

New axially chiral amine organocatalysts

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**This thesis is submitted in partial fulfilment of the
requirements of the degree of Doctor of Philosophy at the
University of East Anglia, UK**



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Preface

The work described within this thesis is, to the best of my knowledge, original and my own work, except where due reference has been made.

Ian Strutt
Norwich, September 2014

For Nell and Ernie, who would have been proud.

0.2 Abstract

Organocatalysis has become one of the most popular areas of research within organic chemistry over the past 15 years. This is due to the fact that, usually under mild conditions, it is possible to access either highly functionalized or previously inaccessible structural motifs using this relatively new type of catalysis.

Firstly, methodology is reported for the synthesis and use of tertiary amine organocatalysts based on the now ubiquitous binaphthyl backbone. The tertiary amines synthesized were shown to be effective nitrogen transfer reagents in the asymmetric aziridination of chalcone substrates, with enantiomeric excesses of up to 37% seen. The first example of an isolated chiral hydrazinium salt being used as a nitrogen transfer reagent for the aziridination of enones is also described.

Secondly, a range of α -substituted secondary amines based on the binaphthyl backbone has been synthesized from easily accessible iminium salts. Preliminary catalyst testing showed them to be interesting alternatives to the more commonly seen proline-derived catalysts for asymmetric conjugate additions reactions between cyclic enones and malonates, with enantiomeric excesses of 24% seen using optimized conditions.

0.3 Acknowledgments

First and foremost, I would like to thank Prof Phil Page for allowing me to work in his group for the four years I was in Norwich. Not only have I enjoyed my time working with him, but also the time spent in his company outside the lab.

Secondly, I would like to thank Dr Yohan Chan. The lab would surely have fallen apart around us without his constant help. He has also proved to be a most excellent drinking partner.

The Page group past and present have been really welcoming and really helpful over the four years I spent in the lab. Chris Pearce, Chris Bartlett and David Day really got me on my feet in the lab when I started and the present Page group were always a pleasure to work with.

Special thanks must go to C  line Bordogna, whose work I continued and also to Amanda Chang and Francesca Kinsey, who have contributed so much to this project and will continue to work on it in the future.

Around the department at UEA, I would like to thank Ketan Panchal, Becky Turner, Doyle Cassar, Mark Walton, Ryan Tinson, Julien Doulcet, Oliver McGaw and everyone else I have had the pleasure to work with. You have all proven to be exception coffee drinking companions for these last four years as we all went through the trials and tribulations of our respective projects.

I would like to thank my parents for their unconditional support, financial or otherwise, over the course of these four years. While I am still not convinced they have the faintest idea what I am doing, they have been unerringly helpful in any way they can.

Finally, Libby Dawes made the final year of my PhD so much more bearable by being there for me outside of the lab. She always managed to pick me up when that one reaction had failed for the 5th time or when I'd dropped something important on the floor. For this, I will forever be grateful.

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0.5 Abbreviations

Ac Acetyl

AIBN Azobisisobutyronitrile

atm Atmosphere

BINAP 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

BINOL 1,1'-Bi-2-naphthol

Boc *tert*-butyloxycarbonyl

Bs *p*-bromobenzenesulfonyl

Bz Benzyl

Cat* Catalyst

Cbz Benzyloxycarbonyl

cy Cyclohexyl

DBSPINOL 4,4'-Dibromo-1,1'-spirobiindane-7,7'-diol

DCM Dichloromethane

DCE 1,2-Dichloroethane

de Diastereoisomeric excess

DIPEA Diisopropylethylamine

DMAP *N,N'*-Dimethylaminopyridine

DME 1,2-Dimethoxyethane

DMF *N,N'*-dimethylformamide

DMSO Dimethylsulfoxide

Dpp Diphenylphosphinyl

Dppp 1,3-Bis(diphenylphosphino)propane

ee Enantiomeric excess

Et Ethyl

HOSA Hydroxylamine *O*-sulfonic acid

HPLC High performance liquid chromatography

*i*Pr Isopropyl

Me Methyl

MSH Mesitylsulfonylhydroxylamine

NBS *N*-bromosuccinimide

NHC *N*-heterocyclic carbene

NMM *N*-methylmorpholine

NMR Nuclear magnetic resonance
NMP *N*-methylpyrrolidine
NOESY Nuclear Overhauser effect spectroscopy
OTf Trifluoromethanesulfonate (triflate)
Oxone[™] Potassium peroxymonosulfate
Pf Phenylfluoren-9-yl
ppm Parts per million
p-TSA *p*-Toluenesulfonic acid
py Pyridine
Red-Al Sodium bis(2-methoxyethoxy)aluminium hydride
R_f Retention factor
rt Room temperature
TASF Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBS Tert-butylsilyl
^tBu *tert*-Butyl
TEA Triethylamine
TFA Trifluoroacetic acid
THF Tetrahydrofuran
TLC Thin layer chromatography
Tol Toly
Ts Tosyl

1.1 Organocatalysis – An Introduction

Ever since it was realized that the spatial arrangement of atoms within molecules could dramatically affect their properties, there has been an exponential increase in the amount of research going into the enantioselective synthesis of compounds. The most cost-effective way to synthesize these molecules is to use a small amount of an enantiomerically pure catalyst to effect the transformation and it is these enantioselective reactions that have had the greatest impact on organic chemistry in the last three decades. In 2000, it was estimated that approximately one third of all marketed drugs contained at least one centre of chirality.¹ Today, it is possible to separate the massive array of enantioselective catalysts available into three main categories:

- Organometallic complexes, which utilize reactive metal centres and chiral organic ligands to effect enantioselective reactions
- Bioorganic catalysts (e.g. enzymes), which utilize biological macromolecules
- Organocatalysts, which utilize small enantiopure organic molecules as catalysts without the need for metal centres

The earliest examples of highly selective asymmetric catalysis generally utilized organometallic complexes due to the fact that their properties could be easily tuned by altering either the metal centre or the ligand. However, organometallic catalysis does have its problems, normally associated with either the expense of the metal concerned or with the toxicity of the metal residues left in the products of these reactions. Although enantioselectivity is generally extremely high in these processes, it is sometimes the case that cost is prohibitive on a large (industrial) scale due to the cost of the catalyst itself or its removal from the waste stream following the completion of the reaction. The same thing can be said for enzymatic transformations, as isolation of the required enzymes on a large scale can be extremely expensive in practice.

A currently burgeoning area of catalytic organic chemistry is that of asymmetric organocatalysis. That is, the use of small organic molecules to effect enantioselective reactions. This area of chemistry has exploded onto the scene in the past decade with close to 2000 articles published on the subject between the

coining of the term in 1998 and 2008. These publications have described enantioselective variants of over 130 different chemical manipulations.²

Organocatalysis has many advantages over other forms of catalysis. It is often the case that organocatalysts are far more stable than their organometallic counterparts, making them generally far more tolerant of air or moisture, negating the need for rigorously anhydrous conditions. They are also generally less expensive to prepare than other catalysts with many being available directly from the chiral pool. Finally, their relative stability allows for facile covalent attachment to solid supports and also allows for their possible use (and subsequent reuse) in high throughput screening and continuous flow chemistry. These factors have clearly contributed to the burgeoning area of organocatalysis as it means that any research group can now partake in this area of research without the need for expensive equipment or reagents. This is exemplified in figure 1, whereby the number of papers containing the word “organocatalysis” published in the years 2000 – 2007 is presented.³

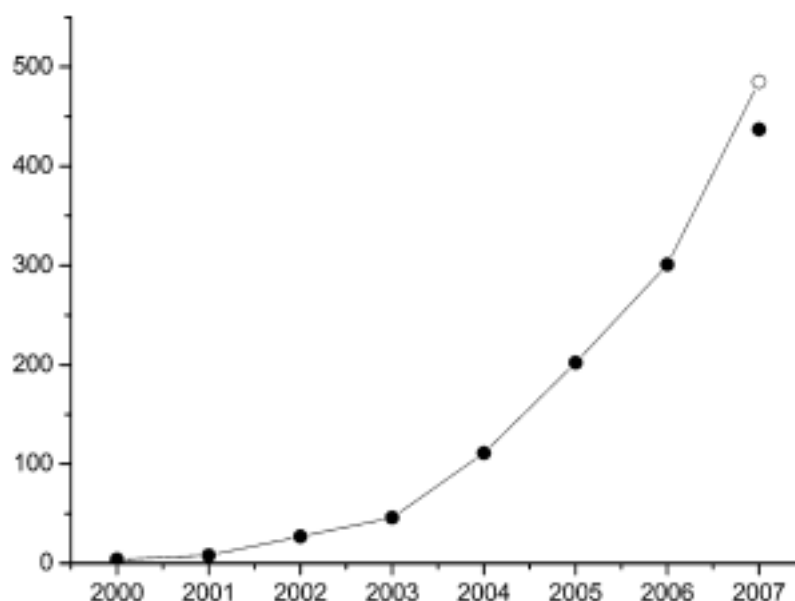
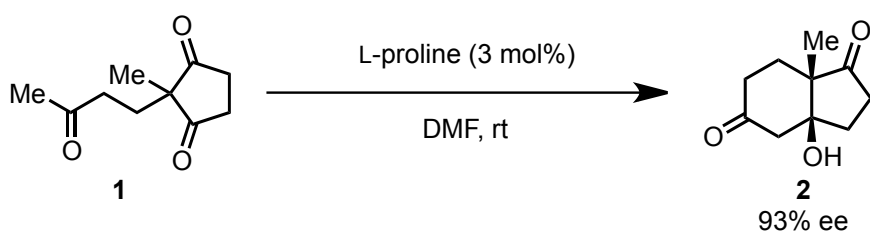
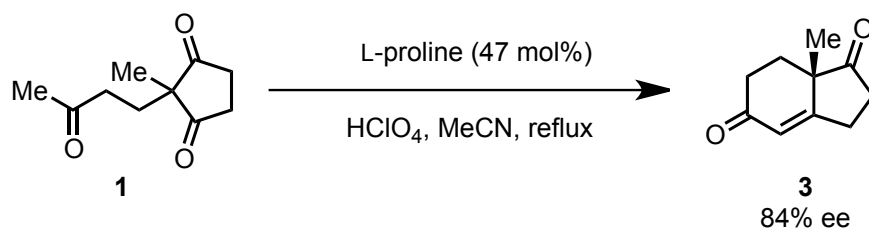


Figure 1 Publications containing the word “organocatalysis” published between 2000 & 2007

The first examples of what we now know as organocatalysis were seen nearly a century ago, when organic chemistry was still in its infancy. Several accounts, including those by Bredig,^{4,5} Ostwald,⁶ Marckwald,⁷ and Langenbeck⁸ exist from the first half of the last century. Unfortunately, none of these were particularly selective and sustained work in the area was not forthcoming. Even over the second half of the century there have only been sporadic publications on organocatalytic processes. The discovery of DMAP and related structures as esterification catalysts by Steglich was a bright spot.⁹ However, this was clearly not an enantioselective catalyst. The first publications of note on the subject of enantioselective organocatalysis were simultaneous papers by Hajos and Parrish,¹⁰ and Eder, Sauer, and Wiechert¹¹ in 1974, which showed that the asymmetric intermolecular aldol reaction between triketone **1** catalysed by (S)-(-)-proline, yielded either the bicyclic ketol **2** or the α,β -unsaturated ketone **3** depending on the conditions used (Schemes 1 & 2).



Scheme 1 The Hajos-Parrish reaction



Scheme 2 The Eder-Sauer-Wiechert reaction

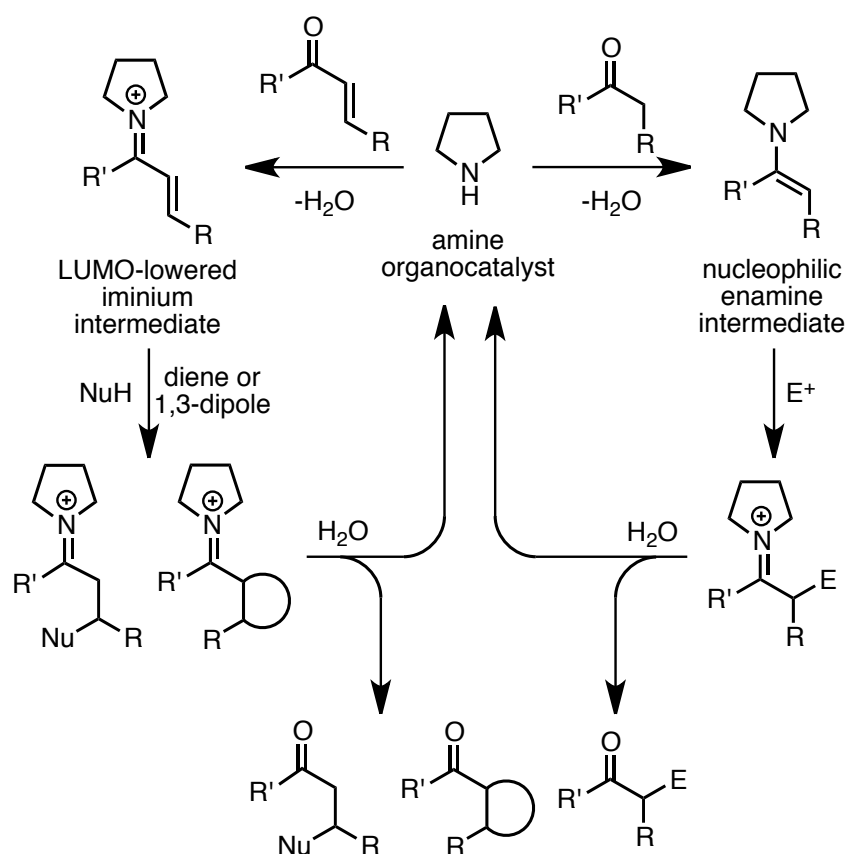
Unfortunately, while this work was well received it did not spur any sustained research in the field, possibly due to the fact that it was seen as more of an anomaly than as something that could spawn a whole new connected area of homogeneous catalysis. A 25-year hiatus unfortunately then occurred, presumably due to the impetus put on metal-based catalysts such as those developed by Evans and

others.¹² This is supported by two facts, one being that not a single review of this type of chemistry was published before 1998 and also the fact that the world renowned chemist Dieter Seebach published an article in 1990 on the future of organic chemistry stating that the discovery of truly new reactions is likely to be limited to the realm of transition-metal organic chemistry, which will almost certainly provide us with additional miracle reagents in the years to come whilst completely failing to mention the concept of organocatalysis at all.¹³

It was not until the work of Shi,¹⁴ Denmark,¹⁵ Yang,¹⁶ and Page¹⁷ on organocatalytic dioxirane and iminium salt mediated epoxidation in the late 1990's that the area of organic catalysis truly took off. While these were clearly important steps forward, the problem with these catalysts are that they are single catalysts with a single use for one transformation. As such, even though organocatalysis as we know it today was discovered many years ago, mainstream research into its use has truly exploded in the past decade following the simultaneous discovery of iminium and enamine based secondary amine organocatalysis by MacMillan and List in 2000. The seminal publications in the area were List's paper on proline-catalysed intramolecular aldol reactions¹⁸ and MacMillan's papers on organocatalytic Diels-Alder and 1,3-dipolar cycloaddition reactions.¹⁹ In both cases, many different reactions are catalysed by the same simple secondary amines. From these beginnings, in subsequent years single catalysts capable of catalysing highly enantioselective organocatalytic asymmetric variants of ubiquitous reactions such as the Mannich, Michael, aza-Henry, and Baylis-Hillman reactions as well as asymmetric oxidations, aminations and other cycloadditions have been discovered.²⁰ This has led one commentator to state that organocatalysis has truly matured "from infancy into adolescence" in recent years.²¹

1.2 Secondary Amine Organocatalysis

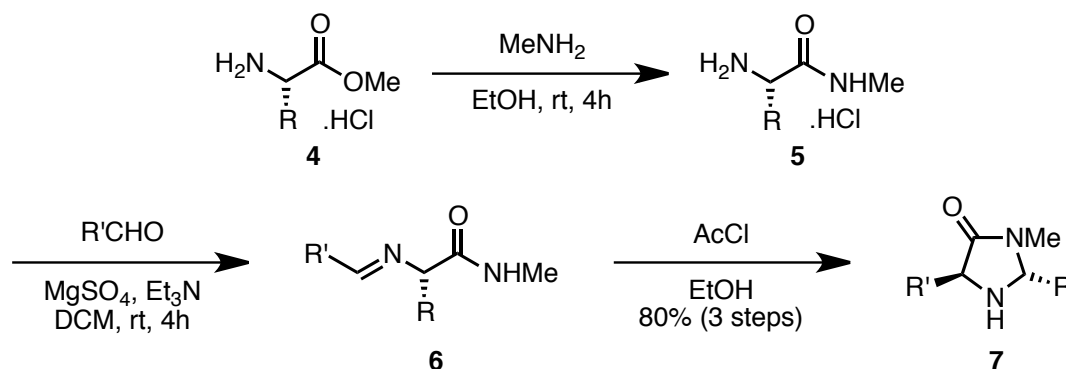
The publications by MacMillan and List discussed above defined two different paths that amine organocatalysis can proceed by. Iminium catalysis activates α,β -unsaturated aldehyde and ketone systems in the same way that Lewis acids do, by lowering the LUMO of one reactant in relation to the HOMO of the other, thus allowing the reaction to proceed. Enamine catalysis on the other hand is essentially a catalytic version of the Stork enamine reaction.²² Whereas enols exist as tautomers of ketones and aldehydes, amine organocatalysts allow chiral enamines to form far more readily, thus allowing for asymmetric α -functionalization of carbonyl substrates. In order for both of these types of transformations to be highly selective, different things must be considered when designing the catalysts. These two catalyst modes are represented in Scheme 3.²³



Scheme 3 The two most well-known forms of organocatalytic activation

1.2.1 Iminium Organocatalysis

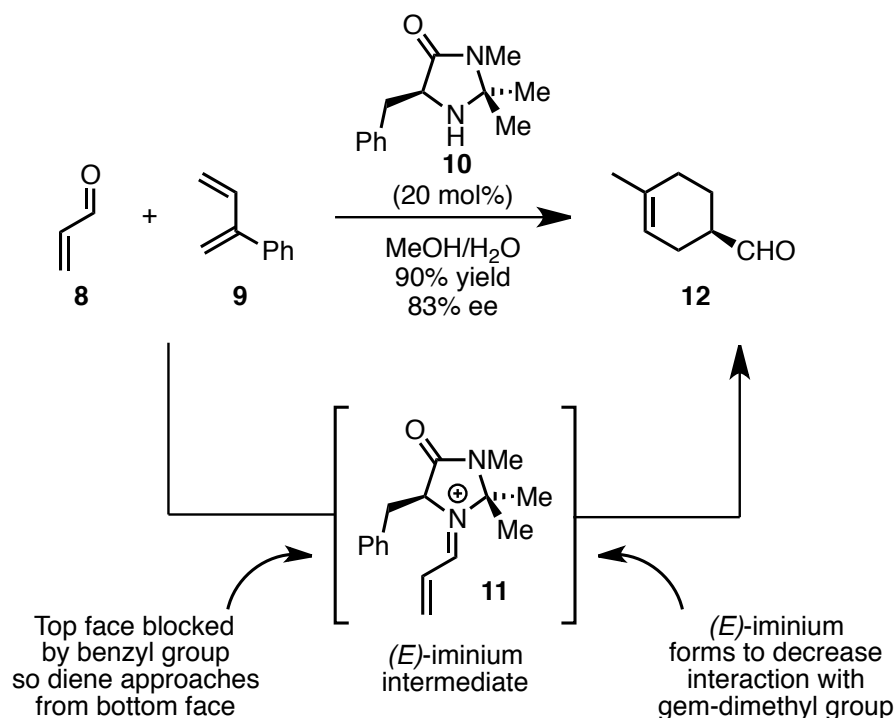
In the case of iminium amine organocatalysts, MacMillan has shown that the geometry of the iminium salt itself is one determining factor in the stereochemical outcome of the reaction.²⁴ This was the driving force behind the design of MacMillan's organocatalysts of the type **7**, which are derived in three steps from commercially available starting materials (Scheme 4).



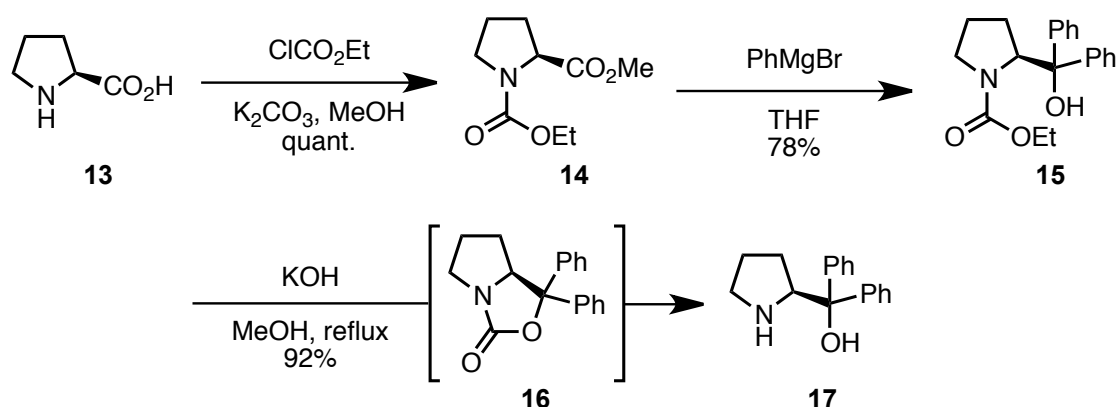
Scheme 4 General synthesis of MacMillan-type imidazolidinone organocatalysts

In the example shown in Scheme 5, the iminium intermediate **11** in the Diels-Alder reaction between acrolein **8** and 1,3-butadien-2-ylbenzene **9** catalysed by catalyst **10** will selectively form the (*E*)-isomer shown in order to avoid high-energy interactions between the acrolein moiety and the *gem*-dimethyl group present. This in turn means that any cycloaddition to the activated intermediate would have to be from the direction shown. The benzyl group effectively shields one face of the iminium intermediate, meaning that one enantiomer should form preferentially over the other. This proved to be the case, with good conversions and high ees seen throughout, giving compound **12** in 90% yield and 83% ee.

The diarylprolinol catalysts **17** simultaneously published by Jørgensen²⁵ and Hayashi²⁶ are also well-known iminium amine organocatalysts. The bulky TMS ether moiety effectively blocks one face of the formed iminium ion, allowing for selective reactions to occur. They are synthesized from proline according to a procedure published by Kanth and Periasamy (Scheme 6).²⁷



Scheme 5 Organocatalysed Diels-Alder reaction

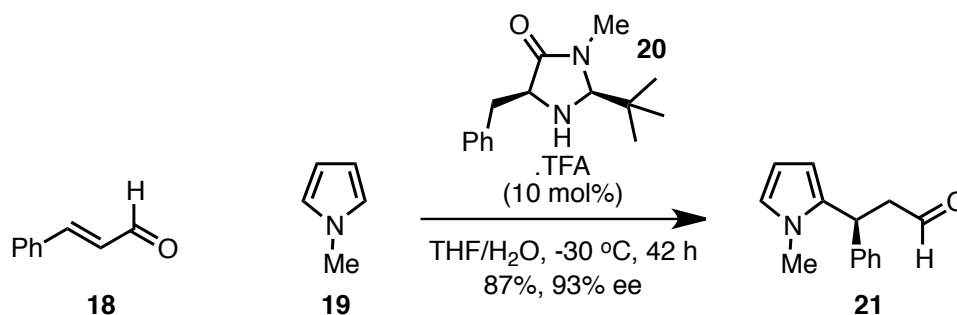


Scheme 6 General synthesis of Jørgensen-type diarylprolinol organocatalysts

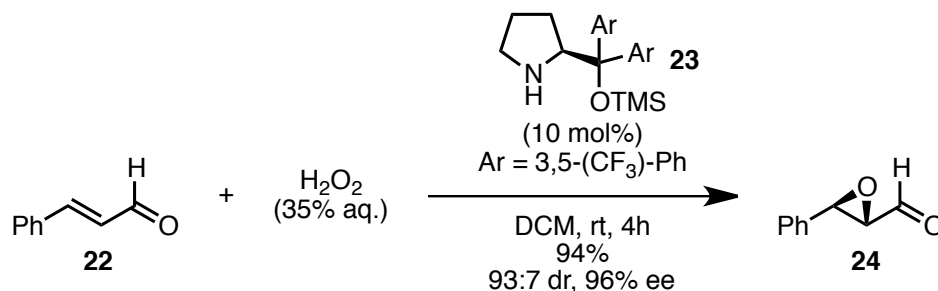
This synthesis is highly optimized and avoids drawbacks such as the instability of intermediates and the use of toxic reagents such as phosgene, which have been used in previous syntheses. A simple silylation yields the desired catalyst. Altering the Grignard reagent used can form a wide variety of potential catalysts with varying properties.²⁸

1.2.2 Examples of Iminium Organocatalysis

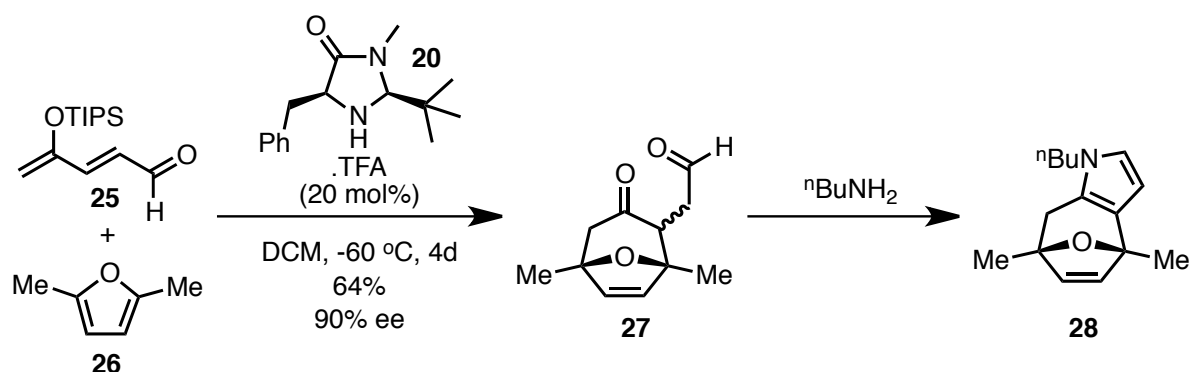
After the initial discovery of iminium catalysis by MacMillan, there have been countless examples of reactions of this type published in the literature.²⁹ A vast array of conjugate additions have been discovered, including conjugate hydride reductions using Hantzsch esters,³⁰ as well as the additions of malonates,³¹ nitroalkanes,³² and heterocycles such as pyrrole (Scheme 7),³³ to enals and enones, which form a wide range of architectures such as **21**. If a specialised type of nucleophile is used, it is also possible form epoxides of the type **24** (Scheme 8),³⁴ aziridinations,³⁵ and cyclopropanations.³⁶ Finally, there are several examples of 4+2,²⁴ 3+2,³⁷ and 4+3 (Scheme 9)³⁸ type cycloadditions in the literature that are effectively catalysed by organocatalysts, giving compounds such as **27**.



Scheme 7 Organocatalytic Friedel-Crafts Alkylation

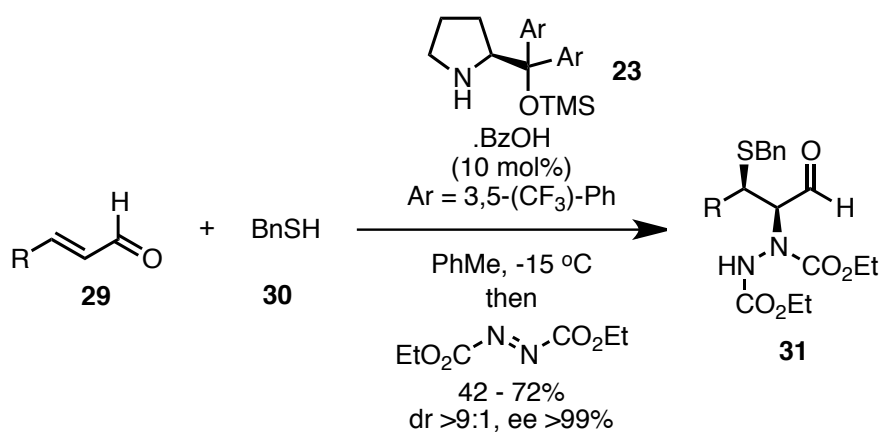


Scheme 8 Organocatalytic Epoxidation of Enals



Scheme 9 Organocatalytic 4+3 cycloaddition

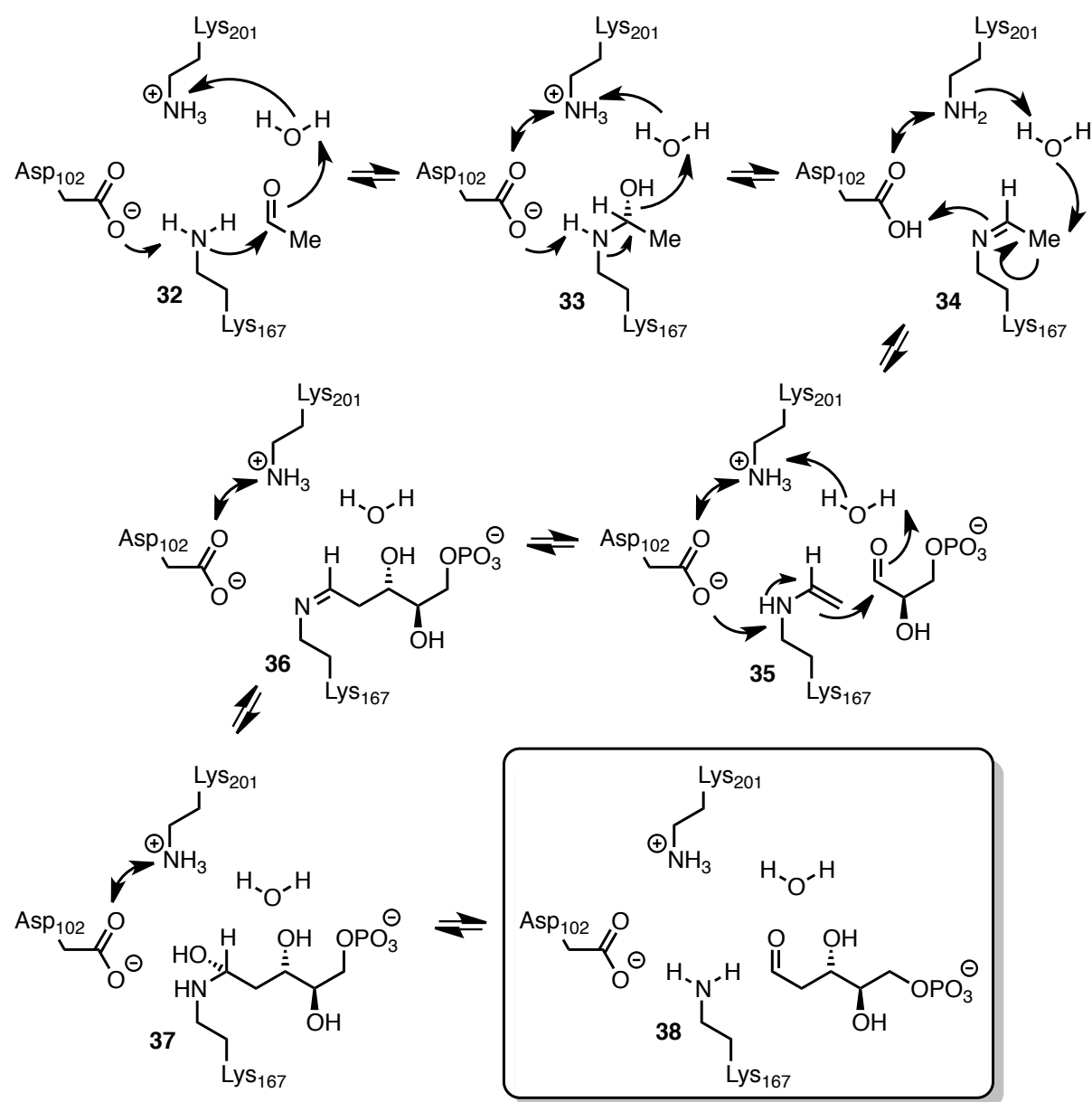
Finally, there are limited examples of reactions employing first iminium catalysis and subsequently enamine catalysis. Thus, many novel compounds have been discovered in this manner. An example, published by Jørgensen, is shown in Scheme 10.³⁹ Here, novel aminothiols such as **31** exhibiting leukotriene A4-hydrolase inhibition were synthesized in a facile, one-pot manner that would not have been possible using conventional organic chemistry techniques.



