyl groups greatly improved reactivity and selectivity. The large trimethylsilyl group and the biaryl system always favour the (*E-s-trans)* enamine, believed to have the lowest energy profile. Although organocatalyst **95** does not contain any Brønsted acid catalytic

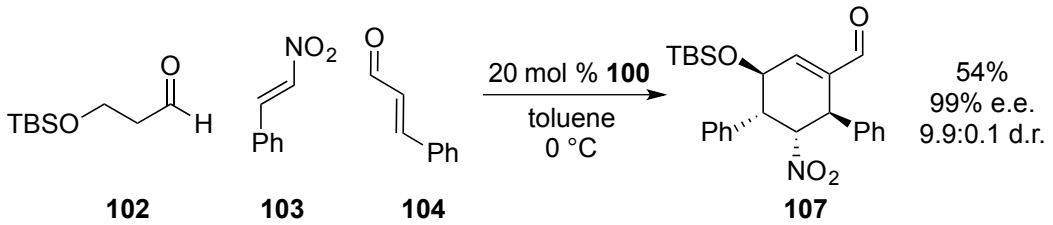
sites, the asymmetric induction occurs through face-shielding stereocontrol, in a manner similar to MacMillan's imidazolinone catalysts.



Scheme 34: Catalyst **99** deactivation through oxazolidine formation

Jørgensen's TMS-protected diarylprolinol catalyst **95** can induce high enantioselectivity and turnover for both HOMO and LUMO pathways. It has since been employed in the benzylation of α,β-unsaturated aldehydes,[98] cycloaddition reactions,[99,100] aziridinations of 2,4-dienals,[101] epoxidations of α-β unsaturated aldehydes,[102] α-aminations of aldehydes[103] and α-fluorinations of aldehydes.[104]

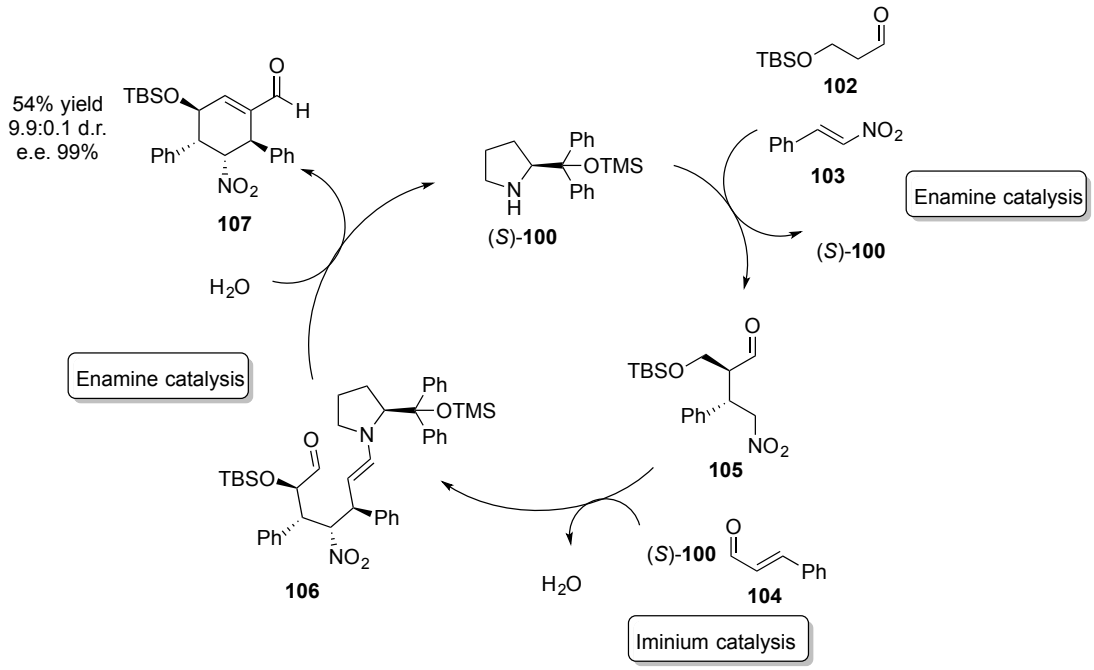
Furthermore, as catalysts of this type are capable of both forms of activation, they can participate in cascade reactions as the formation of consecutive enamine and iminium ion is controlled to produce targets with multiple stereogenic centres. Recently, Enders employed diarylprolinol catalyst **100** in a Michael/Michael/aldol condensation sequence to produce tetra-substituted cyclohexene carbaldehydes.[105]



Scheme 35: Michael/Michael/aldol condensation 'domino' reaction sequence

Four stereocentres are formed with complete enantioselectivity and high diastereoselectivity from a three-component reaction catalysed by 20 mol % of **100**. First, aliphatic aldehyde **102** condenses with catalyst **100** to form an enamine intermediate, which undergoes a Michael-type addition reaction with β-nitrostyrene **103**. As β-nitrostyrene is a more reactive Michael acceptor than

cinnamaldehyde, the first step is completely chemoselective. Once the reaction is complete, the enamine adduct is hydrolysed to furnish the γ-nitroaldehyde product **105**, the only observable intermediate (using gas chromatography) as the subsequent steps are too fast. Catalyst **100** is then free to participate in the activation of cinnamaldehyde, generating the corresponding iminium ion. The iminium ion combines with the γ-nitroaldehyde and the resulting enamine **106** undergoes ring closure through an intramolecular aldol condensation step to yield the polyfunctional cyclohexene derivative **107**. Although the final product is an α,β-unsaturated aldehyde, its steric bulk prevents it from participating further in the catalytic cycle.



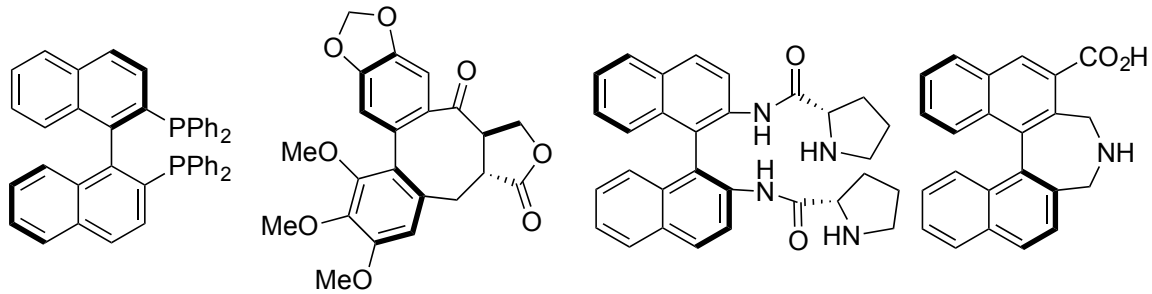
Scheme 36: Catalytic cycle of Enders cascade reaction

Theoretically, the production of 16 different stereoisomers (2^4 stereoisomers) is possible in a reaction that generates four stereogenic centres. In fact, only two enantiomerically pure diastereoisomers are formed. The selectivity is attributed to the first Michael addition step, which was previously shown to be highly selective when (*S*)-proline was used as the catalyst.[106] The selectivity of the Michael reaction generates a product that allows, through sterically favourable interactions, the selectivity to be retained and improved in the following steps.

5.0 Axial chirality

Although the most commonly encountered type of chirality arises from a chiral centre, such as a tetrahedral carbon atom with four different substituents, chirality in a compound can also originate from chiral planes, axes or helices. Axial chirality results from the non-planar arrangement of four groups in pairs about a chiral axis and is observed in compounds such as allenes, 2,2-disubstituted binaphthyls and tetra-ortho-substituted biphenyl compounds where steric hindrance prevents rotation about the Ar-Ar bond.

In the biaryl systems, if the energy barrier to bond rotation is sufficiently large then isolation of separate rotational conformers, known as atropoisomers (from the Greek, *a* = not, *tropos* = turn), can be achieved.[107,108] Atropoisomers with large rotational barriers to racemization have been used extensively as ligands in asymmetric catalysis.[109] These axially chiral scaffolds are popular because they are configurationally stable and possess permanent stereochemical environments. Consequently, mechanistic studies are simplified due to a reduced number of possible diastereoisomeric pathways.[110] Atropoisomerism is also a key feature in a number of natural products, chiral auxiliaries, drugs and, more recently, organocatalysts. Locked bridging aryl bonds have been shown to dramatically alter the chemistry of compounds; from completely changing natural product binding capacities to altering catalyst activity.



108 **109** **110** **111**

Figure 10: Examples of axially chiral compounds

BINAP **108**, perhaps the most widely studied axially chiral compound, has been successfully used as a very selective ligand due to its rotationally stable axis and flexibility in coordinating a wide variety of metals.[111] The natural product (–)-

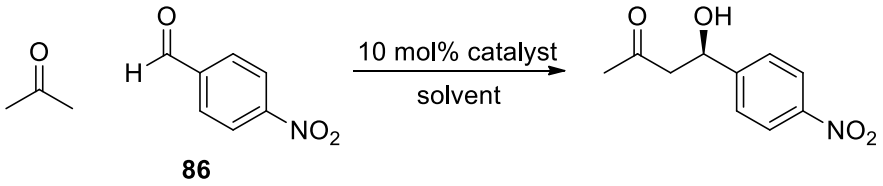
steganone **109** is biologically active and displays anticancer activity. The conformation of steganone is fixed at room temperature due to the rigidity of its eight membered ring. Only the $(S)_{ax}$ conformation can bind to the tubulin active site, inhibiting *in vitro* and *in vivo* polymerization of microtubules (halting cell division).[112]

5.1 Axially chiral aminocatalysts

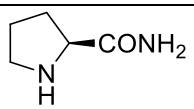
Many of the most widely studied organocatalysts are derivatives of proline. However, as discussed above, proline can undergo decarboxylative decomposition upon condensation with electron-deficient aldehydes, removing it from the catalytic cycle.[113] Alterations can be made to the structure of proline; however, due to difficulty in modifying the pyrrolidine scaffold, modifications are limited to functional group manipulations on the carboxylic acid functionality. These manipulations have led to far more soluble and reactive variants than the parent proline structure and have shown impressive catalytic activity (catalysts **90**, **92**, **95**). Despite these successes, there is still great interest in developing more structurally varied organocatalysts with greater molecular diversity, steric influence and additional sources of chirality.

Prolinamide (*S*)-**110**, synthesised from optically active 1,1'-binaphthyl-2,2'-diamine and (*S*)-proline, and '*synthetic amino acid'* catalyst (S)-**111** are both examples of successful axially chiral organocatalysts. Shi first synthesised compound **110** to catalyse the aldol reaction of ketone and aryl aldehyde substrates. High enantioselectivities (up to 98%) and diastereoselectivities (>98:2) were obtained when acetic acid was used as additive (10 mol%).[114] For aldol reaction catalysis, Maruoka targeted catalyst **111**, featuring a rigid binaphthyl backbone with a pendant carboxylic acid group.[113] Catalyst **111** was designed to ease enamine formation: without an α-substituent, the steric hindrance would be lower, promoting the initial condensation step. Furthermore, because basicity and nucleophilicity profiles of **111** are lower than that of proline, selectivity should also improve. Shi and Maruoka independently assessed their axially chiral catalyst variants against the corresponding prolinol species in the aldol reaction of **86** and acetone.

Table 7: Aldol reaction assessment[114]



86

Entry	Catalyst	Catalyst loading (mol %)	Solvent	Time (h)	Yield (%)	Ee (%)
1	 **112**	10	Acetone	48	80	30 (*R*)
2	**110**	10	Acetone	72	58	65 (*R*)
3	**27**	5	DMSO	24	18	71 (*R*)
4	**111**	5	DMSO	24	70	93 (*R*)

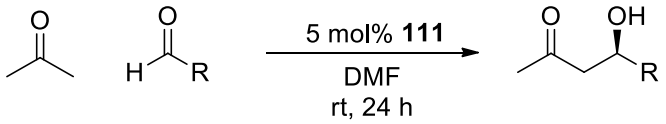
When compared to proline-derived amide **112**, axially chiral prolinamide **110** was found to improve the selectivity, although a longer reaction time was needed.[115,116] The increase in enantioselectivity could be attributed to the extra aminocatalytic centre, increased steric bulk and chiral influence, arising from the binaphthyl backbone.

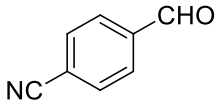
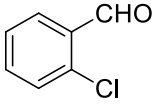
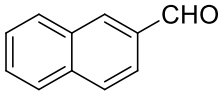
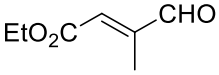
When azepine **111** was used (**Entry 4**), improvements in yield and enantioselectivity were observed when compared to proline; the aldol product was generated in 71% yield and 93% ee.[113] A kinetic study of amino acid catalysts **111** and **27** was performed under the same reaction conditions and the yield of the aldol product was monitored over a 24 h period.[117] Although the rate of reaction with proline was initially higher, the conversion quickly stopped (18%) due to proline consumption through oxazolidine formation (48%). The design of catalyst **111** prevents degradation by decarboxylation, providing greater chemical stability while retaining the enantioselective hydrogen bonding ability.

The success of catalyst **111** led it to be screened further with different solvents: high enantioselectivities identified *N*,*N*-dimethylformamide as optimal.[116] Aldehyde substrate scope studies revealed that heteroaromatic, electron-deficient aromatic and

olefinic aldehydes were best tolerated, whereas simple aromatic aldehydes gave excellent enantioselectivities but disappointing yields (**Entry 3**).

Table 8: Aldol reaction of acetone with aldehydes catalysed by (*S*)-**111**

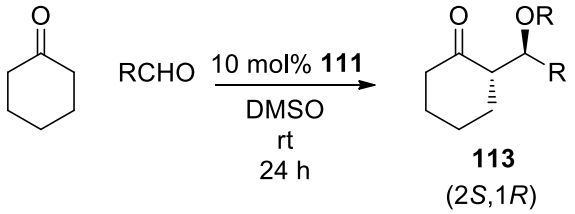


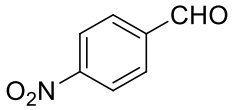
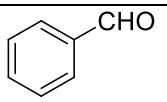
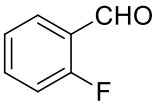
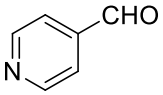
Entry	Aldehyde	Yield (%)	Ee (%)
1		80	95 (*R*)
2		91	95 (*R*)
3		35	96 (*R*)
4[a]		81	96[b]

[a)] 108 equivalents of acetone, entries **1-3**; 27 equivalents [b)] absolute configuration not determined

When cyclohexanone was used as the nucleophile with 4-nitrobenzaldehyde, the highest yields and diastereoselectivities were obtained using dimethylsulfoxide as the solvent alongside increasing the catalyst loading to 10 mol%.[117]

Table 9: Aldehydes screening in (*S*)-**111** catalysed reaction with cyclohexanone



Entry	Aldehyde	Yield (anti:syn)	Anti ee (%)	Syn ee (%)
1		98 (95:5)	98	5
2		38 (91:9)	98	16
3		99 (>95:5)	99	-
4		93 (>95:5)	97	12

Screening aldehydes with cyclohexanone revealed that despite β-naphthyl- and benzaldehyde giving low yields, all the aldehydes employed gave outstanding levels of diastereoselectivity and enantioselectivity (**Entry 1**).[116] The stereochemistry of the major *anti*-aldol product **113** was determined to be (2*S*,1*R*) which allowed the proposal of a tentative transition state in which the *re* face of the aldehyde approaches the *re* face of the enamine (**Figure 11**).

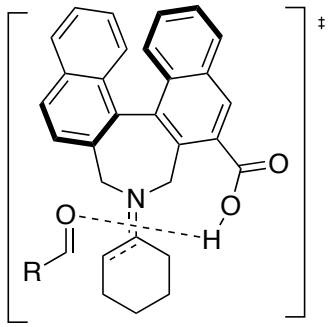
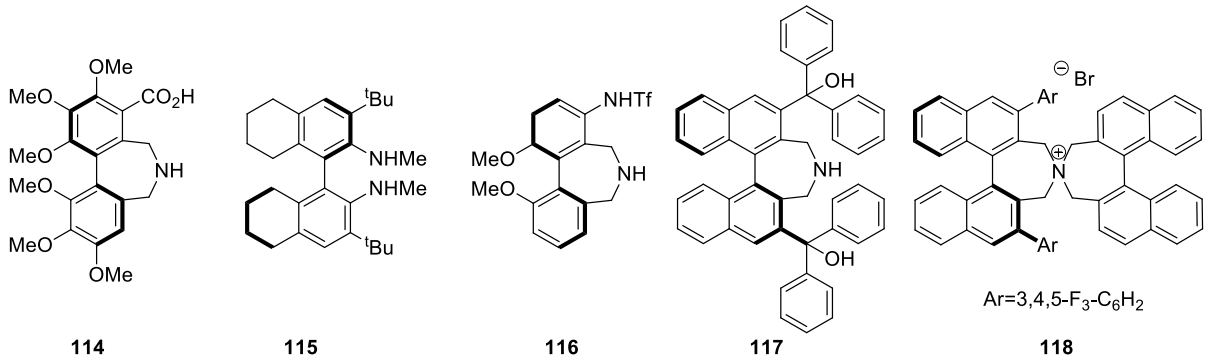


Figure 11: *E-s-trans* transition state of (*S*)-**111** enamine[116]

The enamine derived from **111** must therefore adopt an *anti* conformation with respect to the aryl carboxylic acid directing group, in a similar manner to the *anti*-enamine postulated in the proline-catalysed aldol reaction (**Scheme 16**).

5.2 Maruoka's organocatalysts

Maruoka synthesized a range of very successful axially chiral organocatalysts that operate by enamine (**114**, **116**, **117**),[118] iminium (**115**),[119] or phase transfer (**118**)[120] catalysis.



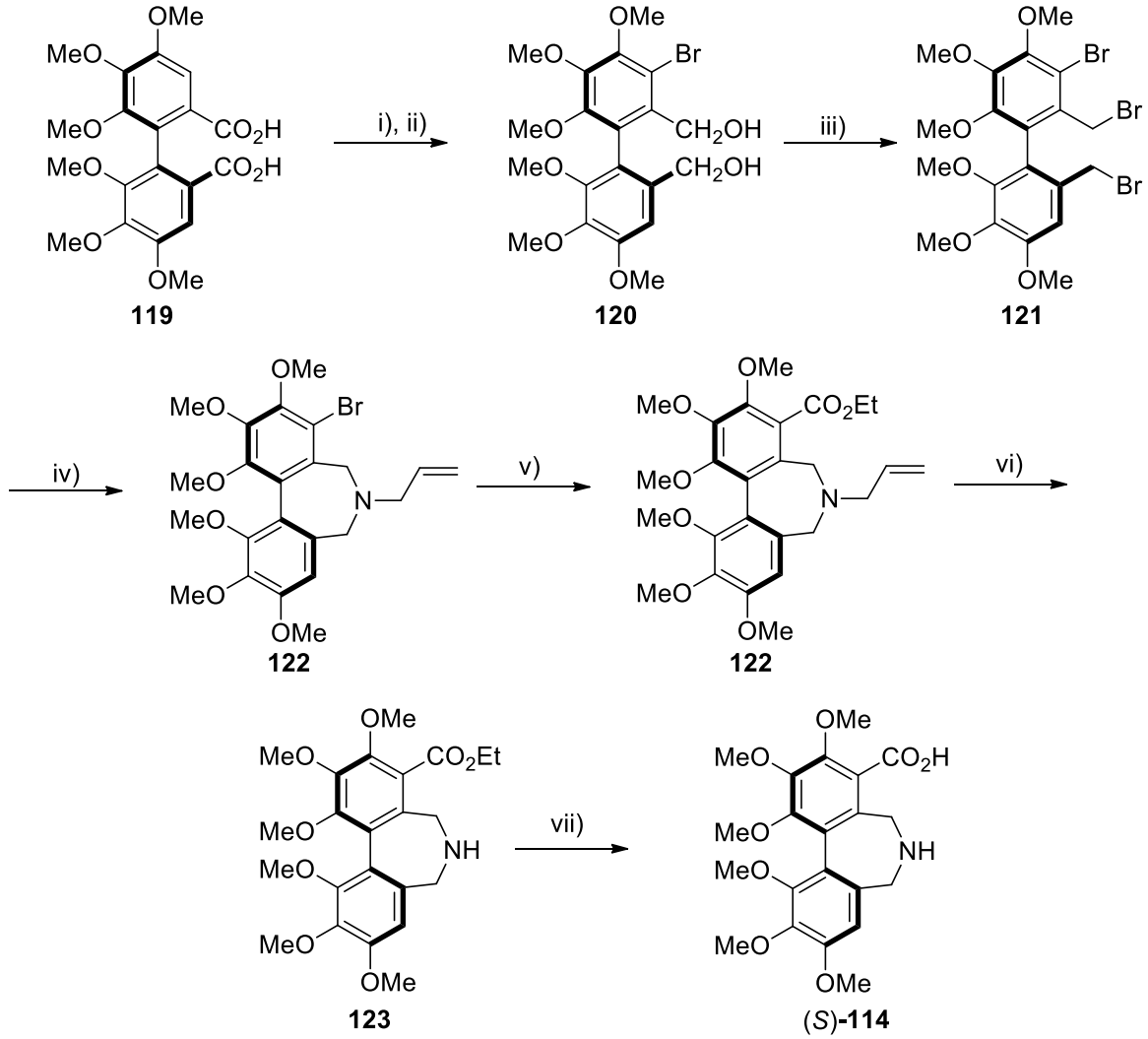
114 **115** **116** **117** **118**

Figure 11: Maruoka's biphenyl and binaphthyl catalysts

The Maruoka catalysts share a common feature: a biaryl axially chiral backbone, which provides chemical stability and allows for potential extensive derivatization.[122] Indeed, the group has capitalized on this tuneable feature to design a range of sophisticated organocatalysts with a variety of aryl pendant functionalities that dramatically alter the steric and electronic properties of each catalyst, allowing them to be tailored to fit the exacting conditions of each reaction type.

5.2.1 Aldol reaction

Despite the success of catalyst **111**, a possible drawback was the high catalyst loading (10 mol%) required in the aldol reaction, hypothesized to be caused by the moderate nucleophility of the benzylic amine. To improve the activity, catalyst (*S*)-**114** was synthesized (**Scheme 38**).[121]



Reagents and conditions: i) BH_3-SMe_2, $B(OMe)_3$, 0 °C → rt, 5 h; ii) Br_2, pyridine, –20 °C → 0 °C, 5 h, 95% over two steps; iii) PBr_3, CH_2Cl_2, rt, 5 h, 78%; iv) allylamine, CH_3CN, 50 °C, 12 h, 99%; v) *n*-BuLi, THF, –78 °C, 1 h, then $(EtO)_2CO$, rt, 1 h, 48%; vi) $Pd(OAc)_2$, PPh_3, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2, 35 °C, 12 h, 98%; vii) 1M NaOH, MeOH-THF, reflux, 10 h, 98%.

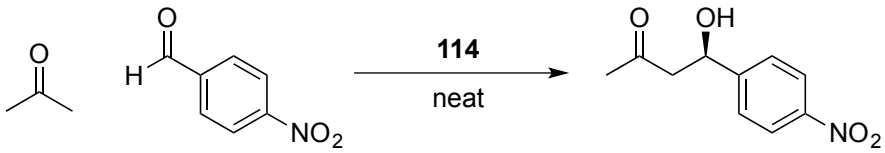
Scheme 37: Synthesis of catalyst (*S*)-**114**

The synthesis of the catalyst commences with dicarboxylic acid compound **119**, which is reduced to the corresponding diol using borane-dimethyl sulfide (BMS) followed by aromatic bromination using molecular bromine and pyridine at low temperature, affording **120** in 95% yield over the two steps. Using the Appel reaction, diol **120** was converted into the corresponding dibromide using phosphorus tribromide at room temperature in 78% yield. Ring closure using a double nucleophilic substitution with allylamine gave **122** in high yield. Lithiation with *n*-BuLi and substitution with ethyl carbonate furnished ethyl ester **123** in 48% yield. A

palladium-catalysed deallylation and saponification of the ethyl ester gave **114** in almost quantitative yield over two steps.

The presence of electron-donating methoxy groups on the biphenyl backbone of **114** increases the nucleophilicity of the catalyst, making it far more reactive. As a result, the catalyst loading can be reduced to as little as 0.1 mol%, delivering the aldol product in comparable enantioselectivities albeit with longer reaction times (**Table 7** and **10**).[120]

Table 10: (*S*)-**114** catalyst loading studies



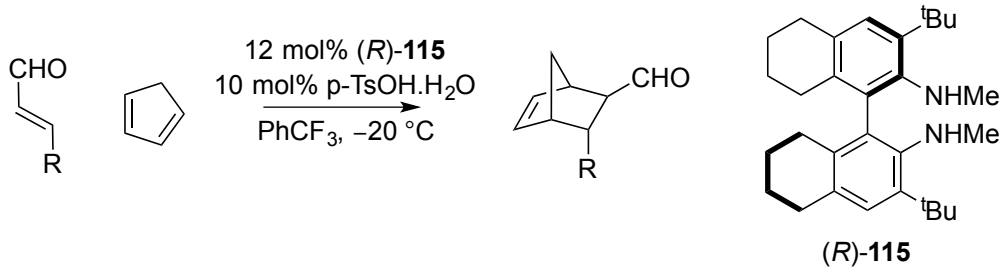
86

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

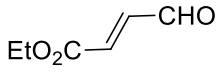
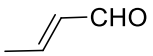
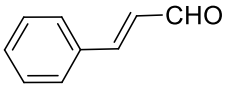
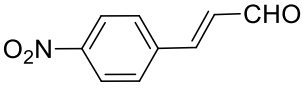
5.2.2 Diels-Alder reaction

A highly selective *exo*-selective Diels-Alder reaction was reported using diamine binaphthyl catalyst (*R*)-**115** in the presence of co-catalyst *p*-toluenesufonic acid.[122] High diastereo- (up to 20:1) and enantioselectivities (up to 95% ee) were obtained in the reaction between α,β-unsaturated aldehydes and cyclopentadiene. Unfortunately, the scope of this reaction is limited as other dienes were not as well tolerated (**Table 11**).

Table 11: Aldehyde screening in Diels-Alder reaction



(*R*)-**115**

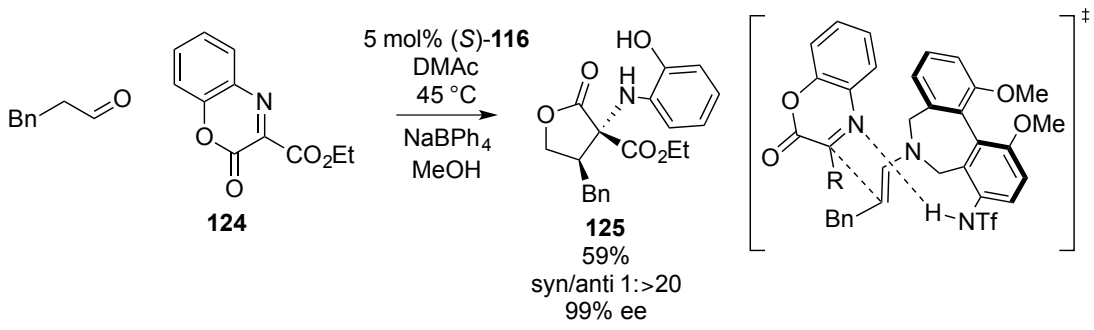
Entry	Aldehyde	Yield (%) (*Exo*:*endo*)	Ee *exo* (%)
1[a]		90 (5.5:1)	83
2		72 (>20:1)	88
3		80 (13:1)	92
4		99 (7.4:1)	95

[a)] Reaction conducted in toluene at −60 °C

The design of catalyst **115** was developed over several screening steps. Substituents on the amine, both electron-donating and -withdrawing were tested: 2,2'-bis(methylamino) derivatives were found to have the best activity, facilitating both fast iminium salt formation and hydrolysis. Introduction of increasingly large groups at the 3- and 3'-positions on the octahydrobinaphthyl rings resulted in increasing levels of *exo* selectivity and enantioselectivity. The large *tert*-butyl substituents at the 3- and 3'-positions block one face of the iminium intermediate, leaving the other face free for the approach of cyclopentadiene.[123] Mechanistic and NMR studies found that the presence of both methylamine functionalities on the catalyst is essential for rapid iminium formation and acceptable turnover. It is hypothesized that the condensation of the methylamine and aldehyde moieties is aided by the presence of an ammonium unit formed after protonation of the remaining amine moiety by *p*-toluenesufonic acid.

5.2.3 Mannich reaction

Amino sulfonamide (*S*)-**116** (**Figure 11**) has been successfully used as a catalyst for the *anti*-Mannich reaction of activated ketimine **124** with aldehyde substrates.[124]



Scheme 38: *Anti*-Mannich reaction using axially chiral amino sulfonamide catalyst **116**

The stereochemistry of the products from this reaction have led to the proposal of a transition state model (**Scheme 38**) which suggests that while both the *E-s-trans* and *E-s-cis* enamines are formed upon condensation of catalyst **116** with 3-phenyl propanal, only the *E-s-cis* enamine is reacts to give the (3*S*,4*R*)-isomer predominantly.[125]

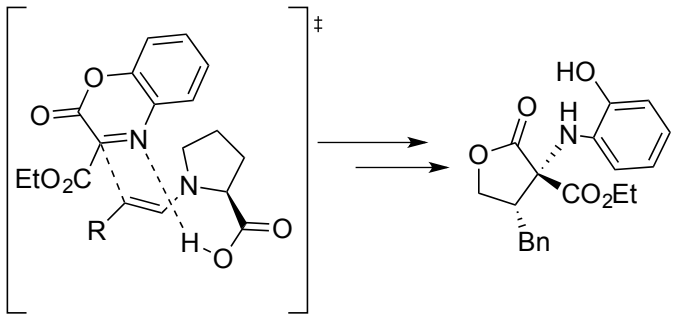


Figure 12: (*S*)-Proline transition state E-*s-trans* model leading to the syn-isomer[123,124]

In comparison, in the (*S*)-proline catalysed reaction, the dominant species is the E-*s-trans* enamine which reacts from its *re* face with the *re* face of **124** resulting in the major *syn* (3*S*,4*S*) isomer (**Figure 12**).

5.2.4 Hydroxyamination of aldehydes

In addition to axially chiral proline analogues (*S*)-**111** and (*S*)-**114,** Maruoka has also synthesized an axially chiral version of Jørgensen's diaryl prolinol catalyst **95**. Catalyst (*S*)-**117** was used in the *α*-aminoxylation reactions between aldehydes and nitrosobenzene.[122]

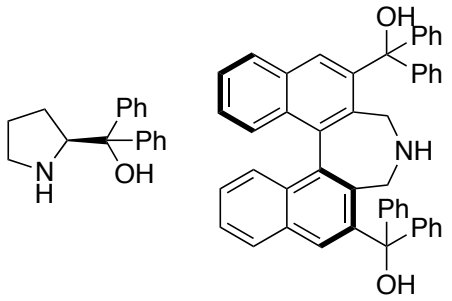
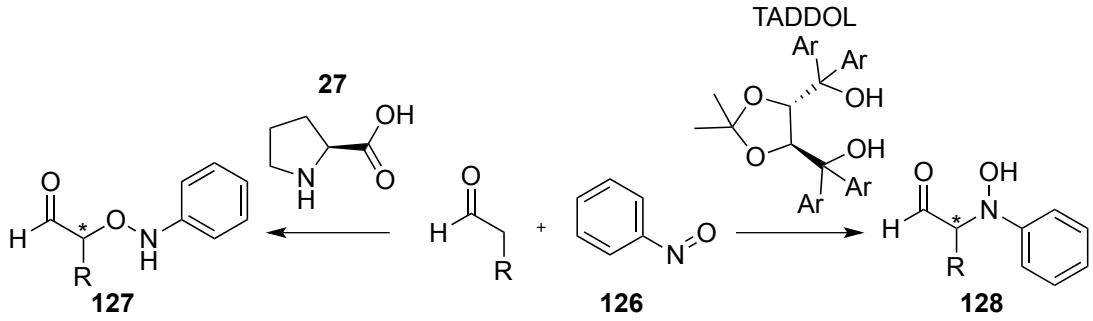


Figure 13: Axially chiral version of Jørgensen's diaryl prolinol catalyst

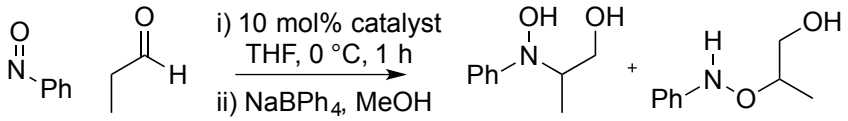
Reactions between aldehydes and nitrosobenzene **126** can result in either the *O*-nitroso aldol product or the *N*-nitroso aldol product depending on the catalyst used. Catalysts with mild acid functionalities, such as tetrazole **90**, proline **27** and glycolic acid, have been shown to afford the aminooxylation product **127** (*O*-nitroso product).[126,127,128] The hydrogen bonding generated by the presence of an acid functionality causes nitrosobenzene **126** to behave as an oxy-electrophile, resulting in the introduction of oxygen at the α-position in aldehydes. Tertiary alcohols, such as TADDOL, in combination with pre-formed enamines result in the exclusive formation of the hydroxyamination product **128** (*N*-nitroso product).



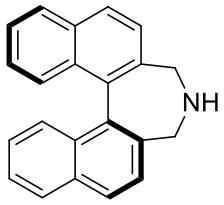
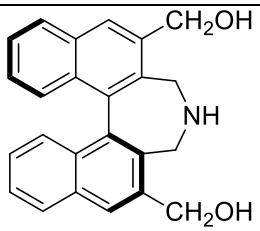
Scheme 39: *N*-nitroso **128** and *O*-nitroso **127** products

Maruoka wanted to create a catalyst that could activate both the aldehyde and nitrosobenzene component, through *in situ* enamine formation and hydrogen bonding, respectively, to provide a convenient route to hydroxyamination products. The group screened the reaction of propanal and nitrosobenzene with (*S*)-**129**, which contains no acid or alcohol functionality. Following a reduction with sodium borohydride, the resulting amino-alcohol was produced with excellent chemoselectivity. However, the reaction was low-yielding and gave poor ee. The addition of alcohol solvents, such as methanol or *tert*-butanol, was found to have a beneficial impact on enantioselectivity. Accordingly, catalyst **132**, possessing two hydroxyl groups, was tested under the same reaction conditions, and improvements in yield and enantioselectivity were observed. Sterically congested catalyst **117** gave high yields and excellent regio- and enantioselectivity, whereas **99** gave very poor conversion; deactivation of **99** is thought to have occurred through oxazolidine formation.[129]

Table 12: Catalyst screening for the hydroxyamination of propanal

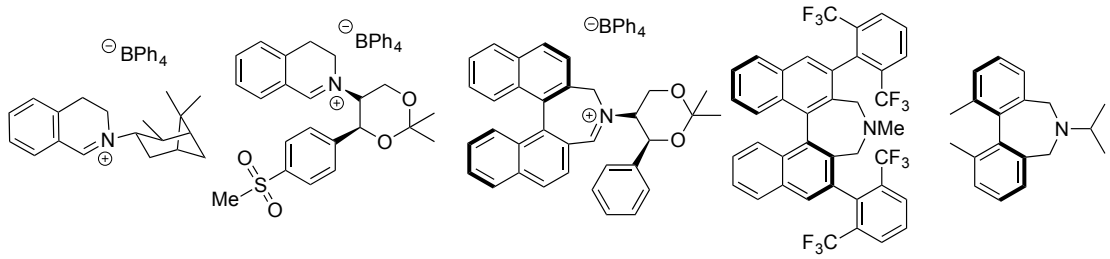


126 **130** **131**

Entry	Catalyst	Ratio 130/131	Yield (%)	Ee (%)
1	 **129**	>99/1	22	29 (*S*)
2	 **132**	>99/1	55	77 (*S*)
3	**117**	>99/1	90	99 (*S*)
4	**99**	>99/1	9	23 (*R*)

5.3 Page's axially chiral atom transfer catalysts

The Page group is well established in the field of organocatalysis; specializing in the development of electrophilic atom-transfer catalysts. These catalysts have evolved from dihydroisoquinoline-based such as **133** and **134**, to more complex axially chiral backbones, such as **135** for epoxidations,[20] and **136** and **137** for aziridinations.[21]



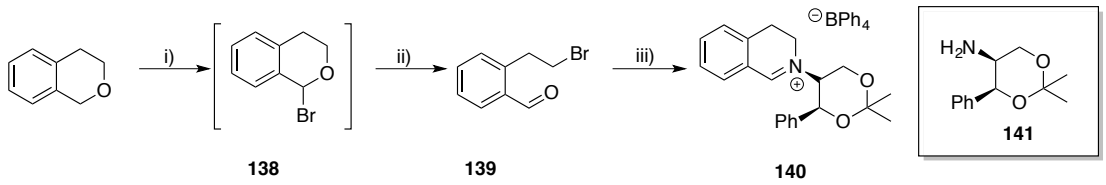
133 **134** **135** **136** **137**

Figure 14: Page's epoxidation and aziridination catalysts

5.3.1 Epoxidation catalysts

In 1998, Page prepared catalysts using a dihydroisoquinoline backbone and a variety of primary amines.[129] These catalysts were the first in the family to possess chiral exocyclic groups on the iminium nitrogen, a feature that was theorised to enhance the enantioselectivity by bringing a chiral element closer to the reaction centre.

The dihydroisoquinoline-based catalyst synthesis began with the bromination of isochroman to afford 1-bromo-isochroman **138**. Without purification, **138** was converted into 2-(2-bromoethyl)benzaldehyde **139** in the presence of hydrobromic acid (48% in water) in good yield. Condensation of **139** with a primary amine, acetonamine **141** in this case, led to the formation of the iminium moiety. Anion exchange with sodium tetraphenylborate allowed for the easy isolation of catalyst **140** as a crystalline solid.[129]

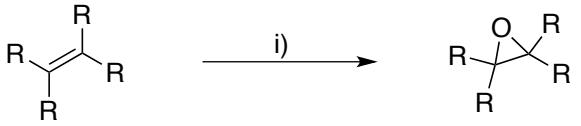


Reagents and conditions: i) Br_2, CCl_4, reflux, 1 h; ii) HBr (48% in water), reflux, 10 min, 65%; iii) **141**, $NaBPh_4$, $EtOH/CH_3CN$, 2 h, 0 °C

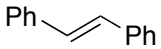
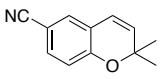
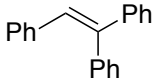
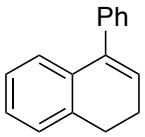
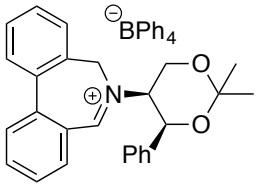
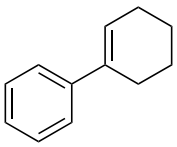
Scheme 40: Synthesis of dihydroisoquinoline catalyst **140**[133]

Iminium salt catalysts, in the presence of an oxidant (Oxone or TPPP), are thought to be converted into the corresponding oxaziridinium ions *in situ*, which, in turn, transfer the oxygen atom to the alkene substrates.[130] This class of epoxidation catalysts were thoroughly investigated and the most successful combination was proved to involve the incorporation of chirality in the form of an axially chiral biphenyl or binaphthyl backbone and the use of acetonamine **141**.[131,132,133]

Table 13: Page's iminium salt-catalyzed epoxidations

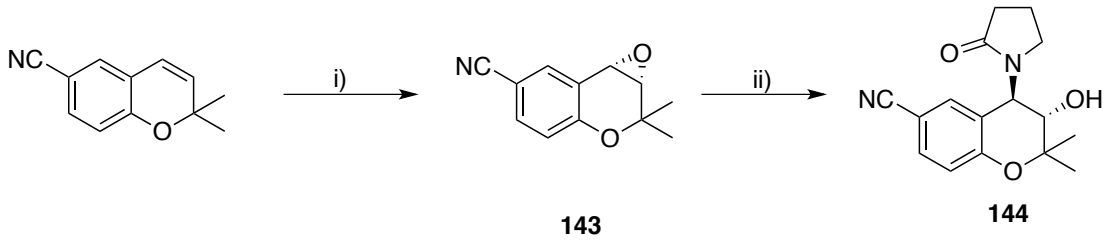


Reagents and conditions i); [a)] Oxone (2 equiv.), Na_2CO_3 (4 equiv.), CH_3CN:H_2O (1:1), 0 °C 1- 12 h; [b)] TPPP, $CHCl_3$, −40 °C

Entry	Catalyst (mol%)	Alkene	Yield (%)	Ee (%)	Major Epoxide
1[a]	**133** (10 mol%)		78	73	(+)-(1*R*,2*R*)
2[b]	**134** (10 mol%)		59	97	(−)-(1*S*,2*S*)
3[a]	**140** (5 mol%)		54	59	(−)-(*S*)
4[a]	**135** (5 mol%)		66	95	(+)-(1*R*,1*S*)
5	 **142**		100	60	(−)-(1*S*,2*S*)

The nature of the chiral exocyclic amine group was shown to be of great importance, with isopinocampheyl amine catalyst **133** giving the most promising result in early testing with *trans*-stilbene (**Entry 1**).[129] Later, catalysts synthesized from amines containing a dioxane moiety and a pendant aryl group (or acetonamines), such as **134**, **135**, **140** and **142** were found to impart increased enantioselectivity. In particular, catalyst **134** with a *p*-methylsulfonylphenyl group gave outstanding enantiomeric excesses for low-temperature epoxidation reactions of cyclic *cis*-alkenes using TPPP (tetraphenylphosphonium mono-peroxysulfate)[134] as an oxidant (**Entry 2**). The antihypertensive (−)-cromakalim was synthesized using Page's conditions following the ring opening of epoxide **143** with 2-pyrrolidinone, giving

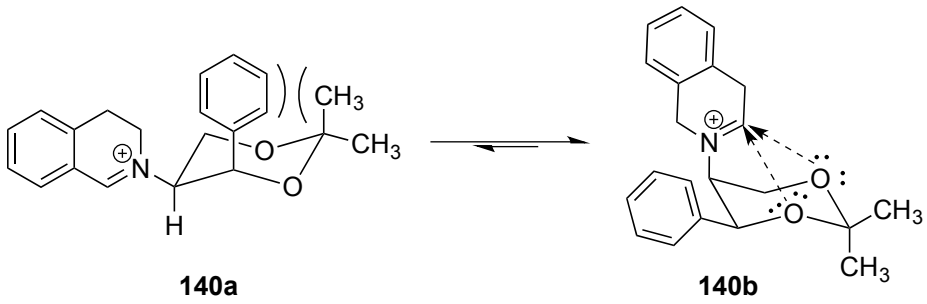
the (−)-(3*S*,4*R*) enantiomer in 52% yield (**Scheme 41**).[135]



Reagents and conditions: i) 10 mol% **134**, TPPP, $CHCl_3$, −40 °C, 24 h, 59%, 97% ee; ii) 2-pyrrolidone, NaH, DMSO, rt, 4h, 52%

Scheme 41: Total synthesis of (−)-cromakalim **144**

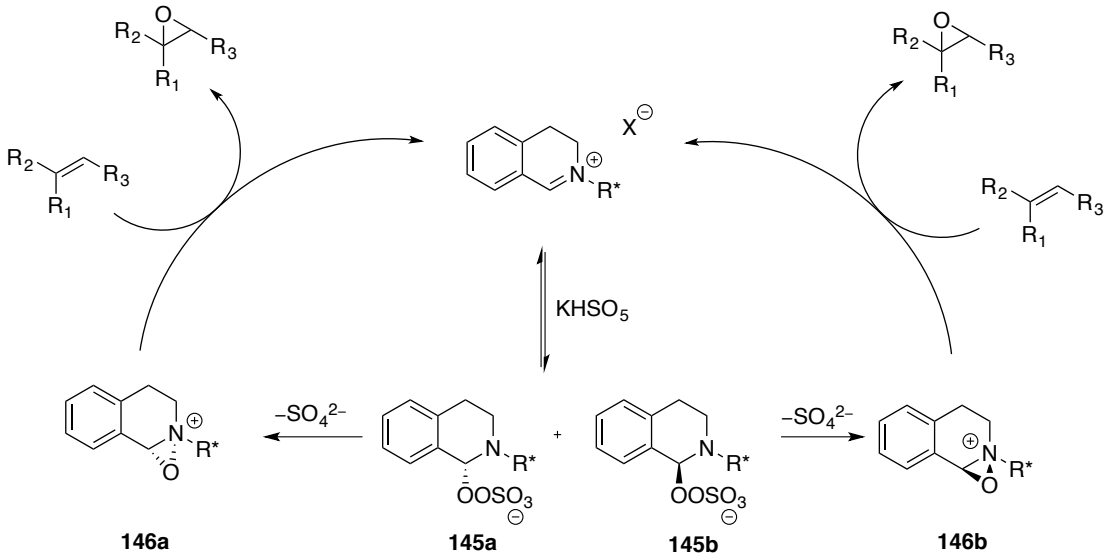
Catalyst **140** gave good selectivity (59% ee) in the epoxidation of triphenylethylene (**Entry 3**).[136] The selectivity of catalyst **140** has been attributed to the rigid chair conformation of the dioxane substituent, in which requires the dihydroisoquinoline appears to be axial; the conformation has also been observed in the solid state using single crystal X-ray crystallography (**Scheme 42**).136



Scheme 42: Two possible conformations of **140**

The preferred thermodynamic conformer is believed to be **140b** because the potential disfavoured 1,3-di-axial interaction present in conformer **140a** is avoided. Additionally, conformer **140b** is favoured by the gauche effect. The lone pairs of the oxygen atoms could help stabilize the electron-deficient iminium carbon, contributing to the overall preference for **140b**. The favoured conformation **140b** seemingly results in the phenyl group shielding one face of the iminium double bond of catalyst **140**. The nucleophilic attack of the oxidant to either the *si* or *re* face of the iminium unit is the starting point of the catalytic cycle and results in the formation of two diastereoisomers: **145a** and **145b** (**Scheme 43**). It is hypothesized that the initial

attack onto the iminium unit is strongly influenced by the bulky phenyl group of catalyst **140** hindering the oxidant's approach towards one face, resulting in an uneven rate of formation of these diastereoisomeric ions.[129] Consequently, following ring-closure and predominant generation of one of the oxaziridinium species **146a** and **146b**, the oxygen atom is transferred to the prochiral alkene substrate, and, depending on the approach of the catalyst, gives rise to the observed enantiomeric excesses.

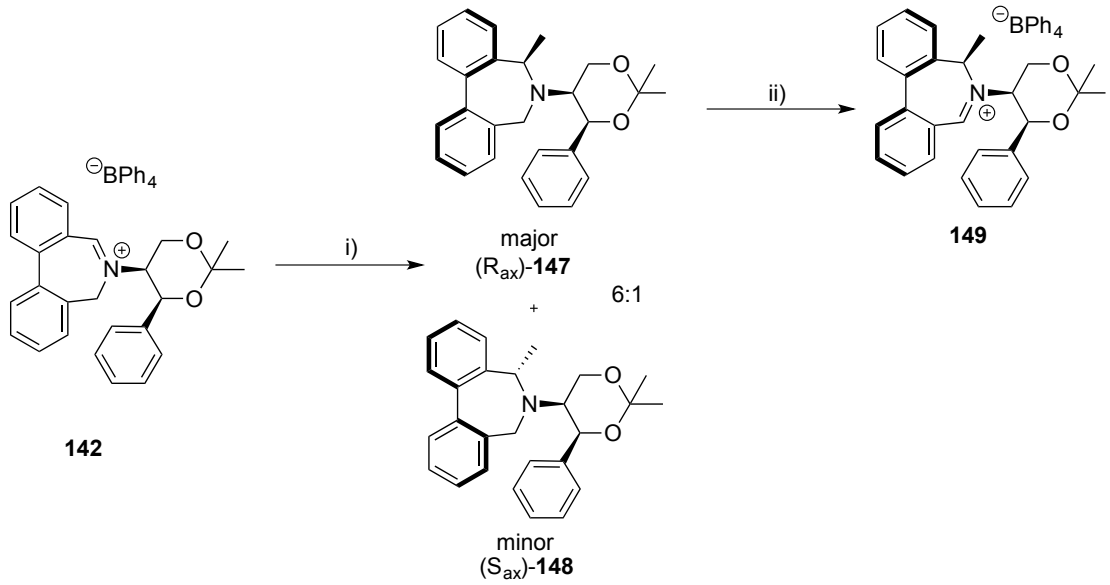


Scheme 43: Proposed catalytic cycle using Oxone[136]

Third generation catalyst **135** (**Figure 14**), a (*S*)-binaphthyl azepinium salt, was shown to be exceptionally efficient, affording phenyl-1,2-dihydronaphthalene oxide in 95% ee within 2 h (**Entry 4**, **Table 13**).[20] As the fixed axial chirality of the binaphthyl backbone led to higher enantioselectivity, further improvements to the family of iminium catalysts were targeted: it was envisaged that the introduction of a substituent in the α-position to the azepinium nitrogen atom might improve selectivity by increasing the steric constraint about the iminium double bond. Additionally, in the case of biphenyl catalyst **142** (**Entry 5, Table 13**), it was hypothesized that the presence of the substituent could shift the equilibrium towards a single atropoisomer.

Low-temperature ^{1}H NMR experiments were performed on **142** to investigate the preferred lowest energy conformer. Four conformers, resulting from rotation around

the biphenyl C-C and N-C bonds, were identified. Analysis of the spectra showed the R_{ax} conformation (89:11) was favoured for the biphenyl unit in order to reduce interactions with the nitrogen substituent. Indeed, the addition of Grignard reagents (MeMgX, iPrMgX, PhMgX, BnMgX) to iminium **142** at low temperature resulted in mixtures of two diastereoisomers. When MeMgBr was used, (R_{ax},*R*,*S*,*S*)-**147** was isolated as the major diastereoisomer alongside (S_{ax},*S*,*S*,*S*)-**148**.[136] NBS oxidation of (R_{ax},*R*,*S*,*S*)-**147** produced catalyst **149** where the iminium double bond is positioned exclusively on the opposite side of the newly introduced Grignard substituent. We believe the remaining pseudoaxial proton is more exposed and therefore more reactive kinetically (**Scheme 44**).



Reagents and conditions: i) MeMgBr, THF, −78 °C, 2 h, d.r. 6:1, 74%; ii) NBS, CH_2Cl_2, Δ, 30 min, $NaBPh_4$, CH_3CN, 10 min, 68%

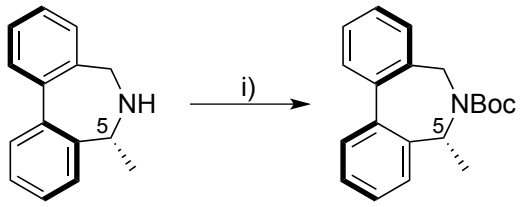
Scheme 44: Addition of a Grignard reagent onto iminium **142**

As predicted, the introduction of the new substituent prevented the rotation around the biaryl axis as the substituent assumed a pseudoaxial position to minimize the steric interaction with the acetonamine (**Scheme 44**). The orientation of the methyl group was deduced from characteristic ^{1}H NMR chemical shifts (for **147** δ_{Me} 0.68 ppm and for **148** δ_{Me} 0.41 ppm) as the protons on the pseudoaxial methyl group experienced significant deshielding because of the ring current effect. The absolute configuration of (R_{ax},*R*,*S*,*S*)-**147** was then confirmed using single crystal X-ray

crystallography.[136]

The diastereoselective formation of the two atropoisomers was described as the result of a 'double stereochemical relay': the chiral appendage on the nitrogen atom enforced a preference for a favoured atropoisomer of **142**, which in turn influenced the addition of the Grignard reagent onto the iminium moiety. [137]

Wallace, well-known for his dynamic axial chirality studies, explored a similar 'stereochemical relay' using a different approach. Wallace studied the effect of a *N*-Boc substituent on the biaryl axial configuration of mono-alkylated 6,7-dihydro-5H-dibenz[c,e]azepine **150** (**Scheme 45**).[138]



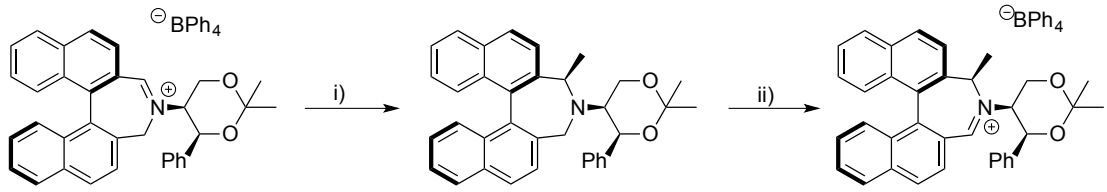
(S_{ax},5*R*) (−)–**150** (R_{ax},5*R*) (+)-**151**

Reagents and conditions: i) Boc_2O, *t*BuOH, r.t., 92%

Scheme 45: Conformational 'switch' of *N*-Boc derivatized **151**

In a similar manner to catalyst **142** (**Scheme 44**), where the axial conformation was directed by the steric interactions between the methyl group and the *N*-substituent, the conversion of **150** to *tert*-butylcarbamate derivative **151** triggered a conformation change: a 'switch' in the orientation of the methyl group at the C5 position from pseudoequatorial to pseudoaxial, and, as indicated by the change in the specific rotation, a concomittant inversion of the chirality at the biphenyl backbone from (S_{ax}) to (R_{ax}) occurred.

Page's 'double stereochemical relay' hypothesis was confirmed when the addition of Grignard reagents onto binaphthyl compound **135**, a compound with fixed axial chirality, was found to be completely diastereoselective (**Scheme 46**).[136]

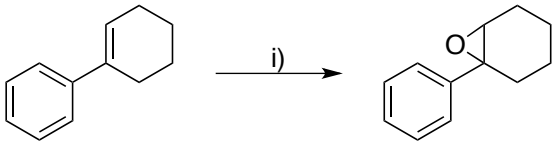


Reagents and conditions: i) MeMgBr, THF, −78 °C, 12 h; ii) NBS, CH_2Cl_2, rt, 10 min, $NaBPh_4$, EtOH, 1 h

Scheme 46: Diastereoselective Grignard reagent addition onto iminium salt **135**

Azepines (R_{ax},*R*,*S*,*S*)-**147** and (R_{ax},*R*,*S*,*S*)-**152** were oxidized to the corresponding iminium salt catalysts using NBS (**Schemes 44** and **46**). The novel catalysts, **149** and **153**, were evaluated using the epoxidation of 1-phenyl-1-cyclohexene. The presence of the substituent in the α-position to the azepinium nitrogen atom, in both the biphenyl and binaphthyl species, led to improvements in selectivity (**Table 14**).

Table 14: Biphenyl and binaphthyl-based catalyst screening



Reagents and conditions: i): (a) Oxone (2 equiv.), Na_2CO_3 (4 equiv.), CH_3CN:H_2O (1:1), 0 °C 1- 12 h; (b) Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), CH_3CN:H_2O (1:1), 0 °C, 17 min - 13 h

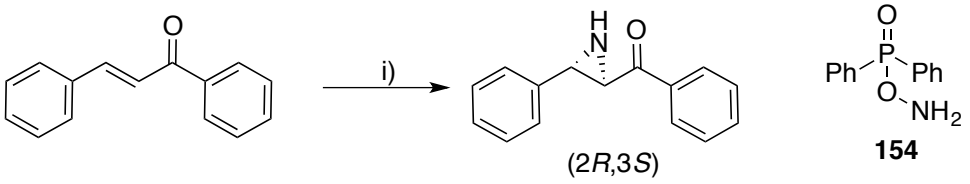
Entry	Catalyst	Conversion (%)	Ee (%)	Major Epoxide
1[a]	**142**	100	60	(−)-(1*S*,2*S*)
2[a]	**149**	100	82	(−)-(1*S*,2*S*)
3[b]	**135**	99	91	(−)-(1*S*,2*S*)
4[b]	**153**	99	94	(−)-(1*S*,2*S*)

5.3.2 Aziridination catalysts

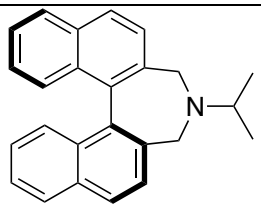
Similarly, Page has investigated the effect of structural modifications on the activity and selectivity of binaphthyl azepine catalysts, such as **136** and **137**, used in the aziridination of *trans*-chalcone. The structural changes surveyed include the

introduction of substituents at the 3- or 3,3'-positions (C_2 symmetric catalysts) and the steric bulk of the nitrogen substituent. The use of nitrogen transfer reagent *O*-(diphenylphosphinyl)-hydroxylamine **154** ($DppONH_2$) and NaOH as the base in dichloromethane were found to be the optimum conditions. *N*-Isopropyl azepine **137** was shown to impart moderate enantioselectivity and allow for a reasonable turnover of substrate (**Entries 1** and **3**). The highest enantioselectivity (43% ee) was obtained using 3,3'-disubstituted catalyst **136**, albeit with disappointing conversion, probably due to the sterically demanding 3,5-bis(trifluoromethyl)phenyl groups (**Entry 2**).

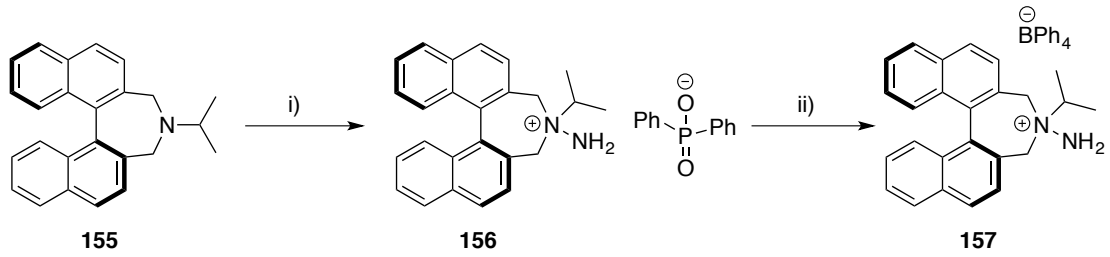
Table 15: Page's aziridination conditions



Reagents and conditions: Catalyst (1 equiv.), **154** (1.1 equiv.), NaOH (1 equiv.), CH_2Cl_2, r.t.

Entry	Catalyst	Time h	Conversion (%)	Ee (%)
1	**137**	48	70	35
2	**136**	48	10	43
3	 **155**	24	38	34

Furthermore, azepine **155** and a stoichiometric amount of $DppONH_2$ were submitted to the reaction conditions, leading to the isolation of the corresponding hydrazinium salt **156** in 77% yield. A counter-ion exchange with sodium tetraphenylborate gave product **157** in quantitative yield as a long-term bench stable aziridination reagent.



Reagents and conditions: i) $DppONH_2$ (1.1 equiv.), CH_2Cl_2, r.t., 18 h, 77%; ii) $NaBPh_4$, CH_3CN, 100%.

Scheme 47: Isolation of hydrazinium salts **156** and **157**

When either salt **156** or **157** was stirred with *trans*-chalcone under the reaction conditions described above, the same ee and yield were observed (**Entry 3**), supporting the contention that the hydrazinium is the active catalytic species.[21]

5.3.3 Page's axially chiral aminocatalysts

Due to the successes of Page's axially chiral atom transfer organocatalysts, the next logical step was the development of related azepines for aminocatalysis. Aminocatalysis is a relatively recent endeavour for the Page group, and as such screening began with simple binaphthyl aminocatalyst **129** and mono-alkylated catalyst **158** for the aldol reaction of *p*-nitrobenzaldehyde **81** and acetone. Maruoka's '*synthetic amino acid'* catalyst (*S*)-**111** was shown to be very successful in this reaction and we envisaged that our catalysts, which share structural similarities, would show promising preliminary results.[113]

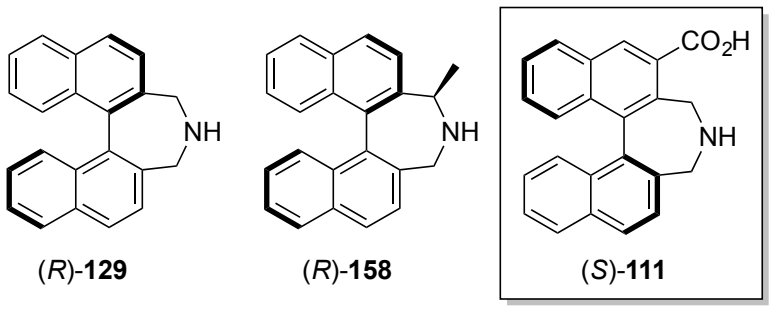
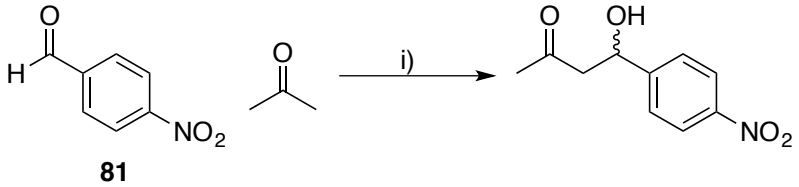


Figure 15: Page's group aminocatalysts

Catalyst **129** was screened using optimum solvents as described by Maruoka **(***N*,*N*-dimethylformamide and dimethylsulfoxide); however, both attempts led to racemic

products and very poor conversions (<5%) (**Entries 4** and **6, Table 15**). Conversely, aprotic solvents such as tetrahydrofuran, acetone and acetonitrile gave full conversion to the hydroxyketone product, albeit with very low ee (**Entries 2**, **3** and **5**). Most polar and every non-polar solvents studied gave low enantioselectivities (<5%), and the (*S*)-enantiomer was the major enantiomer observed. Surprisingly, when water was used, the (*R*)-enantiomer was isolated in 16% ee (**Entry 1**). The same result was obtained, albeit with a poorer conversion, when catalyst **158** was used in a reaction conducted in water (**Entry 11**).

Table 15: Some preliminary screening of catalysts in aldol reaction



81

Reagents and conditions: i) catalyst (10 mol%), $PhCO_2H$ (20 mol%), solvent, r.t. 72 h

Entry	Catalyst	Temp.	Solvent	Conv. (%)	ee (%)
1	**(*R*)-129**	r.t.	H_2O	50	16 (*R*)
2	**(*R*)-129**	r.t.	neat	100	-
3	**(*R*)-129**	r.t.	THF	100	3 (*S*)
4	**(*R*)-129**	r.t.	DMF	<5	-
5	**(*R*)-129**	r.t.	CH_3CN	100	2 (*S*)
6	**(*R*)-129**	r.t.	DMSO	<5	3 (*S*)
7	**(*R*)-129**	r.t.	Et_2O	100	4 (*S*)
8	**(*R*)-129**	r.t.	MeOH	30	2 (*S*)
9	**(*R*)-129**	r.t.	EtOH	50	3 (*S*)
10	**(*R*)-129**	r.t.	*i*PrOH	40	3 (*S*)
11	**(*R*)-158**	r.t.	H_2O	10	16 (*R*)
12	**(*R*)-158**	r.t.	CH_3CN	65	6 (*S*)
13	**(*R*)-158**	0 °C	CH_3CN	25	30 (*S*)
14	**(*R*)-158**	r.t.	THF	70	7 (*S*)
15	**(*R*)-158**	0 °C	THF	15	5 (*S*)
16	**(*R*)-158**	r.t.	Et_2O	50	6 (*S*)
17	**(*R*)-158**	0 °C	Et_2O	15	11 (*S*)
18	**(*R*)-158**	r.t.	Toluene	75	5 (*S*)
19	**(*R*)-158**	0 °C	Toluene	15	5 (*S*)

Catalyst **158** was screened with several different solvents, and rather disappointing enantioselectivities were observed. Encouragingly, a reaction conducted in acetonitrile at 0 °C afforded the (*S*)-product in 30% ee (**Entry 13**). When aprotic solvents, such as THF and acetone, were used, full conversion to the hydroxyketone product, albeit in very low ee, was observed.

6.0 This project

The aim of the project is to design and synthesize catalysts that are analogous in structure to previously reported organocatalysts such as amino acid proline **27**, tetrazole **90**,[139] diarylprolinol silyl ether **100**[140] and binaphthyl functionalized amino acid **111**. Our target catalysts are novel structures with axial chirality and a chiral centre on the azepine ring to exert enantiofacial selectivity. The R substituent should interact with the *in situ* generated iminium/enamine species by hydrogen bonding, ionic and/or steric interactions to induce enantiofacial selectivity, resulting in a highly enantioselective reaction. Installation of functionalities contained in **27**, **90** and **100** were sought in order to provide assessment of the effect of axial chirality on the selectivity of aminocatalysts (**Figure 16**).