Scheme 10 General synthesis of Jørgensen-type diarylprolinol organocatalysts

1.3.1 Enamine Organocatalysis

Enamine type catalysts are often compared with type I aldolase enzymes, which are found *in vitro* and are essential cogs in glycolysis pathways, gluconeogenesis, and in the Calvin cycle.⁴⁰ Aldolases react in a similar manner to the previously described standard mechanism for enamine-based organocatalysis. This has been elegantly proven by Wong, Wilson and co-workers, who managed to obtain X-ray structures of proposed covalently bonded intermediates of a biochemical pathway involving an aldolase enzyme (Scheme 11).⁴¹



Scheme 11 Mechanism of Aldolase I catalysed aldol reactions
(double-headed arrows represent proton shuttling between Lys₂₀₁ & Asp₁₀₂)

These findings were also backed up by NMR studies of the same reaction pathway. It was this type of reactivity that List and Barbas were attempting to mimic in their initial publication on the proline-catalysed aldol reaction.¹⁸

The fact that these types of reactions do in fact proceed through an enamine intermediate has been the topic of debate over the years. Concerning the Hajos-Parrish intramolecular aldol reaction, there are several models that have been postulated over the years, by Hajos,¹⁰ Agami,⁴² Swaminathan,⁴³ and Houk.⁴⁴ Hajos initially dismissed the possibility of an enamine intermediate and instead proposed the formation of an aminocarbiniol intermediate (Figure 2) formed by direct nucleophilic addition of proline to one of the cyclic ketones in the starting material. This would then be attacked by the enol (present in equilibrium with the acyclic ketone) in the molecule.

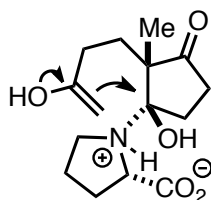


Figure 2 Hajos' initial postulation for the mechanism of the proline-catalysed asymmetric aldol condensation

This theory was discredited by List, who showed that ^{18}O was incorporated into the product when ^{18}O labelled H_2O was added to the reaction mixture after rigorously removing other water from the DMSO solvent used. This confirms that an iminium ion (and subsequently an enamine) must form that is subsequently hydrolysed by water in the reaction mixture once the reaction is complete.⁴⁵

Swaminathan proposed that this type of catalysis occurred heterogeneously, with the reaction occurring on the surfaces of the insoluble, crystalline proline in the reaction mixture, with the enantioselectivity arising from a templating effect (Figure 3).

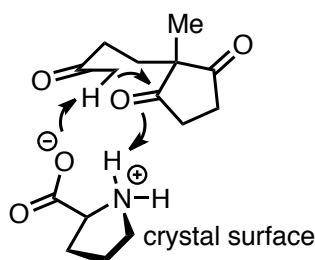


Figure 3 Heterogeneous template model postulated by Swaminathan

Swaminathan also stated that if a reaction containing solid proline as a catalyst was filtered, the reaction ceased to occur, and also quoted a patent by Hajos and co-workers that described the solventless proline catalysed aldol condensation soon after their initial publication.⁴⁶ This was again discredited by List, who stated simply that many aldol condensations catalysed by proline are completely homogeneous.

Thirdly, Agami has postulated a transition state for this reaction that involves two proline molecules taking part at the same time, with one forming the nucleophilic enamine and one acting as a proton donor (Figure 4).

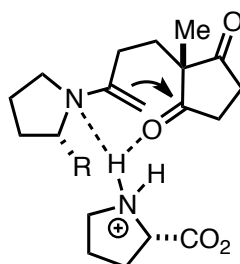


Figure 4 Two-proline model suggested by Agami

This process can be compared to the aldolase enzyme-mediated aldol reactions. He also stated that non-linear effects are at play in this type of reaction, which confirmed in his mind the need for two proline molecules in the transition state. List and co-workers, upon repeating this work, observed no such non-linear effects. Also, if two proline molecules were required for the transition state to form, one would expect a diminished rate and enantioselectivity if dilution were increased. Again, List found no evidence of this.⁴⁵

The most commonly accepted model for this type of reaction is that proposed by List and Houk. They propose a transition state containing only a single proline molecule with the carboxylate acting as the required proton donor, with a stabilized 6-membered ring formed. This can be described as a metal-free Zimmerman-Traxler model,⁴⁷ and accurately predicts the enantioselectivity seen in a variety of proline-catalysed aldol-type reactions. The favoured and disfavoured transition states of the reaction between acetone and acetaldehyde are shown in Figure 5.

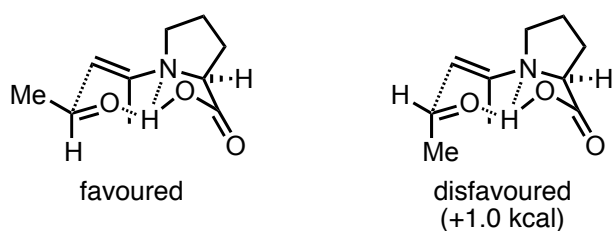


Figure 5 List-Houk model for the proline-catalysed asymmetric aldol reaction

The favoured model has the methyl group of the acetaldehyde in an equatorial position whereas it is axial in the disfavoured orientation. This reduces any steric hindrance that could occur. This effect would obviously be more pronounced with a larger aldehyde (p-nitrobenzaldehyde is the one most often used for catalyst testing). Also, for this 6-membered ring to form the enamine has to be in the *anti* configuration with respect to the carboxylic acid sidechain. Any other conformations result in a much higher energy transition state.

When considering the Hajos-Parrish reaction, this model also explains the selectivity seen. When compared to both the initial transition state proposed by Hajos as well as the uncatalysed transition state, modelling studies have shown the List-Houk intermediate to be lower in energy by upwards of 10 kcal mol⁻¹ (Figure 6).⁴⁸

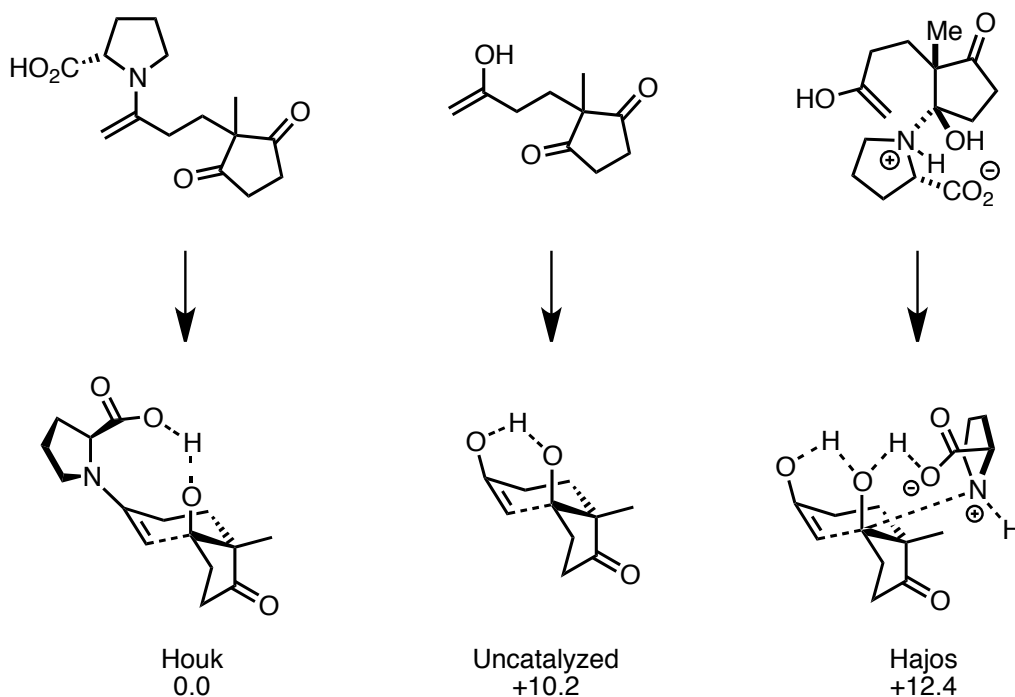
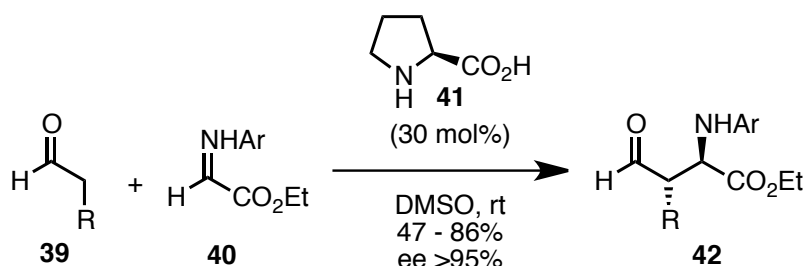


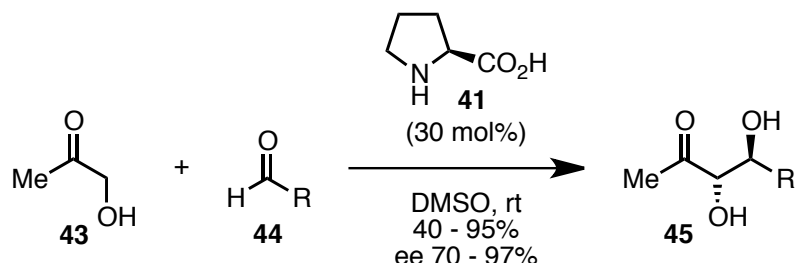
Figure 6 Comparison of three different models for the Hajos-Parrish reaction

1.3.2 Examples of Enamine Organocatalysis

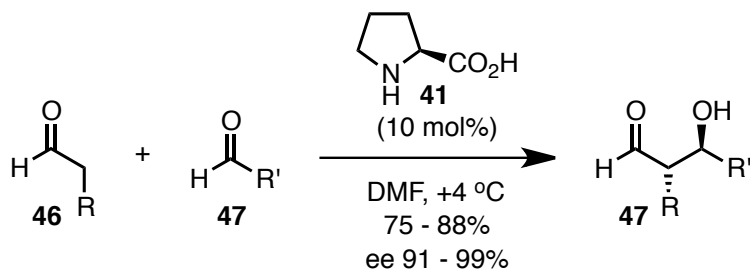
The initial publication by List instigated a rich period of investigation in this area.¹⁸ Within a few years, there were many variations of this aldol reaction published. The most important of these were published by List himself as well as MacMillan and co-workers. By altering the substrates of the reactions, methodologies were discovered for the proline-catalysed Mannich reaction to give compounds of the type **42**⁴⁹ (Scheme 12) and cross aldol couplings to give compounds of the type **45** & **47** (Scheme 13 & 14),⁵⁰ as well as an aldol reaction between β -hydroxyketones and aldehydes that yielded *trans*-diol products.⁵¹ This method is complementary to the well-known Sharpless methodology for the asymmetric synthesis of *cis*-diols⁵² using his version of the Upjohn dihydroxylation.⁵³



Scheme 12 Asymmetric proline-catalysed Mannich reaction

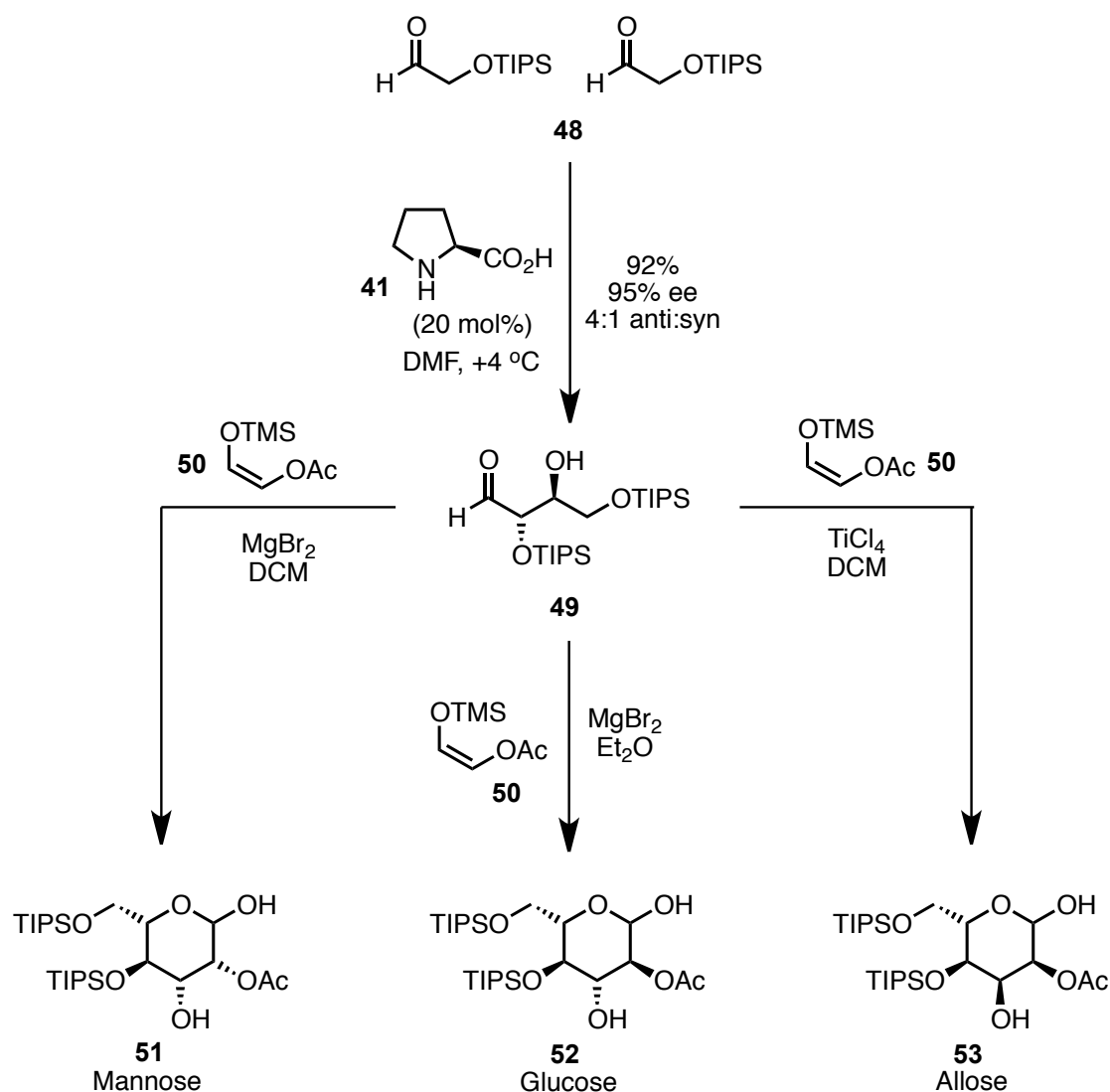


Scheme 13 Asymmetric proline-catalysed aldol reaction



Scheme 14 Asymmetric proline-catalysed cross aldol aldol reaction

Another excellent example of enamine activation is the organocatalytic synthesis of carbohydrates published by MacMillan. Using a proline-catalysed cross aldol reaction between two molecules of TIPS-protected β -hydroxyaldehyde **48**, it was possible to isolate **49** in high yield and with high selectivity. From there, Mukaiyama aldol reactions (under a variety of conditions) were used to access a variety of hexoses including mannose **51**, glucose **52**, and allose **53**, which previously would have required many more steps to obtain (Scheme 15).^{54,55}

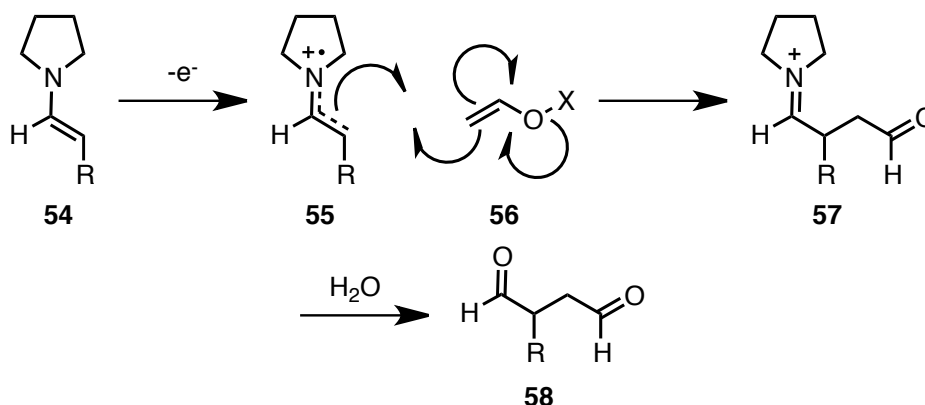


Scheme 15 Asymmetric proline-catalysed cross aldehyde aldol reaction

Further examples include a variety of α -functionalizations such as halogenations,^{56,57,58} aminations,^{59,60} and oxygenations,⁶¹ as well as other carbon-carbon bond forming reactions including conjugate additions of aldehydes to nitroalkanes⁶² and inter- and intramolecular conjugate additions to enones.^{63,64,65}

1.4.1 SOMO Organocatalysis

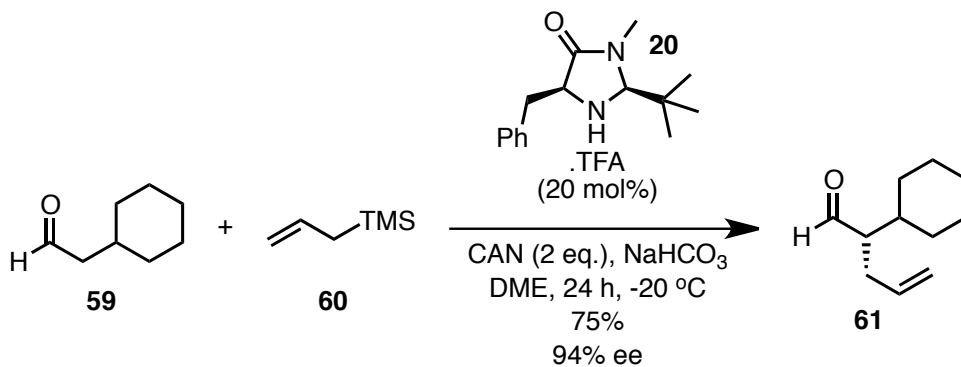
In recent years, a third mode of organocatalysis has been discovered by MacMillan. This mode is referred to as singly occupied molecular orbital (SOMO) catalysis, and involves the oxidation of a well-known enamine intermediate using a stoichiometric single-electron oxidant such as ceric ammonium nitrate (CAN) to form a radical anion intermediate that will react with different substrates from the other two modes, thus opening up a whole new area of enantioselective organocatalysis.⁶⁶ The proposed intermediate **55** for this type of process is shown in Scheme 16.



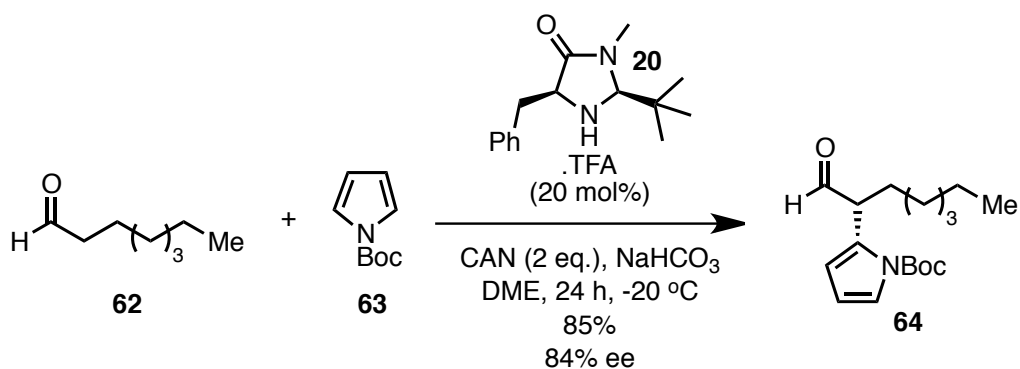
Scheme 16 SOMO organocatalysis

1.4.2 Examples of SOMO Catalysis

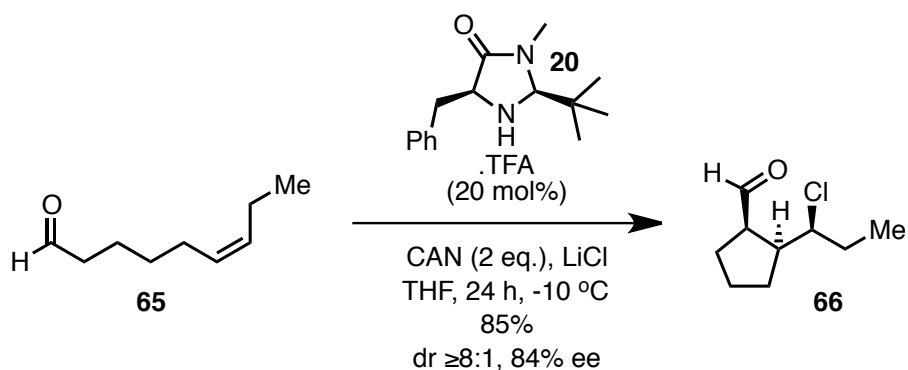
While examples of this type of activation are sparse compared to the more ubiquitous enamine and iminium-type processes, there are several important transformations that use SOMO catalysis. MacMillan initially developed an asymmetric α -allylation of aldehydes to give compounds such as **61** (Scheme 17) as well as preliminary work on an asymmetric heteroarylation to give **64** (Scheme 18) and an asymmetric cyclization-chlorination cascade to give **66** (Scheme 19), all of which demonstrate the broad utility of this type of catalysis. Since then, the α -allylation has been extended to include ketone substrates,⁶⁷ and related α -oxidations⁶⁸ and α -arylations⁶⁹ of aldehydes have been published by Sibi and Nicolaou respectively.



Scheme 17 Asymmetric α -allylation of aldehydes



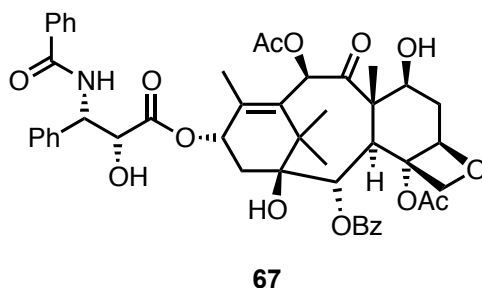
Scheme 18 Asymmetric α -heteroarylation of aldehydes



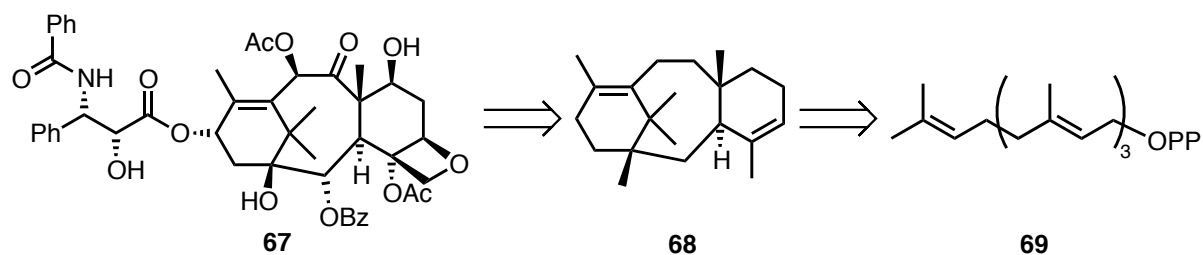
Scheme 19 Asymmetric cyclization-chlorination cascade

2.1 The use of Amine Organocatalysis in Natural Product Synthesis

A publication by MacMillan in 1997 suggested that the current state of organic synthesis was not enabling the pharmaceutical industry to keep up with the need for new (or existing) drugs.⁷⁰ The example he used was Taxol® **67**, a potent anti-cancer drug that was initially isolated from the bark of the Pacific Yew tree in 1966, but its complex structure was not elucidated until 1971.⁷¹



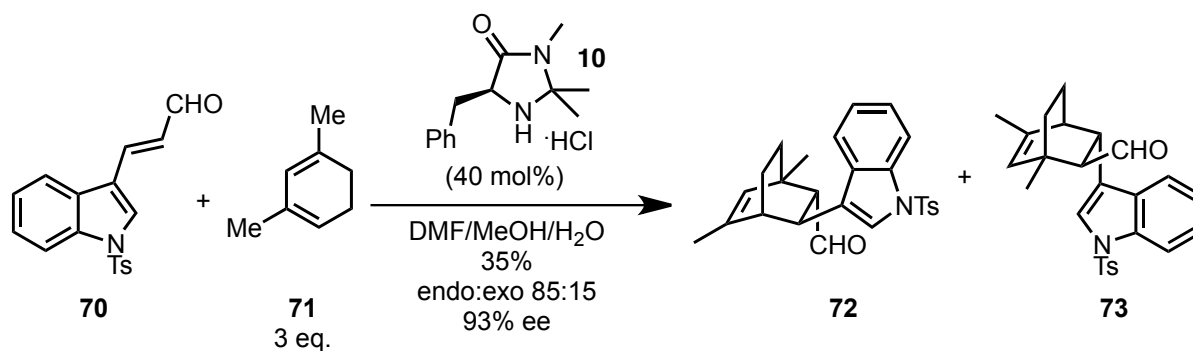
Taxol has succumbed to total synthesis on a number of occasions. The earliest syntheses were reported by Nicolaou, Horton, Danishefsky, Wender, Mukaiyama, and Kuwajima.⁷² However, as a result of its intricate structure, the number of steps required to complete the compound has ranged from 37-51 chemical steps. This initially made biological testing incredibly difficult, as the isolation of Taxol from natural sources was also prohibitively difficult. From 10 kg of dry bark (corresponding to five whole trees), 1 g of Taxol was isolated. Considering that a ton of Taxol was required to meet worldwide need every year, MacMillan proposed the wider use of cascade synthesis as a means to decrease the number of steps required to introduce complexity into compounds. This theory is well-known by examples in nature, including the biosynthesis of Taxol by a variety of enzymes from the well-known terpene precursor geranylgeranyl diphosphate (GGPP) **69** via an intermediate known as taxadiene **68** (Scheme 20). MacMillan envisaged that using his newly discovered iminium activation chemistry it would be feasible to carry out these transformations in the laboratory.



Scheme 20 Taxol biosynthesis

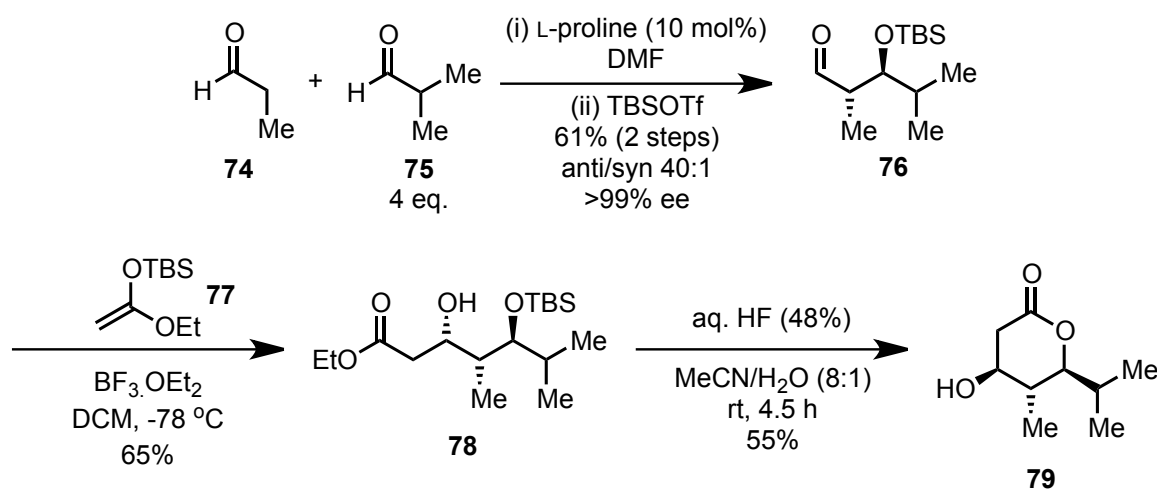
While organocatalysis has been shown to work in a vast array of model systems, the true test of this relatively new system has been the use of these catalysts in the synthesis of complex natural products. This “trial by fire” as one commentator put it,⁷³ has fortunately led to elegant, streamlined syntheses of highly complex natural products that hitherto required lengthy routes or were simply inaccessible using more conventional chemistry. Several of these syntheses are highlighted in reviews by Christmann.⁷³⁻⁷⁴ While it would not be prudent to attempt to describe every example in the literature, the syntheses presented in this chapter show the remarkable diversity of targets that have succumbed to total synthesis through routes employing organocatalysis.

One of the earliest and yet most elegant syntheses using this new methodology was that of hapalindole Q **9** by the group of Kerr.⁷⁵ An asymmetric Diels-Alder reaction between an enal dienophile **70** and 1,3-dimethyl-1,3-cyclohexadiene **71** using MacMillan’s imidazolidinone catalyst **10** gave the critical intermediate **72** required in low yield but with good endo selectivity and high ee (Scheme 21). Interestingly, and gratifyingly for both MacMillan and Kerr, more well-known Lewis acid mediated Diels-Alder reactions all failed due to polymerisation of the diene in each case.



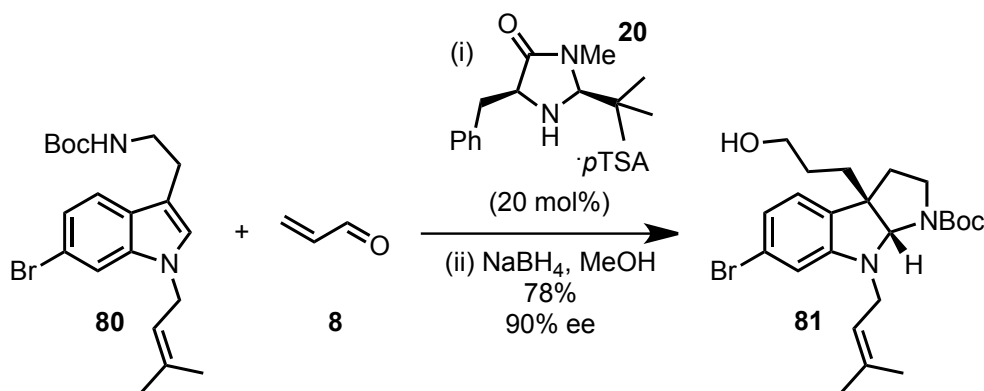
Scheme 21 Key organocatalytic asymmetric Diels-Alder reaction in the total synthesis of hapalindole Q

Another excellent and somewhat simpler early example of total synthesis using a simple L-proline catalyst is that of prelactone **79** by Pihko and co-workers.⁷⁶ A cross-aldol reaction between isovaleraldehyde **74** and propionaldehyde **75** yielded the desired intermediate in high yield along with excellent ee and dr. Only three further steps were required to furnish the natural product **79** in good overall yield (Scheme 22). A comparison between this synthesis and the others in the literature shows that this was the most economical synthesis published at that time, with TBSOTf being the most expensive reagent used throughout. Three more syntheses of prelactone B were known at the time. A racemic 6-step synthesis by Kocienski,⁷⁷ a chiral auxiliary based 6-step synthesis by Staunton,⁷⁸ as well as a comparatively long 13-step synthesis by Chakraborty⁷⁹ all paled into relative insignificance when compared to the streamlined synthesis of Pihko. A related synthesis of prelactone C by Kobayashi gave a similar natural product, also in 4 steps, but utilized non-commercially available starting materials as well as a relatively expensive Zr-based chiral catalyst.⁸⁰



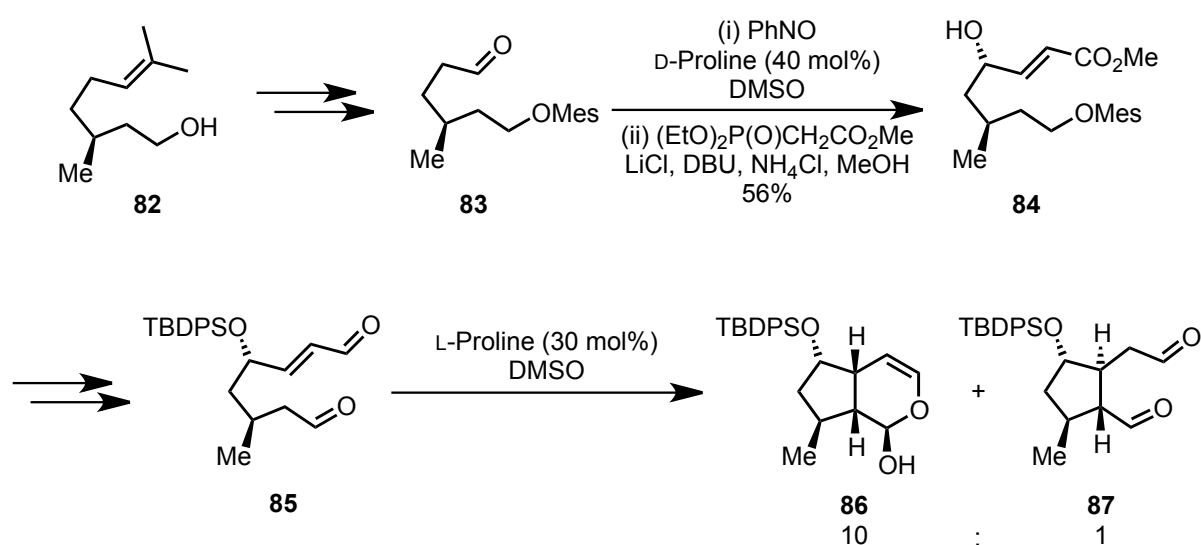
Scheme 22 Total synthesis of Prelactone B

MacMillan's first foray into total synthesis was the use of an asymmetric 1,4-addition of a tryptamine analogue to acrolein using one of his imidazolidinone-based organocatalysts to form the core structure of several of the pyrroloindoline alkaloids with very high selectivity. This is exemplified here by the synthesis of the natural product (–)-flustramine B **11**, a potassium channel inhibitor that shows muscle relaxant properties.⁸¹ In this case, the pendant *N*-Boc protected ethylamine intercepts the iminium-type intermediate formed following the initial 1,4-addition to acrolein in a favoured 5-*exo*-heterocyclization. The tricyclic structure so generated is the desired pyrroloindoline motif. A few simple functional group transformations gave (–)-flustramine B in excellent overall yield (Scheme 23).



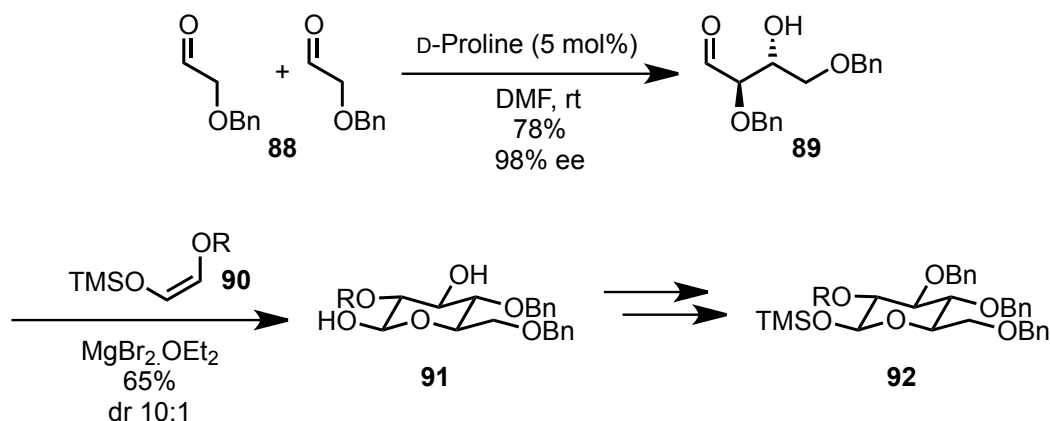
Scheme 23 Organocatalytic synthesis of a key intermediate in the total synthesis of flustramine B

Another excellent use of organocatalysis in total synthesis is that which led to the first synthesis of littoralisone, again by MacMillan.⁸² In this case, molecular complexity is built up very quickly starting from the aldehyde **83** (itself derived from (–)-citronellol **82** in two steps) using a one-pot proline-catalysed aminoxylation and a Horner-Wadsworth-Emmons reaction to form **84** in high yield and ee. A standard reduction/oxidation protocol gave bis aldehyde **85**, which was then subjected to the lynchpin reaction of this synthesis, a contra-thermodynamic Michael addition to form iridoid **86**. By carefully selecting the reaction conditions the desired kinetic product was formed as opposed to the monocyclic thermodynamic product **16** (Scheme 24).



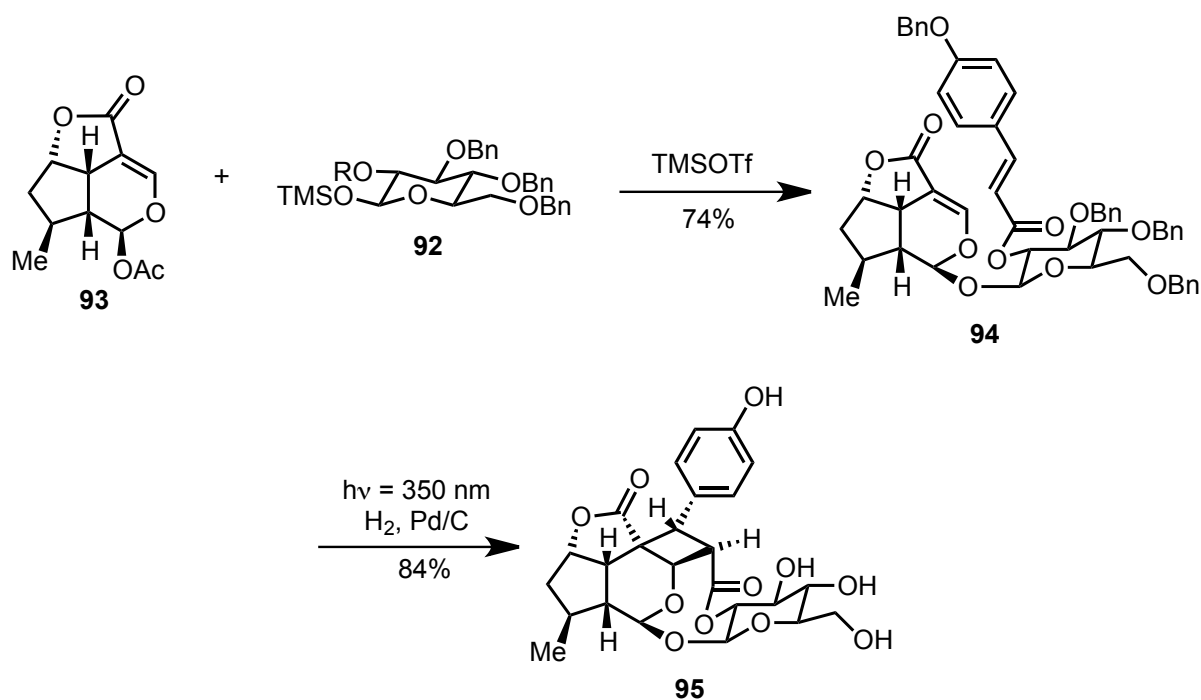
Scheme 24 Organocatalytic synthesis of advanced intermediate **86**

The previously mentioned paper by MacMillan on carbohydrate synthesis has also been used in natural product synthesis.⁵⁵ Thus, compound **19** was synthesized using a 5-step protocol *via* compound **18** (Scheme 25).



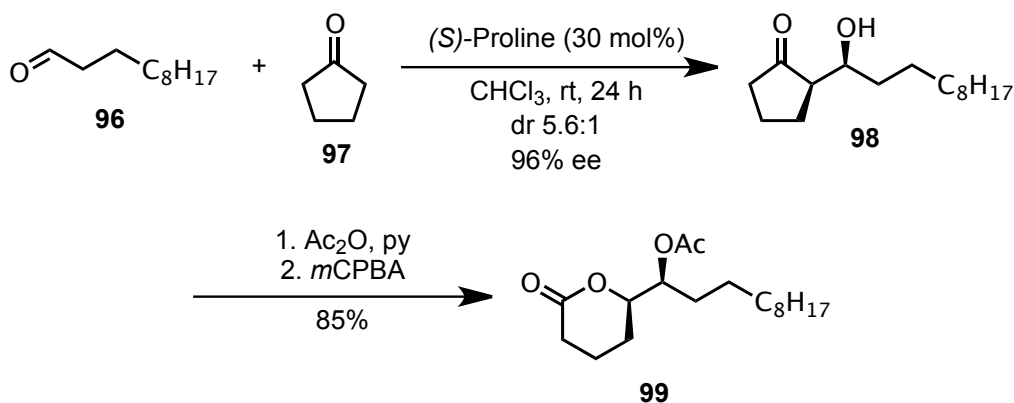
Scheme 25 Organocatalytic carbohydrate synthesis

TMSOTf-catalysed coupling of **93** (derived from **86**) and **92** gave advanced intermediate **94**, which was then irradiated to facilitate a 2+2 cycloaddition. Finally, hydrogenolysis of the benzyl protecting groups furnished littoralisone **95** in 13% yield over 13 steps (Scheme 26).



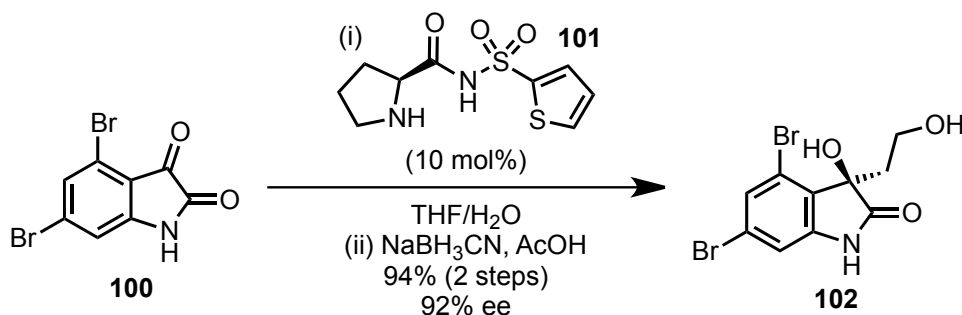
Scheme 26 Completion of the synthesis of littoralisone

One of the most succinct syntheses using organocatalysis is that of (–)-(5*R*,6*S*)-6-acetoxylhexadecanolide **99**, a natural mosquito attractant pheromone, by the group of Li.⁸³ A simple, highly selective proline-catalysed asymmetric aldol reaction led to the β-hydroxyketone intermediate **98**. A simple acetylation and Baeyer-Villiger oxidation gave the natural product **99** in an impressive overall yield (Scheme 27).



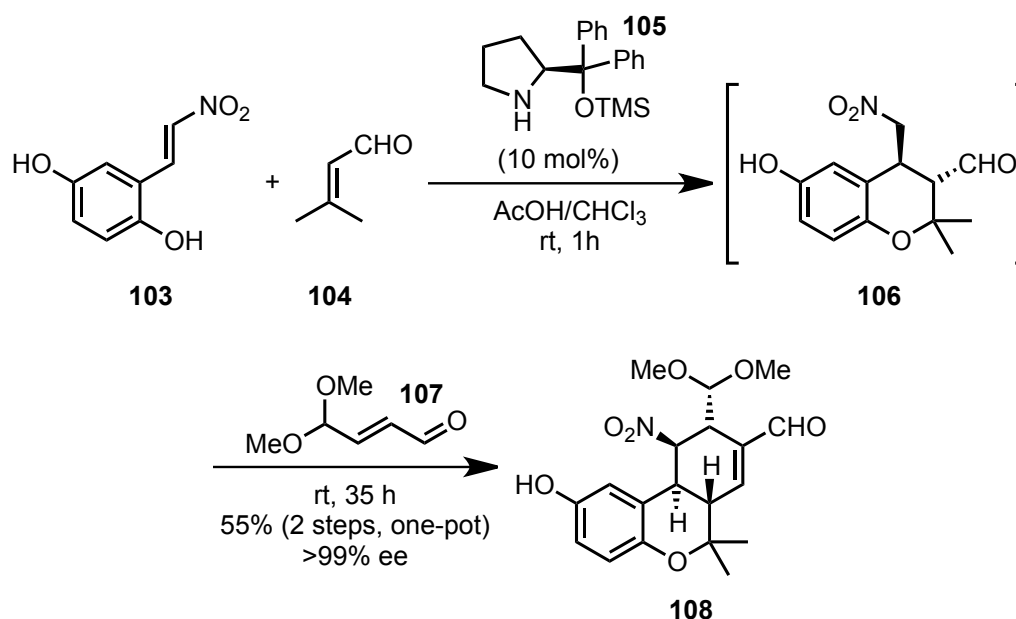
Scheme 27 Total synthesis of (–)-(5*R*,6*S*)-6-acetoxylhexadecanolide

Several members of the convolutamydine family of natural products have succumbed to total synthesis involving organocatalysis, this time at the hands of Nakumura and co-workers.⁸⁴ In this case, the enamine is derived from a variety of aldehydes, and the aldol acceptor is brominated isatin derivative **100** (Scheme 28), which was shown after much optimization to give the highest selectivity for these substrates. Previous attempts to synthesize these compounds were hampered by poor selectivity,⁸⁵ but by using *N*-(2-thiophenesulfonyl)prolinamide **101** as catalyst, it was found that the addition of a second unit with H-bonding ability increased the ee of the final product presumably due to a more ordered transition state.



Scheme 28 Total synthesis of (*R*)-convolutamydine

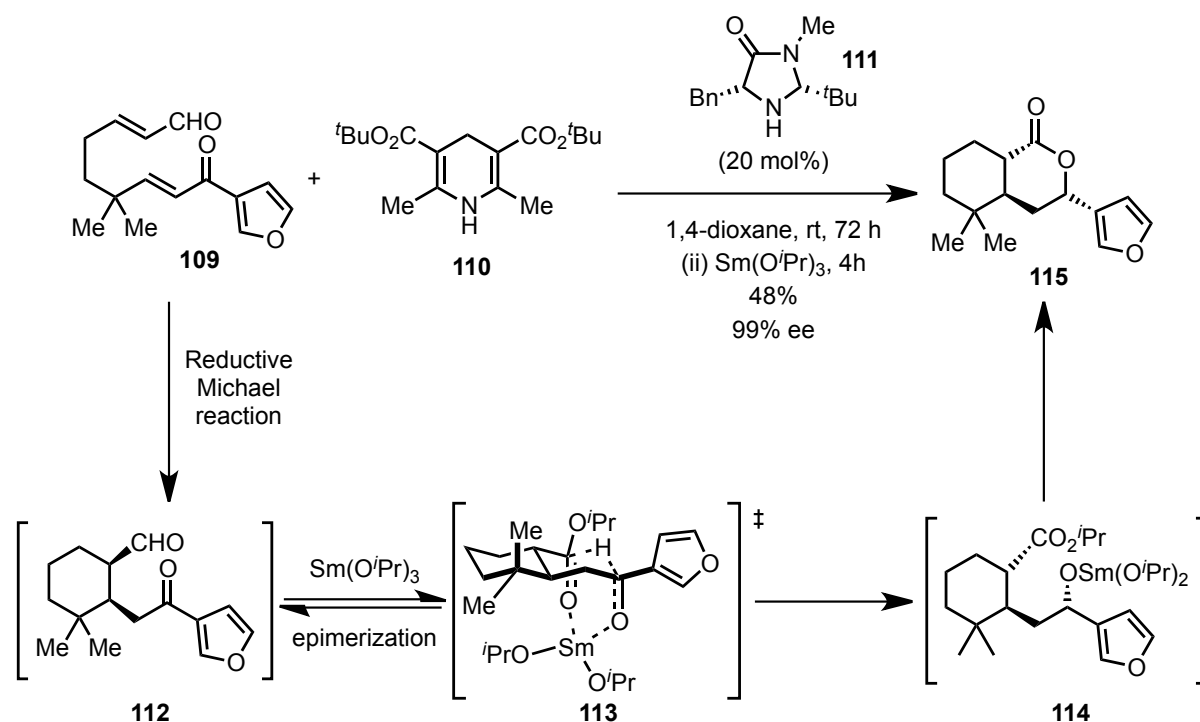
Organocatalysis also lends itself well to use in natural product synthesis because the operational simplicity and robustness of the catalysts generally mean that cascade and one-pot reactions can be designed in order to increase molecular complexity quickly and highly efficiently. This is shown exceptionally well in the synthesis of (+)-conicol by Hong and co-workers.⁸⁶ Starting from the nitrostyrene **103** and two α,β -unsaturated aldehydes (**104** and **107**) as well as Jørgensen's diphenylprolinol catalyst **105**, two cycles and four contiguous stereocentres could be built up in >99% ee in a simple one-pot process in reasonable yield (Scheme 29). The initial Henry reaction proceeds with complete stereoselectivity, and **106** can be isolated if desired. Subsequent addition of a second aldehyde leads to the chromene derivative **108**. Several more steps were then required to access the natural product. Nonetheless, this remains the only synthesis of (+)-conicol, which has potential anti-cancer properties against a variety of cell lines.



Scheme 29 Initial organocatalytic steps in the total synthesis of (+)-conicol

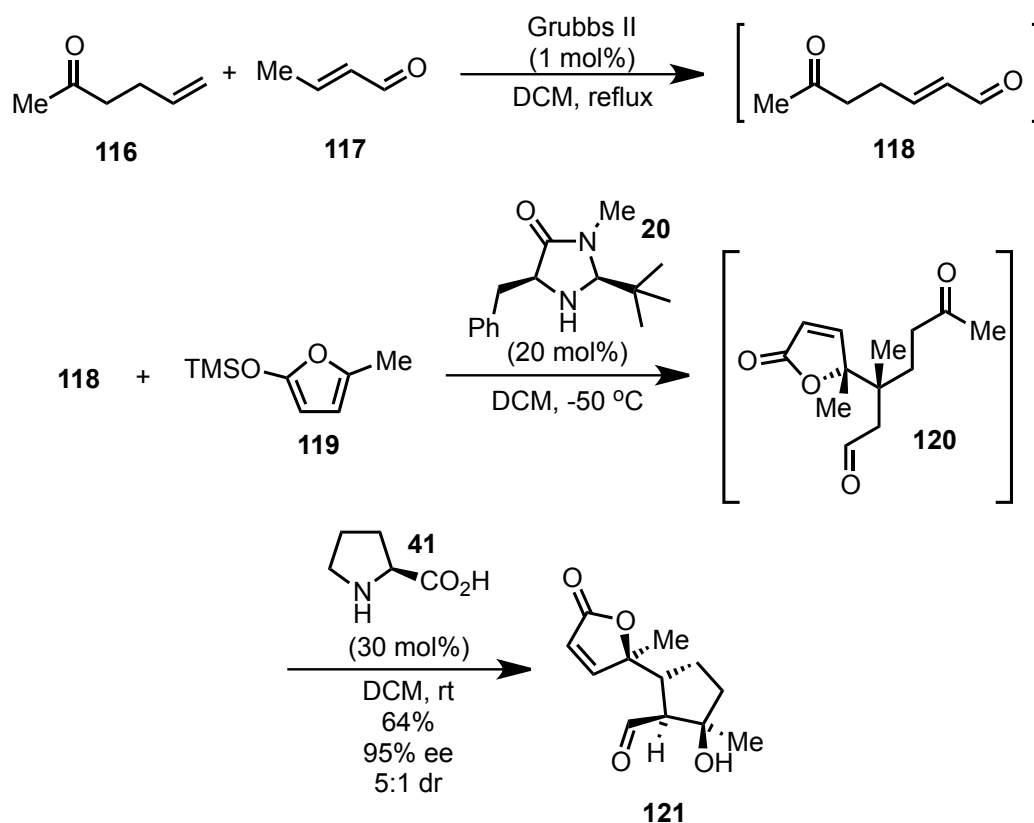
Not only can a single organocatalyst be used in a single pot with multiple substrates, it is also the case that they can be used in the same pot as other metal-based catalysts and even, in some cases, other organocatalysts with different properties. This is exemplified by two recently published total syntheses; ricciocarpin A by List⁸⁷ and (–)-aromadendranediol by MacMillan.⁸⁸

The synthesis of ricciocarpin involves an innovative one-pot reductive Michael cyclization and Tishchenko reaction (Scheme 30). In this case the initially formed *cis*-substituted cyclohexane **112** is epimerized by $\text{Sm}(\text{O}^i\text{Pr})_3$, which incidentally also acts as the catalyst for the second step of the cascade. Thus, the lactone ring forms with complete diastereoselectivity, giving the natural product in high yield. This completed the shortest recorded synthesis of ricciocarpin **115**, which is a potent molluscicidal agent that acts against the water snail *Biomphalaria glabrata*, a vector for the parasites known to cause the potentially deadly disease schistosomiasis.



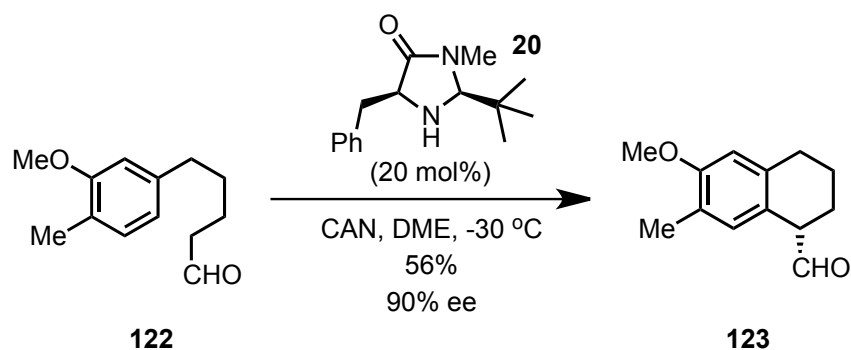
Scheme 30 One-pot organocatalytic reductive cyclization and Tishchenko reaction to form the molluscicide ricciocarpin

In order to show how far this methodology can be pushed, MacMillan and co-workers have shown that a cascade involving three separate catalytic cycles in one pot can be implemented using three different catalysts. A number of highly functionalized motifs can be synthesized depending on the substrates and reagents chosen. For example, in the first reported synthesis of the analgesic and sedative natural product (–)-aromadendranediol, a ring-closing metathesis, an asymmetric Mukaiyama-Michael addition, and finally an asymmetric aldol reaction all occur sequentially in one pot, forming a complex bicyclic intermediate from the three commercially available starting materials shown. Standard cross-metathesis yielded intermediate **118**. Subsequent addition of the silyloxyfuran **119** and the imidazolidinone catalyst **20** led to intermediate **120**, and finally addition of proline led to an intermolecular aldol condensation, giving **121**. This set four of the five contiguous stereocentres seen in the natural product, and a further eight steps led to the completion of synthetic (–)-aromadendranediol, which proved to be identical to the natural isolate (Scheme 31).



Scheme 31 One-pot, three step synthesis of an intermediate in the synthesis of (–)-aromadendranediol utilizing three different catalysts

Nicolaou has recently even used the relatively new concept of SOMO catalysis (described in detail in section 1.4) in their brief synthesis of the potent cytotoxic natural product demethyl calamenene.⁸⁹ A Friedel-Crafts type α -arylation of aldehyde **122** using a combination of MacMillan's catalyst and CAN yielded bicycle **123** with high selectivity and in good yield. Compound **123** was then converted into the natural product using standard chemical techniques (Scheme 32).



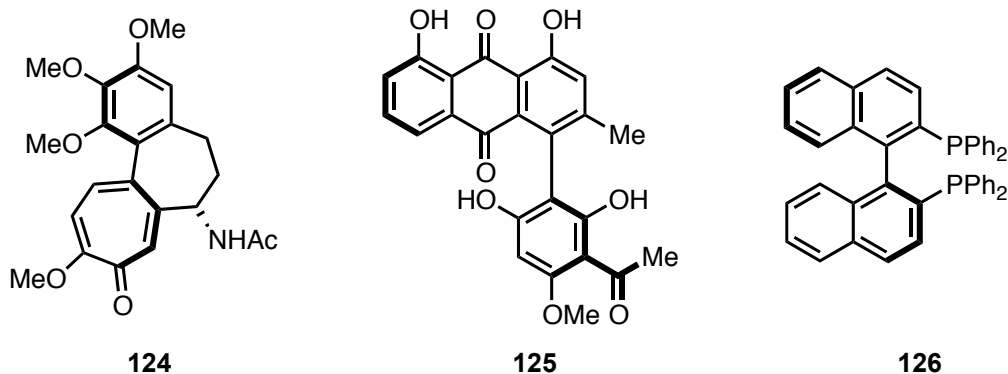
Scheme 32 Asymmetric synthesis of demethyl calamenene utilizing SOMO catalysis

This brief review of work in this area shows that there have clearly been massive breakthroughs in the use of organocatalysis in natural product synthesis. The use of organocatalysts gives a valid alternative to the use of the better-known chiral auxiliary based synthetic protocols for introducing chirality into substrates early in total syntheses. However, there are still drawbacks in this area. With certain exceptions, including some from within the Page group,⁹⁰ catalyst loadings are still generally very high (20-30 %) compared to those generally seen when using organometallic catalysts. This is something that needs to be addressed in the future. Also, whereas in the case of chiral auxiliary-based chemistry the chromatographic separation of diastereoisomers is often facile, the same cannot be said of organocatalytic reactions, where the products are usually enantiomeric and thus cannot be separated using normal methods. Thus, while all of these elegant syntheses do exist, there is still huge room for improvement in this relatively new field.

3.1 Axial Chirality and the Work of Maruoka

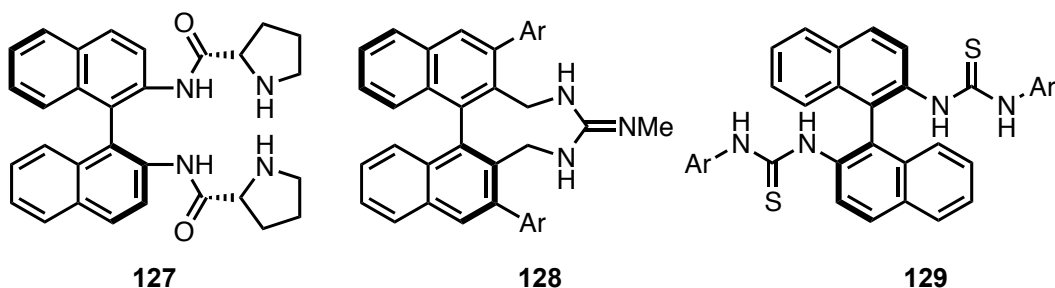
The phenomenon of atropoisomerism (from the Greek, *a* = not, *tropos* = turn) arises when there is sufficient hindrance to rotation around a biaryl single bond at a given temperature that the two optically pure atropoisomers can be isolated.⁹¹ The substitution required around a biaryl system for restricted rotation has been studied extensively. The general definition of the presence of atropoisomerism in a given substrate given by Oki is that, at room temperature, one isomer can be isolated from the other and have a half-life of 1000 s (16.7 minutes).⁹² Generally, the requirement for this is a tetra-substituted biaryl, although other substitution patterns have also been shown to prevent rapid racemization.⁹³

While there are many examples of axially chiral natural products (colchicine **124**⁹⁴ and knipholone **125**⁹⁵ are shown), the most well-known atropoisomeric compounds in the literature are biaryl ligands and catalysts exemplified by BINAP **126**. This was first described as a ligand for the Rh-catalysed asymmetric hydrogenation of α -(acylamino)acrylic acids by Noyori and co-workers in 1980.⁹⁶

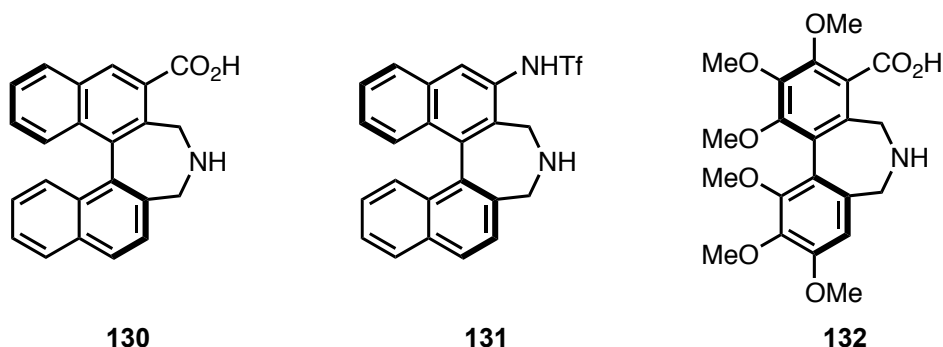


Since then, BINAP has been shown to be a highly selective ligand for a variety of metals, due in equal parts to the flexibility of the system (allowing chelation of a variety of metals) and to its conformational stability (allowing it to form well-defined complexes).⁹⁷ This is exemplified by the fact that the Ru-BINAP complex, also described by Noyori, has been shown to catalyse an unprecedented array of chemical manipulations, including the highly enantioselective reductions of allylic alcohols,⁹⁸ α -keto acids,⁹⁹ and β -keto esters¹⁰⁰ as well as a variety of kinetic resolutions.^{101,102}

With these successes in the area of organometallic catalysis, it was only a matter of time before axially chiral organocatalysts were seen in the chemical literature. There are many examples of this, including prolinamide **127**,¹⁰³ guanidine **128**,¹⁰⁴ and thiourea **129**,¹⁰⁵ which have been used to catalyse a variety of processes.