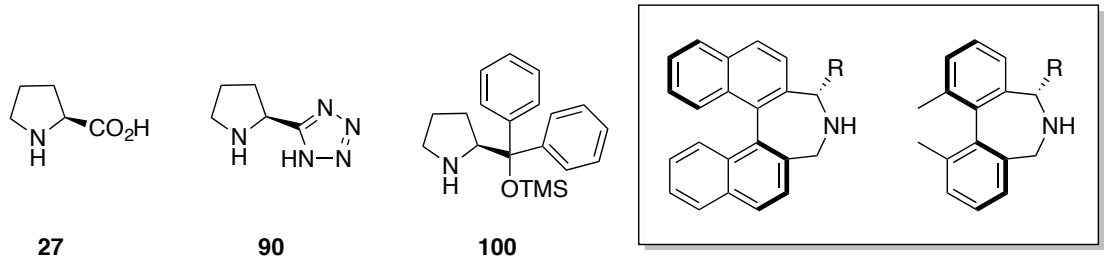


Figure 16*:* Our catalyst design

Introduction references

[1] H. Caner, E. Groner, L. Levy, *Drug Disc. Today*, **2004**, 9, 3, 105−110

[2] L. A. Nguyen, H. He, C. Pham-Huy, *Int. J. Biomed. Sci.,* **2006**, 2, 85−100

[3] G. W. Parshall, R. E. Putscher, *J. Chem. Ed*., **1986,** 63, 3, 189−191

[4] W. S. Knowles, *Angew. Chem.,* **2002**, 41, 1998−2007

[5] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.,* **1987**, 52, 3174–3176

[6] A. Ault, *J. Chem. Ed. Chem*., **2002**, 79, 5, 572−577

[7] J. M. Klunder, T. Onami, K. B. Sharpless, *J. Org. Chem.*, **1989,** 54, 1295–1304

[8] B. E. Rossiter, T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc*., **1981**, 103, 464−465

[9] W. Leuchtenberger, K. Huthmacher, K. Draus, *Appl. Microbiol. Biotechnol.,* **2005**, 69, 1−8

[10] H. Wynberg, *Top. Stereochem.,* **1986**, 16, 87–129

[11] C. Bolm, I. Schiffers, C. L. Dinter, A. Gerlach, *J. Org. Chem.,* **2000**, 65, 6984–6991

[12] T. Hashimoto, K. Maruoka, *Chem. Rev.,* **2007**, 107, 5656–5682

[13] C. E. Song, Cinchona Alkaloids in Synthesis and Catalysis, Wiley-VCH, Verlag GmbH & Co. KGaA, 2009 Online ISBN: 9783527628179

[14] G. Bredig, P. S. Friske, *Bichem. Z.,* **1912**, 46, 7–23

[15] H. Pracejus, *Justus Liebigs Ann. Chem.,* **1960**, 634, 9–22

[16] H. Pracejus, H. Matje, *J. Prakt. Chem.,* **1964**, 24, 195−205

[17] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.,* **1997**, 119, 12414−12415

[18] P. Vachal, E. N. Jacobsen, *Org. Lett.,* **2000**, 2, 6, 867−870

[19] A. H. Mermerian, G. C. Fu, *J. Am. Chem. Soc*., **2003**, 125, 4050–4051

[20] P. C. B. Page, B. R. Buckley, M. M. Farah, A. J. Blacker, *Eur. J. Org. Chem.,* **2009**, 3413–3426

[21] P. C. B. Page, C. Bordogna, I. Strutt, Y. Chan, B. R. Buckley, *Synlett*., **2013**, 24, 2067–2072

[22] D. Bethell, P. C. B. Page, H. Vahedi, *J. Org. Chem.,* **2000**, 65, 6756–6760

[23] P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington, D. M. Andrews, *Synlett,* **1995**, 773–775

[24] P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington, D.M. Andrews, *Tetrahedron: Asymmetry*, **1995**, 6, 2911–2914

[25] P. C. B. Page, J. P. Heer, D. Bethell, A. Lund, E. W. Collington, D. M. Andrews, *J. Org. Chem.*, **1997**, 62, 6093–6094

[26] S. E. Denmark, R. A. Stavenger, K. T. Wong, X. Su, *J. Am. Chem. Soc*., **1999**, 121, 21, 4982–4991

[27] S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.,* **2000**, 33, 432–440

[28] J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.,* **2002**, 124, 7, 1172–1173

[29] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.,* **1963**, 85, 207–222

[30] E. Knoevenagel,; *Ber. Dtsch. Chem. Ges.,* **1896**, 29, 172–174

[31] B. List, *Angew. Chem.,* **2010**, 49, 1730–1734

[32] H. D. Dakin, *J. Biol. Chem.,* **1909**, 7, 49–55

[33] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.,* **1971**, 10, 496–497

[34] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.,* **1974**, 39, 1615–1621

[35] P. Wieland, K. Miescher, *Helv. Chim.,* **1950**, 33, 2215–2228

[36] T. A. Spencer, T. W. Flechtner, R. A. Zayle, *Tetrahedron Lett.*, 43, **1965**, 3889–3897

[37] C. Agami, G. Meynier, C. Puchot, *Tetrahedron,* **1984**, 40, 1031–1038

[38] C. F. Barbas III. *Angew. Chem.,* **2007**, 46, 2–8

[39] C. F. Barbas III. *Angew. Chem.,* **2008**, 47, 42–47

[40] W. J. Rutter, *Fed. Proc.,* **1964**, 23, 1248−1257

[41] C. Y. Lai, N. Nakai, D. Chang, *Science*, **1974**, 183, 1204–1206

[42] J. Wagner, R. A. Lerner, C. F. Barbas III, *Science,* **1995**, 270, 1797–1800

[43] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. U. S. A*., **2004**, 101, 16, 5839–5842

[44] S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.,* **2001**,123, 12911–12912

[45] L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc*., **2003,** 125, 16–17

[46] S. Danishefsky, P. Cain, A. Nagal, *J. Am. Chem. Soc.,* **1975**, 97, 380–387

[47] J. Ruppert, U. Eder, R. Wiechert, *Chem Ber.,* **1973**, 106, 3636–3644

[48] B. List, *Tetrahedron*, **2002**, 58, 5573–5590

[49] E. J. Corey, S. C. Virgil, *J. Am. Chem. Soc.,* **1990**, 112, 6429–6431

[50] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.,* **2000**, 122, 2395

[51] Aldolase Antibody 38C2, AL-207, *Aldrich Catalog.*, **1999**, 47, 995–1000

[52] M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem.,* **2010**, 49, 4997–5003

[53] B. List, *Chem. Commun*., **2006**, 819–824

[54] D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Hel. Chim.,* **2007**, 90,

425–471

[55] B. List, D. A. Bock, C. W. Lehmann, *Proc. Natl. Acad. Sci. U. S. A*., **2010**, 107, 48, 20636–20641

[56] B. List, *J. Am. Chem. Soc*., **2000**, 9336–9337

[57] S. Hanessian, V. Pham., *Org. Lett.,* **2000**, 2, 2975–2978

[58] W. Notz, B. List, *J. Am. Chem. Soc*., **2000**, 122, 7386–7387

[59] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc*., **2002**, 124, 6798–6799

[60] S. P. Brown, M. P. Brochu, C. J. Sinz, D.W. C. MacMillan, *J. Am. Chem. Soc*., **2003**, 125, 10808–10809

[61] B. List, *J. Am. Chem. Soc.,* **2002**, 124, 5656–5657

[62] N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.,* **2002**, 124, 6254–6255

[63] O. Diels, K. Alder**,** *Annalen*, **1928**, 460, 98–122

[64] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, W. M. McLamore, *J. Am. Chem. Soc.*, **1952**, 74, 4223–4251

[65] E. J. Corey, R. L. Danhouser, S. Chandrasekaran, P. Siret, G. E. Keck, J.-L. Gras, *J. Am. Chem. Soc.*, **1978**, 100, 8033–8034

[66] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *Tetrahedron*, **1958**, 2, 1–57

[67] P. A. Jacobi, C. A. Blum, R. W. DeSimone, E. S. Udodong, *Tetrahedron Lett*., **1989**, 30, 51, 7173–7176

[68] S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature*, **2011**, 475, 183–188

[69] X. Chen, S. Duan, C. Tao, H. Zhai, F. G. Qiu, *Nature Comm.,* **2015**, 6, 7204, 1–7

[70] P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc.,* **2001**, 123, 10772–10773

[71] M. Y. Chu-Moyer, S. J. Danishefsky, G. K. Schulte, *J. Am. Chem. Soc.,* **1994**, 25, 11213−11228

[72] C. Nicolauo, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem.*, **2002**, 41, 1668−1698

[73] K. Fukui, T. Yonezawa, H. Shingu, *J. Chem. Phys*., **1952**, 4, 722−725

[74] R. B. Woodward, R. Hoffmann, *Angew. Chem.*, **1969**, 8, 781−932

[75] I. Fleming, 'Pericyclic reactions', *Oxford Science Publications*, **1999,** ISBN 978-0-19-850307-1

[76] J. S. Baum, H. G. Viehe, *J. Org. Chem.,* **1976**, 41, 183–187

[77] M. E. Jung, W. D. Vaccaro, K. R. Buszek, *Tetrahedron Lett.,* **1989**, 30, 1893–1896

[78] O. Riant, H. B. Kagan, L. Ricard, *Tetrahedron*, **1994**, 50, 4543−4554

[79] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc*., **2000**, 122, 4243–4244

[80] S. Ma, 'Handbook of Cyclization Reactions', **2010**, *WILEY-VCH Verlag GmbH & Co. KGaA*, ISBN: 978-3-527-32088-2

[81] R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.,* **2006**, 128, 3543−3553

[82] R. Gordillo, J. Carter, K. N. Houk, *Adv. Synth. Catal*., **2004**, 346, 1175–1185

[83] W. S. Jen, J. J. M. Wiener, D. W.C. MacMillan, *J. Am. Chem. Soc.,* **2000**, 122, 9874–9875

[84] M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2004**, 126, 4108−4109

[85] N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, 123, 4370−4371

[86] Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.,* **2006**, 128, 9328−9329

[87] S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.,* **2005**, 127, 32−33

[88] J. E. Wilson, A. D. Casarez, D. W. C. MacMillan, *J. Am. Chem. Soc.,* **2009**, 131, 11332−11324

[89] L. Samulis, N. C. O. Tomkinson, *Tetrahedron*, **2011**, 67, 4263−4267

[90] S. B. Jones, B. Simmons, A. Mastrachio, D. W. C. MacMillan, *Nature*, **2011**, 475, 183−188

[91] B.-F. Sun, *Tetrahedron Lett*., **2015**, 56, 2133–2140

[92] A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett*, **2004**, 3, 558–560

[93] R. G. Almquist, C. J. Jennings-White, W. R. Chao, T. Steeger, K. Wheeler, R. Rogers, C. Mitoma, *J. Med. Chem.,* **1985**, 28, 1062−1066

[94] L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc*., **2003,** 125, 16−17

[95] A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.,* **2005**, 3, 84–96

[96] B. Maji, H. Yamamoto, *Angew. Chem.,* **2014**, 53, 8714–8717

[97] M. Marigo, T. C. Wabnitz, D. Fielenbach, and K. A. Jørgensen, *Angew. Chem.,* **2005**, 44, 794–797

[98] L. D. Amico, X. Companyó, T. Naicker, T. M. Bräuer, K. A. Jørgensen, *Eur. J. Org. Chem*., **2013**, 5262–5265

[99] H. Jiang, C. Roriguez-Escrich, T. K. Johansen, R. L. Davis, K. A. Jørgensen, *Angew. Chem.*, **2012**, 51, 10271–10274

[100] T. K. Johansen, C. V. Gomez, J. R. Bak, R. L. Davis, K. A. Jørgensen, *Chem. Eur. J.,* **2013**, 19, 16518–16522

[101] K. S. Halskov, T. Naicker, M. E. Jensen, K. A. Jørgensen, *Chem. Commun.,* **2013**, 49, 6382−6384

[102] M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, and K. A. Jørgensen, *J. Am. Chem. Soc*., **2005**, 127, 6964−6965

[103] J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc*., **2005**, 127, 18296–18304

[104] P. Diner, A. Kjærsgaard, M. A. Lie, K. A. Jørgensen, *Chem. Eur. J*., **2008**, 14, 122–127

[105] D. Enders, M. R. M. Hüttl, C. Grondal , G. Raabe, *Nature*, **2006**, 441, 861−863

[106] D. Enders, A. Seki, *Synlett*, **2002**, 1, 26–28

[107] R. Kuhn in *Stereochemie*, K. Freudenberg, Ed., F. Deuticke, Leipzig, **1933**, 803–810

[108] M. Oki, *Top. Stereochem*., **1983**, 14, 1−81

[109] G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.,* **2005**, 44, 5384–5427

[110] J. K. Whitesell, *Chem. Rev.,* **1989**, 89, 1581−1590

[111] R. Noyori, H. Takaya, *Acc. Chem. Res*., **1990**, 23, 345–350

[112] A. Bradley, W.B. Motherwell, F. Ujjainwallen, *Chem. Commun.*, **1999**, 917–918

[113] F. Orsini, F. Pelizzoni, M. Forte, R. Destro, P. Gariboldi, *Tetrahedron*, **1988**, 2, 519−541

[114] T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem.,* **2005**, 44, 3055–3057

[115] G. –N. Ma, Y.-P. Zhang, M. Shi. *Synthesis*, **2007**, 2, 197−208

[116] Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Qi. Mi, Y.-Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci. U.S.A.*, **2004**, 101, 5755–5760

[117] T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Chem. Asian. J.*, **2006**, 1-2, 210−215

[118] T. Kano, R. Sakamoto, K. Maruoka, *Org. Lett.,* **2014**, 16, 944−947

[119] T. Kano, Y. Tanaka, K. Maruoka, *Tetrahedron Lett.,* **2006**, 47, 3039–3041

[120] K. Maruoka, T. Ooi and T. Kano, *Chem. Commun.,* **2007**, 1487–1495

[121] T. Kano, O. Tokuda and K. Maruoka, *Tetrahedron Lett.,* **2006**, 47, 7423–7426

[122] T. Kano, Y. Tanaka, K. Maruoka, *Chem. Asian. J.*, **2007**, 2, 1161–1166

[123] T. Kano, K. Maruoka, *Bull. Chem. Soc. Jpn.*, **2010**, 83, 12, 1421–1438

[124] T. Kano, S. Song, Y. Kubota, K. Maruoka, *Angew. Chem.*, **2012**, 51, 1191–1194

[125] T. Kano, Y. Yamaguchi, K. Maruoka, *Chem. Eur. J.,* **2009**, 15, 6678–6687

[126] N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.,* **2005**, 127, 1080-1081

[127] N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. U.S.A.,* **2004**, 101, 5374–5378

[128] A. Bøgevig, H. Sunden, A. Cordova, *Angew. Chem.,* **2004**, 43, 1109–1112

[129] T. Kano, M.Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.,* **2006**, 128, 6046–6047

[130] P. C. B. Page, G. A.; Rassias, D. Bethell, M. B. Schilling, *J. Org. Chem.,* **1998**, 63, 2774–2777

[131] P. C. B. Page, B. R. Buckley, A. J. Blacker, *Org. Lett.,* **2004**, *6*, 1543–1546

[132] P. C. B. Page, M. M. Farah, B. R. Buckley, A. J. Blacker, *J. Org. Chem*., **2007**, 72, 4424–4430

[133] M. M. Farah, P. C. B. Page, B. R. Buckley, A. J. Blacker, M. R. J. Elsegood, *Tetrahedron*, **2013**, 69, 758–769

[134] S. Campestrini, F. Di Furia, G. Labat, F. Novello, *J. Chem Soc., Perkin Trans.,* **1994**, 2, 2175–2180

[135] P. C. B. Page, B. R. Buckley, H. Heaney, A. J. Blacker, *Org. Lett.,* **2005**, 7, 3, 375–377

[136] P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, B. Buckley, D. Bethell, T. A. D. Smith, A. M. Z. Slawin, *J. Org. Chem.,* **2001**, 66, 21, 6926–6931

[137] Page, P. C. B., Barlett, C. J., Chan, Y., Day, D., Parker, P., Buckley, B. R., Rassias, G. A., Slawin, A. M. Z., Allin. S. M., Lacour, J., Pinto, A., *J. Org. Chem*., **2012**, 77, 6128−6138

[138] S. L. Pira, T. W. Wallace, J. P. Graham, *Org. Lett.*, **2009**, 11, 7, 1663−1666

[139] A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B Gold, S. V. Ley, *Org. Biomol. Chem.,* **2005**, 3, 84–96

[140] M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.,* **2005**, 127, 6284–6289

Chapter two: Results and Discussion

1.0 Aim of project

The project targeted the synthesis of novel axially chiral organocatalysts (**Figure 17**) and the evaluation of their effectiveness in a number of asymmetric processes. Maruoka's aryl bifunctionalized organocatalysts, such as **111**, have been shown to impart high levels of selectivity; however, the impact of a substituent in close proximity to the aminocatalytic centre has not yet been investigated in these systems. Our newly synthesized catalysts possess conformational stability, enforced by the presence of a fixed chiral backbone, and retain the chiral centre in the α-position, with regards to the azepine nitrogen atom, that has proven so successful in pyrrolidine species and in Page's epoxidation catalysts.

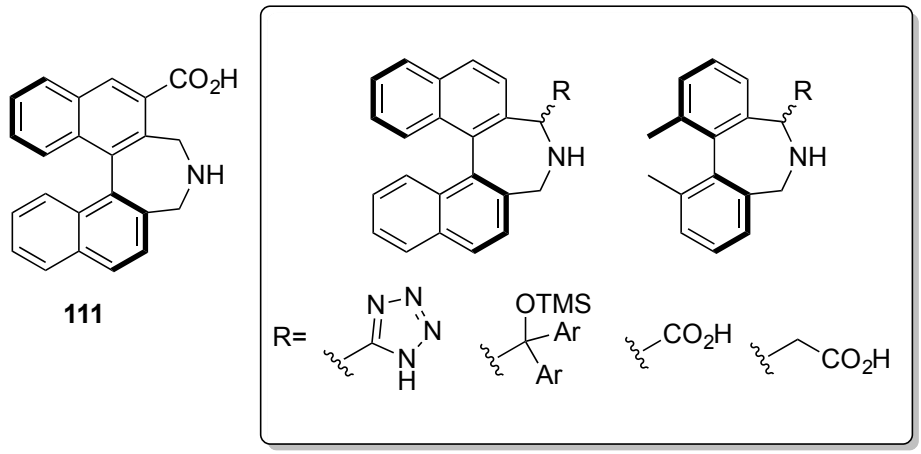
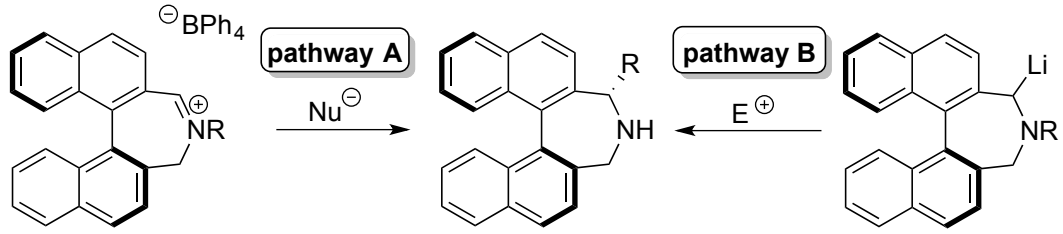


Figure 17: Targeted catalysts

Synthetic strategies toward binaphthyl azepines are well documented;[1,2,3] however, the introduction of a substituent at the 2-position of the azepine ring is less thoroughly reported, with only a handful of asymmetric additions of alkyl groups reported. To date, two approaches have been successful: Page's diastereoselective addition of a Grignard reagent onto an iminium salt,[4] or a base-mediated alkylation methodology as used by Superchi,[1] Meyers,[5] and Wallace (**Scheme 48**).[6]

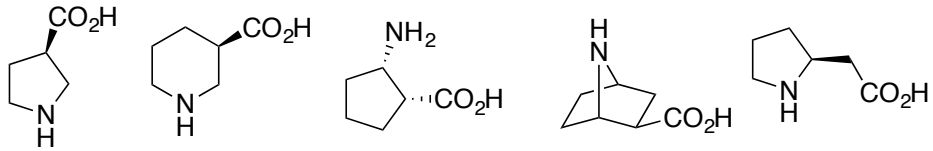


Scheme 48: Approaches towards the synthesis of α-functionalized catalysts

The choice of protecting group is integral to the reactivity of azepines: electron-donating nitrogen protecting groups stabilize the iminium moiety and therefore would be preferred for **pathway A**, whereas electron-withdrawing substituents activate the position α to the azepine nitrogen for deprotonation and could be used in **pathway B**.

2.0 Synthesis of the β-amino acid catalyst

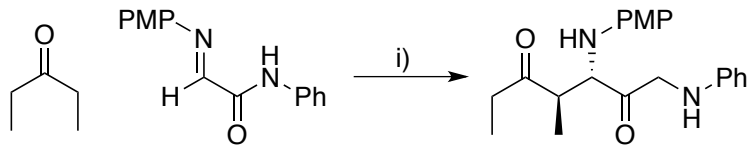
A catalyst analogous to proline was our primary objective, and consequently the installation of a carboxylic acid group was targeted. Several constrained or spatially modified β-amino acid proline analogues have been investigated in depth and their application tested in Mannich, such as **159** and **160**,[7] aldol, such as **161** and **162**,[8] and Michael reactions, such as **163**.[9]



159 **160** **161** **162** **163**

Figure 17: β-Amino acid catalysts

The additional conformational flexibility allows these catalysts to exceed, in several examples, the catalytic activity obtained when using proline.[10] For example, the Mannich reaction between 3-pentanone and α-imino amide **164** is catalysed effectively by **159** in 73% yield after 3 days whereas the (*S*)-proline catalysed reaction is very slow; <10% conversion after 4 days (**Scheme 49**).[7]

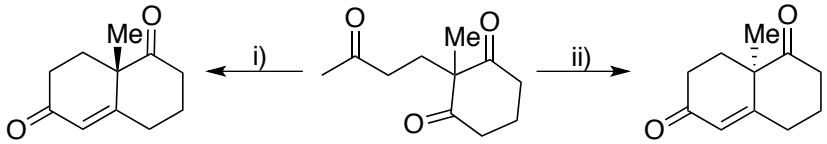


164

Reagents and conditions: i) **159** (20 mol%), DMSO:*i*PrOH (1:1), 3 d, r.t., 73%, anti/syn 83:17, 93% ee anti

Scheme 49: **159** Catalysed *anti*-Mannich reaction

Furthermore, an improvement in selectivity in the Hajos-Parrish-Eder-Sauer-Wiechert reaction of **165** was observed when performed using (1*R*,2*S*)-cispentacin **161** (86% ee), compared to (*S*)-proline (72% ee, **Scheme 50**).[8]



165

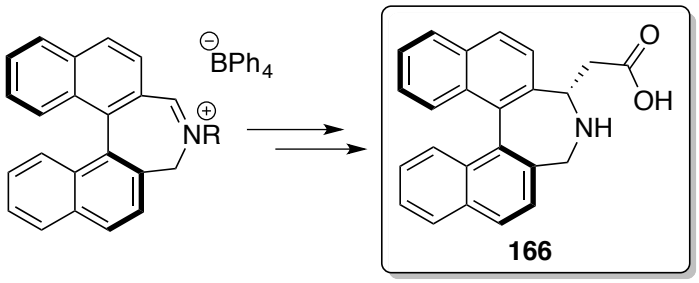
Reagents and conditions: i) (*S*)-Proline (30 mol%), DMF, r.t., TsOH, toluene, Δ, 72% ee; ii) **161** (30 mol%), DMF, r.t., TsOH, toluene, Δ, 86% ee

Scheme 50: Harrish-Eder-Sauer-Wiechert reaction

Axially chiral β-amino acids therefore appeared to be interesting and highly desirable synthetic targets for catalytic design.

2.1 Initial retrosynthetic approaches to the β-amino acid catalyst

The iminium salt pathway was the first route explored (**pathway A**) in the synthesis of catalyst **166** (**Scheme 51**), as the Page group developed the methodology. Indeed, as the addition of a Grignard reagent onto a binaphthyl azepinium species is fully diastereoselective, the selective introduction of a suitable nucleophilic reagent followed by conversion into the corresponding carboxylic acid **166** was targeted (**Scheme 51**).

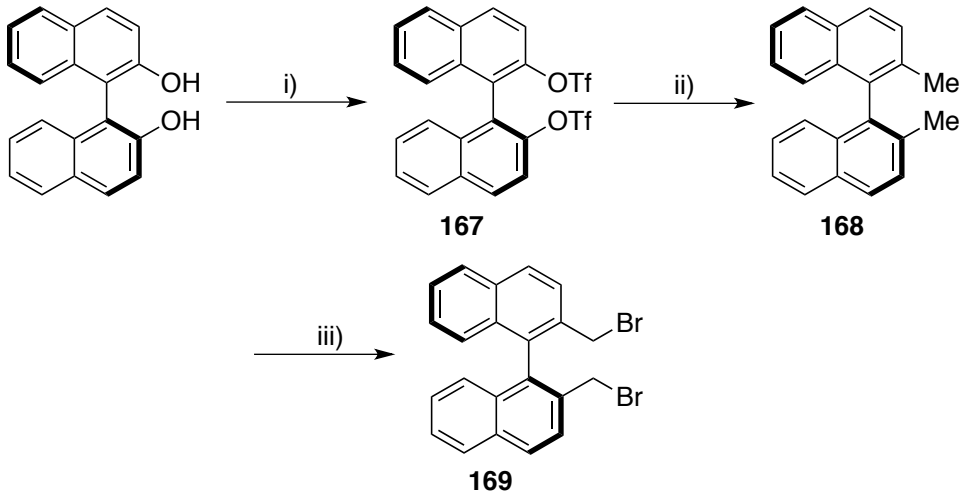


Scheme 51: β-Amino acid catalyst target

The nitrogen protecting group is required to allow iminium salt formation as well as subsequent synthetic steps and easy removal; indeed, tolerance of oxidizing, basic and nucleophilic conditions is needed. Thus, the *p*-methoxybenzyl group was chosen, as electron-rich groups provide extra stability to the iminium moiety. The allyl-azepine analogue was also prepared as Maruoka successfully used it as a precursor in the synthesis of his binaphthyl catalysts.[11]

3.0 Azepine synthesis

The synthesis of the first range of binaphthyl catalysts started with enantiopure (*S*)-BINOL (**Scheme 52**).[12] A DMAP-mediated triflate formation at low temperature using triflic anhydride and 2,6-lutidine provided bis-triflate **167** in quantitative yield. A Kumada cross-coupling reaction employing 1,2-bis-(diphenylphosphino)ethane dichloronickel(II) ($Ni(dppe)_2Cl_2$) as the catalyst and methyl magnesium bromide afforded **168** as a colourless solid following recrystallization in near quantitative yield. A benzylic radical bromination reaction, using initiator azobisisobutyronitrile and *N*-bromosuccimide, led to the formation of **169** in variable yields (usually upwards of 50%, but as high as 77%).[2] The procedure is an improvement on the previous synthesis of **169**, which consisted in heating the substrate under reflux in carbon tetrachloride and under visible light irradiation.[1]



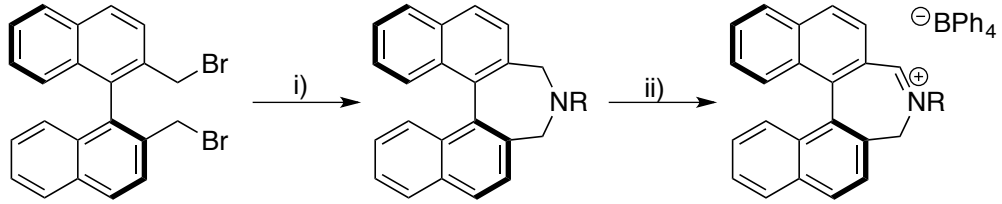
Reagents and conditions: i) Tf_2O, DMAP, 2,6-lutidine, CH_2Cl_2, −78 °C → r.t., quantitative; ii) MeMgBr, $NiCl_2(dppe)_2$, Et_2O, −78 °C → r.t., 95%; iii) AIBN, NBS, cyclohexane, reflux, 4 h, 77%

Scheme 52: Synthesis of dibromobinaphthyl **169**

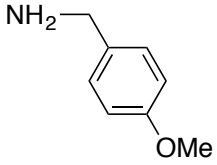
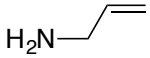
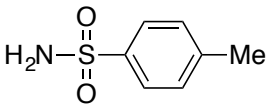
Favourably, purification using column chromatography was not required during the first three steps as the products can be recrystallized or precipitated in very high purity with complete retention of absolute configuration.[1] In addition, the reactions can be easily scaled up: the first step was performed regularly on 20g of BINOL.

A double nucleophilic substitution reaction can then provide a variety of tertiary azepines for further derivatization. A general purpose reaction procedure, previously reported by Page for the synthesis of highly substituted biphenyl azepines,[13] was employed to afford the azepines in moderate to high yields: the dibromo compound **169** and a small excess of a primary amine were heated under reflux in the presence of anhydrous potassium carbonate in acetonitrile (**Table 16**). The reaction has previously been conducted at reflux in tetrahydrofuran with triethylamine; however, our method was considered more environmentally friendly yet equally effective.[2]

Table 16: Synthesis of *N*-protected azepines and iminium salts



Conditions and reagents: i) amine (1.1 equiv.), K_2CO_3 (3 equiv.), CH_3CN, reflux, 16 h; ii) NBS (1.05 equiv.) CH_2Cl_2, 1 h, $NaBPh_4$ (1.05 equiv.), EtOH, CH_3CN, 10 min, r.t.

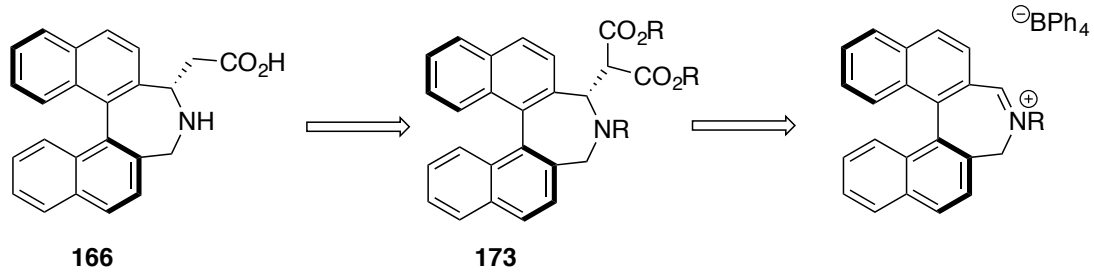
Entry	Reagent	Amine	Yield (%) of amine	Iminum	Yield (%) of iminium
1		**170**	91	**175**	93
2		**171**	84	**176**	81
3		**172**	71	-	-

The corresponding iminium salts were then prepared using an NBS oxidation followed by an anion exchange using sodium tetraphenylborate (**Table 16**).[4] Both the PMB and allyl protecting groups responded well to oxidation, and their respective iminium salts were isolated in high yields. Notably, iminium species **175** was produced in 93% yield (**Entry 1, Table 16**) as a brightly coloured yellow salt, which was found to be exceptionally bench-stable and showed no degradation after two years at room temperature. Compound **172** was prepared in moderate yield (**Entry 3**). However, when **172** was subjected to our oxidative conditions, the desired iminium salt was not observed, probably due to the strongly electron withdrawing nature of the sulfonyl substituent. With iminium species **175** and **176** in hand, we turned our attention to the diastereoselective addition of nucleophiles.

4.0 Diastereoselective addition to binaphthyl azepiniums

4.1 Route 1: the malonate route

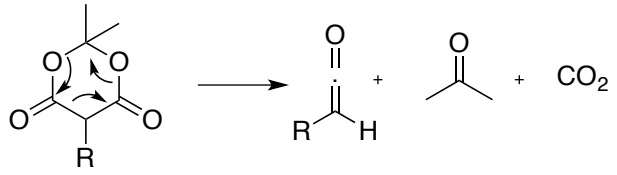
Malonates were envisaged as good nucleophilic reagents, utilizing bases such as *n*-butyllithium as depronating agents or employing cross coupling conditions to afford target **166**. Decarboxylative procedures employing classical Krapcho conditions,[14] high temperature,[15] strongly acidic conditions,[16] or microwave irradiation under basic conditions[17] followed by saponification could provide a route to the desired β-acid.



166 **173**

Scheme 53: Route to the β-acid catalyst

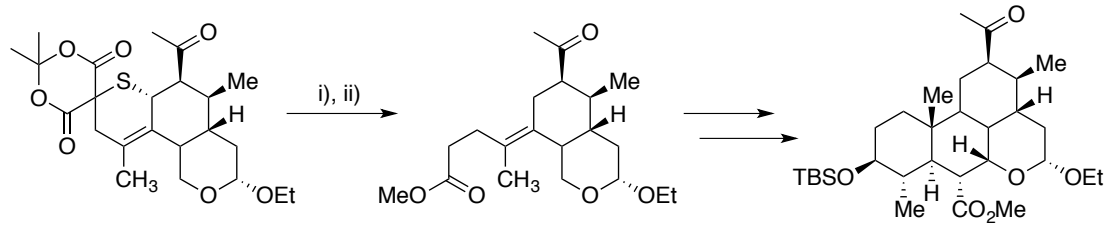
2,2-Dimethyl-[1,3]-dioxane-4,6-dione, or Meldrum's acid, was also chosen as a potential addition substrate because of its well documented thermal instability resulting in the generation of highly reactive ketene intermediates, which could allow access to carboxylic acid, ester and amide catalysts (**Scheme 54**).[18,19]



174

Scheme 54: Pyrolysis of Meldrum's acid

Alternatively, nickel(II) acetylacetonate has been shown to facilitate the decarboxylation and methanolysis of Meldrum's acid derivatives (**Scheme 55**), Spino *et al.* demonstrated the synthesis of anti-cancer quassinoid intermediate **178**, in which a key step was the methanolysis and decarboxylation of the Meldrum's acid moiety in **177**.[20]



177 **178**

Reagents and conditions: i) $Ni(acac)_2$, MeOH, 65 °C, 98%; ii) Ra-Ni, THF-H_2O, 94%

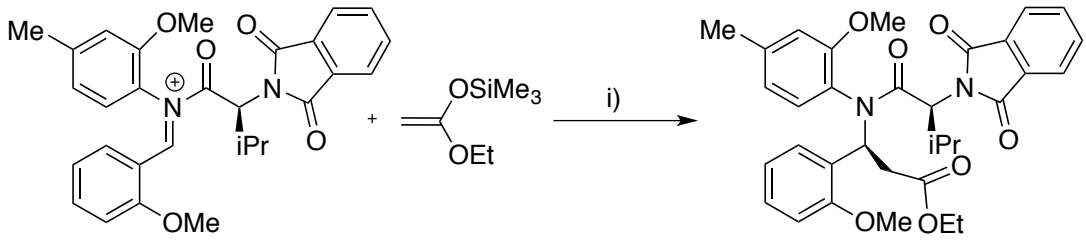
Scheme 55: Meldrum's acid methanolysis in synthesis of anticancer compound **178**

This procedure could provide access to an ester derivative of our catalyst; saponification would then yield β-amino acid **166**.

4.2 Route 2: silyl-based reagents

Similarly, the nucleophilic addition of pre-formed silyl enol ethers could provide a convenient route to β-amino acid **166**. Silyl enol ethers are reactive nucleophiles and very important reagents in the formation of C-C bonds. Silyl enol ethers are produced from enolizable carbonyl compounds with either silyl halides or triflates in the presence of an amine.

Conditions reported by Müller (**Scheme 56**), showed that silyl ketene acetals could add, in high yield and almost complete diastereoselectivity, to *N*-acyl iminium ions, such as **179**, at room temperature in dichloromethane in the absence of Lewis acids.[21]

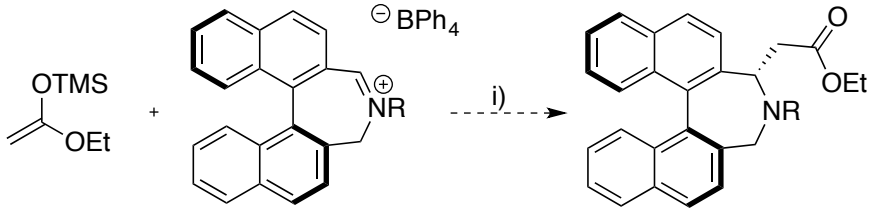


179

Conditions and reagents: CH_2Cl_2, r.t., 72 h, then 10% aq. $NaHCO_3$, d.r. >99:1, 68%

Scheme 56: Silyl ketene acetal addition to *N*-acyl iminium ion **179**

We envisaged that our iminium salts would have similar reactivity, and therefore would allow the facile installation of an ester group (**Scheme 57**).

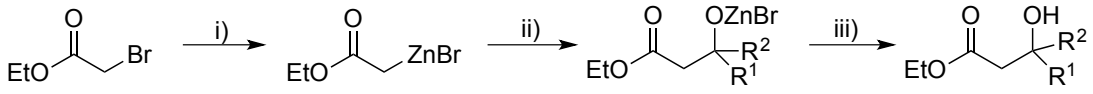


Reagents and conditions: i) CH_2Cl_2, TBAF, 0 °C→r.t.

Scheme 57: Silyl ketene acetal addition to iminium salt

4.3 Route 3: the Reformatsky reaction

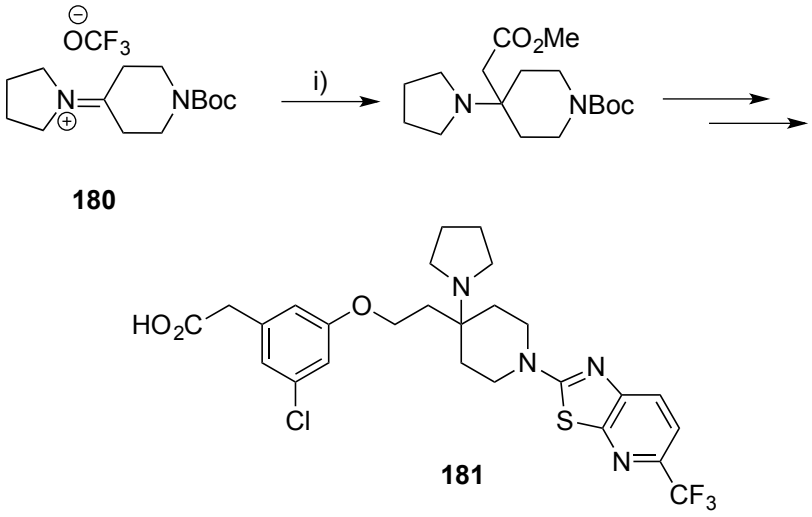
The Reformatsky reaction utilizes organo-zinc reagents, which, despite their similarities with Grignard reagents, have greater functional group tolerance. Traditionally, Reformatsky reagents are formed from the oxidative insertion of zinc into carbon-halide bonds of α-halo esters.[22] Structural determination and X-ray crystallography of Reformatsky reagent ethyl bromozincacetate has established that it exists as THF stabilized dimer $(BrZnCH_2CO_2Et \cdot THF)_2$.[23,24] Organo-zinc reagents add to carbonyl groups resulting in β-hydroxy ester products (**Scheme 58**).



Reagents and conditions: i) Zn dust; ii) R^1COR^2; iii) H_3O^+

Scheme 58: Traditional Reformatsky reaction

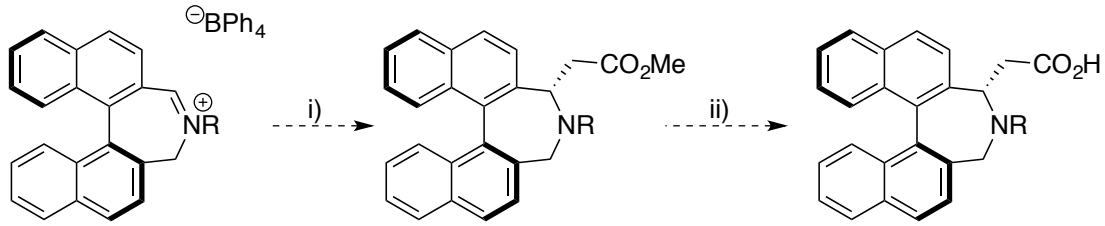
The Reformatsky reaction has been used to install functionality onto various substrates, the most widely studied being aldehydes and ketones; however, rare additions to both imine and iminium moieties have also been reported.[25] Encouragingly, a large-scale procedure for the addition of α-haloesters to iminium salt **180** was found, detailing the scale-up synthesis of anti-arteriosclerotic intermediate **181** (**Scheme 59**).[26]



Reagents and conditions: i) Zn (zinc activation: Zn, $BrCH_2CH_2Br$, THF, reflux), iminium salt, 10 °C, methyl bromoacetate, 3 h, 42%

Scheme 59: Reformatsky reaction in anti-arteriosclerotic intermediate **181** synthesis

Using this approach, the required ester group could be installed in one step and the corresponding acid would be obtained after saponification.



Reagents and conditions: i) Zn, $BrCH_2CO_2Me$, THF; ii) NaOH, THF, r.t.

Scheme 60: Reformatsky reaction

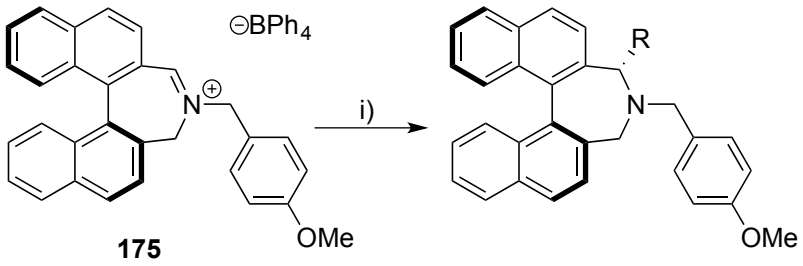
5.0 *p*-Methoxybenzyl azepine

The synthesis towards our desired acid catalyst **166** (**Scheme 49**) commenced with *p*-methoxybenzyl azepine **170**: the azepine was obtained in high yield and the protecting group removal procedure was expected to be a facile high-yielding hydrogenation procedure using palladium on carbon.[27]

5.1 Nucleophile additions

Reagents diethyl malonate and Meldrum's acid were first treated with *n*-butyllithium at low temperature. The lithium enolate solutions were then added to solutions of the *p*-methoxybenzyl iminium salt **175** at −78 °C and the mixtures were allowed to reach ambient temperature over 12 h.

Table 17: Nucleophile additions to iminium salt **175**



175

Conditions and reagents: i) Nucleophile (5 equiv.), base (5 equiv.), THF, −78 °C →r.t., 12 h

Entry	Nucleophile	Base	Yield (%)
1	Diethyl malonate	*n*-BuLi	-
2	Meldrum's acid	*n*-BuLi	20

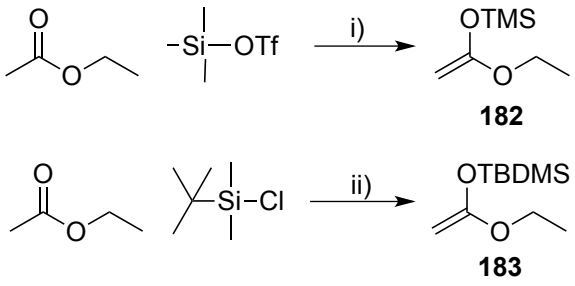
The reaction mixtures were analysed using ^{1}H NMR spectroscopy, and the desired products were observed in both cases. Unfortunately, in the case of the diethyl malonate addition, the product was not stable enough and decomposed on contact with silica gel (**Entry 1, Table 17**). The addition of Meldrum's acid afforded the desired product, albeit in low yield (**Entry 2**). Regrettably, the route was considered

too impractical to continue due to the low yield of the addition and the further synthetic steps still required to obtain the desired catalysts.

Assignments of the new stereocentres were made based on the assumption the substituents would follow experimentally observed preference and adopt the pseudoaxial orientation, as observed in the diastereoselective addition the Grignard reagents (**Scheme 46**).[28]

5.2 Silyl enol ether additions

The silyl enol ether addition was next targeted on azepinium salt **175**. Silyl enol ethers were prepared from ethyl acetate and lithium diisopropylamide (LDA) in THF at −78 °C followed by addition of the corresponding silyl triflate or chloride (**Scheme 61**). The silyl enol ether solutions were used following an aqueous work up without any further purification.

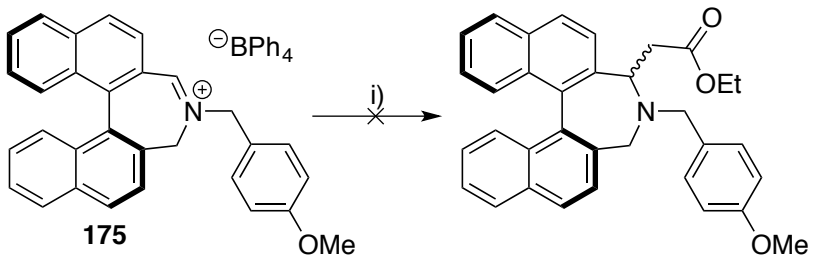


Reagents and conditions: i) TMSOTf (1.2 equiv.), EtOAc (1 equiv.), *n*-BuLi (1.1 equiv.), *i*Pr_2NH (1.2 equiv.), THF, −78 °C, 3 h; ii) TBDMSCl (1.2 equiv.), EtOAc (1 equiv.), DMPU, *n*-BuLi (1.1 equiv.), *i*Pr_2NH (1.2 equiv.), THF, −78°C, 3 h

Scheme 61: Synthesis of silyl enol ethers

Accordingly, trimethylsilyl enol ether **182** (**Entry 1, Table 18**) and *tert*-butyldimethylsilyl enol ether **183** (**Entry 2**) were stirred in dichloromethane with iminium salt **175** at 0 °C, and the reactions monitored using thin layer chromatography. Complex mixtures were obtained, and neither showed any formation of the desired ester product after 3 days. We presume that part of the reason these reactions were unsuccessful is because **182** and **183** are not particularly stable reagents and they used without purification.

Table 18: Silyl enol ether additions

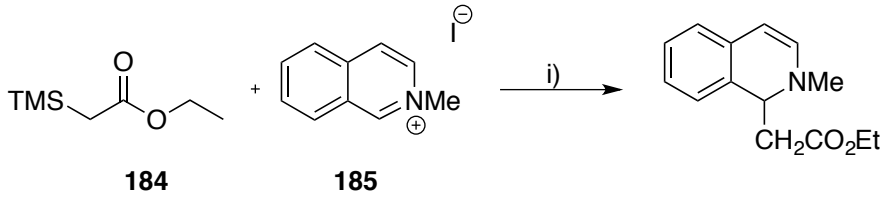


Conditions and reagents: i) Silyl enol ether (1.5 equiv.), CH_2Cl_2, 0 °C, 72 h

Entry	Nucleophile	Additive	Yield
1	**182**	-	-
2	**183**	-	-
3	**183**	TBAF (5 equiv.)	-
4	**183**	$AlCl_3$ (3 equiv.)	-

As the reactions with the enol ethers were unsuccessful, activation of the enol ether was tested. Fluoride-mediated desilylation using tetrabutylammonium fluoride (**Entry 3**)[29] and Lewis acid activation (**Entry 4**) were attempted. Discouragingly, neither of these additives resulted in any conversion. We hypothesized that iminium salt **175**, without an activating electron-withdrawing *N*-acyl group, lacked reactivity under these conditions to allow for the formation of the desired β-amino ester. Indeed, the electron-donating *p*-methoxybenzyl group might lower the electrophilicity of the iminium moiety.

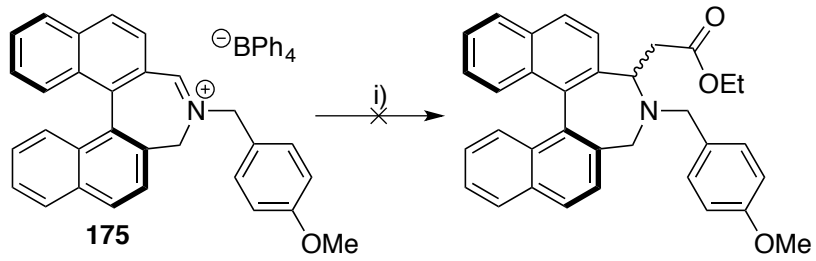
Another silyl-based reagent, ethyltrimethyl silyl acetate **184** (ETSA), has been shown, in combination with CsF, to add to *N*-methylquinolinium iodides (**Scheme 62**).[30]



Reagents and conditions: CsF (1.1 equiv.), ETSA (1.1 equiv.), CH_3CN, reflux, 1 h, 70%

Scheme 62: ETSA addition to methylquinolinium salt **185**

The procedure is attractive because ETSA is a commercially available material and therefore the constraints and problems associated with silyl enol ethers and their syntheses, such as anhydrous reaction conditions and decomposition, can be avoided. Iminium **175** was submitted to the reaction conditions described in the literature. Unfortunately, only starting material was detected after three days (**Scheme 63**).



Reagents and conditions: CsF (1.1 equiv.), ETSA (1.1 equiv.), CH_3CN, reflux, 3 d

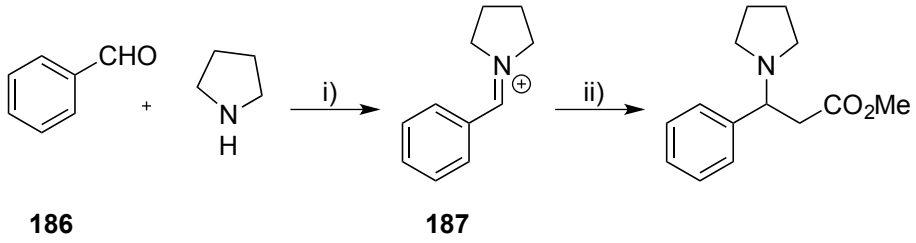
Scheme 63: Attempted ETSA addition

5.3 Reformatsky reaction

After assessing the efficacy of silyl enol reagents with iminium species **175**, the Reformatsky reaction was explored. The first step is the *in situ* generation (or isolation) of the organo-zinc reagent, formed from the addition of zinc into the carbon-halide bond. For this step to occur the zinc must first be sufficiently activated. Activation involves removal of the surface coat of zinc oxide and distributing the metal powder to provide as large a surface area as possible. Several activation methods can be employed, such as addition of iodine, trichloromethylsilane, copper halides, 1,2-dibromoethane in ethereal solvents

(generally at high temperature) or by washing with HCl.[31]

Saidi reported a high yielding Reformatsky reaction onto iminium species **187**, produced from the treatment of aldehyde **186** with pyrrolidine and lithium perchlorate (**Scheme 64**).[34] Zn/Cu couple use has been used extensively since its first reported use in the Simmons-Smith cyclopropanation of alkenes,[32] and has since been used successfully in the Reformatsky reaction.[33] The levels of copper in these alloys vary from 1-3% composition, and no activation is required for their use.[34]

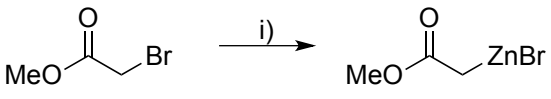


186 **187**

Reagents and conditions: i) $LiClO_4$, Et_2O, r.t. 30 min; ii) $BrZnCH_2CO_2Me$ (zinc activation: Zn-Cu, TMSCl, THF, reflux), Et_2O, r.t., 2 h, 89%

Scheme 64: Organo-zinc reagent nucleophilic addition to iminium species **187**

We adapted this method and large excesses of both zinc, in the form of zinc dust, and methyl bromoacetate were used initially. The zinc was stirred in tetrahydrofuran in the presence of trimethylsilyl chloride at room temperature followed by the addition of methyl bromoacetate. The resulting slurry was used without any purification.

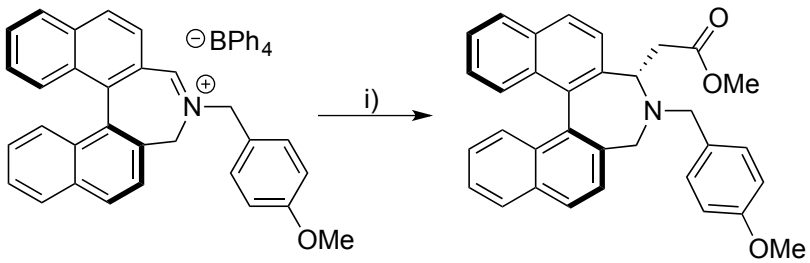


188

Reagents and conditions: i) Zn, TMSCl, THF, r.t., 1 h

Scheme 65: Formation of the Reformatsky reagent

Iminium salt **175** was added to the slurry and the reaction mixture allowed to stir for 1 h. The desired product was isolated in low yield (**Entry 1, Table 19**). Again, as only one diastereoisomer was isolated, an assumption was made that the new stereocentre would follow the trend of previously reported diastereoselective Grignard additions (**Scheme 46**) and the new substituent would solely occupy the pseudoaxial orientation (**Scheme 66**).[28]



175 **189**

Reagents and conditions: i) **188**, THF, r.t., 1 h, 14%

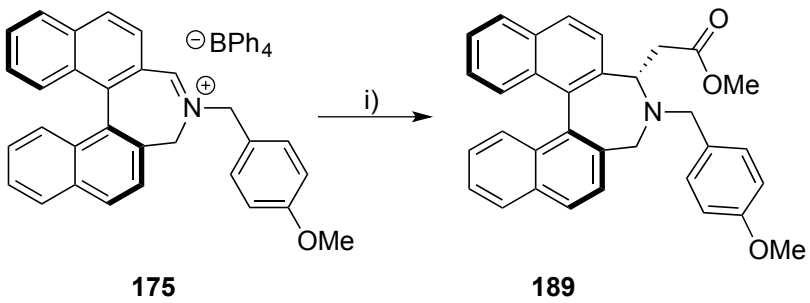
Scheme 66: Reformatsky reagent addition

In order to improve the yield, different methods of activating the zinc and higher temperatures were tested.[35,36] The zinc dust was activated as a suspension in aqueous HCl (10 mol%), isolated through filtration, and washed using water and acetone.[37] The activated zinc was heated under reflux in anhydrous tetrahydrofuran while methyl bromoacetate was added dropwise and it was observed that the reaction mixture turned green. A solution of iminium salt **175** in anhydrous tetrahydrofuran was then transferred into the heated zinc slurry through a cannula, turning the reaction mixture bright red. The remaining methyl bromoacetate was added over 1 h. The reaction mixture was then quenched and product **189** was isolated in 43% yield, suggesting that the *p*-methoxybenzyl iminium species **175** is stable even at high temperature (**Entry 2**).[38] Zinc activation using a more concentrated solution of HCl did not significantly impact upon the reaction yield (**Entry 3**).

The yield of **189** was improved to 50% when the zinc dust was activated using a different methodology (**Entry 4**). A catalytic amount of 1,2-dibromoethane (5 mol%) and trimethylsilyl chloride (4 mol%) were added to the zinc suspension under

reflux. After 30 min, the slurry was allowed to reach room temperature and methyl bromoacetate was added. A solution of iminium **175** in tetrahydrofuran was added and the reaction was stirred at 30 °C for 12 h.[39]

Table 19: Reformatsky reaction conditions



175 **189**

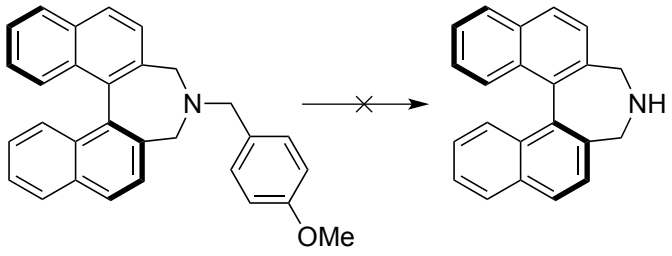
Reagents and conditions: i) Zinc powder (18 equiv.), methyl bromoacetate (15 equiv.), THF, reflux

Entry	Zinc Activation	Temp (°C)	Time (h)	Yield (%)
1	TMSCl (5 mol%)	r.t.	1	14
2	10% HCl	65	1	43
3	35% HCl	65	1	40
4	TMSCl (4 mol%) 1,2-$BrCH_2CH_2Br$ (5 mol%)	65→25→30	12	50

5.4 *p*-Methoxybenzyl group removal

With β-methyl ester substituted azepine **189** now in hand, it was necessary to remove the *p*-methoxybenzyl protecting group (PMB) to obtain the desired catalyst. PMB groups can be removed by hydrogenolysis, chemical or electrolytic oxidation, strongly acidic or by catalytic Lewis acid conditions.[40] Surprisingly, the conventional Pd/C hydrogenation conditions, used by Maruoka,[27] did not successfully yield the desired azepine **129**, and only starting material was

recovered.[41]

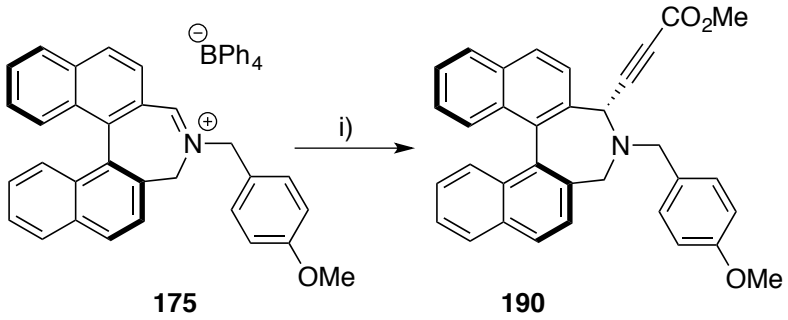


170 **129**

Reagents and conditions: i) Pd/C, H_2, MeOH, 16 h

Scheme 67: Hydrogenolysis of **170**[40]

Due to the poor yields obtained in the syntheses of the β-amino ester **189**, a test substrate was prepared for the optimization of the deprotection reaction. Within our research group, a number of related compounds were prepared, and compound **190**, possessing similar functional groups, was obtained in high yield.[40] Ester **190** was synthesized through the addition of methyl propiolate to iminium salt **175** using a procedure employing copper catalysis in terminal alkyne additions to isoquinoline iminiums.[42] The substituent was assumed to occupy solely the pseudoaxial orientation (**Scheme 68**).[28]



175 **190**

Reagents and conditions: methyl propiolate (1.1 equiv.) CuI (5 mol%), DIPEA (1 equiv.), CH_3CN, r.t., 2 h, 81%

Scheme 68: Synthesis of deprotection test substrate **190**[40]

Stoichiometric single electron oxidants DDQ (2,3-dichloro-3,6-dicyano-1,4-benzoquinone) and CAN (ammonium cerium IV nitrate) are well-known benzylic protecting group removal reagents.[43,44]

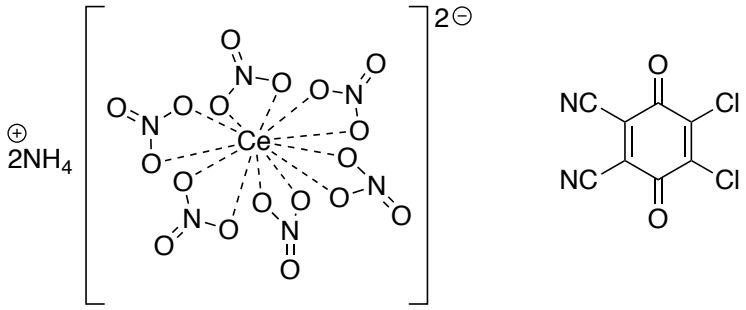
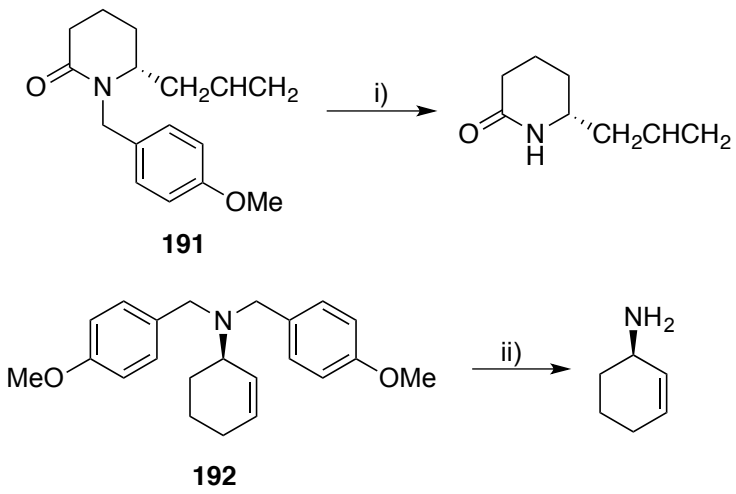


Figure 18: Oxidants DDQ and CAN

Indeed, Wee reported the CAN-mediated oxidative debenzylation of δ-lactam **191**, under mild conditions in short reaction times, and Uozumi utilized CAN in his deprotection of cyclic allylamine **192** (**Scheme 69**). [45]

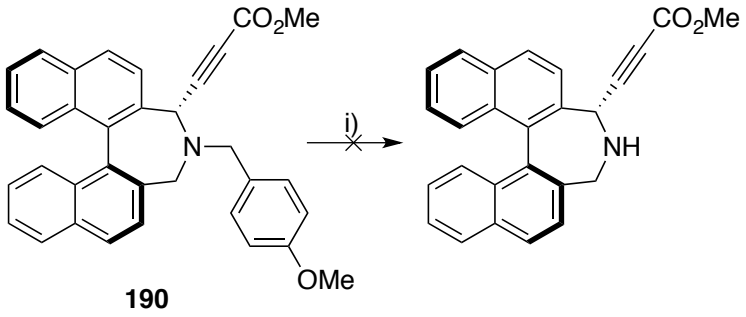


Reagents and conditions: i) $(NH_4)_2Ce(NO_3)_6$ (4 equiv.), CH_3CN:H_2O, 0 °C, 30 min, 44%; ii) $(NH_4)_2Ce(NO_3)_6$ (5 equiv.), CH_2Cl_2:H_2O, r.t. 1 h, 60-90%

Scheme 69: *p*-Methoxybenzyl group removal using CAN

Regrettably, these methods failed to cleave the PMB group of **190**, and the starting material was recovered. Unfortunately, increasing the quantity of CAN (7 equiv.) present in solution resulted in the decomposition of the starting material (**Entry 1, Table 20**).[46] Decomposition of starting material **190** was also observed when DDQ was used **(Entry 2)**.[43]

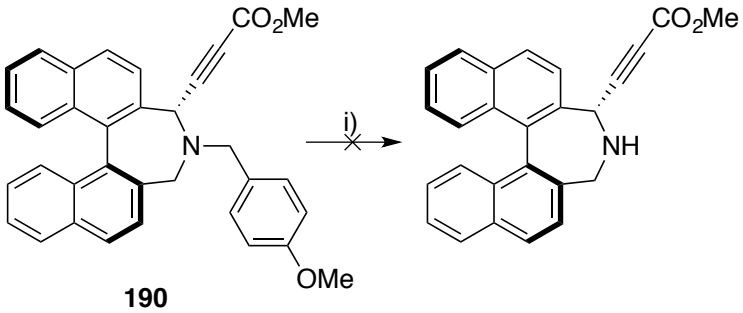
Table 20: Attempted conventional DDQ and CAN removals of PMB group



190

Entry	Reagent	Solvent	Temp (°C)	Time (h)	Yield (%)
1	CAN (7 equiv.)	$CH_3CN:H_2O$	0	24	Decomposition
2	DDQ (4 equiv.)	CH_2Cl_2	r.t.	3	Decomposition

The deprotection of PMB ethers can be achieved using DDQ in combination with an excess of ferric chloride. $FeCl_3$ is used to regenerate DDQ from DDHQ (dichlorodicyanohydroquinone) and therefore only a catalytic amount of DDQ is required. We hoped that these mild conditions would be effective to remove the PMB group of **190**; however, this failed to give the deprotection product, and starting material was recovered (**Scheme 70**).[47]

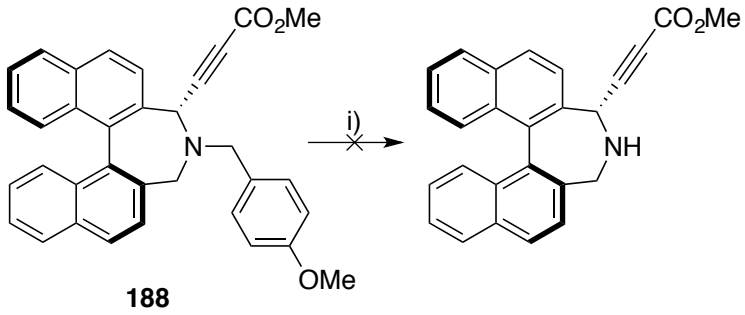


190

Conditions and reagents: i) $FeCl_3$ (3 equiv.), DDQ (10 mol %), CH_2Cl_2:H_2O, 0 °C, 24 h

Scheme 70: Attempted deprotection using 2,3-dichloro-3,6-dicyano-1,4-benzoquinone with ferric chloride

Lewis acids such as $ZrCl_4$, $SnCl_4$, $TiCl_4$ and $AlCl_3$ are frequently employed to cleanly cleave PMB groups in high yield.[48,49] Thiophenol is commonly used as an additive in these reactions, and helps to shorten reaction times.[50] However, when deprotection using $TiCl_4$ in combination with PhSH was attempted, only starting material was isolated and no conversion to the product was observed (**Scheme 71**).

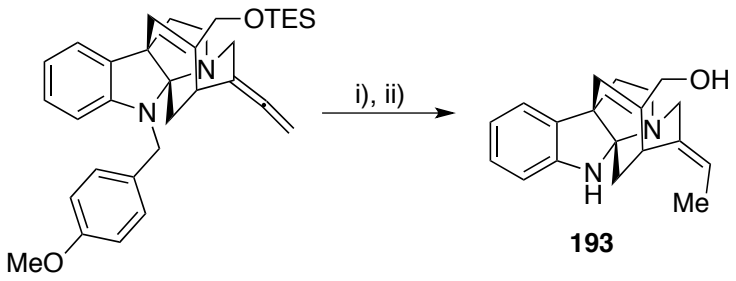


188

Conditions and reagents: i) $TiCl_4$ (1.05 equiv.), PhSH (1.2 equiv.), CH_2Cl_2, −78 °C, 24 h

Scheme 71: Lewis acid $TiCl_4$ use for the removal of PMB group

Fortunately, many other alternatives exist to these reagents, driven by the expense of reagents such as DDQ and the environmental and health concerns when using metal halides. MacMillan used strongly acidic conditions of PhSh and TFA in a global deprotection step in the total synthesis of (+)-minfiensine **193 (Scheme 72)**.[51]

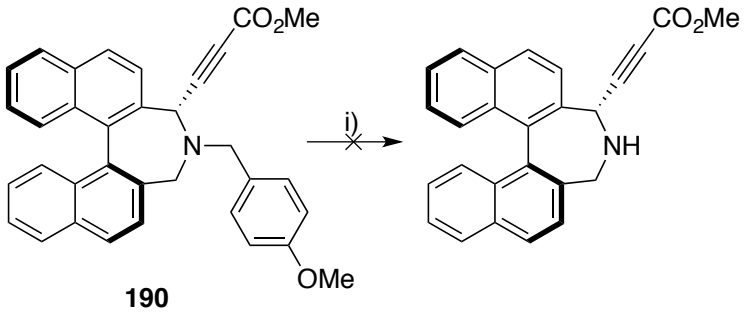


193

Conditions and reagents: i) Pd/C, H_2, THF, −15 °C; >20:1 E/Z; ii) PhSH, TFA, r.t., 90% over two steps

Scheme 72: Final deprotection step in the synthesis of (+)-Minfiensine

These conditions also failed to provide our target product (**Scheme 73**).

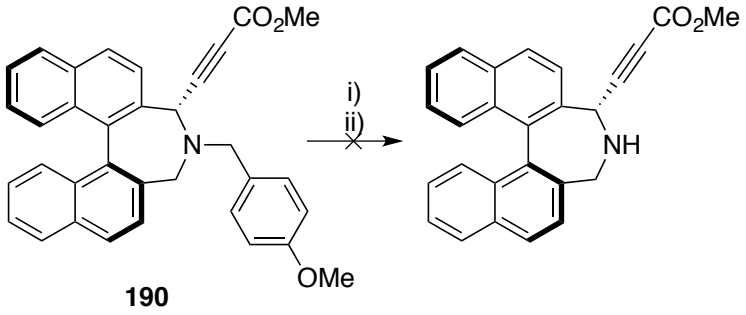


190

Conditions and reagents: i) PhSH (10 equiv.), TFA (excess), r.t.

Scheme 73: Attempted deprotection using MacMillan's reported conditions

Due to its low cost and toxicity, cerium (III) chloride in combination with soft nucleophiles such as sodium iodide has been used for the cleavage of PMB ethers, although high temperature and long reaction times are typically required (typically 24 h).[52] Unfortunately, we observed no conversion after 48 h (**Scheme 74**). Alternative oxidative cleavage procedures, such as the use of (diacetoxyiodo)benzene, $PhI(OAc)_2$, also failed.[53]



190

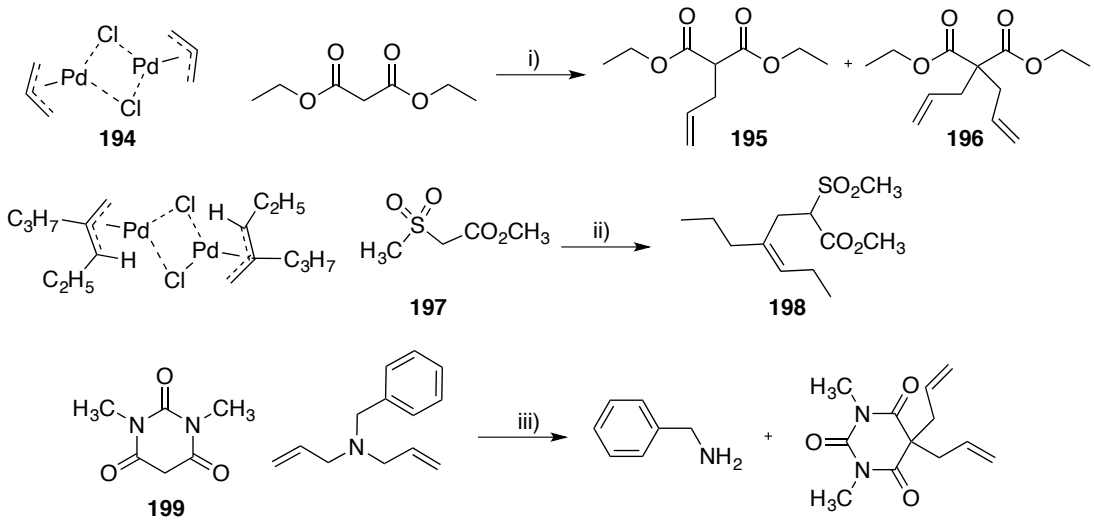
Conditions and reagents: i) $CeCl_3$ (1.5 equiv.), NaI (1 equiv.), CH_3CN, 80 °C, 48 h or; ii) $PhI(OAc)_2$ (4 equiv.), HCl (10 %), MeOH:EtOH, r.t., 12 h

Scheme 74: Attempted removals of *p*-methoxybenzyl protecting group

6.0 Allyl protecting group

As the PMB protecting group proved challenging to remove, we turned our attention to allyl analogue **171**, previously used by Maruoka.[11] Allyl groups have been used widely for the protection of alcohol and amine moieties since the emergence of a convenient deprotection procedure of the conjugate base based on the Tsuji-Trost

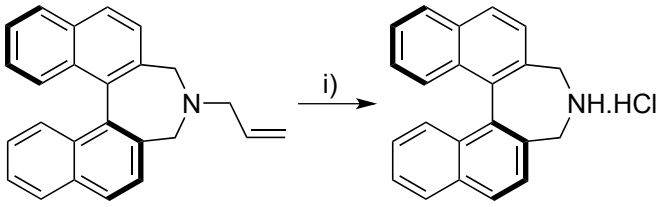
reaction.[54] Tsuji's original palladium mediated allylation reaction proceeds by nucleophilic addition of diethyl malonate to the η^3-diallyl dichlorodipalladium complex **194**, affording both mono- and bis-allyl products.[55] Further work by Trost showed that the addition of triphenylphosphine could reduce reaction time dramatically, and that the addition to η^3 complex is dictated by both the steric and electronic properties of the nucleophile, as shown in the reaction of methyl (methylsulfonyl acetate) **197** where only one product (**198**) is isolated.[56] This reaction has since evolved for removal of allyl groups using *N*,*N*-dimethylbarbituric acid **199** as a nucleophilic allyl scavenger (**Scheme 75**).[57]



Reagents and conditions: i) $[PdCl(allyl)]_2$, sodium, EtOH, DMSO, r.t., **195** 37%, **196** 40%;
iii) $[PdCl(2\text{-propyl-1-pentene})]_2$, PPh_3, THF/DMF, r.t., 80%
iii) $Pd(PPh_3)_4$, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2, 30 °C, 1.5 h, 100%

Scheme 75: Allylation and deallylation procedures based on the Tsuji-Trost reaction

N-Allyl **171** was prepared in high yield (Table **16**, Entry **2**), and, correspondingly, a facile palladium(0)-catalysed deallylation, employing tetrakis(triphenylphosphine) palladium and *N*,*N*-dimethylbarbituric acid, was performed (**Scheme 76**).[56] The product was isolated as the corresponding hydrochloride salt **200** in excellent purity following recrystallization from hot chloroform.



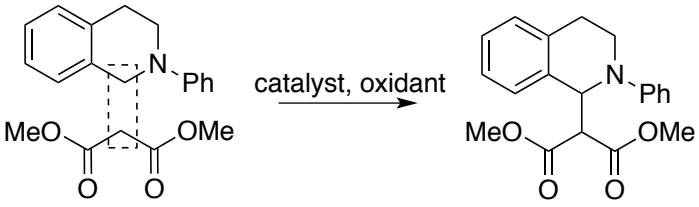
171 **200**

Reagents and conditions: i) $Pd(PPh_3)_4$ (2 mol %), *N*,*N*-dimethylbarbituric acid (3 equiv.), CH_2Cl_2, 50 °C, 16 h; then CH_2Cl_2, $HCl_{(aq)}$, 5 min, 80%

Scheme 76: Palladium-catalysed deallylation of **171**

6.1 Oxidative cross coupling reactions

Following the failure to install the α-functionality by classical coupling reactions of enols and enolates with azepinium salt **175**, a series of 'cross dehydrogenative coupling' C-C bond forming reactions were attempted. CDC reactions typically occur where one reaction partner is converted into an electrophile through *in situ* oxidisation while the electron-rich coupling partner attacks. These reactions have high functional group tolerance and are efficient in functionalizing sp^3 C-H bonds with sp, sp^2 and sp^3 hybridized starting materials, using inexpensive copper or iron salt catalysts.[58]

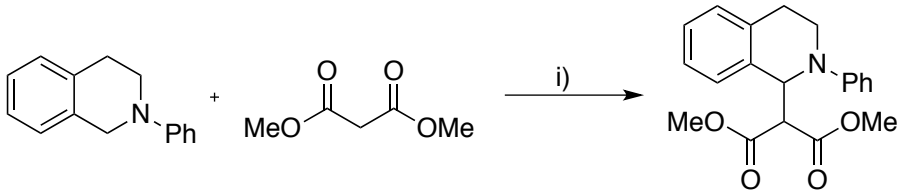


Scheme 77[62]: CDC reaction between sp^3 centers

Fortunately, there are many reported oxidations of C-H bonds adjacent to nitrogen atoms in tertiary amines.[59] Li *et al*. reported a coupling reaction between tetrahydroisoquinoline **201** and dimethyl malonate in the presence of *t*-BuOOH (TBHP) and catalytic quantities of copper bromide.[60] Mild conditions afforded β-diester tetrahydroisoquinoline derivative **202** at ambient temperature in 90% yield when dimethyl malonate was used as the solvent (**Entry 1**, **Table 21**). Itoh published

the first catalytic metal-free oxidative CDC reaction of tertiary amines using iodine as the catalyst in the presence of hydrogen peroxide (**Entry 2, Table 21**), producing tetrahydroisoquinoline derivative **202** in 73% yield.[61]

Table 21: C-H sp^3 CDC reaction of tetrahydroisoquinoline and dimethyl malonate

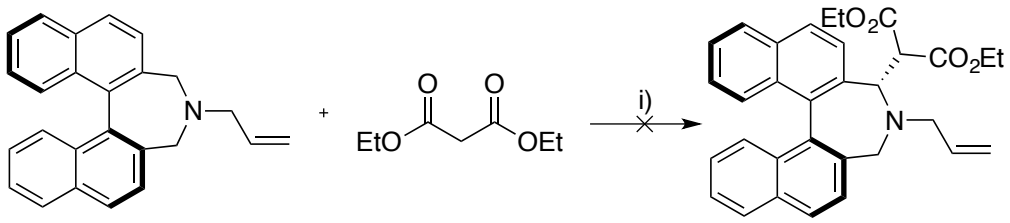


201 **202**

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

Accordingly, azepine **171** was subjected to Li's copper-catalysed reaction conditions with diethyl malonate. After 24 h, only starting material was detected in the reaction mixture (**Entry 1**, **Table 22**). Again, it was assumed that the newly introduced substituent would occupy solely the pseudoaxial orientation (**Table 22**).[28] It was postulated that the poor solubility of azepine **171** in diethyl malonate was inhibiting the reaction. When dichloromethane was used as the solvent, no conversion was observed (**Entry 2**). When a combination of iodine and hydrogen peroxide was used at room temperature and at 50 °C (**Entries 3, 4** and **5**), no conversion was seen.

Table 22: Oxidative coupling of azepine **171** and diethyl malonate



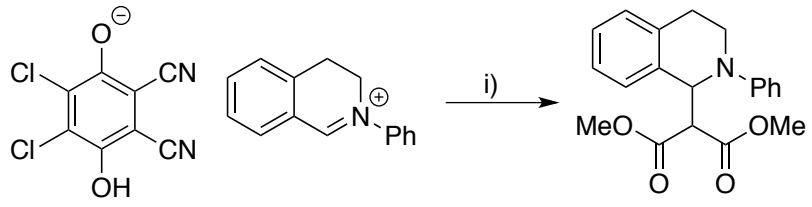
171 **203**

Reagents and conditions: i) Oxidant, catalyst, solvent, temperature, 24 h

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

[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.), H_2O_2 (2 equiv.), I_2 (10 mol%)

Mechanistically, both CDC reactions rely on the generation of an electrophilic iminium ion. Li proposed that the role of copper is twofold: coordinating to **201** to facilitate the formation of an iminium intermediate by hydrogen abstraction at the α-position of tetrahydroisoquinoline while also activating dimethyl malonate. Itoh hypothesized that hypoiodous acid (HOI), generated from iodine and hydrogen peroxide, is the active oxidant in the conversion of **201** into the iminium species. Interestingly, Todd published a CDC reaction between tetrahydroisoquinoline **201** and dimethyl malonate using DDQ as an oxidant. However, the reaction only proceeded if iminium ion **204** was first isolated and then added to a solution of dimethyl malonate, producing **202** in 73% yield after 30 min (**Scheme 78**).[61]



204 **202**

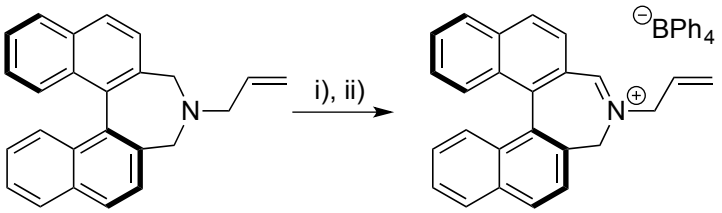
Reagents and conditions: i) dimethyl malonate (1.1 equiv.), CH_2Cl_2, r.t., 30 min, 73%

Scheme 78: Coupling reaction with isolated DDQ iminium salt **204**

When the cross coupling was attempted as a one-pot two-step reaction, a complex mixture of products was obtained, as DDQ was thought to react preferentially with the malonate.[61] We suspected that this could explain why the CDC reactions with azepine **171** were unsuccessful, and we therefore decided to first isolate the iminium salt and trial the copper-catalysed coupling conditions.