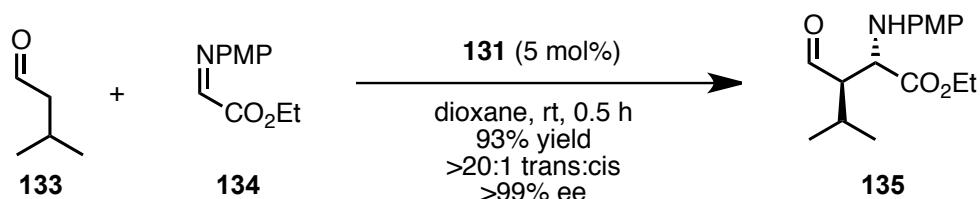


These catalysts, while sometimes highly selective, are not particularly well known. However, the work of Maruoka, who developed amino acid and amino sulfonamide catalysts such as **130**, **131** and **132** for enamine type organocatalysis, has received more widespread acclaim. These catalysts have proven to be highly stable, highly selective catalysts for asymmetric aldol^{106,107} and Mannich^{108,109} reactions.



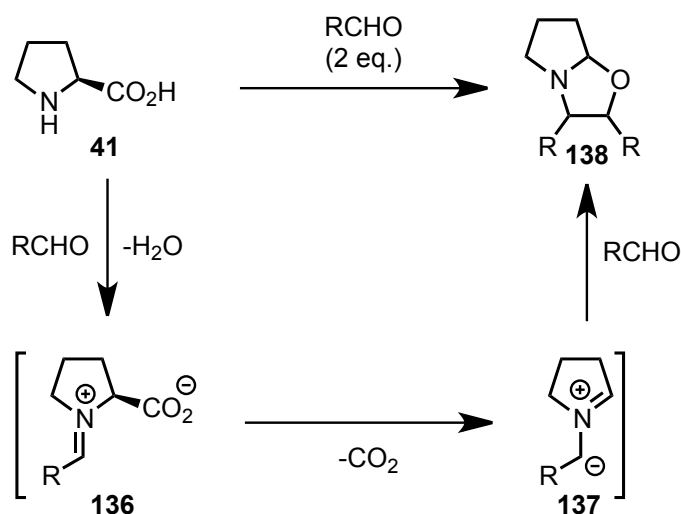
These compounds were designed with several ideas in mind. Firstly, this would be one of very few organocatalysts associated with enamine activation that is not derived from proline. In practice, this led to a difference in *syn/anti* selectivity in the asymmetric Mannich reaction between 3-methylbutanal **133** and the N-PMP imine **134** derived from ethyl glyoxylate, with excellent *anti* selectivity seen when using **131** (Scheme 33). This is the opposite selectivity from that seen when L-proline was used as a catalyst for the same reaction.⁴⁹ Secondly, it was suggested that a lack of an α -substituent in these catalysts would increase the rate of enamine formation by reducing steric constraints in that particular step. Thirdly, these types of amines are

associated with low nucleophilicity and low basicity, both traits that are desirable in selective organocatalysts.



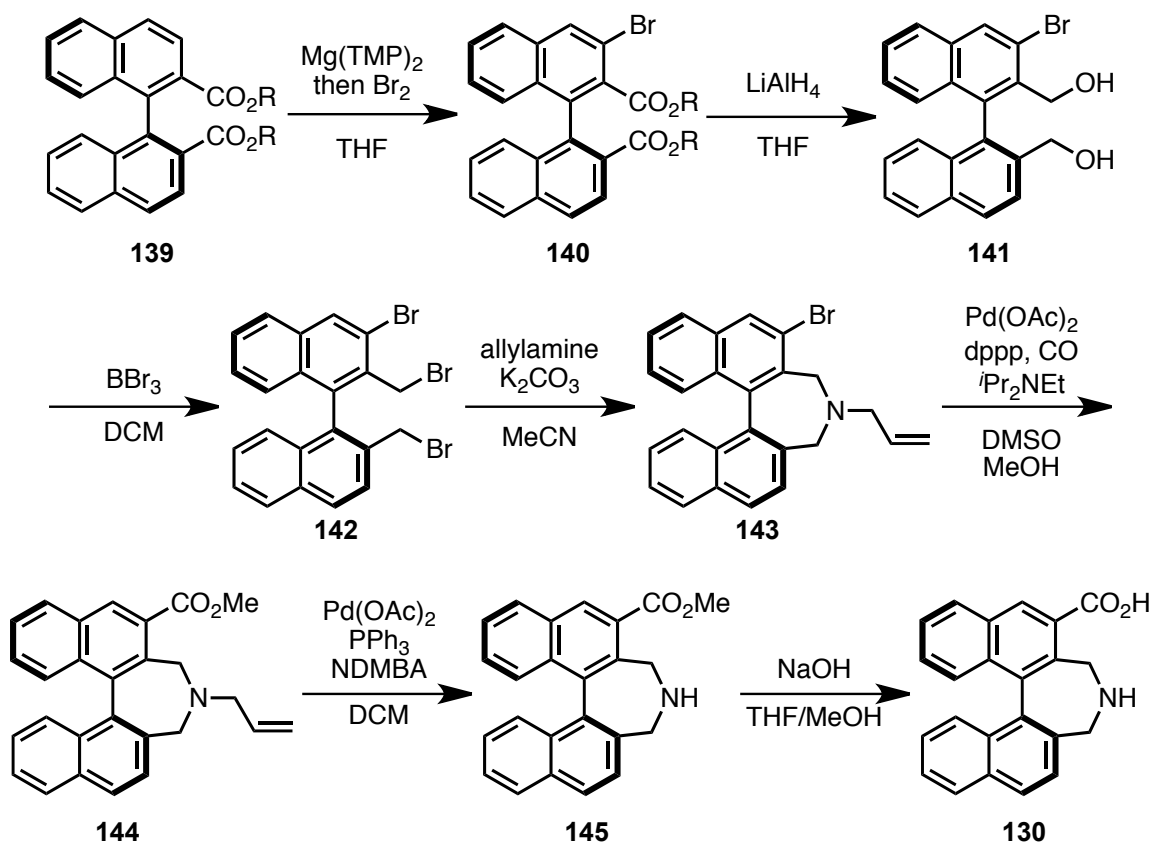
Scheme 33 Asymmetric Mannich reaction catalysed by **131**

Finally, it was hypothesized that not having an α -amino acid moiety in the organocatalyst would increase its stability. For example, side reactions in organocatalytic reactions that utilize proline are prone to catalyst deactivation due to decarboxylative azomethine ylide formation (conversion of **136** into **137**) under standard reaction conditions (Scheme **34**). Utilizing a catalyst that does not contain an α -amino acid motif would prevent these side reactions from occurring.



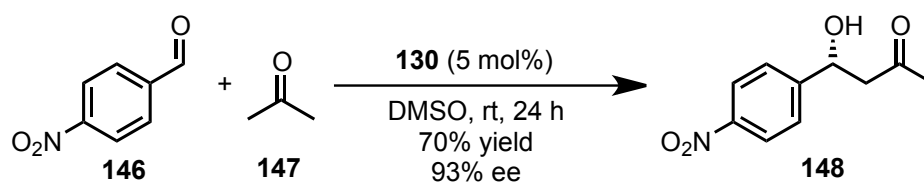
Scheme 34 Decarboxylative decomposition of proline

The initial publication by Maruoka described the synthesis of amino acid **130**. It was synthesized in 7 steps from diester **139** (R = neopentyl). Bromination using $\text{Mg}(\text{TMP})_2$ and molecular bromine afforded monobromide **140**. Subsequent LiAlH_4 reduction and bromination yielded tribromide **142**, which was then easily converted to azepine **143** using standard conditions. A Pd-catalysed carbonylation yielded ester **140**, which was then deprotected in two steps to give the desired compound **130** (Scheme **35**).¹⁰⁶



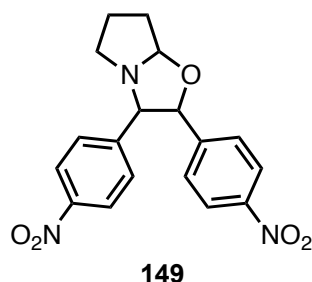
Scheme 35 Synthesis of amino acid **130**

This type of synthesis was employed for all the catalysts mentioned above. The initial catalyst testing was for the asymmetric aldol reaction between p-nitrobenzaldehyde and acetone (Scheme 36).



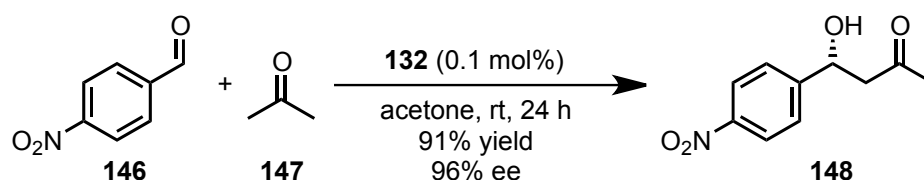
Scheme 36 Aldol reaction catalysed by amino acid **130**

This reaction proceeded as expected, giving the β -hydroxyketone product in 70% yield and 93% ee. In comparison, running the same reaction using L-proline as catalyst gave only 18% conversion to the desired product with only 71% ee. The decomposition pathway discussed above was seen to occur in this case, with 1,3-oxazolidine **149** isolated in 48% yield with respect to the 5 mol% of catalyst used.



After optimization, it was found that a wide variety of heteroaromatic, alkenyl and electron-deficient aromatic aldehydes could be used along with a variety of acyclic and cyclic ketones. In the case of the cyclic ketones, excellent *trans/cis* selectivity (>95:5) was seen in all cases.

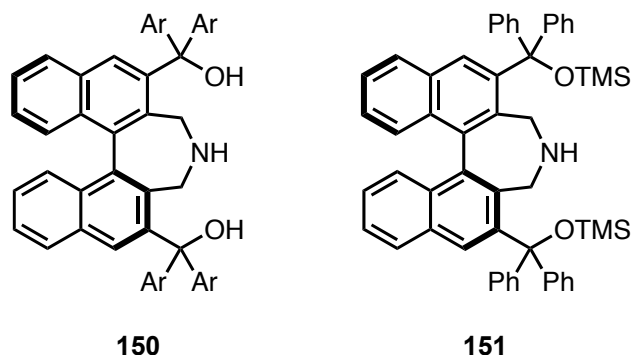
Generally in this initial publication catalyst loadings were quite high (10 mol%). In an effort to decrease this loading, catalyst **130** was synthesized.¹⁰⁷ It was hoped that the electron-donating nature of the biphenyl system would increase the nucleophilicity of the amine moiety, thus increasing the rate of formation of a potential enamine intermediate. This did prove to be the case, with catalyst loadings as low as 0.1 mol% able to catalyse the same aldol reaction as before in a selective manner after a similar reaction time (Scheme 37).



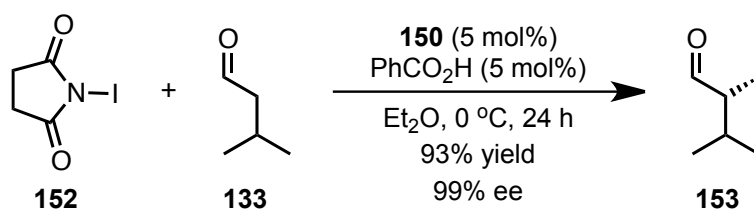
Scheme 37 Aldol reaction catalysed by amino acid **132**

In an effort to subtly alter the characteristics of this type of catalyst, Maruoka also synthesized sulfonamide **131** (see Scheme 33).¹⁰⁹ It was hypothesized that this alteration would increase the distance between the amine moiety and the required acidic proton, thus altering the preference of the orientation of the intermediate enamine. This had the effect of changing the diastereoselectivity of the product.

As well as synthesizing highly selective catalysts **130** – **132**, Maruoka has also synthesized other catalysts for a variety of α -functionalizations of aldehydes. This includes asymmetric metal-free iodinations,¹¹⁰ aminoxylations,¹¹¹ and brominations.¹¹² The properties of these new catalysts **150** and **151** were tailored to the different potential reactions they would be utilized for.



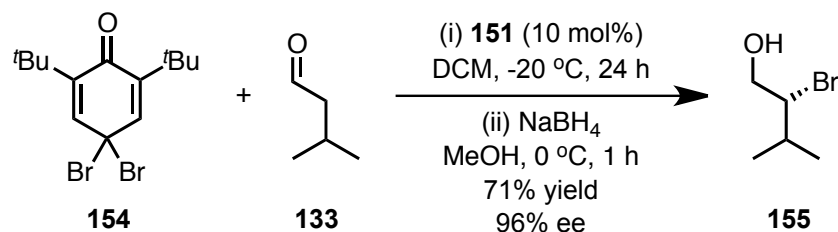
Organocatalytic asymmetric iodinations are scarcely seen in the chemical literature, due in part to the propensity of the products to racemize easily under basic conditions.¹¹³ Compound **150** (Ar = C₆F₅) was synthesized as a catalyst for asymmetric iodination in the hope that the alcohol moiety would activate the NIS iodinating agent and the electron withdrawing pentafluorophenyl groups would decrease the nucleophilicity of the amine. This proved to be the case, and α -iodoaldehydes were formed in high yield and enantiomeric excess (Scheme 38).



Scheme 38 Asymmetric iodination of aldehydes catalysed by **150**

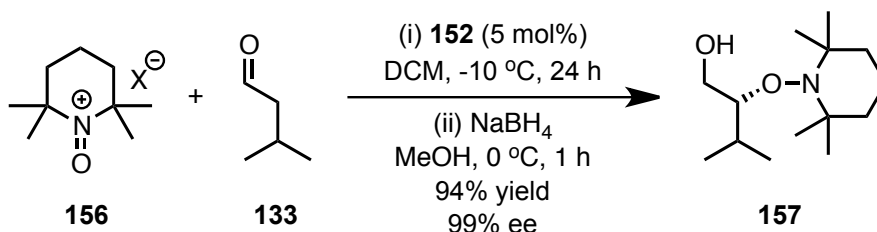
The same catalyst was tested for asymmetric brominations using NBS. Unfortunately, the selectivities proved to be lower. Altering the brominating agent increased the selectivity, albeit with very low conversions. After NMR experiments, it was shown that the tertiary alcohol in **150** was decomposing the brominating agent. Thus, silyl ether **151** was synthesized. This gave similar selectivities to **150** whilst increasing the conversions seen from <10% to >80%. The selectivity was attributed to the steric bulk now present at the 3-positions as opposed to any sort of attractive

interaction between the brominating agent and the ether. After optimization, selectivities were seen to be universally high when a range of substrates was tested (Scheme 39).



Scheme 39 Asymmetric bromination of aldehydes catalysed by **53**

The same also proved to be the case for the asymmetric aminooxylation, with products isolated in good yield with excellent ee using catalyst **152** (Scheme 40).

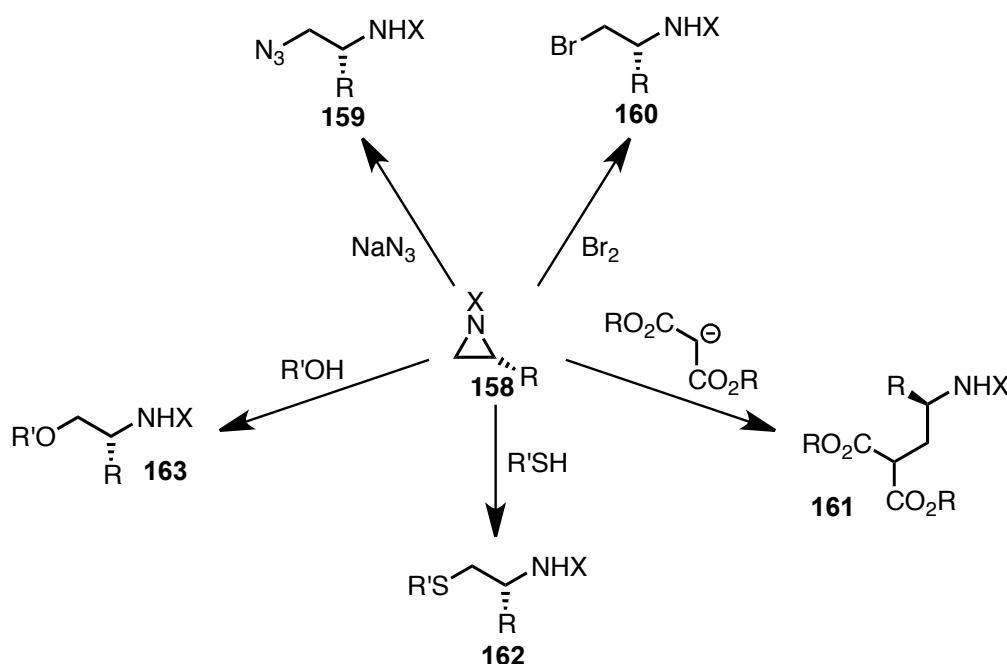


Scheme 40 Asymmetric aminooxylation of aldehydes catalysed by **53**

This chapter reports only a small number of the organocatalytic processes that this type of catalyst can be used for. They are generally more selective than related proline-derived catalysts and are also more easily tuned. There are other related reactions that Maruoka has published including conjugate additions of aldehydes to methylenemalonates¹¹⁴ and nitroalkanes,¹¹⁵ cross aldol reactions between aldehydes and glyoxylic acid derivatives,¹¹⁶ and Mannich reactions between aldehydes and ketimines.¹¹⁷ We hoped that similar catalysts formed *via* a methodology based on α -functionalization of binaphthyl-derived iminium salts would also prove to be just as selective. Our work to this end is described in the following sections.

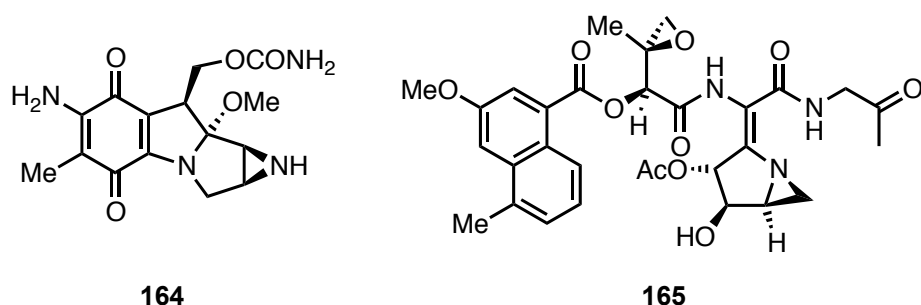
4.1 Asymmetric Aziridination

Aziridines are three membered rings containing two carbon atoms and one nitrogen atom. They are analogues of epoxides, the well-known three-membered cyclic ethers. While not as reactive as epoxides, there is still an appreciable ring strain associated with them (approximately 27 kcal mol⁻¹). As a result, they are highly susceptible to ring opening by a wide variety of nucleophiles (Scheme 41). There are several reviews on aziridine chemistry where these ring openings and other reactions are discussed in detail.^{118,119}

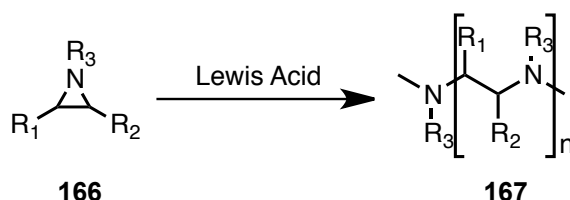


Scheme 41 Ring opening of epoxides by a variety of nucleophiles

The inherent reactivity of aziridines (and epoxides) make them valuable intermediates in both the pharmaceutical industry and in bulk industrial processes to produce chemicals including epoxy resins, ethylene glycol and polyethylenimine. There are also several known examples of natural products containing aziridines that show potent antimicrobial and anti-cancer properties. These compounds include the mitosanes¹²⁰ (mitomycin C, **164**), which are isolated from *Streptomyces verticillatus* and the azinomycins¹²¹ (azinomycin A, **165**), which are isolated from *Grieseofuscus* S42227. Both of these families of compounds show potent anti-cancer properties due to their ability to alkylate DNA through their aziridine (and epoxide) moieties and subsequently initiate apoptosis.



The propensity of aziridines towards ring opening means that there are relatively few ways to synthesize them selectively, especially in their N-unprotected form.¹²² There are countless methods for asymmetric epoxidation in the literature for a wide range of substrates.¹²³ Conversely, there are often compatibility issues with other functional groups when N-unprotected aziridines are formed due to the ability of the aziridine nitrogen to act as a nucleophile. This can cause unwanted side reactions, including polymerization to give compounds of the type **167** (Scheme 42).¹²⁴



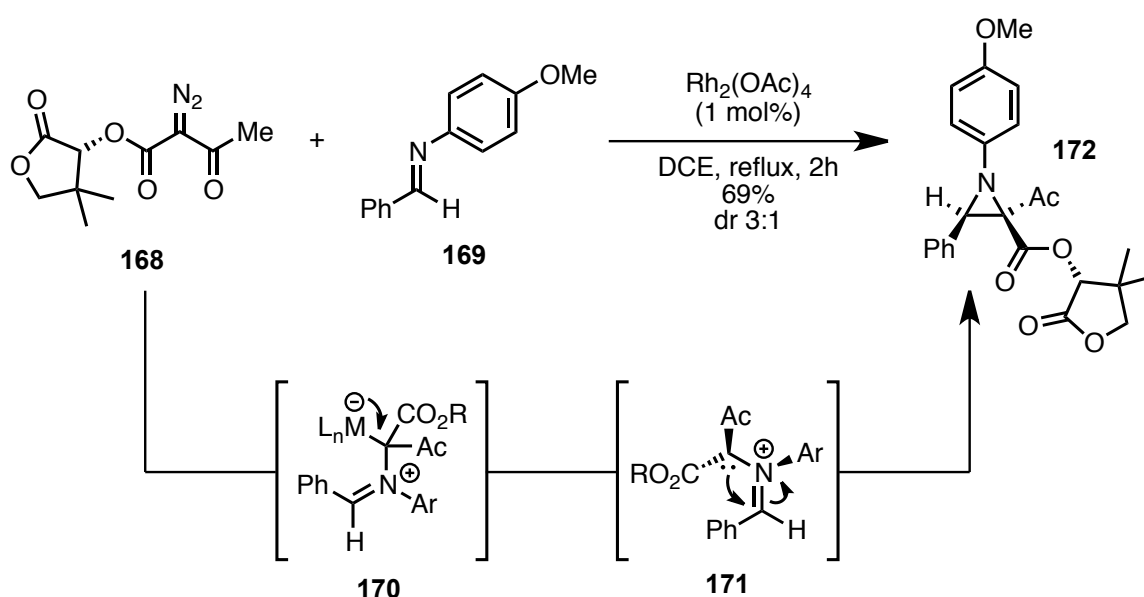
Scheme 42 Lewis acid promoted polymerization of aziridines

There are several reviews on asymmetric aziridination in the literature covering early chiral auxiliary chemistry¹²⁵ as well as more up-to-date reviews incorporating organometallic and organocatalytic methods.^{126,127} It is worth pointing out here that the vast majority of asymmetric aziridination methodology deals solely with *N*-protected aziridines and that a lot of even the most recently published aziridination protocols utilize chiral auxiliary chemistry. This highlights how difficult it is to form aziridines enantioselectively. There are several methods for the formation of aziridines from a variety of substrates, including carbon transfer to imines, reactions of azirines, cyclizations, *aza*-Darzens-type reactions and finally nitrogen transfer to alkenes. Some of these methods are discussed in the following sections.

4.1.1 Addition to imines

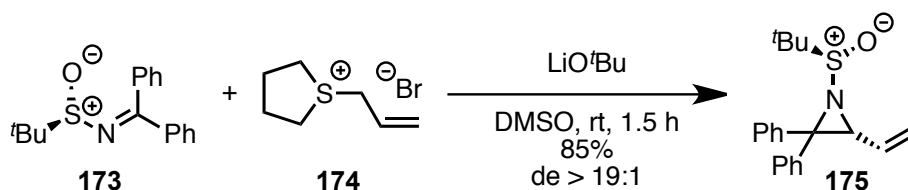
One of the well-known methods for synthesizing aziridines is through formal addition of a carbon atom to an imine. There are three distinct ways this can occur; addition of a carbene, addition of a ylide, and using an aza-Darzens reaction. Examples are shown below.

Huang and co-workers showed that reactions between (*R*)-pantolactone-derived diazoacetates **168** and *N*-aryl imines **169** would form highly functionalized aziridines such as **172** with reasonable levels of diastereoselectivity.¹²⁸ The mechanism is proposed to proceed *via* a metal carbene complex **170** that subsequently decomposes to an azomethine ylide **171** before finally forming the aziridine **172** (Scheme 43). These compounds are valuable intermediates in the preparation of α -hydroxy- β -amino acids, which have been shown to be precursors for a variety of drugs and natural products.¹²⁹



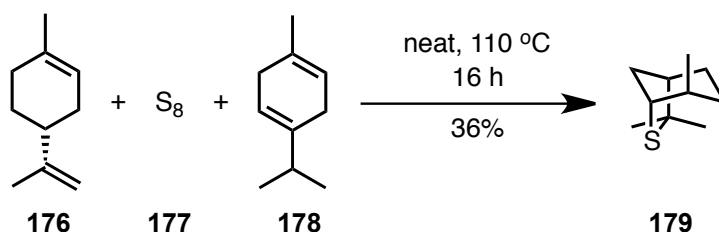
Scheme 43 Carbene addition to *N*-PMP imines

Stockman and co-workers have shown that through reaction of an enantiopure *N*-sulfinylketimine **173** derived from benzophenone with a ylide formed by deprotonation of *S*-allyltetrahydrothiophenium bromide **174**, it was possible to form 2-vinylaziridines such as **175** in excellent yield and with >19:1 diastereoselectivity (Scheme 44).¹³⁰



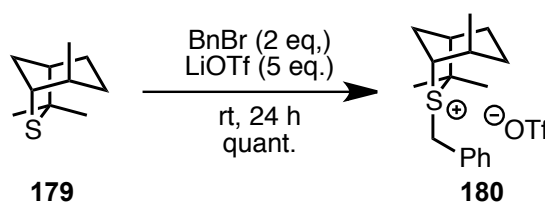
Scheme 44 Addition of an ylide to enantiopure *N*-sulfinyl imines

A similar application of this work is from the group of Aggarwal.¹³¹ By utilizing a chiral sulfur ylide derived in two steps from either (+)- or (–)-limonene it was possible to form a wide range of both aziridines and epoxides with extremely high enantio- and diastereoselectivity. Reaction of either enantiomer of limonene **176** with elemental sulphur at elevated temperatures allows for the facile isolation of either (+)- or (–)-isothiocieneole **179** with >98% ee after a simple distillation (Scheme 45).



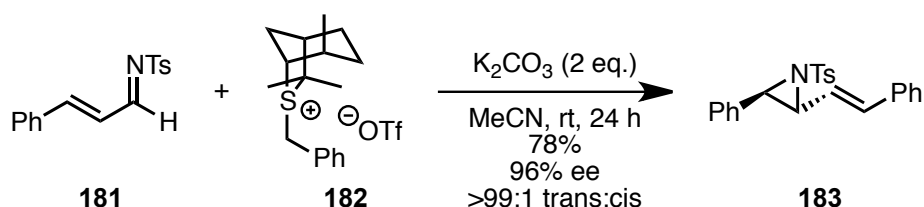
Scheme 45 Preparation of (+)-isothiocieneole **179**

From there, alkylation with benzyl bromide at room temperature affords the precursor to the desired chiral ylide **180** (Scheme 46).



Scheme 46 Preparation of chiral sulfonium salt **180**

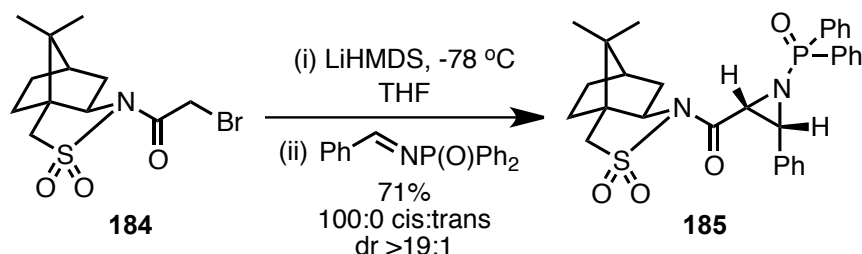
Deprotonation at the benzylic position followed by subsequent reaction of this ylide intermediate with either an aldehyde (to form an epoxide) or an imine (to form an aziridine) then proceeds smoothly at room temperature (Scheme 47).



Scheme 47 Aziridination of *N*-tosyl imines to give *trans*-aziridine products

When considering this type of imine chemistry, this work represents the highest level of diastereoselectivity ever recorded for these types of reactions. However, the limited availability of imine precursors and the requirement for a tosyl group in the imine substantially limits the potential uses of the products from this methodology.

Finally, the other method for facilitating the formal addition of a carbon atom to an imine is through an aza-Darzens reaction. One of the more well-known examples of this was published by Sweeney and co-workers.¹³² Using an α -bromoacetate derived from camphorsultam and an *N*-diphenylphosphinyl imine in the presence of LiHMDS, it was possible to isolate the aziridine shown with high regio- and stereoselectivity (Scheme 48).

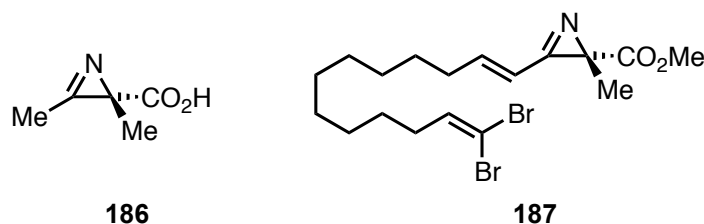


Scheme 48 Aziridination of *N*-tosyl imines to give *trans*-aziridine products

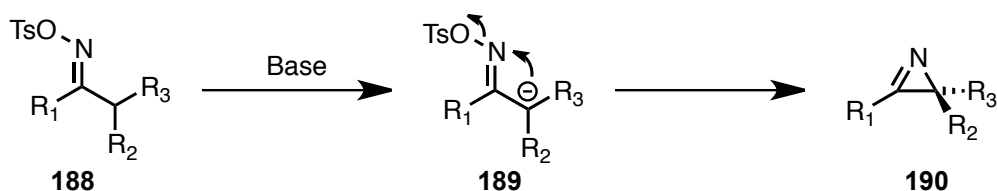
Subsequent hydrolysis of the camphorsultam auxiliary proved to be facile, allowing for the isolation of carboxylic acids, which as indicated above are valuable intermediates in organic synthesis.

4.1.2 Reactions of azirines

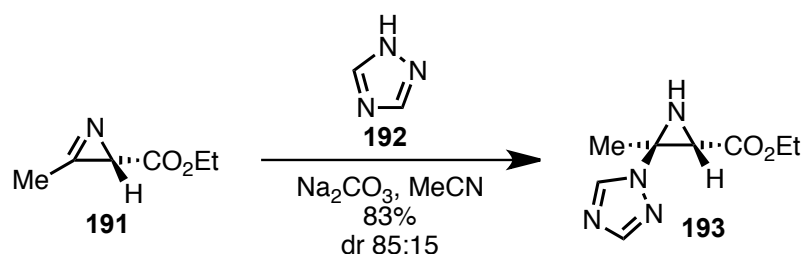
Azirines are the smallest unsaturated N-heterocycles. Once formed, they are then highly susceptible to nucleophilic attack at the imine carbon, a process that forms aziridines. While relatively rare in the literature, azirines are stable enough to have been isolated in a number of natural products including azirinomycin **186**¹³³ and (S)-(+)-antazirine **187**.¹³⁴



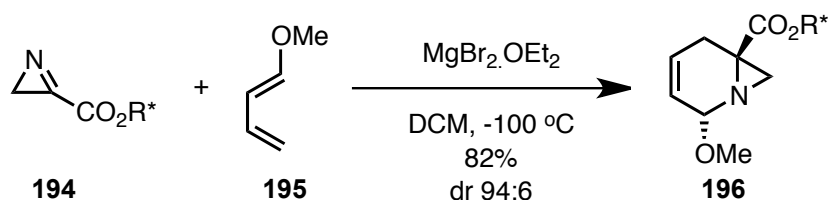
Azirines are generally synthesized from O-tosyl oximes under basic conditions. This is known as the Neber reaction (Scheme **49**).¹³⁵ From there, aziridines can be produced by a subsequent nucleophilic addition reaction. An example where nitrogen-containing heterocycles such as **192** were added to chiral azirine-2-carboxylic esters **191** (Scheme **50**) was published by Alves and co-workers.¹³⁶ Finally, it is also possible to utilize azirines in aza-Diels-Alder reactions. Under Lewis acid catalysis, azirines such as **194** will act as dienophiles with a range of dienes **195** thus forming highly functionalized fused aziridines **196** with high dr (Scheme **51**).¹³⁷



Scheme 49 Neber reaction to form azirines from O-tosyl oximes



Scheme 50 Nucleophilic addition to azirines to form aziridines



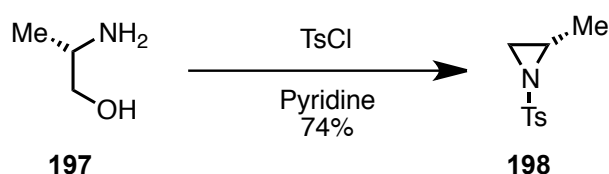
Scheme 51 aza-Diels-Alder reaction of a diene and an azirine

While currently relatively rare in the literature, recent advances in azirine chemistry have been reviewed.¹³⁸ There has also been a recent publication in this area, with an organocatalytic asymmetric synthesis of azirine-2-carboxylates published recently by Takemoto and co-workers using a thiourea-catalysed Neber reaction.¹³⁹ This type of process could prove to be fruitful in the future and push forward this little known area of small-ring chemistry.

4.1.3 Intramolecular substitution

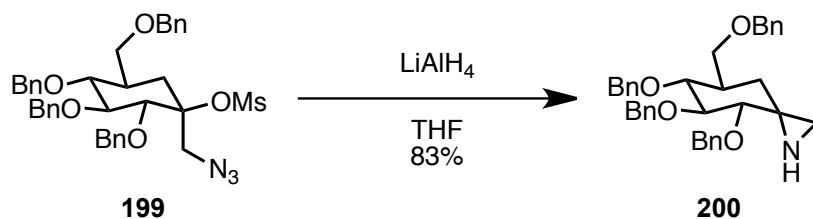
The best-known method for synthesizing aziridines is by intramolecular nucleophilic substitution. There are examples in the literature of aziridine formation from enantiopure 1,2-amino alcohols, 1,2-azido alcohols and 1,2-amino sulfides. All furnish aziridines stereospecifically.

There are countless examples of aziridine formation from 1,2-amino alcohols. An example of this is the synthesis of enantiopure *N*-tosyl aziridines **198** from amino acid derived amino alcohols **197** published by Jabin and co-workers (Scheme 52).¹⁴⁰



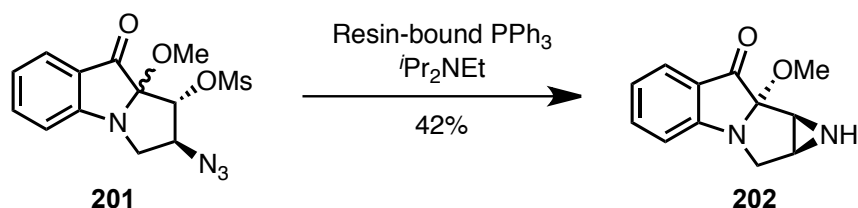
Scheme 52 Aziridine synthesis using 1,2-amino alcohol as starting material

This method is useful for the synthesis of protected aziridines. A more useful method for the synthesis of NH aziridines is through the reduction of a 1,2-azido alcohol and subsequent cyclization. Vasella has used this methodology in the synthesis of spiroaziridine glycosidase inhibitors such as **200**.¹⁴¹ It is notable in this case that other methods for the synthesis of these aziridines failed, making this route a valuable alternative to more well-known procedures (Scheme 53).



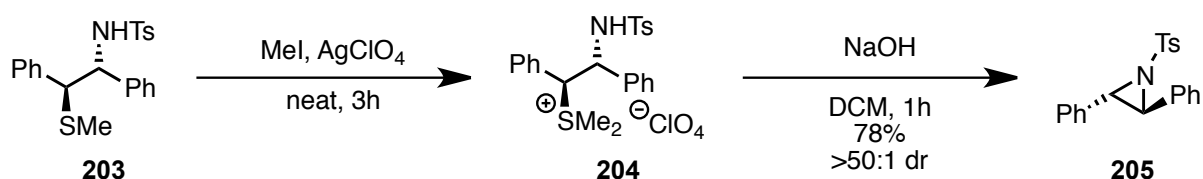
Scheme 53 Synthesis of spiroaziridine glycosidase inhibitors

Miller employed a similar method as the final step in his synthesis of aziridinomitosane (Scheme 54).¹⁴²



Scheme 54 Final step in the total synthesis of aziridinomitosane

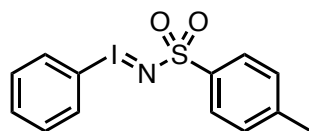
Finally, Arroyo has described a method for the synthesis of aziridines from 1,2-amino sulphides **203**. This first involves formation of a sulfonium cation **204** followed by base-induced ring closure to form the protected aziridine **205** in high yields (Scheme 55).¹⁴³ This methodology proved to be very robust, with no racemization (*via* the formation of an intermediate benzylic carbocation) occurring. There is also no base-induced epimerization and no formation of the imine and ylide decomposition products sometimes associated with this kind of system.



Scheme 55 Synthesis of aziridines from 1,2-amino sulfides

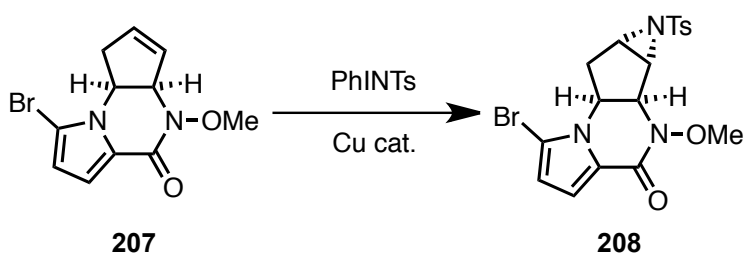
4.1.4 Addition of nitrenes to alkenes

The formal addition of a nitrogen atom to an alkene is an attractive method for synthesizing aziridines because of the availability of a vast array of alkene precursors. One such method, first reported by Mansuy and co-workers,¹⁴⁴ uses nitrene precursors such as (N-tosylimino)phenyliodinane (PhINTs) **206**.



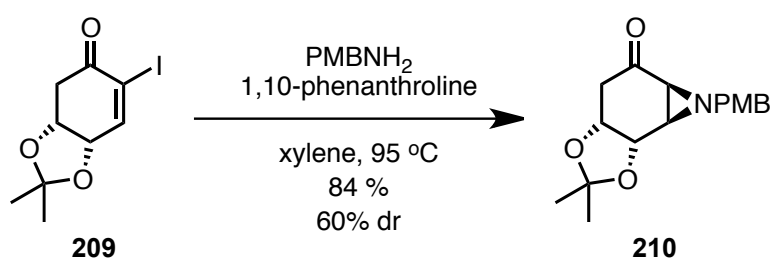
206

Using non-chiral Cu catalysts, it has been possible to form aziridines from a wide range of alkene substrates with these species. For example, Trost reported the synthesis of (+)-agelastatin where an aziridine motif was added to an advanced intermediate **207** with complete stereocontrol using PhINTs and a Cu catalyst (Scheme 56), giving compound **208**.¹⁴⁵



Scheme 56 Late stage aziridination in the synthesis of (+)-agelastatin

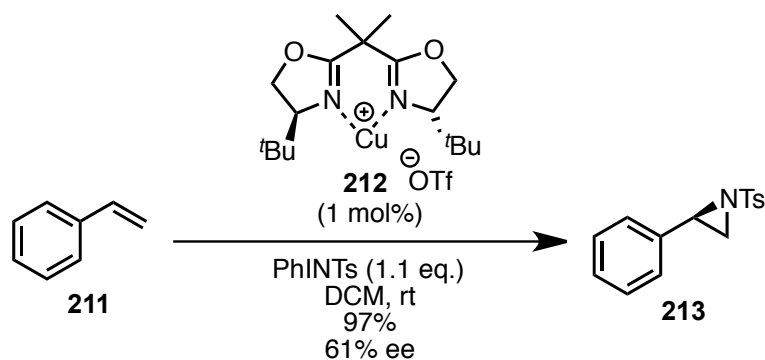
It is also possible to formally add nitrenes to α -haloacrylates in a process known as the Gabriel-Cromwell reaction. In this reaction there is an initial aza-Michael addition of an amine followed by subsequent protonation and ring closure to form the aziridine. This is exemplified by the work of Maycock and co-workers who used this methodology in their synthesis of (+)-bromoxone (Scheme 57).¹⁴⁶



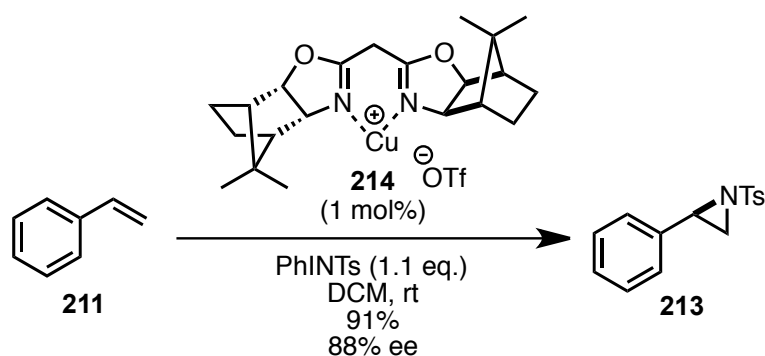
Scheme 57 Example of the Gabriel-Cromwell reaction

While the reactions described above rely on asymmetric induction from the substrates involved, there are countless examples of chiral ligands for asymmetric Cu-catalysed aziridinations, exemplified by the bisoxazoline (BOX) type ligands first

discovered by Brunner,¹⁴⁷ Nishiyama,¹⁴⁸ and Masamune¹⁴⁹ in the late 1980's. It was not until 1991 that, independently, Masamune¹⁵⁰ and Evans¹⁵¹ published single examples of styrene aziridination catalysed by Cu-BOX complexes (Schemes **58** & **59**).

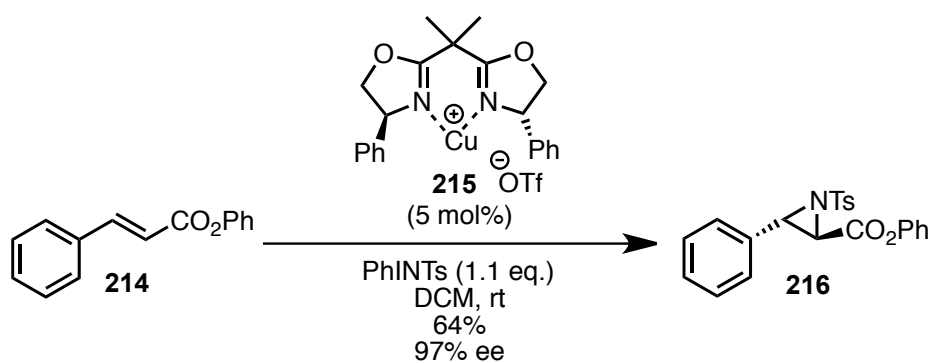


Scheme 58 Evans asymmetric aziridination



Scheme 59 Masamune asymmetric aziridination

While these catalysts were not particularly selective, they did instigate more research in this area. Evans went on to publish further work on these reactions, this time the aziridination of cinnamate esters using a related BOX-type catalyst **215**. Selectivities were universally higher using this system (Scheme **60**).¹⁵²

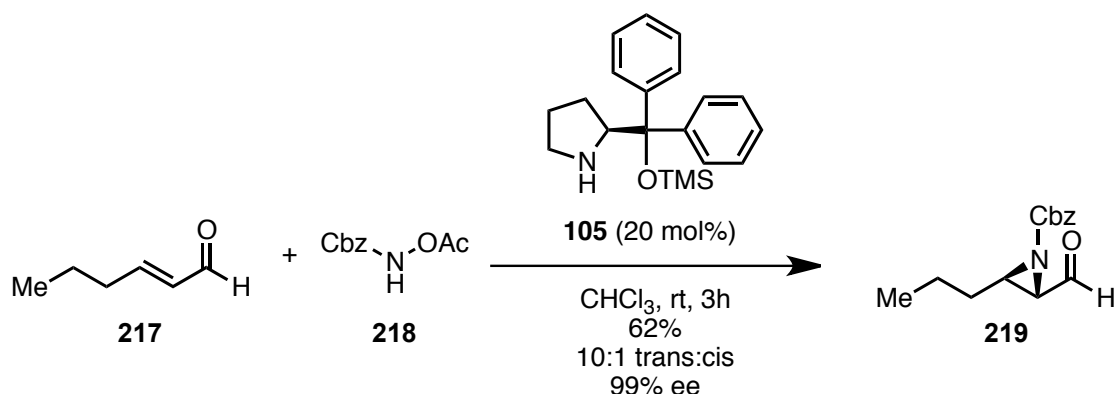


Scheme 60 Evans asymmetric aziridination of cinnamate esters

This work cemented the status of this reaction as a viable means to synthesize enantioenriched aziridines. There have been countless examples of similar reactions in the literature, which have been reviewed.¹²⁶ This remained the state of the art for this type of reaction until organocatalytic methods were developed over a decade later.

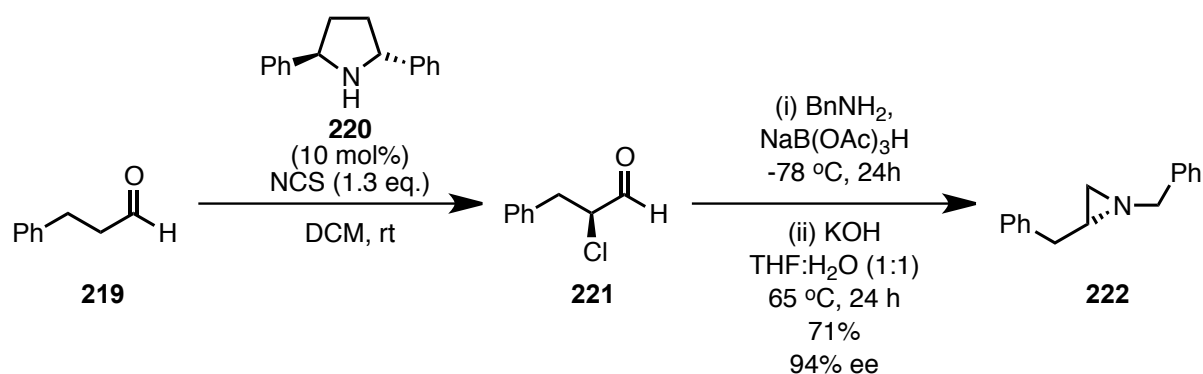
4.1.5 Organocatalysed Aziridinations

A publication by Córdova in 2007¹⁵³ describing the first example of an organocatalysed asymmetric aziridination of linear enals such as **217** (Scheme 61) led to the development of a wide variety of similar reactions on a variety of substrates,¹²² including a publication by the same group on the aziridination of α -substituted- α,β -unsaturated enals to give 2-alkyl-2-formylaziridines, again in high yield and with good selectivity.¹⁵⁴



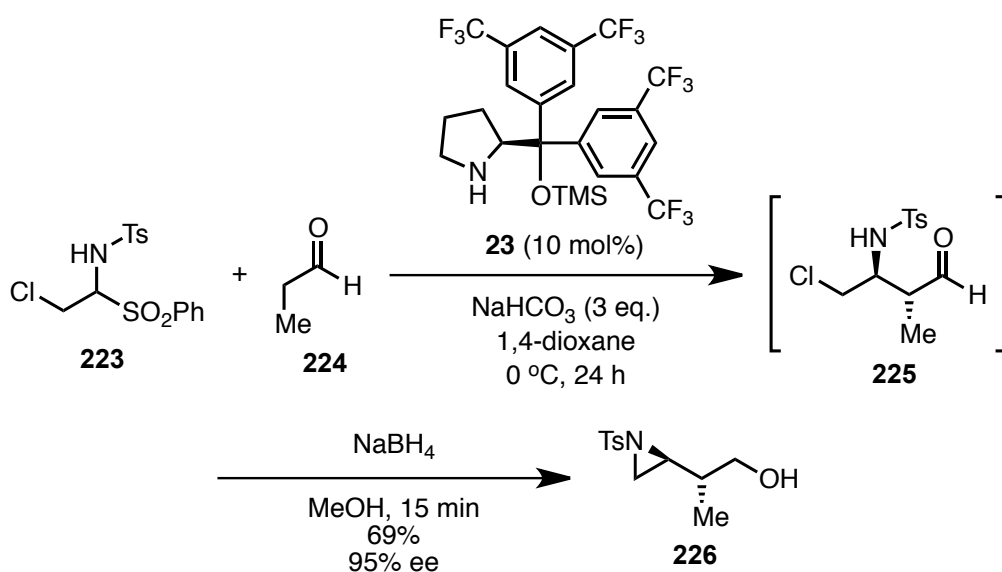
Scheme 61 The first organocatalytic asymmetric aziridination

Other methods for organocatalytic aziridination include those of Lindsley, who showed that an asymmetric α -chlorination of aldehydes to give compounds such as **221** followed by a reductive amination and subsequent cyclization to give **222** would yield terminal aziridines in high yield (Scheme 62).¹⁵⁵ While this does involve more than a single step, there are no other methods for synthesizing this type of compound using organocatalytic activation.



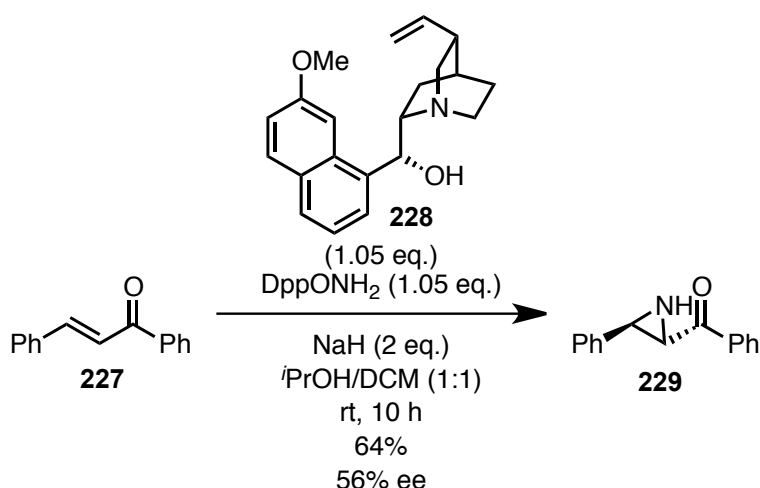
Scheme 62 Synthesis of terminal aziridines using organocatalysis

Another interesting application of enamine activation in aziridination chemistry is the work of Hayashi and co-workers.¹⁵⁶ By using the imine precursor **223**, a desulfonylation and subsequent asymmetric Mannich reaction yield the intermediate **225**. Subsequent cyclization and reduction of the resulting aldehyde give aziridines such as **226** in Scheme **63**.

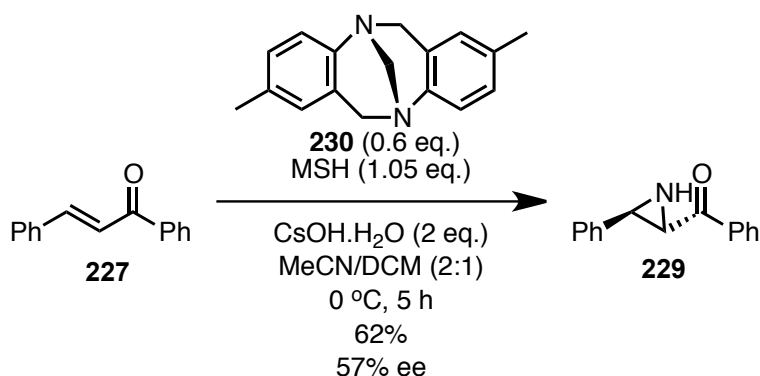


Scheme 63 Asymmetric aziridination using an organocatalytic Mannich reaction

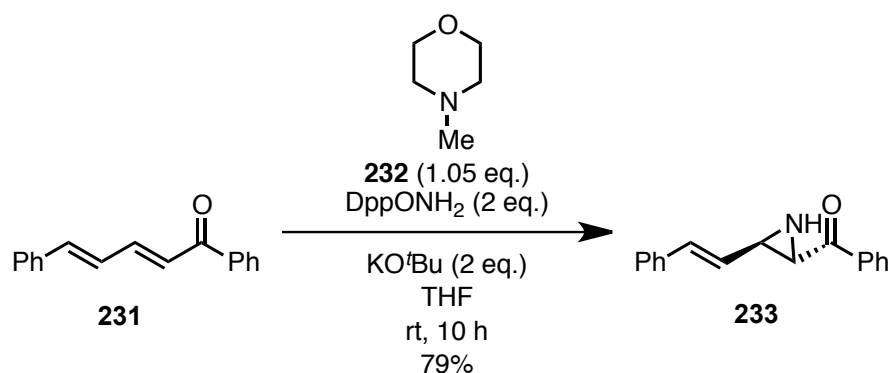
Finally, there has been some work on the tertiary amine catalysed asymmetric synthesis of *NH*-aziridines from enones such as *trans*-chalcone. This type of reaction is often not possible using metal catalysts due to the chelating nature of the products potentially destroying any catalyst used. Using initial work published by Ikeda¹⁵⁷ and co-workers, Shi¹⁵⁸ and Armstrong¹⁵⁹ were both independently able to show that a catalytic amount of tertiary amine, in the presence of an electrophilic amine source such as *O*-diphenylphosphinyl hydroxylamine (DppONH₂)¹⁶⁰ or *O*-mesitylsulfonyl hydroxylamine (MSH)¹⁶¹ (see section 5.1 for more details), was able to transfer a nitrogen atom to the double bond of the enone, forming *NH*-aziridines in the process. Whereas Shi favoured Tröger's base **230** (Scheme 64), Armstrong showed that quinine **228** behaved in a very similar manner (Scheme 65). Both catalysts gave in the region of 57% ee for the aziridination of *trans*-chalcone. In both cases, only the *trans*-aziridine was observed.



Scheme 64 Tertiary amine catalysed asymmetric aziridination



Scheme 65 Tertiary amine catalysed asymmetric aziridination

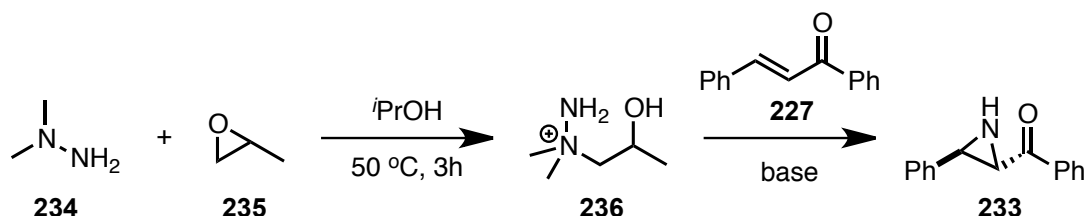


Scheme 66 Synthesis of vinylaziridines using tertiary amine mediated asymmetric aziridination

Armstrong has also continued to work in this area and has shown that it is possible to synthesize N-unsubstituted vinylaziridines **233** from $\alpha,\beta,\gamma,\delta$ -unsaturated enones **231** (Scheme 66).¹⁶² It is interesting to note in this case that the reaction is completely regioselective, with none of the other potential aziridine product seen in any case. This lends support to the proposed mechanism for the reaction, which is discussed in more detail in section 5.1.

5.1 Asymmetric aziridination

At the outset of this research, the focus was on the synthesis of new axially chiral tertiary amine organocatalysts for asymmetric aziridination, based on the methodology first reported by the groups of Ikeda, Hamelin and Bottaro.^{163,164,165} Ikeda showed that hydrazinium salts **236** could be formed *in situ* in a reaction between a hydrazine **234** and an epoxide **235** and could subsequently be deprotonated at the terminal nitrogen, forming a nitrogen-nitrogen ylide or aminimide. The newly formed nitrogen anion is appreciably more nucleophilic than a standard nitrogen-centred anion (such as those found in, for example, lithium diisopropylamide or lithium hexamethyldisilazide). This is due to the phenomenon of the alpha effect, whereby a nucleophile directly bonded to another heteroatom exhibits a much higher reactivity than would be expected if the second heteroatom were not present. Well-known examples include the hypochlorite anion, peroxide anion, hydroxamides and hydrazines. The exact reasoning behind this is not well understood, but the several theories proposed have been the topic of an in-depth review by Fina and Edwards.¹⁶⁶ Subsequent *aza*-Michael addition of these ylids to the substrate followed by reaction of the resultant enolate with the same nitrogen atom yields the aziridine product after loss of the parent tertiary amine (Scheme 67).



Scheme 67 Ikeda's initial work

Subsequent advances in this area of research were sparse until the publications of Shi¹⁶⁷ and Armstrong¹⁶⁸ in 2006 and 2007. By altering the reaction conditions, a tertiary amine could be used as the catalyst for the aziridination of enones, which is a major advantage as tertiary amines are far more readily available than the hydrazines used by Ikeda. The tertiary amine reacts with an electrophilic source of nitrogen, of which there are several reported in the literature. These include *O*-diphenylphosponylhydroxylamine (DppONH₂),¹⁶⁹ *O*-mesitylsulfonylhydroxylamine (MSH),¹⁷⁰ *O*-(2,4-dinitrophenyl)hydroxylamine (DnpONH₂),¹⁷¹ and *O*-benzoylhydroxylamine.¹⁷² This forms the desired hydrazinium salt, which can then

react as described below (Figure 9, where *N*-methyl morpholine represents the tertiary amine catalyst). Tröger's base and quinine were found to give the highest enantioselectivities by Shi and Armstrong, respectively. Both were in the region of 55-56% ee. While the level of selectivity observed was appreciable, it was by no means a perfect system.

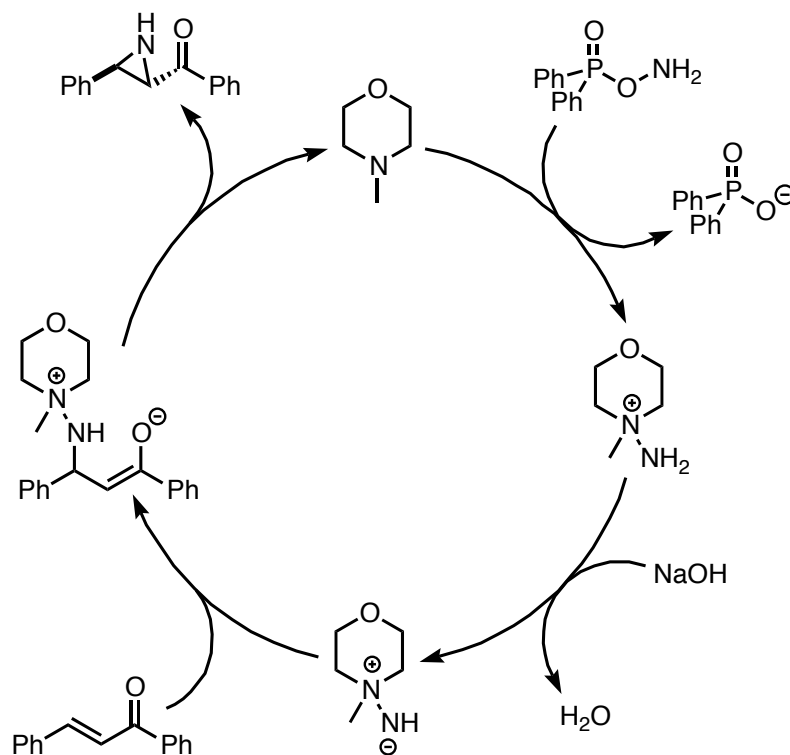
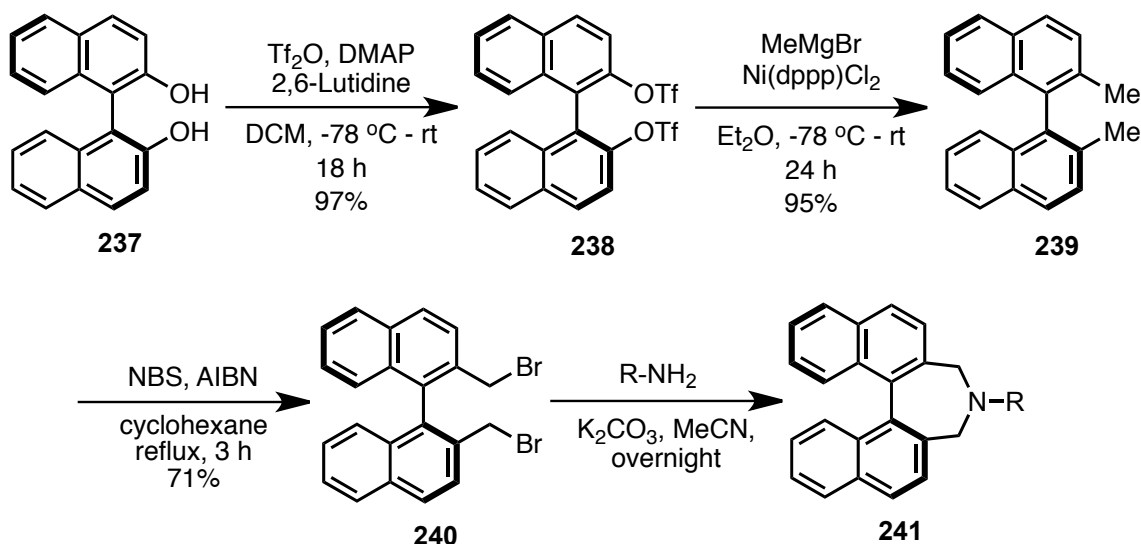


Figure 9 The proposed catalytic cycle

Previous work within the Page group had shown that novel binaphthyl-based axially chiral tertiary amines could catalyze the aziridination of chalcone substrates in up to 38% ee. The synthesis of these dihydroazepines has been utilized extensively within the group to access chiral iminium salts, which are used as oxidation catalysts, and as such is highly optimized (Scheme 68).¹⁷³

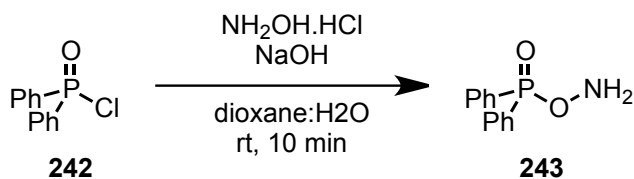
The starting material for this work is (*S*)-BINOL **237** in all cases. Triflation using Trf_2O , DMAP and 2,6-lutidine gave **238** in near quantitative yield. Subsequent Kumada coupling¹⁷⁴ using dichloro(1,3-bis(diphenylphosphino)propane)nickel (II) and methylmagnesium bromide yielded dimethylbinaphthalene **239**, again in high yield. A radical bromination using the typical NBS/AIBN mixture yields the dibromide **240** in a reasonable 71% yield after a simple filtration. Finally, ring closure through a double

nucleophilic substitution occurs using any of a wide number of primary amines in the presence of potassium carbonate in acetonitrile, giving products of the type **241**. Yields are universally high for this step, ranging from 80% to near quantitative using only a very small excess of the amine. This late stage variation in the preparation of different potential nitrogen transfer reagents allowed for the simple screening of a wide variety of tertiary amines.