NBS or DDQ oxidation, followed by counter-ion exchange with sodium tetraphenylborate, allowed for the generation and easy isolation of iminium salt **176** as an orange solid. However, NBS oxidation at room temperature was found to be too severe and resulted in some decomposition and rather disappointing yields (**Entry 1, Table 23**). Consequently, low temperature oxidation was performed, leading to higher yields (**Entry 2**). A DDQ-mediated oxidation was also investigated,[62] and, although DDQ oxidation afforded **176**, the yield was lower than would be acceptable for large-scale synthesis (**Entry 3**).

Table 23: Oxidation of allyl **171**

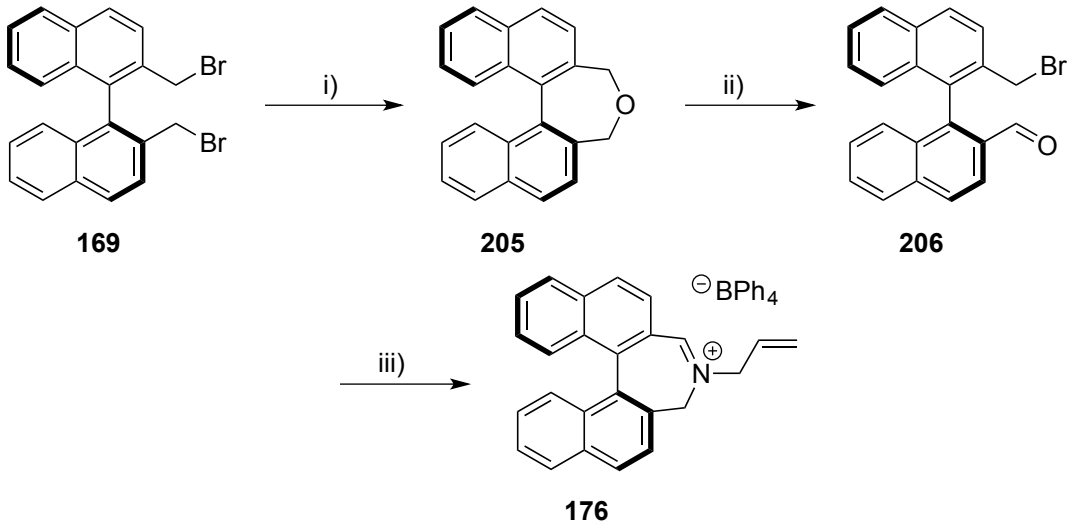


171 **176**

Reagents and conditions: i) Oxidant, CH_2Cl_2; ii) $NaBPh_4$ (1.1 equiv.), EtOH, CH_3CN, 10 min

Entry	Reagent	Temp (°C)	Time (h)	Yield (%)
1	NBS (1.05 equiv.)	r.t.	1	54
2	NBS (1.05 equiv.)	0	2	81
3	DDQ (2 equiv.)	r.t.	1	46

An alternative route to allyl iminium species **176** was explored. Dibromo compound **169** was heated in a mixture of 1,4-dioxane and saturated aqueous sodium carbonate to form oxepine **205**.[20] A ring-opening reaction using molecular bromine afforded bromoaldehyde **206** in moderate yield. Finally, a cyclocondensation reaction with allylamine in ethanol followed by addition of sodium tetraphenylborate resulted in the desired iminium salt in 65% yield (**Scheme 79**).

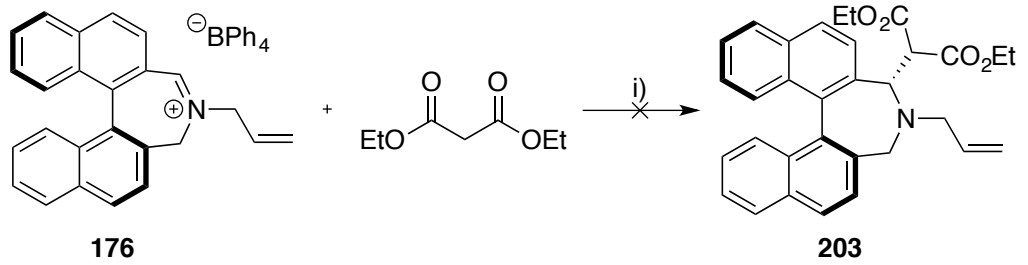


Reagents and conditions: i) Sodium carbonate (sat. aq.), 1,4 dioxane (1:1), reflux, 12 h, 87%; ii) Br_2 (1.125 equiv.), cyclohexane, 0 °C→reflux, 1 h, 50%; iii) allylamine (1 equiv.), EtOH, 40 °C, 12 h, $NaBPh_4$ (1.1 equiv.), CH_3CN, 65%

Scheme **79**: Alternative synthesis of iminium salt **176** from bromoaldehyde **206**

With allyl iminium salt **176** in hand, the coupling conditions reported by Li were explored, both in the presence and absence of oxidant *t*-BuOOH (**Entry 1** and **2**, **Table 24**). The substituent would be assumed to occupy solely the pseudoaxial orientation (**Table 24** and **25**).[28]

Table 24: Coupling reactions on preformed iminium salt **176**



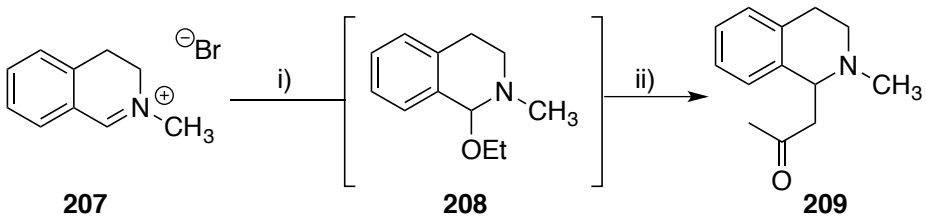
Reagents and conditions: i) Diethyl malonate, TBHP (1 equiv.), CuBr (5 mol%), r.t., 16 h

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

3	CuBr	-	CH_2Cl_2	-

Unfortunately, after 16 h, complete decomposition of starting material iminium salt **176** was observed with no formation of the anticipated diester product **203** (**Table 24**).

Promotion of CDC reactions by generation of a reactive ethoxy intermediate **208** has been reported.[63] Intermediate **208**, prepared from isoquinolinium bromide **207** and sodium ethoxide, was subjected to displacement by various ketones using either an ambient temperature 'one-pot' route or a higher temperature procedure after isolating ethoxide intermediate **208**. The route employed and the yield of the reaction depended upon the ketone substrates used; acetone, for example, was one of the highest yielding substrates (**Scheme 80**).



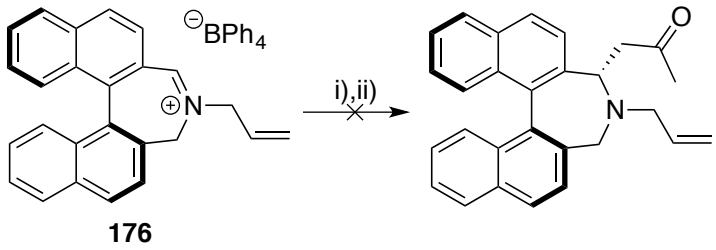
207 **208** **209**

Reagents and conditions: i) EtONa (2 equiv.), EtOH, 0 °C, 20 min; ii) CH_3COCH_3 (2 equiv.), r.t., 5 h, 97%

Scheme 80: Preparation of **209** by active intermediate **208**

Unfortunately when these conditions were replicated without attempting to isolate the reaction intermediate, addition of acetone at low temperature resulted in none of the desired product after 16 h (**Entry 1** and **2**). Reactions at higher temperature were also trialled; however, only starting material was recovered.

Table 25: Nucleophilic addition to iminium salt **176**



176

Reagents and conditions: i) EtONa (2 equiv.), EtOH, 0 °C, 20 min; ii) CH_3COCH_3 (2 equiv.), temperature

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

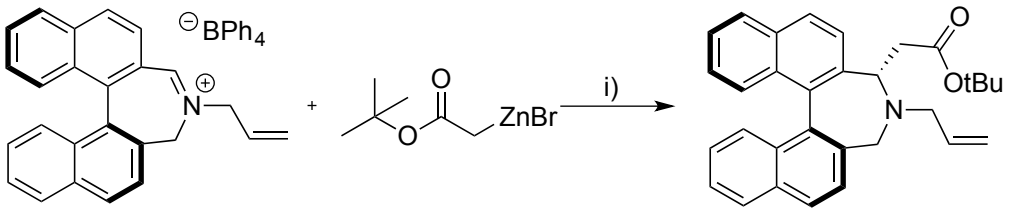
6.2 Reformatsky reaction

As described above (**Table 19**), ester **189** was prepared from iminium salt **175** using Reformatsky conditions in low to moderate yields; hence, allyl iminium salt **176** was also evaluated as a Reformatsky reagent acceptor. Haloester *t*-butyl bromoacetate was employed as we envisaged that the subsequent saponification step would require milder conditions.

Zinc activation was achieved through heating a zinc suspension in tetrahydrofuran under reflux in the presence of additives 1,2-dibromoethane and chlorotrimethylsilane for 1 h. The optimum conditions described for the synthesis of **189** were employed; unfortunately, only trace amounts of the desired *t*-butyl ester **211** were observed (**Entry 1**). When the quantities of reagents necessary to prepare the organo-zinc reagent were increased, compound **211** was isolated in 19% yield as a colourless solid and a single diastereoisomer (**Entry 2**). Increasing the reaction time to 48 h and increasing the quantities of zinc activating additives to

stoichiometric quantities resulted in a minor improvement in yield to 23% (**Entry 3**). To further improve the yield, the reaction was conducted at 65 °C; however, no product **211** was observed (**Entry 4**). This led us to conclude that either the Reformatsky reagent **210** or iminium salt **176** were not stable at higher temperatures.

Table 26: Reformatsky conditions

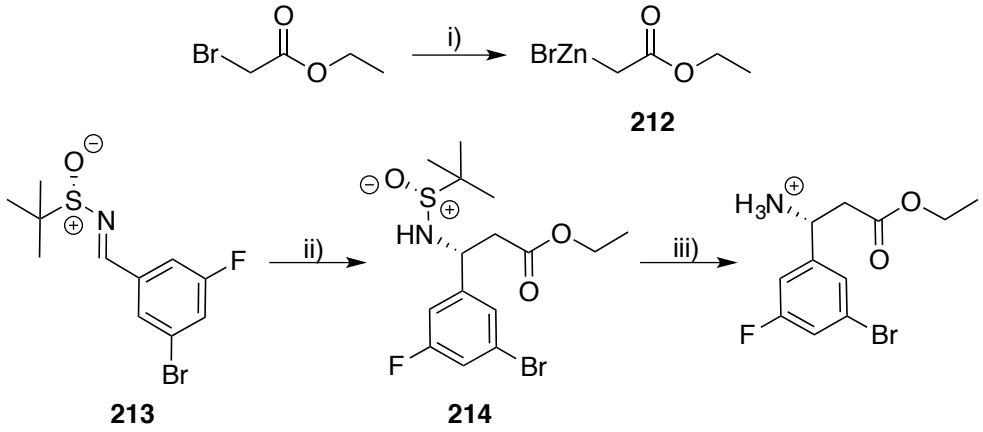


176 **210** **211**

Reagents and conditions: **210** (zinc activation: 65 °C, THF, additives), THF

Entry	*t*-butyl bromo-acetate	Zinc powder	Activation of zinc		Temp (°C)	Time (h)	Yield (%)
			1,2-$BrCH_2CH_2Br$	TMSCl			
1	5 equiv.	6 equiv.	5 mol%	4 mol%	25→30	12	trace
2	10 equiv.	10 equiv.	10 mol%	10 mol%	25→30	24	19
3	10 equiv.	10 equiv.	1 equiv.	1 equiv.	25→30	48	23
4	5 equiv.	6 equiv.	10 mol%	10 mol%	65	12	-

Due to the possible instability of iminium salt **176** at elevated temperature, an alternative procedure was sought: chiral *N*-sulfinyl imine **213** had been reported to undergo Reformatsky reactions at low temperature to yield the corresponding ester **214** in quantitative yield (**Scheme 81**). Interestingly, a novel zinc activation method employing DIBAL was also reported to be convenient for large-scale synthesis.[64]

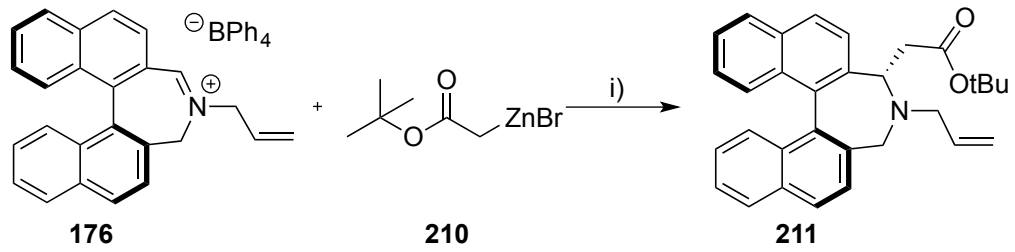


Reagents and conditions: i) Zn (3.5 equiv.), THF, 30 °C, ethyl bromoacetate (0.1 equiv.), 20% wt DIBAL in toluene (4 mol%), 40 °C, ethyl bromoacetate (1.7 equiv.), 2 h; ii) **212**, THF, −8 °C, 14 h, *quant.*; iii) 5M HCl/isopropanol, 20 °C, 18 h, 62%

Scheme 81: DIBAL zinc activation and low temperature Reformatsky reaction of imine **213**

In our hands, DIBAL zinc activation and the substrate addition at low temperature afforded ester **211** in 28% yield (**Entry 1**, **Table 27**). Encouraged by the increase in yield, we focused our attention on the addition of iminium salt **176** at low temperature. The zinc was activated with a stoichiometric amount of TMSCl, and iminium salt **176** was added to the activated zinc slurry at 0 °C, providing a further increase in yield (**Entry 2**). Addition of the iminium species at −78 °C gave ester **211** as a single diastereoisomer in 71% yield (**Entry 3**).

Table 27: Low temperature addition of **210**



176 **210** **211**

Reagents and conditions: i) **210** (zinc activation: 40-65 °C, THF, additive, 1 h), THF, 0 or −78 °C→r.t.

Entry	*t*-butyl bromoacetate	Zinc powder	Zinc Activation		Temp* (°C)	Time (h)	Yield (%)
			Additive	°C			
1	1.7 equiv.	3.5 equiv.	DIBAL (4 mol%)	40	−78→r.t.	12	28
2	10 equiv.	10 equiv.	TMSCl (1 equiv.)	65	0→r.t.	48	43
3	10 equiv.	10 equiv.	TMSCl (1 equiv.)	65	−78→r.t.	48	71

*Temperature at which iminium salt **176** is added to zinc slurry, the reaction is then allowed to reach r.t.

Crystals of **211**, suitable for single crystal X-ray crystallography, were obtained, and the relative conformation, where the β-*t*-butyl ester adopts a pseudo-axial orientation, was confirmed.[40]

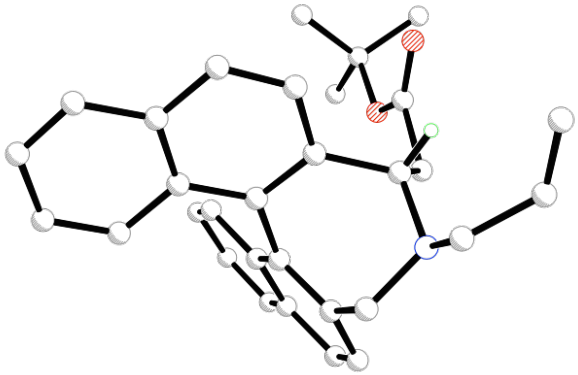
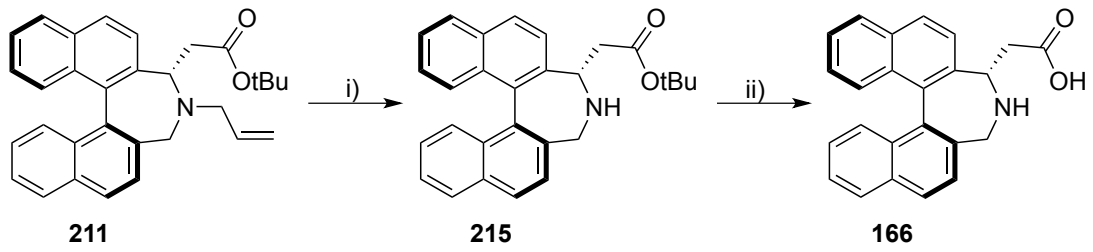


Figure 19: Crystal structure of **211**[40]

Unfortunately, the synthesis of **211** can be capricious and the yields can vary greatly: very low yields were also obtained when the reaction conditions described in **Entry 3** were employed. Two factors could explain the variable yields: stringently dry conditions are essential as the smallest amount of moisture can drastically lower the yield, and freshly prepared starting material **176** is vital as the iminium salt decomposes over time.

Deallylation of **211** was accomplished using the reported conditions,[11] and azepine **215** was obtained in 84% yield. *t*-Butyl group removal using trifluoroacetic acid afforded *β*-amino acid **166** in 94% yield **(Scheme 82)**.



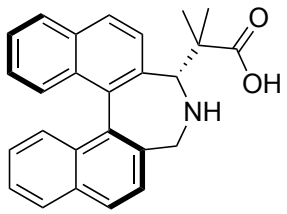
211 **215** **166**

Reagents and conditions: i) $Pd(PPh_3)_4$ (2 mol %), *N*,*N*-dimethylbarbituric acid (3 equiv.), CH_2Cl_2, 50 °C, 24 h, 84%; ii) TFA (12 equiv.), CH_2Cl_2, r.t., 16 h, 94%

Scheme 82: Protecting groups removal

We predicted that a more sterically congested version of β-amino acid **166** might

provide further selectivity by increasing crowding close to the aminocatalytic centre, and consequently β-amino acid **216** was sought.

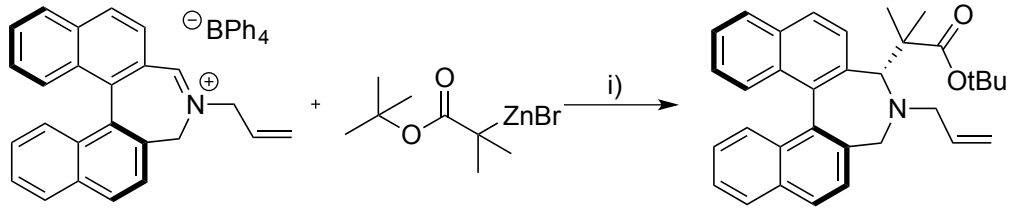


216

Figure 20: Sterically congested β-amino acid **216**

Using *t*-butyl bromoisobutyrate as a Reformatsky substrate, different reaction temperatures were screened. Ambient temperature addition surprisingly gave a better yield (**Table 28**, **Entry 1**) than seen previously using the *t*-butyl bromoacetate reagent (**Table 26, Entry 4**). Indeed, lower temperature additions were also higher yielding as compound **218** was isolated in up to 76% yield (**Entry 3**).

Table 28: Reformatsky conditions



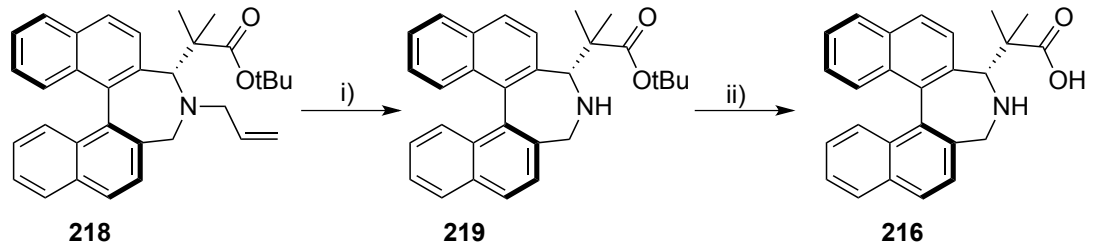
176 **217** **218**

Reagents and conditions: i) **217** (zinc activation: 65 °C, THF, additives, 1 h), THF, 48 h

Entry	*t*-Butyl bromo isobutyrate	Zn powder	Zinc Activation		Temp* (°C)	Yield (%)
			1,2-$BrCH_2CH_2Br$	TMSCl		
1	10 equiv.	10 equiv.	1 equiv.	1 equiv.	25→30	45
2	15 equiv.	15 equiv.	-	1 equiv.	0→r.t.	53
3	10 equiv.	10 equiv.	-	1 equiv.	−78→r.t.	76

*Temperature at which iminium salt **176** is added to the zinc slurry, then the reaction is allowed to warm to r.t.

Exposure of **218** to palladium-catalysed deallylation conditions gave **219** in 69% yield. Finally, a trifluroacetic acid-mediated saponification afforded β-amino acid **216** in moderate yield (**Scheme 83**).



218 **219** **216**

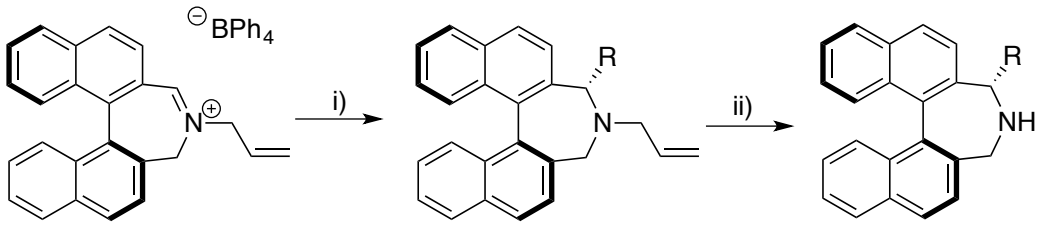
Reagents and conditions: i) $Pd(PPh_3)_4$ (2 mol %), *N*,*N*-dimethylbarbituric acid (3 equiv.), CH_2Cl_2, 50 °C, 24 h, 62%; ii) TFA (12 equiv.), CH_2Cl_2, r.t., 16 h, 61%

Scheme 83: Protecting groups removal

To assess the effect of the Brønsted acidic sites of β-amino acid catalysts **166** and **216**, and to separate that effect from the steric influence, a comparative study of the

catalysts with a variety of alkyl groups was needed. Therefore, increasingly bulky alkyl substituents were introduced onto iminium species **176** using Grignard reagent addition (**Table 29**). The Grignard reagent in THF solutions were added to iminium species **176** at low temperature and were allowed to reach ambient temperature overnight. Addition of methylmagnesium bromide gave the highest yield (**Entry 1**) providing a single diastereoisomer with a characteristic upfield shifting of the pseudoaxial methyl group (δ 0.54 ppm, doublet). Similarly, addition of ethynylmagnesium bromide gave a single diastereoisomer with the newly introduced group occupying the pseudoaxial position (δ 1.27 ppm, doublet). Whereas addition of benzylmagnesium chloride gave only trace amounts of the product (**Entry 3**). Identification of trace quantities of the benzyl addition product were made by ^{1}H NMR analysis of the reaction mixture, based on the expected number of aromatic signals (17 Ar*H*) and a doublet of doublet signal (δ 4.03 ppm) which could correspond to the NC*H*CH_2 coupling to the diastereotopic CH_2 group of the benzyl. Deprotection gave moderate yields, and slightly longer reaction times and further additions of $Pd(PPh_3)_4$ were necessary.

Table 29: Grignard reagent additions



176

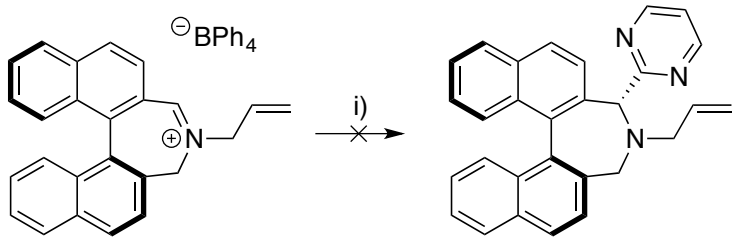
Reagents and conditions: i) Grignard reagent solution (10 equiv.), THF, −78 °C→r.t., 12 h; ii) $Pd(PPh_3)_4$ (2-4 mol %), *N*,*N*-dimethylbarbituric acid (3 equiv.), CH_2Cl_2, 50 °C, 36 h

Entry	Grignard solution	i) Yield (%)	ii) Yield (%)
1	MeMgBr	70	55
2	EthynylMgBr*	37	-
3	Benzyl MgCl	Trace	-

*15 equiv. used

With a successful route to both β-amino acids **166** and **216** achieved, the installation of other hydrogen bonding functional groups was targeted. First, the addition of 2-bromopyrimidine was examined using Reformatsky and Grignard conditions (**Table 30**). Zinc was activated at 65 °C with TMSCl (5 mol%), 1,2 dibromoethane (3 mol%), and magnesium was activated using iodine; 2-bromopyrimidine was then added over 1 h. After cooling, the organometallic reagents were added to a solution of allyl azepinium salt **176** in tetrahydrofuran at −78 °C and the reactions allowed to reach ambient temperature overnight. Surprisingly, neither the Reformatsky reaction nor the Grignard conditions produced the desired compound **220** and Grignard conditions resulted only in decomposition of starting material **176**.

Table 30: 2-Bromopyrimidine additions

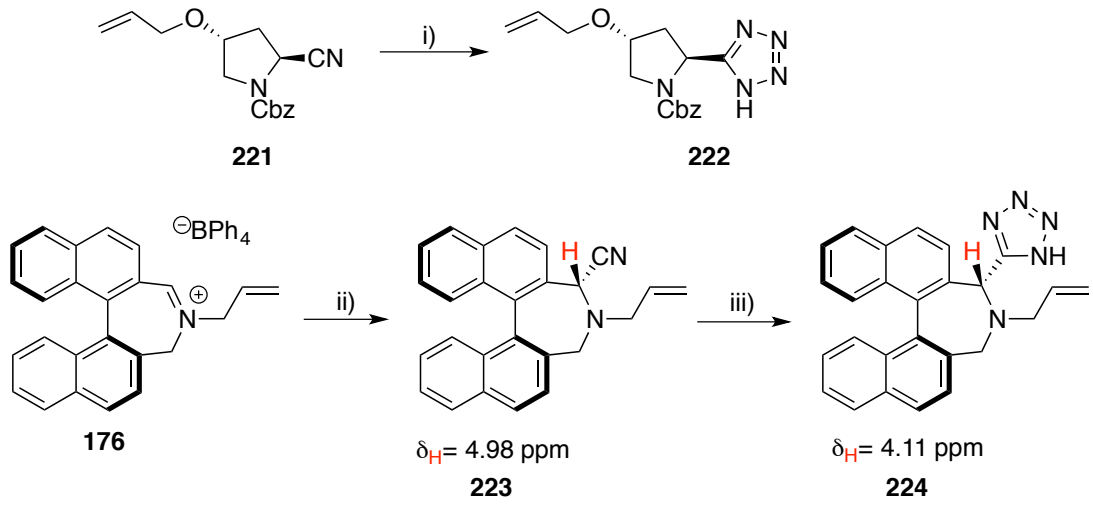


Reagents and conditions: i) Activated metal, 2-bromopyrimidine, THF, 65 °C, 1 h, −78 °C→r.t., 16 h

Entry	2-Bromopyrimidine	Metal	Activation	Yield (%)
1	5 equiv.	Zn (3.5 equiv.)	TMSCl, 1,2 dibromoethane	-
2	10 equiv.	Mg (14 equiv.)	Iodine	-

An axially chiral version of Ley's tetrazole **90** was also targeted. Addition of sodium cyanide to iminium salt **176** afforded α-amino-nitrile **223**, isolated cleanly following an aqueous work up. Compound **223** decomposed on silica gel and therefore was used without further purification in the attempted [3+2]-cycloaddition reaction with sodium azide and triethylamine hydrochloride (**Scheme 84**). [65,66,67] Trace amounts of

tetrazole **224** were detected by ^{1}H NMR analysis of the reaction mixture after 24 h. The assignment was based on the full consumption of starting material **223**, as observed by the disappearance of a singlet signal at δ 4.98 ppm (corresponding to the C*H*CN proton) and the appearance of a singlet at δ 4.11 ppm which we believe corresponds to C*H*C-tetrazole proton (tetrazole **90** C*H*NH δ 4.77 ppm[68], **Scheme 85**). Formation of **224** occurred alongside degradation of the starting material and so the reaction was not considered viable for continuing further synthetic steps. Acidic hydrolysis, to afford the α-acid derivative, was not considered at the time because of the unstable nature of compound **223**.[69,70]

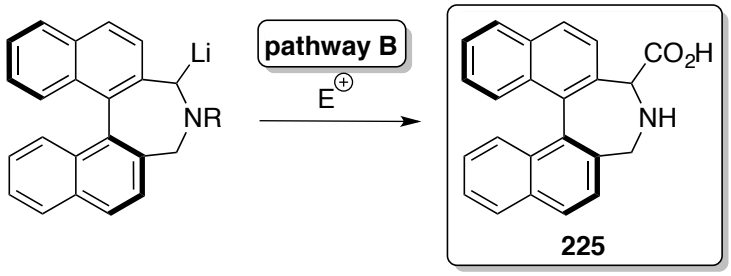


Reagents and conditions: i) NaN_3 (1.3 equiv.), $Et_3N.HCl$ (1.3 equiv.), toluene, 100 °C, 24 h, 75%[65] ii) NaCN (5 equiv.), CH_2Cl_2, H_2O, r.t., 2 h; iii) NaN_3 (1.3 equiv.), $Et_3N.HCl$ (1.3 equiv.), toluene, 100 °C, 24 h, traces

Scheme 84: Synthesis of tetrazole **224**

7.0 Initial retrosynthetic approaches to the α-amino acid catalyst

With a route to β-amino acids **166** and **216** achieved, a comparison was necessary to assess the effect of the carboxylic acid group on the selectivity. The next synthetic target chosen for catalytic evaluation was α-amino acid **225**, which could be generated asymmetrically through a lithiation and electrophilic trapping route **(Scheme 85)**.

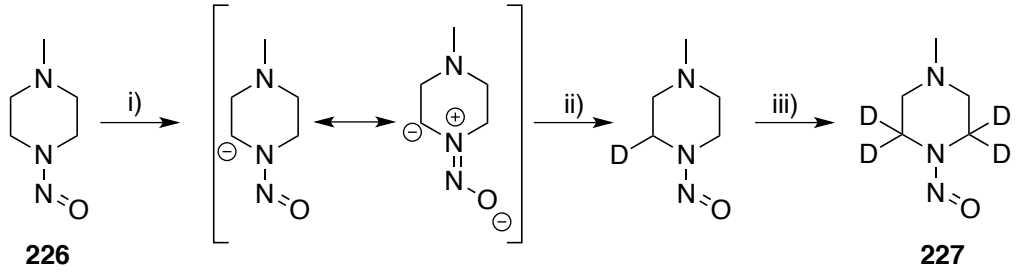


Scheme 85: α-Amino acid catalyst target **225**

Pathway B, a deprotonation route, requires metallation of our binaphthyl azepines using either an organo-lithium or a metal hydride base. The abstraction of the proton at the α-position requires the use of electron-withdrawing *N*-protecting groups, which increase the acidity at the α-position by stabilization of the intermediate anion.[71] The anion can then be quenched by the addition of an electrophilic reagent, resulting in the production of an α-functionalized catalyst. Accordingly, the nitroso and Boc protected azepines were targeted as potential anion precursors.

7.1 Nitroso protecting group

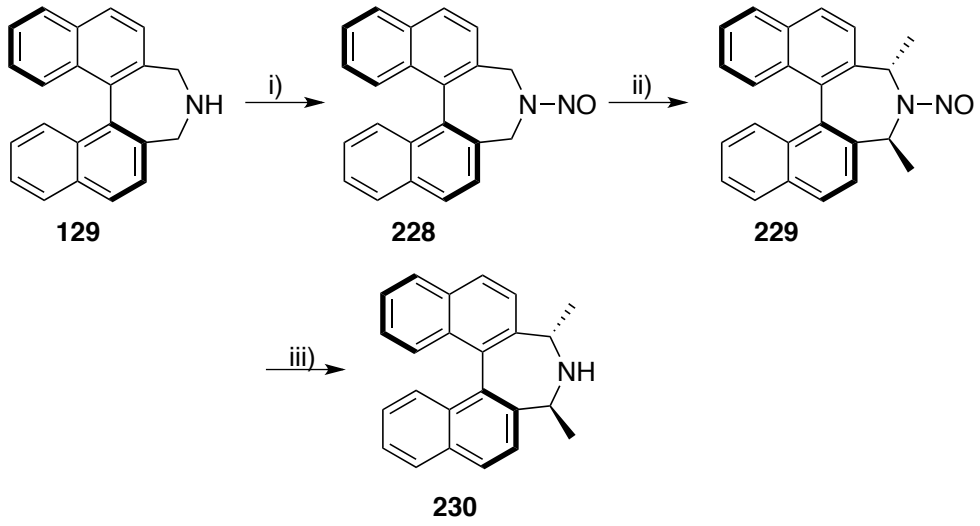
Under basic conditions and at elevated temperature, the protons at the α-position of nitroso-protected methylpiperazine **226** have been shown to be labile, undergoing deuterium exchange (**Scheme 86**).[72] This observation has been taken as evidence for the involvement of a stabilizing 'α-nitrosoamino carbanion', and consequently use of this protecting group has been explored in α-functionalization reactions.



Reagents and conditions: i) 1.3 M NaOD; ii) D_2O; iii) NaOD, D_2O, 100 °C, 2.5 h, 100% incorporation

Scheme 86: Influence of *N*-nitroso group[70]

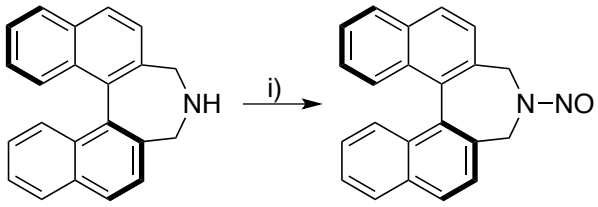
For example, Superchi used the nitroso protecting group in his synthesis of binaphthyl azepine ligands for dialkylzinc addition to aldehydes.[73] *N*-Nitroso **228** was synthesized from **129** by treatment with sodium nitrite in acetic acid. Compound **228** was then dimethylated by deprotonation using potassium hydride in tetrahydrofuran and addition of an excess of methyl iodide. Dimethyl *N*-nitroso **229** was then deprotected in 59% yield using a Raney Nickel-mediated hydrogenolysis producing C_2 symmetric **230**, where the two pseudoaxial methyl groups are in a *trans*-configuration, as confirmed by analysis of the ^{1}H NMR spectrum (**Scheme 87**).



Reagents and conditions: i) $NaNO_2$ (3 equiv.), H_2O, AcOH, r.t., 2 h, 87%; ii) KH (4 equiv.), THF, r.t., 30 min, MeI (16 equiv.), reflux, 18 h, 84%; iii) EtOH, Ra-Ni, H_2, 16 h, 59%

Scheme 87: Ligand synthesis employing nitroso-protecting group

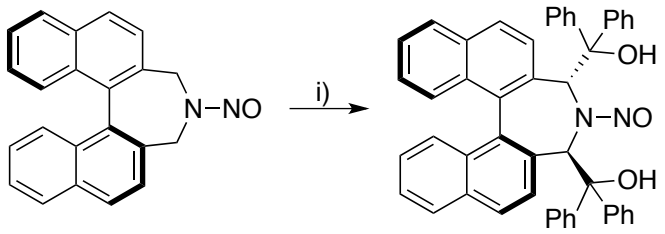
Accordingly, we synthesized *N*-nitroso compound **228** in high yield, following the same procedure (**Scheme 88**).



Reagents and conditions: i) $NaNO_2$ (3 equiv.), H_2O, AcOH, r.t., 2 h, 76%

Scheme 88: *N*-Nitroso azepine synthesis

Preparation of an axially chiral analogue of Jørgensen's biarylalcohol **99** species was targeted first. *N*-Nitroso **228** was stirred in tetrahydrofuran at 0 °C as potassium hydride was added in one portion. Benzophenone was added, as a solution in THF, and the mixture was allowed to reach ambient temperature overnight. The reaction was quenched and analysed using ^{1}H NMR spectroscopy of the reaction mixture; but, unfortunately, only starting material was observed.



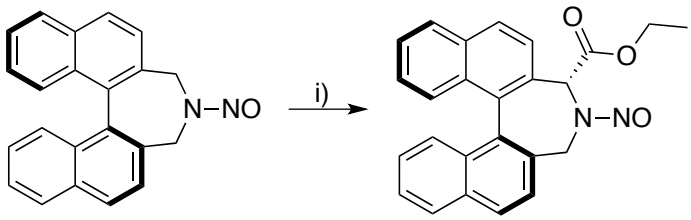
228 **231**

Reagents and conditions: i) KH (4 equiv.), THF, 0 °C, 30 min, $PhCO_2Ph$ (6 equiv.), r.t., 16 h

Scheme 89: Attempted synthesis of an axially chiral version of Jørgensen's diaryl alcohol catalyst

Nitroso-azepine **228** was deprotonated at –78 °C and the resulting anion next trapped with an electrophile that could be manipulated to obtain the α-amino acid. Ethyl chloroformate was chosen and a range of bases were screened (**Table 31**). Potassium hydride, employed by Superchi, and *sec*-BuLi provided trace amounts of the desired ester **232** (**Entry 4**), identified by the increasing complexicity in the aromatic signal region (suggesting the formation of an unsymmetrical monosubstituted azepine product) and the appearance of multiplet signals (δ 1.00-1.80 ppm) which could correspond to the two diastereotopic CH_2CH_3 ester signals. Sodium hydride and potassium hydride did not lead to the formation of the product (**Entries 1 and 2**). Sodium hydride did not lead to the formation of the product. Similarly, treatment with lithium diisopropylamide gave no conversion (**Entry 3**), presumably due to steric hindrance.

Table 31: Base screening for deprotonation of **228**



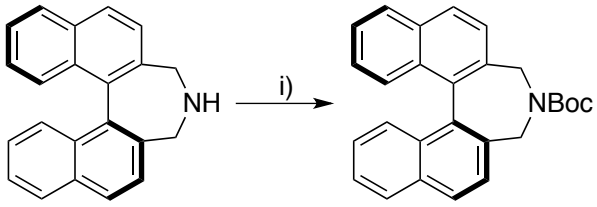
228 **232**

Reagents and conditions: i) Base, ethyl chloroformate, 16 h

Entry	Base	Solvent	Temp (°C)	Yield (%)
1	KH (1.2 equiv.)	THF	0→ r.t.	Starting material
2	NaH (1.2 equiv.)	THF	0→ r.t.	Starting material
3	LDA (2 equiv.)	THF	−78 °C→ r.t.	Starting material
4	*s*-BuLi (1.2 equiv.)	THF	−78 °C→ r.t.	Trace

7.2 Boc protecting group

With disappointing preliminary results observed when using the nitroso group, *N*-Boc azepine **233** was synthesized. Initially, addition of di-*tert*-butyl carbamate to **129** afforded **233** in excellent yield. However, as with nitroso compound **228**, the starting material required for this method is produced from the deprotection of *N*-allyl azepine **171**, causing this route to be neither time nor atom efficient.



129 **233**

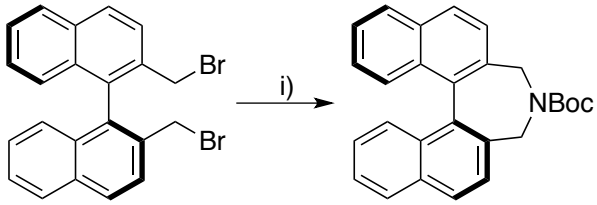
Reagents and conditions: i) di-*tert*-butyl carbamate (1.05 equiv.), *t*BuOH, r.t., 16 h, 92%

Scheme 90: Boc protection of azepine **233**

Therefore, a procedure employing dibromo compound **169** and *tert*-butyl carbamate

alongside sodium hydride in DMF, was adopted, and after 4 days, **233** was isolated in moderate yield (**Entry 1, Table 32**).[74] Increasing the number of equivalents of base used resulted in improvements in yield (**Entries 2** and **3**). To reduce reaction time, gentle heating of the reaction mixture was trialled, following reagent addition at 0 °C, but, this resulted in reduced yields and an increasing number of inseparable side products (**Entry 4**).

Table 32: Optimization of the synthesis of *N*-Boc azepine

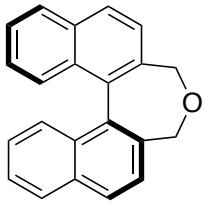


169 **233**

Reagents and conditions: i) NaH, *tert*-butyl carbamate (1 equiv.), DMF

Entry	NaH	Time (d)	Temp (°C)	Yield (%)
1	2.1 equiv.	4	0→ r.t.	58
2	3 equiv.	4	0→ r.t.	65
3	4 equiv.	4	0→ r.t.	87
4	4 equiv.	1	0 → 50	37

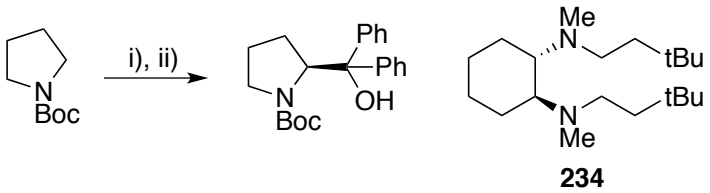
A significant quantity of side product oxepine **205** was detected when the *N*,*N*-dimethylformamide was not freshly distilled or sufficiently dry and, unfortunately, this impurity co-eluted with *N*-Boc azepine **233** when purification was carried out using silica gel column chromatography.



205

Figure 21: Oxepine side product **205**

Blakemore's asymmetric *N*-Boc pyrrolidine lithiation methodology was next tested.[73] Blakemore employed 1.3 equivalents of *sec*-butyllithium and 3 equivalents of electrophile in the presence of (*S*, *S*)-diamine **234,** for the synthesis of the *N*-Boc derivative of Jørgensen's catalyst in 82% yield (**Scheme 91**).

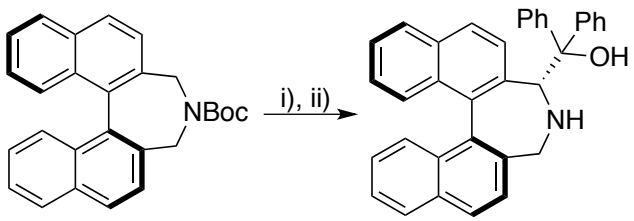


234

Reagents and conditions: i) *s*-BuLi (1.3 equiv.), (*S*,*S*)-**234**, Et_2O, −78 °C, 1 h; ii) Ph_2CO (3 equiv.), 82%, 95% ee

Scheme 91: Blakemore's asymmetric *N*-Boc pyrrolidine lithiation methodology

Diaryl alcohol analogue **235** was again targeted through the addition of benzophenone. When *sec*-butyllithium was added to the Boc-azepine **233**, the reaction mixture changed from pale yellow to black with the colour persisting until the addition of benzophenone had been made. Unfortunately, starting materials were the major compounds isolated from the reaction mixture, alongside **235** in trace quantities (**Scheme 92**). Trace quantities of **235** were identified based on ^{1}H NMR analysis of the reaction mixture: aromatic signals matching the number of aromatic protons expected (22 Ar*H)* and a deshielded singlet signal at δ 6.44 ppm which could correspond to the C*H*C(Ph)$_2$OH proton. This signal is at a high chemical shift compared to that of the pyrrolidine catalyst **99** (C*H*C(Ph)$_2$OH δ 4.26 ppm).[75,76,77] However, as the proton is positioned between two aromatic systems and it may be experiencing a ring current deshielding effect from both enviroments. We hypothesize that the acidic nature of silica may have promoted the deprotection of the Boc derivative during silica gel column chromatography purification.



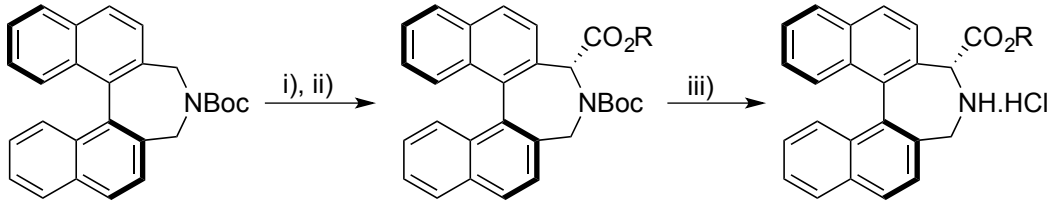
233 **235**

Reagents and conditions: i) *s*-BuLi (1.3 equiv.), Et_2O, –78 °C, 1 h; ii) $PhCO_2Ph$ (3 equiv.), −78 °C→ r.t., 16 h, traces

Scheme 92: Addition of benzophenone and unintentional deprotection

To obtain the α-amino acid **225**, Boc-azepine **233** was deprotonated at –78 °C and the addition of alkyl chloroformates was next attempted (**Table 33**). Blakemore's conditions were successful for the addition of alkyl chloroformates, although only starting material was recovered in the addition of *tert*-butyl anhydride (**Entry 3**).[78] An attempt at Boc-deprotection of **233** using mild microwave heating in water was unsuccessful as only starting material was observed.[79] Deprotection of Boc-azepines **236** and **237** was achieved using an excess of trifluoroacetic acid in dichloromethane, producing the free amine species in moderate to high yields. Heating under reflux with aqueous hydrochloric acid (6M) led to the isolation of the product in the highest yield. Furthermore, the hydrochloride salt product was easily purified by recrystallisation.[80]

Table 33: Ester catalyst synthesis

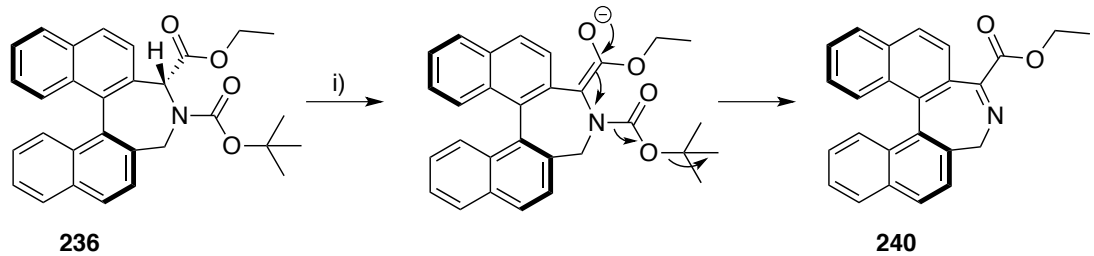


233

Reagents and conditions: i) *s*-BuLi (1.3 equiv.), Et_2O, −78 °C, 1 h; ii) electrophile (3 equiv.), −78 °C→ r.t., 16 h; iii) HCl_{aq} (6M), acetone, 70 °C, 16 h

Entry	Electrophile	i) Yield (%)	Product	ii) Yield (%)	Product
1	Ethyl chloroformate	73%	**236**	*Quantitative*	**238**
2	Methyl chloroformate	81%	**237**	*Quantitative*	**239**
3	Boc anhydride	Starting material	-	-	-

On one occasion, **240** was isolated following treatment of **233** with *s*-BuLi and ethyl chloroformate, but only in trace quantities. We hypothesized that a double deprotonation could account for the formation of **240** (**Scheme 93**).



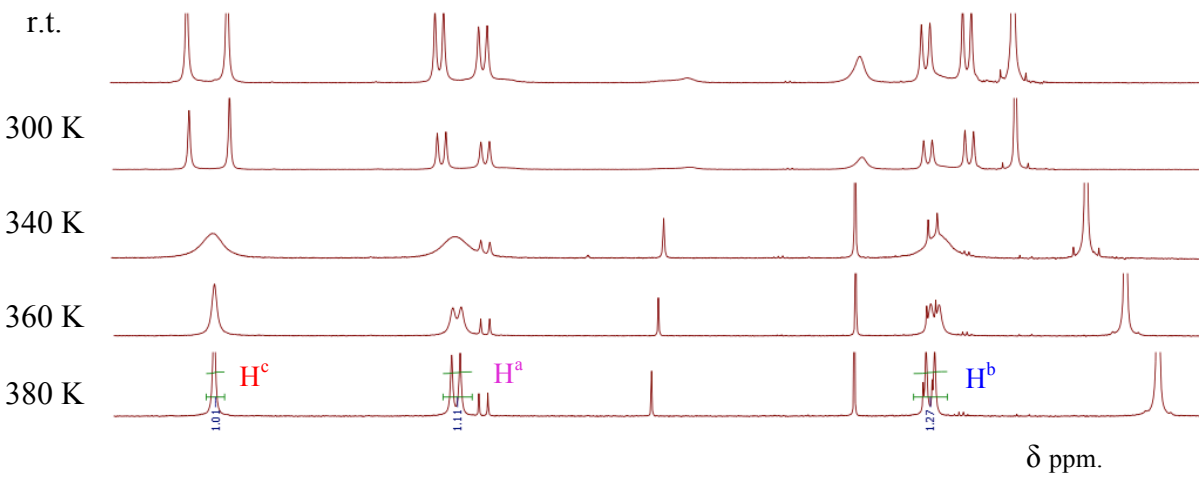
236 **240**

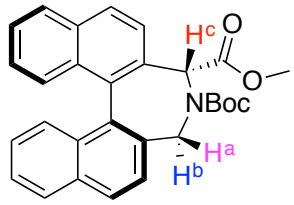
Reagents and conditions: i) *s*-BuLi, Et_2O, −78 °C→ r.t., 16 h, traces

Scheme 93: Unexpected side product form ethyl chloroformate addition

Both the methyl and ethyl ester exist as mixtures of two rotamers due to the conformational restrictions of the bulky *tert*-butyl ester. Variable temperature ^1H

NMR experiments confirmed the presence of rotamers: coalescence of the duplicate peaks can be observed when increasing the temperature to 380 Kelvin (**Figure 22**).

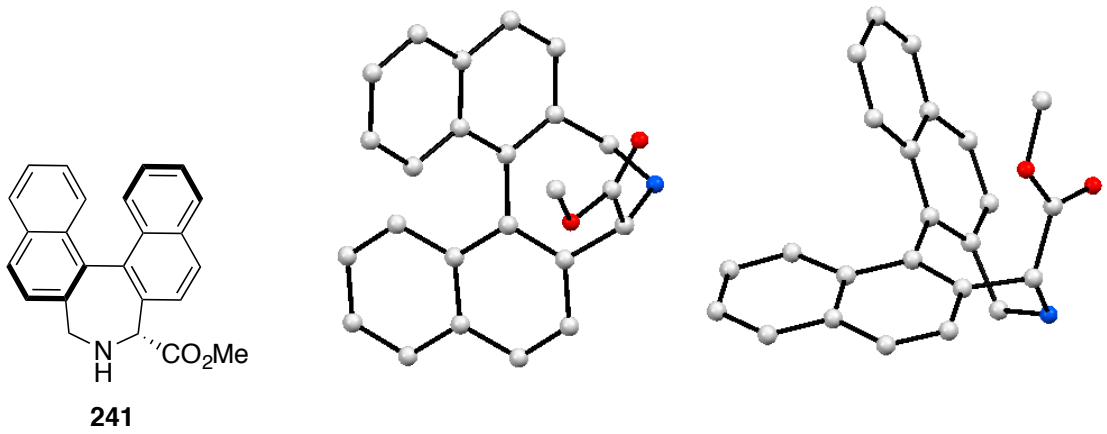




237

Figure 22: Variable temperature NMR of **237**

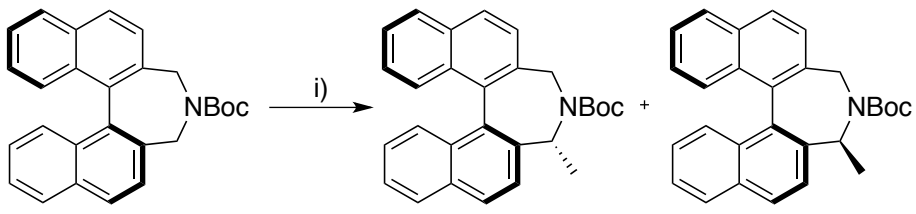
Alkyl chloroformate additions were fully diastereoselective, and single crystal X-ray crystallography of **241** confirmed that the ester group adopts a pseudo-axial orientation (**Figure 23**).



241

Figure 23: Pseudoaxial orientation of the ester group

Interestingly, the selectivity observed on addition of alkyl chloroformates was a welcome, but unexpected outcome. Meyer's lithiation of **233** with *sec*-BuLi and trapping with iodomethane was shown to result in a mixture of S_{ax},*S* and S_{ax},*R* diastereoisomers in a 1.5:1 ratio (**Scheme 94**). Upon repeating Meyer's experiment, the same ratio of products was observed using ^{1}H NMR spectrum analysis through the integration of the signals corresponding to the methyl group protons (S_{ax},*R*-**242** δ_{Me} 1.95 ppm and S_{ax},*S*-**243** δ_{Me} 0.70 ppm).[5] Whilst we are uncertain why we observe a diastereoselective addition when using chloroformates and not with iodomethane, we tentatively suggest that the selectivity may be affected by the size of the electrophile (Discussed further, **Table 35**).



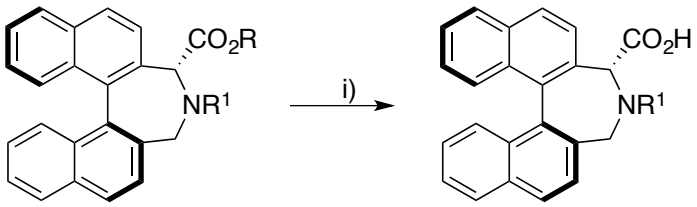
233 **242** **243**

Reagents and conditions: i) *s*-BuLi (2 equiv.), THF, −78 °C, 30 min, MeI (1.3 equiv.), 1 h, 68%

Scheme 94: Results from repeating Meyer's *N*-Boc methylation conditions

Surprisingly, all conventional attempts to saponify the methyl and ethyl esters failed (**Table 34**). Both esters were subjected to strongly basic, acidic and high temperature conditions for prolonged periods of time, yet only starting materials were detected (**Table 34**). [81] Further, TMSCl (2 equiv.) used in combination with NaI (2 equiv.) failed to saponify the methyl ester, and instead these conditions favoured the deprotection of the Boc group (**Entry 7**).[82] Heating under reflux in hydrochloric acid also resulted in the removal of the Boc group (**Entry 9**). When 18-crown-6 was used with potassium hydroxide, starting materials were the only products observed. Finally, when hydrazine was used, a complex mixture was obtained (**Entry 11**).[83]

Table 34: Attempted saponification of methyl and ethyl esters



Reagents and conditions: Base, solvent, temperature, 12-72 h

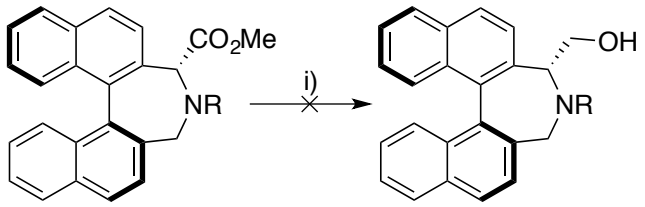
Entry	R	R^1	Reagent	Solvent	Temp (°C)	Yield (%)
1	Et	H	LiOH (1 equiv.)	THF:H_2O	r.t. *	Starting material
2	Et	H	LiOH (1 equiv.)	MeOH:H_2O	r.t.	Starting material
3	Et	H	LiOH (6 equiv.)	CH_3CN:H_2O	r.t.*	Starting material
4	Et	H	NaOH (3 equiv.)	MeOH:H_2O	r.t.	Starting material
5	Et	H	LiOH (6 equiv.)	EtOH:H_2O	r.t.	Starting material
6	Me	Boc	NaOH (1 equiv.)	MeOH:H_2O	r.t.*	Starting material

7	Me	Boc	TMSCl and NaI	CH_3CN	r.t.	**241**
8	Me	H	TMSCl and NaI	CH_3CN	r.t.	Starting material
9	Et	Boc	HCl (6 M)	-	70	**238**
10	Me	Boc	KOH 18-crown-6	$MeOH:H_2O$	r.t.	Starting material
11	Me	Boc	NH_2NH_2 (80%)	H_2O	r.t.	Complex mixture

*also performed at reflux

Extraordinarily, the inertness of the ester group also extended to lithium aluminium hydride reduction conditions. When three equivalents of reducing agent were used with **237**, the desired product was not formed and only starting material was isolated (**Entry 1**, **Table 35**). We believed the bulkiness of the *tert*-butyl group could have prevented the reduction, and accordingly **241** was subjected to the same conditions, but only starting material was recovered (**Entry 2**).

Table 55: Lithium aluminium hydride reduction attempts

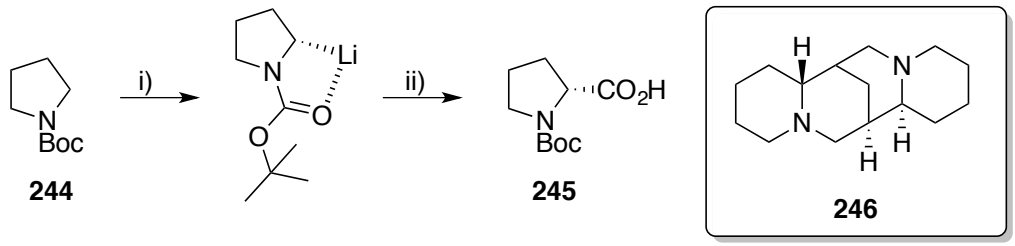


Reagents and conditions: $LiAlH_4$ (3 equiv.), Et_2O, 0 °C→ r.t., 16 h

Entry	R	Compound	Yield (%)
1	Boc	**237**	Starting material
2	H	**241**	Starting material

As the saponification of esters **236** and **237** proved surprisingly difficult, we

endeavoured to find an alternative approach for the synthesis of **225**. Asymmetric lithiation/carboxylation of Boc-pyrrolidine **244**, reported by Beak, in the synthesis of (*R*)-proline was an encouraging lead.[84] Beak employed the chiral additive (−)-sparteine alongside *sec*-butyllithium to create a chiral organolithium reagent which could, in turn, selectively deprotonate **244** leading to the preferential formation of one enantiomer. Carbon dioxide gas was bubbled into the reaction mixture to generate **245** in moderate yield and 88% enantiomeric excess (**Scheme 94**).

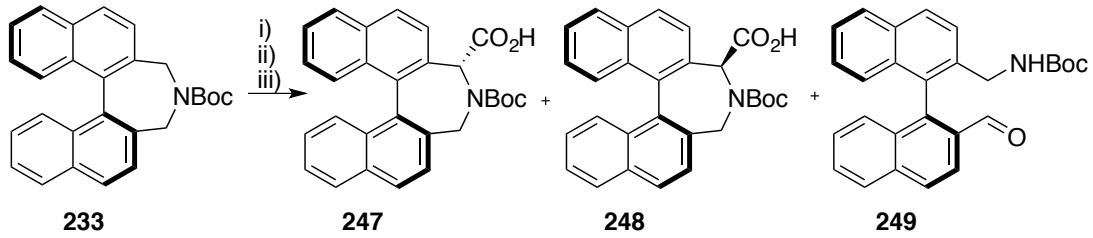


Reagents and conditions: i) (−)-sparteine **246** (1.2 equiv.), Et_2O, −78 °C, *s*-BuLi (1.2 equiv.), 15 min, pyrrolidine (1 equiv.), −78 °C, 4 h; ii) CO_2, −78 °C, 3 h, 55%, 88% ee

Scheme 94: (−)-Sparteine mediated asymmetric lithiation

Accordingly, we attempted a similar methodology: *sec*-BuLi was added to a solution of **233** at −78 °C and left for 1 h and CO_2 gas, from sublimation of cardice, was bubbled into the reaction mixture via a $CaCl_3$ drying tube. The reaction mixture allowed to stir for 1 h before it was quenched using saturated aqueous ammonium chloride. Diastereoisomeric acids **247** and **248** were isolated in 34% and 31% yield, respectively (**Entry 1**, **Table 35**). Side product **249** was also isolated in 13% yield. Increasing the reaction time to 16 h did not greatly affect the yield; however, increasing the quantity of *sec*-butyllithium and the reaction time, following the addition of CO_2, resulted in a significant reduction in the yield (**Entry 3**). Addition of carbon dioxide in the form of dry ice pellets resulted in a slight decrease in the yield of products **247** and **248** (**Entries 4** and **5**).

Table 35: Addition of CO_2



233 **247** **248** **249**

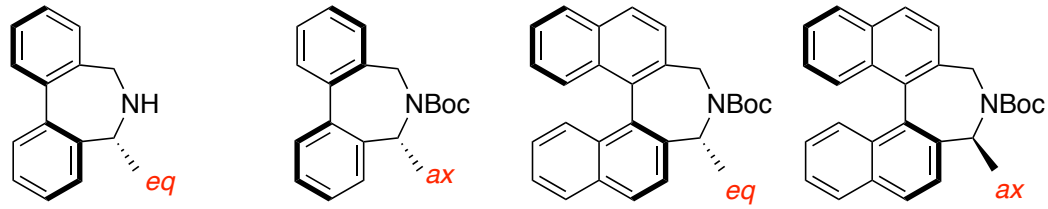
Reagents and conditions: i) *s*-BuLi, Et_2O, −78 °C, 1 h; ii) CO_2, −78 °C→ r.t. iii) NH_4Cl solution

Entry	*s*-BuLi	CO_2	Time (h)	Yield of 247 (%)	Yield of 248 (%)	Yield of 249 (%)
1	1.3	Gas	2	34	31	13
2	1.3	Gas	16	30	33	17
3	2	Gas	24	12	12	14
4	1.3	Solid	2	25	28	7
5	2	Solid	16	24	23	10

We are not able to confidently explain how side product **249** is produced; the suggested structure matches all the assignments made using mass, NMR and IR spectral analysis. The yield of **249** seems unaffected by the quantity of *sec*-butyllithium used or by reaction time, and it was not isolated in any of the alkyl chloroformate addition reactions.

The identification of **247** and **248** was based on the differing chemical shifts of the signals corresponding to the pseudoaxial and pseudoequatorial protons on the carbon atom α to the acid group. This technique has been employed widely in conformational assignments of this type of azepinal structure (**Figure 24**). Pseudoaxial substituents experience a clear upfield shifting in ^1H NMR spectrum, compared to their pseudoequatorial counterparts, due to the effect of the

neighbouring aromatic ring or 'ring current effect'.[5,85,86,87,88]



δ_{Me}= 1.50 ppm — **150**

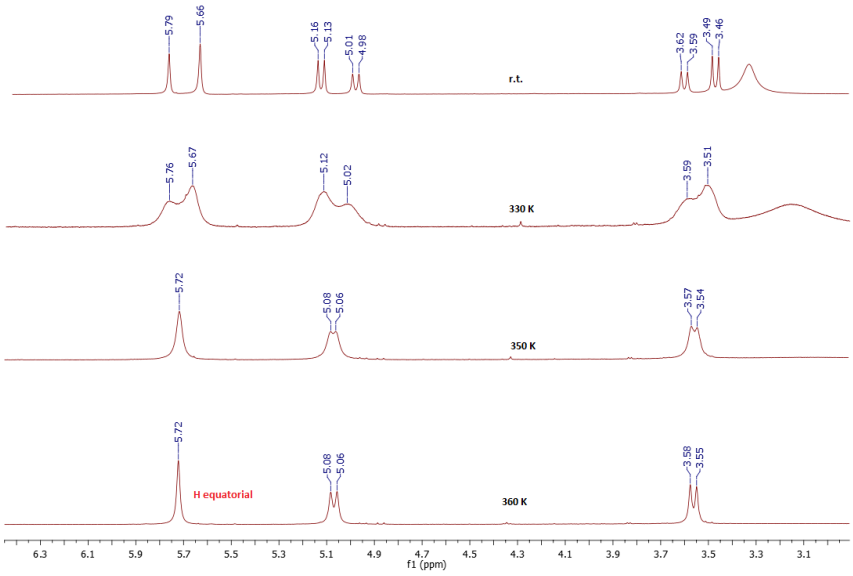
δ_{Me}= 0.86 ppm — **151**

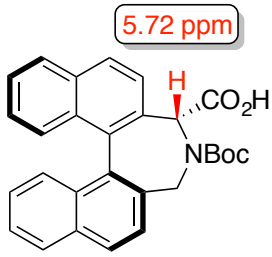
δ_{Me}= 1.95 ppm — **242**

δ_{Me}= 0.70 ppm — **243**

Figure 24: Conformational assignments based on ^{1}H NMR spectroscopy

Variable temperature ^{1}H NMR experiments (up to 360 K) were performed in order to increase the resolution to identify the splitting patterns for diastereoisomer (S_{ax},*S*)-**248** and to define the chemical shifts of the protons for diastereoisomer (S_{ax},*R*)-**247** as the presence of rotamers doubled the number of signals (**Figure 25**). In (S_{ax},*S*)-**248**, the pseudoaxial proton experiences greater shielding from the proximal naphthalene group and therefore the signal is found further upfield (δ_H 4.36 ppm) compared to the pseudoequatorial proton in (S_{ax},*R*)-**247** (δ_H 5.72 ppm).[6]





247

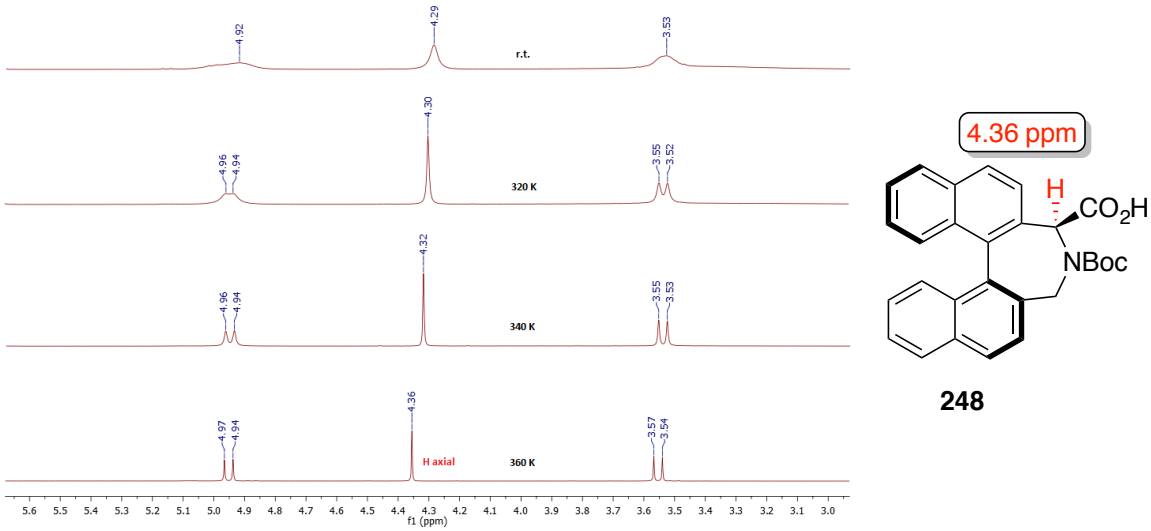
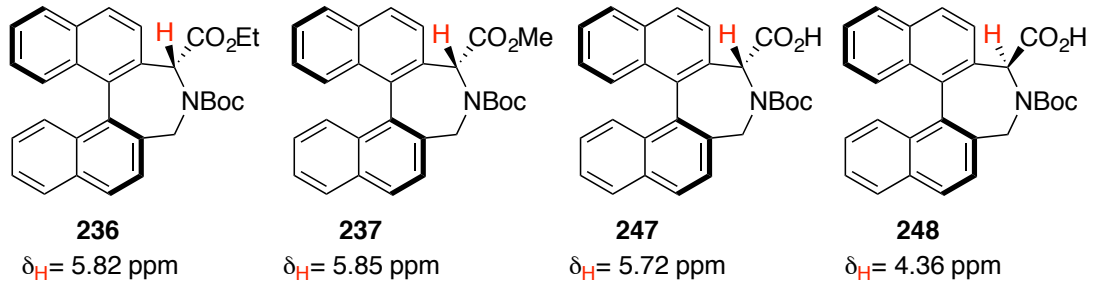


Figure 25: Variable temperature ^{1}H NMR chemical shifts of methylene protons of diastereoisomers **247** and **248** at increasing temperature

When analysing the ^{1}H NMR spectra of (S_{ax},*S*)-**248**, the pseudoaxial proton (shown in red) experiences greater shielding from the proximal naphthalene group and therefore the signal is found further upfield (δ_H 4.36 ppm) compared to the pseudoequatorial proton in (S_{ax},*R*)-**247** (δ_H 5.72 ppm).[6]

Accordingly, compound **247** was assigned as having a pseudoaxial carboxylic acid substituent based on the chemical shift corresponding to the α-proton, indicating a pseudoequatorial orientation. In addition this value follows the trend of the other catalyst precursors with pseudoaxial substituents (**Figure 26**). Compounds **236**, **237** and **247**, all of which have alpha substituents in the pseudoaxial orientation, have very similar chemical shift values for the signal corresponding to their pseudoequatorial protons (δ_H 5.82 ppm, δ_H 5.85 ppm, δ_H 5.72 ppm, respectively). These assignments are further supported by the absolute configuration of **236**, following Boc group removal, which has been confirmed by X-ray crystallography (**Figure 23**).



236 δ_H= 5.82 ppm

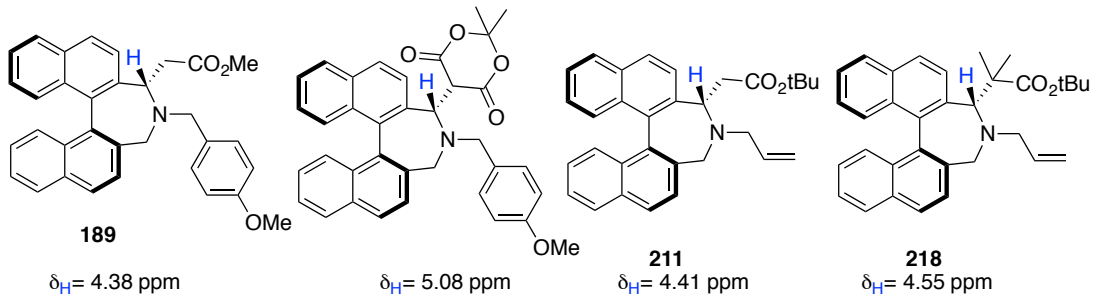
237 δ_H= 5.85 ppm

247 δ_H= 5.72 ppm

248 δ_H= 4.36 ppm

Figure 26: Chemical shifts of α-amino esters and acids, **236**, **237**, **247** and **248**

If we extend this reasoning, we can be confident of our previous assignments of the β-amino acid catalyst precursors, such as **189**. The absolute configuration of **211** has been confirmed by X-ray crystallography (**Figure 19**) where the β-amino ester group was shown to occupy the pseudoaxial position. The chemical shift values for the C*H*CR$_2$COOR protons of compounds **189**, **211** and **218** (**Figure 27**) are very similar (δ_H 4.38 ppm, δ_H 4.41 ppm, δ_H 4.55 ppm, respectively) which supports our previous stereochemical assignment for compound **189**. Whilst the recorded chemical shift values for the pseudoequatorial protons appear upfield, compared to the pseudoequatorial protons of the α-acids and esters, the distance to the electron-withdrawing carbonyl explains the difference. Conversely, in the Meldrum's acid derived compound, the pseudoequatorial proton is close to two electron withdrawing substituents which leads to a chemical shift value (δ_H 5.08 ppm) nearer to that of **236**, **237** and **247**.