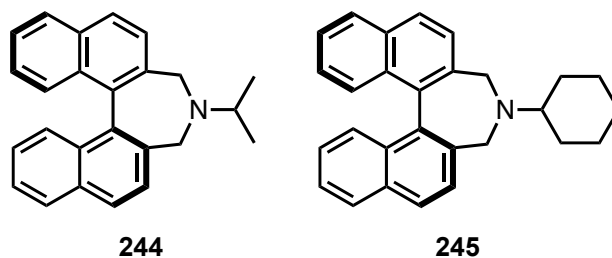
Scheme 68 General synthesis of binaphthyl azepines

The electrophilic nitrogen source used was O-diphenylphosphinyl hydroxylamine (DppONH₂) **243**.¹⁶⁹ It is easily accessed in one step from commercially available diphenylphosphinic chloride **242** and hydroxylamine hydrochloride (Scheme 69).

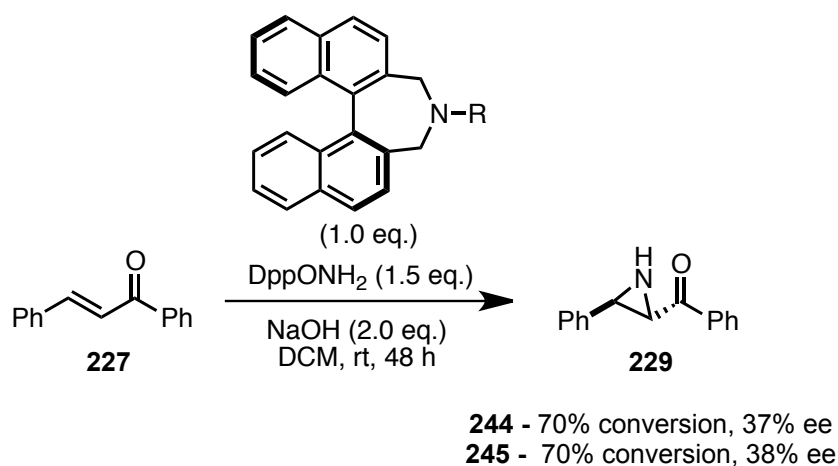


Scheme 69 Synthesis of DppONH₂

Other known electrophilic sources of nitrogen such as O-mesitylsulfonylhydroxylamine (MSH) have been shown to be explosive under relatively mild conditions and as such were not used in this work.¹⁷⁵



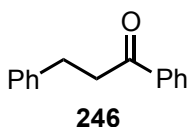
It was shown previously that *N*-isopropyl **244** and *N*-cyclohexyl **245** substituted dihydroazepines gave the best compromise between reactivity and selectivity in the aziridination of *trans*-chalcone (the chosen test reaction) (Scheme **70**).¹⁷⁶



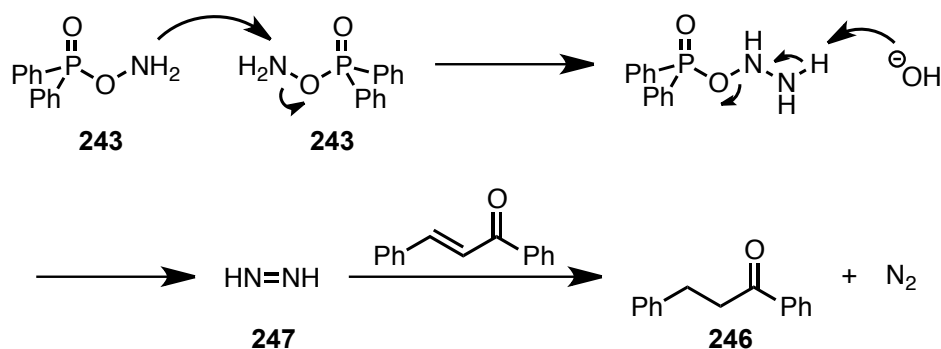
Scheme 70 Aziridination of *trans*-chalcone using previously optimized conditions

Using optimized conditions and after 48 h, the aziridination proceeds in 70% conversion and 38% ee when *N*-cyclohexyl azepine **245** is used as the catalyst. Other *N*-substituents have been tested and have been discussed at length in previous work.¹⁷⁷

In all cases, reactions were sluggish. Attempts to increase the rate of reaction by increasing the reaction temperature or the number of equivalents of DppONH₂ in the reaction mixture also failed to help increase the rate of conversion. In the latter case, the reduced ketone product **246** was seen in small but isolable quantities.



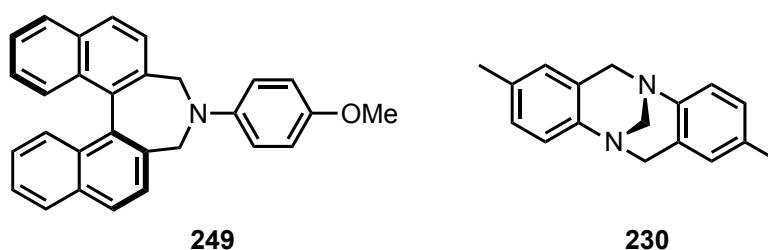
This is presumably due to the formation of small quantities of the strong reducing agent diazene (or diimide) forming *in situ* from the condensation of two molecules of DppONH₂. Presumably, DppONH₂ is both electrophilic and nucleophilic enough to condense in this manner, with the side reaction presumably proceeding through the mechanism shown (Scheme 71).



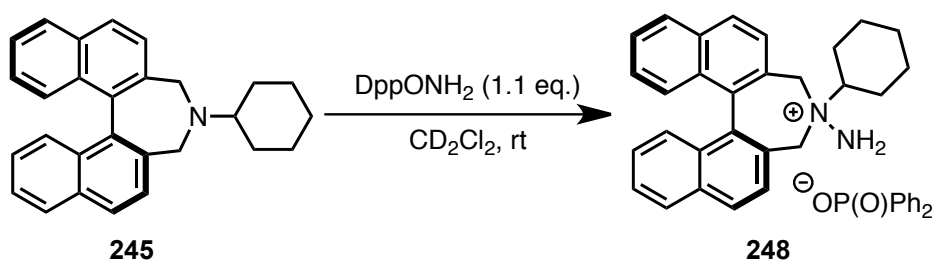
Scheme 71 Reduction of chalcone by diimide formed *in situ* from two equivalents of DppONH₂

These side reactions and long reaction times led us to consider a different approach. Previously isolated achiral hydrazinium salts could be used not as catalysts but as stoichiometric nitrogen transfer reagents.¹⁷⁸ One equivalent of tertiary amine was usually required for good conversion to take place in the one-pot procedure anyway, suggesting that catalyst turnover was not occurring at a satisfactory rate. It has also been shown in previous work that the formation of hydrazinium salts from the parent binaphthyl azepines was a very quick reaction as long as the *N*-substituent was an alkyl (Figure 10) rather than an aryl group (Figure 11).

As can be seen in figure 10, the conversion from **245** to the hydrazinium salt **248** is complete within 10 minutes in CD₂Cl₂ solution at room temperature. Conversely, using the electron rich aniline derivative **249** (which contains an *N*-benzylaniline moiety similar to Tröger's base **230** used by Shi¹⁶⁷) required over 4 hours for the same reaction to occur, forming **250**.



In Scheme **72**, for the *N*-cyclohexyl substrate **245**, the reaction was monitored using ^1H NMR spectroscopy, recording the advancement of the reaction at regular intervals: the disappearance of the pair of doublets at $\delta = 3.25$ and 3.90 ppm and the formation of four doublets at $\delta = 4.12$, 4.21 , 5.47 , and 5.58 ppm, corresponding to the four non-equivalent benzylic protons in the hydrazinium salt, can be seen to be largely complete within five minutes. In the case of the *N*-PMP azepine **249** in Scheme **73**, the corresponding pair of doublets at $\delta = 3.76$ and 4.38 ppm give way to doublets at $\delta = 4.21$, 4.52 , 4.86 , and 5.21 ppm, but the process is incomplete after four hours.



Scheme 72 Conversion of **245** to **248** using DppONH₂ in CD₂Cl₂ solution

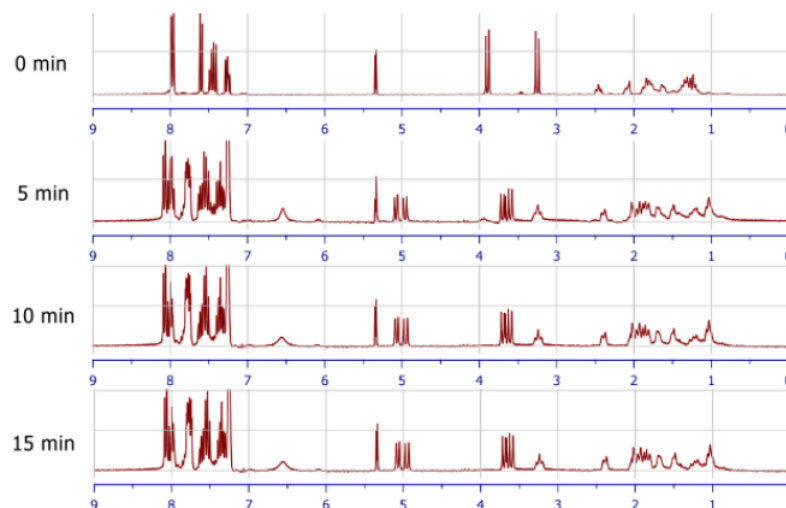
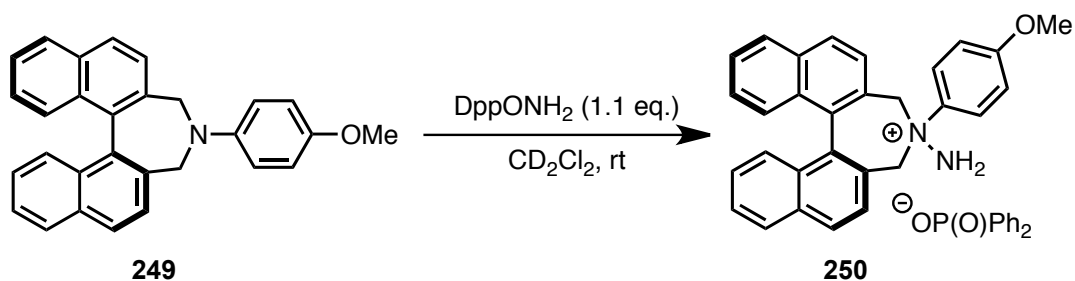


Figure 10 Monitoring conversion from **245** to **248** using ¹H NMR spectroscopy



Scheme 73 Conversion of **249** to **250** using DppONH₂ in CD₂Cl₂ solution

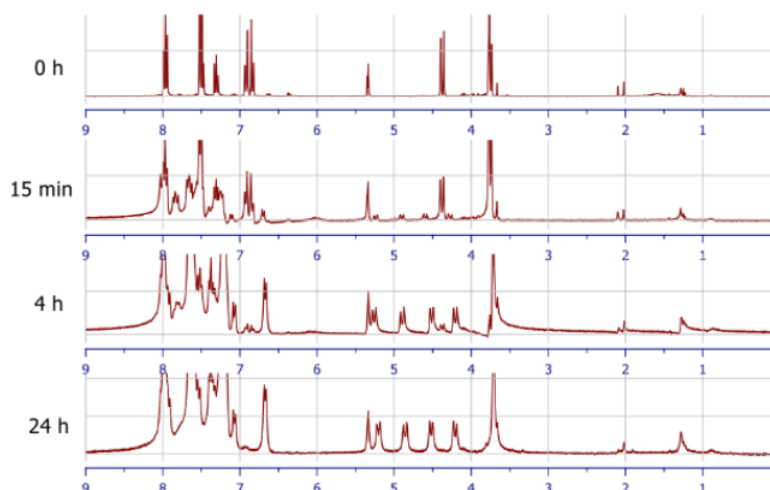
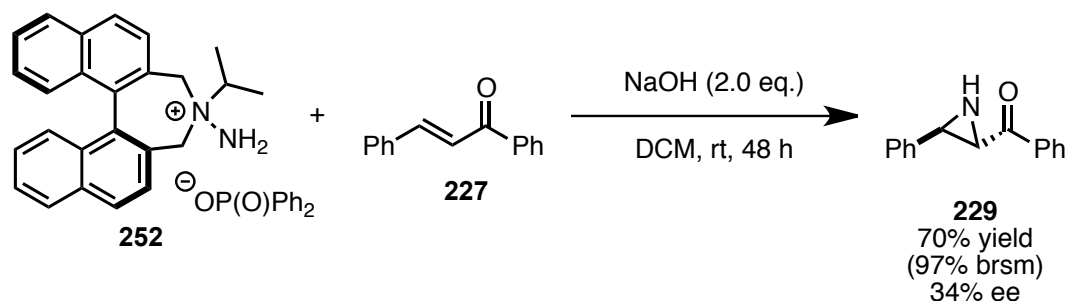


Figure 11 Monitoring conversion from **249** to **250** using ¹H NMR spectroscopy

This clean, quantitative process, with no other discernable products detected using ^1H NMR spectroscopy, suggested to us that it would be feasible to isolate these hydrazinium salts and then use them in aziridination reactions with only a base additive to form the desired aminimide.

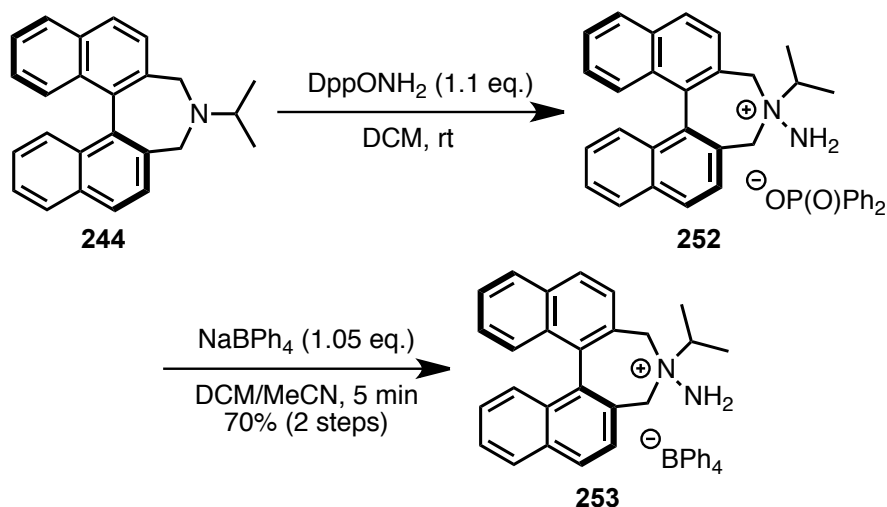
Thus, solid DppONH_2 **243** (1.1 equivalents) was added to **244** (1 equivalent) in dichloromethane (not dried, under air atmosphere). DppONH_2 is an incredibly insoluble material in the vast majority of organic solvents and as such the only work-up required to isolate the desired product was a simple filtration through Celite to remove the unreacted aminating agent. Analysis of the ^1H NMR spectrum of the resulting crude product showed completely clean hydrazinium diphenylphosphinate **251**, which was isolated as a yellow hygroscopic foam. This was then tested as a nitrogen transfer reagent with *trans*-chalcone and gratifyingly, the aziridine was obtained in 70% yield and 34% ee, results which are almost identical to those obtained when the one-pot procedure was used, albeit in a cleaner manner (the starting material, the aziridine product and tertiary amine were the only visible spots on the TLC plate after the work-up) (Scheme 74).



Scheme 74 Aziridination of *trans*-chalcone using a preformed hydrazinium salt

Although this result was promising, the hygroscopicity of the hydrazinium diphenylphosphinate salt **70** meant that it was not suitable for storage for any length of time and had to be used quickly after its synthesis. As a result, a counterion exchange was attempted to replace the diphenylphosphinate anion with the more stable, non-nucleophilic tetraphenylborate anion using the method that has been used for many years in the Page group for the isolation of iminium salts.¹⁷⁹ To our delight, the non-hygroscopic hydrazinium tetraphenylborate salt **71** was isolated as a colourless powder in 70% yield over two steps. This compound has proven to be

completely bench-stable even over the course of two years while taking no precautions to exclude air or moisture (Scheme 75).



Scheme 75 Isolation of highly stable hydrazinium tetraphenylborate salt **253**

This salt also proved to be just as reactive as its less stable precursor in the aziridination protocol, with a similarly clean reaction taking place under the standard reaction conditions. Enantioselectivity was also not affected in this case.

In conclusion for this chapter, a series of novel axially chiral tertiary amines have been shown to be effective nitrogen transfer reagents when used in conjunction with DppONH₂, an electrophilic nitrogen source. Also, what we believe to be the first example of an isolable chiral hydrazinium salt was isolated and fully characterized. It acts as an enantioselective nitrogen transfer reagent in itself for the aziridination of trans-chalcone, giving NH-aziridine products in good yield and moderate enantioselectivity. This is in complete agreement with the work of Ikeda and Armstrong, who suggest that the formation of a hydrazinium salt is an integral part of the catalytic cycle for the tertiary amine catalyzed synthesis of aziridines from chalcone substrates.¹⁶⁸

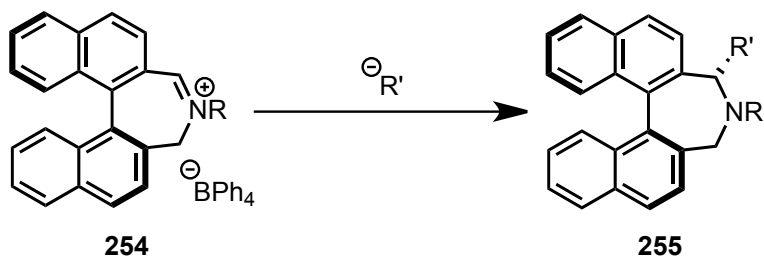
6.1 New Axially Chiral Secondary Amines

At around the time our work on tertiary amine mediated asymmetric aziridination was published,¹⁷⁶ Cordova reported the asymmetric aziridination of enals using a secondary amine diarylprolinol organocatalyst that has been popularized by Jørgensen over the past decade.¹⁸⁰ Having modified axially chiral tertiary amines in a variety of ways in attempts to increase selectivity, the next logical step was to synthesize some axially chiral secondary amines and test them as catalysts for a variety of standard asymmetric organocatalytic processes.

While there are some highly selective organocatalytic systems in the literature, there are relatively few structural motifs that are regularly seen. L-Proline, which was used by Hajos & Parrish,¹⁰ Eder, Sauer & Wiechert,¹⁸¹ List,¹⁸² and others as well as the now ubiquitous MacMillan imidazolidinone catalysts¹⁸³ and the diarylprolinol catalysts first used by Jørgensen¹⁸⁴ and Hayashi¹⁸⁵ are highly selective in the majority of cases but lack much in the way of structural diversity. We envisaged that the highly constrained dihydroazepine system in our binaphthyl amines could act as a selective organocatalytic system.

Maruoka has previously shown that similar functionalized systems can be stable, highly selective catalysts for enamine-type organocatalytic processes including aldol and Mannich reactions that have been discussed above (in section 3.1).¹⁰⁶ However, the synthesis of the catalysts themselves rely on an early stage Pd-catalyzed carbonylation to insert the desired functionality. It was hoped that using a previously utilized methodology from within the Page group it would be possible to synthesize a large variety of potential organocatalysts from a single late stage precursor.

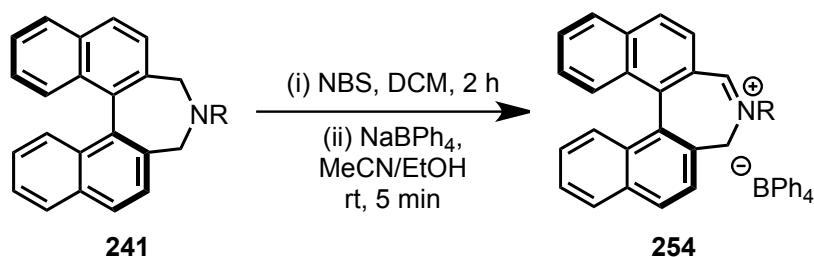
A 2012 publication by the Page group showed that addition of nucleophiles to iminium salts **254** derived from BINOL occurs completely diastereoselectively, with the product always having the newly attached pendant group in a pseudoaxial configuration with respect to the 7-membered dihydroazepine ring (Scheme 76).¹⁸⁶



Scheme 76 Highly diastereoselective nucleophilic addition to iminium salts

This configuration can easily be determined by analysis of the 1H NMR spectrum of the product. If the R' group is in the expected pseudoaxial orientation, an associated pronounced upfield shift of the signal corresponding to the protons located on the first carbon of the group will be clearly apparent in the spectrum. This occurs due to shielding interactions between the protons of the R group and the ring current that flows through the delocalized aromatic system in the naphthyl group in the backbone. It is the opposite phenomenon to that of why protons in aromatic compounds experience a pronounced downfield shift compared with protons in similar, albeit non-aromatic compounds (e.g. benzene appearing at ~ 7.3 ppm in a 1H NMR spectrum and the vinylic proton in cyclohexene appearing at ~ 5.6 ppm). The pseudoaxial orientation of these newly introduced substituents has also been unequivocally proven by single crystal X-ray analysis. This will be mentioned below.

Our hypothesis was that if simple Grignard reagents could be added diastereoselectively into iminium salts, it would also be the case that more exotic nucleophiles could also be added in the same way. It was envisaged that we would be able to synthesize a wide range of potential organocatalysts from the single iminium salt of the type **254** that was itself available upon oxidation of *N*-substituted azepines **241** (accessible in four steps as described above in scheme **68**) by the action of *N*-bromosuccinimide in dichloromethane (Scheme **77**). Generally, a counterion exchange to form the iminium tetraphenylborate is then carried out in order to stabilize the iminium salt in an identical manner to the isolation of hydrazinium salt **253**.

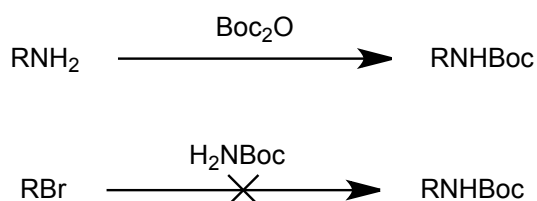


Scheme 77 Formation of iminium salts from their parent azepines

6.1.1 Initial Work and Choice of Protecting Group

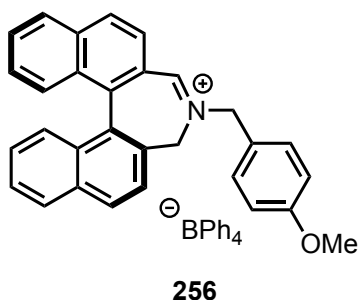
The choice of nitrogen protecting group was important considering the wide variety of conditions it would be subjected to throughout any potential synthesis. The primary amine required for reaction would have to be either commercially available or easily made on multi-gram scale, and it would have to be stable to the acidic conditions of the crucial oxidation step from amine to iminium salt as well as the strongly basic conditions required for addition of Grignard reagents. It must also then be easily deprotected in the presence of other functional groups in the molecule. This narrowed down our potential choices substantially from the outset.

The carbamate protecting groups (Boc, Fmoc etc.) are probably the most well known group of nitrogen protecting groups. However, protection normally occurs through reaction of a primary or secondary amine with the anhydride of the desired protecting group (Scheme 78). For this to happen in our synthesis, a cumbersome deprotection and reprotection route would have to be devised, thus increasing the number of steps required for any potential synthesis. The stability of potential iminium salts containing a carbamate was also called into question, and for these reasons, none of the carbamate protecting groups were considered further.

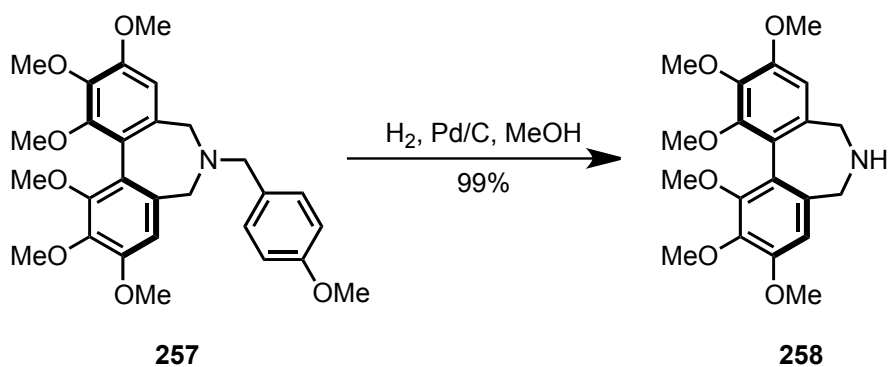


Scheme 78 Potential synthesis of NBoc derivatives

Our initial synthetic route to new secondary amine organocatalysts proceeded through the *N*-*p*-methoxybenzyl protected iminium salt **256**.

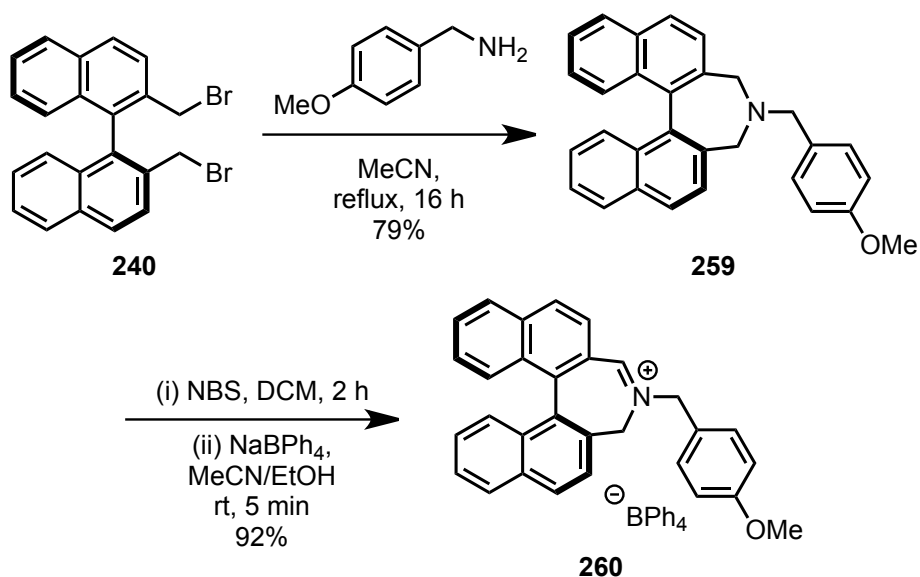


There was literature precedent from a patent by Maruoka for the removal of a PMB group from a related scaffold using a standard hydrogenolysis protocol (Scheme **79**),¹⁸⁷ and we hoped that the same would be true in our binaphthyl-based system.



Scheme 79 Hydrogenolysis of a PMB protecting group in a biphenyl-based system

Thus, azepine **259** was synthesized from dibromide **240** and commercially available *p*-methoxybenzylamine. Iminium salt **260** was then isolated in excellent yield after oxidation with NBS to the iminium bromide salt and subsequent counterion exchange using NaBPh₄ (Scheme **80**).



Scheme 80 Synthesis of iminium salt **260**

At this point, some test deprotection reactions were also attempted on the parent azepine **259** (Table 1).

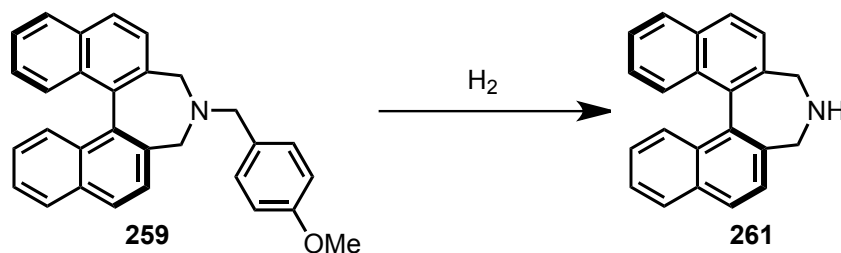


Table 1 Attempted hydrogenolysis of **259**

Catalyst	Solvent	Time (h)	Result
Pd/C	MeOH	16	SM
Pd(OH) ₂ /C	MeOH	16	SM
Pd/C	AcOH	16	SM
Pd/C	THF	16	Decomposition

Unfortunately, Maruoka's method for deprotection was unsuccessful, giving only starting material in all cases. Supposedly, the amine is converted to the corresponding ammonium salt in acidic media (i.e. AcOH solvent), which should facilitate deprotection. This was not the case in our system, and again only starting material was isolated. Finally, when tetrahydrofuran was used as the solvent,

complete decomposition of the azepine ring was observed, presumably showing that the two other benzylic positions within the molecule were also highly susceptible to hydrogenolysis under the right conditions.

Next, a simple acidic cleavage such as the one employed by MacMillan in his total synthesis of minfiensine was attempted.¹⁸⁸ Thus, the azepine **259** was stirred in a solution of triethylsilane and trifluoroacetic acid in dichloromethane (Scheme **81**). In our hands, this method merely protonated the amine and the corresponding ammonium trifluoroacetate **262** was isolated in quantitative yield.



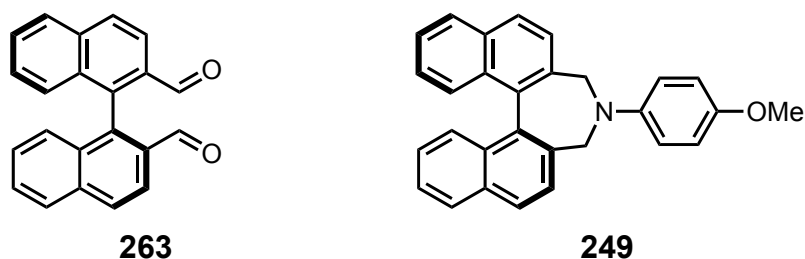
Scheme 81 Synthesis of amine trifluoroacetate **262**

Finally, a variety of oxidative cleavages were tested. This is the standard method for removing PMB groups from ethers but is less used when considering PMB protected amines (Table **2**).

Table 2 Attempted oxidative deprotections of **259**

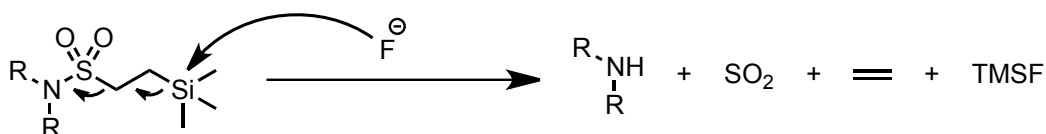
Conditions	Solvent	Temperature (°C)	Time (h)	Result
CeCl ₃ /NaI	MeCN	reflux	24	SM
DDQ	dry DCM	rt	3	Decomposition
FeCl ₃ /cat. DDQ	DCM/H ₂ O	rt	3	263 (30%)
SnCl ₄ /PhSH	DCM	-50	1	SM
Ph ₃ C ⁺ BF ₄ ⁻	DCM	rt	0.1	Decomposition
CAN	MeCN/H ₂ O	rt	0.1	Decomposition

Unfortunately, all attempts were unsuccessful, with mild oxidants leading to the recovery of the starting material and stronger oxidants resulting in decomposition. A notable exception was observed when iron trichloride and DDQ were used; the bisaldehyde **263** was isolated in low yield after column chromatography. This did prove that the naphthyl benzylic positions were definitely susceptible to the types of oxidative cleavage that one normally expects to see only in the case of highly electron rich aromatic systems such as the PMB group.



The *p*-methoxyphenyl (PMP) protecting group (compound **249**) was also tested, as it is also susceptible to this type of oxidative cleavage.¹⁸⁹ Unfortunately, this only led to the same results as before, with none of the desired secondary amine seen when analysing the ¹H NMR spectra of any of the crude reaction mixtures.

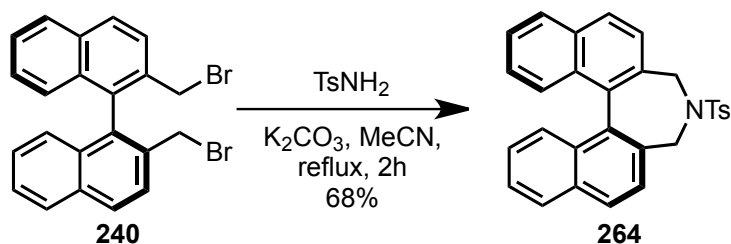
The next class of protecting groups that we considered was the sulfonyl-based groups, exemplified by the *p*-toluenesulfonyl or tosyl group. While notoriously difficult to remove (dissolving metal reductions or strongly acidic conditions), there are several protecting groups in this class that are susceptible to deprotection under a wide range of conditions. The one that caught our eye in this case was the little-used trimethylsilyl ethanesulfonyl (SES) group, which can be selectively deprotected in the presence of other sensitive functionalities using a source of fluoride.¹⁹⁰ This occurs via a fragmentation of the protecting group into one equivalent each of trimethylsilyl fluoride, as well as gaseous ethylene and sulfur dioxide. After workup, the amine is generally isolated cleanly (Scheme **82**).



Scheme 82 Deprotection of the SES protecting group

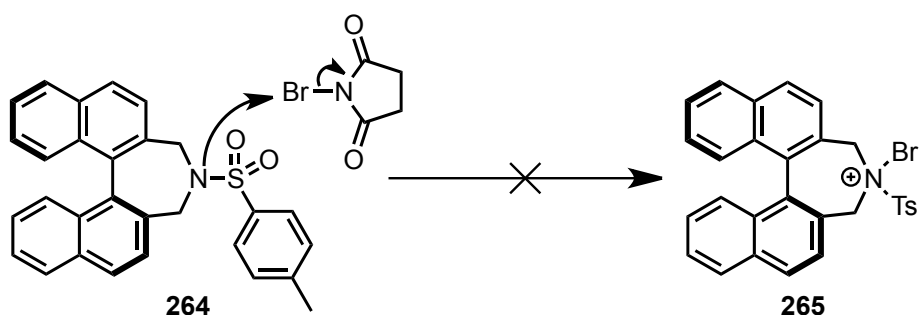
Unfortunately the desired amine is prohibitively expensive and even the related chloride is only available on relatively small scale, which would hinder scale up attempts.¹⁹¹

In order to test the compatibility of sulfonyl protecting groups with our synthetic route, *N*-tosylazepine **264** was synthesized from the standard dibromide precursor **240** using commercially available *p*-toluenesulfonamide (Scheme 83).



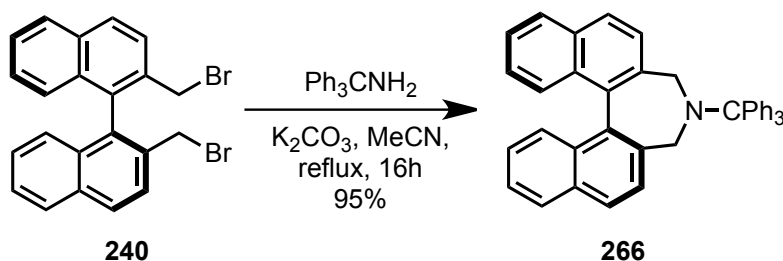
Scheme 83 Synthesis of sulfonamide **264**

The hope was that the electron-withdrawing sulfonyl group would still allow for NBS oxidation to occur to give the *N*-tosyl iminium salt. Unfortunately, this proved not to be the case. Even under forcing conditions with 3 eq. of the NBS oxidant at reflux in dichloromethane or 1,2-dichloroethane, the starting material was recovered completely in each case. This shows just how stable tertiary sulfonamides are and also that their electron-withdrawing nature renders the amine non-nucleophilic to the point that the proposed intermediate of the oxidation (the *N*-bromo intermediate **265**) cannot form (Scheme 84). Bhandarkar has discussed this mechanism in depth.¹⁹² Unfortunately, as a result of this failure, the search for a protecting group continued.



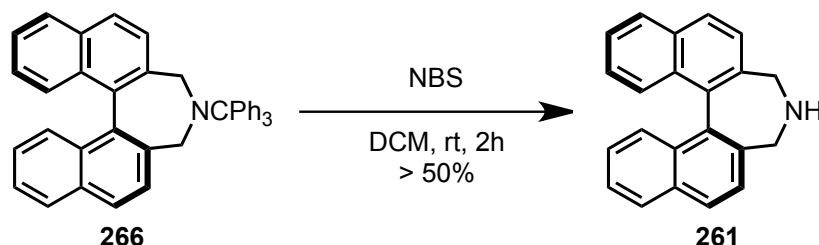
Scheme 84 Attempted oxidation of **264** to give *N*-bromo intermediate **265**

Next on the list of potential protecting groups was the highly labile trityl group.¹⁹³ The stability of the triphenylcarbenium cation is well known and is often exploited when using this protecting group. The synthesis of compound **266** proceeded without issue (Scheme 85).



Scheme 85 Synthesis of *N*-trityl azepine **266**

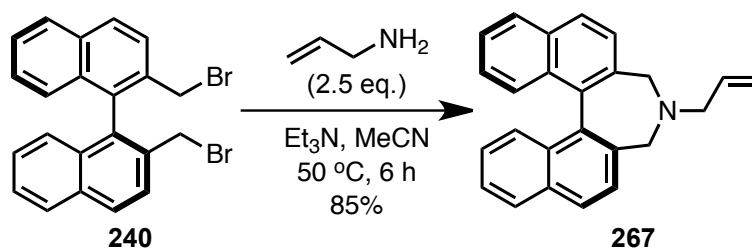
However, we feared that the trityl group would not survive the mildly acidic conditions of the oxidation step (due to residual HBr present in the *N*-bromosuccinimide). This unfortunately proved to be the case, with appreciable amounts of the unwanted secondary amine seen after several oxidation attempts using even freshly recrystallized NBS (Scheme 86).



Scheme 86 Unwanted deprotection of compound **266**

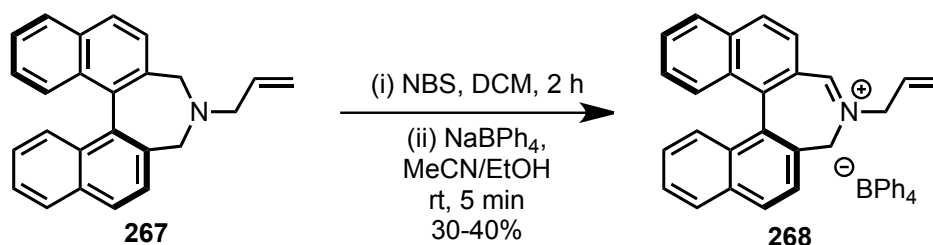
Our final choice of protecting group was the allyl group, which had been used previously in a literature synthesis of related compounds by Hawkins.¹⁹⁴ The only potential issue we foresaw was whether the alkene part of the protecting group would be stable to the NBS oxidation step to form the required iminium salt.

Due to the low boiling point of allylamine, our general method for dihydroazepine synthesis had to be altered slightly. As such, 2.5 equivalents of allylamine were used in this case at a lower than standard temperature. Purification of compound **267** was found to be facile. A single wash with cold acetone removed any impurities from the solid azepine product (Scheme 87).



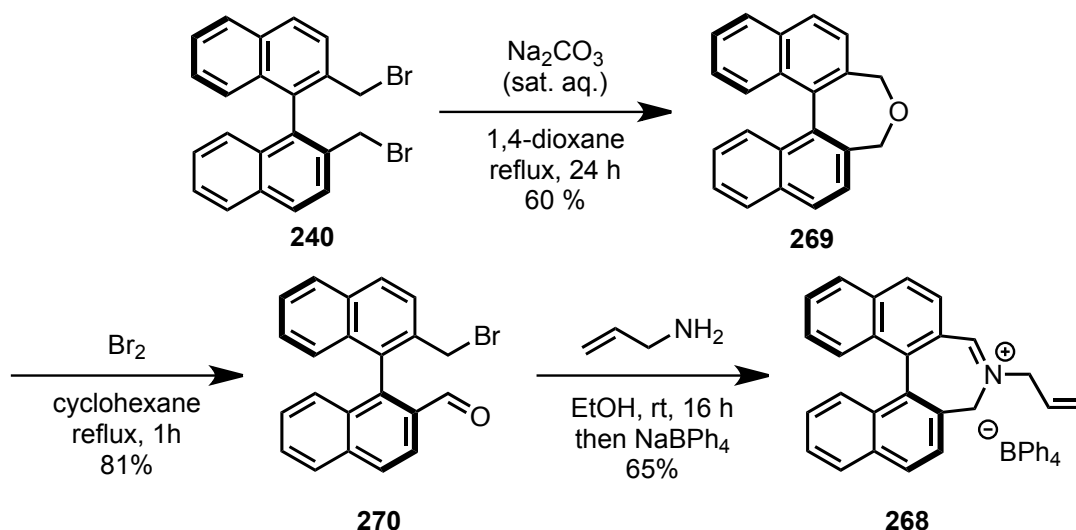
Scheme 87 Synthesis of *N*-allyl azepine **267**

Our initial attempts at the oxidation of **267** to iminium salt **268** were unsuccessful, as purification of the salt proved to be extremely difficult (Scheme **88**). There is literature precedent for the dibromination of *N*-allyl groups by NBS and, although nothing was ever isolated from these reaction mixtures, we assumed that this is one of several decomposition pathways that could be at play in this case.¹⁹⁵



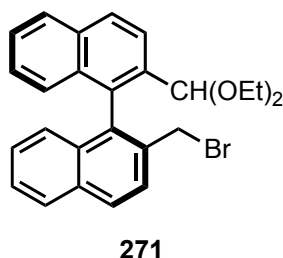
Scheme 88 First synthesis of *N*-allyl iminium salt **268**

Another potential route to the iminium salt **268** was *via* bromoaldehyde **270**, which has been used extensively within the Page group for the synthesis of iminium salts (Scheme **89**).¹⁷³



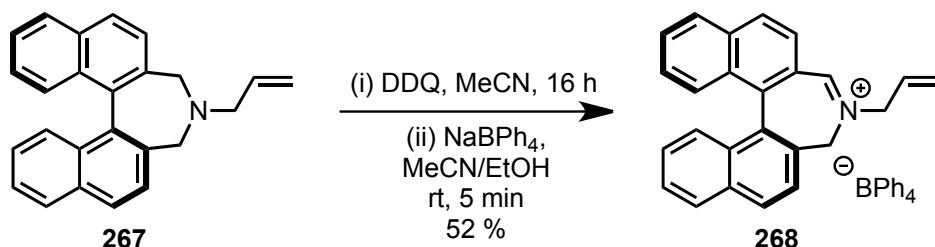
Scheme 89 Synthesis of **268** via bromoaldehyde intermediate **270**

However, this three step protocol (which required two cumbersome chromatography steps) was found to give an unacceptably low yield of the desired iminium salt, which was difficult to separate from unreacted **270**, as well as small but isolable amounts of the diethyl acetal byproduct **271**, which was seen repeatedly when analyzing ^1H NMR spectra of crude reaction mixtures.



Attempts to form the desired *N*-tosyl iminium salt by this method also failed, with a complex mixture of products formed. None of them corresponded to the desired cyclized iminium salt.

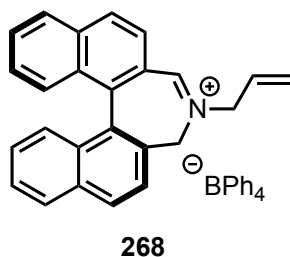
DDQ-mediated oxidation of azepine **267** was attempted which yielded the iminium salt **268** in unacceptably low yields after an extremely drawn out purification to remove DDQ by-products (Scheme 90).



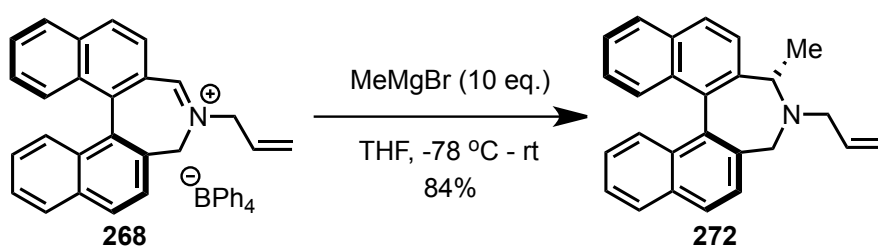
Scheme 90 DDQ oxidation to form **268**

Gratifyingly, we eventually found that after optimization of the reaction conditions that the *N*-allyl iminium tetraphenylborate could be isolated in useful quantities using a drastically modified procedure compared with that used for the synthesis of PMB iminium salt **260**. We found that by slowly adding NBS to a dilute solution of **267** in dichloromethane and monitoring the reaction closely by TLC, it was possible to form the desired iminium bromide cleanly in good yield. However, this compound proved to be highly unstable and as such counterion exchange was carried out without isolation of the intermediate bromide.

The standard method for purification of iminium tetraphenylborates is to recrystallize from hot ethanol. This was not suitable in this case, as it caused appreciable decomposition of the desired compound. Instead, it transpired that excess NaBPh₄ could be removed from the mixture due to its insolubility in acetone and that other impurities could be largely removed due to their insolubility in chloroform. This gave us appreciable quantities of **268**, which had been inaccessible to this point, allowing us to continue on with our proposed synthetic route.



It was then necessary to prove that our methodology was sound and that the diastereoselectivity of nucleophilic addition to our iminium salts was not controlled by the chiral *N*-substituents that were used in our previous work but by the axial chirality of the binaphthyl backbone.¹⁸⁶ Thus, a simple addition of MeMgBr was attempted onto iminium salt **268**. As before, a large excess of the Grignard reagent was required to afford good conversion to the desired product. Thus, after addition of 10 equivalents of MeMgBr to the iminium salt in dry THF, the methylated product **272** was isolated in an excellent 84% yield as a single diastereoisomer after column chromatography (Scheme 91).



Scheme 91 MeMgBr addition to iminium salt **268** to give **272**

This result shows that our methodology should allow us to synthesize a wide array of compounds based upon this structural motif. As discussed above, the orientation of the methyl group in compound **272** can be inferred from analysis of its ¹H NMR

spectrum (Figure 11). The doublet corresponding to the methyl group appears at $\delta = 0.55$ ppm, which is much further upfield than one would expect for protons in a similar environment. Compared with the terminal protons in α -methylbenzylamine ($\delta = 1.34$ ppm), it is clear to see the large effect that the ring current effect of the binaphthyl backbone has on these protons.

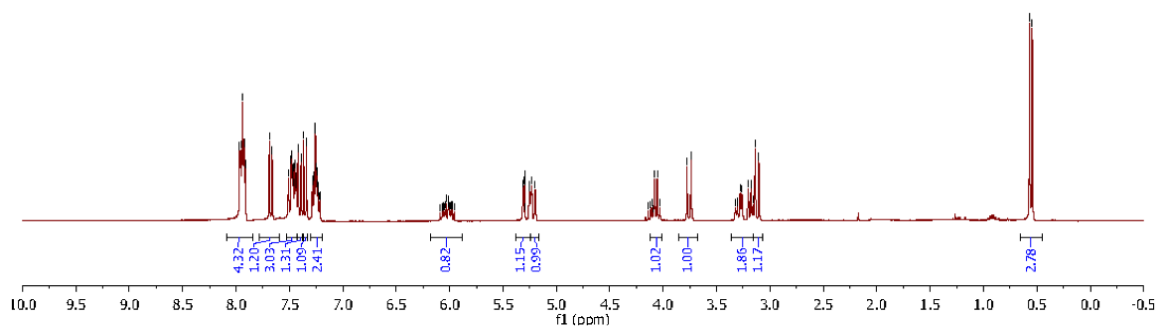
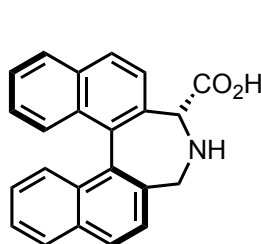


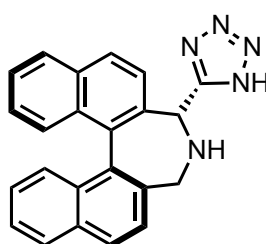
Figure 12 ^1H NMR spectrum of compound **272**

6.1.2 Towards the synthesis of α -amino acid **273**

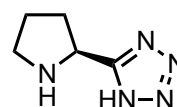
We had two compounds in mind when it came to designing novel organocatalysts. The α -amino acid **273** appeared to be an appropriate target due to its similarity to the well-known amino acid organocatalyst proline. Tetrazoles have been shown to be bioisosteres for carboxylic acids in several drugs.¹⁹⁶ Compounds such as **275** have also previously been shown to act as excellent organocatalysts by Ley and co-workers so we also deemed compound **274** to be a valuable target.¹⁹⁷



273

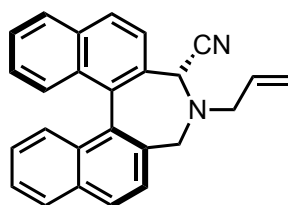


274



275

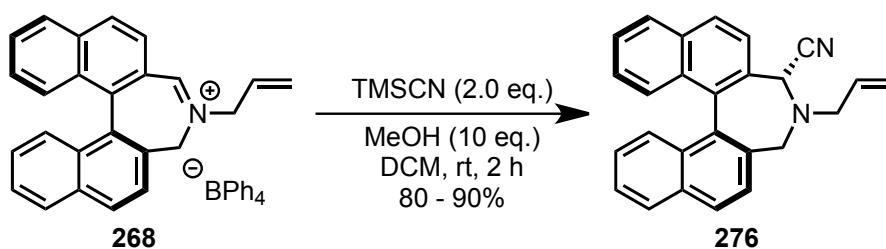
Thus, our first potential target compound was α -amino nitrile **276**, which we hoped would provide access to both of these compounds after further derivatization. Hydrolysis could presumably lead to **273**, while a 3+2 cycloaddition with sodium azide could lead to **274**.



276

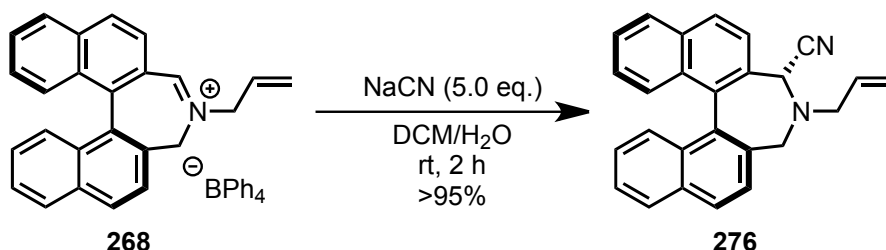
6.1.2.1 The α -amino nitrile

Our initial route to **276** was using conditions generally used in well-known asymmetric Strecker reactions. That is, the use of trimethylsilyl cyanide (TMSCN) in dichloromethane along with several equivalents of an alcohol (usually MeOH), which liberates the cyanide anion and allows it to react with the imine (or in our case, the iminium salt).¹⁹⁸ This worked well and gave near quantitative formation of the desired product (Scheme **92**).



Scheme 92 Initial synthesis of **276**

However, it also unfortunately led to a product contaminated with several silicon-containing byproducts (characterized by a large number of peaks at $\delta = \sim 0$ ppm in the ^1H NMR spectrum). Attempted column chromatography resulted in considerable decomposition of a compound that was unstable to acidic conditions. Instead, it was found that a simple biphasic mixture of **268** and NaCN in dichloromethane/water was found to give far cleaner **276**, meaning the crude product could be taken through to the next step without further purification (Scheme **93**).



Scheme 93 Optimized synthesis of **276**

At this point, it was also possible to grow crystals of **276** suitable for X-ray analysis. The structure is shown in figure **13**, where it is clearly possible to see the pseudoaxial orientation of the newly introduced nitrile with respect to the azepine ring.

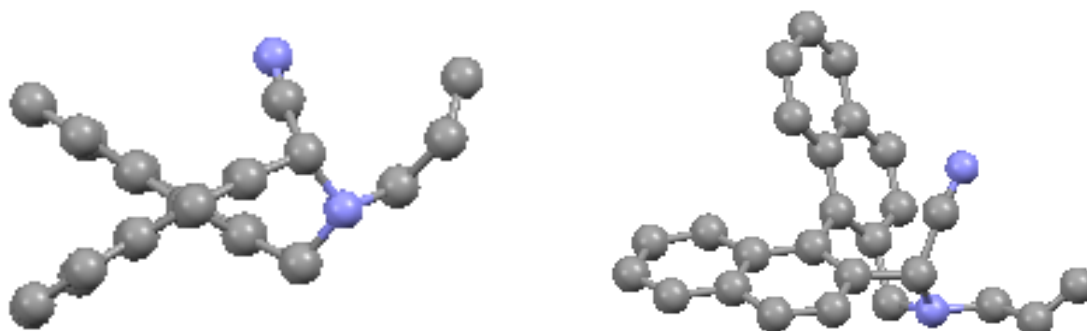


Figure 13 Crystal structure of α -amino nitrile **276**

There were then several possible reactions we were hoping to perform on compound **276**. As mentioned above, **273** and **274** were our primary targets, but it would also be interesting to attempt reductions of **276** to potentially form other compounds that could prove useful. Attempts at hydrolysis using both basic and acidic conditions unfortunately were generally met with complete failure, with either the starting material reisolated or complete decomposition seen in all cases (Table 3).

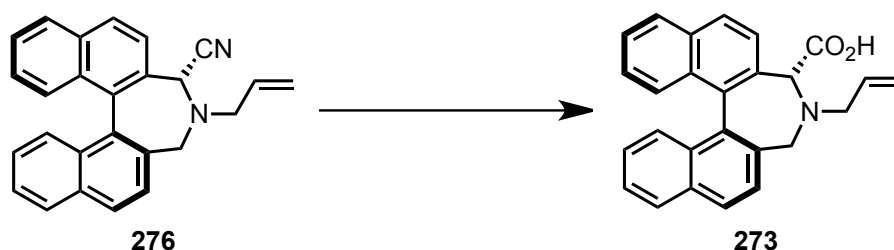


Table 3 Attempts to hydrolyze **276**

Conditions	Temperature (°C)	Time (h)	Result
conc. HCl	reflux	16	Decomposition
conc. HCl	0	48	SM
3M NaOH	reflux	16	Decomposition
80% aq. H ₂ SO ₄	50 °C	16	Decomposition

Attempts to synthesize tetrazole **274** also met with failure. Either no reaction occurred whatsoever, or decomposition of the starting material occurred. These results are presented in table 4.

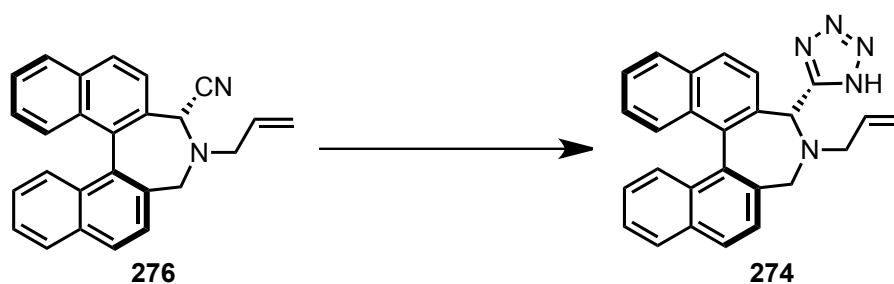
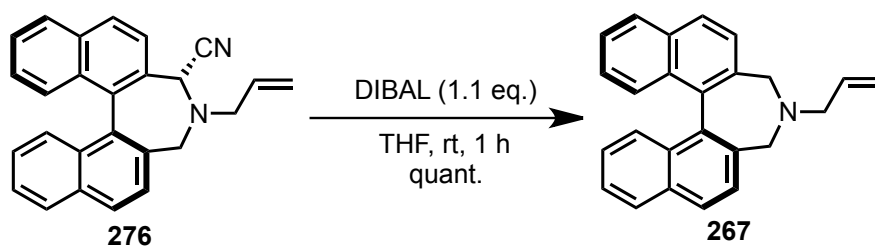


Table 4 Attempted synthesis of tetrazole **274**

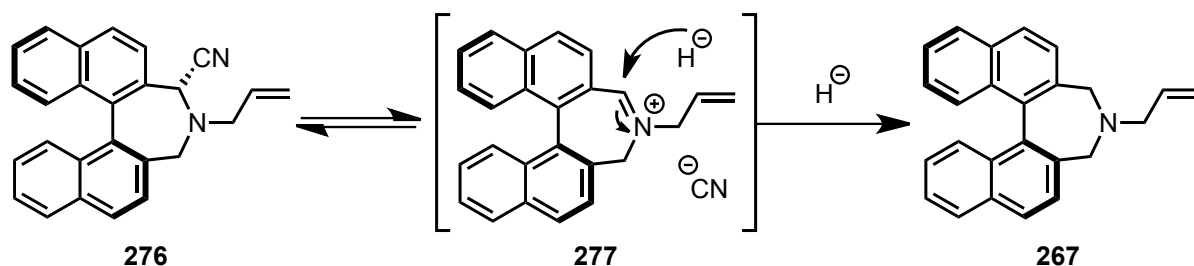
Solvent	Temperature (°C)	NaN ₃ (eq.)	Additive	Result
PhMe	100	2	-	SM
PhMe	100	1.5	Et ₃ N.HCl	SM
PhMe	130	5	Et ₃ N.HCl	SM
NMP	200	2	TMSCl	decomp.
DMF	140	1.5	NH ₄ Cl	SM
<i>i</i> PrOH:H ₂ O	100	2	ZnBr ₂	decomp.

Seeing as cyanide is an excellent leaving group and that iminium salt **268** is more stable than other iminium salts due to its cyclic nature, it was not surprising that the harsh conditions resulted in decomposition. This was further exemplified by attempting to reduce the nitrile, either to the aldehyde or to the primary amine. Use of lithium aluminium hydride resulted in decomposition of the compound, whereas addition of an excess of the less harsh reducing agent diisobutylaluminium hydride (DIBAL) resulted in complete conversion of **276** to the parent azepine **267** (Scheme 94).



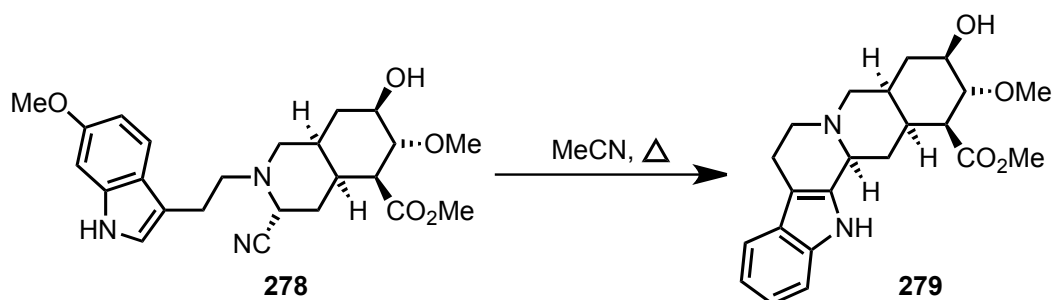
Scheme 94 Attempted reduction of **276**

Even slow addition of a single equivalent of the reducing agent at $-30\text{ }^{\circ}\text{C}$ resulted in the same reaction occurring, albeit at a much slower rate. This lends further evidence to the hypothesis that the facile decomposition of **276** proceeds due to the fact that the formation of iminium cyanide **277** and subsequent loss of cyanide is a favourable process with loss of gaseous HCN driving the reaction forward. Presumably this newly formed iminium ion is then quickly reduced by the hydride source in the reaction mixture to give **267** (Scheme 95).



Scheme 95 Formation of **267** by reduction of iminium cyanide **277**

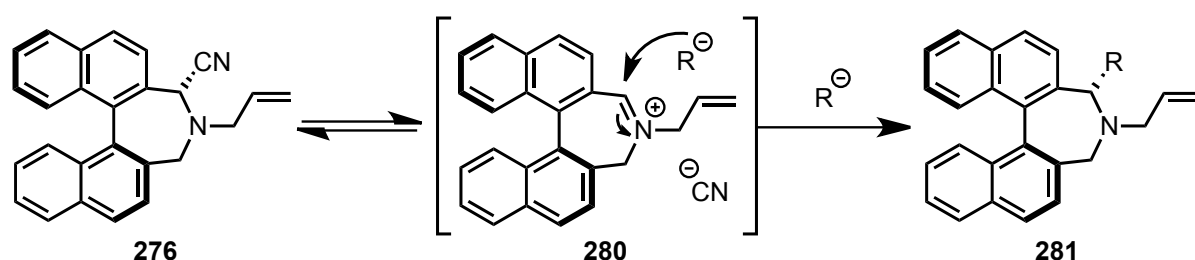
While there are countless examples of α -amino nitrile hydrolysis in the literature, there are also many examples of their use as precursors to iminium ions. A publication by Stork on the total synthesis of the alkaloid reserpine illustrates this fact.¹⁹⁹ The α -amino nitrile, itself formed in a similar method to ours, was refluxed in acetonitrile causing loss of cyanide. A subsequent Friedel-Crafts reaction formed the desired 6 membered ring of the natural product (Scheme 96).



Scheme 96 Use of an α -amino nitrile as an iminium salt precursor

Finally, another reaction which suggests that this type of equilibrium occurs in α -amino nitriles is the little known Bruylants reaction, where an α -amino nitrile reacts directly with a Grignard reagent, causing what would appear to be a nucleophilic substitution with cyanide acting as a leaving group.²⁰⁰ However, it is far more likely that an iminium cyanide is forming in the reaction mixture resulting in direct addition

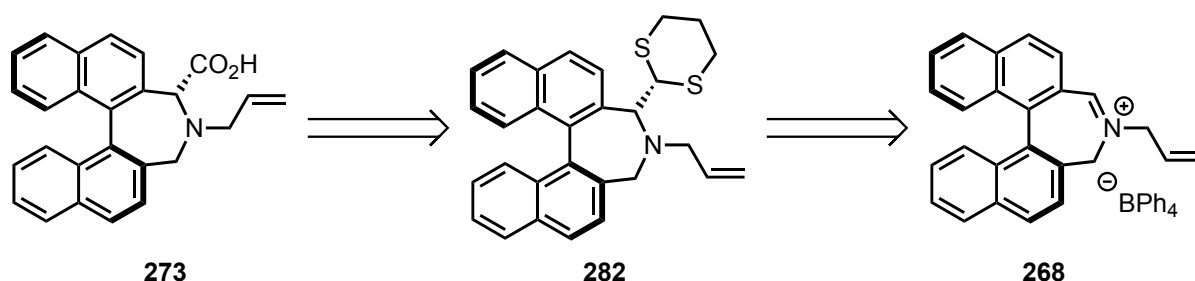
of the Grignard reagent to the electrophilic iminium portion of the ion pair (Scheme 97 where **276** is used as an example of an α -amino nitrile).



Scheme 97 Use of an α -amino nitrile as an iminium salt precursor in the Bruylants reaction

6.1.2.2 Dithiane additions

Our next potential route to the α -amino acid was via the addition of a dithiane derivative to iminium salt **268** in a modification of the Corey-Seebach reaction.²⁰¹ There are very few examples²⁰² in the literature of this type of addition to iminium salts, but it was deemed that the synthesis of compounds such as **282** could potentially lead to the desired compound **273** from iminium salt **268**. This retrosynthesis is shown in scheme 98.