189 δ_H= 4.38 ppm

δ_H= 5.08 ppm

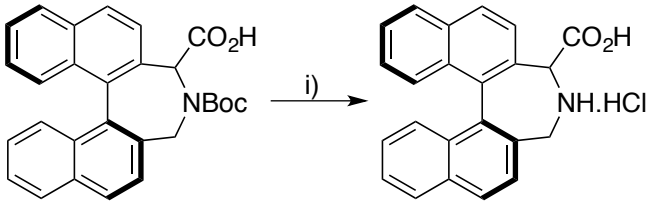
211 δ_H= 4.41 ppm

218 δ_H= 4.55 ppm

Figure 27: Chemical shifts of beta-amino esters and derivatives

In both cases, deprotection of **247** and **248** was achieved in quantitative yield through heating under reflux in a mixture of acetone and aqueous hydrochloric acid overnight (**Table 36**).

Table 36: Deprotection of **247** and **248**

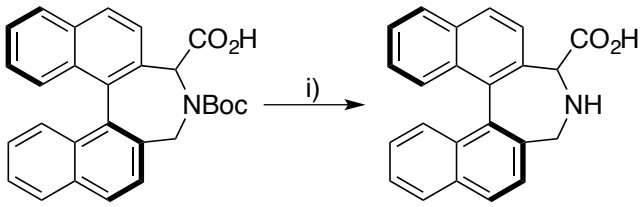


Reagents and conditions: i) HCl_{aq} (6M), acetone, 70 °C, 16 h

Entry	Compound	Yield (%)	Compound
1	**247**	*Quantitative*	**250**.HCl
2	**248**	*Quantitative*	**251**.HCl

Alternatively a trifluoroacetic acid-mediated deprotection afforded amines **250** and **251** in high yields (**Table 37**).[89]

Table 37: Trifluoroacetic acid deprotection



Reagents and conditions: i) TFA (14 equiv.), CH_2Cl_2, r.t., 16 h

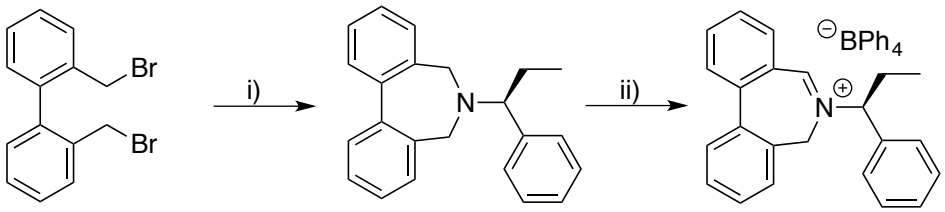
Entry	Compound	Yield (%)	Compound
1	**247**	82	**250**
2	**248**	71	**251**

8.0 Biphenyl catalysts

Having successfully synthesized a series of novel binaphthyl-based axially chiral amino acids for screening in catalysis, we turned our attention to the biphenyl analogues. Indeed, as mentioned previously, Maruoka reported that compared to **111**, compound **144** was more a reactive catalyst, due its biphenyl structure and activating aryl methoxy groups, and consequently required much lower catalyst loadings (**Table 10**).[90]

Our synthesis of the related biphenyl catalysts started from achiral dibromo compound **252** (**Scheme 96**). From this achiral starting material, we intended to introduce a chiral nitrogen-protecting group, and observe whether this substituent would induce any selectivity in nucleophilic additions to the corresponding iminium salt derivative.[4]

A double nucleophilic substitution ring closing reaction, using (*R*)-(+)-1-phenylpropylamine, afforded **253** in 88% yield, and an NBS oxidation and counter-ion exchange gave iminium salt **254** in 64% yield (**Scheme 95**).



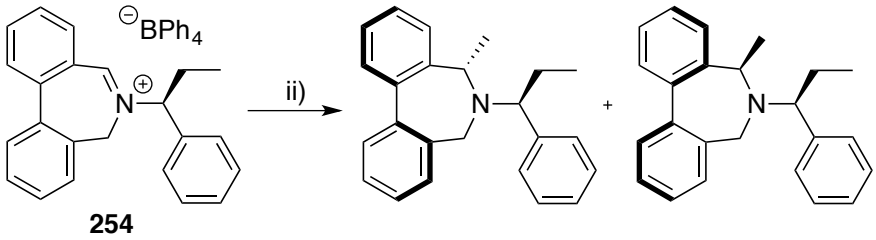
252 **253** **254**

Reagents and conditions: i) (*R*)-(+)-1-phenylpropylamine (1 equiv.), $CsCO_3$ (1.8 equiv.), CH_3CN, 80 °C, 16 h, 88%; ii) NBS (1.05 equiv.), CH_2Cl_2, 0 °C, 2 h, then $NaBPh_4$ (1.05 equiv.), $MeCH_3$, EtOH, 64%

Scheme 95: Synthesis of iminium salt **254**

As a test reaction, we had hoped that the presence of a chiral nitrogen-protecting group would provide some selectivity in the addition of methyl Grignard reagent

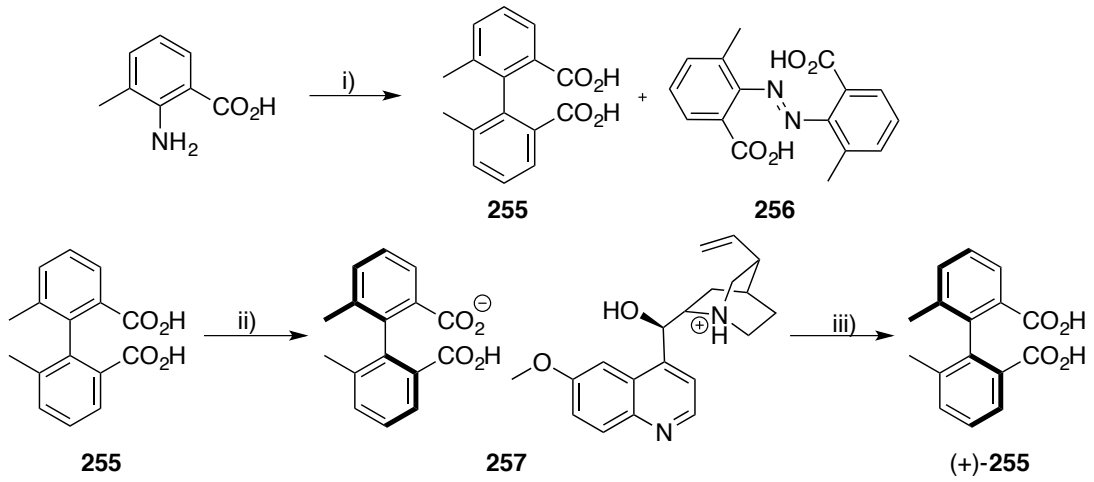
onto iminium salt **254**. Ideally, had the addition demonstrated some diastereoselectivity, Reformatsky reactions would have been attempted to synthesize the β-amino acid analogues. Disappointingly, the addition resulted in an inseparable mixture of diastereoisomers in a 1:1 ratio (**Scheme 96**).



Reagents and conditions: i) MeMgBr (10 equiv.), THF, −78 °C→ r.t., 16 h, d.r. 1:1, 86%

Scheme 96: Addition of methyl Grignard reagent to iminium salt **254**

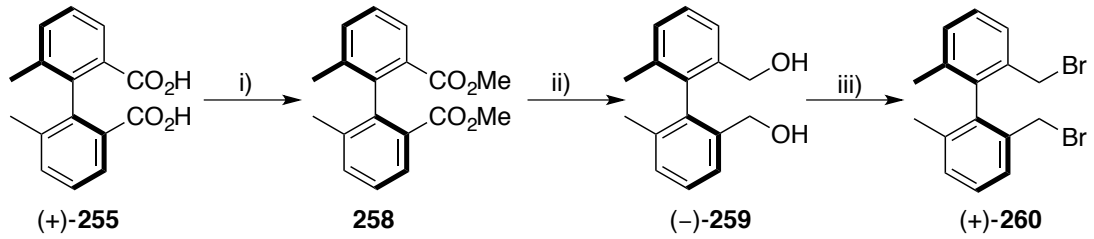
As the addition proved non-selective, we turned our attention to the preparation of an axially chiral biphenyl backbone, hoping that a fixed chirality, as observed in the case of the binaphthyl analogue, would afford the addition products as single diastereoisomers. Such an axially chiral biphenyl backbone has been reported by Denmark,[91] and was used to prepare epoxidation catalysts within the Page group.[92] Our target aminocatalysts would then be accessed using the methodology described above for the binaphthyl analogues. The first step was a copper(I) diazonium salt homocoupling reaction of commercially available 2-amino-3-methylbenzoic acid, affording racemic 6,6'-dimethyl-dicarboxylic acid **255** and the azo-containing side product **256** in 54% and 18% yields, respectively (**Scheme 97**). Resolution of (±)-**255** was achieved using quinine, and the resulting salt was recrystallized from hot ethanol (90%) to achieve the selective isolation of diastereoisomerically pure quinine salt **257**. Treatment of salt **257** with hydrochloric acid led to the formation of (+)-**255** as a single diastereoisomer, as confirmed by optical rotation measurements.[86]



Reagents and conditions: i) NaOH (1.3 equiv.), $NaNO_2$ (1 equiv.), H_2O, 0 °C, 4M HCl, $CuSO_4.5H_2O$ (1.7 equiv.), 30 % NH_4OH, NH_2OH (prepared from $(NH_2OH)_2.H_2SO_4$ (1.9 equiv.), 3M NaOH, 0 °C), 110 °C, 1 h, conc. HCl, r.t. 12 h, **255** 54%, **256** 18%; ii) Quinine (1 equiv.), 90% EtOH, 70 °C→ r.t.; iii) EtOAc, 3M HCl, 16 h, 37%

Scheme 97: Synthesis and resolution of bis-acid **255**

Bis-acid (+)-**255** was then converted into the corresponding bis-methyl ester **258**. Reduction of both ester moieties using $LiAlH_4$ afforded bis-alcohol (−)-**259** in quantitative yield. An Appel reaction employing phosphorus tribromide and pyridine gave dibromo compound (+)-**260** in 88% yield (**Scheme 98**).

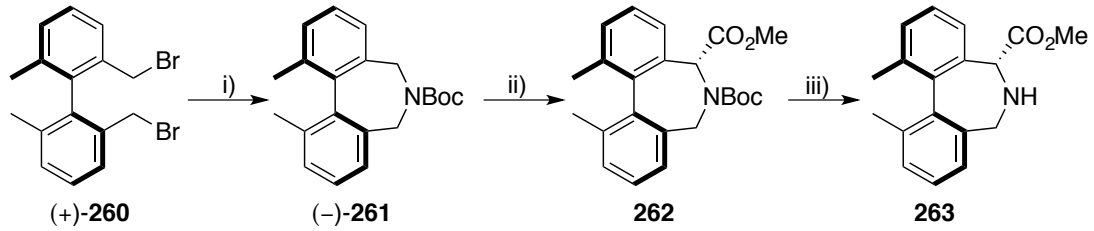


Reagents and conditions: i) MeOH, conc. H_2SO_4, 70 °C, 16 h, 82%; ii) Et_2O, $LiAlH_4$, 0 °C, *quant*.; iii) pyridine (0.1 equiv.), toluene, PBr_3 (3 equiv.), 60 °C, 3 h, 88%

Scheme 98: Synthesis of dibromo compound **260**

With (+)-**260** in hand, and employing the conditions used in the synthesis of the binaphthyl analogue **233**, *N*-Boc analogue (−)-**261** was isolated in high yield, despite

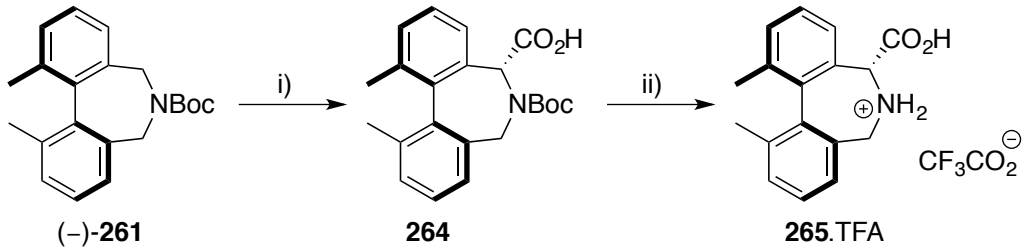
small amounts of the corresponding oxepine impurity detected. Azepine (−)-**261** was lithiated using *sec*-butyllithium, causing the reaction mixture to change from a pale yellow to a deep red colour; the anion was trapped using methyl chloroformate to form **262** in 79% yield. A trifluoroacetic acid-mediated deprotection gave free amine **263** in 74% yield (**Scheme 99**).



Reagents and conditions: i) DMF, NaH (2.05 equiv.), 0 °C, *tert*-butyl carbamate (1 equiv.), 88%; ii) Et_2O, −78 °C, *s*-BuLi (2 equiv.), 1 h, $ClCO_2Me$ (1.5 equiv.), 1 h, −78 °C, 79%; iii) TFA, DCM, r.t., 1 h, 74%

Scheme 99: Synthesis of methyl ester catalyst **263**

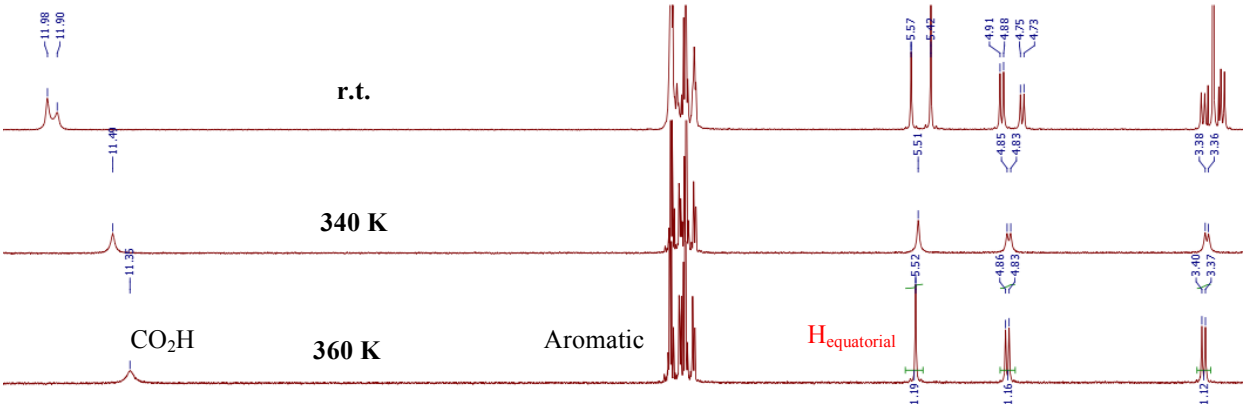
Finally, α-amino acid derivative **264** was isolated in 45% yield when CO_2 gas was used as the electrophile (**Scheme 101**). Deprotection of **264** could be achieved by trifluoroacetic acid treatment, producing **265**.TFA in 50% yield (**Scheme 100**).

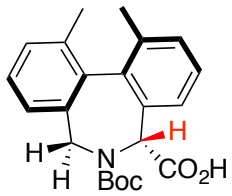


Reagents and conditions: i) Et_2O, −78 °C, *s*-BuLi (2 equiv.), 1 h, CO_2 gas, 1 h, −78 °C→ r.t., 45 %; iii) TFA, DCM, r.t., 1 h, 50%

Scheme 100: Synthesis of **265**

Variable temperature ^{1}H NMR experiments were performed on **264** to resolve signals corresponding to the two rotamers present at room temperature in solution. At 360 K we observed coalescence of the rotameric signals (**Figure 28**).

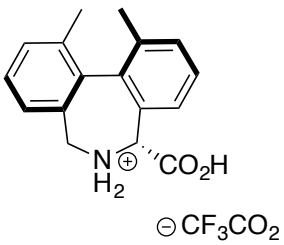




264

Figure 28: Variable temperature NMR of **264**

The absolute configuration of the acid group of **265** was confirmed by single crystal X-ray crystallography and the acid group adopts a pseudoaxial conformation (**Figure 29**).



265.TFA

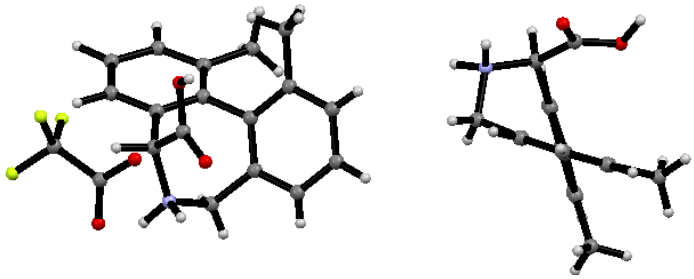


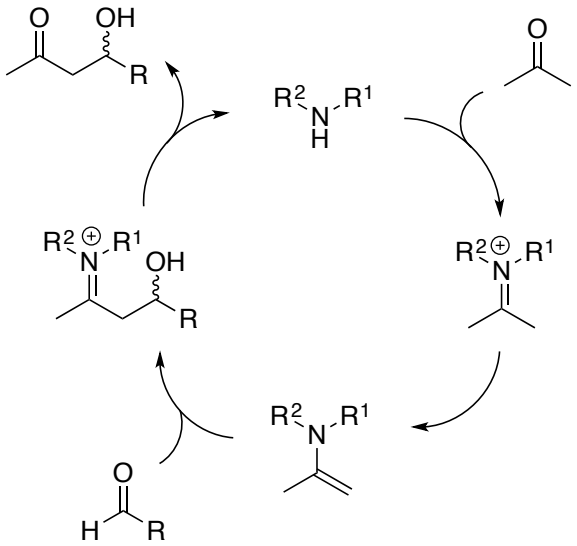
Figure 29: Crystal structure of **265**

Interestingly, the complete diastereoselectivity observed in the synthesis of **264** does not follow the selectivity observed when preparing binaphthyl acids **247** and **248**, where a mixture of diastereoisomeric acids was generated from the same lithiation and decarboxylation conditions.

9.0 Catalyst testing

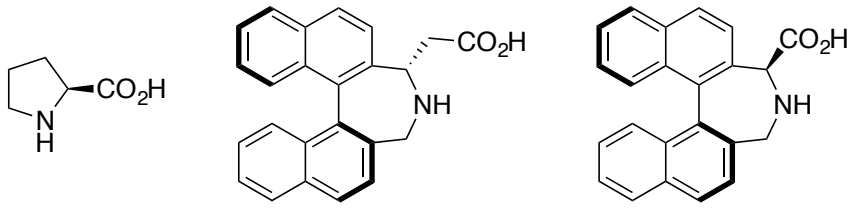
9.1 Aldol reaction

Aminocatalysis is a relatively recent endeavor for the Page group and as such, screening began with catalysts **166** and **251** for the aldol reaction of nitrobenzaldehyde **81** and acetone. This reaction relies on enamine activation of the ketone substrate by aminocatalyst (**Scheme 101**).



Scheme 101: General catalytic cycle of organocatalysed aldol reaction

As seen above, Maruoka's '*synthetic amino acid'* catalyst (*S*)-**111** was shown to be very successful in this reaction, affording aldol products in up to 99% ee (**Tables 8** and **9**). We envisaged that our catalysts, which share structural similarities, especially in the case of **166** and **251**, would show equally promising preliminary results.[113]

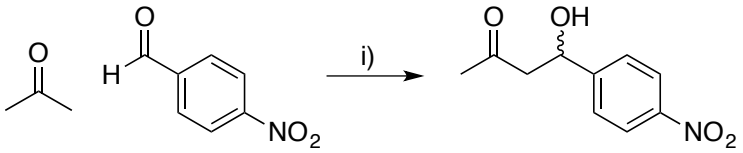


27 **166** **251**

Figure 30: Previous studies of Page group aminocatalysts for the aldol reaction

Catalyst **166** and **251** were screened using the optimum solvent described by Maruoka and List (DMSO); however remarkably, in both cases, no conversion was detected after several days (**Entries 4** and **6**, **Table 38**).[113,93] Similarly, when acetonitrile was used as a solvent for **251** and **216**, no conversion to the hydroxyketone was observed (**Entries 3** and **5**).

Table 38: Aldol reaction



81

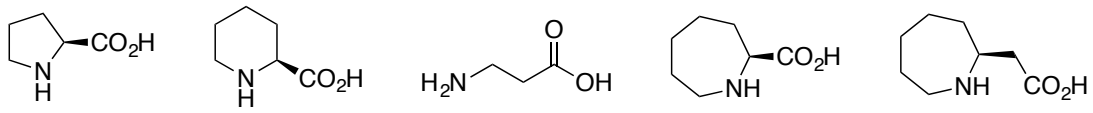
Reagents and conditions: Catalyst (10 mol%), acetone (27 equiv.), nitrobenzaldehyde (1 equiv.), solvent, r.t., 72 h

Entry	Catalyst	Temp (°C)	Solvent	Conversion (%)[a]	ee (%)[b],[c]
1	**-**	r.t.	neat	**-**	**-**
2	**27**[d],[e]	r.t.	DMSO	80	34 (*R*)
3	**166**	r.t.	CH_3CN	-	-
4	**166**[d],[e]	r.t.	DMSO	-	-
5	**251**	r.t.	CH_3CN	-	-
6	**251**[d],[e]	r.t.	DMSO	-	-

7	**251**	r.t.	MeOH	-	-
8	**251**	r.t.	toluene	-	-

[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture [b] Enantiomeric excess was determined using HPLC with Chiralcel® IC column: (hexane/iPrOH=92:8, λ=220 nm), 0.5 mL; tR= major enantiomer 45.5 min, minor enantiomer 43.1 min. [c] absolute configuration was determined by comparison with known HPLC retention times [d] 30 mol% [e] additive $PhCO_2H$ used (20 mol%)

It was surmised that the inactivity of **166** compared to (*S*)-proline could be explained by the reduced acidity of the carboxylic acid group and its larger distance from the aminocatalytic centre. Indeed, α-amino acids (*S*)-proline, 2-piperidinecarboxylic acid and **268** have carboxylic acid pKa values of 2.0, 2.5 and 2.5 respectively, whereas β-alanine and **269** are much less acidic, with values of 3.6 and 4.0 (**Figure 31**).[94,95] It was concluded that a more acidic group and nucleophilic nitrogen may be required for this reaction to proceed smoothly.

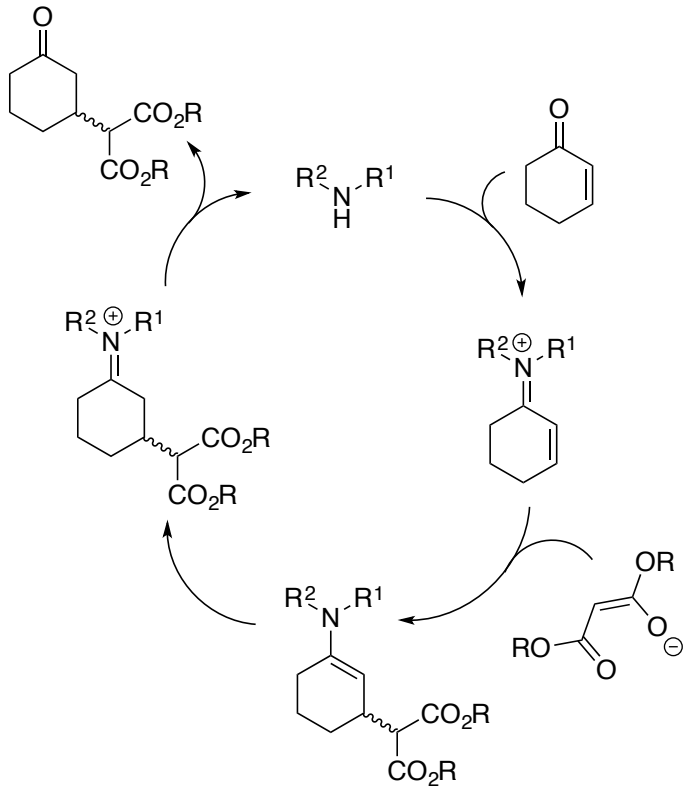


pKa 2.0 | pKa 2.5 **266** | pKa 3.6 | pKa 2.5 **268** | pKa 4.0 **269**

Figure 31: Computational and experimental pKa values of α- and β-amino-acid derivatives

9.2 Michael reaction

As the aldol reaction showed little in the way of encouraging results, we decided to evaluate the Michael reaction, hoping that our catalysts would be more successful in an iminium activation pathway. Indeed, secondary amines such as MacMillan's **70** and Jørgensen's **100** have proven very effective in catalysis through such an iminium ion activation mechanism (**Scheme 102**).[96,97] The conjugate 1,4-addition of malonates to α,β-unsaturated enones was explored first (**Table 39**).

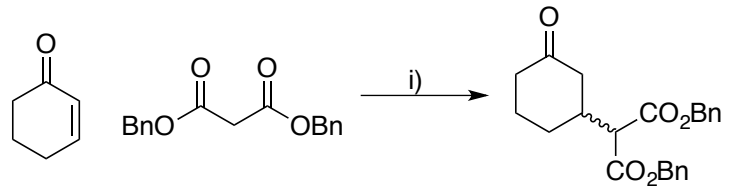


Scheme 102: General catalytic cycle of organocatalysed Michael reaction

We selected catalysts **166**, **216** and **251** to screen and followed conditions reported by Ley, who employed tetrazole catalyst **90** in combination with a stoichiometric quantity of base in the reaction of dibenzyl malonate additions to cyclohexenone.[98] Ley reported that tetrazole catalyst **90**, when employed alongside piperidine, provided the product in 62% yield and 82% ee in two days.[94] The reaction is promoted by a bifunctional Lewis/Brønsted basic type activation; the chiral amine catalyst activates the α,β-unsaturated carbonyl compound *via* an iminium

intermediate whilst the addition of a basic additive activates the nucleophilic reagent by deprotonation.[99] Ley reported piperidine was the most successful base of those screened;[99] however, previous work within our group showed that piperidine was not suitable in combination with catalysts **166** and **216** and that, surprisingly, inorganic base LiOH gave the best enantioselectivities.[40] Thus, initially we explored the effect of other bases and preliminary results suggested the reaction occurs, albeit slowly, in the absence of our catalysts, when LiOH and K_2CO_3 are used (**Entries 1-3**). We hoped that because the base-mediated reaction was slow, the contribution of our aminocatalysts would be significant: conferring enantioselectivity and increasing the speed of reaction.

Table 39: Michael addition of dibenzyl malonate onto cyclohexenone



270

Reagents and conditions: i) Enone (1 equiv.), malonate (1 equiv.), catalyst (10 mol%), additive (1 equiv.), solvent, r.t.

Entry	Catalyst	Additive	Solvent	Temp (°C)	Time (h)	Conversion (%)[a]	Ee (%)[b],[c]
1	**-**	LiOH	CH_2Cl_2	r.t.	144	100	-
2	**-**	K_2CO_3	CH_2Cl_2	r.t.	144	100	-
3	**166**	LiOH	CH_3CN	r.t.	24	100	5
4	**166**	LiOH	THF	r.t.	24	100	5
5	**166**	LiOH	xylene	r.t.	30	100	4
6	**166**	LiOH	H_2O	r.t.	24	100	12
8	**216**	LiOH	toluene	− 5	120	100	12
9	**216**	LiOH	CH_2Cl_2	− 5	120	-	-

10	**216**	LiOH	toluene	r.t.	24	100	4
11	**251**	LiOH	CH_2Cl_2	r.t.	144	100	-
12	**251**	-	Neat	r.t.	144	-	-
13	**251**	-	Et_2O	r.t.	144	-	-
14	**251**	-	CH_3CN	r.t.	144	-	-
15	**251**	$PhCO_2H$ [d]	$CHCl_3$	r.t.	144	-	-

[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture [b] Enantiomeric excess was determined using HPLC with Chiralcel® AI-3 column: (hexane/iPrOH=60:40, λ=220 nm), 0.7 mL; tR= major enamtiomer 20.2 min, minor enantiomer 20.6 min [c] absolute configuration was determined by comparison of the HPLC in the literature [d] 10 mol% additive used

The reaction conditions employing stoichiometric quantities of inorganic base, and 10 mol% of catalyst, led to full conversion; however, the addition products were obtained in very low ee or as racemic mixtures. Unsurprisingly, considering the water has a pKa value of 15.7, and, is therefore far more basic than Ley's favoured base, piperidine (pKa 12).[100] Indeed, when no base was used and the reaction was stirred for six days no formation of product was detected (**Entry 12**). In order to ascertain whether the catalyst was forming the activated iminium intermediate, a periodic ^{1}H NMR experiment was performed: 1 equivalent of catalyst **251** and 1 equivalent of cyclohexenone **270** in $(CD_3)_2SO$, were monitored using ^{1}H NMR spectroscopy over a 24 h period. $(CD_3)_2SO$ was used for NMR spectral analysis as the solvent as it did not interfere with substrate signals and signals were found to be better resolved when using this solvent.

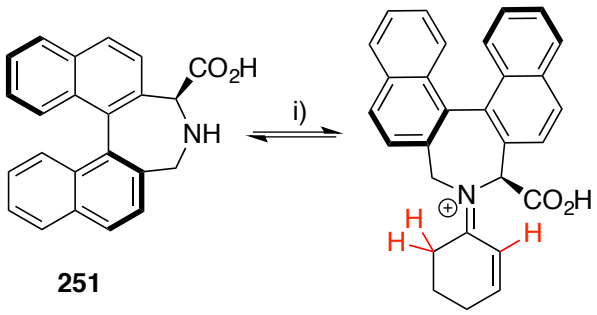


Figure 32: Catalyst **251** and cyclohexenone **270** in d_6-DMSO

A change in splitting patterns and/or chemical shifts would indicate the formation of the active iminium intermediate. After 24 h, no sign of activation was observed (conducted with and without the presence of benzoic acid) using NMR spectral analysis and consequently cyclohexenone was abandoned as a substrate for catalysis (**Figure 33**).

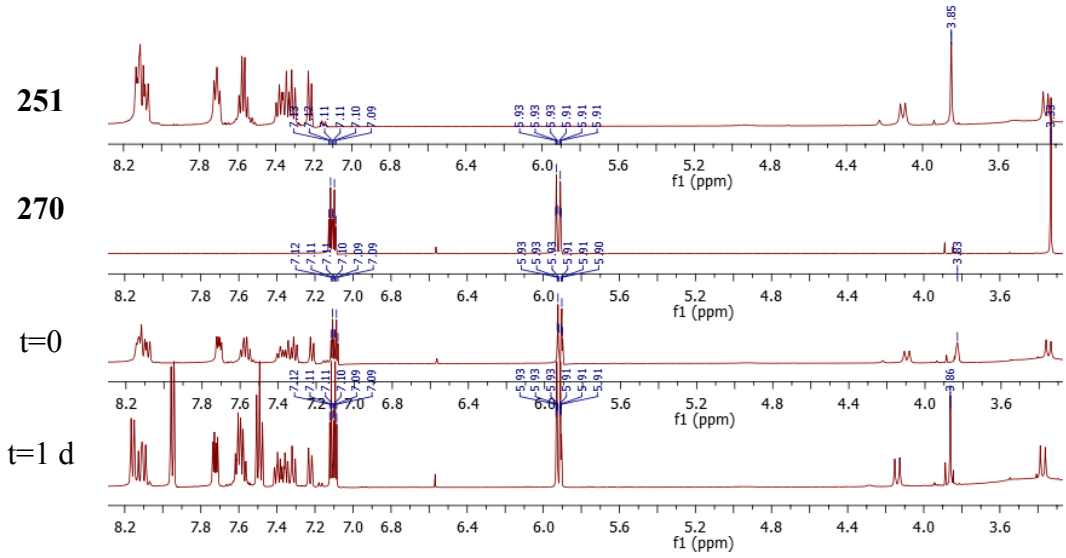


Figure 33: Evolution of the ^{1}H NMR spectrum of a mixture of catalyst **251** and cyclohexenone over 1 d

A more reactive α,β-unsaturated carbonyl substrate was considered; a mixture of *trans*-cinnamaldehyde (**271**) and catalyst **251** was examined by periodic ^{1}H NMR experiments over a 24 h period (**Figure 34**).

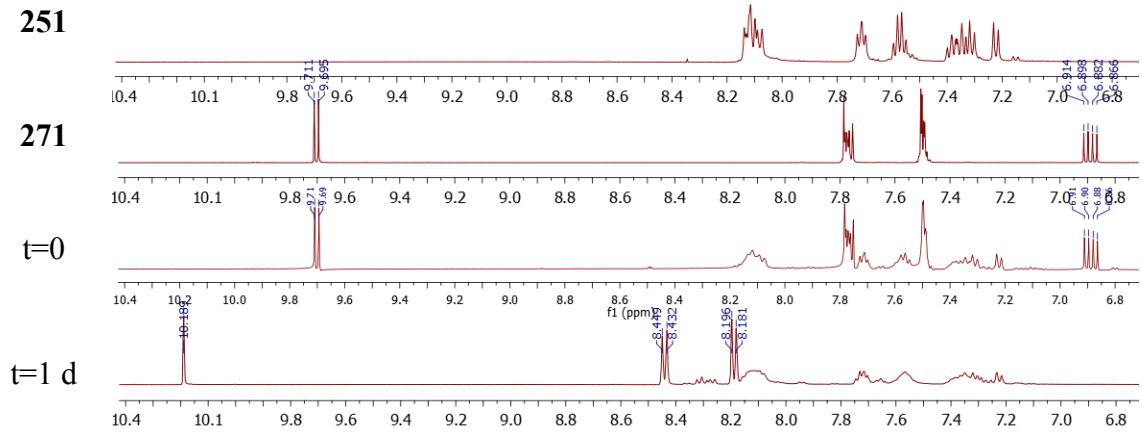


Figure 34: Evolution of the ^{1}H NMR spectrum of a mixture of catalyst **251** and *trans*-cinnamaldehyde **271** over 1 d

An obvious shifting of signals was observed over 24 h, as the peaks corresponding to substrate **271** were shifted downfield (**Figures 34** and **35**). This suggests that these sp^2 hybrized proton environments were becoming progressively more deshielded, an observation consistent with the formation of a positively charged iminium intermediate **272 (Figure 35)**.[101,102]

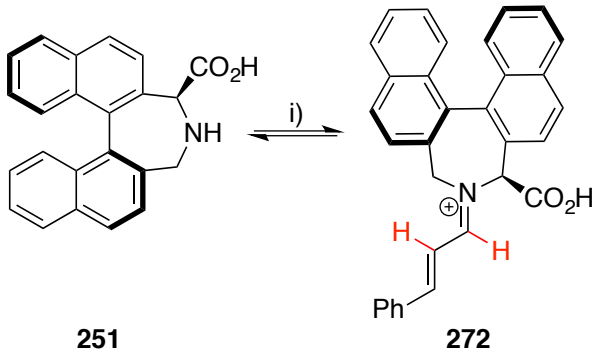
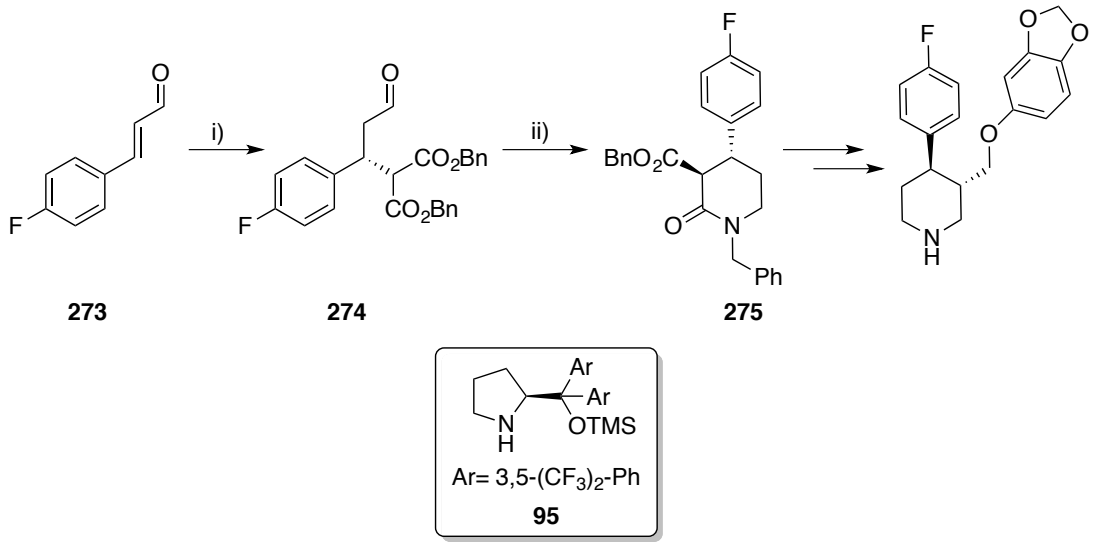


Figure 35: Catalyst **251** and *trans*-cinnamaldehyde **271** in d_6-DMSO

The Michael addition of dibenzyl malonate onto *trans*-cinnamaldehyde has been widely used for comparative studies of asymmetric catalysis.[103,104,105,106,107] Excellent

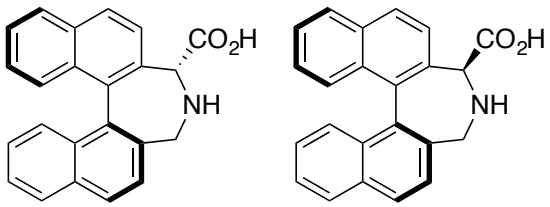
enantioselectivities are frequently reported for 1,4-additions of nucleophiles to electron-deficient alkenes. Therefore, this reaction is considered one of the most selective for the stereocontrolled formation of carbon-carbon bonds.[108] The Michael reaction employing iminium ion catalysis of α,β-unsaturated aldehydes has only recently been established; consequently, development of this reaction is in demand,[104] as it can be used in the synthesis of important pharmaceutical compounds. Indeed, Jørgensen used this very selective reaction in the first step of the synthesis of antidepressant (−)-paroxetine (**Scheme 103**).[109] Compound **273** undergoes a selective Michael addition reaction with dibenzyl malonate affording **274** in 86% ee. Imine formation, reduction and lactamization gave **275** in high yield, and (−)-paroxetine can then be accessed using literature procedures.[110,111,112,113]



Reagents and conditions: Dibenzyl malonate (0.5 equiv.), catalyst **95** (10 mol%), EtOH, 0 °C, 96 h, 72%, 86% ee; ii) $PhCH_2NH_2$, $NaBH(OAc)_3$, dioxane, 70% d.r.: 13:1; further steps

Scheme 103: Synthesis of (−)-paroxetine

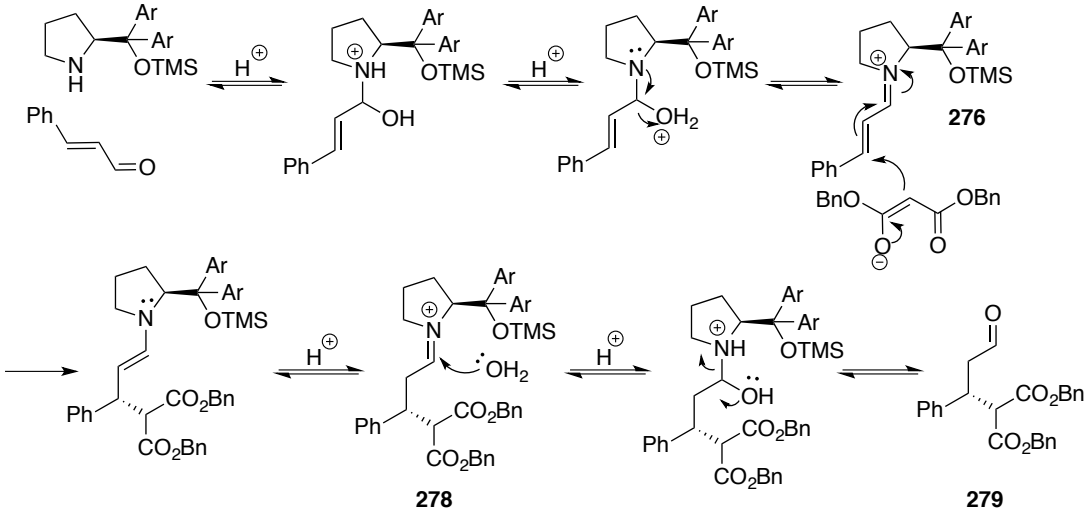
As *trans*-cinnamaldehyde was identified as a suitable substrate, catalyst screening was carried out using catalysts **250** and **251** (**Figure 34**, **Table 40**).



250 **251**

Figure 34: Catalysts **250** and **251**

Jørgensen reported that the optimum solvent for the Michael reaction of cinnamaldehyde and dibenzyl malonate was ethanol and, other than DMSO, no conversion was noted using non-alcoholic solvents.[104,114] Additionally, Pfaltz discovered that the addition of water and benzoic acid accelerated the reaction when using Jørgensen's diaryl prolinol catalyst **95**.[97] The presence of an acid additive has been extensively explored in this reaction as it is hypothesized to aid the formation of the iminium species **276**. In addition, the presence of acid may also favour the iminium species **278** in the iminium/enamine equilibrium of the reaction product; the iminium species subsequently undergoes hydrolysis to form **279** (**Scheme 104**).[97]

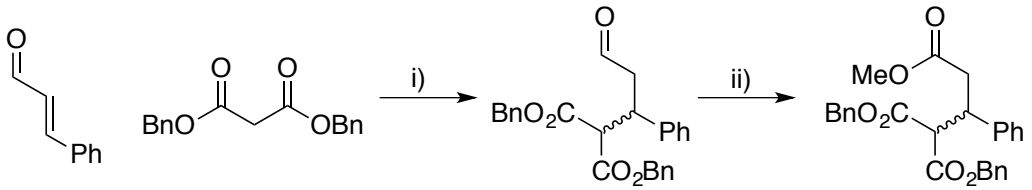


Scheme 104: Lewis acid/Brønsted acid catalysis using Jørgensen's catalyst **95**

We tested acid and base additives, as they have been shown to significantly affect

the rate and selectivity of organocatalytic reactions.[115] In particular, the effect of benzoic acid was investigated as Lewis acid/Brønsted acid catalysis has been shown to have a sizeable influence in this reaction. Following the isolation of conjugate addition product **280**, it was converted into methyl ester derivative **281** to allow for resolution of the peaks corresponding to each enantiomer using chiral stationary phase HPLC. Transformation to **281** was achieved by treatment of **280** with potassium permanganate and trimethylsilyldiazomethane.[103]

Table 40: Michael addition of dibenzyl malonate onto *trans*-cinnamaldehyde **271**



Reagents and conditions: i) Catalyst (10 mol%), dibenzyl malonate (1 equiv.), additive, solvent, r.t.; ii) 1M $KMnO_4$, 1M NaH_2PO_4, $NaHSO_3$, 1M HCl, $TMSCHN_2$

Entry	Catalyst (10 mol%)	Additive (10 mol%)	Solvent	Time (d)	Conversion (%)[a]	Ee (%) [b],[c]
1	**-**	**-**	90% EtOH	5	-	-
2	-	$PhCO_2H$	EtOH (90%)	5	-	-
3	**129**.HCl	$PhCO_2H$	EtOH (90%)	1	80	4 (*S*)
4	(*S*)-proline	$PhCO_2H$	EtOH (90%)	1	11	4 (*R*)
5	**251**	-	EtOH (90%)	8	31	3 (*S*)
6	**251.HCl**	$PhCO_2H$	EtOH (90%)	1	53	3 (*S*)
7	**251**	$PhCO_2H$	EtOH (90%)	1	31	14 (*S*)
8	**251**	-	CH_2Cl_2	8	77	20 (*S*)

9	**251**	NaOH[d]	CH_2Cl_2	1	28	0
10	**251**	-	$CHCl_3$	3	27	17 (*S*)
11	**251**	$PhCO_2H$	$CHCl_3$	8	23	22 (*S*)
12	**251**	$PhCO_2H$[e]	$CHCl_3$	7	74	20 (*S*)
13	**251**	-	CCl_4	8	5	-
14	**251**	-	toluene	8	20	10 (*S*)
15	**251**	-	DMSO	5	-	-
16	**250**	-	EtOH (90%)	8	23	4 (*S*)
17	**250**	$PhCO_2H$	EtOH (90%)	8	38	8 (*S*)
18	**250**.HCl	$PhCO_2H$	EtOH (90%)	1	43	6 (*S*)
19	**250**	-	CH_2Cl_2	7	50	16 (*S*)
20	**250**	-	$CHCl_3$	8	28	14 (*S*)
21	**250**	$PhCO_2H$	$CHCl_3$	7	64	18 (*S*)

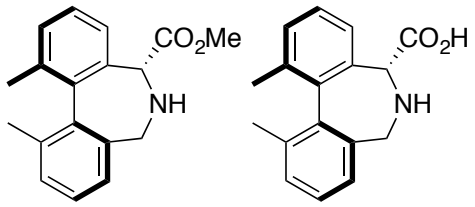
[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture [b] Enantiomeric excess was determined using HPLC with Chiralcel® AD-H column: (hexane/*i*PrOH=80:20, λ=254 nm), 1.0 mL; tR= major enantiomer 26.5 min, minor enantiomer 18.7 min [c] absolute configuration was determined by comparison with known HPLC retention times [d] 1 equiv. [e] 2 equiv.

When EtOH (90%) was used in combination with benzoic acid and a catalyst **251** was used, **281** was obtained in 14% ee with a disappointing conversion (**Entry 7**). The reaction conditions show that the reaction is heavily solvent-dependent: indeed, when DMSO was used, no product formation was detected after four days (**Entry 15**). Chloroform provided the highest ee (22%, **Entry 11**), whereas dichloromethane showed a reduction in both conversion and ee, and carbon tetrachloride suppressed the reaction completely (**Entries 8** and **13**). Increasing the quantities of benzoic acid to stoichiometric quantities accelerated the reaction, though at the expense of a

reduction in selectivity (**Entry 12**). Basic additives have been shown, in combination with LUMO-lowering catalysts, to provide high turnover and enantioselectivity.[99] However, when NaOH was used (**Entry 9**), a racemic product was obtained; presumably, the base-catalysed pathway was faster than the aminocatalysed reaction.

Similar results were obtained when the reaction was performed in EtOH (90%) using catalyst **250 (Entry 16)**. Likewise, the addition of benzoic acid slightly improved the conversion and ee. Halogenated solvents gave higher enantioselectivities and the highest ee was observed when chloroform was used with benzoic acid (**Entry 21**).

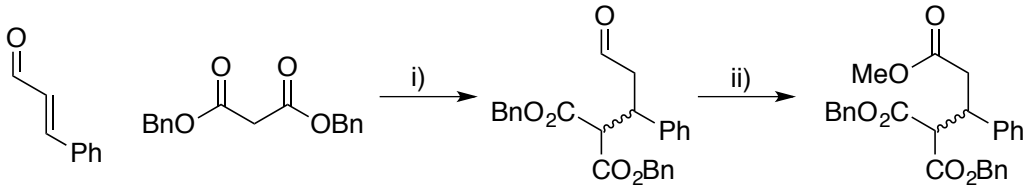
Axially chiral biphenyl catalysts **263** and **265** were also tested under the same reaction conditions (**Table 41**).



263 **265**

Figure 37: Catalysts **263** and **265**

Table 41: 1,4-Michael addition of dibenzyl malonate to *trans*-cinnamaldehyde



271 **280** **281**

Reagents and conditions: i) Catalyst (10 mol%), dibenzyl malonate (1 equiv.), additive (1 equiv.), solvent, r.t.; ii) 1M $KMnO_4$, 1M NaH_2PO_4, $NaHSO_3$, 1M HCl, $TMSCHN_2$

Entry	Catalyst	Additive	Solvent	Time (d)	Conversion (%)[a]	Ee (%)[b], [c]
1	**265**.TFA	$PhCO_2H$[d]	90% EtOH	1	71	3 (*S*)
2	**265.**TFA	NaOH[e]	CH_2Cl_2	5	30	0
3	**263**	-	90% EtOH	3	95	2 (*S*)
4	**263**	-	$CHCl_3$	8	39	1 (*S*)

[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/*i*PrOH=80:20, λ=254 nm), 1.0 mL; tR= major enantiomer 26.5 min, minor enantiomer 18.7 min [c] absolute configuration was determined by comparison with known HPLC retention times [d] 10 mol% [e] 1 equiv.

Conversely, when EtOH (90%) and **263** or **265** were used, high conversion was observed, although the product isolated was racemic in both cases (**Entries 1** and **3**). Halogenated solvents slowed the rate of conversion whilst also giving racemic products (**Entries 2 and 4**).

9.3 Diels-Alder Reaction

trans-Cinnamaldehyde **271** was also employed as the dienophile for Diels-Alder reactions. As with the Michael reaction, the organocatalytic Diels-Alder reaction relies on the activation of the dienophile through LUMO energy lowering due to iminium ion formation. The [4+2] reaction is wide-reaching, with an extensive application for the synthesis of six membered rings with defined stereo- and regio-chemical control. The use of chiral amines as organocatalysts for this type of Diels-Alder reaction has exploded in popularity since MacMillan's seminal publication in 2000.[116,117] There are now many examples of total syntheses employing a pivotal aminocatalytic Diels-Alder step.[118,119,120] The rate-determining step, as postulated by MacMillan, is the condensation step between the amine and carbonyl groups resulting in the formation of an iminium ion. We therefore felt that our bifunctional catalysts with Brønsted acid/Lewis basic character should be ideal for the promotion of this reaction (**Figure 38**).

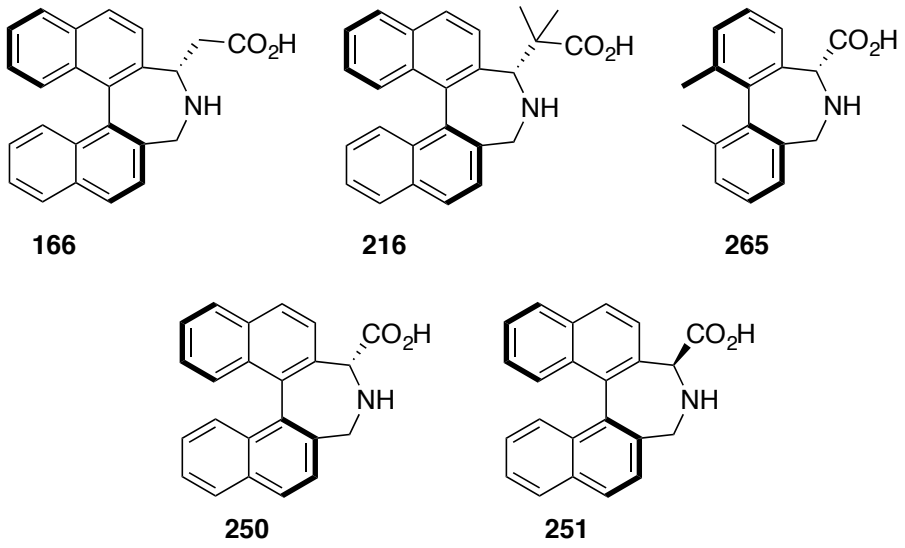
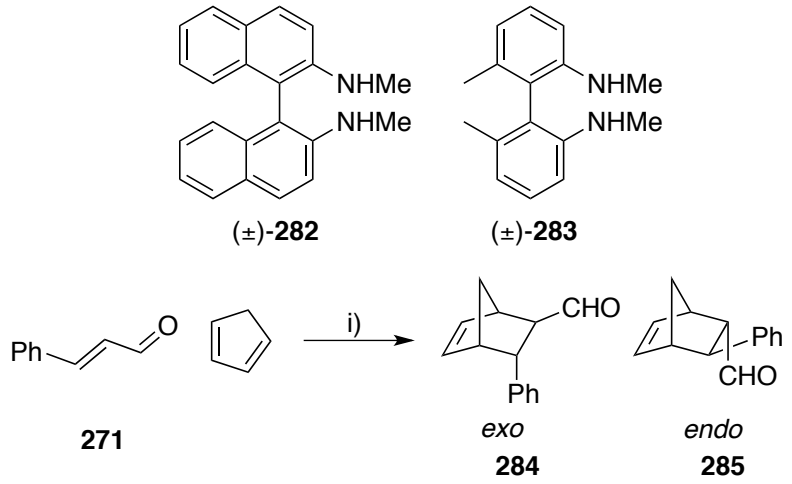


Figure 38: Amino acid catalysts screened

In addition to the effect on the selectivity of a chiral acid functionality, we were intrigued to see if the backbone had a noticeable effect, and specifically, whether our binaphthyl or biphenyl backbone catalysts provided a higher degree of *exo*:*endo* selectivity. Indeed Maruoka found that, in the reaction of cinnamaldehyde and cyclopentadiene, (±)-binaphthyl **282** gave slightly improved selectivity compared to

(±)-biphenyl **283** (**Table 42**).[121]

Table 42: Maruoka's binaphthyl and biphenyl diamine catalysts



Reagents and conditions: i) 12 mol% catalyst, 10 mol% TfOH, CH_2Cl_2, r.t.

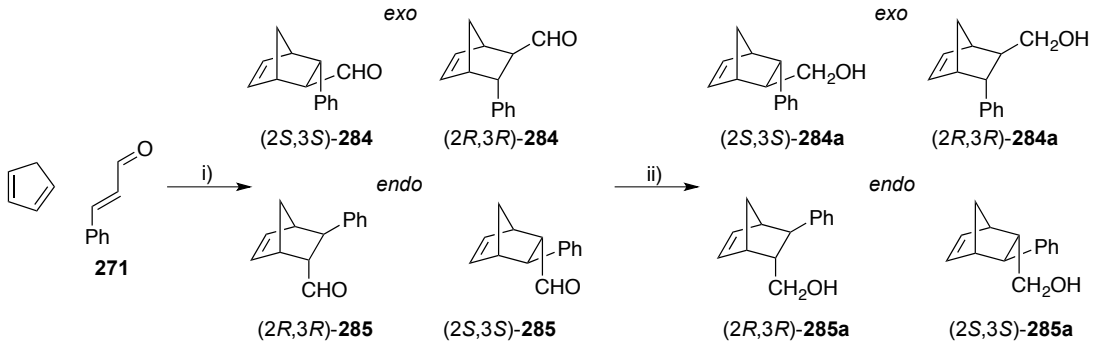
Entry	Catalyst	Time (h)	Yield (%)	***exo:endo*** **284:285**
1	(±)-**282**	20	99	9.2:1
2	(±)-**283**	23	83	8.0:1

Utilizing conditions optimized for the reaction of *trans*-cinnamaldehyde and cyclopentadiene, reported by MacMillan using imidazolidinone catalyst **70**, we began screening carboxylic acid catalysts (**Figure 38**).[111] In addition, as MacMillan utilized **70** as the corresponding hydrochloride salt, we assessed both the free amine and hydrochloride salt derivatives of many of our catalysts.

The products, **284** and **285**, were partially converted *in situ* to corresponding dimethyl acetals. TFA mediated hydrolysis allowed the conversion to be calculated by crude NMR analysis and assignment of the diastereomeric ratio of aldehydes (***exo*** δ 9.86 (1H, d, *J*= 2.0 Hz, C*H*O): ***endo*** δ 9.59 (1H, d, *J*= 2.2 Hz, C*H*O)). Following isolation of the bicyclic *exo* and *endo* products **284** and **285**, respectively,

compounds **284** and **285** were converted into the corresponding alcohols **284a** and **285a**, respectively, through a lithium aluminium hydride-mediated reduction, to allow the separation of enantiomers on chiral stationary phase HPLC (**Table 43**). Assignments of the major enantiomers could be made by comparison with literature HPLC elution times.[120]

Table 43: Amino acid catalyst screening



Reagents and conditions: i) cyclopentadiene (3 equiv.), cinnamaldehyde (1 equiv.), catalyst (10 mol%), MeOH:H_2O (95:5 *v/v*), r.t.; ii) $LiAlH_4$, Et_2O, 0 °C, 2 h

Entry	**Catalyst**	**Time (d)**	**Conv. (%)**[a]	***exo*:*endo* 284:285**[b]	***endo* ee (%)**[c],[d]	***exo* ee (%)**[c],[d]
1	-	5	-	-	-	-
2[e]	Pyrrolidine	5	73	1:1	0	0
3	(*S*)-proline	5	74	1:0.6	21 (2*S*,3*S*)	43 (2*S*,3*S*)
4	**70**.HCl	2	100	1:1.1	95 (2*R*,3*R*)	89 (2*R*,3*R*)
5	**166**.HCl	7	44	1:0.5	14 (2*R*,3*R*)	26 (2*R*,3*R*)
6	**216**.HCl	7	68	1.0.5	13 (2*R*,3*R*)	30 (2*R*,3*R*)
7	**265**.TFA	5	14	1:0.8	9 (2*R*,3*R*)	43 (2*R*,3*R*)
8	**251**	5	21	1:1.6	2 (2*S*,3*S*)	1 (2*R*,3*R*)

9	**251**.HCl	7	3	1.1.6	4 (2*S*,3*S*)	7 (2*R*,3*R*)
10	**250**	7	23	1:1.2	4 (2*S*,3*S*)	4 (2*R*,3*R*)
11	**250**.HCl	7	12	1:1.4	1 (2*S*,3*S*)	11 (2*R*,3*R*)

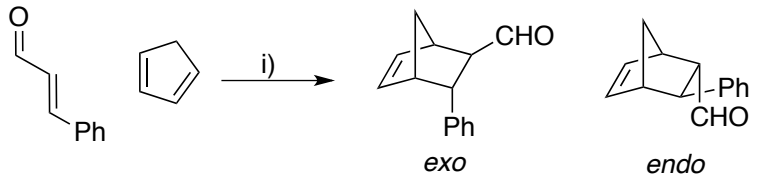
[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture of bicyclic aldehydes **284** and **285** [b] Ratio determined by ^{1}H NMR spectra analysis of crude reaction mixture [c] Enantiomeric excess was determined using HPLC with Chiralcel® OJ column (hexane/iPrOH=90:10, λ=222 nm), 1.0 mL; ***endo*** isomer (t_R1 15 min, 35 min) ***exo*** isomer (t_R1 47 min, 65 min)) [d] configuration was determined by comparison with known HPLC retention times [e] reaction performed in toluene

In order to assess the effect of the carboxylic acid functionality in a non-axially chiral system, (*S*)-proline was also evaluated under these conditions (**Entry 3, Table 43**). (*S*)-Proline provided modest *exo* selectivity and delivered the *exo* adduct in 43% ee. In addition, we tested MacMillan's imidazolidinone catalyst **70 (Entry 4**); a fast reaction time and excellent enantioselectivity were noted; but poor diastereoselectivity was observed. Strikingly, in contrast to the Diels-Alder class of reaction, catalysts **166**, **216** and **265** favoured the formation of the *exo* isomer (**Entries 5-7**). β-Amino acid species **166** and **216**, employed as their respective hydrochloride salts, produced moderate diastereoselectivities in favour of the *exo* isomer (**Entries 4** and **5**). Salt **216.**HCl out-performed **166**.HCl in terms of reactivity, perhaps surprisingly due to its crowded structure, as well as enantioselectivity. Supporting Maruoka's observations, biphenyl **265** did indeed give reduced *exo*:*endo* selectivity, compared to the corresponding binaphthyl version **250**. However, **265** imparted higher levels of enantioselectivity, affording the *exo* adduct in 43% ee (**Entries 7** and **10**). Interestingly, α-amino acid catalysts **250** and **251** showed slight *endo* selectivity **(Entries 7-10)**. Both salts **250**.HCl and **251**.HCl showed reduced activity compared to the free amine form, alongside lower enantioselectivities.

The α-effect, related to the increasing nucleophilicity of an atom bearing a lone pair as a result of an adjacent heteroatom, was explored by Tomkinson in the Diels-Alder

reaction utilizing acyclic hydrazines as catalysts.[122] In addition, Tomkinson found that while pyrrolidine hydrochloride **286** was a poor catalyst for this reaction, proline methyl ester hydrochloride **287** was efficient in affording adducts **284** and **285** in 85% yield, suggesting that an electron-withdrawing ester functional group can also help facilitate generation of the iminium intermediate (**Table 44**).

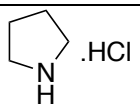
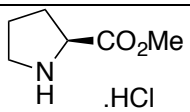
Table 44: Diels-Alder reaction of cinnamaldehyde and cyclopentadiene



exo *endo*

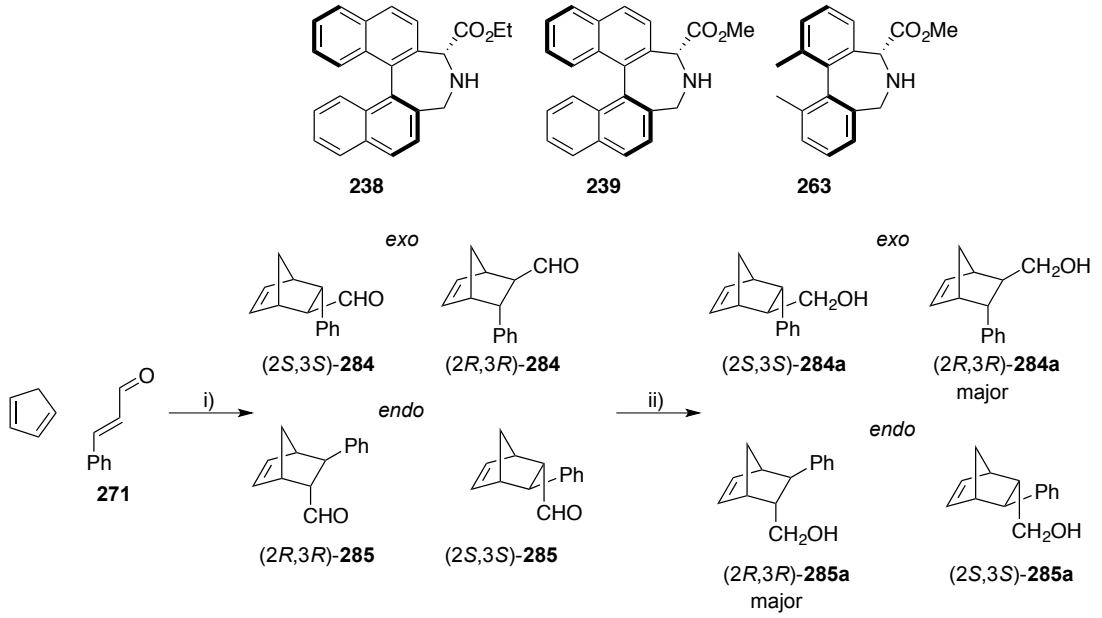
271 **284** **285**

Reagents and conditions: i) Catalyst (10 mol%), MeOH:H_2O (19:1), r.t.

Entry	Catalyst	Time (h)	*exo:endo* 284:285	Yield (%)
1	 **286**	24	68:32	9
2	 **287**	48	71:29	85

Consequently, we were curious to discover whether our α-ester functionalised catalysts **238**, **239** and **263** (**Table 45**) would show improved reactivity and *endo*/*exo* diastereoselectivity.

Table 45: α-Ester catalyst screening



Reagents and conditions: i) cyclopentadiene (3 equiv.), cinnamaldehyde (1 equiv.), catalyst (10 mol%), MeOH:H_2O (95:5 *v/v*), r.t; ii) $LiAlH_4$, Et_2O, 0 °C, 2 h

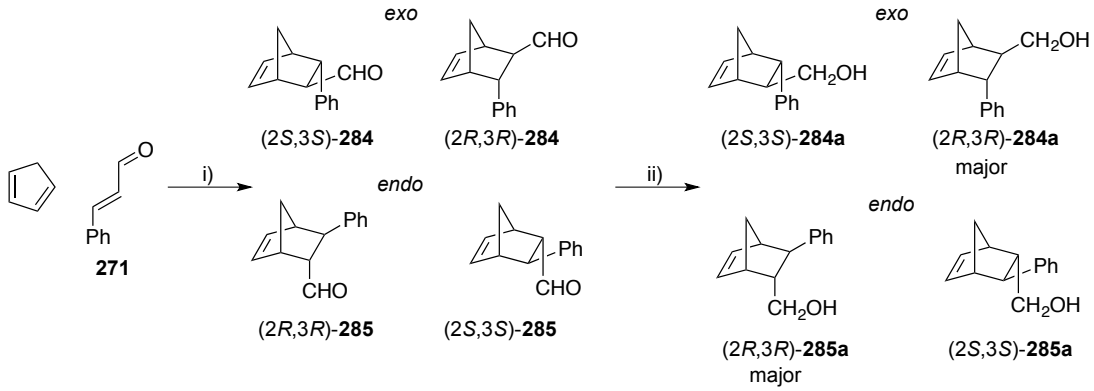
Entry	Catalyst	Solvent	Time (d)	Conv. (%)[a]	*exo:* *endo* 284:285 [b]	*endo* ee (%)[c],[d]	*exo* ee (%)[c],[d]
1	**287**.HCl	MeOH:H_2O	7	100	1:0.4	43 (2*S*,3*S*)	47 (2*S*,3*S*)
2	**263**	MeOH:H_2O	5	70	1:0.7	21 (2*R*,3*R*)	51 (2*R*,3*R*)
3	**239**	MeOH:H_2O	5	26	1.0.7	17 (2*R*,3*R*)	43 (2*R*,3*R*)
4	**239**.HCl	MeOH:H_2O	5	100	1:0.5	34 (2*R*,3*R*)	56 (2*R*,3*R*)
5	**238**	MeOH:H_2O	4	36	1:0.4	31 (2*R*,3*R*)	57 (2*R*,3*R*)
6	**238.**HCl	MeOH:H_2O	5	92	1:0.4	34 (2*R*,3*R*)	58 (2*R*,3*R*)

[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture of bicyclic aldehydes **284** and **285** [b] Ratio determined by ^{1}H NMR spectra analysis of crude reaction mixture [c] Enantiomeric excess was determined using HPLC with Chiralcel® OJ column (hexane/iPrOH=90:10, λ=222 nm), 1.0 mL; ***endo*** isomer (t_R1 15 min, 35 min) ***exo*** isomer (t_R1 47 min, 65 min)) [d] configuration was determined by comparison with known HPLC retention times

We evaluated (*S*)-proline methyl ester hydrochloride salt **287** under our conditions (**Entry 1**) and discovered a much improved *endo* ee and slightly enhanced diastereoselectivity compared to (*S*)-proline (**Table 43**). In contrast to the amino acid catalysts screened (**Table 43**), the α-ester catalysts were *exo* selective and were also, broadly, more active catalysts, requiring shorter reaction times and resulting in higher conversions. Encouragingly, *exo*-selective catalyst-controlled Diels-Alder reactions are uncommon, due to competing *endo*-selective secondary orbital interactions; consequently, methodologies providing the preferential generation of *exo* adducts are highly sought.[123,124] Biphenyl methyl ester **263** gave 51% ee of the *exo* enantiomer whilst **239,** the binaphthyl methyl ester species, as well as being a less reactive catalyst, gave only 43% ee of the *exo* isomer (**Entries 2** and **3**). Conversely, salt **239**.HCl gave higher enantioselectivities and better *exo*:*endo* selectivity (**Entry 4**). Ethyl ester **238** provided improved diastereoselectivity and ee compared to methyl ester **239**, supporting the assumption that an increase in the size of the α-substituent leads to an increase in selectivity.[125] Again, the hydrochloride salt **239**.HCl was more reactive than the free amine **239**, although similar ees were observed (**Entry 6**).

The reaction conditions were then optimized for salt **239**.HCl by screening a variety of solvents (**Table 46**).

Table 46: Solvent screening



Reagents and conditions: i) Cyclopentadiene (3 equiv.), cinnamaldehyde (1 equiv.), catalyst **239**.HCl (10 mol%), solvent, r.t.; ii) $LiAlH_4$, Et_2O, 0 °C, 2 h

Entry	Solvent	Time (d)	Conv. (%) [a]	*exo:endo* 284:285 [b]	*endo* ee (%) [c],[d]	*exo* ee (%) [c],[d]
1	$MeOH:H_2O$	5	100	1:0.5	34 (2*R*,3*R*)	56 (2*R*,3*R*)
2 [e]	$MeOH:H_2O$	7	77	1:0.4	39 (2*R*,3*R*)	62 (2*R*,3*R*)
3	CH_2Cl_2	5	61	1:0.4	28 (2*R*,3*R*)	34 (2*R*,3*R*)
4	MeOH	2	100	1:1	36 (2*R*,3*R*)	58 (2*R*,3*R*)
5	$DMSO:H_2O$	5	69	1:0.6	29 (2*R*,3*R*)	42 (2*R*,3*R*)
6	$THF:H_2O$	5	41	1:0.5	32 (2*R*,3*R*)	42 (2*R*,3*R*)
7	$DMF:H_2O$	5	57	1:0.6	28 (2*R*,3*R*)	42 (2*R*,3*R*)
8	CH_2NO_2: H_2O	5	96	1:0.4	22 (2*R*,3*R*)	47 (2*R*,3*R*)
9	$CH_3CN:H_2O$	5	97	1:0.4	30 (2*R*,3*R*)	46 (2*R*,3*R*)
10	$EtOH:H_2O$	5	94	1:0.5	35 (2*R*,3*R*)	55 (2*R*,3*R*)

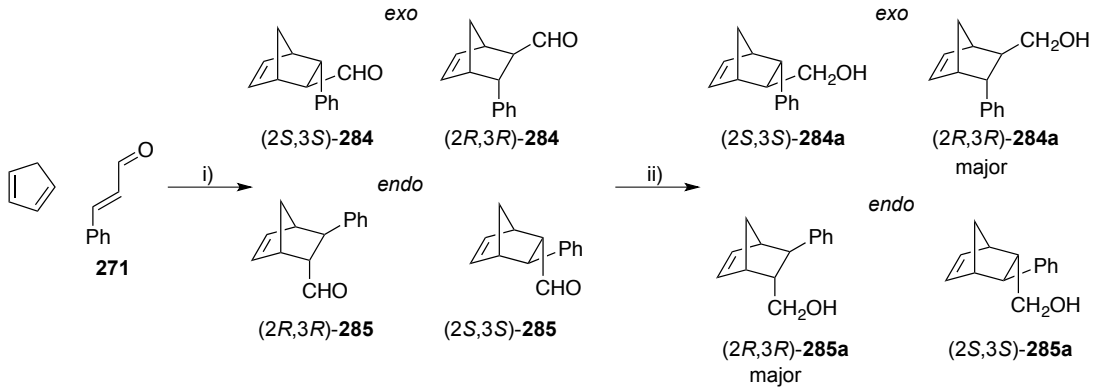
[a] Conversion determined from ^1H NMR spectra analysis of the reaction mixture of bicyclic aldehydes **284** and **285** [b] Ratio determined by ^1H NMR spectra analysis of crude reaction mixture [c] Enantiomeric excess was determined using HPLC with Chiralcel® OJ column (hexane/iPrOH=90:10, λ=222 nm), 1.0 mL; ***endo*** isomer (t_R1 15 min, 35 min) ***exo*** isomer (t_R1 47 min, 65 min)) [d] configuration was determined by comparison with known HPLC retention times [e] conducted at 0°C

When dichloromethane was used, a reduction in the activity of the catalyst and lower ees were observed (**Entry 3**). The highest enantioselectivities were observed when the reaction was conducted in polar solvents, with water and alcoholic mixtures showing a marginal improvement over all others (**Entries 1** and **10**). Water was found to be essential in providing selectivity, as, when the reaction was conducted in methanol, the diastereoisomeric ratio was reduced to 1:1, although the reaction time was reduced (**Entry 4**). Furthermore, lowering the reaction temperature improved both the *exo* selectivity and the enantioselectivity of both adducts (**Entry 2**).

We were further encouraged by results published by Maruoka, who improved the enantioselectivity attained when using axially chiral diamine **115** (**Figure 11**) in an *exo*-selective Diels-Alder by addition of trifluoromethanesulfonic acid (10 mol%).[126] The behaviour of methyl ester catalyst **239**.HCl was therefore assessed alongside various Brønsted acid co-catalysts **(Table 47)**. Blank reactions were run, without catalyst, to determine whether the acid co-catalysts were capable of catalysing the reaction in a competing achiral process, but no conversion was noted.

The addition of Brønsted acid additives increased the reaction rate in all cases, postulated to be as a result of accelerated iminium ion formation and subsequent hydrolysis, as mentioned above (**Scheme 104**). When using salt **239**.HCl with most co-catalysts, enantioselectivities were not greatly affected. (±)-Camphorsulfonic acid was an exception as the *exo* isomer ee dropped to 31% (**Entry 5**). When triflic acid was employed, a slight decrease in yield was observed, suggesting that this strong acid additive may cause some decomposition; the ee was, however, unchanged, indicating that strong acids are not detrimental to selectivity (**Entry 6**). Additionally, the *exo*:*endo* ratio was slightly improved when acetic acid was used as additive (**Entry 3**).

Table 47: Brønsted acid additive screening



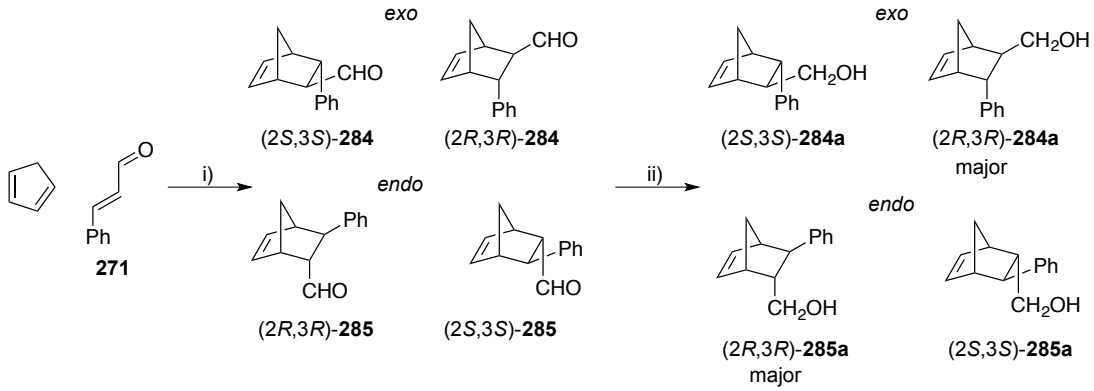
Reagents and conditions: i) Cyclopentadiene (3 equiv.), cinnamaldehyde (1 equiv.), catalyst **239**.HCl (10 mol%), Additive (10 mol%), MeOH:H_2O (95:5 *v/v*), r.t.; ii) $LiAlH_4$, Et_2O, 0 °C, 2 h

Entry	Co-catalyst	pKa [127]	Time (d)	Conv. (%)[a]	*exo:endo* 284:285 [b]	*endo* ee (%)[c],[d]	*exo* ee (%)[c],[d]
1	-	-	5	100	1:0.5	34 (2*R*,3*R*)	56 (2*R*,3*R*)
2	CH_3CO_2H	4.8	3	98	1:0.4	33 (2*R*,3*R*)	57 (2*R*,3*R*)
3	$PhCO_2H$	4.2	3	94	1:0.5	35 (2*R*,3*R*)	56 (2*R*,3*R*)
4	CF_3CO_2H	−0.3	4	100	1:0.5	34 (2*R*,3*R*)	56 (2*R*,3*R*)
5	(±)-CSA	−3	3	97	1:0.5	31 (2*R*,3*R*)	36 (2*R*,3*R*)
6	CF_3SO_3H	−14	3	82	1:0.5	36 (2*R*,3*R*)	57 (2*R*,3*R*)

[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture of bicyclic aldehydes **284** and **285** [b] Ratio determined by ^{1}H NMR spectra analysis of crude reaction mixture [c] Enantiomeric excess was determined using HPLC with Chiralcel® OJ column (hexane/iPrOH=90:10, λ=222 nm), 1.0 mL; ***endo*** isomer (t_R1 15 min, 35 min) ***exo*** isomer (t_R1 47 min, 65 min)) [d] configuration was determined by comparison with known HPLC retention times

The effect of catalyst loading was investigated under the optimized reaction conditions (**Table 48**). Upon increasing the catalyst loading to 20 mol%, a faster reaction time and a minor increase in enantioselectivity from 31% to 39% in the case of the *endo* isomer was detected (**Entry 3**).

Table 48: Effect of catalyst loading



Reagents and conditions: i) Cyclopentadiene (3 equiv.), cinnamaldehyde (1 equiv.), catalyst **239**.HCl, MeOH:H_2O (95:5 *v/v*), r.t.; ii) $LiAlH_4$, Et_2O, 0 °C, 2 h

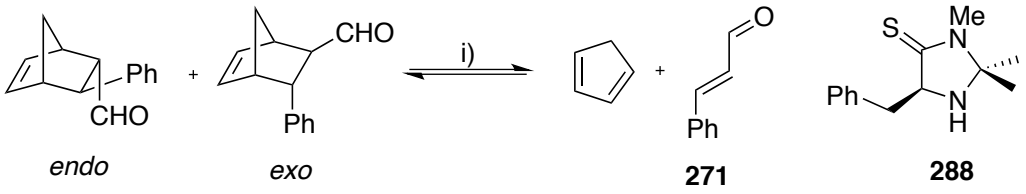
Entry	Cat. loading (mol%)	Time (d)	Conv. (%)[a]	*exo:endo*[b]	*endo* ee (%)[c],[d]	*exo* ee (%)[c],[d]
1	10	5	100	1:0.5	34 (2*R*,3*R*)	56 (2*R*,3*R*)
2	5	5	77	1:0.5	31 (2*R*,3*R*)	56 (2*R*,3*R*)
3	20	2	96	1:0.5	36 (2*R*,3*R*)	59 (2*R*,3*R*)

[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture of bicyclic aldehydes **284** and **285** [b] Ratio determined by ^{1}H NMR spectra analysis of crude reaction mixture [c] Enantiomeric excess was determined using HPLC with Chiralcel® OJ column (hexane/iPrOH=90:10, λ=222 nm), 1.0 mL; ***endo*** isomer (t_R1 15 min, 35 min) ***exo*** isomer (t_R1 47 min, 65 min)) [d] configuration was determined by comparison with known HPLC retention times

The Diels-Alder reaction can be a reversible process, depending on the reaction conditions. Due to the modest ees and the long reaction times observed using catalyst **239**.HCl, we sought to determine whether a competing retro-Diels-Alder (rDA) was occurring. The imidazolethione **288**-catalysed DA reaction using cinnamaldehyde and cyclopentadiene was investigated by Su (**Table 49**).[128] Deracemization experiments were performed on racemic DA adducts and reaction parameters varied: the effect of catalyst and co-catalyst loading was explored, alongside temperature and solvent system. It was found that the reaction conducted in CH_3CN:H_2O resulted in slight changes in the dr and ees of the adducts (**Entries 2**

and **3, Table 49**), suggesting that a rDA reaction was occurring. An increased ratio in favour of the *exo* isomer was observed and the ees of the (2*S*)-adducts were slightly reduced in comparison to the (2*R*)-adducts, which could suggest a more facile rDA for the *endo* and (2*S*)-adducts, in an CH_3CN:H_2O solvent system

Table 49: Evidence for rDA reaction[128]



endo *exo* **271** **288**

1:1.2

Reagents and conditions: catalyst **288** (equiv.), TFA (equiv.), solvent system, r.t., 48 h

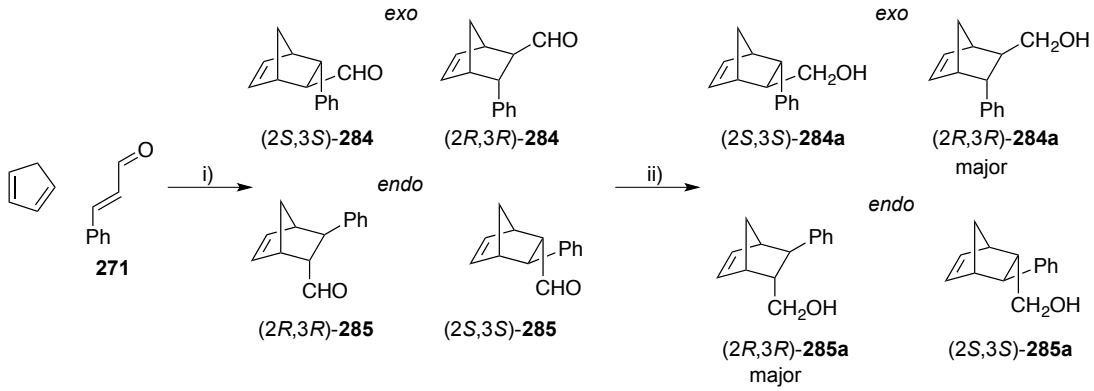
Entry	**Catalyst (mol%)**	**TFA (mol%)**	**Solvent**	***exo*:*endo***	***exo* ee (%)**	***endo* ee (%)**
1	-	0.2	CH_3CN:H_2O	1.2:1	0	0
2	0.2	0.2	CH_3CN:H_2O	1.4:1	2	6
3	0.2	0.2	CH_3OH:H_2O	1.2:1	0	0
4	0.2	1	CH_3CN:H_2O	1.7:1	8	10
5	1	1	CH_3CN:H_2O	1.8:1	8	12
6[a]	0.2	1	CH_3CN:H_2O	1.8:1	30	40

[a] Reaction performed at 50 °C

We therefore set out to ascertain whether our reaction conditions could be facilitating a rDA process. We examined whether the ees of the adducts or the relative ratios of the *endo* and *exo* diastereoisomers changed after 25 days using catalyst **239**.HCl (**Table 50**). After 25 days, no reduction in diastereoselectivity and a (very slight) increase in ee of the (2*R*)-adduct were observed. From this we can conclude that very little, if any, rDA is taking place. Our results match Su's reported observation that when the reaction was performed in a CH_3OH:H_2O mixture, the

ratio of *exo*:*endo* isomers, and their ee values, are stable. Su hypothesized this to be as a result of formation of the dimethyl acetal derivatives of the aldehyde adducts, which prevent the reverse reaction.

Table 50: Evaluating changes in enantioselectivity with time



Reagents and conditions: i) Cyclopentadiene (3 equiv.), cinnamaldehyde (1 equiv.), catalyst **239**.HCl (10 mol%), MeOH:H_2O (95:5 *v*/*v*), r.t., .; ii) $LiAlH_4$, Et_2O, 0 °C, 2 h

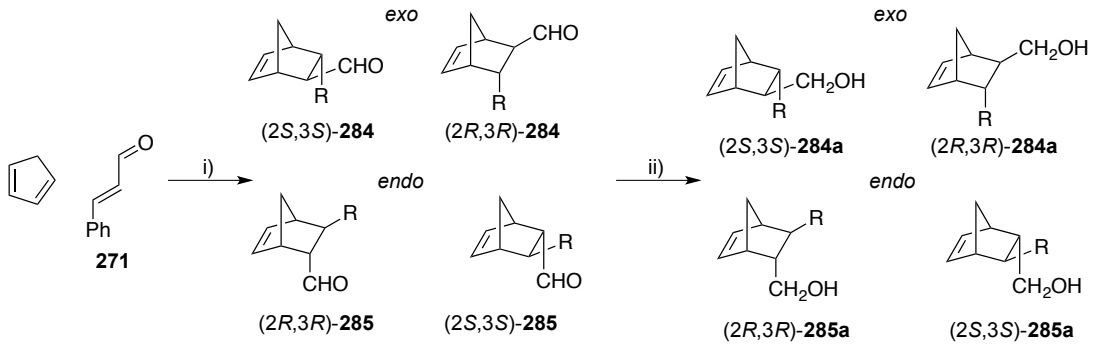
Entry	**Time (d)**	**Conv. (%)**[a]	***exo:endo* 284:285**[b]	***endo* ee (%)**[c],[d]	***exo* ee (%)**[c],[d]
1	5	100	1:0.5	32 (2*R*,3*R*)	56 (2*R*,3*R*)
2	25	100	1:0.5	35 (2*R*,3*R*)	56 (2*R*,3*R*)

[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture of bicyclic aldehydes **284** and **285** [b] Ratio determined by ^{1}H NMR spectra analysis of crude reaction mixture [c] Enantiomeric excess was determined using HPLC with Chiralcel® OJ column (hexane/iPrOH=90:10, λ=222 nm), 1.0 mL; ***endo*** isomer (t_R1 15 min, 35 min) ***exo*** isomer (t_R1 47 min, 65 min)) [d] configuration was determined by comparison with known HPLC retention times

We next sought to extend the substrate scope, and used salt **239**.HCl in the Diels-Alder reaction between cyclopentadiene and *o*- and *p*-substituted cinnamaldehyde derivatives with electron-withdrawing and -donating groups (**Table 51**). When possible, catalyst **70** was screened to provide a standard comparison against salt **239**.HCl. We found the electronic nature of the aromatic ring to have little impact in

the outcome of the reaction: both substrates with electron-donating and -withdrawing substituents were well tolerated and gave comparable ees. Favourably, catalyst **239**.HCl provided greater dr than **70** in the reactions screened. In most cases we were able to assign the major enantiomers by comparison with literature HPLC retention times.[124,125] We noted an increased *endo* enantioselectivity in all cases, with respect to employing cinnamaldehyde **271**. Electron-withdrawing *p*-nitrocinnamaldehyde gave the best conversion, presumably because of the increased reactivity of this substrate, while also providing the greatest *exo*/*endo* selectivity (**Entry 5**). [129,130]

Table 51: Screening dienophiles



Reagents and conditions: i) Cyclopentadiene (3 equiv.), dienophile (1 equiv.), Catalyst (10 mol%), MeOH:H_2O (95:5 *v*/*v*), r.t., .; ii) $LiAlH_4$, Et_2O, 0 °C, 2 h

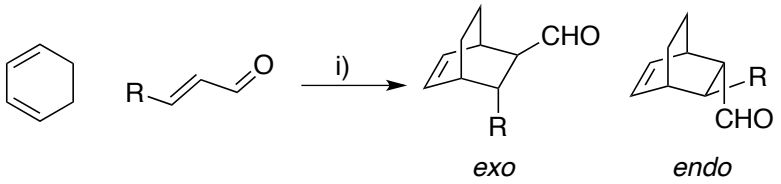
Entry	Catalyst	Dienophile	Time (d)	Conv. (%)[a]	*exo:* *endo* 284:285[b]	*endo* ee (%)	*exo* ee (%)
1[c]125	**70**	*p*-C_6H_5OMe	4	62	1:0.8	90 (2*S*,3*S*)	76 (2*S*,3*S*)
2[c]125	**239**.HCl	*p*-C_6H_5OMe	4	20	1:0.6	54 (2*S*,3*S*)	30 (2*S*,3*S*)
3[d]	**70**	*o*-C_6H_5OMe	4	100	1:0.7	93	90
4[d]	**239**.HCl	*o*-C_6H_5OMe	4	78	1:0.6	46	29

5[e]125	**239**.HCl	*p*-$C_6H_5NO_2$	4	90	1:0.5	53 (2*R*,3*R*)	30 (2*S*,3*S*)
6[f]124	**239**.HCl	*o*-$C_6H_5NO_2$	4	57	1:0.8	54 (2*S*,3*S*)	51 (2*R*,3*R*)

[a] Conversion determined from ^{1}H NMR spectra analysis of the reaction mixture of bicyclic aldehydes [b] Ratio determined by ^{1}H NMR spectra analysis of crude reaction mixture [c] Enantiomeric excess was determined using Chiralcel® AS-3 column (hexane/iPrOH=95:5, λ=222 nm), 0.5 mL; ***endo*** isomer (t_R1 35 min, 59 min) ***exo*** isomer (t_R1 39 min, 56 min)) [d] Chiralcel® AD-H column (hexane/iPrOH=98:2, λ=222 nm), 0.5 mL; ***endo*** isomer (t_R1 65 min, 80 min) ***exo*** isomer (t_R1 57 min, 69 min)) [e] Chiralcel® AD-H column (hexane/iPrOH=90:10, λ=254 nm), 0.5 mL; ***endo*** isomer (t_R1 49 min, 57 min) ***exo*** isomer (t_R1 43 min, 53 min)) [f] Chiralcel® AD-H column (hexane/iPrOH=95:5, λ=254 nm), 0.5 mL; ***endo*** isomer (t_R1 37 min, 39 min) ***exo*** isomer (t_R1 41 min, 50 min)).

Unfortunately, attempts using a different diene failed; the reactions employing 1,3-cyclohexadiene were unsuccessful and only trace amounts of cycloadducts were observed alongside starting material (**Table 52**).

Table 52: Screening dienes

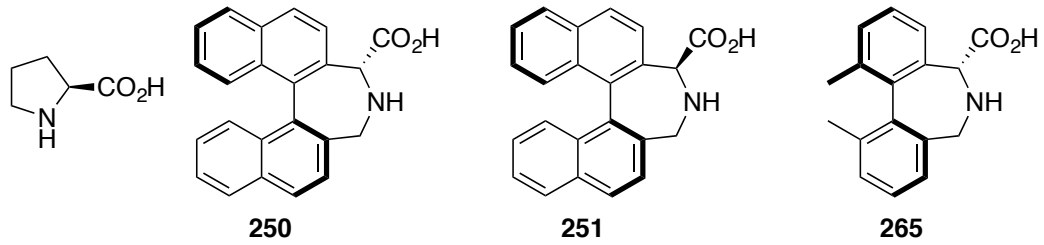


Reagents and conditions: i) 1,3 cyclohexadiene (1 equiv.), dienophile (1 equiv.), Catalyst **239**.HCl (10 mol%), MeOH:H_2O (95:5 *v*/*v*), r.t.,

Entry	R	Time (d)	Conv. (%)	*Exo*:*endo*	*Endo* ee (%)	*Exo* ee
1	CH_3	5	-	-	-	-
2	H	5	-	-	-	-
3	Ph	5	-	-	-	-

10.0 General conclusion

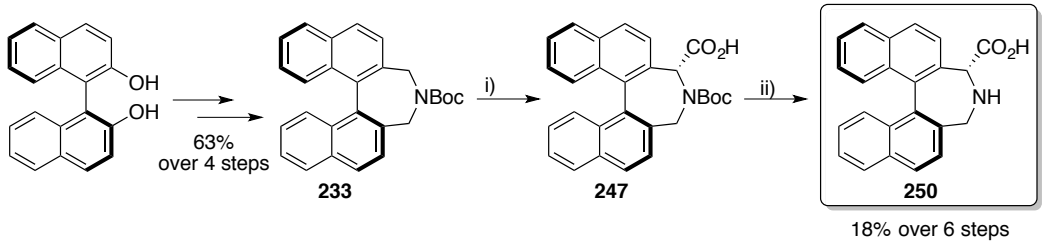
The aim of this project was to develop a route toward axially chiral aminocatalysts, inspired from known successful pyrrolidine analogues. With the recent successes reported using organocatalysis, it is now crucial to understand and evaluate what structural features aminocatalysts are required to possess in order to induce even greater degrees of selectivity. Accordingly, we have pioneered the synthesis of three novel axially chiral proline-type aminocatalysts, possessing Lewis basic/Brønsted acidic bifunctionality (**Figure 39**).



250 **251** **265**

Figure 39: α-Amino acid-type organocatalysts

The binaphthyl α-amino acid derivatives are bench-stable and prepared following a 6-step procedure, with a key divergent lithiation/carboxylation step, simplifying access to both α-acid diastereoisomeric catalysts. Compounds **251** and **250** were obtained in 14% and 18% yield overall, respectively (**Scheme 105**).



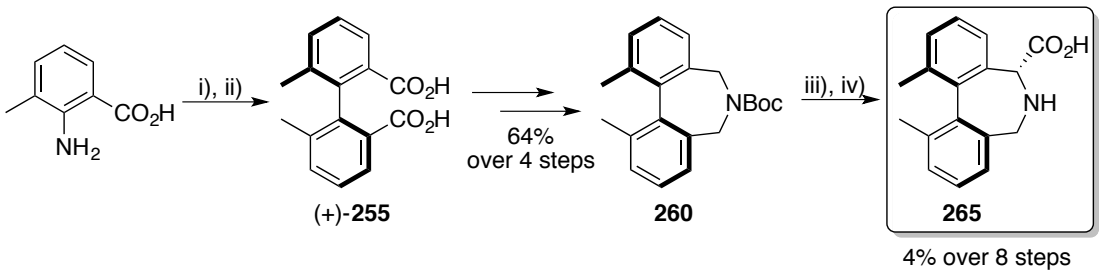
233 **247** **250**

18% over 6 steps

Key steps: i) Lithiation and carboxylation; ii) Boc deprotection

Scheme 105: Synthetic route to compound **250**

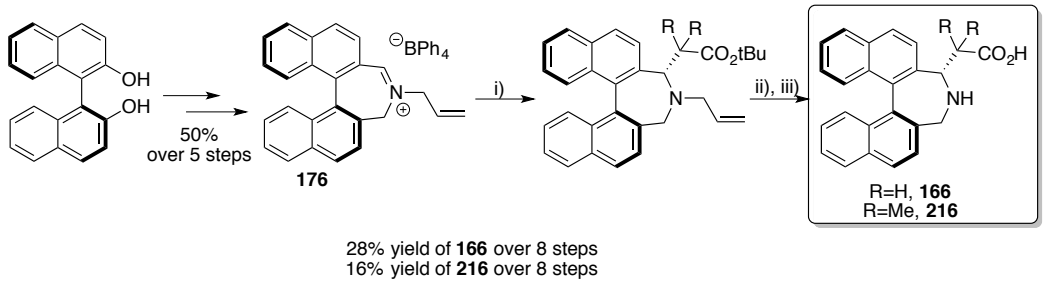
In addition, we have developed the synthesis of biphenyl catalyst **265**, which was prepared in 8 steps in 4% overall yield from 2-amino-3-methylbenzoic acid. The key steps in the synthesis include a diazonium salt homocoupling, a quinine-mediated resolution and a diastereoselective lithiation/carboxylation step (**Scheme 106**).



Key steps: i) Copper-mediated homocoupling, ii) Resolution, iii) Lithiation and carboxylation, iv) Boc deprotection

Scheme 106: Preparation of biphenyl catalyst **265**

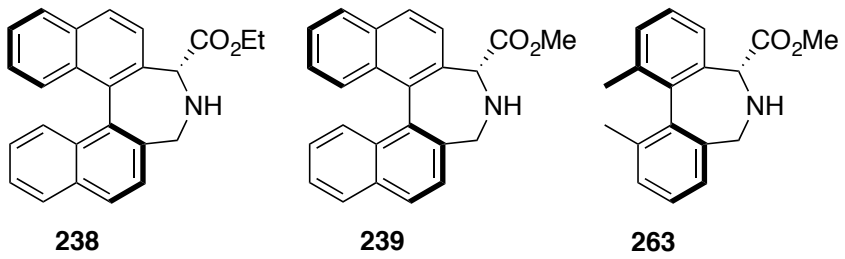
We envisaged that the introduction of an additional carbon unit between the amino and carboxylic acid group functionalities would allow us to assess the influence of distal Brønsted acidic sites. Optimization of the synthesis of β-amino acid **166** was accomplished, following an 8-step procedure, which included a diastereoselective Reformatsky addition to iminium salt **176**. The synthesis was complete in 28% yield overall. We anticipated increased conformational flexibility with this system, and therefore sought to derivatize the β-carbon unit, with respect to the amino functionality, to provide a more selective catalyst. Consequently, we directed the synthesis toward bulkier catalyst **216**, which we were able to isolate in a 16% overall yield (**Scheme 107**).



Key steps: i) Reformatsky reaction, ii) Deallylation reaction, iii) tButyl group removal

Scheme 107: Synthesis of β-amino acid catalysts

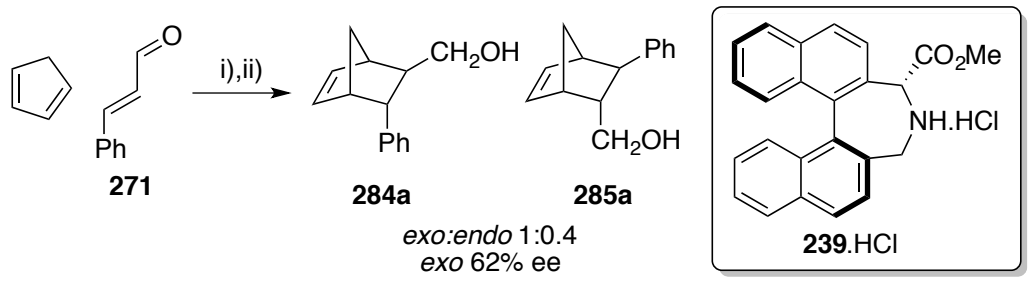
In addition, we have also synthesized the corresponding biphenyl and binaphthyl α-ester derivatives of these amino acid aminocatalysts (**Figure 40**). The synthesis of these esters was high-yielding and fully diastereoselective.



238 **239** **263**

Figure 40: α-Ester derivatives

In order to assess whether our axially chiral species have increased reactivity and selectivity over non-axially chiral analogues, we have applied them in several asymmetric processes. Assessments of their ability to activate substrates by HOMO energy raising enamine and LUMO energy lowering iminium activation were made, and the majority of our catalysts were screened in three separate organocatalytic transformations; the aldol, Michael and Diels-Alder reactions. After discouraging results in the aldol reaction, catalyst **251** was assessed using ^{1}H-NMR spectral analysis with ketone, enone and enal substrates, and demonstrated suitable iminium ion activation with cinnamaldehyde. Correspondingly, this substrate was used in the addition of malonates in the Michael reaction (**Table 39**). The most encouraging results were found when **239**.HCl was applied in the Diels-Alder reaction of cinnamaldehyde, and several derivatives, with cyclopentadiene (**Scheme 108**).



271 **284a** **285a** **239**.HCl

exo:endo 1:0.4
exo 62% ee

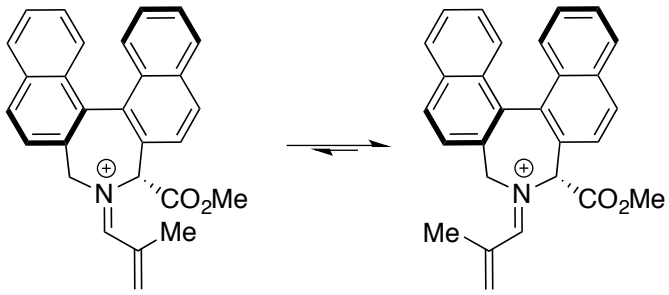
Key steps: i) 10 mol% **239**.HCl, MeOH:H_2O, 0 °C ii) $LiAlH_4$ reduction

Scheme 108: Low temperature Diels-Alder reaction employing catalyst **239**.HCl

In creating these novel aminocatalysts, we have been able to further understand the structural characteristics necessary for the design of highly selective catalysts. From assessing α-amino acid catalysts, we can conclude that carboxylic acid sites on an azepine ring with an axially chiral backbone were not selective catalysts in our chosen screening reactions. α-Ester derivatives, however, promote the formation of the active iminium intermediates in the Michael and Diels-Alder reactions. Moderate diastereoselectivity and enantioselectivity were obtained, implying steric influence is an important feature in this type of reaction.

10.1 Future work: Substrate screening

Further screening of the Diels-Alder reaction is necessary, with simple α,β-unsaturated aliphatic aldehydes such as acrolein and crotonaldehyde requiring assessment. Methacroleins would be interesting substrates to evaluate because, aside from the generation of highly sought-after quaternary stereocentres, α,β-unsaturated aldehydes, possessing an α-alkyl substituent, should have more demanding steric constraints (**Scheme 109**). Consequently the generation of the iminium intermediate should be more discriminatory and induce greater selectivity.

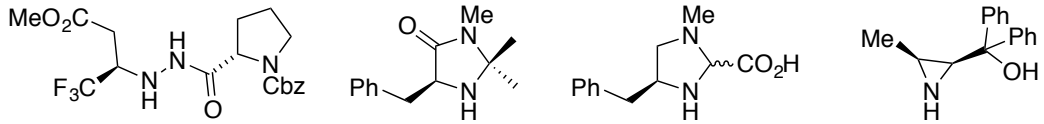


Scheme 109: Proposed preferred iminium ion conformation of catalyst **239** and methacrolein

In addition, reactions conditions require optimization to allow other substrates (other cyclic dienes, such as 1,3-cyclohexadiene, 1,3-pentadiene and acyclic dienes, such as 2-methylbutadiene) to be studied.

10.2 Catalyst design

From the preliminary results acquired using catalyst **239**, it has become apparent that, in order to achieve superior enantioselectivities, our catalysts need to possess greater structural complexity. It appears that it is not sufficient to have one enantiofacial-discriminating substituent; indeed, many of the most successful catalysts possess features that encourage double asymmetric control (**Figure 41**).

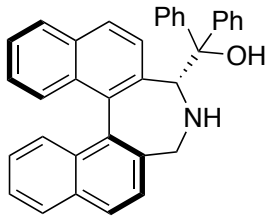


288 **70** **289** **290**

Figure 41: Highly selective catalysts possessing two-fold enantiofacial control

Smith described acyclic chiral hydrazide catalyst **288** affording excellent *endo*-diastereoselectivity and good enantioselectivity in the Diels-Alder reaction (up to 86% ee).[131] He attributed the selectivity of this catalyst to the stereoinduction of both chiral influencing groups; particularly the (5*S*)-trifluoromethyl group. nOe spectral analysis confirmed the *Z*-geometry of the C=N bond of the iminium salt of **288** with substrate cinnamaldehyde, leaving the *re* face of the dienophile free for the reaction with cyclopentadiene. In a similar manner, MacMillan reported the importance of the stereodirecting germinal methyl substituents of catalyst **70**, which influence the predominant formation of an iminium C=N bond with *E*-geometry, facilitating benzyl group *re* face shielding, promoting selective *si* face cycloaddition.[111,132] Second generation imidazolidinone catalyst, with a sterically hindered *tert*-butyl substituent in place of the geminal dimethyl groups of **70**, resulted in superior yields and enantioselectivities in intramolecular Diels-Alder reactions.[133] Again, computational modelling predicted that the *E*-geometry is the preferred isomer, due to repulsive non-bonding interactions of the substrate and the *tert*-butyl substituent, whilst the benzyl substituent shields the *re* face.[134] Jørgensen's catalyst **289**, which was employed as a mixture of diastereoisomeric acids, also confers selectivity through *re* face shielding from the benzyl group or proposed π-stacking interactions

between the benzyl group and cinnamaldehyde's phenyl group.[135] Furthermore, Bonini's aziridine-type catalyst **290** provided good selectivity in Diels-Alder and Friedel-Crafts alkylation reactions.[136] Conversely, Hayashi, employing **95**, found that the steric bulk of a singular CF_3-disubstituted diphenyl OTMS α-substituent was sufficient to produce excellent ees.[137,138] Therefore instalment of a single sterically demanding substituent should also be targeted. Optimization of the synthesis of **234** (**Scheme 92**) and silyl protection, would provide bulky Jørgensen-type catalyst for future catalysis screening (**Figure 42**).



234

Figure 42: Catalyst for screening

To assess the extent of predicted facial selectivity when employing the most selective of these catalysts, we decided to investigate the energy minima of iminium isomers derived from catalysts **70** and **100**, and their enal substrates (cinnamaldehyde and acrolein), using MM2 calculations (software Chem3D Pro). While the calculations are not as accurate as the MM3 methodology used by MacMillan, they can give us a broad idea of the preferred isomer of the reaction intermediates.[111] The *trans* isomer was the favoured intermediate in both cases and, as anticipated, we saw dramatically different energy differences in the *trans* and *cis* isomers, which could explain the high degree of selectivity, observed when using these catalysts (**Figure 43**).

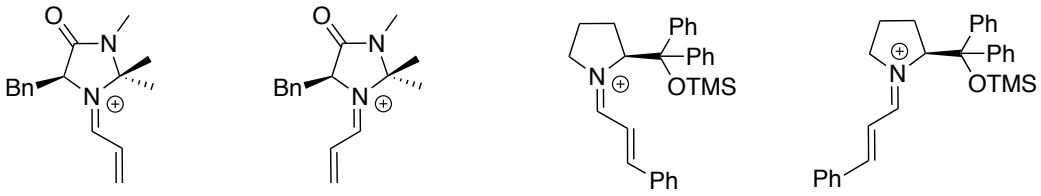
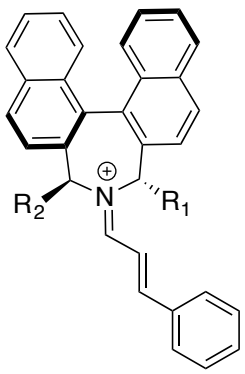
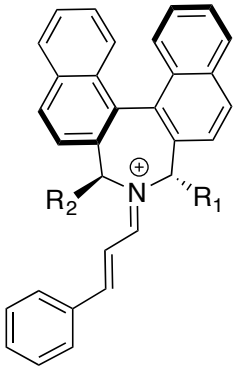


Figure 43: Calculated energy minima values of cinnamaldehyde- and acrolein-derived iminium species

Applying this set of calculations to catalyst **239**, a much smaller energy difference between the *cis* and *trans* isomers was seen (**Entry 1, Table 53**). This estimate of a much-reduced energy difference in the *trans*/*cis* isomers was confirmed experimentally, as both catalysts **70** and **100** outperform **239** in the Diels-Alder reaction. We then set out to identify the optimum substitution pattern for future binaphthyl azepine catalyst structures.

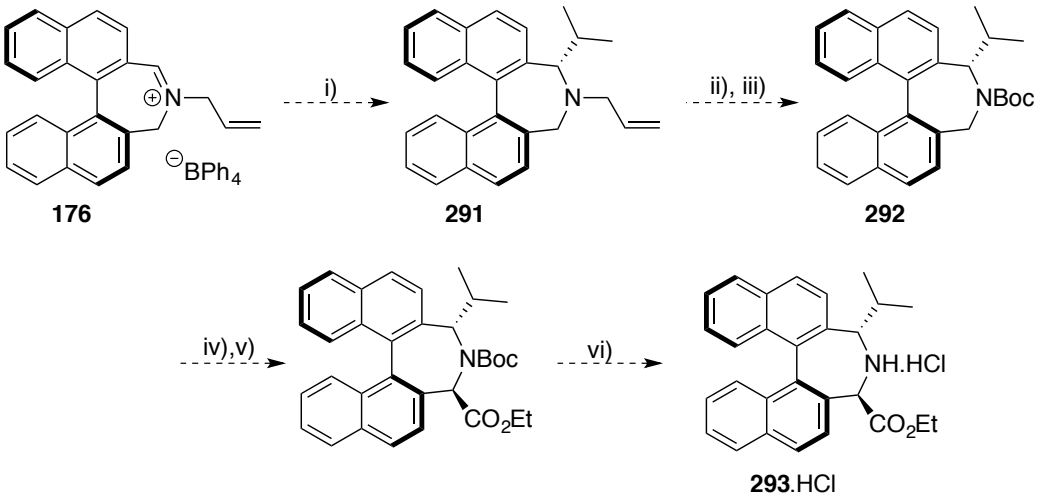
Table 53: Predicted energy minima values using MM2





Entry	R_1	R_2	*Cis* isomer (kcal/mol)	*Trans* isomer (kcal/mol)
1	CO_2Me	H	21.4958	22.5201
2	$C(C_6H_5)_2OTMS$	H	40.7286	41.5442
3	Bn	Me	24.4785	25.4070
4	Bn	*n*Pr	25.2676	26.3338
5	Ph	*i*Pr	24.8141	25.6477
6	*i*Pr	CO_2Me	30.7768	26.0680
7	*i*Pr	CO_2Et	30.3076	25.5896

Assuming these calculations are broadly predictive of experimental observations, as postulated by MacMillan,[111] future modifications of our catalyst design should be directed toward the installment of two enantiodiscriminating groups in both the α positions. **Entry 6** and **7** show the highest degree of energy differentiation between the *cis* and *trans* isomers and, gratifyingly, these catalysts could be synthesized using steps previously explored in this body of work. An NBS oxidation and diastereoselective nucleophilic Grignard addition could furnish **291**, followed by an allyl/Boc deprotection and protection step. An asymmetric lithiation and chloroformate addition and deprotection sequence could theoretically provide us with a route toward a better catalyst, such as **293** (**Scheme 101**).[4]



176 **291** **292** **293**.HCl

Reagents and conditions: i) *i*PrMgBr, THF, − 78 °C; ii) $Pd(PPh_3)_4$, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2, 50 °C; iii) di-*tert*-butyl carbamate, *t*BuOH, r.t.; iv) *s*-BuLi, Et_2O, −78 °C; v) ethyl chloroformate, −78 °C→ r.t; vi) HCl_{aq} (6M), acetone, 70 °C

Scheme 110: Future catalyst design

Results and discussion references

[1] T. Mecca, S. Superchi, E. Giorgio, C. Rosini, *Tetrahedron: Asymmetry*, **2001**, 12, 1225−1233

[2] M. Ikunaka, K. Maruoka, Y. Okuda, T. Ooi, *Org. Proc. Res. Dev.*, **2003**, 7, 644−648

[3] P. C. Bulman Page, B. R. Buckley, M. M. Farah, A. J. Blacker, *Eur. J. Org. Chem.,* **2009**, 3413−3426

[4] Page, P. C. B., Barlett, C. J., Chan, Y., Day, D., Parker, P., Buckley, B. R., Rassias, G. A., Slawin, A. M. Z., Allin. S. M., Lacour, J., Pinto, A., *J. Org. Chem*., **2012**, 77, 6128−6138

[5] A. I. Meyers, T. H. Nguyen, *Tetrahedron Lett.*, **1995**, 36, 5873−5876

[6] S. L. Pira, T. W. Wallace, J. P. Graham, *Org. Lett.*, **2009**, 11, 7, 1663−1666

[7] H. Zhang, S. Mitsumori, N. Utsuni, M. Imai, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.,* **2008**, 130, 875−886

[8] S. G. Davies, A. J. Russell, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Org. Biomol. Chem.,* **2007**, 5, 3190−3200

[9] D. Terakado, M. Takano, T. Oriyama, *Chem. Lett.,* **2005**, 35, 7, 962−963

[10] A. Armstrong, Y. Bhonoah, A. J. P. White, *J. Org. Chem*., **2009**, 74, 5041−5048

[11] T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem.,* **2005**, 44, 3055−3057

[12] S. N. Khong, O. Kwon, *Molecules*, **2012**, 17, 5626−5650

[13] M. M. Farah, P. C. B. Page, B. R. Buckley, A. J. Blacker, M. R. J. Elsegood, *Tetrahedron*, **2013**, 69, 758−769

[14] A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E.G. E. Jahngen, Jr., A. J. Lovey, W. P. Stephens, *J. Org. Chem.,* **1978**, 43, 138−147

[15] R. R. Jagadeeshwar, R. F. Schinazi, C. K. Chu, *Bio. Med. Chem.,* **2007**, 15, 839−846

[16] M. Nejman, A. Sliwinska, A. Zwierzak, *Tetrahedron*, **2005**, 61, 8536−8541

[17] J. D. Mason, S. S. Murphree, *Synlett*, **2013**, 13, 1391−1394

[18] F.A. Leibfarth, M. Wolffs, L.M. Campos, K. Delany, N. Treat, M. J. Kade, B. Moon, J. Hawker, *Chem. Sci.,* **2012**, 3, 766−771

[19] H. McNab, *Chem. Soc. Rev.*, **1978**,7, 345−358

[20] S. Perreault, C. Spino, *Org. Lett*., **2006**, 8, 20, 4385−4388

[21] H. Müller, H. Rottele, H. Henke, H. Waldmann, *Chem. Eur. J*., **2000**, 6, 11, 2032−2043

[22] S. Reformatsky, *Ber.*, **1887**, 20, 1210−1211

[23] A. Fürstner, *Synthesis*, **1988**, 571−590

[24] J. Dekker, P. H. M. Budzelaar, J. Boersma, G. J. M. van der Kerk, *Organometallics,* **1984**, 3, 1403−1407

[25] A. Fürstner, *Angew. Chem.*, **1993,** 32, 164−189

[26] H. Osato, M. Osaki, T. Oyama, Y. Takagi, T. Hida, K. Nishi, M. Kabaki, *Org. Proc. Res. Dev.,* **2011**, 15, 1433−1437

[27] K. Maruoka, Y. Nishimoto, Y. Yamamoto, Japan, *Patent No*. WO2006104226

[28] P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, B. Buckley, D. Bethell, T. A. D. Smith, A. M. Z. Slawin, *J. Org. Chem.,* **2001**, 66, 21, 6926−6931

[29] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc*., **1972**, 94, 17, 6190−6191

[30] F. Diaba, C. L. Houeron, M. Grignon-Dubios, B. Rezzonico, P. Gerval, *Eur. J. Org. Chem*., **2000**, 2915−2921

[31] M. Miki, K. Nakamoto, J. Kawakami, S. Handa, S. Nuwa, *Synthesis*, **2008**, 3, 409−412

[32] R. Shank, H. Shechter, *J. Org. Chem.*, **1959**, 24, 11, 1825−1826

[33] E. Santaniello, A.Manzocchi, *Synthesis*, **1977**, 10, 698−699

[34] L09811, *Alfa Aesar catalogue*, CAS 53801-63-1, MDL number MFCD00084851

[35] M. R. Saidi, M. Nazari, *Monatsh. Chem.,* **2004**, 135, 309−312

[36] R. Moumne, S. Lavielle, P. Karoyan, *J. Org. Chem.*, **2006**, 71, 3332−3334

[37] B. P. Bandgar, S. N. Chavare, S. S. Pandit, *J. Chem. Soc.,* **2005**, 52, 125−128

[38] M. R. Saidi, N. Azizi, H. Zali-Boinee, *Tetrahedron*, **2001**, 57, 6829−6832

[39] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.,* **2006**, 45, 6040−6044

[40] S. A. Weissman, D. Zewge, *Tetrahedron*, **2005**, 61, 7833−7863

[41] I. Strutt, *Ph.D thesis*, University of East Anglia, 2014

[42] A. M. Taylor, S. L. Schreiber, *Org. Lett*., **2006**, 8, 1, 143−146

[43] J. A. Wright, J. Yu, J. B. Spencer, *Tetrahedron Lett.*, **2001**, 42, 4033−4036

[44] V. Jurcik, K. Arai, M. M Salter, Y. Yamashita, S. Kobayashi, *Adv. Synth. Catal*., **2008**, 350, 5, 647−651

[45] K. Annadi, A. G. H. Wee, *Arkivoc*, **2014**, 6, 108−126

[46] A. Jarrahpour, M. Zarei, *Molecules*, **2007**, 12, 2364−2379

[47] S. Chandrasekhar, G. Sumithra, J. S. Yadav, *Tetrahedron Lett.*, **1996**, 37, 10, 1645−1646

[48] W. Yu, M. Su, X. Gao, Z. Yang, Z. Jin, *Tetrahedron Lett*., **2000**, 41, 4015−4017

[49] T. Akiyama, Y. Takesue, M. Kumegawa, H. Nishimoto, S. Ozaki, *Bull. Chem. Soc. Jpn.*, **1991**, 64, 7, 2266−2269

[50] J. H. Rigby, V. Gupta, *Synlett*, **1995**, 547−548

[51] S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2009**, 131, 13606−13607

[52] A. Cappa, E. Marcantoni, E. Torregiani, *J. Org. Chem.,* **1999**, 64, 15, 5696−5699

[53] J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *Org. Lett.*, **2003**, 5, 18, 3273−3275

[54] B. M. Trost, D. L. V. Vranken, *Chem. Rev.*, **1996**, 96, 1, 395−422

[55] J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.*, **1965**, 49, 4387−4388

[56] B. M. Trost, T. J. Fullerton, *J. Am. Chem. Soc.*, **1972**, 95, 1, 292−294

[57] F. Garro-Helion, A. Merzouk, F. Guibe, *J. Org. Chem*., **1993**, 58, 6109−6113

[58] C.-J. Li, *Accounts. Chem. Res*., **2009**, 42, 2, 335−344

[59] C. S. Yeung, Vy, M. Dong, *Chem. Rev*., **2011**, 111, 1215−1292

[60] Z. Li, C.-J. Li, *Euro. J. Org. Chem.*, **2005**, 3173−3176

[61] T. Nobuta, N. Tada, A. Fujiya, A. Kariya, T. Miura, A. Itoh, *Org. Lett.*, **2013**, 15, 3, 574−577

[62] A. S.-K. Tsang, P. Jensen, J. M. Hook, A. S. K. Hashmi, M. H. Todd, *Pure Appl. Chem.*, **2011**, 83, 11, 655−665

[63] K. Hashigaki, S. Ishikawa, W. Wan, M. Yamato, *Synthesis*, **1988,** 12, 1001−1003

[64] G. Loh, R. Tanigawara, S. M. Shalik, K. Sa-ei, L. Wong, P. N. Sharrat, *Org. Proc. Res. Dev.*, **2012**, 16, 959−966

[65] O. Bortolini, L. Caciolli, A. Cavazzini, V. Costa, R. Greco, A. Massi, L. Pasti, *Green Chem.,* **2012**, 14, 992−1000

[66] S.-T. Tong, P. W. R. Harris, D. Barker, M. A. Brimble, *Eur. J. Org. Chem*., **2008**, 168−170

[67] S. Delacroix, J.-P. Bonnet, M. Courty, D. Postel, A. N. V. Nhien, *Carbohydr. Res*., **2013**, 381, 12−18

[68] V. Aureggi, V. Franckevicius, M. O. Kitching, S. V. Ley, D. A. Longbottom, A. J. Oelke, G. Sedelmeier, *Org. Synth.,* **2008**, *85*, 72−87

[69] F. Zhang, X. Wen, Q.-L. Xu, H. Sun, *Eur. J. Org. Chem*., **2014**, 8101−8109

[70] M. Yauda, S. Saito, Y. Arakawa, S. Yoshifuji, *Chem. Pharma. Bull.*, **1995**, 43, 8, 1318−1324

[71] P. Beak, W. J. Zajdel, D. B. Reitz, *Chem. Rev.*, **1984**, 84, 471−523

[72] L. K. Keefer, C. H. Fodor, *J. Am. Chem. Soc*., **1970**, 92, 19, 5748−5749

[73] L. Pisani, S. Superchi, *Tetrahedron; Asymmetry*, **2008**, 19, 1784−1789

[74] N. Momcilovic, P. G. Clark, A. J. Boydston, R. H. Grubbs, *J. Am. Chem. Soc.*, **2011**, 133, 19087−19089

[75] P. Beak, S. T. Kerrick, S. Wu, J. Chu, *J. Am. Chem. Soc.*, **1994**, 116, 8, 3231−3239

[76] S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.*, **1991**, 113, 25, 9708−9710

[77] Z. Zhenghong, T. Yilong, W. Lixin, Z. Guofeng, Z. Qilin, T. Chuchi, *Synthesis*, **2004**, 2, 217−220

[78] G. Gelardi, G. Barker, P. O'Brien, D. C. Blakemore, *Org. Lett.,* **2013**, 15, 21, 5424−5427

[79] A. Thaqi, A. McCluskey, J. L. Scott, *Tetrahedron*, **2008**, 49, 6962−6964

[80] D. S. Coffey, M. K. Hawk, S. W. Pederson, S. J. Ghera, P. G. Marler, P. N. Dodson, M. L. Lytle, *Org. Proc. Res. Dev*., **2004**, 8, 945−947

[81] F. Kelleher, S. Kelly, J. Watts, V. McKee, *Tetrahedron*, **2010**, 66, 3525−3536

[82] A. C. Murphy, M. I. Mitova, J. W. Blunt, M. H. G. Munro, *J. Nat. Prod.*, **2008**, 71, 806−809

[83] G. Mloston; *Tetrahedron: Asymmetry*, **2012**, 23, 795–801

[84] S. T. Kerrick, P. Beak, *J. Am. Chem. Soc*., **1991**, 113, 25, 9708−9710

[85] P. Kasak, K. Mereiter, M. Widhalm, *Tetrahedron: Asymmetry*, **2005**, 16,

3416−3426

[86] M. Bourghida, M. Widhalm, *Tetrahedron: Asymmetry*, **1998**, 9, 1073−1083

[87] S. D. Rychnovsky, T. L. McLernon, H. Rajapakse, *J. Org. Chem.*, **1996**, 61, 1194−1195

[88] L. A. Saudan, G. Bernardinelli, E. P. Kündig, *Synlett*, **2000**, 4, 483−486

[89] F. Kelleher, S. Kelly, J. Watts, V. McKee, *Tetrahedron*, **2010**, 66, 3525−3536

[90] T. Kano, O. Tokuda and K. Maruoka, *Tetrahedron Lett.,* **2006**, 47, 7423−7426

[91] S. E. Denmark, H. Matsuhashi, *J. Org. Chem.,* **2002**, *67*, 3479−3486

[92] P. C. B. Page, C. J. Bartlett, Y. Chan, S. M. Allin, M. J. McKenzie, J. Lacour, G. A. Jones, *Org. Biomol. Chem.,* **2016**, Advance Article

[93] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.*, **2000**, 122, 2395−2396

[94] Paula Yurkanis Bruice, 'Organic Chemistry Paperback, 6th edition', *Pearson*, **2010**, SBN-10: 0321697685

[95] V. Stella, R. Borchardt, M. Hageman, R. Oliyai, H. Maag, J. Tilley, 'Prodrugs Challenges and Rewards', *Springer*, **2007**, ISBN: 9780387497853

[96] S. Bertelsen, P. Diner, R. L. Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.*, **2007**, 129, 1536−1537

[97] N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc*., **2002**, 124, 27, 7894−7896

[98] V. Wascholowski, K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Eur. J.,* **2008**, 14, 6155−6165

[99] K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.,* **2006**, 66−68

[100] T. N. Sorrell, 'Organic Chemistry**,** 2nd Edition', **2005,** *University Science Books*, ISBN-10: 1891389386

[101] S. Zhou, E. Sánchez-Larios, M. Gravel, *J. Org. Chem*., **2012**, 77, 3576−3582

[102] I. Fleischer, A. Pfaltz, *Chem. Eur. J.*, **2010**, 16, 95−99

[103] S. K. Ghosh, K. Dhungana, A. D. Headley, B. Ni, *Org. Biomol. Chem.*, **2012**, 10, 8322−8325

[104] Y. Wang, P. Li, X. Liang, J. Ye, *Adv. Synth. Catal.,* **2008**, 350, 1383−1389

[105] A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.,* **2008**, 49, 3075−3077

[106] K. S. Feu, A. M. Deobald, S. Narayanaperumal, A. G. Corrêa, M. W. Paixão, *Eur. J. Org. Chem.*, **2013**, 5917−5922

[107] C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á. Puente, S. Vera, *Angew. Chem.*, **2007**, 46, 8431−8435

[108] D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry*, **2007**, 18, 299−365

[109] S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem*., **2006**, 45, 4305−4309

[110] M. S. Yu, I. Lantos, Z. –Q. Peng, J. Yu, T. Cacchio, *Tetrahedron Lett*., **2000**, 41, 5647−5651

[111] M. Amat, J. Hidalgo, J. Bosch, M. Cantó, M. Pérez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque, *J. Org. Chem*., **2000**, 65, 3074−3084

[112] L. Czibula, A. Nemes, F. Sebök, C. Szántay, Jr., M. Mák, *Eur. J. Org. Chem.*, **2004**, 44, 3336−3339

[113] T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtius, P. Beak, *J. Am. Chem. Soc.*, **2002**, 124, 11689−11698

[114] O. V. Maltsev, A. S. Kucherenko, S. G. Zlotin, *Eur. J. Org. Chem.*, **2009**, 5134–5137

[115] P. I. Dalko, 'Enantioselective Organocatalysis', *Wiley-VCH*, Weinheim, **2007**

[116] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc*., **2000**, 122, 4243−4244

[117] A. Moyano, R. Rios, *Chem. Rev*., **2011**, 111, 4703−4832

[118] X. Chen, S. Duan, C. Tao, H. Zhai, F. G. Qiu, *Nature Communications*, **2015**, 6, 7204, 1−7

[119] S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature*, **2011**, 475, 183−188

[120] B.-F. Sun, *Tetrahedron Lett.,* **2015**, 56, 2133−2140

[121] T. Kano, Y. Tanaka, K. Maruoka, *Chem. Asian J*., **2007**, 2, 1161−1165

[122] J. L. Cavill, R. L. Elliot, G. Evans, I. L. Jones, J. A. Platts, A. M. Ruda, N. C. O. Tomkinson, *Tetrahedron*, **2006**, 62, 410−421

[123] K. Maruoka, H. Imoto, H. Yamamoto, *J. Am. Chem. Soc*., **1994**, 116, 12115−12116

[124] J. L. Cavill, J.-U. Peters, N. C. O. Tomkinson, *Chem. Commun*., **2003**, 728−729

[125] H. Gotoh, Y. Hayashi, *Org. Lett.,* **2007**, 9, 15, 2859−2862

[126] T. Kano, Y. Tanaka, K. Maruoka, *Org. Lett.,* **2006**, 8, 13, 2687−2689

[127] D.H. Ripin, D.A. Evans, 'pKa Table', Publisher: Havard.edu, (http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf), **2005**

[128] N. Li, X. Liang, W. Su, *RSC Adv.*, **2015**, 5, 106234−106238

[129] A. Puglisi, M. Benaglia, R. Annunziata, V. Chiroli, R. Porta, A. Gervasini, *J.Org. Chem.*, **2013**,78, 11326−11334

[130] C. A. Wang, Y. Zhang, J. Y. Shi, W. Wang, *Chem. Asian. J*., **2013**, 8, 6, 1110−1114

[131] E. Gould, T. Ledbl, A. M.Z. Slawin, M. Reid, T. Davies, A. D. Smith, *Org. Biomol. Chem.,* **2013**, 11, 7877−7892

[132] S. Guizzetti, M. Benaglia, J. S. Siegel, *Chem. Commun*., **2012**, 48, 3188−3190

[133] R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc*., **2005**, 127, 11616−11617

[134] I. K. Mangion, A. B. Northup, D. W. C. MacMillan, *Angew. Chem*., **2004**, 43,

6722−6724

[135] N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem*., **2002**, 67, 8331−8338

[136] B. F. Bonini, E. Capitò, M. Commes-Franchini, M. Fochi, A. Ricci, B. Zwanenburg, *Tetrahedron: Asymmetry*, **2006**, 17, 3135−3143

[137] Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem.*, **2008**, 47, 6634−6637

[138] Y. Hayashi, D. Okamura, T. Yamazaki, Y. Ameda, H. Gotoh, S. Tsuzuki, T. Uchimaru, D. Seebach, *Chem. Eur. J*., **2014**, 20, 17077−17088

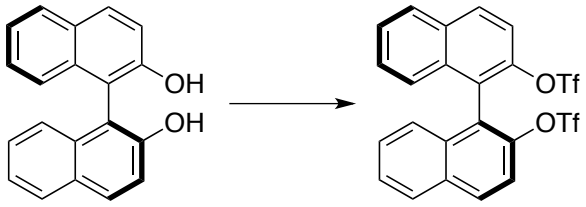
Chapter three: Experimental section

Melting points were recorded using a Büchi B-545 Melting Point apparatus. Optical rotations were obtained using a Bellingham and Stanley Ltd ADP440 polarimeter and the solvents used for these measurements were of HPLC-grade quality. IR spectra were recorded on a Perkin-Elmer 100 FT-IR spectrophotometer and samples were used as thin film DCM solutions on KBr plates. 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 or the residual deuterated solvents peak. 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. Toluene, 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. Dicyclopentadiene was cracked on the day of use to distil cyclopentadiene.

1.0 Synthesis of azepines

(S)-[1,1']-Binaphthalene-2,2'-diol bis-trifluoromethanesulfonate 167[2]

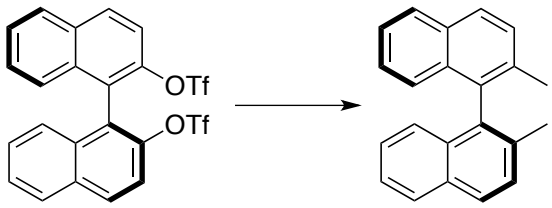


167

(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 anhydrous dichloromethane (300 mL). The reaction mixture was cooled to –78 °C. 2,6-Lutidine (12.2 mL, 104 mmol, 3.0 equiv.) and trifluoromethanesulfonic anhydride (18.0 mL, 104 mmol, 3.0 equiv.) were added to the mixture. The solution turned from yellow to pink and was allowed to reach room temperature overnight. Over this time period the reaction mixture turned from pale pink to dark brown. Silica gel was added (~10 g) and the solvent was removed under reduced pressure. Silica gel was placed on a sintered funnel and washed repeatedly with petroleum ether (~2 L). The petroleum ether fractions were combined and the solvents removed under reduced pressure to yield the title compound as a colourless solid (19.2 g, *quant*.). This was employed in the next step without further purification.

m.p. 86-88 °C (Lit 83-85 °C)[1,2]; $[\alpha]_D^{22.5}$ +144 ° [(*c*=1.00, $CHCl_3$); Lit $[\alpha]_D^{21}$: +148 º, (*c* 1.00, $CHCl_3$)][1,2]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3060 (*C-H aromatic stretch*), 1592, 1509, 1423 (*C=C aromatic stretch, multiple*), 1219 (*C-F stretch, strong*), 1140 (*S=O stretching*), 1066, 963, 941, 739, 704, 634; ^{1}H NMR (500 MHz; $CDCl_3$) 8.14 (2H, d, *J*= 9.0 Hz, C*H* arom), 8.01 (2H, d, *J*= 8.2 Hz, C*H* arom), 7.62 (2H, d, *J*= 9.0 Hz, C*H* arom), 7.59 (2H, ddd, *J*= 8.1, 6.8, 1.1 Hz, C*H* arom), 7.41 (2H, ddd, *J*= 8.1, 6.8, 1.1 Hz, C*H* arom), 7.27-7.23 (2H, m, C*H* arom); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5, 133.2, 132.4, 132.1, 128.4, 128.0, 127.4, 126.8, 123.5, 119.4, 118.1 (q, J_{C-F}= 316.5 Hz).

***(S)*-2,2'-Dimethyl-[1,1']binaphthalene 168**[2]

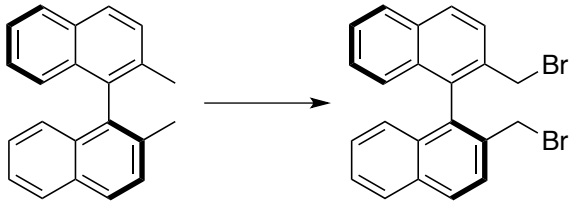


167 **168**

(S)-[1,1']-Binaphthalene-2,2'-diol-bis-trifluoromethanesulfonate (15.50 g, 28 mmol) and 1,3-bis(diphenylphosphino)propane nickel (II) chloride (1.07 g, 1.97 mmol, 0.07 equiv.) were dissolved in anhydrous Et_2O (300 mL). The reaction mixture was cooled to −78 °C. A solution of methyl magnesium bromide (3M in Et_2O, 38 mL, 113 mmol, 4.0 equiv.) was added slowly and the reaction mixture was allowed to reach room temperature overnight. The excess Grignard reagent was quenched at 0 °C with H_2O (50 mL) and the reaction mixture was diluted with Et_2O (100 mL). The solution was stirred for 30 min. The solids were filtered over a plug of celite and washed with Et_2O (~50 mL). The filtrate was transferred to a separating funnel and a few drops of aqueous HCl (37%) were added. The organic layer was washed with H_2O (5 x 50 mL), a saturated brine solution (2 x 30 mL), dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure. The residue was recrystallized (hot methanol) to yield the title compound as colourless crystals (7.5 g, 95%).

m.p. 75–77 °C (Lit 77–79 °C)[3]; $[\alpha]_D^{22.5}$ +36.5 ° [(*c* 1.00, $CHCl_3$); Lit $[\alpha]_D^{21}$ +37.7 °, (*c* 1.00, $CHCl_3$)][3]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3049 (*C-H aromatic stretch, strong*), 3007, 2858 (*C-H stretch*), 1506 (*C=C aromatic stretch),* 1443, 1421, 1351 (*C-H bending*), 1219; ^{1}H NMR (500 MHz, $CDCl_3$) 7.88 (4H, t, *J*= 8.0 Hz, C*H* arom) 7.50 (2H, d, *J*= 8.5 Hz, C*H* arom) 7.38 (2H, ddd, *J*= 8.0, 6.8, 1.1 Hz, C*H* arom), 7.20 (2H, ddd, *J*= 8.0, 6.8, 1.1 Hz, C*H* arom), 7.04 (2H, d, *J*= 8.1 Hz, C*H* arom), 2.03 (6H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 134.3, 132.8, 132.2, 128.7, 127.9, 127.4, 126.1, 125.6, 124.9, 20.0.

(*S*)-2,2'-*Bis*-bromomethyl-[1,1']binaphthalene 169[4]

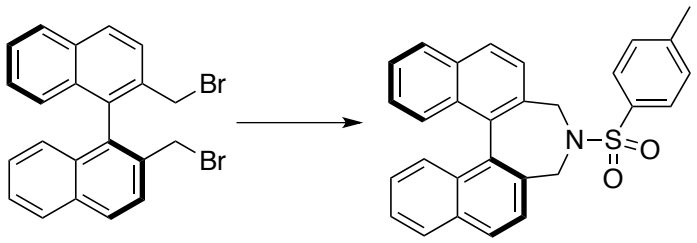


168 **169**

(S)-2,2'-Dimethyl [1,1'] binaphthalene (4.00 g, 14.2 mmol), *N*-bromosuccinimide (6.30 g, 35.4 mmol, 2.5 equiv.) and azobisisobutyronitrile (0.23 g, 1.4 mmol, 0.1 equiv.) were dissolved in cyclohexane (28 mL, 14 % *w/v* solution). The reaction was heated at reflux for 4 h until completion was observed using TLC. The reaction mixture was cooled to 0 °C and EtOAc (9 mL, 1/3 of the volume of cyclohexane) and distilled water (56 mL, twice the volume of cyclohexane) were added. The biphasic solution was stirred for 1 h to allow for precipitation and filtration yielded the title compound as a beige solid (4.76 g, 77%).

m.p. 188-190 °C (Lit 180-183 °C)[2] $[\alpha]_D^{22.5}$ −174.4 ° [(*c* 1.00, $CHCl_3$); Lit $[\alpha]_D^{20}$ (for (*R*)-2,2'-*Bis*-bromomethyl-[1,1']binaphthalene) +186.4 °, (*c* 1.00, benzene)][2]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*C-H aromatic stretch*), 2986 (*C-H stretch*), 2305, 1723 (*C=C aromatic stretch*), 1421, 1265 (*C-H bending*), 896, 740, 705 (*C-Br stretch, strong*); ^{1}H NMR (500 MHz, $CDCl_3$) 8.02 (2H, d, *J*= 8.6 Hz*,* C*H* arom), 7.92 (2H, d, *J*= 8.2 Hz*,* C*H* arom), 7.75 (2H, d, *J*= 8.6 Hz*,* C*H* arom), 7.49 (2H, ddd, *J*= 8.0, 6.8, 1.0 Hz*,* C*H* arom), 7.27 (2H, ddd, *J*= 8.0, 6.8, 1.1 Hz*,* C*H* arom), 7.08-7.07 (2H, d, *J*= 8.5 Hz, C*H* arom), 4.25 (4H, s, CH_2Br); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.2, 134.1, 133.3, 132.5, 129.4, 128.0, 127.8, 126.9, 126.8, 126.8, 32.6.

***(S)*-4-Tosyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 172**

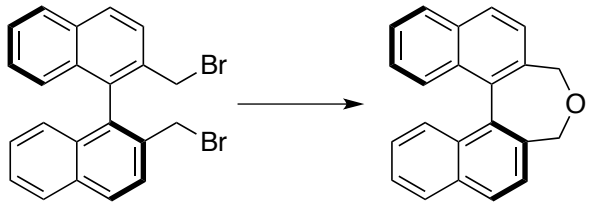


169 **172**

p-Toluenesulfonamide (0.43 g, 2.5 mmol, 1.1 equiv.), (*S*)-2,2'-bis-(bromomethyl)-[1-1']-binaphthalene (1.00 g, 2.27 mmol) and potassium carbonate (0.94 g, 6.81 mmol, 3.0 equiv.) were dissolved in acetonitrile (10 mL). The reaction mixture was heated at reflux overnight or until completion was observed using TLC. The reaction mixture was allowed to reach room temperature, dichloromethane (30 mL) was added and the solution filtered to remove excess potassium carbonate. The filtrate was transferred to a separating funnel and the organic layer was washed with H_2O (4 x 10 mL), a saturated brine solution (2 x 20 mL), dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure to give an orange solid. The residue was purified using column chromatography on silica gel (light petroleum ether/EtOAc, 15:1) to yield the title compound as a yellow solid (0.73 g, 71%).

m.p. 164-166 °C; $[\alpha]_D^{21.4}$ +105.6 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*C-H aromatic stretch)*, 2986 (*C-H stretch*), 2932, 2685, 2525, 2418, 2305, 1597 (*C=C aromatic stretch*), 1508, 1421(*C-H bending*), 1339 (*C-O stretch*), 1329, 1265, 1158 (*C-N stretch*), 1094, 1038, 928, 896, 820; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (2H, d, *J*= 8.2 Hz, C*H* arom), 7.84 (2H, d, *J*= 8.4 Hz, C*H* arom), 7.73–7.68 (2H, m, C*H* arom), 7.46 (2H, ddd, *J*= 8.1, 6.7, 1.2 Hz, C*H* arom), 7.36 (4H, t, *J*= 8.4 Hz, C*H* arom), 7.27–7.20 (4H, m, C*H* arom), 4.75 (2H, d, *J*= 13.0 Hz), 3.67 (2H, d, *J*= 13.0 Hz), 2.39 (3H, s, Ar-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 136.8, 135.0, 133.4, 131.2, 131.0, 129.6, 129.1, 128.3, 127.4, 127.4, 127.3, 126.1, 126.0, 49.2, 21.5; HRMS (CI^+): *m/z* found for $[M+H]^+$: 450.1522; $[C_{29}H_{24}NO_2S]^+$ requires 450.1522.

***(S)*-3,5-Dihydrodinaphtho[2,1-c:1',2'-e]oxepine 205**[2]

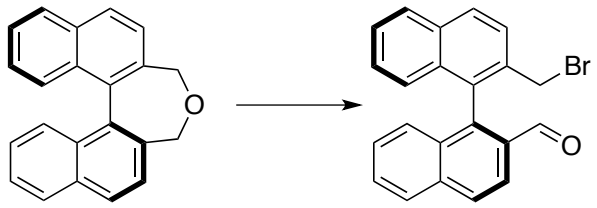


169 **205**

(S)-2,2'-Bis(bromomethyl)-[1-1']-binaphthalene (3.20 g, 7.3 mmol) was suspended in a mixture of saturated aqueous sodium carbonate solution and 1,4-dioxane (1:1, 100 mL) and heated at reflux for 12 h. The reaction mixture was allowed to cool to room temperature and the mixture transferred to a separating funnel and extracted with Et_2O (3 x 30 mL). The organic layers were combined and washed with H_2O (20 mL), a saturated brine solution (2 x 40 mL), dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the resultant yellow oil was purified using column chromatography on silica gel (100:0-90:10 light petroleum ether/EtOAc) to give a colourless solid. Recrystallization of the solid ($CHCl_3$ in hexane) yielded the title compound as a colourless solid (1.88 g, 87%).

m.p. 170-173 °C (Lit 180-183 °C)[2]; $[\alpha]_D^{20}$ +527.0 ° [(*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*C-H aromatic stretch*), 2986 (*C-H stretching*), 2304, 1420 (*C-H bending, C=C aromatic bending*), 1265, 1055 (*C-O stretch, strong*), 896, 820; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (2H, d, *J*= 8.2 Hz), 7.98 (2H, d, *J*= 8.2 Hz), 7.64 (2H, d, *J*= 8.3 Hz, C*H* arom), 7.55 (2H, dd, *J*= 8.6, 0.6 Hz, C*H* arom), 7.51 (2H, ddd, *J*= 8.1, 6.8, 1.2 Hz, C*H* arom), 7.31 (2H, ddd, *J*= 8.3, 6.8, 1.3 Hz, C*H* arom) 4.65 (2H, d, *J*= 11.3 Hz, CH_2O), 4.21 (2H, d, *J*= 11.3 Hz, CH_2O); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 134.0, 133.6, 131.2, 129.2, 128.4, 127.7, 127.4, 126.0, 126.0, 67.5.

(*S*)-2'-Bromomethyl-[1,1']binaphthalene-2-carboxaldehyde 206[2]

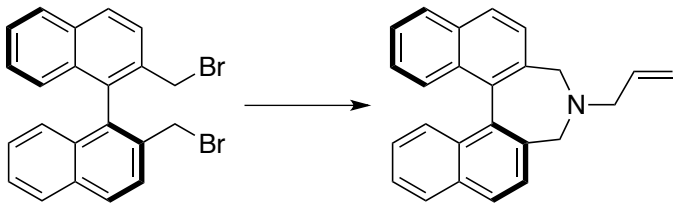


205 **206**

(*S*)-2,7-Dihydrodinaphtho[2,1-c;1',2'-e]oxepine (4.80 g, 16.2 mmol) was dissolved in cyclohexane (80 mL) and the solution cooled in an ice bath. The solution turned dark red as molecular bromine (0.9 mL, 18.2 mmol, 1.125 equiv.) was added slowly. The ice bath was removed and the reaction mixture heated at reflux for 1 h, which caused the reaction mixture to turn yellow in colour. The solvent was removed under reduced pressure and the residue redissolved in Et_2O (70 mL). The solution was transferred to a separating funnel and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (2 x 50 mL), a saturated brine solution (2 x 60 mL), dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and was purified using column chromatography on silica gel (9:1 light petroleum/EtOAc) to yield the title compound as a colourless solid (3.04 g, 50%).

m.p. 147-149 °C (Lit 151-153 °C)[2]; $[\alpha]_D^{22.5}$ −142.0 ° [(*c* 1.00, $CHCl_3$); Lit $[\alpha]_D^{20}$ (for (*R*)-2'-Bromomethyl-[1,1']binaphthalene-2-carboxaldehyde) +144.7 ° (*c* 1.02, $CHCl_3$)][2]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*C-H aromatic stretch*), 2986 (*C-H stretch, =C-H stretch*), 2305, 1689 (*C=O, strong*), 1422 (*C-H bend*), 1265, 896, 740, 705, 600 (*C-Br stretch*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (1H, d, *J*= 1.0 Hz, C*H*O), 8.24 (1H, d, *J*= 8.5 Hz, C*H* arom), 8.13 (1H, d, *J*= 8.5 Hz, C*H* arom), 8.09 (1H, d, *J*= 8.5 Hz, C*H* arom), 8.03 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.98 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.76 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.66 (1H, ddd, *J*= 8.0, 7.0, 1.0 Hz, C*H* arom), 7.53 (1H, ddd, *J*= 8.0, 7.0, 1.0 Hz, C*H* arom), 7.38 (1H, ddd, *J*= 8.5, 7.0, 1.5 Hz, 1H, C*H* arom), 7.32 (1H, ddd, *J*= 8.5, 7.0, 1.5 Hz, C*H* arom), 7.27 (1H, dd, *J*= 8.0, 0.5 Hz, C*H* arom), 7.05 (1H, dd, *J*= 8.5, 0.5 Hz, C*H* arom), 4.37 (1H, d, *J*= 10.0 Hz, CH_2Br), 4.12 (1H, d, *J*= 10.0 Hz, CH_2Br); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.8, 141.6, 136.3, 134.6, 133.6, 133.0, 132.5, 132.42, 132.42, 129.9, 129.4, 129.3, 129.2, 128.5, 128.2, 127.41, 127.40, 127.0, 126.6, 122.4, 31.9.

***(S)*-Allyl-4,5-dihydro-3H-4-aza-cyclohepta[2,1-a;3,4-a']dinaphthalene 171[5]**

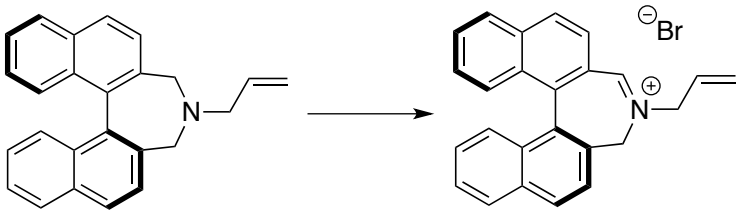


169 **171**

(S)-2,2'-Bis-(bromomethyl)-[1-1']-binaphthalene (2.50 g, 5.7 mmol) and allylamine (0.5 mL, 6.25 mmol, 1.1 equiv.) were dissolved in acetonitrile (25 mL). Anhydrous potassium carbonate (2.36 g, 17.1 mmol, 3.0 equiv.) was added and the reaction mixture heated at reflux overnight or until completion was observed using TLC. The reaction mixture was cooled to room temperature, diluted with dichloromethane (40 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 saturated brine solution (2 x 20 mL), dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure yielding an orange solid. Recrystallization (hot acetone) yielded the title compound as a pale yellow solid (1.60 g, 84%).

m.p. 167-169 °C (Lit 148-149 °C)[6]; $[\alpha]_D^{22.5}$ +396.2 ° (*c* 1.80, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3944, 3054 (=*C-H stretch*, *C-H aromatic stretch, strong*), 2987 (*C-H stretch, strong*), 2829, 2685, 2410, 2305, 1508 (*C-C aromatic stretch*), 1421 (*C-H bending*), 1263 (*C-N stretch*), 1156, 896, 820; ^{1}H NMR (500 MHz, $CDCl_3$) 8.00 (4H, d, *J*= 8.3 Hz*,* C*H* arom), 7.59 (2H, d, *J*= 8.2 Hz, C*H* arom), 7.52-7.49 (4H, m, C*H* arom), 7.31 (2H, ddd, *J*= 8.3, 6.8, 1.1 Hz*,* C*H* arom), 6.09-6.01 (1H, m, NCH_2CHCH_2), 5.32 (1H, dd, *J*= 17.1, 1.3 Hz, NCH_2CHCH_2), 5.28 (1H, d, *J*= 10.0 Hz, NCH_2CHCH_2), 3.79 (2H, d, *J*= 12.5 Hz*,* $ArCH_2N$), 3.21 (2H, d, *J*= 12.5 Hz, $ArNCH_2$), 3.21-3.13 (2H, m, NCH_2CHCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) 136.3, 135.1, 133.4, 133.2, 131.4, 128.4, 128.3, 127.8, 127.5, 125.8, 125.5, 118.1, 58.5, 54.8.

***(S)*-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium bromide**

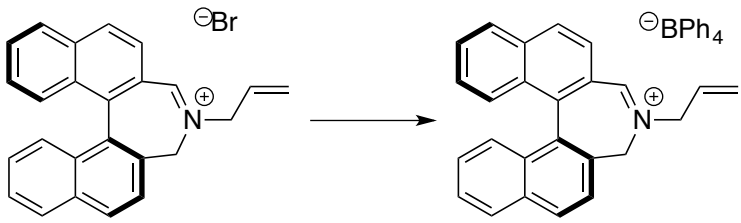


171

(*S*)-Allyl-4,5-dihydro-3H-4-aza-cyclohepta[2,1-a;3,4-a']dinaphthalene (1.00 g, 3.0 mmol) was dissolved in dichloromethane (50 mL). The flask was placed in an ice bath and *N*-bromosuccimide (0.56 g, 3.13 mmol, 1.05 equiv.) was added and the solution 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 (3.83 g crude mass, not routinely isolated).

m.p.* 110 °C (**decomp*); $[\alpha]_D^{22.5}$ +316.0 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3684, 3409, 3019 (*=C-H stretch, C-H aromatic stretch*), 2956 (*C-H stretch, strong*), 2400, 1780, 1753, 1722, 1650, 1521 (*C-C aromatic stretch*), 1430 (*C=N stretching, C-H bending*), 1343, 1160 (*C-N stretch*), 1016; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.88 (1H, s, ArC*H*N^+), 8.50 (1H, d, *J*= 8.6 Hz, C*H* arom), 8.16 (1H, d, *J*= 8.8 Hz, C*H* arom), 8.10 (1H, d, *J*= 8.4 Hz, C*H* arom), 8.05 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.96 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.70 (1H, ddd, *J*= 8.1, 6.8, 1.1 Hz*,* C*H* arom), 7.61 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.53–7.49 (2H, m, C*H* arom), 7.37 (1H, ddd, *J*= 8.1, 6.8, 1.2 Hz*,* C*H* arom), 7.25 (1H, ddd, *J*= 8.1, 6.8, 1.2 Hz, C*H* arom), 7.06-7.05 (1H, d, *J*= 8.4 Hz, C*H* arom), 5.92 (1H, m, NCH_2CHCH_2), 5.71 (1H, d, *J*= 17.0 Hz, NCH_2CHCH_2 *trans*), 5.57 (1H, d, *J*= 10.0 Hz, NCH_2CHCH_2 *cis*), 5.35 (1H, dd, *J*= 14.2, 6.6 Hz, NCH_2CHCH_2), 5.23 (1H, dd, *J*= 14.2, 6.6 Hz*,* NCH_2CHCH_2), 5.02 (1H, d, *J*= 13.3 Hz*,* $ArCH_2N$), 4.57 (1H, d, *J*= 13.3 Hz, $ArCH_2N$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 169.9, 141.4, 135.4, 134.7, 133.7, 132.0, 131.52, 131.48, 130.3, 129.6, 129.4, 128.7, 128.6, 127.5, 127.4, 127.3, 127.22, 127.18, 127.0, 125.3, 125.2, 64.6, 56.6, 29.6.

***(S)*-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium tetraphenylborate 176**

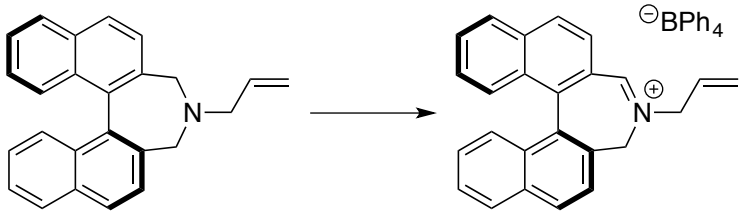


176

Crude *(S)*-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium bromide (3.83 g) was dissolved in a minimum volume of ethanol and sodium tetraphenylborate (1.13 g, 3.3 mmol, 1.1 equiv., in the minimum volume of acetonitrile) was added. The solution was stirred for 10 min. A bright yellow precipitate formed instantly, the solid was collected by filtration and washed with cold ethanol to yield the title compound as a yellow solid which was dried at 70 °C overnight (1.55 g, 80%).

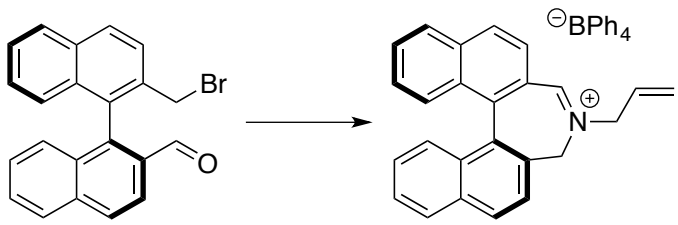
m.p.* 160 °C (**decomp.*); $[\alpha]_D^{22.5}$ +410.5 ° (*c* 1.00, MeCN); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*=C-H stretch, C-H aromatic stretch*), 2987 (*C-H stretch, strong*), 2685, 2410, 2305, 1521 (*C-C aromatic stretch*), 1263 (*C=N stretch*), 1156 (*C-N stretch*), 896; ^{1}H NMR (500 MHz, DMSO) δ 9.58 (1H, s, ArC*H*N$^+$), 8.40 (1H, d, *J*= 8.6 Hz, C*H* arom), 8.28 (2H, t, *J*= 8.8 Hz, C*H* arom), 8.10 (2H, dd, *J*= 14.3, 8.3 Hz, C*H* arom), 7.87 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.81 (1H, t, *J*= 7.4 Hz, C*H* arom), 7.57 (1H, t, *J*= 7.5 Hz, C*H* arom), 7.51 (1H, t, *J*= 7.6 Hz, C*H* arom), 7.46 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.32 (1H, t, *J*= 7.7 Hz, C*H* arom), 7.20 (8H, s, BPh_4 *arom*), 7.01 (1H, d, *J*= 8.7 Hz, C*H* arom), 6.94 (8H, t, *J*= 7.3 Hz, BPh_4 *arom*), 6.81 (4H, t, *J*= 7.1 Hz, BPh_4 *arom*), 6.04–5.90 (1H, m, $NHCH_2CHCH_2$), 5.67 (1H, d, *J*= 17.5 Hz, $NHCH_2CHCH_2$ *trans*), 5.55 (1H, d, *J*= 10.1 Hz, $NHCH_2CHCH_2$ *cis*), 5.16 (1H, d, *J*= 13.5 Hz, $ArCH_2N$), 4.86 (2H, d, *J*= 5.5 Hz, $NHCH_2CHCH_2$), 4.71 (1H, d, *J*= 13.6 Hz, $ArCH_2N$); ^{13}C NMR (126 MHz, DMSO) δ 179.9, 164.5, 164.1, 163.7, 163.3, 141.0, 136.6, 136.0, 135.2, 133.8, 131.8, 131.5, 131.3, 131.2, 130.5, 129.8, 129.6, 129.5, 129.2, 128.1, 127.5, 127.2, 126.9, 126.7, 125.80, 125.78, 125.76, 125.74, 124.3, 122.0, 64.1; HRMS (NSI^+) *m/z* found for $[M\text{-}BPh_4]^+$: 334.1595 $[C_{25}H_{20}N]^+$ requires 334.1590.

Alternative procedures for the synthesis of (*S*)-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium tetraphenylborate 176:



171 **176**

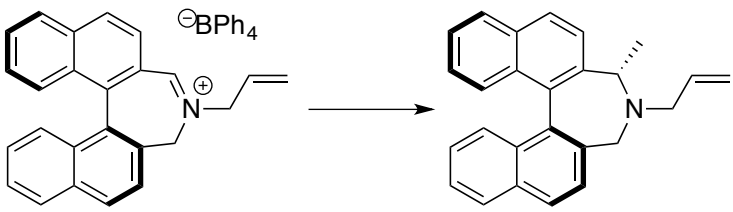
(*S*)-Allyl-4,5-dihydro-3H-4-aza-cyclohepta[2,1-a;3,4-a']dinaphthalene (2.12 g, 6.3 mmol) was dissolved in anhydrous dichloromethane (100 mL). Dried crushed molecular sieves and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.87 g, 12.6 mmol, 2 equiv.) were added. The solution was stirred at ambient temperature for 2 h or until completion was observed using TLC. Sodium tetraphenylborate (2.37 g, 6.93 mmol, 1.1 equiv., in the minimum volume of acetonitrile) was added and the reaction stirred for a further 10 min. The solvent was removed under reduced pressure and the orange residue triturated in hot EtOH to yield the title compound as a bright yellow solid (1.9 g, 46%).



206 **176**

(*S*)-2'-Bromomethyl-[1,1']binaphthalene-2-carboxaldehyde (1.41 g, 3.76 mmol) was dissolved in EtOH (15 mL) and allylamine (0.3 mL, 3.76 mmol, 1 equiv., as a solution in ethanol, 0.5 mL) was added dropwise. The reaction mixture was warmed to 35 °C and stirred for 4 h or until consumption of starting material was seen by TLC. The solution was allowed to reach room temperature and sodium tetraphenylborate (1.42 g, 4.14 mmol, 1.10 equiv., in the minimum volume of acetonitrile) was added. After 10 min of stirring, the solvents were removed under reduced pressure and the crude residue triturated in hot EtOH to yield the title compound as a bright yellow solid (1.59 g, 65%).

(3S,11cS)-4-Allyl-3-methyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine

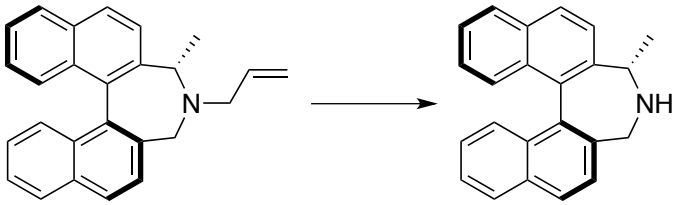


176

(*S*)-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium tetraphenylborate (843 mg, 1.29 mmol) was dissolved in anhydrous THF (20 mL). The solution was cooled to –78 °C and a solution of methyl magnesium bromide (3M in Et_2O, 2.2 mL, 6.45 mmol, 5 equiv.) was added slowly. The reaction mixture was allowed to reach room temperature overnight. The excess Grignard reagent was quenched with H_2O (5 mL) and the reaction mixture was diluted with Et_2O (30 mL). The organic layer was washed with H_2O (20 mL), a saturated brine solution (10 mL), dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified using column chromatography on silica gel (7:3 light petroleum/EtOAc 3% TEA) to yield the title compound as a colourless oil (388 mg, 86%).

$[\alpha]_D^{24.8}$ +317 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3048 (C-*H* aromatic stretch), 3005, 2959 (*C-H stretch*), 2928, 2904, 2805, 2866, 1506 (*C-H bend*), 1366 (*C-C aromatic stretch*), 1264, 1112 (*C-N stretch*), 819, 750, 738; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.87 (4H, m, C*H* arom), 7.65 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.48 (1H, dd, *J*= 8.6, 0.7 Hz, C*H* arom), 7.44–7.38 (3H, m, C*H* arom), 7.33 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.21 (2H, *appt* dddd, *J*= 8.1, 7.0, 5.7, 1.3 Hz, C*H* arom), 6.00 (1H, dddd, *J*= 17.6, 10.1, 7.6, 5.5 Hz, CH_2CH=CH_2), 5.25 (1H, dd, *J*= 17.0, 1.5 Hz, NCH_2CH=CH_2 *trans*), 5.19 (1H, dd, *J*= 11.0, 1.0 Hz, NCH_2CH=CH_2 *cis*), 4.04 (1H, q, *J*= 7.3 Hz, C*H*CH_3), 3.72 (1H, d, *J*= 11.0 Hz, NCH_2Ar), 3.26 (1H, *appt* ddt, *J*= 13.6, 5.4, 1.4 Hz, NCH_2CH=CH_2), 3.15 (1H, dd, *J*= 13.7, 7.6 Hz, NCH_2CH=CH_2), 3.10 (1H, d, *J*= 11.0 Hz, NCH_2Ar), 0.54 (3H, d, *J*= 7.4 Hz, CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4, 136.6, 135.8, 135.1, 133.3, 133.2, 132.9, 132.1, 132.0, 129.2, 128.8, 128.4, 128.1, 128.0, 127.42, 127.40, 125.9, 125.7, 125.5, 117.9, 61.9, 61.0, 56.8, 22.2; HRMS (NSI^+) *m/z* found for $[M+H]^+$: 350.1902; $[C_{26}H_{24}N]^+$ requires 350.1903.

(3*S*,11cS)-3-Methyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 267

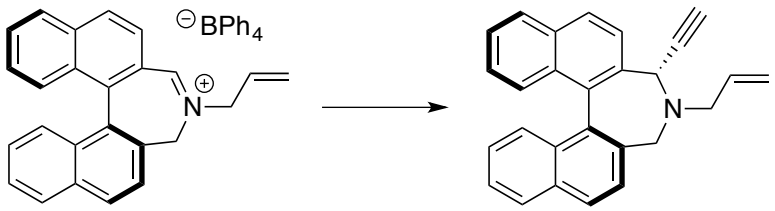


267

(3*S*,11cS)-4-Allyl-3-methyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine (700 mg, 2.00 mmol) was dissolved in anhydrous dichloromethane (20 mL). $Pd(PPh_3)_4$ (92 mg, 0.08 mmol, 0.04 equiv.) and 1,3-dimethylbarbituric acid (937 mg, 6.00 mmol, 3 equiv.) were added and the reaction mixture was heated at reflux overnight or until TLC showed complete consumption of the starting material. The reaction was cooled to room temperature and the organic layers washed with 1 M NaOH (2 x 15 mL), H_2O (2 x 10 mL), a saturated brine solution (2 x 10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product purified using column chromatography on silica gel (10% MeOH in CH_2Cl_2) to yield the title compound as a yellow foam (341 mg, 55%).

m.p. 110-112 °C, $[\alpha]_D^{22.6}$ +498.0 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3049 (*N-H bend, C-H aromatic stretch*), 2951 (*C-H stretch*), 2923, 2864, 1673, 1594 (*C-H bend*), 1075 (*br*, *NH wag*), 819, 750; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.89 (4H, m, C*H* arom), 7.61 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.50–7.45 (3H, m, C*H* arom), 7.41 (1H, d, *J*= 8.2 Hz), 7.37 (1H, d, *J*= 8.3 Hz) 7.29–7.21 (2H, m, C*H* arom), 4.41 (1H, q, *J*= 7.3 Hz, C*H*CH_3), 3.86 (1H, d, *J*= 12.4 Hz, CH_2), 3.78 (1H, d, *J*= 12.3 Hz, CH_2), 2.31 (1H, s, N*H*), 0.72 (3H, d, *J*= 7.2 Hz, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 135.4, 133.5, 133.3, 133.2, 132.20, 132.17, 129.2, 129.1, 128.4, 128.2, 127.3, 127.2, 127.0, 126.1, 125.8, 125.7, 125.7, 57.3, 48.4, 22.5; HRMS (NSI^+) *m/z* found for $[M+H]^+$: 310.1589; $[C_{23}H_{20}N]^+$ requires 310.1590.

(3S,11cS)-4-Allyl-3-ethynyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine

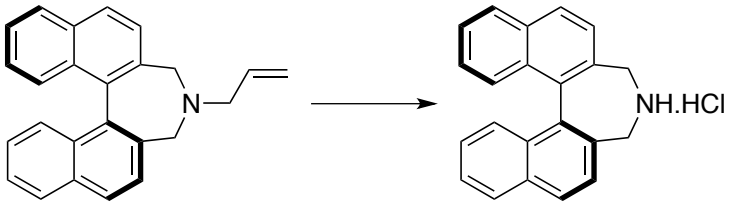


176

(*S*)-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium (1.00 g, 1.52 mmol) was dissolved in anhydrous THF (30 mL). The reaction mixture was cooled to –78 °C and a solution of ethynylmagnesium bromide (0.5M solution in THF, 46 mL, 22.8 mmol, 15 equiv.) was added slowly. The reaction was allowed to reach room temperature overnight. The reaction mixture was quenched at 0 °C with saturated ammonium chloride solution (5 mL) and diluted with Et_2O (50 mL). The mixture was transferred to a separating funnel and the organic layer washed with H_2O (2 x 10 mL), saturated brine solution (10 mL), dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified using column chromatography on silica gel (10:1, light petroleum ether/EtOAc) to yield the title compound as a colourless solid (200 mg, 37%).

$[\alpha]_D^{22.5}$ +271 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3921, 3092 (=*C-H stretch*, *C-H aromatic stretch, strong*), 2767 (*C-H stretch, strong*), 2825, 2684, 2680, 2201 (C≡C stretch), 1503 (*C-C aromatic stretch*), 1470 (*C-H bending*), 1206 (*C-N stretch*), 1152; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01-7.89 (4H, m, C*H* arom), 7.59-7.57 (2H, m, C*H* arom), 7.50 (1H, ddd, *J*= 8.1, 6.8, 1.1 Hz, C*H* arom), 7.45-7.42 (3H, m, C*H* arom), 7.30 (1H, ddd, *J*= 8.1, 6.7, 1.5 Hz C*H* arom), 7.26-7.22 (1H, m, C*H* arom), 6.03 (1H, dddd, *J*= 17.6, 10.1, 7.7, 5.5 Hz, NCH_2CHCH_2), 5.34 (1H, dd, *J*= 17.1, 1.3 Hz, $NCH_2CHCH_{2\ trans}$), 5.27 (1H d, *J*= 10.2 Hz, $NCH_2CHCH_{2\ cis}$), 4.85 (1H, d, *J*= 2.6 Hz, C*H*C≡CH), 3.76 (1H, d, *J*= 11.9 Hz, NCH_2Ar), 3.36-3.28 (1H, m, NCH_2CHCH_2), 3.22-3.17 (1H, m, NCH_2CHCH_2), 3.18 (1H, d, *J*= 12.0 Hz, NCH_2Ar), 1.27 (1H, d, *J*= 2.6 Hz, CHC≡C*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 135.7, 134.7, 133.3, 133.3, 132.8, 132.3, 131.9, 128.9, 128.8, 128.6, 128.2, 128.1, 127.8, 127.5, 127.5, 127.4, 126.0, 125.9, 125.7, 125.3, 118.6, 82.1, 70.4, 58.1, 55.5, 55.1; HRMS (NSI^+) *m/z* found for $[M+H]^+$ 360.1750; $[C_{27}H_{22}N]^+$ requires 360.1747.

(*S*)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepinium hydrochloride 200

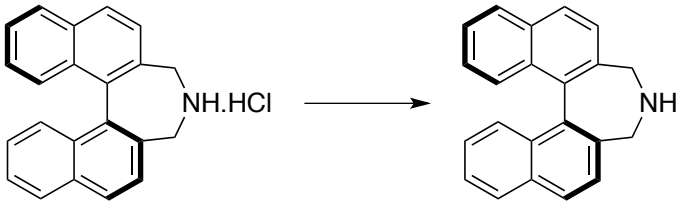


171 **200**

(*S*)-Allyl-4,5-dihydro-3H-4-aza-cyclohepta[2,1-a;3,4-a']dinaphthalene (760 mg, 2.26 mmol) was dissolved in anhydrous dichloromethane (20 mL). 1,3-Dimethylbarbituric acid (1060 mg, 6.8 mmol, 3 equiv.) and $Pd(PPh_3)_4$ (52 mg, 0.045 mmol, 0.02 equiv.) were added. The solution was heated at reflux overnight or until full consumption of the starting material was seen by TLC. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was redissolved in Et_2O (30 mL) and the organic layer washed with 1 M NaOH (2 x 20 mL), H_2O (2 x 20 mL) and a saturated brine solution (2 x 20 mL). The organic layers were dried over anhydrous $MgSO_4$. To the filtrate a few drops of HCl (37%) were added and solution stirred for 10 min. The solvent was removed reduced pressure and the residue was recrystallized (hot $CHCl_3$) to yield the title compound as a pale beige solid (600 mg, 80%).

m.p.* 320-322 °C (**decomp.*); $[\alpha]_D^{21.9}$ +436.4 ° (*c* 1.00, MeOH); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3944, 3689, 3054 (*=C-H aromatic stretching*), 2986 (*N-H streching, strong*), 2827, 2726, 2600, 2410, 2305, 1596 (*C=C aromatic stretch*), 1581, 1421 (*C-H stretch, C=C aromatic stretch*), 1263, 1217 (*C-N stretch*), 896, 819 (*N-H wag*); ^{1}H NMR (500 MHz, DMSO) 10.16 (1H, s, NH.*H*Cl) 9.89 (1H, s, N*H*.HCl), 8.22 (2H, d, *J*= 8.0 Hz, C*H* arom), 8.15 (2H, d, *J*= 8.0 Hz, C*H* arom), 7.81 (2H, d, *J*= 7.0 Hz, C*H* arom), 7.41 (2H, t, *J*= 8.0 Hz, C*H* arom), 7.61 (2H, t, *J*= 7.5 Hz, C*H* arom), 7.29 (2H, d, *J*= 8.5 Hz, C*H* arom), 4.38 (2H, d, *J*= 13.0 Hz, CH_2), 3.54 (2H, d, *J*= 12.5 Hz, CH_2); ^{13}C NMR (126 MHz, d6-DMSO) δ 134.7, 133.6, 130.6, 129.3, 128.9, 128.63, 128.56, 128.1, 128.0, 126.7, 45.0; HRMS (NSI^+) *m/z* found for $[M\text{-}Cl]^+$: 296.1432; $[C_{22}H_{18}N]^+$ requires 296.1434.

(*S*)-4,5-Dihydro-3H-4-aza-cyclohepta[2,1-a;3,4-a']dinaphthalene 129[4]

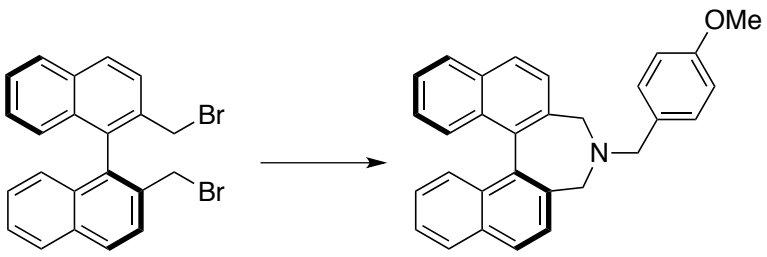


200 **129**

(*S*)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepinium hydrochloride (696 mg, 2.09 mmol) was dissolved in dichloromethane (5 mL) and saturated sodium hydrogen carbonate solution (5 mL) was added. The biphasic solution was stirred for 30 min at room temperature. The organic layer was separated, washed with H_2O (3 x 5 mL), saturated brine solution, dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield the title compound as a yellow foamy solid (620 mg, *quant.*).

M.p. 80-89 °C; (Lit 73-84 °C)**7**; $[\alpha]_D^{22.3}$ +578 ° [(*c* 1.00, $CHCl_3$); Lit $[\alpha]_D^{20}$ +620 °(*c* 0.78, $CHCl_3$)][7]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3040 (=*C-H aromatic stretch, N-H bend*), 2967, 2823, 1578 (*C=C aromatic stretch*), 1490, 1412, 1389, 1325 (*C-H stretch*), 1058 (*C-N stretch*), 1022, 812 (*N-H wag*), 751; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (4H, dd, *J*= 11.7*,* 8.5 Hz*,* C*H arom*), 7.61 (2H, d, *J*= 8.5 Hz*,* C*H arom*), 7.48-7.51 (4H, m, C*H arom*), 7.29-7.32 (2H, m, C*H arom*), 3.89 (2H, d, *J*= 12.4 Hz, CH_2), 3.56 (2H, d*,* *J*= 12.5 Hz, CH_2) 2.74 (1H, s, NH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.0, 134.9, 133.2, 131.4, 128.9, 128.3, 127.4, 127.1, 125.8, 125.4, 48.7.

(*S*)-4-(4-Methoxybenzyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 170

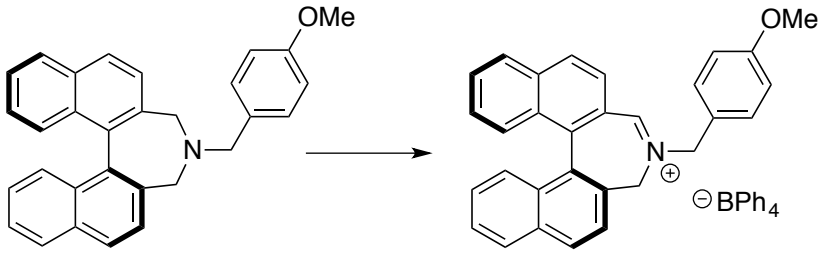


169 **170**

(S)-2,2'bis(bromomethyl)-[1-1']binaphthalene (2.21 g, 5.0 mmol) and *p*-methoxy-benzylamine (0.72 mL, 5.5 mmol, 1.1 equiv.) were dissolved in acetonitrile (20 mL). Anhydrous potassium carbonate (2.10 g, 15.0 mmol, 3 equiv.) was added and the reaction was heated at reflux for 4 h or until consumption of the starting material was observed by TLC. The reaction mixture was diluted with dichloromethane (40 mL) and filtered to remove potassium carbonate. The filtrate was transferred to a separating funnel and washed with H_2O (2 x 60 mL), saturated brine solution (2 x 20 mL) and dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. Purification using column chromatography on silica gel (0.5 % MeOH:CH_2Cl_2) afforded the title compound as a colourless solid (1.9 g, 91%).

m.p. 207-209 °C; $[\alpha]_D^{22.5}$ +129 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3945, 3688, 3054 (*=C-H aromatic stretch*), 2987, 2685, 2305, 1512 (*C=C aromatic stretch, C-C stretch aromatic*), 1422 (C-H stretch), 1264 (*C-O stretch, C-N stretch*), 896; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (4H, d, *J*= 8.2 Hz, C*H* arom), 7.53 (2H, d, *J*= 8.3 Hz, C*H* arom), 7.49-7.42 (4H, m, C*H* arom), 7.34 (2H, d, *J*= 8.7 Hz, C*H* arom), 7.29-7.25 (2H, m, C*H* arom), 6.90 (2H, d, *J*= 8.7 Hz, C*H* arom), 3.83 (3H, s, O*Me*), 3.66 (2H, d, *J*= 12.3 Hz, CH_2), 3.62 (2H, d, *J*= 12.8 Hz, NCH_2PhOMe), 3.51 (2H, d, *J*= 12.8 Hz, NCH_2PhOMe), 3.18 (2H, d, *J*= 12.3 Hz, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 135.1, 133.7, 133.2, 131.5, 131.2, 130.4, 128.3, 128.3, 127.9, 127.5, 125.7, 125.4, 113.8, 59.1, 55.3, 55.1; HRMS (CI^+) *m/z* found for $[M+H]^+$: 416.2010; $[C_{30}H_{26}NO]^+$ requires 416.2009.

(*S*)-4-(4-Methoxybenzyl)-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium 175



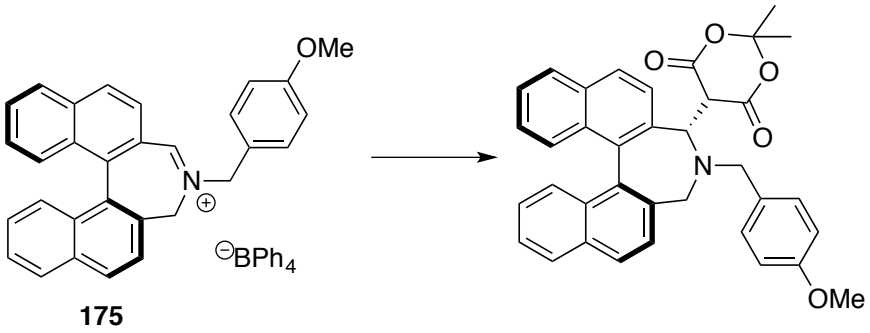
170 **175**

(*S*)-4-(4-methoxybenzyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine (1.90 g, 4.58 mmol) and *N*-bromosuccinimide (0.86 g, 4.80 mmol, 1.05 equiv.) were dissolved in dichloromethane (50 mL). The reaction mixture was stirred for 1 h at room temperature or until full consumption of the starting material was seen by TLC. The solution was transferred to a separating funnel and the organic layer was washed with H_2O (30 mL), saturated brine solution (2 x 30 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The iminium bromide (3.20 g) was isolated as an orange foam and dissolved in a minimum volume of EtOH. Sodium tetraphenylborate (1.65 g, 4.80 mmol, 1.05 equiv., dissolved in the minimum volume of acetonitrile) was added and the solution was stirred for 10 min. The solvent was removed under reduced pressure and the residue triturated in hot EtOH to yield the title compound as a bright yellow solid (3.12 g, 93%).

m.p.* 188-189 °C (**decomp.*); $[\alpha]_D^{22.4}$ +234 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*=C-H aromatic stretch*), 3005, 1693 (*C=N stretch*), 1638, 1610, 1594 (*C-C stretch aromatic*), 1547, 1513, 1462 (*C=C aromatic stretch, C-H stretch*), 1429, 1360, 1255 (*C-O stretch*), 1180 (*C-N stretch)*, 1030, 869, 818, 734, 705, 612; ^{1}H NMR (400 MHz, DMSO) δ 9.86 (1H, s, ArC*H*N$^+$), 8.40 (1H d, *J* = 8.6 Hz, C*H* arom), 8.25 (1H d, *J* = 8.3 Hz, C*H* arom), 8.12 (1H d, *J* = 8.6 Hz, C*H* arom), 8.03 (2H t, *J* = 8.0 Hz, C*H* arom), 7.78 (1H, t, *J*= 7.5 Hz, C*H* arom), 7.52 (3H, t, *J* = 7.4 Hz, C*H* arom), 7.46 (1H, d, *J* = 7.1 Hz, C*H* arom), 7.39 (1H, d, *J* = 8.5 Hz, C*H* arom), 7.29 (1H, d, *J* = 7.9 Hz, C*H* arom), 7.25 (1H, d, *J* = 8.5 Hz, C*H* arom), 7.18 (8H, d, *J* = 1.1 Hz, C*H* arom), 6.94 (11H, dt, *J* = 14.6, 7.4 Hz, C*H* arom), 6.79 (4H, t, *J* = 7.1 Hz, C*H* arom), 5.35 (2H, s,), 5.08 (1H, d, *J* = 13.6 Hz,), 4.65 (1H, d, *J* = 13.5 Hz,), 3.79 (3H, s, OMe); ^{13}C NMR (101 MHz, DMSO) δ 169.2, 164.6, 164.1, 163.6, 163.1, 160.6, 136.8, 136.0, 136.0, 132.0 131.6, 130.9, 130.4, 129.6, 129.4, 129.1,

129.1, 128.0, 127.4, 127.4, 127.1, 127.1, 126.7, 126.2, 125.8, 125.8, 125.7, 124.2, 122.0, 114.8, 64.2, 55.8; HRMS (CI^+): *m/z* found for $[M\text{-}BPh_4]^+$: 414.1853; $[C_{30}H_{24}NO]^+$ requires 414.1852.

5-((3S,11cS)-4-(4-Methoxybenzyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione



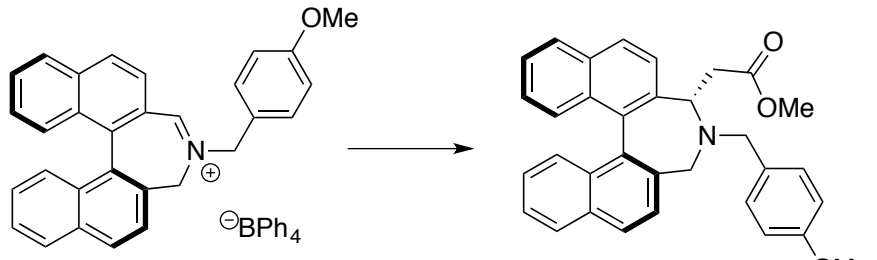
175

2,2 Dimethyl [1, 3] dioxane 4, 6 dione (490 mg, 3.40 mmol, 5 equiv.) was dissolved in THF (20 mL) and cooled to −78 °C. *n*-BuLi (2.5 M in hexane, 1.36 mL, 3.40 mmol, 5 equiv.) was added and the reaction mixture was stirred for 1 h. This solution was then transferred to a flask containing the (*S*)-4-(4-methoxybenzyl)-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium (500 mg, 0.68 mmol), in THF (30 mL), cooled to −78 °C. The reaction was allowed to reach ambient overnight. The reaction mixture was quenched with saturated solution of ammonium chloride (10 mL), diluted with Et_2O (50 mL) and washed and separated with H_2O (2 x 20 mL). The organic layers were dried using saturated brine solution (30 mL) and $MgSO_4$. Purified by column chromatography (2:1 light petroleum ether/ CH_2Cl_2) afforded the title compound as a yellow oil (100 mg, 26%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3055 (*=C-H aromatic stretch)*, 2987 (*=C-H aromatic stretch)*, 2306, 1674 (*C=O aromatic stretch)*, 1596 (C=*C aromatic stretch, C-H stretch)*, 1421 (*C-N stretch, C-O stretch*), 896, 747, 704; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (1H, br s, NCHC*H*), 8.05 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.96 (2H, t, *J*= 8.8 Hz, C*H* arom), 7.86 (2H, dd, *J*= 8.5, 2.8 Hz, C*H* arom), 7.54 (1H, ddd, *J*= 8.1, 6.8, 1.1 Hz, C*H* arom), 7.51 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.46 (1H, d, *J*= 8.1 Hz, C*H* arom), 7.41 (1H, ddd, *J*= 8.1, 5.7, 2.2 Hz, C*H* arom), 7.37 (2H, d, *J*= 8.7 Hz, C*H* arom), 7.31 (1H, ddd, *J*= 8.3, 6.8, 1.2 Hz, C*H* arom), 7.15 (2H, dd, *J*= 5.7, 1.1 Hz, C*H* arom), 6.97-6.93 (2H, m, C*H* arom), 5.08 (1H, d, *J*= 7.5 Hz, NC*H*CH), 4.48 (1H, d, *J*= 13.7 Hz, NCH_2C$_6$H$_4$OMe), 3.88 (1H, d, *J*= 13.3 Hz, NCH_2Ar), 3.78 (3H, s, OMe), 3.76-3.68 (1H, m, NCH_2Ar), 3.68-3.60 (1H, m, NCH_2C$_6$H$_4$OMe), 1.92 (3H, s, CH_3), 1.70 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 165.7, 160.7, 137.2, 134.8, 134.3, 134.1, 132.1, 132.0, 131.5, 131.1, 129.8, 129.5, 128.4, 128.4,

128.3, 127.6, 127.4, 127.4, 127.0, 126.7, 126.4, 126.0, 124.6, 122.9, 115.2, 103.3, 67.8, 65.0, 55.5, 53.5, 49.2, 31.0, 27.7, 25.0.

Methyl 2-((3S,11cS)-4-(4-methoxybenzyl)-4,5-dihydro-3H dinaphtho[2,1c:1',2'e] azepin-3-yl) acetate 189



175 **189**

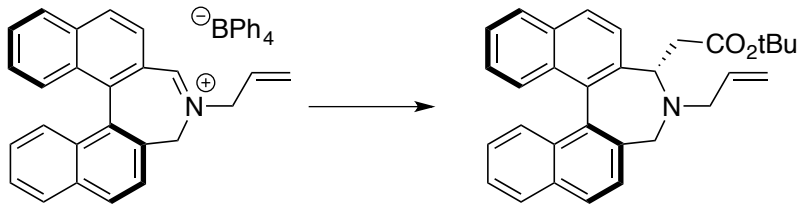
Zinc powder (800 mg, 12.2 mmol, 18 equiv.) and anhydrous THF (30 mL) were added to a flame-dried nitrogen-purged round-bottom flask. 1,2 $BrCH_2CH_2Br$ (2.9 mL, 0.034 mmol, 0.05 equiv.) and TMSCl (3.4 mL, 0.027 mmol, 0.04 equiv.) were added and the reaction was stirred at reflux for 30 min. The reaction mixture was removed from the heat and allowed to reach room temperature. Methyl bromoacetate (3 drops) was added and the reaction was stirred for a further 15 min. (*S*)-4-(4-methoxybenzyl)-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium (500 mg, 0.68 mmol) was added in one portion. Methyl bromoacetate (1 mL, 10.2 mmol, 15 equiv.) was added slowly over the course of over 1 h, causing the reaction mixture to turn red. The reaction mixture was stirred for 12 h at 30 °C after which it was diluted with Et_2O (45 mL) and filtered through a pad of celite. Potassium carbonate solution (50% *w/v*, 15 mL) was added and the biphasic solution was stirred for 30 min. The solution was then transferred to a separating funnel and the organic layers washed with H_2O (3 x 10 mL), saturated brine solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified using column chromatography on silica gel (6:1 light petroleum ether/EtOAc) to isolate the title compound as a colourless solid (166 mg, 50%).

m.p. 76-78 °C; $[\alpha]_D^{22.5}$ +152 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (=*C-H aromatic stretch*), 2987, 1776 (*C=O stretch*), 1533 (*C=C aromatic stretch*), 1437 (*C-H stretch*), 1265 (*C-N stretch*), 1320 (*C-O stretch*) 1010, 739; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93-7.80 (4H, m, C*H* arom), 7.45 (1H, d, *J*= 8.3 Hz, C*H* arom),

7.42-7.35 (4H m, C*H* arom), 7.28 (1H, d, *J*= 8.1 Hz, C*H* arom), 7.23-7.14 (2H, m, C*H* arom), 6.89-6.73 (2H, m, C*H* arom), 4.38 (1H, t, *J*= 7.6 Hz, NC*H*$CH_2CO_2CH_3$), 3.76 (1H, d, *J*= 13.0 Hz, NC*H*$_2$PhOCH_3), 3.75 (3H, s, PhOC*H*$_3$), 3.57 (1H, d, *J*= 12.8 Hz, NC*H*$_2$PhOCH_3), 3.55 (1H, d, *J*= 10.8 Hz, N*CH*$_2$Ar), 3.28 (3H, s, CO_2C*H*$_3$), 2.91 (1H, d, *J*= 10.9 Hz, N*CH*$_2$Ar), 1.64-1.59 (2H, m, NCHC*H*$_2CO_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 158.8, 135.4, 135.2, 135.2, 133.5, 133.2, 133.1, 131.9, 131.8, 131.7, 130.0, 129.5, 129.0, 128.4, 128.4, 128.1, 127.9, 127.4, 127.3, 125.8, 125.8, 125.6, 125.6, 119.5, 119.4, 113.7, 64.9, 62.1, 55.5, 55.3, 51.1, 41.2; HRMS (CI^+): *m/z* found for $[M+H]^+$: 488.2240; $[C_{33}H_{30}NO_3]^+$ requires 488.2209.

2.0 Synthesis of of β-amino acid and derivatives

Tert-butyl 2-((3S,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e] azepin-3-yl) acetate 211[8]



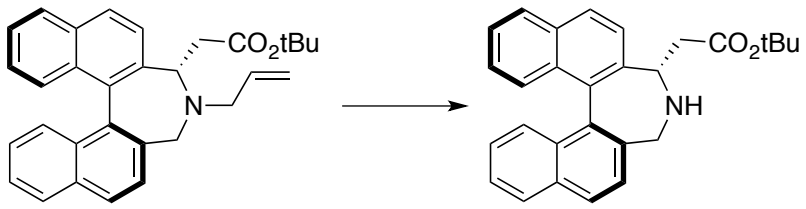
176 211

Zinc dust (1.90 g, 29.1 mmol, 10 equiv.), anhydrous THF (40 mL) and TMSCl (0.37 mL, 2.9 mmol, 1 equiv.) were added to a flame-dried nitrogen-purged round-bottom flask. The reaction mixture was heated at reflux for 30 min. tert-Butyl bromoacetate (0.43 mL, 2.9 mmol) was added and the reaction was heated at reflux for a further 30 min. The mixture was cooled to –78 °C. (*S*)-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium (1.90 g, 2.9 mmol) was dissolved in anhydrous THF (40 mL) in a separate flame-dried round-bottom flask. The iminium salt solution was then transferred into the zinc slurry at –78 °C using a cannula. The reaction mixture was stirred at –78 °C for 1 h and t-butyl bromoacetate (4.3 mL, 29.1 mmol, 10 equiv.) was added in small portions over 20 min, whilst maintaining the temperature. The reaction vessel was allowed to reach room temperature and monitored by TLC. The reaction mixture 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), saturated brine solution (3 x 20 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. The product was purified using column chromatography on silica gel (9:1 light petroleum ether/ EtOAc) to yield the title compound as a colourless oil (932 mg, 71%).

$[\alpha]_D^{22.4}$ +158 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3052 (*=C-H stretch,=C-H aromatic stretch*), 2978, 1724 (*C=O stretch*), 1507 (*C=C stretch, C=C aromatic stretch*), 1367, 1264 (*C-O stretch*), 1150 (*C-N stretch*), 820; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98-7.90 (4H, m, C*H* arom), 7.62 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.48-7.41 (4H, m, C*H* arom), 7.36 (1H, d, *J*= 8.1 Hz, C*H* arom), 7.27-7.19 (2H, m, C*H* arom),

5.97 (1H, m, NCH_2CHCH_2), 5.25 (1H, dd, *J*= 17.1, 1.5 Hz, NCH_2CHCH_2) 5.19 (1H, *appt* d, *J*= 10.2 Hz, NCH_2CHCH_2) 4.41 (1H, t, *J*= 7.8 Hz, $CHCH_2CO_2tBu$), 3.71 (1H, d, *J*= 10.9 Hz, NCH_2Ar), 3.35–3.20 (2H, m, NCH_2CHCH_2), 3.08 (1H, d, *J*= 10.9 Hz, NCH_2Ar), 1.73 (1H, dd, *J*= 15.1, 7.0 Hz, $CHCH_2CO_2tBu$), 1.51 (1H, dd, *J*= 15.1, 8.4 Hz, $CHCH_2CO_2tBu$), 1.15 (9H, s, $CHCH_2CO_2tBu$); ^{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, 129.9, 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; HRMS (CI^+): *m/z* found for $[M+H]^+$: 450.2424; $[C_{31}H_{32}NO_2]^+$ requires 450.2428.

Tert-butyl 2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl) acetate 215



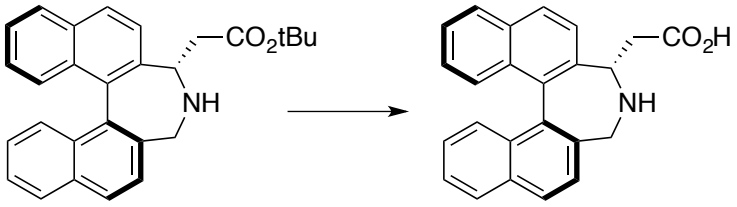
211 **215**

tert-Butyl 2-((3S,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetate (1.20 g, 2.67 mmol) was dissolved in anhydrous dichloromethane (60 mL). 1,3-Dimethylbarbituric acid (1.25 g, 8.00 mmol, 3 equiv.) and $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol, 0.02 equiv.) were added and reaction mixture gently heated at 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. The residue was redissolved in Et_2O (50 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), saturated brine solution (10 mL), dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified using column chromatography on silica gel (6:4 light petroleum ether/EtOAc, elution with EtOAc) to yield the title compound as a fluffy pale yellow foam (0.92 g, 84%).

m.p. 78-79 °C; $[\alpha]_D^{22.4}$ +206 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3052 (=*C-H aromatic stretch, N-H bend*), 2976, 1719 (*C=O stretch*), 1507, 1437 (*C=C aromatic stretch*, *C-H stretch*), 1366, 1293, 1219 (*C-N stretch*), 1148 (*C-O stretch*), 1118; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02-7.91 (4H, m, C*H* arom), 7.59 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.52 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.50-7.43 (2H, m, C*H* arom), 7.40 (1H, d, *J*= 8.6 Hz, C*H* arom), 7.35 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.29–7.20 (2H, m, C*H* arom), 4.63 (1H, t, *J*= 7.6 Hz, C*H*CH_2CO_2tBu), 3.79 (1H, d, *J*= 12.2 Hz, ArCH_2N), 3.72 (1H, d, *J*= 12.2 Hz, ArCH_2N), 2.50 (1H, s), 1.77 (1H, dd, *J*= 15.3, 7.6 Hz, CHCH_2CO_2tBu), 1.71 (1H, dd, *J*= 15.2, 7.7 Hz, CHCH_2CO_2tBu), 1.18 (9H, s, $CHCH_2CO_2$*tBu*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 137.4, 136.7, 134.9, 133.83, 133.2, 133.1, 132.2, 132.1, 129.3, 129.1, 128.8, 128.6, 128.5, 128.3, 128.1, 127.5,

127.4, 127.0, 125.9, 125.7, 125.6, 125.5, 80.2, 59.1, 48.8, 43.0, 27.9; HRMS (CI^+): *m/z* found for $[M+H]^+$: 410.2114; $[C_{28}H_{28}NO_2]^+$ requires 410.2115.

2-((3S,11cS)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetic acid 166



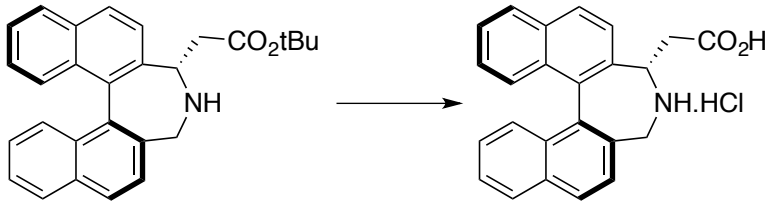
215 **166**

tert-Butyl 2-((3S,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetate (660 g, 1.6 mmol) was dissolved in dichloromethane (30 mL) and trifluoroacetic acid (1.5 mL, 19.3 mmol, 12 equiv.) was added. The reaction was stirred until consumption of the starting material was seen by TLC. A saturated sodium hydrogen carbonate solution was added until the pH of the solution was neutral. The biphasic mixture was transferred to a separating funnel and the organic layer washed using H_2O (15 mL), a saturated brine solution (2 x 10 mL), dried over anhydrous $MgSO_4$. 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 (535mg, 94%).

m.p. 228–230 °C; $[\alpha]_D^{22.4}$ +264 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3345 (*O-H stretch*), 3072 (*=C-H aromatic stretch*), 2971, 1719 (*C=O stretch*), 1597, 1507 (*C=C aromatic stretch*, *C-H stretch*), 1375, 1204 (*C-N stretch*), 1152 (*C-O stretch*); ^{1}H NMR (400 MHz, DMSO) δ 8.09 (2H, d, *J* = 8.3 Hz, C*H* arom), 8.06 (2H, d, *J* = 8.3 Hz, C*H* arom), 7.72 (1H, d, *J* = 8.3 Hz, C*H* arom), 7.62 (1H, d, *J* = 8.4 Hz, C*H* arom), 7.57-7.48 (2H, m, C*H* arom), 7.37-7.28 (2H, m, C*H* arom), 7.23 (1H, d, *J* = 8.5 Hz, C*H* arom), 7.15 (1H, d, *J* = 8.4 Hz, C*H* arom), 4.73 (1H, dd, *J* = 10.5, 5.8 Hz, NC*H*CH_2CO_2H), 4.02 (1H, d, *J* = 12.0 Hz, ArCH_2N), 3.54 (1H, d, *J* = 11.9 Hz, ArCH_2N), 1.74 (1H, dd, *J* = 16.2, 5.8 Hz, CHCH_2CO_2H), 1.37 (1H, dd, *J* = 16.2, 5.8 Hz, CHCH_2CO_2H); ^{13}C NMR (101 MHz, DMSO) δ 135.3, 133.5, 133.4, 133.3, 131.7, 131.6, 129.7, 129.6, 129.4, 129.0, 128.8, 128.1, 126.9, 126.8, 126.7, 126.6,

57.2, 46.6, 38.1; HRMS (CI^+): *m/z* found for $[M+H]^+$: 354.1487; $[C_{24}H_{20}NO_2]^+$ requires 354.1489

2-((3S,11cS)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetic acid 166.HCl



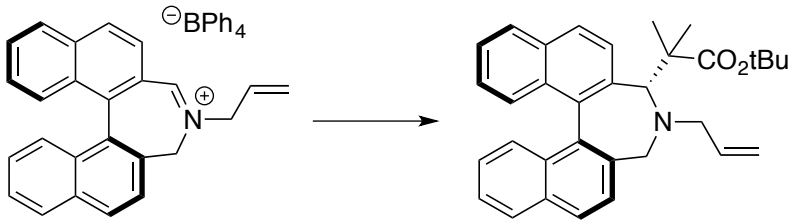
215 **166**.HCl

tert-Butyl 2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetate (481 mg, 1.2 mmol) was dissolved in dichloromethane (20 mL) and trifluoroacetic acid (1.3 mL, 16.4 mmol, 14 equiv.) was added. The reaction was stirred until consumption of the starting material was seen by TLC. A saturated sodium hydrogen carbonate solution was added until the pH of the solution was neutral. The biphasic mixture was transferred to a separating funnel and the organic layer washed using H_2O (10 mL), a saturated brine solution (2 x 10 mL), dried over anhydrous $MgSO_4$. HCl (37%, 3 drops) was added and the solution stirred for 10 min. The solvent was removed under reduced pressure and the residue recrystallized (hot $CHCl_3$) to yield the title compound as a white solid (398 mg, 85%).

m.p. 293-295 °C; $[\alpha]_D^{22.8}$ +378 ° (*c* 0.5, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2916 (*=C-H aromatic stretch, N-H bend*), 2811 (*O-H bend*), 2720, 2433, 1723 (*C=O stretch*), 1587, 1413 (*C=C aromatic stretch, C-H stretch*), 1398, 1289, 1191 (*C-N stretch*), 899 (*O-H bend*); ^{1}H NMR (500 MHz, DMSO) δ 12.46 (1H, s, CO_2H), 10.21 (1H, s, NH.*H*Cl), 9.53 (1H, s, N*H*) 8.21 (2H, dd, *J*= 19.0, 8.4 Hz, C*H* arom), 8.14 (2H, dd, *J*= 13.0, 8.5 Hz, C*H* arom), 7.79 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.72 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.62 (2H, dd, *J*= 15.6, 8.3 Hz, C*H* arom), 7.46-7.34 (2H, m, C*H* arom), 7.26-7.16 (2H, dd, *J*= 13.5, 8.5 Hz, C*H* arom), 5.11 (1H, t, *J*= 7.0 Hz, C*H*CH_2CO_2H), 4.30 (1H, d, *J*= 13.0 Hz, ArCH_2N), 3.78 (1H, d, *J*= 13.0 Hz, ArCH_2N), 1.94 (2H, m, CHCH_2CO_2H); ^{13}C NMR (126 MHz, DMSO) δ 171.3, 135.5, 134.00, 133.98, 133.8, 132.9, 131.6, 131.5, 130.0, 129.78, 129.76, 129.6, 129.1, 128.9, 128.68, 128.67, 127.41, 127.35, 127.1, 127.0, 126.9, 56.6, 46.1, 36.8;

HRMS (NSI$^-$) *m/z* found for $[M-H]^-$: 388.1118; $[C_{24}H_{19}ClNO_2]^-$ requires 388.1110.

Tert-butyl 2-((3R,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate 218



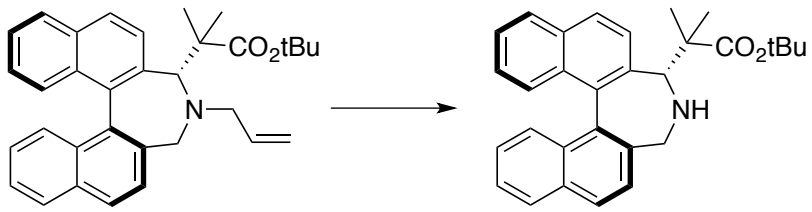
176 **218**

Zinc dust (2.0 g, 30.6 mmol, 10 equiv.) and anhydrous THF (40 mL) were added to a flame-dried nitrogen-purged round-bottom flask. TMSCl (0.4 mL, 3.06 mmol, 1 equiv.) was added and the reaction mixture was heated at reflux for 30 min. tert-Butyl α-bromoisobutyrate (0.57 mL, 3.06 mmol, 1 equiv.) was added and the reaction mixture heated at reflux for a further 30 min. The reaction mixture was cooled to –78 °C. (*S*)-4-Allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium (2.0 g, 3.06 mmol) was dissolved in anhydrous THF (40 mL) in a separate flame-dried one-necked round-bottom flask and transferred into the activated zinc slurry using a cannula. The reaction was stirred for 1 h at –78 °C. tert-Butyl α-isobromobutyrate (5.7 mL, 30.6 mmol, 10 equiv.) was added in small portions over 20 min, maintaining the temperature at –78 °C. The reaction vessel was allowed to reach room temperature and monitored by TLC. The reaction was quenched using a saturated ammonium chloride solution (5 mL), diluted with Et_2O (50 mL) and 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), saturated brine solution (3 x 20 mL), dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified using column chromatography on silica gel (9:1 light petroleum ether/EtOAc) to yield the title compound as a colourless oil (1.1 g, 76%). (NB: inseparable impurities).

$[\alpha]_D^{18.9}$ +102.8 ° (*c* 1.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2977 (*=C-H aromatic stretch*, *=C-H stretch*), 2934, 2872, 1722 (*C=C stretch, C=O stretch*), 1475 (*C=C aromatic*

stretch), 1458 (*C-H stretch*), 1391, 1367, 1254 (*C-O stretch*), 1141 (*C-N stretch*), 1119, 918, 850, 819, 755, 667; 1H NMR (500 MHz, $CDCl_3$) δ 7.89–7.87 (4H, m, C*H* arom), 7.55 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.46–7.39 (3H, m, C*H* arom), 7.37 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.30 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.25–7.20 (1H, m, C*H* arom), 7.20–7.15 (1H, m, C*H* arom), 5.93 (1H, dddd, *J*= 17.1, 10.0, 7.0, 5.6 Hz, NCH_2CHCH_2), 5.23 (1H, dd, *J*= 17.2, 1.6 Hz, NCH_2CHCH_2), 5.13 (1H, dd, *J*= 10.7, 1.4 Hz, NCH_2CHCH_2), 4.54 (1H, s, $CHC(CH_3)_2CO_2tBu$), 3.65 (1H, d, *J*= 11.4 Hz, NCH_2Ar), 3.53–3.44 (2H, m, NCH_2CHCH_2), 3.41 (1H, d, *J*= 11.3 Hz, NCH_2Ar), 1.29 (9H, s, *tBu*), 0.42 (3H, s, CH_3), 0.29 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 136.6, 136.2, 136.1, 135.9, 134.3, 133.2, 133.1, 132.9, 132.3, 128.8, 128.44, 128.37, 128.3, 128.1, 127.9, 127.7, 125.9, 125.7, 125.5, 125.3, 117.3, 80.0, 64.7, 55.2, 51.2, 28.1, 25.3, 24.0, 22.7, 22.5; HRMS (CI^+) *m/z* found for $[M+H]^+$: 478.2735 $[C_{33}H_{36}NO_2]^+$ requires 478.2741.

Tert-butyl 2-((3R,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate 219



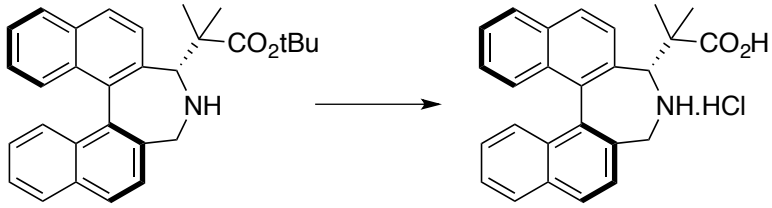
218 **219**

tert-Butyl 2-((3R,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate (1.12 g, 2.3 mmol) was dissolved in anhydrous dichloromethane (70 mL). 1,3-Dimethylbarbituric acid (1.08 g, 6.9 mmol, 3 equiv.) and $Pd(PPh_3)_4$ (0.05 g, 0.046 mmol, 0.02 equiv.) were added and the reaction mixture was heated at reflux overnight or until full consumption of the starting material was observed by TLC. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was redissolved in Et_2O (60 mL) and transferred to a separating funnel. The organic layer was washed with 1M NaOH (2 x 15 mL), H_2O (2 x 20 mL), saturated brine solution (2 x 20 mL) and dried over anhydrous $MgSO_4$.

The solvent was removed under reduced pressure and column chromatography on silica gel (1:1 light petroleum ether/EtOAc) yielded the title compound as a colourless foam (623 mg, 62%).

m.p. 87-89 °C; $[\alpha]_D^{20.1}$ +314.0 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3019 (=*C-H aromatic stretch, N-H bend*), 2980, 2935, 2400, 1710 (*C=O stretch*), 1598, 1509 (*C=C aromatic stretch*), 1437 (*C-H stretch*), 1420, 1366 (*C-O stretch*), 1215 (*C-N stretch*), 1153, 1132, 1031, 928, 849 (*N-H wag*), 819; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (4H, dd, *J*= 8.0, 5.0 Hz, C*H* arom), 7.49 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.45 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.42- 7.38 (2H, m, C*H* arom), 7.26- 7.24 (2H, m, C*H* arom), 7.20 (1H, ddd, *J*= 8.2, 6.7, 1.5 Hz, C*H* arom), 7.15 (1H, ddd, *J*= 8.2, 6.7, 1.5 Hz, C*H* arom), 4.89 (1H, s, C*H*C$(CH_3)_2CO_2$tBu), 3.95 (1H, d, *J*= 12.5 Hz, NCH_2Ar), 3.73 (1H, d, *J*= 12.5 Hz, NCH_2Ar), 1.35 (9H, s, *tBu*), 0.73 (3H, s, CH_3), 0.23 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 138.9, 136.4, 134.8, 134.6, 133.4, 132.9, 132.8, 132.7, 132.4, 128.8, 128.4, 128.1, 127.9, 127.7, 127.5, 126.7, 125.8, 125.7, 125.4, 125.0, 80.1, 70.3, 50.7, 49.4, 28.0, 23.7, 19.6; HRMS (CI^+) *m/z* found for $[M+H]^+$: 438.2424; $[C_{30}H_{32}NO_2]^+$ requires 438.2428.

2-((3R,11cS)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoic acid hydrochloride 216.HCl



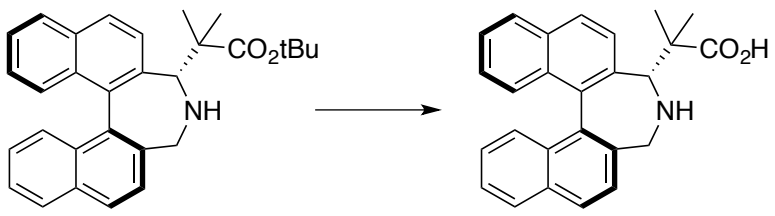
219 **216.HCl**

tert-Butyl 2-((3R,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methyl propanoate (643 mg, 1.47 mmol) was dissolved in dichloromethane (20 mL). Trifluoroacetic acid (1.3 mL, 17.6 mmol, 12 equiv.) was added and the reaction 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 biphasic mixture was transferred to a separating funnel and the organic

layer washed H_2O (15 mL), saturated brine solution (2 x 15 mL), dried over anhydrous $MgSO_4$. The residue was subjected to column chromatography on silica gel (EtOAc). HCl_{aq} (37%, 3 drops) was added and the reaction stirred for 10 min. The solvent was then removed under reduced pressure and the residue was recrystallized (Et_2O and light petroleum ether) to yield the title compound as a colourless solid (469 mg, 76%).

m.p. 222-225 °C; $[\alpha]_D^{22.7}$ +283 ° (*c* 0.5, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3500 (*broad O-H stretch*), 2928 (*=C-H aromatic stretch*), 2833 (*N-H bend*), 2728, 1703 (*C=O stretch*), 1566 (*C=C aromatic stretch*), 1460 (*C-H stretch*), 1189 (*C-O stretch*), 1154, 1134, 1034, 726; ^{1}H NMR (500 MHz, DMSO) δ 13.01 (1H, s, CO_2H), 10.92 (1H, s, NH.*H*Cl), 9.05 (1H, s, N*H*), 8.13 (2H, t, *J*= 8.5 Hz, C*H* arom), 8.07 (2H, dd, *J*= 8.0, 4.5 Hz, C*H* arom), 7.75 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.69 (1H, dd, *J*= 8.0, 3.3 Hz, C*H* arom), 7.59-7.55 (2H, m, C*H* arom), 7.35 (1H, t, *J*= 8.5 Hz, C*H* arom), 7.27 (1H, t, *J*= 8.5 Hz, C*H* arom), 7.15 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.08 (1H, d, *J*= 8.5 Hz, C*H* arom), 5.24 (1H, s, C*H*C$(CH_3)_2CO_2H$), 4.25 (1H, d, *J*= 13.5 Hz, NCH_2Ar), 3.88 (1H, d, *J*= 13.0 Hz, NCH_2Ar), 0.82 (3H, s, CH_3), 0.18 (3H, s, *CH*$_3$); ^{13}C NMR (126 MHz, DMSO) δ 176.6, 135.2, 133.41, 133.35, 133.2, 132.1, 131.6, 131.5, 131.1, 129.5, 129.1, 129.1, 128.9, 128.7, 128.5, 128.2, 127.2, 126.9, 126.7, 126.5, 126.3, 66.5, 47.4, 47.0, 25.0, 19.3; HRMS (NSI$^+$) *m/z* found for $[M\text{-}Cl]^+$: 382.1791; $[C_{26}H_{24}NO_2]^+$ requires 382.1802.

2-((3S,11cS)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoic acid 216



219 **216**

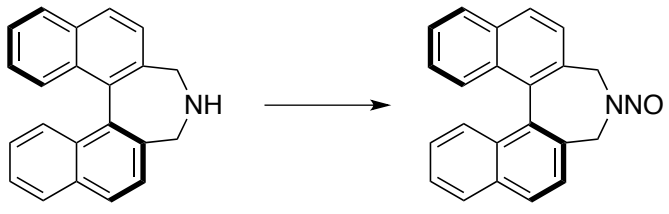
tert-Butyl 2-((3R,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate (300 mg, 0.69 mmol) was dissolved in dichloromethane (20 mL)

and trifluoroacetic acid (0.63 mL, 8.2 mmol, 12 equiv.) was added. The reaction was stirred until consumption of the starting material was seen by TLC. A saturated sodium hydrogen carbonate solution was added until the pH of the solution was neutral. The biphasic mixture was transferred to a separating funnel and the organic layer washed using H_2O (20 mL), a saturated brine solution (2 x 10 mL), dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue subjected to column chromatography (EtOAc). Recrystallization ($CHCl_3$ and light petroleum ether) yielded the title compound as a beige solid (161 mg, 61%).

m.p. 192-194 °C; $[\alpha]_D^{24.9}$ +138.1 °(*c* 0.9, $CHCl_3$); *vmax*(CH_2Cl_2)/cm^{-1} 3400 (*OH broad stretch*), 3054, 2979 (*=C-H aromatic stretch*), 2850 (*N-H bend*), 1673 (*C=O stretch*) , 1598 (*C=C aromatic stretch*), 1470 (*C-H stretch*), 1200 (*C-O stretch*), 1135, 821, 751; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.94 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.89 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.78 (1H, d, *J*= 7.8 Hz, C*H* arom), 7.58 (5H, d, *J*= 8.1 Hz, C*H* arom), 7.56-7.46 (3H, m, C*H* arom), 7.26-7.30 (2H, m, C*H* arom), 7.24-7.17 (2H, m, C*H* arom), 5.35 (5H, s), 4.39 (2H, d, *J* = 12.9 Hz), 4.09 (2H, d, *J* = 12.8 Hz), 1.16 (3H, s), 0.01 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.6, 136.1, 133.9, 133.9, 133.6, 132.9, 132.4, 131.7, 131.8, 129.6, 129.4, 129.2, 128.7, 128.1, 128.0, 127.6, 127.5, 126.8, 126.6, 126.3, 126.1, 77.2, 67.8, 47.2, 27.6, 26.6; HRMS (CI^+) *m/z* found for $[M+H]^+$: 382.1803; $[C_{26}H_{24}NO_2]^+$ requires 382.1802.

3.0 Synthesis of α-amino acid derivatives

(*S*)-4-Nitroso-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 228[9]



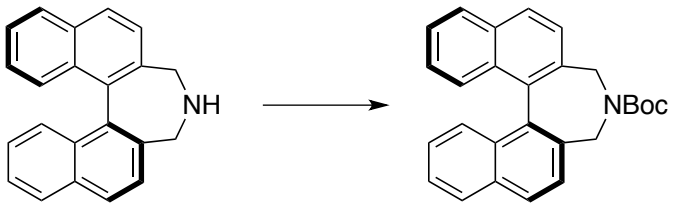
129 **228**

(*S*)-4,5-Dihydro-3H-4-aza-cyclohepta[2,1-a;3,4-a']dinaphthalene (800 mg, 2.71 mmol) was dissolved in acetic acid (28 mL). $NaNO_2$ (561 mg, 8.13 mmol, 3 equiv.)

in H_2O (8 mL) was added and the reaction mixture was stirred for 2 h at room temperature or until full consumption of the starting material was seen by TLC. The reaction mixture was poured into an ice bath-cooled flask cooled and a solution of NaOH (10M, 10 mL) was added and the mixture transferred to a separating funnel. Toluene (2 x 30 mL) was added and the organic layers washed with H_2O (3 x 30 mL), saturated brine solution (2 x 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield the title compound as a foamy pale yellow solid (660 mg, 75%).

m.p. 57-59 °C (Lit 57-58 °C)[9]; $[\alpha]_D^{22.7}$ −197.0 °[(*c* 1.00 $CHCl_3$); Lit $[\alpha]_D^{25}$ −212.3 ° (c 0.68, $CHCl_3$)][9]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*C=H aromatic stretch*), 2987, 2685, 2410, 2305, 1596, 1556 (*N-O stretch*), 1422 (*=C-H stretch, C-H bend*), 1323 (*C-H stretch*), 1345 (*N-O stretch*), 1265, 1127 (*C-N stretch*), 896; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90-7.80 (4H, m, C*H* arom), 7.53 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.43-7.34 (3H, m, C*H* arom), 7.30 (1H, d, *J*= 8.7 Hz, C*H* arom), 7.19-7.13 (2H, m, C*H* arom), 7.05 (1H, d, *J* = 7.2 Hz, C*H* arom), 5.56 (1H, d, *J*= 13.5 Hz), 5.52 (1H, d, *J*= 15.3 Hz), 4.57 (1H, d, *J*= 13.5 Hz), 3.50 (1H, d, *J*= 15.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 134.4, 133.7, 133.5, 131.7, 131.7, 131.4, 130.4, 129.9, 129.5, 128.5, 128.5, 127.7, 127.5, 127.4, 126.6, 126.6, 126.5, 126.5, 54.5, 47.2.

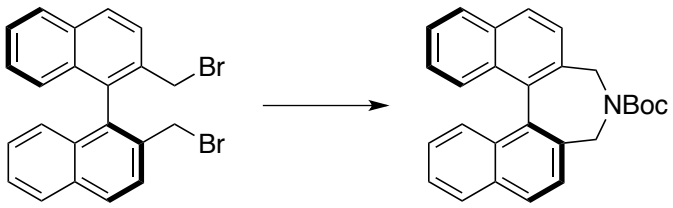
(*S*)-Tert-butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate 233[10,11]



129 **233**

(*S*)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine (1.32 g, 4.5 mmol) was dissolved in warmed *t*-BuOH (30 mL). Di-*tert*-butyl dicarbonate (1.02 g, 4.7 mmol, 1.05 equiv.) in a solution of *t*-BuOH (10 mL) was added and the solution was stirred at room temperature for 3 h. A further portion of di-*tert*-butyl dicarbonate (0.12 equiv.) was added and the solution was stirred until full consumption of the starting material was seen by TLC. The solvent was removed under reduced pressure and the residue redissolved in EtOAc and the organic layer washed with H_2O (2 x 20 mL), saturated brine solution (20 mL), dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield the product as a pale yellow solid; no further purification was required (1.65 g, 92%).

Alternative synthesis:



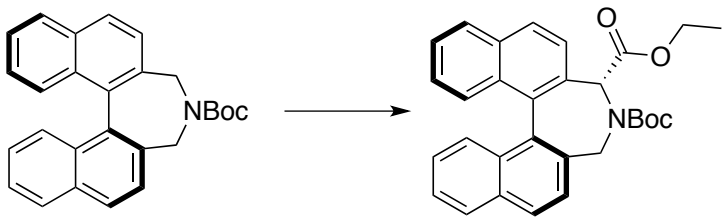
169 **233**

(*S*)-2,2'-Bis-bromomethyl-[1,1']binaphthalene (600 mg, 1.36 mmol) was dissolved in anhydrous DMF (30 mL). The pale 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 in small portions. 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 (10 mL) at 0 °C and the majority of the solvent was removed under reduced pressure. Et_2O (100 mL) was added to the

mixture and the organic layer washed with H_2O (5 x 20 mL), saturated brine solution (3 x 20 mL), and dried over anhydrous $MgSO_4$. Recrystallization (hot acetone) yielded the title compound as a colourless solid (469 mg, 87%).

m.p. 219- 221 °C; $[\alpha]_D^{22.5}$ −7.0 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3057 (=*C-H aromatic stretch*), 2979, 2933, 2253, 1819, 1682 (*C=O stretch*), 1508 (*C=C aromatic stretch*), 1464(*C-H stretch*), 1405, 1367, 1275 (*C-O stretch*), 1252, 1219 (*C-N stretch*), 1163, 1106, 908, 867, 819; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.91 (4H, m, C*H* arom), 7.60 (2H, d, *J*= 8.0 Hz, C*H* arom), 7.47 (2H, ddd, *J*= 8.0, 7.0, 1.0 Hz, C*H* arom), 7.43 (2H, d, *J*= 8.5 Hz, C*H* arom), 7.26 (2H, ddd, *J*= 8.5, 7.0, 1.0 Hz, C*H* arom), 4.93 (2H, br s), 3.65 (2H, d, *J*= 13.0 Hz), 1.51 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 135.0, 133.33, 133.28, 131.5, 129.2, 128.3, 127.51, 127.47, 126.0, 125.8, 85.2, 80.0, 28.6, 27.4; HRMS (NSI^+) *m/z* found 396.1955 $[M+H]^+$; $[C_{27}H_{25}NO_2+H]^+$ requires 396.158.

(3R,11cS)-4-Tert-butyl 3-ethyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)-dicarboxylate 236



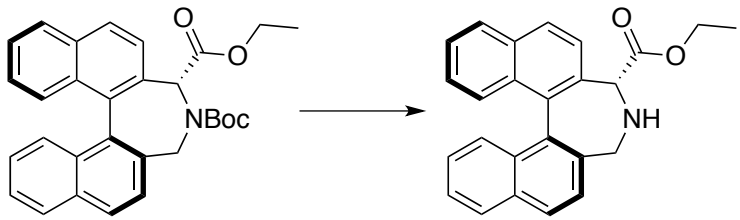
233 **236**

(*S*)-Tert-butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate (200 mg, 0.51 mmol) was dissolved in anhydrous Et_2O (20 mL) and cooled to −78 °C. *sec*-BuLi (0.47 mL, 0.66 mmol, 1.3 equiv., 1.4 M solution in cyclohexane) was added dropwise; the pale yellow solution instantly turned black on addition. The solution was stirred at −78 °C for 1 h. Ethyl chloroformate (0.15 mL, 1.53 mmol, 3 equiv.) was added in one portion causing the solution to turn from black to bright yellow. The reaction was allowed to reach room overnight, or until full consumption of the starting material was seen by TLC. The reaction was quenched with saturated ammonium chloride solution (10 mL) at 0 °C. The organic layers were washed with H_2O (3 x 10 mL), saturated brine solution (3 x 10 mL), dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure. Column chromatography on silica gel (7:3 light petroleum ether/EtOAc) yielded the title compound as a colourless solid (174 mg, 73%).

m.p. 101-103 °C; $[\alpha]_D^{22.1}$ −17.6 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3052 (=*C-H aromatic stretch*), 2976, 2931, 1748 (*C=O stretch*), 1695 (*C=O stretch*), 1508 (*C=C aromatic stretch*), 1475, 1461 (*C-H stretch*), 1392, 1366, 1297, 1252 (*C-N stretch*), 1243 (*C-O stretch*), 1217, 1164, 1155, 1107, 1027, 945, 911, 897, 864, 825, 814; ^{1}H NMR (500 MHz, DMSO at 360 K) δ 8.14 (1H, d, *J*= 8.3 Hz, C*H* arom), 8.09 (1H, d, *J*= 8.2 Hz, C*H* arom), 8.05 (1H, d, *J*= 8.4 Hz, C*H* arom), 8.01 (1H, d, *J*= 8.1 Hz, C*H* arom), 7.79 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.62 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.56 (1H, ddd, *J*= 8.1, 6.7, 1.2 Hz, C*H* arom), 7.50 (1H, ddd, *J*= 8.1, 6.8, 1.1 Hz, C*H* arom), 7.37-7.25 (3H, m, C*H* arom), 7.18 (1H, d, *J*= 8.5 Hz, C*H* arom), 5.82 (1H, s, C*H*CO_2Et), 5.13 (1H, *br* s, NCH_2Ar), 3.59 (1H, *br* s, NCH_2Ar), 2.94-2.85 (1H, m, $CO_2CH_2CH_3$), 2.55-2.53 (1H, *dis* m, $CO_2CH_2CH_3$), 1.52 (9H, s, tBu), 0.46 (3H, t, *J*= 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (126 MHz, DMSO at 360 K) δ 169.5, 153.9, 134.4,

134.2, 134.0, 133.7, 133.5, 133.4, 131.6, 129.8, 129.7, 129.2, 128.8, 128.6, 128.3, 127.1, 127.1, 126.71, 126.68, 126.4, 126.2, 80.4, 62.0, 60.6, 28.6, 13.5; HRMS (NSI^+) *m/z* found 468.2165 $[M+H]^+$; $[C_{30}H_{29}NO_4+H]^+$ requires 468.2169.

(3R,11cS)-Ethyl 4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylate 238

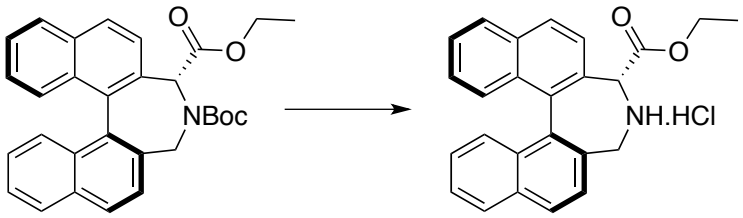


236 **238**

(3R,11cS)-4-Tert-butyl 3-ethyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)-dicarboxylate (90 mg, 0.2 mmol) was dissolved in dichloromethane (5 mL). Trifluoroacetic acid (0.2 mL, 2.8 mmol, 14 equiv.) was added and the reaction mixture was stirred until consumption of the starting material was seen by TLC. Saturated sodium hydrogen carbonate solution was added until the pH of the solution was neutral. The solvent was removed reduced pressure and the residue redissolved in EtOAc (5 mL). The organic layer was then washed with H_2O (3 x 5 mL), saturated brine solution (3 x 5 mL) and dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. Purified by column chromatography on silica gel (EtOAc), which gave product as a yellow oil (60 mg, 81%).

$[\alpha]_D^{23.1}$ +386.0 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3583 (*N-H bend*), 2980 (=*C-H aromatic stretch*), 2253, 1742 (*C=O stretch*), 1710, 1394 (*C=C aromatic stretch*), 1366 (*C-H stretch*), 1222 (*C-N stretch*), 1156, 1109 (*C-O stretch*), 1027, 909 (*N-H wag*), 826; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.98–7.91 (2H, m, C*H* arom), 7.89 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.63 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.51-7.44 (2H, m, C*H* arom), 7.44–7.34 (3H, m, C*H* arom), 7.29-7.20 (2H, m, C*H* arom), 4.59 (1H, s, NC*H*CO_2Et), 3.83 (1H, d, *J*= 13.5 Hz, ArCH_2N), 3.55 (1H, d, *J*= 13.5 Hz, ArCH_2N), 3.36 (1H, s, N*H*), 3.22 (1H, dq, *J*= 10.7, 7.1 Hz, $CO_2CH_2CH_3$), 2.58 (1H, dq, *J*= 10.7, 7.2 Hz, $CO_2CH_2CH_3$), 0.49 (3H, t, *J*= 7.5 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 137.5, 134.9, 134.0, 133.4, 133.3, 132.9, 131.60, 131.57, 129.6, 129.0, 128.8, 128.34, 128.28, 127.4, 127.2, 126.9, 125.98, 125.95, 125.9, 125.4, 62.5, 61.1, 48.5, 13.3; HRMS (ESI^+) *m/z* found 368.1645 $[M+H]^+$; $[C_{25}H_{21}NO_2+H]^+$ requires 368.1645.

(3R,11cS)-Ethyl 4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylate hydrochloride 238.HCl

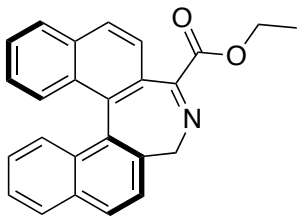


236 **238**.HCl

(3R,11cS)-4-Tert-butyl 3-ethyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)-dicarboxylate (300 mg, 0.64 mmol) was dissolved in acetone (30 mL) and concentrated HCl (3 drops) was added. The reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. Recrystallization (Et_2O and light petroleum ether) yielded the title compound as a yellow solid (260 mg, *quant.*).

m.p.* 219-221 °C (*decomp); $[\alpha]_D^{22.6}$ +340 ° (*c* 1.03, $CHCl_3$); ν_{max}(solid)/cm^{-1} 3394 (*N-H bend*), 2928 (*=C-H aromatic stretch*), 2661, 1736 (*C=O stretch*), 1671, 1595, 1545, 1443 (*C=C aromatic stretch*), 1369 (*C-H stretch*), 1299 (*C-O stretch*), 1236 (*C-N stretch*), 1195, 1055, 1027, 961 (*N-H wag*), 897, 820, 796, 749, 705, 624; ^{1}H NMR (500 MHz, DMSO) δ 10.99 (1H, s, NH.*H*Cl), 9.42 (1H, s, N*H*.HCl), 8.02 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.94 (2H, dd, *J*= 8.3, 4.8 Hz, C*H* arom), 7.88 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.58 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.48 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.45-7.40 (1H, m, C*H* arom), 7.37 (1H, t, *J*= 7.5 Hz, C*H* arom), 7.24-7.14 (2H, m, C*H* arom), 7.03 (1H, d, *J*= 8.6 Hz, C*H* arom), 6.96 (1H, d, *J*= 8.5 Hz, C*H* arom), 5.63 (1H, s, ArC*H*CO_2Et), 4.14 (1H, d, *J*= 13.5 Hz, ArCH_2NH), 3.46 (1H, d, *J*= 13.0 Hz, ArCH_2NH), 3.03 (1H, dq, *J*= 10.8, 7.1 Hz, $CO_2CH_2CH_3$), 2.38 (1H, dq, *J*= 10.8, 7.1 Hz, $CO_2CH_2CH_3$), 0.16 (3H, t, *J*= 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (126 MHz, DMSO) δ 167.3, 134.1, 133.6, 133.4, 130.7, 130.6, 129.9, 129.7, 129.5, 129.2, 129.1, 128.5, 128.0, 127.1, 126.8, 126.8, 126.7, 126.6, 126.5, 61.8, 58.7, 45.4, 12.8; HRMS (ESI^+) *m/z* found 368.1645 $[M-Cl]^+$; $[C_{25}H_{22}NO_2]^+$ requires 368.1645.

Side product (trace): (S)-Ethyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-5-carboxylate 240

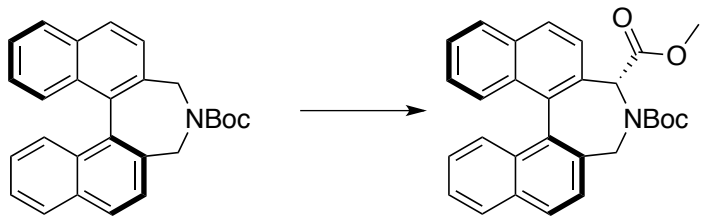


240

Trace amount isolated.

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (=*C-H aromatic stretch*), 2960, 2925, 2853, 1720 (*C=O stretch*), 1609 (*C=N stretch*), 1596, 1506 (*C=C aromatic stretch*), 1367 (*C-H stretch*), 1304, (*C-O stretch*) 1218, 1190 (*C-N stretch*), 1093, 1053, 1029, 866, 821; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1H, d, *J*= 6.6 Hz, C*H* arom), 7.97 (1H, d, *J*= 5.7 Hz, C*H* arom), 7.93 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.90 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.77 (1H, d, *J*= 8.6 Hz), 7.69 (1H, d, *J*= 8.3 Hz), 7.55 (1H, ddd, *J*= 8.1, 6.8, 1.1 Hz, C*H* arom), 7.50 (1H, d, *J*= 8.6 Hz, C*H* arom), 7.42 (1H, ddd, *J*= 8.1, 6.8, 1.1 Hz, C*H* arom), 7.32 (1H, d, *J*= 8.6 Hz, C*H* arom), 7.28 (1H, ddd, *J*= 8.5, 6.8, 1.2 Hz, C*H* arom), 7.20 (1H, ddd, *J*= 8.5, 6.8, 1.2 Hz, C*H* arom), 5.11 (1H, d, *J*= 10.1 Hz, NCH_2), 4.35 (2H, m, $CO_2CH_2CH_3$), 3.99 (1H, d, *J*= 10.1 Hz, NCH_2), 1.36 (3H, t, *J*= 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5 (N=*C*), 160.6 (*C*O_2Et), 140.9, 137.9, 133.3, 133.0, 132.7, 131.1, 130.9, 130.6, 129.1, 128.9, 128.3, 128.3, 127.8, 127.6, 127.4, 126.3, 126.03, 125.96, 125.5, 124.5, 62.3, 56.5, 14.2; HRMS (NSI^+) *m/z* found 366.1486 $[M+H]^+$; $[C_{25}H_{19}NO_2+H]^+$ requires 366.1489.

(3R,11cS)-4-Tert-butyl 3-methyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)-dicarboxylate 237



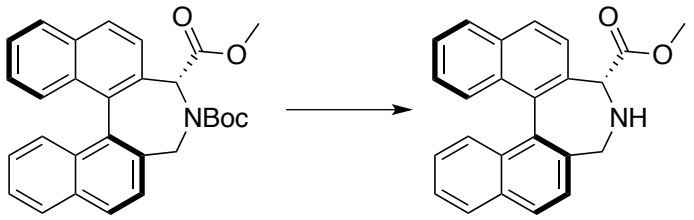
233 **237**

(*S*)-Tert-butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate (900 mg, 2.3 mmol) was dissolved in anhydrous Et_2O (50 mL). The solution was cooled to −78 °C and *sec*-BuLi (2.3 mL, 3.0 mmol, 1.3 equiv., 1.3 M in cyclohexane) was added dropwise causing the pale yellow solution to turn black. The solution was stirred at -78 °C for 1 h then methyl chloroformate (0.53 mL, 6.8 mmol, 3 equiv.) was added causing the solution to turn bright yellow. The reaction was allowed to reach room temperature over 12 h, or until consumption of the starting material was seen by TLC, and quenched with saturated ammonium chloride solution (5 mL) at 0 °C. The organic layer was washed with H_2O (2 x 20 mL), saturated brine solution (2 x 10 mL) and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The title compound was isolated using column chromatography on silica gel (9:1 light petroleum ether/EtOAc) as a colourless fluffy solid (845 mg, 81%).

m.p. 124-126 °C; $[\alpha]_D^{22.6}$ −20.8 ° (*c* 0.5, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3053 (=*C-H aromatic stretch*), 2975, 2946, 2884, 1751 (*C=O stretch*), 1696 (*C=O stretch*), 1508 (*C=C aromatic stretch*), 1456, 1392, 1366 (*C-H stretch*), 1296 (*C-O stretch*), 1164 (*C-N stretch*), 960, 823; ^{1}H NMR (500 MHz, DMSO at 380 K) δ 8.13 (1H, d, *J*= 8.3 Hz, C*H* arom), 8.08 (1H, d, *J*= 8.2 Hz, C*H* arom), 8.04 (1H, d, *J*= 8.3 Hz, C*H* arom), 8.01 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.76 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.60 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.56 (1H, ddd, *J*= 8.1, 6.6, 1.3 Hz, C*H* arom), 7.51 (1H, ddd, *J*= 8.1, 6.8, 1.1 Hz, C*H* arom), 7.37-7.32 (1H, m, C*H* arom), 7.32–7.28 (2H, m, C*H* arom), 7.19 (1H, d, *J*= 8.5 Hz, C*H* arom), 5.85 (1H, s, C*H*CO_2Me), 5.10 (1H, d, *J*= 13.3 Hz, CH_2), 3.61 (1H, d, *J*= 13.4 Hz, CH_2), 2.54 (3H, s, CO_2CH_3), 1.50 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (126 MHz, DMSO at 380 K) δ 169.9, 153.9, 134.5, 134.3, 134.2, 133.7, 133.6, 133.5, 131.63, 131.58, 129.8, 129.7, 128.9, 128.7, 128.6, 128.3, 127.1, 126.9, 126.73, 126.67, 126.4, 126.2, 80.5, 79.6, 51.2, 28.7, 28.6; HRMS

(ESI$^+$) *m/z* found 476.1832 $[M+Na]^+$; $[C_{27}H_{27}NO_4Na]$ requires 476.183.

(3R,11cS)-Methyl 4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylate 239



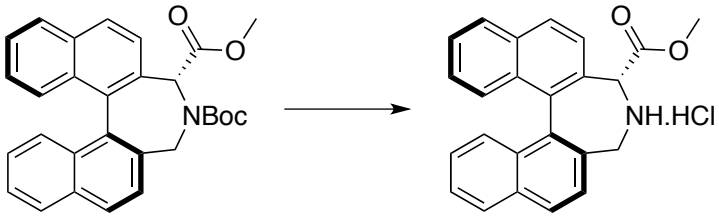
237 **239**

(3R,11cS)-4-Tert-butyl 3-methyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)-dicarboxylate (600 mg, 1.32 mmol) was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (1.4 mL, 18.5 mmol, 14 equiv.) was added. The solution was stirred for 30 min after which time the pH was neutralised by addition of saturated solution of sodium hydrogen carbonate. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (30 mL). The organic layer was then washed with H_2O (3 x 20 mL), saturated brine solution (3 x 20 mL), dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The brown residue was then recrystallized ($CHCl_3$ and light petroleum ether) to yield the title compound (364 mg, 78%).

m.p. 214-216 °C; $[\alpha]_D^{21.4}$ +420 ° (*c* 1.03, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3318 (*N-H bend),* 3050 (*=C-H aromatic stretch*), 2947, 2874, 1730 (*C=O stretch*), 1508 (*C=C stretch*), 1448 (*C-H stretch*), 1432 (*C-O stretch*), 1223, 1207 (*C-N stretch*), 1110, 992, 866 (*N-H wag*), 822; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.97-7.93 (2H, m, C*H* arom), 7.91 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.64 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.52-7.47 (2H, m, C*H* arom), 7.44-7.42 (2H, m, C*H* arom), 7.36 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.28 (1H, d, *J*= 7.6 Hz, C*H* arom), 7.24 (1H, d, *J*= 7.5 Hz, C*H* arom), 4.62 (1H, s, C*H*CO_2Me), 3.84 (1H, d, *J*= 14.0 Hz, ArCH_2N), 3.57 (1H, d, *J*= 13.7 Hz, ArCH_2N), 2.49 (3H, s, CO_2*Me*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 137.4, 135.0, 133.7, 133.4, 133.3, 132.9, 131.5, 131.4, 129.7, 129.1, 128.4,

128.34, 128.29, 127.3, 127.0, 126.8, 126.1, 126.0, 125.9, 125.5, 62.2, 51.6, 48.4; HRMS (ESI^+) *m/z* found 354.1479 $[M+H]^+$; $[C_{24}H_{19}NO_2+H]^+$ requires 354.1489.

(3R,11cS)-Methyl 4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylate hydrochloride 239.HCl

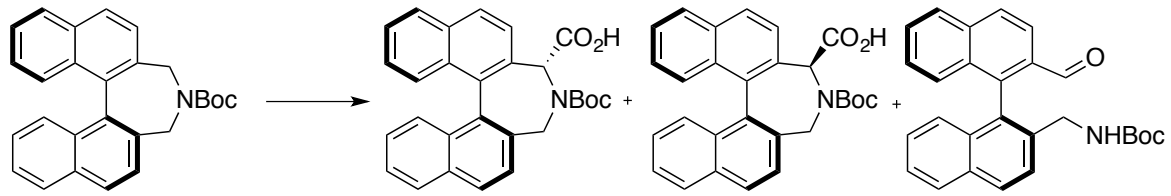


237 **239**.HCl

(3R,11cS)-4-Tert-butyl 3-methyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-3,4(5H)-dicarboxylate (258 mg, 0.57 mmol) was dissolved in acetone (30 mL) and concentrated HCl (3 drops) was added. The reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The product was isolated by recrystallization (MeOH and Et_2O) to give a biege solid (222 mg, *quant.*).

m.p. 220-230 °C; $[\alpha]_D^{21.4}$ + 296.0 ° (*c* 1.00, $CHCl_3$); ν_{max}(solid)/cm^{-1} 3406 (*N-H bend*), 3053 (*=C-H aromatic stretch*), 2950, 2673, 1746 (*C=O stretch*), 1596, 1508 (*C=C aromatic stretch*), 1439 (*C-H stretch*), 1371, 1248 (*C-N stretch*), 1212 (*C-O stretch*), 1058, 864, 822; ^{1}H NMR (500 MHz, DMSO) δ 9.67 (1H, s), 8.26 (1H, d, *J*= 8.0 Hz, C*H* arom), 8.17-8.15 (2H, m, C*H* arom), 8.12 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.81 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.71 (1H, d, *J*= 8.3 Hz, C*H* arom), 7.65 (1H, ddd, *J*= 8.0, 6.6, 1.0 Hz, C*H* arom), 7.61 (1H, ddd, *J*= 8.1, 6.8, 1.0 Hz, C*H* arom), 7.42-7.37 (2H, m, C*H* arom), 7.27 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.16 (1H, d, *J*= 8.5 Hz, C*H* arom), 5.86 (1H, s, C*H*CO_2Me), 4.36 (1H, d, *J*= 13.2 Hz, ArCH_2N), 3.70 (1H, d, *J*= 13.2 Hz, ArCH_2N), 2.45 (3H, s, CO_2*Me*); ^{13}C NMR (126 MHz, DMSO) δ 167.8, 134.2, 134.1, 133.6, 133.4, 130.74, 130.66, 130.5, 130.0, 129.9, 129.5, 129.2, 128.8, 128.5, 127.9, 127.1, 126.9, 126.8, 126.5, 126.3 58.6, 52.0, 45.4; HRMS (NSI^+) *m/z* found for $[M-Cl]^+$: 354.1488; $[C_{24}H_{20}NO_2]^+$ requires 354.1489.

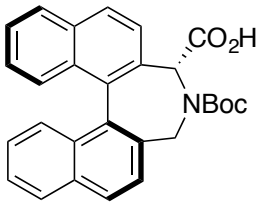
(11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid synthesis



233 **247** **248** **249**

(*S*)-Tert-butyl 3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carboxylate (500 mg, 1.26 mmol) was dissolved in anhydrous Et_2O (30 mL). The reaction mixture was cooled to −78 °C. A positive pressure of argon was continuously bubbled over the reaction as *sec*-Buli (1.2 mL, 1.6 mmol, 1.3 equiv., 1.4 M solution in cyclohexane) was added, causing the solution to turn from a pale yellow solution to a black colour. The reaction was stirred at −78 °C for 1 h. CO_2 gas was bubbled directly into the solution via drying tube filled with $CaCl_3$. The reaction mixture was stirred overnight at −78 °C under an atmosphere of argon. The reaction was quenched at 0 °C with ammonium chloride (10 mL) and EtOAc (20 mL) was added. The organic layers were washed with H_2O (2 x 20 mL), saturated brine solution (2 x 20 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure.

1st eluting diastereoisomer:
(3R,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid 247



247

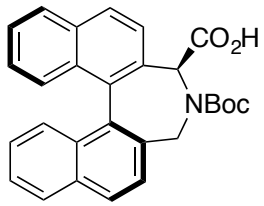
Eluted using column chromatography on silica gel (4:1 light petroleum ether/EtOAc). Title compound isolated as a colourless solid (188 mg, 34%).

m.p. 164-167 °C; $[\alpha]_D^{23.9}$ −47.2 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3056 (*O-H stretch*, *=C-H aromatic stretch*), 2976 (*O-H stretch*), 2937, 1754, 1694 (*C=C*

aromatic stretch, C=O stretch), 1393, 1367 (*C-H stretch*), 1303 (*C=O stretch*), 1245 (*C-N stretch*), 1156, 912 (*O-H bend*), 819, 749; ^{1}H NMR (500 MHz, DMSO, VT at 363 K) δ 8.07 (1H, d, *J*= 8.7 Hz, C*H* arom), 8.02 (1H, d, *J*= 8.7 Hz, C*H* arom), 7.98–7.94 (2H, m, C*H* arom), 7.70 (1H, d, *J*= 8.6 Hz, C*H* arom), 7.57 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.49 (1H, ddd, *J*= 8.1, 6.8, 1.5 Hz, C*H* arom), 7.44 (1H, ddd, *J*= 8.1, 6.8, 1.5 Hz, C*H* arom), 7.25 (2H, m, C*H* arom), 7.20-7.15 (2H, m, C*H* arom), 5.72 (1H, s, C*H*CO_2H), 5.07 (1H, d, *J*= 15.5 Hz, NCH_2Ar), 3.56 (1H, d, *J*= 15.5 Hz, NCH_2Ar), 1.45 (9H, s, *tBu*); ^{13}C NMR (126 MHz, DMSO, VT at 363 K) δ 170.5, 154.0, 134.3, 133.5, 131.8, 131.7, 129.5, 129.4, 128.7, 128.6, 128.4, 127.4, 127.2, 126.5, 126.2, 126.0, 80.2, 62.1, 47.4, 28.7.; HRMS (NSI$^+$) *m/z* found for [M+H]$^+$: 440.1854; [$C_{28}H_{25}NO_4$+H]$^+$ requires 440.1856.

2nd eluting diastereoisomer:

(3S,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid 248



248

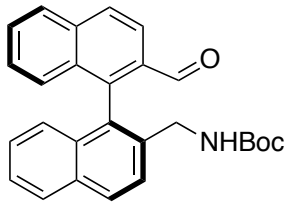
Purified using column chromatography on silica gel (EtOAc), isolated as a colourless solid (170 mg, 31%).

m.p. 255-257 °C; $[\alpha]_D^{23.9}$ +58.4 ° (*c* 1.00, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3052 (=*C-H aromatic stretch, O-H stretch*), 3006, 2976, 2927, 1751 (*C=O stretch*), 1725, 1696 (*C=C aromatic stretch, C=O stretch*), 1395, 1367 (*C-H stretch*), 1251 (*C-N stretch*), 1219, 1151, 820 (*O-H bend*), 772, 759, 677; ^{1}H NMR (500 MHz, DMSO, VT NMR at 353 K) δ 8.07 (2H, d, *J*= 8.3 Hz, C*H* arom), 8.02 (2H, dd, *J*= 11.6, 8.3 Hz, C*H* arom), 7.66 (1H, d, *J*= 9.0 Hz, C*H* arom), 7.58 (1H, d, *J*= 9.0 Hz, C*H* arom), 7.52-7.48 (2H, m, C*H* arom), 7.35-7.31 (2H, m, C*H* arom), 7.27-7.24 (1H, m, C*H* arom), 7.16 (1H, d, *J*= 8.7 Hz, C*H* arom), 4.95 (1H, d, *J* =15.0 Hz, NCH_2Ar), 4.36 (1H, s, C*H*CO_2H), 3.55 (1H, d, *J* =15.0 Hz, NCH_2Ar), 1.40 (9H, s, *tBu*); ^{13}C NMR (126

MHz, DMSO, VT NMR at 353 K) δ 171.4, 155.75, 136.3, 135.1, 133.5, 133.4, 132.6, 132.3, 131.7, 131.5, 129.8, 129.2, 128.9, 128.7, 127.21, 127.16, 126.8, 126.8, 126.7, 126.3, 126.1, 125.2, 81.1, 62.7, 48.7, 28.4; HRMS (NSI^+) *m/z* found for $[M+H]^+$: 440.1852; $[C_{28}H_{25}NO_4+H]^+$ requires 440.1856.

Side product:

(*S*)-Tert-butyl ((2'-formyl-[1,1'-binaphthalen]-2-yl)methyl)carbamate

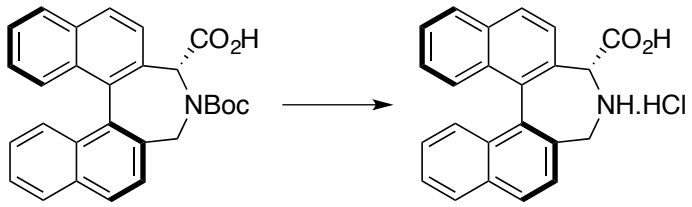


249

Eluted first in on silica gel (4:1 light petroleum ether/EtOAc) as colourless oil (69 mg, 13%).

$[\alpha]_D^{23.7}$ +6.0 ° (*c* 0.5, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3355 (*N-H bend*), 3059 (*=C-H aromatic stretch*), 3008, 2977, 2930, 2867 (*H-C=O stretch*), 1762 (*C=O stretch*), 1690 1594, 1508 (*C=C aromatic stretch*), 1457 (*C-H stretch*), 1429, 1391, 1366, 1324, 1230 (*C-N stretch*), 1168, 1027, 865 (*N-H wag*), 821; ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (1H, s, C*H*O), 8.16 (1H, d, *J*= 8.6 Hz, C*H* arom), 8.04 (2H, dd, *J*= 8.5, 5.7 Hz, C*H* arom), 7.98 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.94 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.72 (1H, d, *J*= 8.6 Hz, C*H* arom), 7.60 (1H, ddd, *J*= 1.0, 6.8, 7.9 Hz, C*H* arom), 7.46 (1H, ddd, *J*= 7.9, 6.8, 1.0 Hz, C*H* arom), 7.33 (1H, ddd, *J*= 7.9, 6.8, 1.0 Hz, C*H* arom), 7.27-7.22 (2H, m, C*H* arom), 7.01 (1H, d, *J*= 8.5, 0.6 Hz C*H* arom), 4.57 (1H, s), 4.02 (2H, d, *J*= 5.9 Hz), 1.36 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.0, 155.6, 142.7, 136.4, 136.2, 133.6, 132.6, 132.2, 130.9, 129.4, 129.2, 129.1, 128.6, 128.1, 127.5, 127.0, 126.8, 126.2, 125.9, 122.3, 79.5, 42.8, 29.4, 28.3; HRMS (NSI^+) *m/z* found 412.1907 $[M+H]^+$; $[C_{27}H_{25}NO_3+H]^+$ requires 412.1907.

(3R,11cS)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid hydrochloride 250.HCl

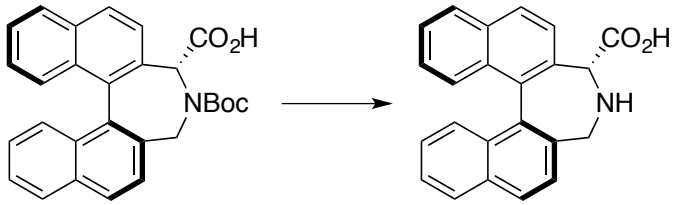


247 **250**.HCl

(3R,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid (230 mg, 0.52 mmol) was dissolved in acetone (20 mL) and concentrated HCl (3 drops) was added. The reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The product was isolated by recrystalization (MeOH and light petroleum ether) to give a pale yellow solid (197 mg, *quant*.)

m.p. 265-267 °C; $[\alpha]_D^{21.5}$ +294 ° (*c* 1.00, MeOH); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3019 (=*C-H aromatic stretch, O-H stretch, N-H stretch*), 2400, 1741 (*C=O stretch*), 1528 (*C=C stretch, C-H stretch*), 1425, 1215 (*C-N stretch, =C-O stretch*), 928, 757, 669 (*N-H wag*), 625; ^{1}H NMR (500 MHz, DMSO) δ 13.26 (1H, s, CO_2H), 11.10 (1H, s, NH.*H*Cl), 9.43 (1H, s, N*H*), 8.23 (1H, d, *J*= 8.4 Hz, C*H* arom), 8.15 (2H, dd, *J*= 8.3, 3.7 Hz, C*H* arom), 8.09 (1H, d, *J*= 8.2 Hz, C*H* arom), 7.80 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.71 (1H, d, *J*= 8.4 Hz, C*H* arom), 7.66-7.54 (2H, m, C*H* arom), 7.43-7.34 (2H, m, C*H* arom), 7.18 (2H, t, *J*= 8.0 Hz, C*H* arom), 5.71 (1H, s, C*H*CO_2H), 4.34 (1H, d, *J*= 13.1 Hz, CH_2), 3.67 (1H, d, *J*= 13.1 Hz, CH_2); ^{13}C NMR (126 MHz, DMSO) δ 168.9, 134.7, 134.6, 134.0, 132.2, 131.34, 131.25, 130.2, 129.9, 129.8, 129.68, 129.65, 129.6, 129.0, 128.9, 128.4, 127.4, 127.3, 127.2, 127.1, 127.0, 59.4, 46.0; HRMS (NSI$^+$) *m/z* found 340.1333 $[M-Cl]^+$; $[C_{23}H_{18}NO_2-Cl]^+$; requires 340.1332.

(3R,11cS)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid 250

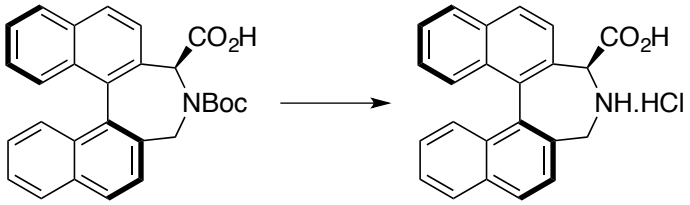


247 **250**

(3R,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid (1.55g, 3.53 mmol) was dissolved in dichloromethane (30 mL) and trifluoroacetic acid (3.8 mL, 49.4 mmol, 14 equiv.) was added. The solution was stirred for 30 min after which time the pH was neutralised by addition of saturated solution of sodium hydrogen carbonate. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (30 mL). The organic layer was then washed with H_2O (3 x 20 mL), saturated brine solution (3 x 20 mL), dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The residue was then recrystallized ($CHCl_3$ and light petroleum ether) to yield the title compound (983 mg, 82%).

m.p. 269-271 °C; $[\alpha]_D^{24.5}$ +272.8 ° (*c* 1.00, $CHCl_3$); ν_{max}(solid)/cm^{-1} 3400 (*O-H stretch*), 3067 (*N-H bend*), 2926 (*=C-H aromatic stretch*), 2876, 2521, 1722 (*C=O stretch*), 1670, 1367 (*C-H stretch*), 1367, 1194 (*C-N stretch*), 1139, 820 (*O-H bend*), 749 (*N-H wag*); ^{1}H NMR (500 MHz, DMSO) δ 8.21 (1H, d, *J*= 8.0 Hz, C*H* arom), 8.13 (2H, dd, *J*= 8.0, 2.0 Hz, C*H* arom), 8.08 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.77 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.69 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.60 (2H, dt, *J*= 15.9, 7.5, C*H* arom), 7.37 (2H, ddd, *J*= 8.0, 6.5, 1.0 Hz, C*H* arom), 7.17 (2H, dd, *J*= 8.5, 5.3 Hz, C*H* arom), 5.49 (1H, s), 4.30 (1H, d, *J*= 13.1 Hz), 3.63 (1H, d, *J*= 13.1 Hz); ^{13}C NMR (126 MHz, DMSO) δ 168.9, 134.7, 134.3, 133.92, 133.86, 131.4, 131.3, 131.3, 131.1, 130.5, 129.9, 129.8, 129.7, 128.9, 128.8, 128.3, 127.4, 127.2, 127.0, 126.92, 126.86, 60.1, 46.1; HRMS (NSI$^-$) *m/z* found 338.1181 $[M-H]^-$; $[C_{23}H_{17}NO_2-H]^-$ requires 338.1187.

(3S,11cS)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid hydrochloride 251.HCl

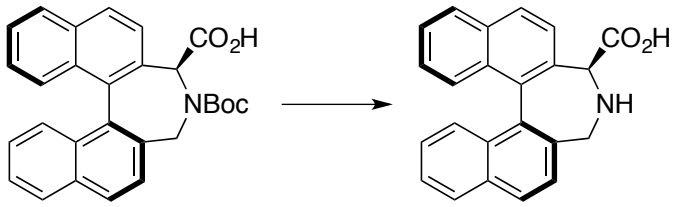


248 **251**.HCl

(3S,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid (346 mg, 0.79 mmol) was dissolved in acetone (35 mL) and concentrated HCl (3 drops) was added. The reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The product was isolated by recrystalization (diethyl ether and light petroleum ether) to give a yellow solid (296 mg, *quant*.)

m.p.* 290-292 °C (**decomp*); $[\alpha]_D^{21.5}$ +282 ° (*c* 1.00, MeOH); ν_{max}(solid)/cm^{-1} 3247 (*=C-H aromatic stretch, O-H stretch*), 2737 (*N-H bend*), 1961, 1714 (*C=O stretch*), 1594, 1461 (*C=C aromatic stretch*), 1430 (*C-H stretch*), 1310 (*C=O stretch*), 1276, 1235(*C-N stretch*), 1028, 816, 780, 665 (*N-H wag*), 640; ^{1}H NMR (500 MHz, DMSO) δ 10.51 (1H, s), 10.09 (1H, s), 8.29 (1H, d, *J*= 8.5 Hz, C*H* arom), 8.24 (1H, d, *J*= 8.0 Hz, C*H* arom), 8.17 (2H, d, *J*= 8.0 Hz, C*H* arom), 7.79 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.68–7.62 (2H, m, C*H* arom), 7.54 (1H, d, *J*= 8.5 Hz, C*H* arom), 7.47-7.42 (2H, m, C*H* arom), 7.35 (1H d, *J*= 8.5 Hz, C*H* arom), 7.29 (1H, d, *J*= 8.6 Hz, C*H* arom), 4.61 (1H, s, C*H*CO_2H), 4.41 (1H, d, *J*= 13.0 Hz, CH_2), 3.45 (*dist,* 1H, d, *J*= 13.0 Hz, CH_2); ^{13}C NMR (126 MHz, DMSO) δ 169.1, 135.7, 134.5, 134.3, 134.1, 131.1, 130.8, 130.4, 130.1, 129.7, 129.1, 128.5, 127.8, 127.6, 127.5, 127.4, 127.34, 127.32, 127.1, 124.6, 58.3, 46.2; HRMS (NSI$^+$) *m/z* found 340.1336 $[M–HCl+H]^+$; $[C_{23}H_{18}NO_2–Cl]^+$ requires 340.1332.

(3S,11cS)-4,5-Dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid 251



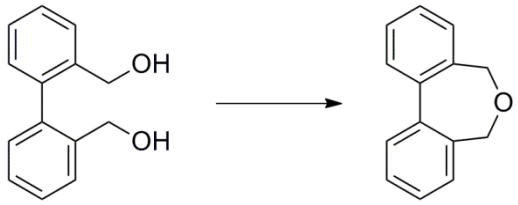
248 **251**

(3S,11cS)-4-(Tert-butoxycarbonyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine-3-carboxylic acid (1.60 g, 3.64 mmol) was dissolved in dichloromethane (30 mL) and trifluoroacetic acid (3.9 mL, 50.96 mmol, 14 equiv.) was added. The solution was stirred for 30 min after which time the pH was neutralised by addition of saturated solution of sodium hydrogen carbonate. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (30 mL). The organic layer was then washed with H_2O (3 x 20 mL), saturated brine solution (3 x 20 mL), dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The residue was then recrystallized ($CHCl_3$ and light petroleum ether) to yield the title compound (877 mg, 71%).

m.p. 276-280 °C; $[\alpha]_D^{24.5}$ +196.0 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3408 (*N-H bend*), 3053 (*O-H stretch*), 3009 (*=C-H aromatic stretch*), 2974, 2974, 2784, 2595, 1760 (*C=O stretch*), 1633 (*C=C aromatic stretch*), 1400 (*C-H stretch*), 1392, 1340 (*C-O stretch*), 1201 (*C-N stretch*), 1029 (*O-H bend*), 820 (*N-H wag*), 739; ^{1}H NMR (500 MHz, DMSO) δ 8.09 (4H, m, C*H* arom), 7.70 (2H, d, *J*= 8.3 Hz, C*H* arom), 7.58 (2H, m, C*H* arom), 7.42–7.26 (3H, m, C*H* arom), 7.22 (1H, d, *J*= 8.6 Hz, C*H* arom), 4.10 (1H, d, *J*= 12.7 Hz, CH_2), 3.85 (1H, s, C*H*CO_2H), 3.35 (1H, *dis* d, *J*= 12.7 Hz, CH_2); ^{13}C NMR (126 MHz, DMSO) δ 134.7, 134.5, 133.2, 133.1, 132.2, 131.0, 130.6, 130.3, 129.0, 128.7, 128.6, 128.4, 127.6, 126.6, 126.6, 126.5, 126.3, 126.3, 126.2, 126.2, 60.2, 45.8; HRMS (NSI^+) *m/z* found 340.1335 $[M+H]^+$; $[C_{23}H_{17}NO_2+H]^+$ requires 340.1332.

4.0 Biphenyl catalyst synthesis

5,7-Dihydrodibenzo[*c*,*e*]oxepine[12]

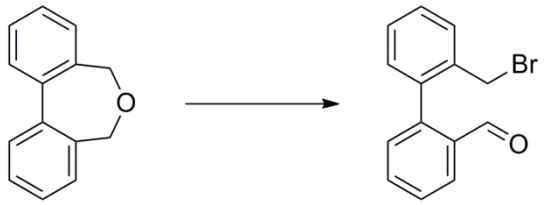


A suspension of 2,2-biphenyl dimethanol (5.90 g, 27.5 mmol) in hydrobromic acid (24% in water, 84 mL) was heated to 100 °C for 40 minutes. The cloudy solution was allowed to cool to room temperature and the aqueous phase extracted with Et_2O (3 x 50 mL). The organic layers were washed with water (2 x 10 mL), sodium hydrogen carbonate solution (50 mL) and saturated brine solution (50 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. Recrystallization (EtOAc and light petroleum ether) of the title compound as a colourless solid was achieved (4.0 g, 74%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1567 (*C=C aromatic stretch*), 1197 (*C-O stretch*), 1073, 1042, 903, 891, 754 (*C-H aromatic stretch*), 602; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (2H, d, *J*= 7.6 Hz, C*H* arom), 7.55 (2H, td, *J*= 7.1, 2.0 Hz, C*H* arom), 7.49-7.44 (4H, m, C*H* arom), 4.41 (4H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.2, 135.2, 129.7, 129.0, 128.3, 127.5, 67.6.

Data in agreement with literature.[14]

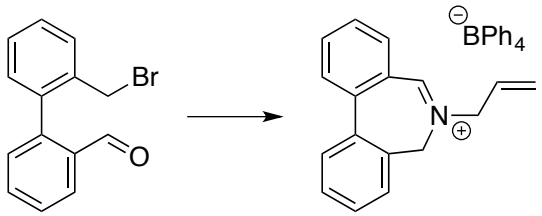
2-[2-(Bromoethyl)phenyl]benzene carbaldehyde[12]



A solution of 5,7-dihydrodibenzo[*c*,*e*]oxepine (2.20 g, 11.2 mmol) in cyclohexane (50 mL) was cooled to 0 °C. Molecular bromine (0.6 mL, 11.8 mmol, 1.05 equiv., as a solution in cyclohexane (5 mL)) was added over a period of 5 minutes causing the solution turned from pale yellow to dark red. After five minutes the ice bath was removed and reaction mixture heated at reflux until pale yellow solution is observed and HBr ceases to be liberated (~1 h). The solvent was removed under reduced pressure and the residue redissolved in Et_2O. The organic layers were washed with saturated sodium hydrogen carbonate solution (20 mL) and saturated brine solution (20 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents removed under reduced pressure to yield yellow oil. The title compound was crystallised as a colourless solid from hexane and $CHCl_3$ (1.50 g, 49%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*C-H aromatic stretch*), 2986 (O=*C-H*), 2861, 2761, 2762, 2662, 2691, 2306, 1694 (*C=O*), 1596 (*C=C aromatic stretch*), 1445, 1421, 1266, 1122, 1196, 896 (*C-H aromatic bend*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (1H, s, C*H*O), 7.97 (1H, d, *J*= 8.0 Hz, C*H* arom), 7.57 (1H t, *J*= 7.5 Hz, C*H* arom), 7.46 (2H, t, *J*= 8.2 Hz, CH arom), 7.35-7.29 (2H, m, C*H* arom), 7.28 (1H, t, *J*= 7.6 Hz, C*H* arom), 7.11 (1H, d, *J*= 7.5 Hz, C*H* arom), 4.26 (1H, d, *J*= 10.2 Hz), 4.16 (1H, d, *J*= 10.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.7, 143.3, 137.9, 136.0, 134.2, 133.6, 131.1, 130.7, 130.7, 129.1, 128.5, 128.4, 127.7, 31.4.
Data in agreement with literature.[12]

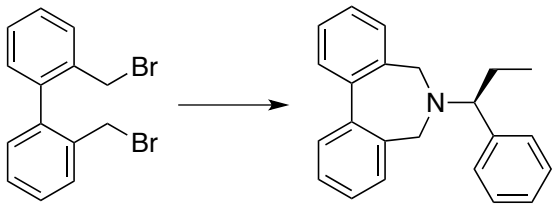
6-Allyl-5H-dibenzo[c,e]azepin-6-ium



2-[2-(Bromoethyl)phenyl]benzene carbaldehyde (4.71 g, 17.1 mmol) was dissolved in ethanol (50 mL) and the solution was cooled to 0 °C. Allylamine (1.4 mL, 18.8 mmol, 1.1 equiv., as a solution in ethanol (10 mL)) was added dropwise to the reaction mixture. The reaction was allowed to reach ambient temperature overnight. Sodium tetraphenylborate (6.43 g, 18.8 mmol, 1.1 equiv.) was dissolved in a minimum volume of acetonitrile and added in one portion. The reaction mixture was stirred for 5 minutes then the solvents removed under reduced pressure. The residue was dissolved in a minimum volume of ethanol and a minimum volume of water was added to facilitate precipitation. The resulting solid was collected by filtration and washed with cold ethanol. The title compound was collected as a bright orange solid after being dried in a vacuum oven at 70 °C overnight (7.00 g, 74 %).

m.p.* 175-177 °C (**decomp*); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3412, 3054 (*C-H aromatic stretch, =C-H stretch*), 2986, 2685, 2305, 1712, 1653 (*C=C stretch*), 1480 (*C=C aromatic stretch*), 1422, 1265, 1223 (*C-N stretch*), 896 (*=C-H bend*), 740 (*C-H aromatic bend*), 600; ^{1}H NMR (500 MHz, DMSO) δ 9.43 (1H, s, N^+=C*H*), 8.11 (1H, d, *J*= 7.5 Hz, C*H* arom), 8.06 (1H, dd, *J*= 7.5, 0.8 Hz, C*H* arom), 8.01 (1H, ddd, *J*= 8.5, 7.5, 1.0 Hz, C*H* arom), 7.85-7.81 (2H, m, C*H* arom), 7.66-7.62 (3H, m, C*H* arom), 7.23-7.18 (8H, m, C*H* arom), 6.94 (8H, t, *J*= 7.5 Hz, C*H* arom), 6.81 (4H, t, *J*= 7.0 Hz, C*H* arom), 6.02 (1H, ddt, *J*= 16.6, 10.0, 6.5 Hz, NCH_2CHCH_2), 5.69 (1H, dd, *J*= 17.0, 1.0 Hz, $NCH_2CHCH_{2\ trans}$), 5.55 (1H, dd, *J*= 10.2, 0.5 Hz, $NCH_2CHCH_{2\ cis}$), 4.85 (2H, d, *J*= 6.0 Hz, NCH_2CHCH_2), 3.33 (2H, m, $ArCH_2N$); ^{13}C NMR (126 MHz, DMSO) δ 170.4, 164.4, 164.1, 163.7, 163.3, 141.4, 137.3, 136.0, 134.9, 134.5, 130.6, 130.5, 130.5, 129.9, 129.8, 129.1, 127.2, 125.8, 125.8, 125.8, 125.8, 124.2, 122.0, 64.2, 55.5; HRMS (NSI^+) *m/z* found 235.1307 $[M–BPh_4]^+$; $C_{17}H_{16}N^+$ requires 235.1311

(S)-6-(1-Phenylpropyl)-6,7-dihydro-5H-dibenzo[c,e]azepine 253

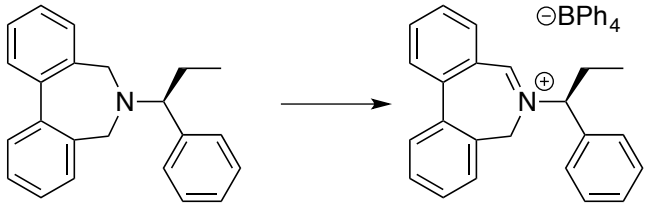


252 **253**

2,2'-Bis (bromomethyl)-1,1'-biphenyl (1.00 g, 2.94 mmol) was dissolved in acetonitrile (30 mL) and $CsCO_3$ (1.73g, 5.29 mmol, 1.8 equiv.) and (*R*)-(+)-1-phenylpropylamine (0.43 mL, 2.94 mmol, 1 equiv.) were added. The reaction mixture was heated at reflux at 80 °C overnight. After consumption of starting material was seen by TLC analysis the reaction mixture was then diluted with dichloromethane (40 mL) and filtered into a separating funnel to remove the excess $CsCO_3$. The organic layers were washed with H_2O (3 x 20 mL) and saturated brine solution (2 x 10 mL) and dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (10:1 light petroleum ether/EtOAc) afforded the title compound as a colourless oil (810 mg, 88%).

$[\alpha]_D^{22.6}$ +64.0 ° (*c* 1.03, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3684, 3019 (*C-H aromatic stretch*), 2975, 2934, 2400, 1492 (*C=C aromatic stretch*), 1480, 1265 (*C-N stretch*), 1215, 928; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, dd, *J*= 7.6, 1.2 Hz, C*H* arom), 7.59-7.55 (2H, m, C*H* arom), 7.53-7.48 (4H, m, C*H* arom), 7.45 (2H, ddd, *J*= 8.5, 7.0, 1.0 Hz, C*H* arom), 7.43-7.38 (3H, m, C*H* arom), 3.71 (2H, d, *J*= 12.5 Hz, ArCH_2N), 3.54 (1H, dd, *J*= 9.6, 3.5 Hz, NC*H*(CH_2CH_3)Ph), 3.42 (2H, d, *J*= 12.5 Hz, ArCH_2N), 2.26-2.13 (1H, m, NCH(CH_2CH_3)Ph), 1.96-1.77 (1H, m, NCH(CH_2CH_3)Ph), 0.81 (3H, t, *J*= 7.5 Hz, NCH(CH_2CH_3)Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 141.4, 135.4, 130.0, 128.9, 128.5, 128.0, 127.7, 127.6, 127.2, 69.1, 53.4, 27.5, 10.6; HRMS (NSI^+) *m/z* found 314.1902 $[M+H]^+$; $[C_{23}H_{23}N]^+$ requires 314.1903.

(*S*)-6-(1-Phenylpropyl)-5H-dibenzo[c,e]azepin-6-ium 254

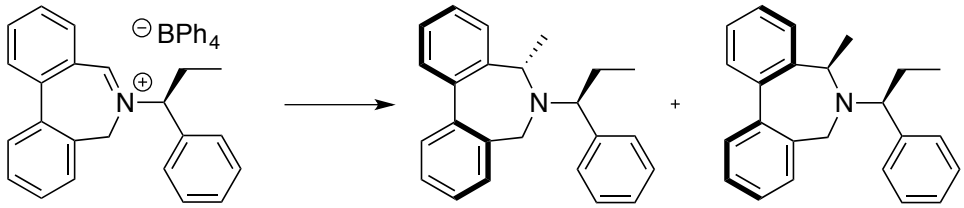


253 **254**

(*S*)-6-(1-Phenylpropyl)-6,7-dihydro-5H-dibenzo[c,e]azepine (810 mg, 2.58 mmol) was dissolved in dichloromethane (50 mL). The solution was cooled to 0 °C and *N*-bromosuccinimide (483 mg, 2.71 mmol, 1.05 equiv.) was added slowly, causing the reaction mixture to turn bright yellow. The reaction mixture was stirred for 2 h or until full consumption of the starting material was seen by TLC. The solvent was removed under reduced pressure and the residue redissolved in a minimum volume of ethanol. Sodium tetraphenylborate (927 mg, 2.71 mmol, 1.05 equiv., in a minimum volume of acetonitrile) was added dropwise. The title compound precipitated as a pale yellow solid (1.05g, 64%).

m.p. 202-204 °C; $[\alpha]_D^{22.2}$ +26.5 ° (*c* 1.60, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3412, 3055 (*C-H aromatic stretch*), 3001, 2984, 1637 (*C=C aromatic stretch*), 1599, 1579, 1556, 1479, 1454, 1426, 1316, 1274, 1265, 1209 (*C-N stretch*), 1135, 1065, 1031, 845; ^{1}H NMR (500 MHz, DMSO) δ 9.73 (1H, s, C*H*=N^+), 8.21 (1H, d, *J*= 8.0 Hz, C*H* arom), 8.07 (1H, d, *J*= 7.95 Hz, C*H* arom), 8.03 (1H, t, *J*= 7.5 Hz, C*H* arom), 7.85 (1H, t, *J*= 8.0 Hz, C*H* arom), 7.78 (1H, d, *J*= 7.5 Hz, C*H* arom), 7.68-7.60 (2H, m, C*H* arom), 7.56 (1H, t, *J*= 7.5 Hz, C*H* arom), 7.50-7.43 (3H, m, C*H* arom), 7.40 (1H, t, *J*= 7.5 Hz, C*H* arom), 7.24-7.21 (8H, m, C*H* arom), 7.09-7.03 (1H, m, C*H* arom), 6.93 (8H, t, *J*= 7.3 Hz, C*H* arom), 6.80 (4H, t, *J*= 7.5 Hz, C*H* arom), 5.53 (1H, t, *J*= 8.0 Hz), 4.72 (2H, s), 2.43 (2H, m), 0.90 (3H, t, *J*= 6.9 Hz); ^{13}C NMR (126 MHz, DMSO) δ 164.4, 164.0, 163.7, 163.3, 141.5, 136.2, 136.0, 130.5, 130.4, 130.1, 130.1, 129.6, 129.6, 129.5, 129.4, 129.4, 129.4, 129.1, 129.1, 127.2, 125.8, 125.8, 125.8, 125.7, 122.0, 94.7, 67.2, 45.8, 10.6; HRMS (NSI^+) m/z found 313.1780 $[M\text{-}BPh_4]^+$; $[C_{23}H_{22}N]^+$ requires 313.1781.

5-Methyl-6-1-phenylpropyl)-6,7-dihydro-5H-dibenzo[c,e]azepine

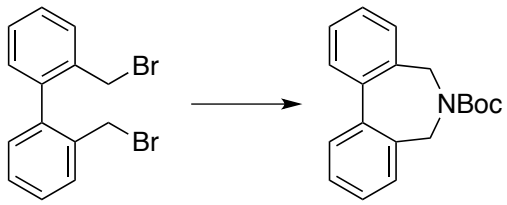


254

(*S*)-6-(1-Phenylpropyl)-5H-dibenzo[c,e]azepin-6-ium (200 mg, 0.32 mmol) was dissolved in anhydrous THF (20 mL) and the solution was cooled to −78 °C. A solution of methyl magnesuim bromide (1.1 mL, 3.2 mmol, 10 equiv., 3M in Et_2O) added. The reaction mixture was allowed to reach ambient temperature overnight and the excess Grignard quenched with H_2O. The solvent was evaporated under reduced pressure and the residue redissolved in dichloromethane and the organic layers washed with H_2O (2 x 10 mL) and dried with saturated brine solution (2 x 10 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The title product was isolated, following column chromatography on silica gel (12:1 light petroleum ether/EtOAc), as colourless oil in a mixture of inseparable diastereoisomers (90 mg, 86%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3061, 3025 (*C-H aromatic stretch*), 2962, 2929, 2873, 2800, 1681, 1619, 1605 (*C=C aromatic stretch*), 1491, 1481, 1377, 1364, 1196, 1087 (*C-N stretch*), 1038; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.18 (24H, m, C*H* arom), 7.01 (1H, dd, *J*= 7.5, 1.0 Hz, C*H* arom), 6.95 (1H, d, *J*= 7.0, 1.0 Hz, C*H* arom), 4.19-4.04 (1H, m), 3.97-3.81 (2H, m), 3.70 (1H, dd, *J*= 9.0, 5.1 Hz), 3.60 (1H, dd, *J*= 9.1, 4.3 Hz), 3.56 (1H, d, *J*= 11.1 Hz), 3.17 (1H, d, *J*= 11.1 Hz), 3.16-3.12 (1H, m), 2.08 (1H, ddd, *J*= 12.7, 7.3, 5.2 Hz), 2.04-1.87 (2H, m), 1.85-1.75 (1H, m), 0.87 (3H, t, *J*= 7.3 Hz), 0.77-0.70 (6H, m), 0.62 (3H, d, *J*= 7.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 142.4, 141.8, 141.2, 140.5, 139.5, 139.3, 139.2, 137.4, 137.2, 131.4, 131.3, 130.3, 130.0, 129.8, 129.3, 129.2, 128.7, 128.7, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.2, 127.0, 126.9, 126.9, 70.9, 70.8, 60.9, 60.3, 53.7, 51.8, 26.7, 25.7, 23.7, 22.9, 11.5, 10.8; HRMS (NSI^+) m/z found 328.2059 $[M+H]^+$; $[C_{24}H_{26}N]^+$ requires 328.2060.

Tert-butyl 5H-dibenzo[c,e]azepine-6(7H)-carboxylate

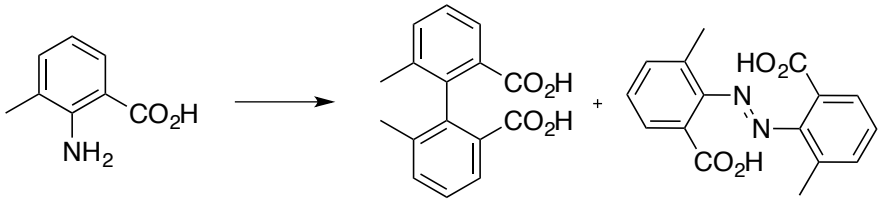


252

NaH (72 mg, 3 mmol, 2.05 equiv.) and 2,2'-bis(bromomethyl)-1,1'-biphenyl (500 mg, 1.47 mmol) were dissolved in anhydrous DMF (12 mL). The flask was then cooled to 0 °C and tert-butyl carbamate (172 mg, 1.47 mmol, 1 equiv., as a solution in anhydrous DMF) was added dropwise to the reaction mixture. The ice bath was removed and the reaction mixture was stirred at ambient temperature for 4 days. To the solution was added a small amount of ice and the solvent was removed under reduced pressure. The residue was redissolved in Et_2O (20 mL) and the ethereal solutions washed with H_2O (3 x 10 mL) and saturated brine solution (2 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (4:1 light petroleum ether/EtOAc) gave the title compound as a yellow oil (247 mg, 57%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3065, 3020 (*C-H aromatic stretch*), 2976, 2930, 2864, 1764, 1693 (*C=O stretch*), 1601, 1481, 1453, 1399, 1248, 1342, 1264, 1224, 1158, 1115 (*C-N stretch*), 1080, 1008, 994, 940, 876; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.28 (8H, m, C*H* arom), 4.14 (4H, s, ArCH_2N), 1.52 (9H, s, NCO_2*tBu*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 141.2, 140.7, 135.1, 134.4, 129.8, 129.7, 129.0, 128.5, 128.5, 128.3, 128.2, 127.5, 80.0, 67.6, 28.6, 28.4; HRMS (NSI$^-$) *m/z* found 294.1490 $[M-H]^-$; $[C_{19}H_{21}NO_2-H]^-$ requires 294.1489.

(+/-) 6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-dicarboxylic acid 255[13]



255 **256**

NaOH (5.88 g, 147 mmol) and 2-amino-3-methylbenzoic acid (17 g, 113 mmol) were dissolved in water and cooled to 0 °C. $NaNO_2$ (7.8 g, 113 mol, 1 equiv.) was added. The solution stirred until homogeneous. 4M HCl (240 mL) was added dropwise keeping the temperature below 8 °C. After addition the reaction mixture was stirred at 0 °C for 30 minutes. In a separate 1 L flask $CuSO_4.5H_2O$ (48 g, 192 mmol) and water (150 mL) were cooled to 0 °C and ammonium hydroxide (95 mL, 215 mmol) was added. NH_2OH was added (prepared from $(NH_2OH)_2.H_2SO_4$ (17.6 g, 107 mmol) with 3M NaOH (75 mL)) and the solution effervesced. The diazonium salt prepared above was added in 40 mL portions via syringe with the needle below the surface of the reaction mixture. The addition was completed as quickly as possible whilst maintaining the temperature below 8 °C. The resulting mixture was refluxed for 30 minutes at 115 °C and then cooled to room temperature and HCl (12M, 80 mL) was added. The solution was left overnight and the precipitate that had formed was filtered giving a brown solid which was dried at 60 °C for 12 h (17.5 g). The solid was dissolved in boiling ethanol and cooled to room temperature from which yellow solid crashes out: the **major side product 256** of this reaction (3.05 g, 18%).

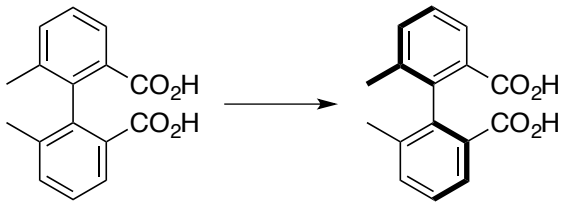
m.p. 252-254 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3944, 3691, 3054 (*C-H aromatic stretch*), 2987, 2685 (*O-H stretch*), 2410, 2305, 1682 (*C=C aromatic stretch, C=O stretch*), 1421 (*O-H bend*), 1314 (*C-O bend*), 1265, 1158, 1125 (*C-N stretch*), 961, 896; ^{1}H NMR (500 MHz, DMSO) δ 12.66 (2H, s, CO_2H), 7.50 (2H, d, *J*= 7.3 Hz, C*H* arom), 7.46 (2H, t, *J*= 7.5 Hz, C*H* arom), 7.37 (2H, d, *J*= 7.2 Hz, C*H* arom), 2.56 (6H, s, CH_3); ^{13}C NMR (126 MHz, DMSO) δ 170.1, 148.8, 137.5, 133.0, 130.6, 126.8, 126.4, 18.2.

The remaining filtrate was rotatory evaporated and redissolved in hot ethanol and

H_2O (100 mL) was added. The **title compound 255** precipitated as a red-brown solid, which was collected by suction filtration (8.2 g, 30.3 mmol, 54%).

m.p. 208-210 °C (Lit 220-230 °C); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 (*C-H aromatic stretch*), 2986, 2923, 2832, 2685, 2560 (*O-H stretch*), 2411, 2305, 1702 (*C=O stretch*), 1682, 1592 (*C=C aromatic stretch*), 1579, 1421, 1296, 1264 (*C-O stretch*), 1187, 1159, 1111, 934, 896 (*C-H bend),* 819; ^{1}H NMR (500 MHz, DMSO) δ 12.39 (2H, s, CO_2H), 7.72 (2H, d, *J*= 7.6 Hz, C*H* arom), 7.46 (2H, d, *J*= 7.4 Hz, C*H* arom), 7.33 (2H, t, *J*= 7.6 Hz, C*H* arom), 1.83 (6H, s, CH_3); ^{13}C NMR (126 MHz, DMSO) δ 168.5, 141.1, 136.4, 133.3, 130.9, 127.7, 127.1, 20.2; HRMS (NSI^-) *m/z* found for $[M-H]^-$: 269.0812; $[C_{16}H_{13}O_4-H]^-$ requires 269.0819.

(S)-6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-dicarboxylic acid (+)-**255**

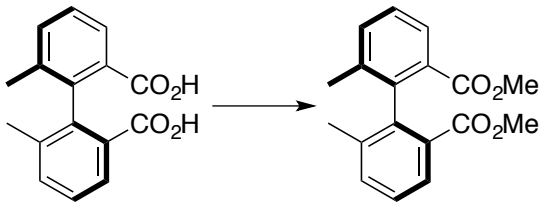


255 (+)-**255**

(±) 6,6'-dimethyl-[1,1'-biphenyl]-2,2'-dicarboxylic acid (3.5 g, 12.9 mmol) was dissolved in 90 % boiling EtOH (16 mL) and quinine (4.2 g, 12.9 mmol, 1 equiv.) was added in one portion. The solution was allowed to cool to room temperature and a white precipitate of the quinine monohydrate salt formed (4.90 g). The quinine salt was then dissolved in EtOAc (70 mL) and 3 M HCl (80 mL) was added. The organic layers were washed and separated with H_2O (3 x 20 mL), dried with saturated brine solution (2 x 10 mL) and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield an orange solid (1.3 g, 37%).

$[\alpha]_D^{20.7}$ +20.8 ° [(*c* 1.00, MeOH) (Lit $[\alpha]_D^{25}$ +19.2 °, *c* 1.00, MeOH)]
m.p. 225-227 °C (Lit 220-230 °C)

***(S)*-Dimethyl 6,6'-dimethyl-[1,1'-biphenyl]-2,2'-dicarboxylate 258**

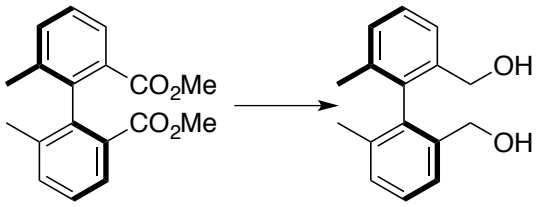


(+)-**255** **258**

6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-dicarboxylic acid (200 mg, 0.74 mmol) was dissolved in MeOH (10 mL). Concentrated H_2SO_4 (95%, 1 mL) was added and the red-brown reaction mixture was heated at refluxed at 70 °C overnight. The reaction was quenched at 0 °C with saturated sodium hydrogen carbonate solution and the solvent was removed under reduced pressure. The residue was redissolved in dichloromethane (20 mL) and the organic layers were washed with H_2O (3 x 10 mL) and saturated brine solution (2 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resultant brown oil was subjected to column chromatography (4:1 light petroleum ether/EtOAc) to give the product as a dark yellow oil (181 mg, 82%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3059 (*C-H aromatic stretch*), 2992, 2951, 2921, 2841, 1727 (*C=O stretch*), 1593 (*C=C aromatic stretch*), 1578, 1460, 1434, 1291, 1267, 1193, 1174, 1141, 1105 (*C-O stretch*), 1016, 877; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.84 (2H, m, C*H* arom), 7.44 (2H, ddd, *J*= 7.6, 1.3, 0.7 Hz, C*H* arom), 7.33 (2H, t, *J*= 7.7 Hz, C*H* arom), 3.58 (6H, s, CO_2CH_3), 1.91 (6H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 141.2, 136.6, 133.6, 129.4, 127.7, 126.9, 51.7, 20.0.

***(S)*-(6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-diyl)dimethanol 259[14]**

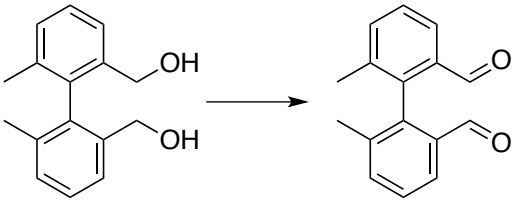


258 **259**

Dimethyl 6,6'-dimethyl-[1,1'-biphenyl]-2,2'-dicarboxylate (144 mg, 0.48 mmol) was dissolved in anhydrous Et_2O (10 mL) and the solution was cooled to 0 °C. $LiAlH_4$ (73 mg, 1.93 mmol, 4 equiv.) was added and the reaction was monitored by TLC. After 5 h the reaction mixture was quenched with H_2O (10 mL). The reaction mixture was filtered through a pad of celite and the organic layers washed with H_2O (3 x 15 mL) with saturated brine solution (2 x 10 mL) then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the product as an orange solid (117 mg, *quant*.). This was employed in the next step without further purification.

m.p. 208-210 °C (Lit 116-118 °C)[16]; $[\alpha]_D^{22.1}$ −74.7 ° [(*c* 1.00, $CHCl_3$); Lit $[\alpha]_D$ −30 ° (*c* 0.4, $CHCl_3$)][16]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3064 (*O-H stretch*), 3018 (*C-H aromatic stretch*), 2970, 2918, 2856, 1459 (*C=C aromatic stretch*), 1437, 1381, 1246, 1210, 1166 (*C-O stretch*), 788 (*C-H aromatic bend*), 755, 735, 626, 613; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (2H, dd, *J*= 7.4, 1.0 Hz, C*H* arom), 7.31 (2H, t, *J*= 7.5 Hz, C*H* arom), 7.26 (2H, t, *J*= 6.1 Hz, C*H* arom), 4.29 (2H, d, *J*= 11.5 Hz), 4.14 (2H, d, *J*= 11.5 Hz), 2.27 (2H, br s, O*H*), 1.87 (6H, s, ArCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 138.2, 136.0, 129.8, 127.9, 127.5, 63.0, 20.1.
Data in agreement with literature values.[16]

(±) 6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-dicarbaldehyde

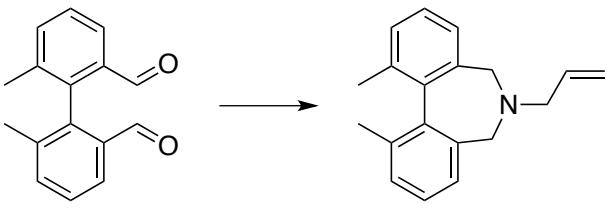


259

(6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-diyl)dimethanol (172 mg, 0.71 mmol) was dissolved in dichloromethane (10 mL) and pyridinium chlorochromate (459 mg, 2.13 mmol, 3 equiv.) was added. The solution was stirred at ambient temperature overnight. Et_2O (20 mL) and a spatula of celite were added to the solution and the reaction mixture was stirred for a further 30 minutes. The solution was then filtered through a pad of celite and the solvent was removed under reduced pressure. The product was isolated without further purification as an orange solid (162 mg, 96%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3063, 3003 (*C-H aromatic stretch*), 2956, 2921, 2852 (*O=C-H stretch*), 2810, 2748, 1685 (*C=O stretch*), 1590 (*C=C aromatic stretch*), 1574, 1457, 1384, 1280, 1238, 1217, 1168, 1001, 918 (*C-H aromatic bend*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (2H, s, ArC*H*O), 7.91 (2H, d, *J*= 7.6 Hz, C*H* arom), 7.59 (2H, d, *J*= 7.4 Hz, C*H* arom), 7.50 (2H, t, *J*= 7.6 Hz, C*H* arom), 1.98 (6H, s, ArCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.4, 139.9, 137.5, 135.9, 134.5, 128.6, 126.4, 19.6.
Data in agreement with literature values.

(±) 6-Allyl-1,11-dimethyl-6,7-dihydro-5H-dibenzo[c,e]azepine

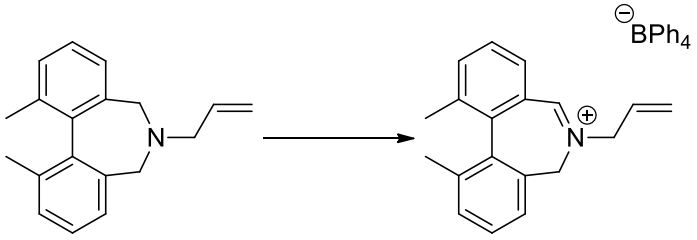


6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-dicarbaldehyde (500 mg, 2.10 mmol) was dissolved in MeOH (80 mL). Allyamine (0.16 mL, 2.10 mmol, 1 equiv.) was added and the solution was stirred for 5 minutes. $NaBH_3CN$ (264 mg, 4.20 mmol, 2 equiv.)

was added in one portion and glacial acetic acid (1 mL) was added immediately after. The reaction mixture was stirred overnight. The reach mixture was quenched by the addition of 1M NaOH (20 mL) and Et_2O (50 mL) was added. The solution was washed and separated with H_2O (2 x 30 mL) and saturated brine solution (2 x 20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield the title compound as an orange oil (352 mg, 64%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3067, 3019 (*C-H aromatic stretch*), 2930, 2877, 2804, 1646 (*C=C aromatic stretch*), 1453, 1377, 1336, 1219, 1163, 1101 (*C-N stretch*), 996, 919, 810 (*C-H aromatic bend*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (4H, d, *J*= 4.8 Hz, C*H* arom), 7.12 (2H, t, *J*= 4.4 Hz, C*H* arom), 5.95 (1H, ddt, *J*= 17.1, 10.1, 6.6 Hz, NCH_2CHCH_2), 5.28-5.15 (2H, m, NCH_2CHCH_2), 3.52 (2H, d, *J*= 12.4 Hz, NCH_2Ar), 3.01 (2H, dd, *J*= 6.7, 1.0 Hz, NCH_2CHCH_2), 2.95 (2H, d, *J*= 12.3 Hz, NCH_2Ar), 2.19 (6H, s, $ArCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 136.3, 135.7, 134.3, 129.5, 127.2, 126.5, 117.8, 57.9, 54.5, 19.8; HRMS (NSI^+) *m/z* found 264.1747 $[M+H]^+$; $[C_{19}H_{22}N]^+$ requires 264.1747.

(±) 6-Allyl-1,11-dimethyl-5H-dibenzo[c,e]azepin-6-ium

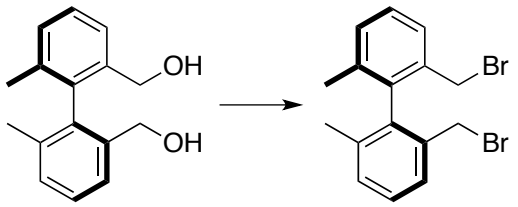


6-Allyl-1,11-dimethyl-6,7-dihydro-5H-dibenzo[c,e]azepine (542 mg, 2.1 mmol) and *N*-bromosuccinimide (385 mg, 2.2 mmol, 1.05 equiv.) were dissolved in dichloromethane (30 mL). The reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure and the residue redissolved in a minimum volume of EtOH. Sodium tetraphenylborate (790 mg, 2.3 mmol, 1.1 equiv., in a minimum volume of acetonitrile) was added to the solution. A bright orange precipitate was collected by suction filtration and washed with cold EtOH to give the title compound as a orange solid which was dried at 70 °C in a vacuum oven (983 mg, 80%).

m.p.* 129-131°C (**decomp.*); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3425, 3054 (*C-H aromatic stretch*),

3002, 2987, 2922, 2845, 1775, 1705, 1648, 1637, 1583 (*C=C aromatic stretch*), 1478, 1440, 1426, 1378, 1348, 1298, 1265, 1183, 1036 (*C-N stretch*), 853, 791 (*C-H aromatic bend*), 733, 707, 706, 612; ^{1}H NMR (500 MHz, DMSO) δ 9.36 (1H, s, ArC*H*=N^{+}), 7.87 (1H, d, *J*= 7.6 Hz, C*H* arom), 7.82 (1H, d, *J*= 7.6 Hz, C*H* arom), 7.70 (1H, t, *J*= 7.7 Hz, C*H* arom), 7.48 (1H, d, *J*= 6.7 Hz, C*H* arom), 7.22-7.15 (9H, m, C*H* arom), 6.94 (9H, t, *J*= 7.4 Hz, C*H* arom), 6.81 (4H, t, *J*= 7.2 Hz, C*H* arom), 5.96 (1H, ddt, *J*= 16.6, 10.3, 6.4 Hz, NCH$_2$C*H*CH$_2$), 5.61 (1H, d, *J*= 17.1 Hz, NCH$_2$CHC*H*$_{2\ trans}$), 5.51 (1H, d, *J*= 10.2 Hz, NCH$_2$CHC*H*$_{2\ cis}$), 4.85 (1H, d, *J*= 13.4 Hz, ArC*H*$_2$N), 4.80-4.68 (2H, m, NC*H*$_2$CHCH$_2$), 4.41 (1H, d, *J*= 13.4 Hz, ArC*H*$_2$N), 2.30 (3H, s, ArC*H*$_3$), 2.09 (3H, s, ArC*H*$_3$); ^{13}C NMR (126 MHz, DMSO) δ 179.9, 170.0, 164.4, 164.0, 163.7, 163.3, 140.0, 139.1, 138.1, 138.1, 136.7, 136.0, 134.6, 132.1, 130.7, 129.7, 129.2, 129.1, 128.8, 128.4, 126.7, 125.8, 125.8, 125.8, 125.7, 124.1, 122.0, 63.8, 56.2, 30.0, 20.2, 20.2; HRMS (NSI^{+}) *m/z* found 262.1592 [M−BPh$_4$]$^{+}$; $C_{19}H_{20}N^{+}$ requires 262.1590.

2,2'-Bis(bromomethyl)-6,6'-dimethyl-1,1'-biphenyl 260



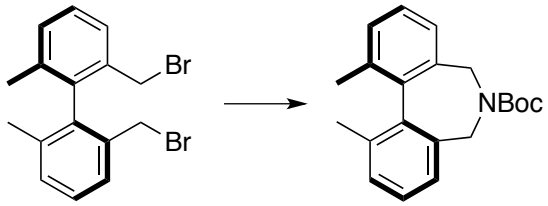
259 **260**

(6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-diyl)dimethanol (500 mg, 2.1 mmol) and pyridine (19 µL, 0.23 mmol, 0.11 equiv.) were dissolved in anhydrous toluene (50 mL). Phosphorous tribromide (0.6 mL, 6.3 mmol, 3 equiv.) was added dropwise to the solution. After the addition was complete, the reaction was heated to 60 °C for 3 h. The reaction was quenched by addition of H_2O (50 mL) and the resulting biphasic mixture was washed with saturated sodium hydrogen carbonate solution (20 mL) and the organic layers dried over anhydrous $MgSO_4$ and decolourised with a spatula of carbon black, filtered and the solvent was removed under reduced pressure to yield the title compound as an orange solid (677 mg, 88%).

m.p. 45-47 °C; $[\alpha]_D^{19.4}$ +35.2 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3064, 3018 (*C-H aromatic stretch*), 2970, 2918, 2856, 1593 (*C=C aromatic stretch*), 1459, 1437,

1381, 1246, 1210, 1166, 1005, 935, 788 (*C-H aromatic bend*), 755, 735, 626, 613; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*= 7.6 Hz, C*H* arom), 7.32 (2H, t, *J*= 7.6 Hz, C*H* arom), 7.26 (2H, d, *J*= 7.6 Hz, C*H* arom), 4.15 (4H, q, *J*= 10.1 Hz), 1.98 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.7, 136.7, 135.4, 130.5, 128.6, 128.4, 32.4, 20.2.

Tert-butyl 1,11-dimethyl-5H-dibenzo[c,e]azepine-6(7H)-carboxylate 261

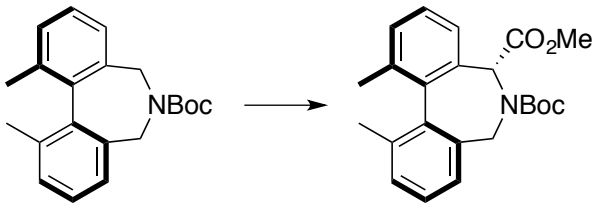


260 **261**

2,2'-Bis(bromomethyl)-6,6'-dimethyl-1,1'-biphenyl (500 mg, 1.36 mmol) was dissolved in anhydrous DMF (30 mL) and NaH (67 mg, 2.78 mmol, 2.05 equiv.) was added. The solution was cooled to 0 °C and tert-butyl carbamate (159 mg, 1.36 mmol, 1 equiv.) was added in one portion. The reaction was monitored by TLC and once complete, DMF was removed under reduced pressure and the residue redissolved in EtOAc (60 mL). The organic layers were washed repeatedly with H_2O (5 x 10 mL) and saturated brine solution (2 x 20 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (9:1 light petroleum ether/EtOAc) afforded the product as a colourless oil (385 mg, 88%). (NB: unable to remove 10% oxepine impurity)

$[\alpha]_D^{22.3}$ −238 ° (*c* 1.50, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3063 (C-H aromatic stretch), 2974, 2927, 2866, 1691 (*C=C aromatic stretch, C=O*), 1459, 1400, 1364, 1036 (*C-O stretch*), 1247, 1216, 1158, 1100 (*C-N stretch*), 869; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.10 (6H, m, C*H* arom), 4.71 (2H, d, *J*= 9.7 Hz), 3.45 (2H, d, *J*= 13.1 Hz), 2.18 (6H, s), 1.48 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 138.2, 136.1, 134.9, 130.0, 127.9, 126.5, 79.7, 47.8, 28.6, 19.7; HRMS (NSI^+) *m/z* found 324.1960 $[M+H]^+$; $[C_{21}H_{25}NO_2+H]^+$ requires 324.1958.

(5R,11bS)-6-Tert-butyl 5-methyl 1,11-dimethyl-5H-dibenzo[c,e]azepine-5,6(7H)-dicarboxylate 262

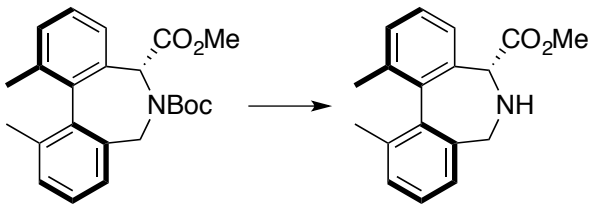


261 **262**

tert-butyl 1,11-dimethyl-5H-dibenzo[c,e]azepine-6(7H)-carboxylate (645 mg, 1.99 mmol) was dissolved in anhydrous Et_2O (60 mL) and cooled to −78 °C. *s*-BuLi (2.85 mL, 3.99 mmol, 2 equiv., 1.4 M in cyclohexane) was added to the solution and the reaction mixture turned from a pale yellow to deep red. The reaction was stirred for 1 h. Methyl chloroformate (0.23 mL, 2.99 mmol, 1.5 equiv.) was added and the reaction mixture returned an orange colour. The reaction mixture was stirred for 1 h at −78 °C and then quenched at 0 °C with saturated ammonium chloride solution. The organic layers were washed and separated with H_2O (2 x 30 mL) and saturated brine solution (2 x 10 mL) and dried over anhydrous $MgSO_4$ and the solvents removed under reduced pressure. Column chromatography (9:1 light petroleum ether/EtOAc) afforded the product as a colourless fluffy solid (600 mg, 79%).

m.p. 74-76 °C; $[\alpha]_D^{22.5}$ −248 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3065, 3002 (*C-H aromatic stretch),* 2975, 2948, 2930, 2872, 2250, 1752 (*C=O stretch*), 1686 (*C=O stretch*), 1600 (*C=C aromatic stretch*), 1474, 1458, 1433, 1392, 1366, 1355, 1308, 1255, 1221, 1206, 1161, 1105 (*C-N stretch*), 1004 (*C-O stretch*), 912, 875 (C-H aromatic bend); ^{1}H NMR (500 MHz, DMSO at 373 K) δ 7.42-7.16 (6H, m, C*H* arom), 5.61 (1H, s, C*H*CO_2Me), 4.85 (1H, d, *J*= 13.3 Hz, CH_2), 3.38 (1H, d, *J*= 13.1 Hz, CH_2), 3.10 (3H, s, CO_2CH_3), 2.13 (3H s, ArCH_3), 2.07 (3H, s, ArCH_3), 1.47 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, at ambient temperature) δ 170.8, 170.5, 154.3, 153.9, 137.5, 137.3, 137.2, 136.9, 136.7, 136.6, 136.4, 135.2, 134.9, 134.7, 134.6, 130.6, 130.4, 129.8, 129.7, 128.5, 128.5, 128.2, 128.1, 128.04, 128.01, 127.3, 127.1, 80.5, 80.4, 62.1, 60.8, 51.7, 47.7, 46.4, 28.5, 28.4, 19.5, 19.4; HRMS (NSI^+) *m/z* found for $[M+H]^+$: 382.2013; $[C_{23}H_{27}NO_4+H]^+$ requires 382.2013.

(5R,11bS)-Methyl1,11-dimethyl-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxylate 263

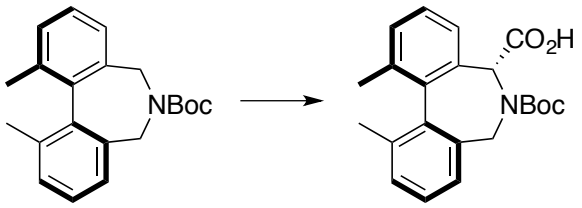


262 **263**

(5R,11bS)-6-Tert-butyl 5-methyl 1,11-dimethyl-5H-dibenzo[c,e]azepine-5,6(7H)-dicarboxylate (100 mg, 0.26 mmol) was dissolved in dichloromethane (8 mL) and trifluoroacetic acid (0.28 mL, 3.64 mmol, 14 equiv.) was added in one portion. The solution was stirred for 30 minutes after which time the pH was neutralised by addition of saturated solution of sodium hydrogen carbonate. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (10 mL). The organic layer was then washed with H_2O (3 x 10 mL) and saturated brine solution (3 x 5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the brown residue recrystallized ($CHCl_3$) as a colourless solid (55 mg, 75%).

$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3316, 3062, 3017 (*C-H aromatic stretch*), 2948, 2926, 2867, 1732 (*C=O stretch*), 1493 (*C=C aromatic stretch*), 1432, 1378, 1302, 1265, 1228, 1211, 1122, 1099 (*C-O stretch*), 994, 785, 770, 741 (*C-H aromatic stretch*), 680; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.29 (2H, m, C*H* arom), 7.29-7.22 (2H, m, C*H* arom), 7.18 (1H, d, *J*= 7.4 Hz, C*H* arom), 7.11 (1H, d, *J*= 7.3 Hz, C*H* arom), 4.44 (1H, s, C*H*CO_2Me), 3.64 (1H, d, *J*= 13.6 Hz, CH_2), 3.35 (1H, d, *J*= 13.6 Hz, CH_2), 3.22 (3H, s, CO_2CH_3), 2.64 (1H, s, N*H*), 2.15 (3H, s, CH_3Ar), 2.12 (3H, s, CH_3Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 138.3, 137.9, 136.9, 136.6, 136.3, 135.1, 130.3, 129.2, 128.5, 128.0, 127.9, 125.6, 62.4, 51.9, 48.3, 19.5, 19.4; HRMS (NSI^+) *m/z* found 282.1489 $[M+H]^+$; $[C_{18}H_{20}NO_2]^+$ requires 282.1489.

(5R,11bS)-6-(Tert-butoxycarbonyl)-1,11-dimethyl-6,7-dihydro-5Hdibenzo[c,e] azepine-5-carboxylic acid 264

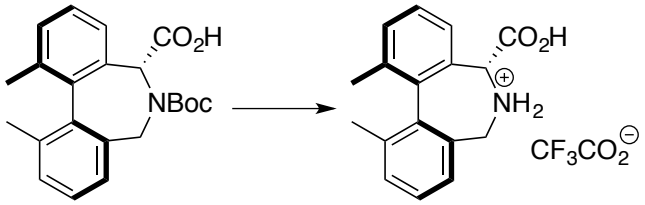


261 **264**

tert-butyl 1,11-dimethyl-5H-dibenzo[c,e]azepine-6(7H)-carboxylate (645 mg, 1.99 mmol) was dissolved in anhydrous Et_2O (60 mL). The solution was cooled to −78 °C and *s*-BuLi (2.85 mL, 4.00 mmol, 2 equiv., 1.4 M in cyclohexane) was added and the reaction mixture turned red. After 1 h at −78 °C CO_2 gas (syringe in directly through a drying tube of $CaCl_2$) was bubbled into reaction mixture for 1 h, this caused the reaction to turn yellow. The reaction was allowed to warm to ambient temperature overnight then quenched with saturated ammonium chloride solution at 0 °C. The resulting biphasic mixture was washed with H_2O (2 x 20 mL) and saturated brine solution (2 x 10 mL) and dried over $MgSO_4$. Organic layers concentrated under reduced pressure and column chromatography (4:1 light petroleum ether/EtOAc) gave the product as a colourless solid (330 mg, 45%).

m.p. 117-119 °C; $[\alpha]_D^{23.6}$ −250 ° (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3066, 3009 (*C-H aromatic stretch*), 2976, 2928, 2782 (*O-H stretch*), 1751, 1717 (*C=O stretch*), 1601 (*C=C aromatic stretch*), 1456, 1394, 1367, 1310 (*C-O stretch*), 1254, 1219, 1160 (*C-N stretch*), 883 (*C-H aromatic bend*), 760, 744; ^{1}H NMR (VT NMR at 380 K, 500 MHz, DMSO) δ 11.35 (1H, s, CO_2H), 7.37-7.32 (2H, m, C*H* arom), 7.29-7.21 (3H, m, C*H* arom), 7.17 (1H dd, *J*= 6.7, 2.0 Hz, C*H* arom), 5.52 (1H, s, C*H*CO_2H), 4.84 (1H, d, *J*= 13.1 Hz, CH_2), 3.39 (1H, d, *J*= 13.2 Hz, CH_2), 2.13 (3H, s, CH_3Ar), 2.08 (3H, s, CH_3Ar), 1.47 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (VT NMR at 380 K, 126 MHz, DMSO) δ 170.7, 153.9, 137.8, 137.7, 136.9, 136.3, 135.7, 135.2, 130.5, 130.0, 128.6, 128.4, 128.3, 127.4, 80.0, 63.4, 28.7, 28.7, 19.7, 19.5; HRMS (NSI$^-$) *m/z* found 366.1702 $[M-H]^-$; $[C_{22}H_{25}NO_4\text{-}H]^-$ requires 366.1711.

(5R,11bS)-1,11-Dimethyl-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxylic acid trifluoroacetic acid 265



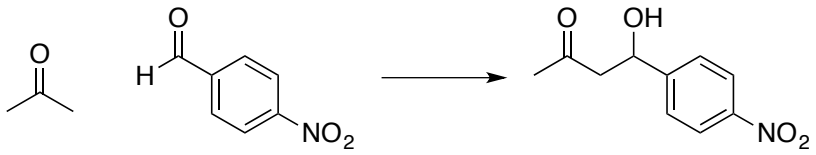
264 **265**.TFA

(5R,11bS)-6-(tert-butoxycarbonyl)-1,11-dimethyl-6,7-dihydro-5H dibenzo[c,e]azepine-5-carboxylic acid (250 mg, 0.68 mmol) was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (0.71 mL, 9.53 mmol, 14 equiv.) was added in one portion. The solution was stirred for 30 minutes. The solvent was removed under reduced pressure and the residue redissolved in EtOAc (10 mL). The organic layer was then washed with H_2O (3 x 10 mL) and dried with saturated brine solution (3 x 5 mL) and anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The brown residue was then recrystallized ($CHCl_3$) as a colourless solid (128 mg, 50%).

m.p. 250-252 °C; $[\alpha]_D^{23.6}$ −34.8 ° (*c* 1.02, MeOH); ν_{max}(solid)/cm^{-1} 3169 (*N-H stretch*), 2800 (*C-H aromatic stretch, O-H stretch*), 1729 (*C=O stretch*), 1643, 1566 (*C=C aromatic stretch*), 1433, 1379, 1348, 1285 (*C-O stretch*), 1249, 1150, 1136, 1059 (*C-N stretch*), 839, 786, 725 (*C-H aromatic stretch*), 675; ^{1}H NMR (500 MHz, DMSO) δ 13.49 (1H, s, CO_2H), 10.10 (1H, s), 9.13 (1H, s), 7.52-7.28 (6H, m, CH arom), 5.43 (1H, s, C*H*CO_2H), 4.09 (1H, d, *J* = 12.9 Hz, CH_2), 3.43 (1H d, *J* = 12.9 Hz, CH_2), 2.11 (3H, s, CH_3), 2.08 (3H, s, CH_3); ^{13}C NMR (126 MHz, DMSO) δ 168.7, 137.2, 136.9, 136.7, 136.4, 131.8, 131.5, 130.5, 130.0, 129.3, 128.5, 128.2, 128.0, 59.0, 45.6, 19.2, 19.0; HRMS (NSI^-) *m/z* found for $[M-CF_3CO_2H_2]^-$: 266.1187; $[C_{17}H_{16}NO_2]^-$ requires 266.1184.

5.0 Catalyst testing

Procedure for the aldol reaction of acetone and nitrobenzaladehyde 81:

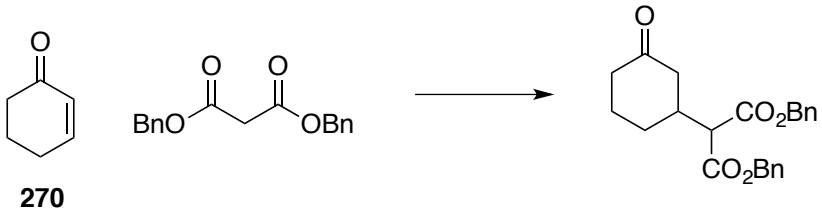


81

Acetone (1 mL, 13.5 mmol, 27 equiv.) and 4-nitrobenzaldhyde **81** (75.6 mg, 0.5 mmol, 1 equiv.) were dissolved in solvent (4 mL). Catalyst (10 mol%) was added and the reaction was stirred for 72 h or until it was observed by TLC that the starting material had been consumed. The reaction mixture was diluted with EtOAc and was treated with saturated ammonium chloride solution (2 mL). The organic layers were washed with water (5 mL) and saturated brine solution (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the title compound isolated as a colourless solid following column chromatography on silica gel (4:1 light petroleum ether/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24-8.18 (2H, m, CH arom), 7.57-7.52 (2H, m, C*H* arom), 5.27 (1H, dd, *J* = 7.6, 4.6 Hz,), 3.69 – 3.59 (1H, s), 2.86 (2H, dd, *J* = 6.1, 2.5 Hz), 2.23 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.5, 150.0, 147.4, 126.4, 123.8, 68.9, 51.5, 30.7. Enantiomeric excess was determined using HPLC with Chiralcel® IC column: (hexane/iPrOH=92:8, λ=220 nm), 0.5 mL; tR= major enantiomer 45.5 min, minor enantiomer 43.1 min.

General procedure for the Michael addition reaction of cyclohexenone 270 and dibenzylmalonate:



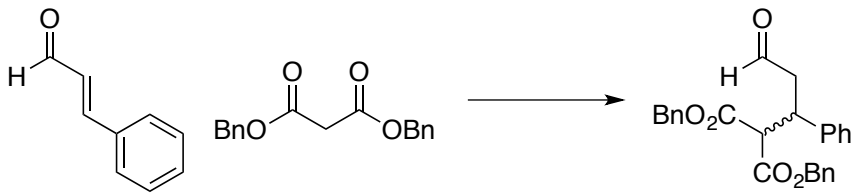
270

Cyclohexenone **270** (24 μL, 0.25 mmol, 1 equiv.) and dibenzyl malonate (62.5 μL, 0.25 mmol, 1 equiv.) were dissiolved in solvent (5 mL). LiOH (6 mg, 025 mmol, 1 equiv.) and catalyst (10 mol%) were added. The reaction was stirred for 6 d or until it was observed by TLC that the starting material had been consumed. The reaction mixture was diluted with DCM and the organic layers were washed with water (10 mL) and saturated brine solution (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the title compound isolated following column chromatography on silica gel (6:4 light petroleum ether/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 6H), 7.29 (4H, m), 5.15 (2H, s), 5.14 (2H, s), 3.41 (1H, d, *J* = 7.7 Hz), 2.56 (1H, m), 2.44 (1H, m), 2.39-2.33 (1H, m), 2.29-2.14 (2H, m), 2.02 (1H, m), 1.94-1.86 (1H, m), 1.67-1.59 (1H, m), 1.46 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.4, 167.5, 135.1, 128.6, 128.3, 67.3, 67.3, 56.8, 45.1, 41.0, 38.1, 28.7, 24.5. Enantiomeric excess was determined using HPLC with Chiralcel® AI-3 column: (hexane/iPrOH=60:40, λ=220 nm), 0.7 mL; tR= major enamtiomer 20.2 min, minor enantiomer 20.6 min

General procedure for the Michael addition reaction of dibenzyl malonate to cinnamaldehyde 271:

Dibenzyl 2-(3-oxo-1-phenylpropyl)malonate 280

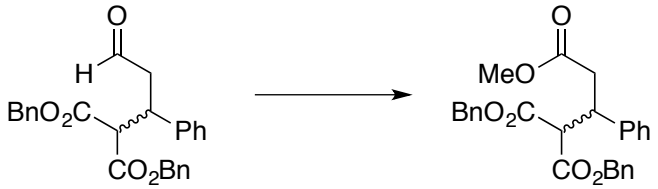


271 **280**

Catalyst (10 mol%) was dissolved in solvent (3 mL) and cinnamaldehyde **271** (63 μL, 0.5 mmol, 1 equiv.) was added followed by the addition of dibenzyl malonate (125 μL, 0.5 mmol, 1 equiv.). The reaction was stirred and monitored by TLC and once judged complete, the reaction mixture was filtered on a pad silica gel and washed with dichloromethane. The solvents were removed under reduced pressure and the crude product by purified by column chromatography on silica gel (9:1 light petroleum ether/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (1H, t, *J*= 1.8 Hz, C*H*O), 7.36-7.19 (13H, m, C*H* arom), 7.06 (2H, dd, *J*= 1.5, 8 Hz, C*H* arom), 5.17-5.11 (2H, m, CO_2CH_2Ph), 4.96-4.81 (2H, m, CO_2CH_2Ph), 4.04-4.06 (1H, m, $CHOCH_2CH$), 3.83 (1H, d, *J*= 9.5 Hz, $CH(CO_2Bn)_2$), 2.95-2.81 (2H, m, $CHOCH_2CH$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0, 167.7, 167.2, 139.6, 135.0, 135.0, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.6, 67.5, 67.3, 57.5, 47.2, 39.5.

General oxidation procedure for HPLC analysis: 1,1-Dibenzyl 3-methyl 2-phenylpropane-1,1,3-tricarboxylate 281



280 **281**

Michael addition product (50 mg, 0.10 mmol, 1 equiv.) was dissolved in *t*-BuOH (3 mL) and NaH_2PO_4 (1 M, *aq*., 3 mL) and $KMnO_4$ (1 M, 3 mL) were added. After stirring for 5 minutes $NaHSO_3$ (5 mL) was added followed by HCl (1 M, dropwise until pH was acidic). The addition of the HCl made the solution colourless. EtOAc (10 mL) was added and the resulting mixture was extracted with EtOAc (2 x 10 mL) and the organic layers were washed with H_2O (2 x 10 mL) and saturated brine solution (10 mL). The organic solvent was removed under reduced pressure and the crude product redissolved in toluene (2 mL) and MeOH (5 mL). $TMSCHN_2$ (2 M in hexane) was added dropwise until the reaction mixture turned from colourless to yellow. The reaction was stirred for 15 min and then the $TMSCHN_2$ was quenched by addition of a small quantity of AcOH. The solvents were removed under reduced pressure and the product was purified by column chromatography (10:1 light petroleum ether/EtOAc) to give a colourless solid.

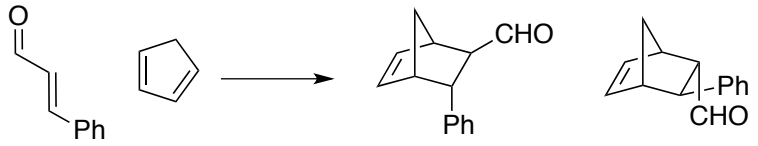
1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.18 (13H, m, C*H* arom), 7.05 (2H, dd, *J*= 8.0, 1.5 Hz, C*H* arom), 5.22-5.11 (2H, m, CO_2CH_2Ph), 4.95-4.80 (2H, m, CO_2CH_2Ph), 3.96 (1H, m, MeO_2CCH_2Ph), 3.87 (1H, d, *J*= 10.5 Hz, $CH(CO_2Bn)_2$), 3.50 (3H, s, OMe), 2.83 (1H, dd, *J*= 16.0, 4.5 Hz, C*H*Ph), 2.73 (1H, dd, *J*= 16.0, 9.5 Hz,

MeO_2CCH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 167.7, 167.3, 139.7, 135.2, 135.0, 128.6, 128.6, 128.5, 128.2, 128.2, 128.1, 127.4, 67.4, 67.2, 57.2, 51.6, 41.5, 38.4. Enantiomeric excess was determined using HPLC with Chiralcel® AD-H column: (hexane/*i*PrOH=80:20, λ=254 nm), 1.0 mL; tR= major enantiomer 26.5 min, minor enantiomer 18.7 min

General procedure for the organocatalytic Diels Alder reaction:

Catalyst (10 mol%) was dissolved in MeOH:H_2O (95/5 *v/v,* 1 mL) and an α-β unsaturated aldehyde (1.0 mmol, 1 equiv.) was added. After 5 minutes the diene was added (3 mmol, 3 equiv.). The reaction mixture was monitored by TLC and upon consumption of cinnamaldehyde the reaction was diluted with Et_2O (5 mL). The reaction mixture was washed with H_2O (3 x 5 mL) and saturated brine solution (2 x 5 mL) and concentrated under reduced pressure. Hydrolysis of the methyl diacetal adduct was performed stirring in TFA:H_2O:$CHCl_3$ (1:1:2) for 2 h. Neutralisation with sodium hydrogen carbonate solution and extraction with Et_2O (2 x 10 mL) and saturated brine solution (2 x 5 mL). Column chromatography to purify the adduct product. Reduction to the corresponding alcohol was performed in anhydrous Et_2O and $LiAlH_4$ to allow separation on HPLC columns.

3-Phenylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde



exo *endo*

271 **284** **285**

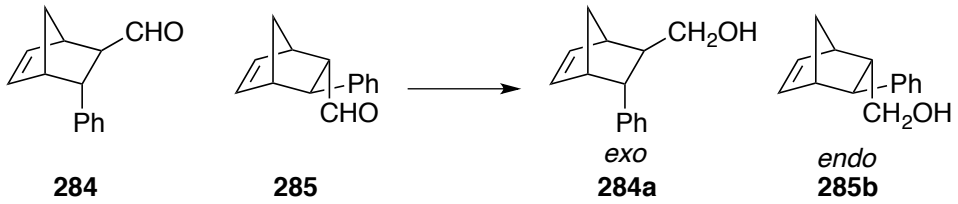
Catalyst (10 mol%) was dissolved in MeOH: H_2O (95/5 *v/v,* 1 mL) and (*E*)-cinnamaldehyde (126 μL, 1.0 mmol, 1 equiv.) was added. The solution stirred for 5 minutes before the addition of cyclopentadiene (252 μL, 3 mmol, 3 equiv., freshly distilled). The reaction was followed by analysis of TLC. After hydrolysis of diacetal, crude NMR analysis allowed conversion to be calculated and assignment of the diastereomeric ratio (***exo*** δ 9.86 (1H, d, *J*= 2.0 Hz, C*H*O): ***endo*** δ 9.59 (1H, d, *J*= 2.2 Hz, C*H*O)). Column chromatography (15% EtOAc in petroleum ether) afforded the product as an inseparable mixture of diastereoisomers as a colourless oil. Data matches literature reported values.[15]

Exo **compound 284** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (1H, d, *J*= 2.0 Hz, C*H*O), 7.30-7.10 (5H, m, C*H* arom), 6.29 (1H, dd, *J*= 5.5, 3.5 Hz, C*H*=CH), 6.03 (1H, dd, *J*= 5.5, 3.0 Hz, CH=C*H*), 3.69 (1H, dd, *J*= 5.0, 3.5 Hz, C*H*Ph), 3.18-3.16 (2H, m, C*H*CH_2), 2.55 (1H, m, C*H*CHO), 1.61-1.54 (2H, m, CHCH_2CH).

Endo **compound 285** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (1H, d, *J*= 2.2 Hz, C*H*O), 7.30-7.10 (5H, m, C*H* arom), 6.37 (1H, dd, *J*= 5.7, 3.2 Hz, C*H*=CH), 6.13 (1H, dd, *J*= 5.7, 2.8 Hz, CH=C*H*), 3.30-3.26 (1H, m, C*H*CH_2), 3.08- 3.07 (1H, m, C*H*CH_2), 3.06 (1H, dd, *J*= 4.5, 1.0 Hz, C*H*Ph), 2.93-2.90 (1H, m, C*H*CHO), 1.79-1.74 (1H, m, CHCH_2CH), 1.51 (1H, m, CHCH_2CH);

For the mixture: $\nu_{max}(CHCl_3)/cm^{-1}$ 3059, 3026, 2970, 2950, 2898, 2828, 1718, 1600, 1496, 1450, 1333, 1131,1059, 720, 699; ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 202.8, 143.6, 142.6, 139.2, 136.6, 136.3, 133.8, 128.6, 128.2, 127.9, 127.4, 126.3, 126.2, 60.9, 59.5, 48.5, 48.4, 47.6, 47.2, 45.7, 45.5, 45.5, 45.2; HRMS (NSI^-) *m/z* found for $[M-H]^-$: 197.0960; $[C_{14}H_{14}O-H]^-$ requires 197.0961.

3-Phenylbicyclo[2.2.1]hept-5-en-2-yl)methanol[16]



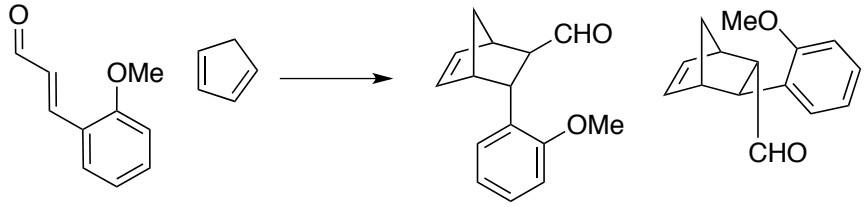
284 **285** *exo* **284a** *endo* **285b**

Following purification, the adduct (150 mg, 0.76 mmol) was dissolved in anhydrous Et_2O (10 mL). $LiAlH_4$ (30 mg, 0.76 mmol, 1 equiv.) was added the reaction stirred until competition was observed by TLC. Purification by column chromatography (4:1 light petroleum ether/EtOAc) afforded the products as an inseparable mixture of diastereoisomers as a colourless oil.

Data of a mixture ***endo***: ***exo***:

$\nu_{max}(CHCl_3)/cm^{-1}$ 3339 (br), 3058, 2965, 2872, 1030, 717, 698; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.14 (10H, m, CH arom), 6.37 (1H, dd, *J*= 5.5, 3.0 Hz), 6.34 (1H, dd, *J*= 5.5, 3.0 Hz), 6.16 (1H, dd, *J*= 5.7, 3.0 Hz), 5.94 (1H, dd, *J*= 5.5, 3.0 Hz), 3.90 (1H, dd, *J*= 10.5, 6.0 Hz), 3.70- 3.62 (2H, m), 3.40 (1H, dd, *J*= 10.5, 9.0 Hz), 3.03 (2H, br m), 2.87 (2H, br m) 2.84 (1H, dd, *J*= 5.0, 3.5 Hz), 2.40-2.32 (1H, m), 2.14 (1H, dd, *J*= 5.5, 2.0 Hz), 1.94-1.90 (1H, m), 1.80-1.77 (1H, m), 1.66-1.64 (1H, m), 1.61-1.57 (1H, m), 1.54 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 144.0, 138.7, 137.6, 134.6, 134.3, 128.5, 128.0, 127.5, 126.0, 125.9, 66.9, 66.5, 50.3, 49.9, 49.0, 48.7, 48.4, 47.8, 47.1, 47.1, 44.8, 44.1; HRMS (NSI^+) m/z found 218.1541 $[M+NH_4]^+$; $[C_{14}H_{20}ON]^+$ requires 218.1539; Enantiomeric excesses were determined using HPLC with Chiralcel® OJ column (hexane/iPrOH=90:10, λ=222 nm), 1.0 mL; ***endo*** isomer (t_R1 15 min, 35 min) ***exo*** isomer (t_R1 47 min, 65 min))

3-(2-Methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde[17]



exo *endo*

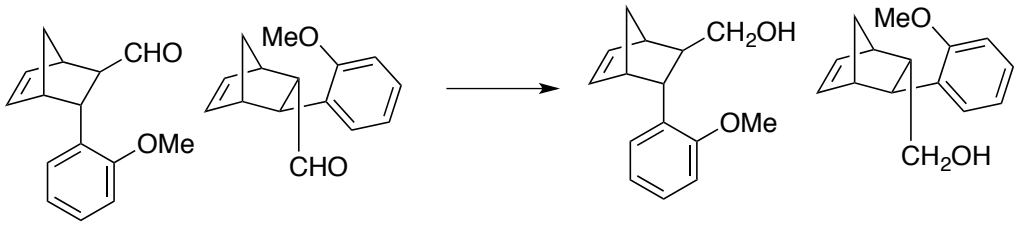
(*E*)- 2-Methoxycinnamaldehyde (162 mg, 1.0 mmol, 1 equiv.) and catalyst (10 mol%) were dissolved in MeOH: H_2O (95/5 *v/v,* 1 mL). The solution stirred for 5 minutes before the addition of cyclopentadiene (252 µL, 3 mmol, 3 equiv., freshly distilled). The reaction was followed by analysis of TLC. After hydrolysis of diacetal, crude NMR analysis allowed conversion to be calculated and assignment of the diastereomeric ratio (***exo*** δ 9.93 (1H, d, *J*= 3.0 Hz, C*H*O): ***endo*** δ 9.50 (1H, d, *J*= 4.0 Hz, C*H*O)). Column chromatography (15% EtOAc in light petroleum ether) afforded the product as an inseparable mixture of diastereoisomers as a colourless oil (210 mg, 0.92 mmol, 92%). In agreement with literature values.[17]

Exo **compound** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (1H, d, *J*= 3.0 Hz, C*H*O), 7.26-6.79 (4H, m, C*H* arom), 6.27 (1H, dd, *J*= 6.0, 3.5 Hz), 6.17 (1H, dd, *J*= 6.0, 3.0 Hz), 3.88 (1H, dd, *J*= 5.5, 3.0 Hz), 3.78 (3H, s, OMe), 3.29 (1H, m), 3.10-3.07 (1H, m), 2.38-2.31 (1H, m), 1.61 (1H, ddd, *J*= 8.5, 3.5, 1.5 Hz), 1.55 (1H, ddd, *J*= 8.5, 3.5, 1.5 Hz);

Endo **compound** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (1H, d, *J*= 4.0 Hz, C*H*O), 7.26 – 6.79 (4H, m, C*H* arom), 6.42 (1H, dd, *J*= 6.0, 3.5 Hz), 6.17 (1H, dd, *J*= 6.0, 3.0 Hz), 3.73 (3H, s, OMe), 3.26-3.22 (1H, m), 3.20 (1H, s), 3.16 (1H, d, *J*= 4.0 Hz), 2.55 (1H, dt, *J*= 5.0, 3.8 Hz), 1.72 (1H, s) 1.57-1.55 (1H, m);

ν_{max}($CHCl_3$)/cm^{-1} 2969, 2716, 1717, 1490, 1243, 1111, 1028, 753, 719; ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.3, 204.2, 157.6, 157.5, 138.5, 136.9, 136.4, 134.2, 132.4, 131.0, 127.3, 127.2, 127.2, 125.6, 120.4, 120.0, 110.0, 109.9, 59.7, 58.0, 55.0, 54.9, 47.8, 47.4, 47.0, 46.3, 46.2, 45.6, 40.8, 40.2; HRMS (NSI^-) m/z found 227.1065 $[M–H]^-$; $[C_{15}H_{15}O_2]^-$ requires 227.1067

3-(2-Methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol



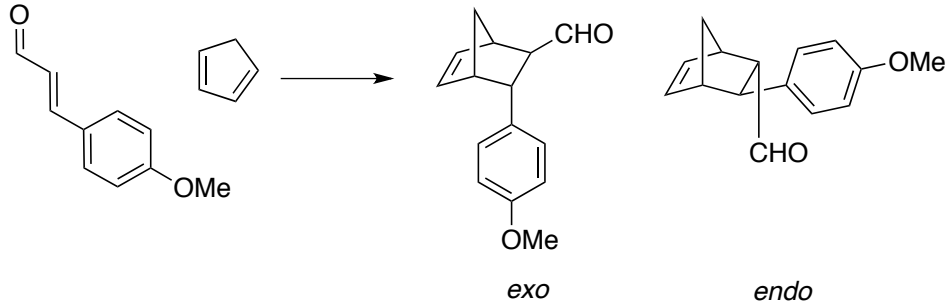
exo *endo*

Following purification, the adduct (210 mg, 0.92 mmol) was dissolved in anhydrous Et_2O (10 mL). $LiAlH_4$ (35 mg, 0.92 mmol, 1 equiv.) was added the reaction stirred until competition was observed by TLC. Purification by column chromatography (9:1, light petroleum ether/EtOAc) afforded the product as an inseparable mixture of diastereoisomers as a colourless oil.

Data of a mixture ***endo***: ***exo***:

$\nu_{max}(CHCl_3)/cm^{-1}$ 3368, 2962, 2941, 1598, 1490, 1463, 1242, 1029, 752, 736, 716; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (1H, dd, *J*= 8.0, 1.5 Hz, CH arom), 7.22-7.16 (1H, m, C*H* arom), 7.16 – 7.12 (1H, m, C*H* arom), 7.05 (1H, dd, *J*= 8.0, 2.0 Hz, CH arom), 6.96 (1H, td, *J*= 7.5, 1.0 Hz, C*H* arom), 6.86 (1H, dd, *J*= 8.2, 1.0 Hz, C*H* arom), 6.83-6.80 (2H, m, C*H* arom), 6.36 (2H, dt, *J*= 5.8, 3.0 Hz), 6.13 (1H, dd, *J*= 6.0, 3.0 Hz), 5.84 (1H, dd, *J*= 6.0, 3.0 Hz), 3.84 (6H, s), 3.83 (1H, m), 3.80 (1H, m) 3.62 (1H, dd, *J*= 10.6, 8.5 Hz), 3.54 (1H, dd, *J*= 10.8, 7.5 Hz), 3.45 (1H, dd, *J*= 10.8, 6.8 Hz), 3.27 (1H, dd, *J*= 5.4, 3.2 Hz), 3.00 (1H, s), 2.96 (1H, s), 2.86 (2H, s), 2.50 (1H, dd, *J*= 5.0, 1.0 Hz), 2.24-2.15 (1H, m), 1.97-1.89 (1H, m), 1.82 (1H, d, *J*= 8.4 Hz), 1.73 (1H, br s), 1.68 (1H, d, *J*= 8.6 Hz), 1.58 (1H, ddd, *J*= 8.4, 3.3, 1.6 Hz), 1.50 (1H, ddd, *J*= 8.6, 3.4, 1.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 156.80, 138.7, 137.3, 134.9, 134.6, 133.7, 131.8, 127.5, 126.8, 126.8, 126.6, 121.1, 120.0, 110.4, 109.9, 67.2, 67.0, 55.4, 50.89, 48.7, 48.6, 47.6, 47.5, 47.4, 44.9, 44.8, 40.9, 40.3; HRMS (NSI^+) m/z found 231.1380 $[M+H]^+$; $[C_{15}H_{19}O_2]^+$ requires 231.1380; Enantiomeric excesses were determined using Chiralcel® AD-H column (hexane/iPrOH=98:2, λ=222 nm), 0.5 mL; ***endo*** isomer (t_R1 65 min, 80 min) ***exo*** isomer (t_R1 57 min, 69 min)).

(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde[17]



exo *endo*

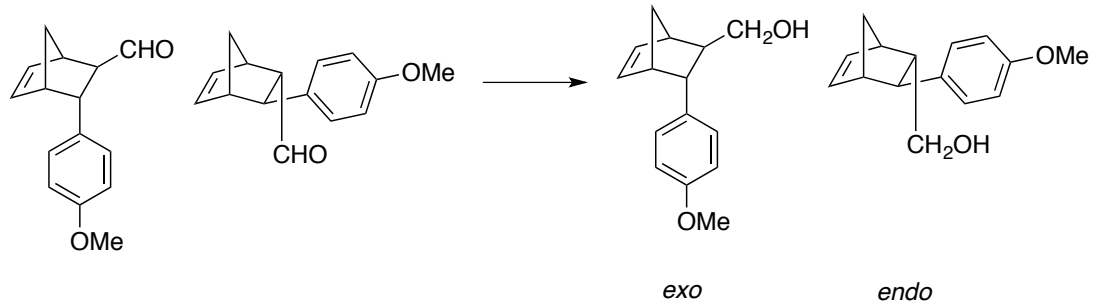
(E)-4-Methoxycinnamaldehyde (162 mg, 1.0 mmol, 1 equiv.) and catalyst (10 mol%) were dissolved in MeOH: H_2O (95/5 *v/v,* 1 mL). The solution stirred for 5 minutes before the addition of cyclopentadiene (252 μL, 3 mmol, 3 equiv., freshly distilled). The reaction was followed by analysis of TLC. After hydrolysis of diacetal, crude NMR analysis allowed conversion to be calculated and assignment of the diastereomeric ratio (***exo*** δ 9.88 (1H, d, *J*= 2.0 Hz, C*H*O): ***endo*** δ 9.56 (1H, d, *J*= 2.3 Hz, C*H*O)). Column chromatography (15% EtOAc in light petroleum ether) afforded the product as an inseparable mixture of diastereoisomers as a colourless oil. Data matches literature reported values.[17]

Exo **compound** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (1H, d, *J*= 2.0 Hz, C*H*O), 7.08-7.03 (2H, m, C*H* arom), 6.79-6.76 (2H, m, C*H* arom), 6.31 (1H, dd, *J*= 5.6, 3.0 Hz, C*H*=CH), 6.05 (1H, dd, *J*= 5.6, 3.0 Hz, CH=C*H*), 3.75 (3H, s, OMe), 3.64 (1H, dd, *J*= 5.2, 3.5 Hz, C*H*Ar), 3.19-3.16 (1H, m, C*H*CH_2), 3.16-3.14 (1H, m, C*H*CH_2), 2.51 (1H, dt, *J*= 5.3, 2.0 Hz, C*H*CHO), 1.61-1.56 (1H, m, CH_2), 1.53 (1H, m, CH_2);

Endo **compound** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (1H, d, *J*= 2.3 Hz, C*H*O), 7.19-7.15 (2H, m, CH arom), 6.87-6.82 (2H, m, CH arom), 6.39 (1H, dd, *J*= 5.6, 3.0 Hz, C*H*=CH), 6.14 (1H, dd, *J*= 5.6, 3.0 Hz, CH=C*H*), 3.76 (3H, s, OMe), 3.31-3.28 (1H, m, C*H*Ar), 3.06-3.03 (1H, m, C*H*CH_2), 3.02-2.99 (1H, m, C*H*CH_2), 2.91 (1H, ddd, *J*= 5.0, 3.4, 2.4 Hz, C*H*CHO), 1.78-1.76 (1H, m, CH_2), 1.61-1.58 (1H, m, CH_2);

For the mixture: ν_{max}($CHCl_3$)/cm^{-1} 2968, 2835, 2718, 1715, 1611, 1513, 1463, 1247, 1180, 1035, 726; ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 202.9, 158.2, 158.0, 139.3, 136.6, 136.3, 135.6, 134.7, 133.7, 128.8, 128.3, 114.0, 113.6, 61.0, 59.7, 55.3, 55.2, 48.7, 48.6, 47.6, 47.1, 45.5, 45.1, 45.1, 44.7.

3-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol

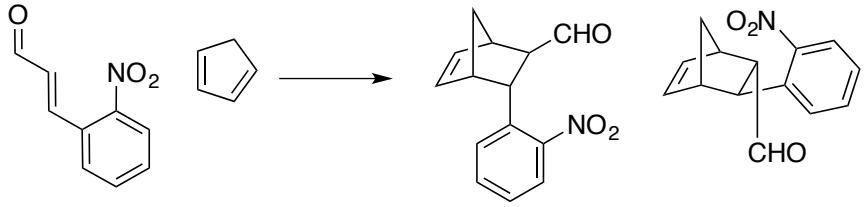


Following purification, the adduct (158 mg, 0.69 mmol) was dissolved in anhydrous Et_2O (10 mL). $LiAlH_4$ (26 mg, 0.69 mmol, 1 equiv.) was added the reaction stirred until competition was observed by TLC. Purification by column chromatography (9:1, light petroleum ether/EtOAc) afforded the product as an inseparable mixture of diastereoisomers as a colourless oil.

Data of a mixture ***endo***:***exo***:

$\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3056, 2964, 1611, 1580, 1511, 1464, 1265, 1246, 1034, 910, 743; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.07 (4H, m, C*H* arom), 6.90-6.73 (4H, m, C*H* arom), 6.37- 6.32 (1H, m), 6.14 (1H, dd, *J*= 5.7, 2.8 Hz), 5.94 (1H, dd, *J*= 5.7, 2.8 Hz), 3.88 (1H, dd, *J*= 10.5, 6.0 Hz), 3.79 (3H, m), 3.76 (3H, m), 3.66 (1H, dd, *J*= 10.5, 9.0 Hz) 3.61 (1H, dd, *J*= 10.5, 6.0 Hz), 3.38 (1H, dd, *J*= 10.5, 9.0 Hz), 3.01 (2H, br d, *J*= 17.5 Hz), 2.84 (1H, dd, *J*= 14.6, 1.5 Hz), 2.79 (1H, dd, *J*= 5.0, 3.5 Hz), 2.37-2.27 (1H, m), 2.11-2.07 (1H, m), 1.88-1.84 (2H, m), 1.75 (1H, d, *J*= 8.5 Hz), 1.63 (1H, d, *J*= 8.5 Hz), 1.59-1.54 (2H, m), 1.54-1.50 (1H, m), 1.26 (1H, s), 1.21 (1H, d, *J*= 6.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 157.8, 138.7, 137.5, 137.0, 136.1, 134.6, 134.1, 129.0, 128.9, 128.4, 113.8, 113.4, 66.9, 66.6, 55.3, 55.2, 50.8, 50.4, 50.1, 49.4, 49.2, 48.8, 47.5, 47.1, 47.0, 47.0, 44.8, 44.1. HRMS (NSI^+) *m/z* found 248.1646 $[M+NH_4]^+$; $[C_{15}H_{22}O_2N]^+$ requires 248.1645; Enantiomeric excesses were determined using Chiralcel® AS-3 column (hexane/iPrOH=95:5, λ=222 nm), 0.5 mL; ***endo*** isomer (t_R1 35 min, 59 min) ***exo*** isomer (t_R1 39 min, 56 min)).

3-(2-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde[17]



exo *endo*

(*E*)-2-Nitrocinnamaldehyde (177 mg, 1.0 mmol, 1 equiv.) and catalyst (10 mol%) were dissolved in MeOH:H_2O (95/5 *v/v*, 1 mL). The solution stirred for 5 minutes before the addition of cyclopentadiene (252 μL, 3 mmol, 3 equiv., freshly distilled). The reaction was followed by analysis of TLC. After hydrolysis of diacetal, crude NMR analysis allowed conversion to be calculated and assignment of the diastereomeric ratio (***exo*** δ 9.80 (1H, d, *J*= 2.2 Hz, C*H*O): ***endo*** δ 9.40 (1H, d, *J*= 3.5 Hz, C*H*O)). Column chromatography (9:1 light petroleum ether/EtOAc) afforded the product as an inseparable mixture of diastereoisomers as a yellow oil. Data matches literature reported values.[17]

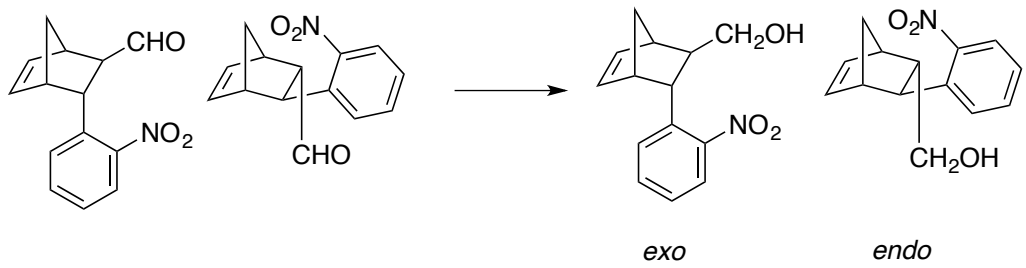
Exo **compound** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (1H, d, *J*= 2.2 Hz, C*H*O), 7.72 (1H, dd, *J*= 8.0, 1.5 Hz, C*H* arom), 7.45-7.41 (1H, m, C*H* arom), 7.36-7.30 (1H, m, C*H* arom), 7.18 (1H, dd, *J*= 8.0, 1.0 Hz, C*H* arom), 6.47 (1H, dd, *J*= 5.6, 3.2 Hz, C*H*=CH), 6.02 (1H, dd, *J*= 5.6, 3.0 Hz, CH=C*H*), 4.09 (1H, dd, *J*= 5.2, 3.3 Hz, C*H*Ar), 3.37 (1H, br s, C*H*CH_2), 3.31-3.26 (1H, m, C*H*CH_2), 2.63-2.58 (1H, m, C*H*CHO), 1.67-1.60 (1H, m, CH_2), 1.60-1.57 (1H, m, CH_2);

Endo **compound** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (1H, d, *J*= 3.5 Hz, C*H*O), 7.82 (1H, dd, *J*= 8.0, 1.5 Hz, CH arom), 7.59-7.52 (2H, m, C*H* arom), 7.39 (1H, ddd, *J*= 8.4, 7.3, 1.5 Hz, C*H* arom), 6.50 (1H, dd, *J*= 5.6, 3.2 Hz, C*H*=CH), 6.22 (1H, dd, *J*= 5.7, 2.8 Hz, CH=C*H*), 3.44 (1H, dd, *J*= 5.0, 1.0 Hz, C*H*Ar), 3.34-3.30 (1H, m, C*H*CH_2), 3.13-3.11 (1H, m, C*H*CH_2), 2.95 (1H, dt, *J*= 5.2, 3.6 Hz, C*H*CHO), 1.84 (1H, dt, *J*= 9.0, 1.5 Hz, CH_2), 1.69-1.68 (1H, m, CH_2);

For the mixture*:* ν_{max}($CHCl_3$)/cm^{-1} 3054, 2986, 2825, 2305, 2254, 1717, 1687, 1527, 1421, 1351, 1263, 746, 705; ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 201.5, 139.2, 137.3, 137.0, 136.3, 136.1, 134.2, 132.8, 131.8, 128.9, 127.9, 127.4, 127.3, 124.8,

124.0, 59.3, 59.0, 49.8, 49.2, 48.2, 47.2, 46.6, 46.3, 41.7, 40.1; HRMS (NSI^-) *m/z* found 242.0811 $[M-H]^-$; $[C_{14}H_{12}NO_3]^-$ requires 242.0812.

3-(2-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol compound

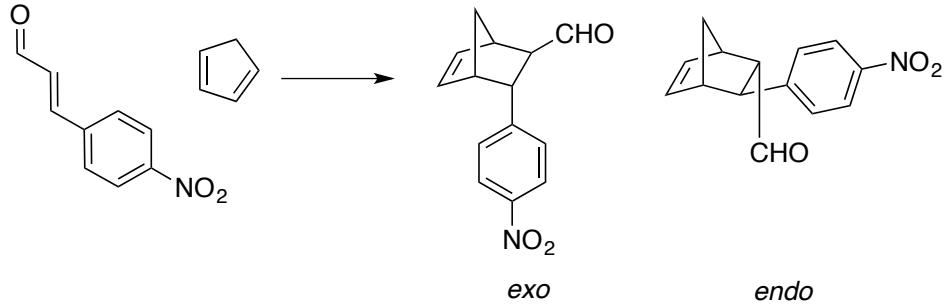


Following purification, the adduct (140 mg, 0.58 mmol) was dissolved in anhydrous Et_2O (10 mL). $LiAlH_4$ (22 mg, 0.58 mmol, 1 equiv.) was added the reaction stirred until competition was observed by TLC. Purification by column chromatography (9:1, light petroleum ether/EtOAc) afforded the product as an inseparable mixture of diastereoisomers as a pale yellow oil.

Data of a mixture ***endo***:***exo***:

$\nu_{max}(CHCl_3)/cm^{-1}$ 3064, 2973, 1717, 1523, 1351, 723; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, dd, *J* = 8.0, 1.4 Hz, C*H* arom), 7.63 (2H, ddd, *J* = 8.0, 3.5, 1.1 Hz, C*H* arom), 7.54 (1H, td, *J* = 7.8, 1.4 Hz, C*H* arom), 7.40 (1H, dd, *J* = 7.3, 1.0 Hz, C*H* arom), 7.36 – 7.26 (3H, m, C*H* arom), 6.47 (1H, dd, *J* = 5.6, 3.2 Hz), 6.42 (1H, dd, *J* = 5.6, 3.1 Hz), 6.15 (1H, dd, *J* = 5.7, 2.9 Hz), 5.89 (1H, dd, *J* = 5.6, 2.9 Hz), 3.76 (1H, dd, *J* = 10.6, 6.3 Hz), 3.63 (1H, dd, *J* = 10.5, 8.2 Hz), 3.45 (1H, dd, *J* = 10.6, 6.0 Hz), 3.35 (1H, dd, *J* = 10.6, 8.0 Hz), 3.18 (1H, dd, *J* = 5.2, 3.2 Hz), 3.11 (2H, dd, *J* = 7.5, 1.8 Hz), 2.91 (1H, d, *J* = 1.4 Hz), 2.80 (1H, d, *J* = 1.4 Hz), 2.58-2.50 (2H, m), 2.00-1.93 (2H, m), 1.77 (2H, d, *J* = 8.9 Hz), 1.69 (2H, d, *J* = 8.8 Hz), 1.58-1.52 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 137.4, 134.0, 131.5, 129.1, 126.8, 123.4, 66.5, 50.7, 49.3, 48.0, 45.1, 42.6, 14.2; HRMS (NSI^+) *m/z* found 246.1124 $[M+H]^+$; $[C_{14}H_{16}NO_3]^+$ requires 246.1125; Enantiomeric excesses were determined using Chiralcel® AD-H column (hexane/iPrOH=95:5, λ=254 nm), 0.5 mL; ***endo*** isomer (t_R1 37 min, 39 min) *exo* isomer (t_R1 41 min, 50 min)).

3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde[17]



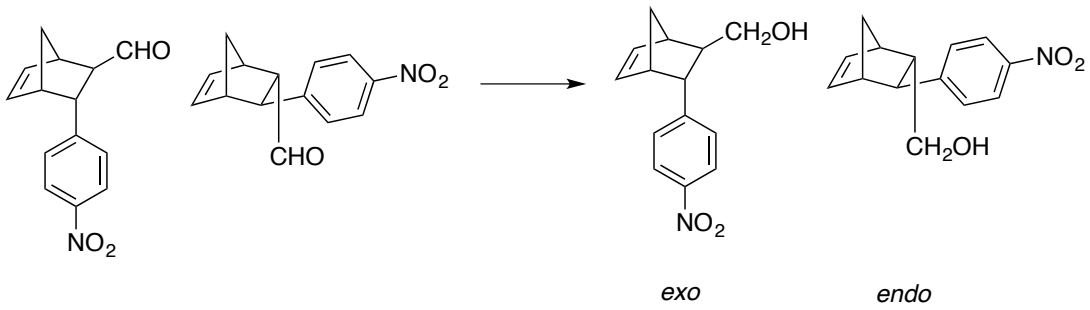
(*E*)-4-Nitrocinnamaldehyde (177 mg, 1.0 mmol, 1 equiv.) and catalyst (10 mol%) were dissolved in MeOH: H_2O (95/5 *v/v,* 1 mL). The solution stirred for 5 minutes before the addition of cyclopentadiene (252 μL, 3 mmol, 3 equiv., freshly distilled). The reaction was monitored by TLC. After hydrolysis of diacetal, crude NMR analysis allowed conversion to be calculated and assignment of the diastereomeric ratio (***exo*** δ 9.92 (1H, d, *J*= 2.0 Hz, C*H*O): ***endo*** δ 9.65 (1H, d, *J*= 2.0 Hz, C*H*O)). Column chromatography (9:1 light petroleum ether/EtOAc) afforded the product as an inseparable mixture of diastereoisomers as a yellow oil. Data matches literature reported values.[17]

Exo **compound** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (1H, d, *J*= 2.0 Hz, C*H*O), 8.12-8.01 (2H, m, C*H* arom), 7.36-7.26 (2H, m, C*H* arom), 6.41 (1H, dd, *J*= 5.5, 3.0 Hz, C*H*=CH), 6.05 (1H, dd, *J*= 5.5, 3.0 Hz, CH=C*H*), 3.89 (1H, dd, *J*= 5.0, 3.5 Hz, C*H*Ar), 3.34-3.29 (1H, m, C*H*CH_2), 3.26 (1H, br s, C*H*CH_2), 2.64 (1H, d, *J*= 5.2 Hz, C*H*CHO), 1.62-1.59 (2H, m, CH_2);

Endo **compound** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (1H, d, *J*= 2.0 Hz, C*H*O), 8.22-8.12 (2H, m, C*H* arom), 7.48-7.35 (2H, m, C*H* arom), 6.44 (1H, dd, *J*= 6.0, 3.5 Hz, C*H*=CH), 6.20 (1H, dd, *J*= 6.0, 3.0 Hz, CH=C*H*), 3.44 (1H, br s, C*H*CH_2), 3.21-3.19 (2H, m, C*H*Ar, C*H*CH_2), 2.98 (1H, ddd, *J*= 5.0, 3.5, 1.7 Hz, C*H*CHO), 1.78-1.68 (2H, m, CH_2);

For the mixture: $\nu_{max}(CHCl_3)/cm^{-1}$ 2972, 1715, 1596, 1515, 1495, 1345, 1107, 721; ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.1, 201.6, 171.1, 151.7, 150.6, 146.5, 146.3, 139.0, 137.0, 135.9, 134.0, 128.7, 128.2, 123.7, 123.3, 61.1, 60.3, 59.5, 48.4, 47.9, 47.6, 47.1, 45.6, 45.5, 45.1, 45.0, 21.0, 14.2; HRMS (NSI^-) *m/z* found 242.0811 $[M-H]^-$; $[C_{14}H_{12}NO_3]^-$ requires 242.0812.

3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol



Following purification, the adduct (210 mg, 0.86 mmol) was dissolved in anhydrous Et_2O (10 mL). $LiAlH_4$ (32 mg, 0.86 mmol, 1 equiv.) was added the reaction stirred until competition was observed by TLC. Purification by column chromatography (9:1, light petroleum ether/EtOAc) afforded the product as an inseparable mixture of diastereoisomers as a colourless oil.

Data of a mixture ***endo**: **exo***:

^1H NMR (500 MHz, $CDCl_3$) δ 8.18-8.12 (2H, m, C*H* arom), 8.10-8.06 (2H, m, C*H* arom), 7.51-7.46 (2H, m, C*H* arom), 7.38-7.34 (2H, m, C*H* arom), 6.40-6.37 (2H, m), 6.19 (1H, dd, *J*= 6.0, 3.0 Hz), 5.91 (1H, dd, *J*= 6.0, 3.0 Hz), 3.85 (1H, dd, *J*= 10.5, 7.0 Hz), 3.75 (1H, dd, *J*= 10.5, 8.0 Hz), 3.58 (1H, dd, *J*= 10.5, 7.0 Hz), 3.51 (1H, dd, *J*= 10.5, 8.0 Hz), 3.09 (1H, s), 3.07 (1H, s), 3.04-2.98 (1H, m), 2.97-2.95 (1H, br m), 2.90-2.89 (1H, br m), 2.38-2.31 (1H, m), 2.31-2.28 (1H, br m), 1.98-1.92 (1H, m), 1.72 (2H, br dd, *J*= 15.5, 8.5 Hz), 1.64 (1H, ddd, *J*= 8.8, 3.3, 1.7 Hz), 1.59 (1H, ddd, *J*= 8.8, 3.3, 1.6 Hz), 1.53 (2H, br s); $\nu_{max}(CHCl_3)/cm^{-1}$ 3418, 3054, 2986, 1265, 739; ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 152.2, 146.4, 146.2, 138.3, 138.3, 134.8, 134.0, 128.8, 128.3, 123.6, 123.2, 66.7, 66.4, 50.8, 50.0, 48.9, 48.8, 48.7, 48.1, 47.4, 47.1, 45.0, 44.4; HRMS (NSI^+) *m/z* found 263.1390 $[M+NH_4]^+$; $[C_{14}H_{19}N_2O_3]^+$ requires 263.1386; Enantiomeric excesses were determined using

Chiralcel® AD-H column (hexane/iPrOH=90:10, λ=254 nm), 0.5 mL; ***endo*** isomer (t_R1 49 min, 57 min) ***exo*** isomer (t_R1 43 min, 53 min)).

Experimental references

[1] The m.p. and αD values recorded in Aldrich catalogue

[2] P. C. B. Page, B. R. Buckley, M. M. Farah, A. J. Blacker, *Eur. J. Org. Chem*., **2009**, 3413–3426

[3] T. Mecca, S. Superchi, E. Giorgio, C. Rosisini, *Tetrahedron: Asymmetry*, **2001**, 12, 1225–1233

[4] M. Ikunaka, K. Maruoka, Y. Okuda, T. Ooi, *Org. Proc. Res. Dev.*, **2003**, 7, 5, 644–648

[5] T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc*., **2003**, 125, 5139–5151

[6] J. M. Hawkins, T. A. Lewis, *J. Org. Chem*., **1994**, 59, 649–652

[7] J. M. Hawkins, G. C. Fu, *J. Org. Chem.,* **1986**, 51, 2822–2824

[8] H. Osato, M. Osaki, T. Oyama, Y. Takagi, T. Hida, K. Nishi, M. Kabaki, *Org. Proc. Res. Dev.,* **2011**, 15, 1433–1437

[9] S. Pisani, S. Superchi, *Tetrahedron Asymmetry*, **2008**, 19, 1784–1789

[10] S. Pira, T.W. Wallace, J.P. Graham, *Organic Letters,* **2009**, 11, 7, 1663–1666

[11] A. I. Meyers, T. H. Nguyen, *Tetrahedron Lett.*, **1995**, 36, 5873–5876

[12] P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, D. Bethell, E. Merifield, *Synlett,* **2002**, 4, 580–582

[13] S. E. Denmark, H. Matsuhashi, *J. Org. Chem*., **2002**, 67, 3479–3486

[14] M. B. Andrus, D. Asgari, J. A. Sclafani, *J. Org. Chem*., **1997**, 62, 26–29

[15] E. Gould, T. Lebl. A. M. Z. Slawin, M. Reid, T. Davies, A. D. Smith, *Org. Biomol. Chem*., **2013**, 11, 7877–7892

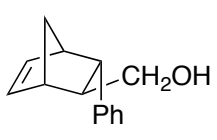
[16] C. A.Wang, , Y. Zhang, J. Y. Shi, W. Wang, *Chem. Asian J.*, **2013**, 8, 1110–1114

[17] H. Gotoh, Y. Hayashi, *Org. Lett*, **2007**, 9, 2859–2862

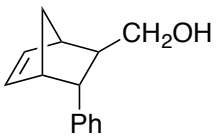
Appendix

HPLC traces

Racemic trace:

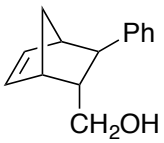


(1*R*,2*S*,3*S*,4*S*)-**284**

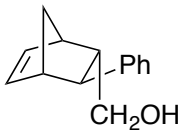


(1*S*,2*R*,3*R*,4*R*)-**284**

exo



(1*R*,2*R*,3*R*,4*S*)-**285**

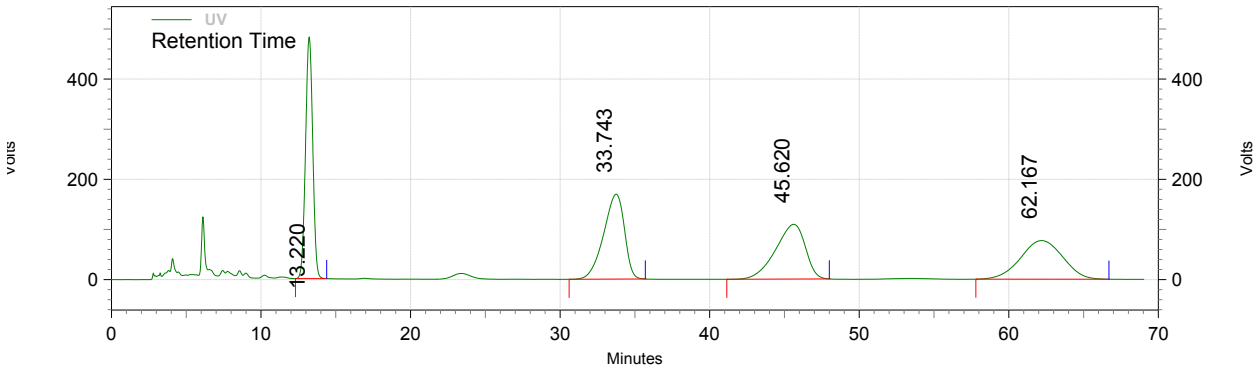


(1*S*,2*S*,3*S*,4*R*)-**285**

endo

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Fran\diels alder\fk80a 80.20 60 min ojnew col 222nm new OJ.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Fran\diels alder\80.20 1ml 222nm 60 min.met
Acquired: 11/08/2015 17:07:43
Printed: 12/08/2015 09:43:30

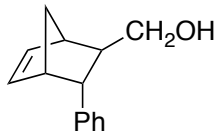


UV Results

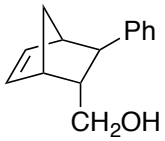
Retention Time	Area	Area %	Height	Height %
13.220	64536756	25.71	1928102	57.55
33.743	65498431	26.09	677564	20.22
45.620	60424958	24.07	436586	13.03
62.167	60578598	24.13	308081	9.20

Totals	251038743	100.00	3350333	100.00

Area % Report
Major products:



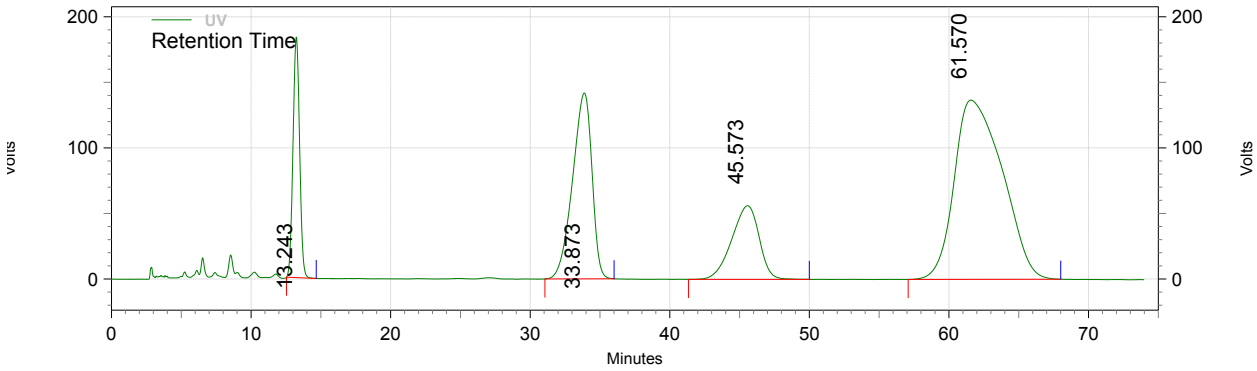
(1*S*,2*R*,3*R*,4*R*)-**284**
45.6 and 61.6 min



(1*R*,2*R*,3*R*,4*S*)-**285**
13.2 and 33.9 min

exo:endo
1:0.4
endo 39% ee
exo 62% ee

Data File: C:\EZChrom Elite\Enterprise\Projects\Fran\diels alder\fk141A 80.20 70 min OJ 222nm 1 ml.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Fran\diels alder\80.20 1ml 222nm 70 min.met
Acquired: 27/08/2015 13:40:54
Printed: 27/08/2015 15:01:49



UV Results

Retention Time	Area	Area %	Height	Height %
13.243	24066176	10.00	733768	35.40
33.873	54790835	22.76	567050	27.36
45.573	30757918	12.78	224860	10.85
61.570	131091183	54.46	546904	26.39

Totals				
	240706112	100.00	2072582	100.00