Scheme 98 Potential retrosynthesis of compound **273** via dithiane **282**

While it has been reported that there are several problems associated with dithiane deprotection (generally to do with the harsh and/or toxic conditions required),²⁰³ this approach was still deemed a worthwhile endeavour. Table 5 details our attempts to make dithiane **282** using both the literature method reported by Duhamel as well as other known methods for the additions of metallated dithianes to various electrophiles.

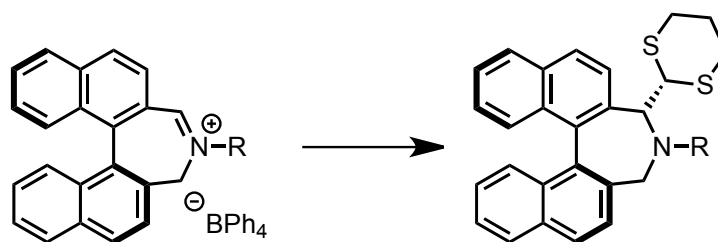


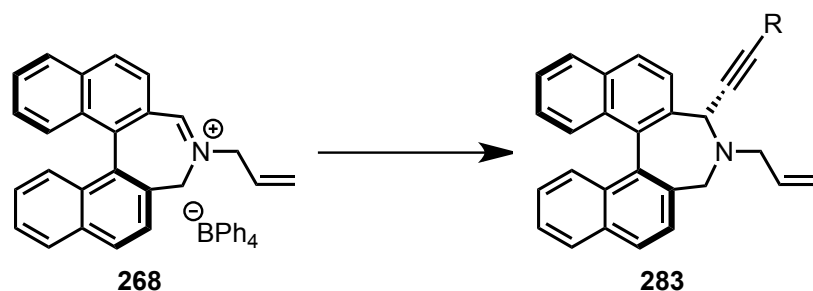
Table 5 Attempted dithiane additions to iminium salt **268**

R	Dithiane (eq.)	Base (eq.)	Additive (eq.)	Temperature (oC)	Time (h)	Yield (%)
allyl	1	<i>n</i> -BuLi (1.1)	-	-78 – rt	16	0
allyl	10	LDA (10)	-	-78 – rt	16	trace
allyl	10	LDA (10)	MgBr ₂ (10)	-78 – rt	16	trace
PMB	10	LDA (10)	MgBr ₂ (10)	-78 – rt	16	<20

As can be seen, only a trace amount of the desired product was ever detected when using *N*-allyl iminium salt **268**. When the same conditions were used for addition to the *N*-PMB iminium salt **260**, a small amount of impure material was isolated after extensive column chromatography, albeit in a less than satisfactory yield and in small enough quantities that further derivatization was not possible.

6.1.2.3 Alkyne additions

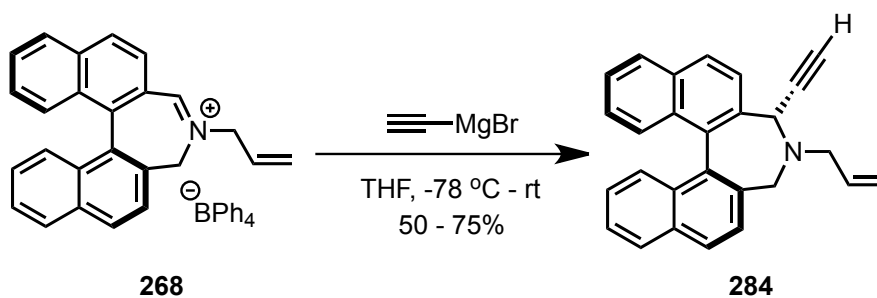
One of the other routes that we proposed for the synthesis of **273** was the addition of various alkynes to iminium salt **268**, yielding propargylamines of the type **283** (Scheme 99).



Scheme 99 Proposed alkyne additions to iminium salts

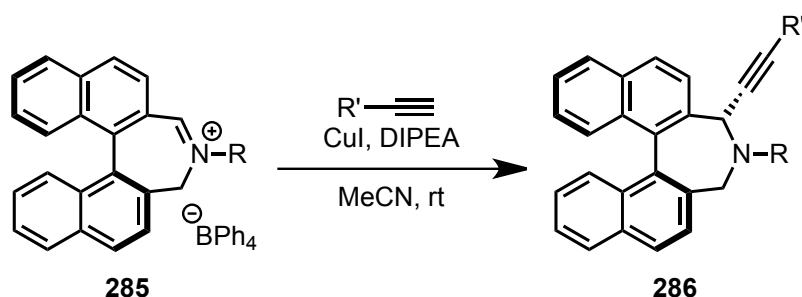
From there, there are a variety of literature procedures for the conversion of alkynes into carboxylic acids, most notably by ozonolysis to the anhydride and subsequent hydrolysis.

We envisaged the synthesis of terminal alkyne **284** would occur initially through the use of ethynylmagnesium bromide. Thus, **268** was subjected to our standard Grignard addition protocol using 10 eq. of a commercially available 0.5 M solution of ethynylmagnesium bromide in THF. The low concentration compared with other available Grignard reagents caused an unavoidable decrease in reaction rate but was infinitely preferable to the preparation of the Grignard reagent ourselves using acetylene gas. Isolated yields were generally in the region of 50 – 75%, which we believe was directly related to the quality of the different batches of the Grignard reagent as received from the supplier (Scheme 100).



Scheme 100 Proposed alkyne additions to iminium salts

This lack of reproducibility led to us contemplating a different route to compound **284** through the use of organocopper chemistry. It is well known that copper has an affinity for terminal alkynes, forming σ -complexes which are known intermediates in the now ubiquitous copper-catalyzed “click” azide-alkyne 3+2 cycloaddition (Huisgen cycloaddition) discovered by Sharpless²⁰⁴ and Meldal.²⁰⁵ However, copper acetylides are also well-known nucleophiles, and a publication by Schreiber and co-workers on their catalytic asymmetric addition of alkynes to isolated iminium salts caught our eye.²⁰⁶ Using a chiral ligand it was possible to obtain excellent enantioselectivities and high yields of the desired products. Consequently, we believed that using a modified procedure (without the chiral ligand) we would be able to add a variety of alkyne nucleophiles to our iminium salts cleanly and efficiently to give compounds of the type **286** (Scheme **101**). Gratifyingly, this proved to be the case. Our results are summarized in table **6**.

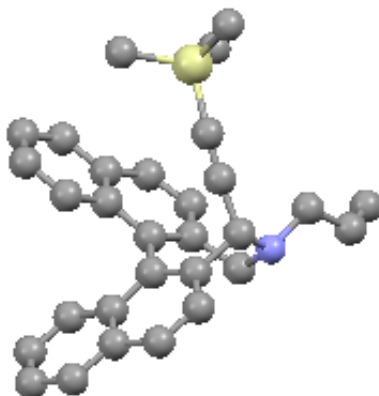


Scheme 101 Proposed alkyne additions using copper catalysis

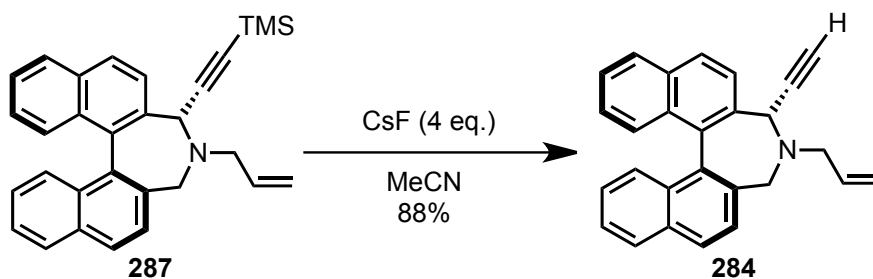
Table 6 Alkyne additions to iminium salt of the type **285**

Product	R	R'	Alkyne (eq.)	Time (h)	Yield (%)
287	allyl	Ph	5	24	74
288	allyl	TMS	5	24	74
289	allyl	CO ₂ Me	1.1	2	88
290	PMB	CO ₂ Me	1.1	2	81

Simple acetylenes (R = TMS and Ph) were added effectively but only when an excess of alkyne was used. It was, however, the electron deficient alkyne methyl propiolate that was really successful, giving 88% yield of the desired compound **289** within two hours at room temperature. As can be seen, both allyl and PMB groups were tolerated, giving similar results in both cases. One of these compounds, **287**, gave crystals suitable for X-ray analysis (figure **14**).

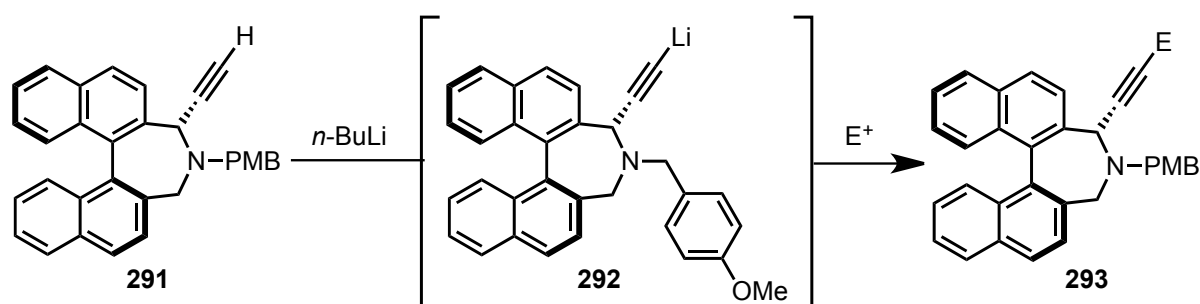
**Figure 14** Crystal structure of compound **287**

Compound **287** was also easily deprotected, giving a similarly yielding route to terminal alkyne **284** but avoiding the variability in yield seen using the Grignard addition (Scheme **102**).



Scheme 102 Deprotection of **287** to give **284**

A potential way of functionalizing **291** would be to lithiate the terminal alkyne using *n*-BuLi (or a similar base) and quench this anion with a variety of electrophiles (Scheme **103**).



Scheme 103 Derivatization of **291** *via* lithiation

This again proved to be fruitful, with both ethyl chloroformate and carbon dioxide gas used to isolate compounds **294** and **295** respectively. It was also possible to form crystals of **294** by recrystallization from hot ethanol (Figure **15**).

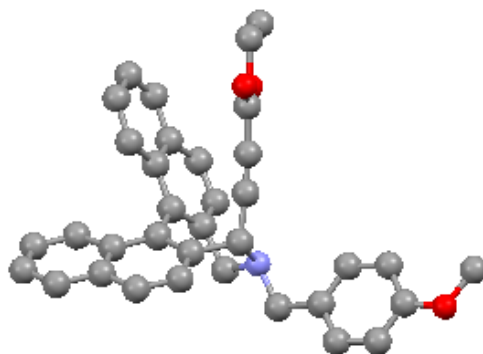
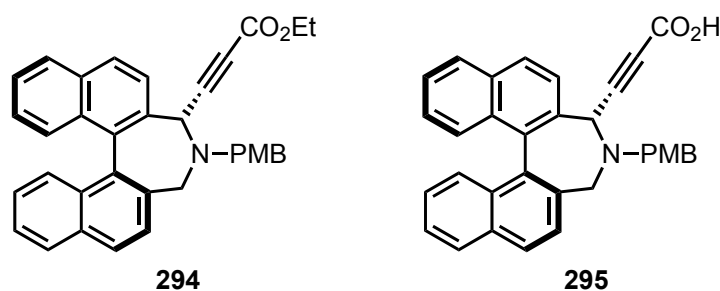
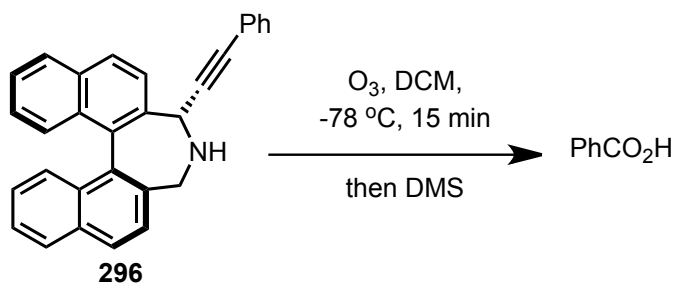
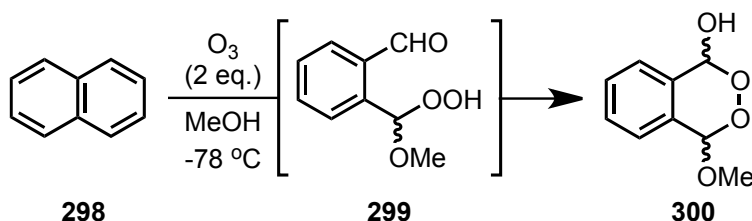


Figure 15 Crystal structure of compound **294**



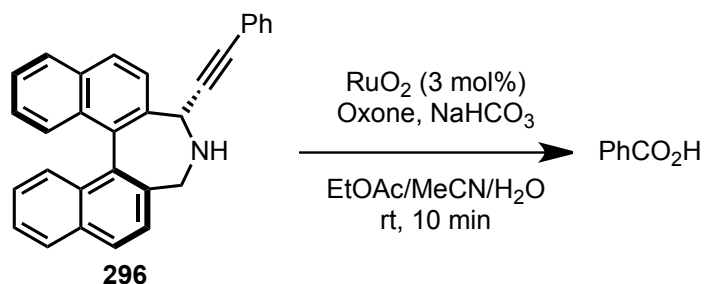
Scheme 106 Attempted ozonolysis of **296**

This result showed that the desired alkyne fragmentation was occurring but unfortunately also that the binaphthyl backbone was not stable to the strongly oxidizing conditions of this reaction. Perusal of the literature showed that this is in fact a known potential pitfall of naphthalenes in general. Bailey showed that upon ozonolysis of naphthalene itself it is in fact possible to isolate peroxides of the type **300** when using alcoholic solvents for the ozonolysis process (Scheme 107).²⁰⁸



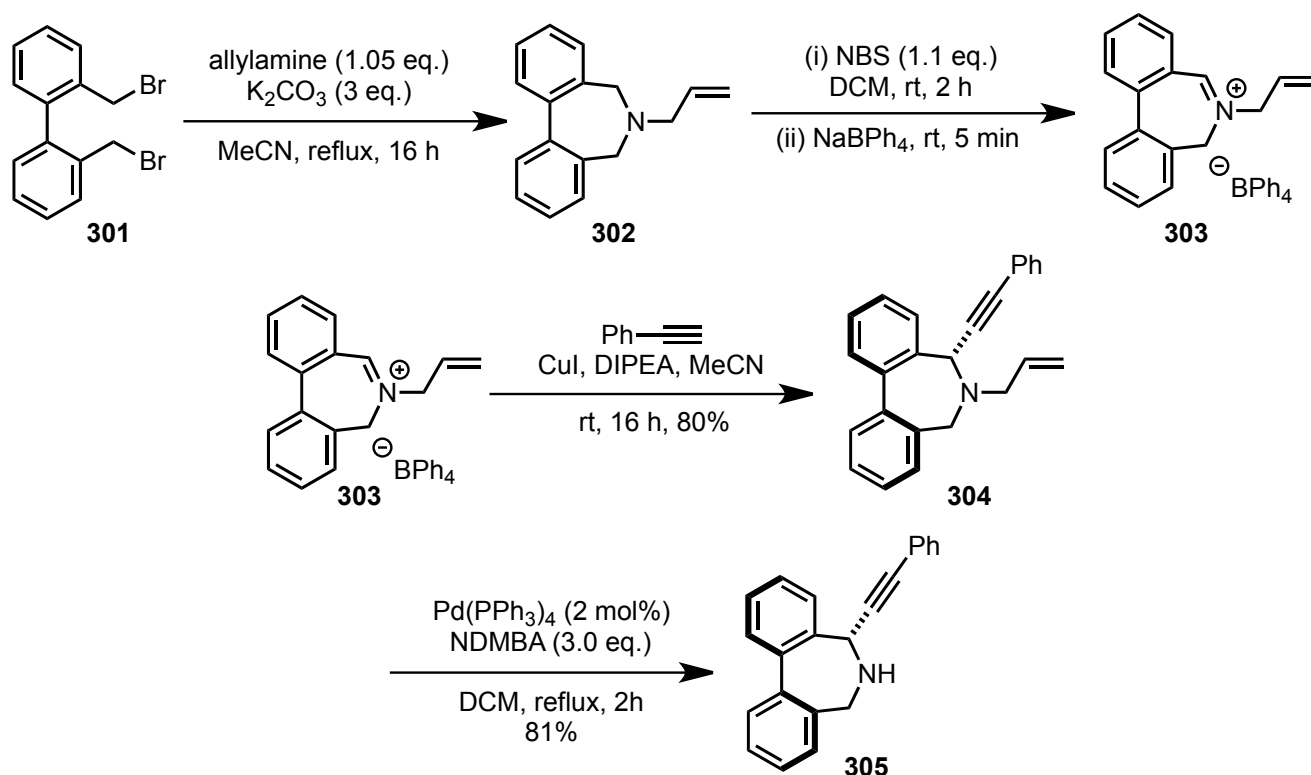
Scheme 107 Ozonolysis of naphthalene

Another possibility that we saw for the functionalization of compound **296** was through the use of a Ru-catalysed oxidation reaction, which would again provide potential access to compound **273** via an intermediate anhydride. This was shown by Yang and co-workers to be a viable route to benzoic acid derivatives from diarylacetylenes.²⁰⁹ Using either ruthenium dioxide or TPAP along with Oxone® as stoichiometric oxidant, the reactions unfortunately met with the same fate as before, with benzoic acid being the only observable compound in the NMR spectrum of the crude reaction mixture (Scheme 108).



Scheme 108 Attempted oxidation of alkyne **296**

We hypothesized at this point that the biphenyl system **305** would hopefully prove to be more stable to these oxidative conditions. As such, compound *rac*-**305** was obtained in two steps from the novel biphenyl iminium salt **303**, itself available in two steps from **301** (synthesis shown in scheme **109**). There are known methods to make these biphenyl systems in an enantiomerically pure manner,²¹⁰ so this would hopefully prove to be a viable route to new axially chiral organocatalysts.



Scheme 109 Synthesis of compound **305**

After submitting compound **305** to both the ozonolysis and Ru-catalysed hydration conditions, the same result was witnessed in both cases, benzoic acid was the only observable compound present.

As a consequence of these failures, we deemed it necessary to alter our choice of targets. The α -amino acid has thus far proved impossible to access using the methods we have attempted. Our future potential synthetic routes to this compound are described in section **7.1**.

6.1.3 Axis-Centre Stereochemical Relays Revisited

As mentioned above, when an R substituent is in a pseudoaxial orientation in a system of the type **255**, there is an associated upfield shift of the R group in the ^1H NMR spectrum (Figure 12). It can thus be possible to infer the orientation of any substituent by looking at this shift and comparing it to the shift that would normally be expected for this type of group in other molecules.

Wallace has synthesized enantiopure **306** & **307** using a modification of the well-known Meyers' lactamization methodology.²¹¹ They showed that in this biphenyl system where there is a very small energy barrier to rotation around the biaryl axis, the orientation of the biaryl backbone is controlled by the orientation of the R group relative to the central 7-membered ring. This is itself controlled by the nature of the *N*-substituent. If the amine is unsubstituted, the methyl group in **306** [δH (500 MHz, CDCl_3) 1.50 (d, 3H, $\alpha\text{-Me}$), 3.64 (q, 1H, $\alpha\text{-H}$)] is found in a pseudoequatorial orientation due to the fact that any hindrance between the NH proton and the methyl group is presumably outweighed by the pseudo 1,3-allylic strain between the methyl group and to closest aromatic proton in the biaryl axis. This is not the case in *N*-Boc derivative **307** [δH (500 MHz, CDCl_3) 0.86 (d, 3H, $\alpha\text{-Me}$), 5.13 (q, 1H, $\alpha\text{-H}$)], where the opposite is true and the methyl group adopts a pseudoaxial orientation to avoid steric clashes with the newly introduced carbamate (Figure 16).

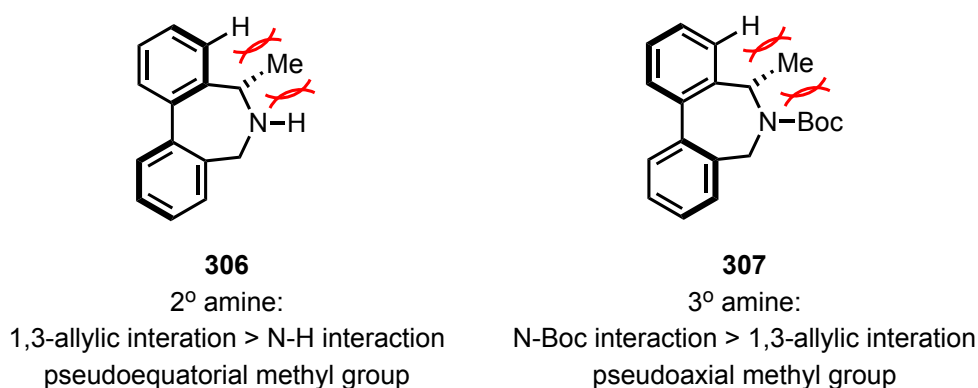
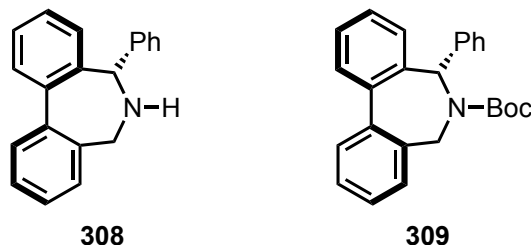


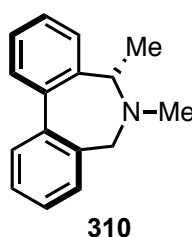
Figure 16 Point-axis stereochemical relay in compounds **306** and **307**

In another publication by Wallace, the phenyl substituted azepine **308** [δ H (500 MHz, CDCl_3) 4.87 (s, 1H, α -H)] and its Boc derivative **309** [δ H (500 MHz, CDCl_3) 6.24 (s, 1H, α -H)] were synthesized.



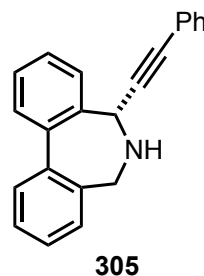
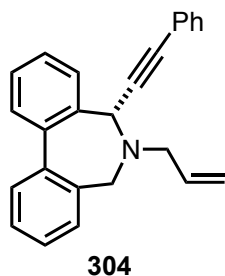
It was shown that the much larger phenyl groups were still subject to the same sort of stereochemical relay that was previously shown. Addition of the Boc group showed that the phenyl group would readily adopt either a pseudoequatorial or a pseudoaxial orientation depending on the nature of the *N*-substituent, documented by marked shifts in the both the aromatic protons of the phenyl group as well as the proton α - to the amine.

In previous work within our group, by synthesizing **310** [δ H (500 MHz, CDCl_3) 1.32 (d, 3H, α -Me), 3.32 (q, 1H, α -H)] it was possible to show that a smaller *N*-Me group in this system still allowed the α -methyl group to maintain a pseudoequatorial orientation as a result of the pseudo 1,3-allylic strain still outweighing any other steric interactions. This is inferred due to the fact that there is very little change in the chemical shift of the α -proton.



However, in the case of allylated rac-**304** [δ H (500 MHz, CDCl_3) 4.40 (s, 1H, α -H)] and deprotected rac-**305** [δ H (500 MHz, CDCl_3) 4.77 (s, 1H, α -H)], which were synthesized as part of this project, we made some interesting observations pertaining to this sort of axis-centre stereochemical relay. We envisaged that upon deallylation of rac-**304** we would see a marked shift in the ^1H NMR chemical shift of

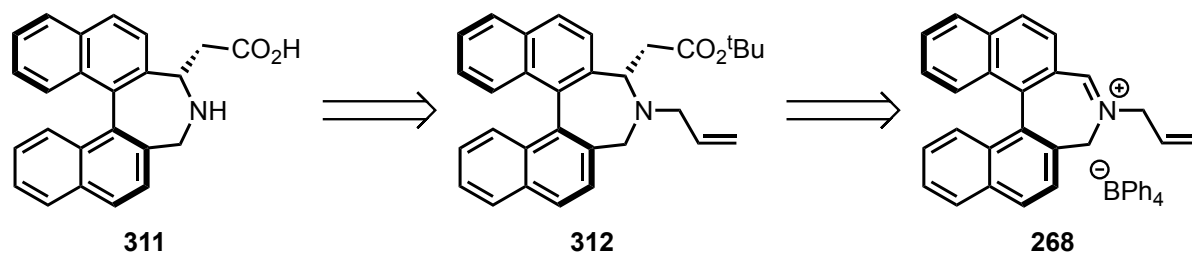
the α -proton in common with these other previously reported cases. This was not the case here, with nowhere near the same shift seen compared with the cases described above.



Preliminary modeling calculations by Wallace suggested that the lowest energy conformation of azepines of this type would be determined by the size of the α -substituent. It is possible that this larger phenylacetylene substituent is now large enough to be permanently locked in a pseudoaxial conformation and at the same time lock the axial chirality of the backbone. While the Boc derivative of **305** has not been synthesized, it would be an interesting future experiment that would confirm this one way or the other. While there is a significant difference in steric burden between the allyl group and Boc group, we believed that the *N*-allyl group should have been large enough to have some effect on the orientation of the α -substituent. Work continues in this area.

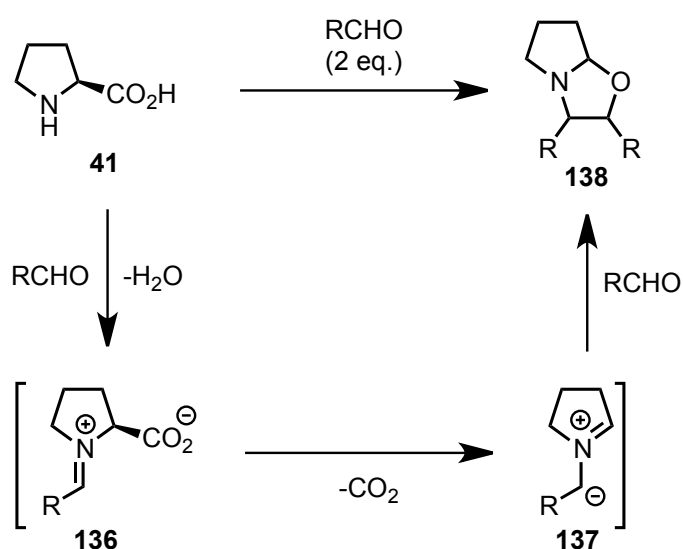
6.2.1 The synthesis of β -amino acid **311**

Given that initial work towards the synthesis of α -amino acid **273** ultimately failed, we set our sights on the addition of some different side chains to iminium salt **268**. We deemed a sensible alternative to **273** would be the β -amino acid **311**, which we hoped to form through a Reformatsky-type reaction using an organozinc reagent derived from *tert*-butyl bromoacetate (retrosynthesis shown in Scheme **110**).



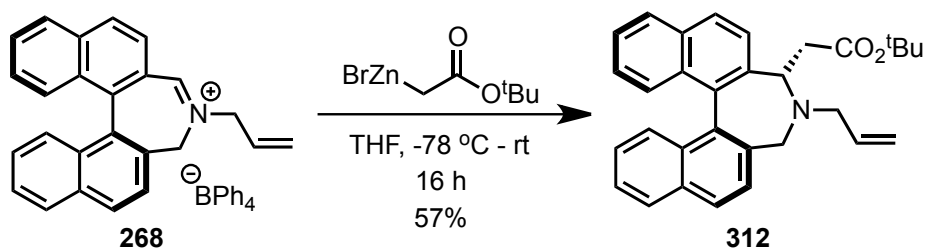
Scheme 110 Proposed retrosynthesis of compound **311**

β -Amino acids have been shown to be selective organocatalysts for a variety of processes, for example in the work by Armstrong and co-workers.²¹² We also envisaged that **311** would be more stable than α -amino acid **273** due to the fact that the reported decomposition pathways that are known to affect compounds of this type in certain organocatalytic processes (usually aldol reactions, Scheme **111**) would not occur when a β -amino acid was used.



Scheme 111 Potential decomposition of proline by decarboxylation

Fortunately for us, the synthesis of **312** proved to be far more straightforward than that of **273**. Using *t*-butyl bromoacetate and zinc powder activated with TMSCl and 1,2-dibromoethane, the Reformatsky product **312** was isolated in a moderate but reproducible 57% yield after column chromatography (Scheme 112).



Scheme 112 Synthesis of intermediate **312**

It was possible to obtain crystals of this product suitable for X-ray analysis (Figure 17).

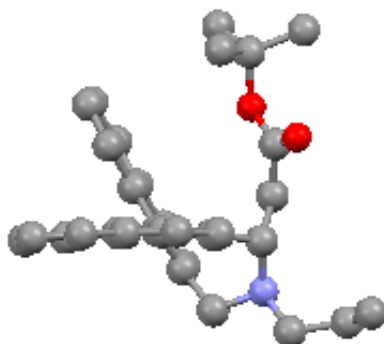
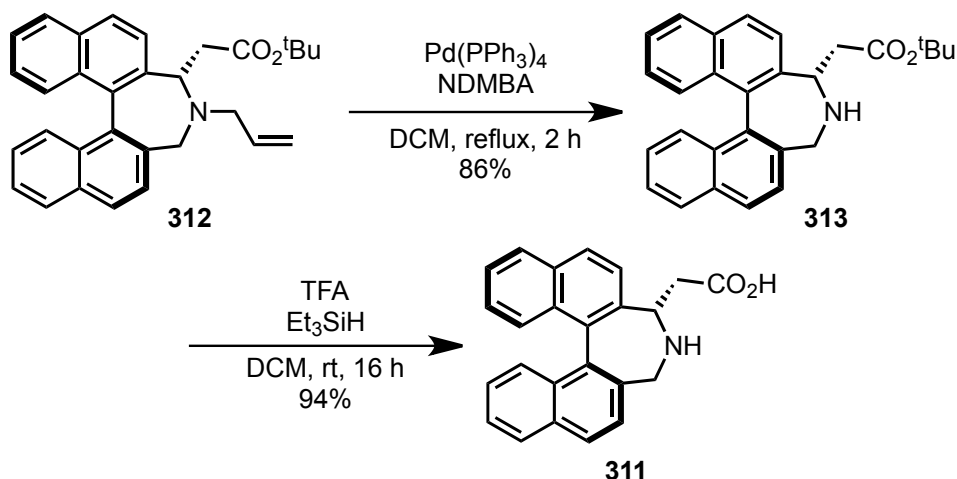


Figure 17 Crystal structure of β -amino ester **312**

Deallylation using standard conditions and subsequent cleavage of the *t*-butyl ester proceeded without any problems, yielding β -amino acid **311** in respectable overall yield (Scheme 113).



Scheme 113 Synthesis of compound **311**

With compound **311** in hand, we set about searching for a reaction that we could use to test the efficacy of this new type of catalyst. We hoped for example that it would catalyze the asymmetric aldol condensation in a similar fashion to that of L-proline in the work of List and co-workers.¹⁸² Modeling studies have shown that the carboxylic acid present in the enamine formed between acetone and the proline catalyst forms a favourable transition state by hydrogen bonding interactions between itself and the aldehyde substrate (Figure **18**).²¹³

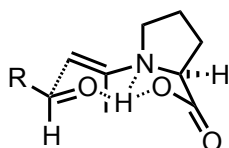
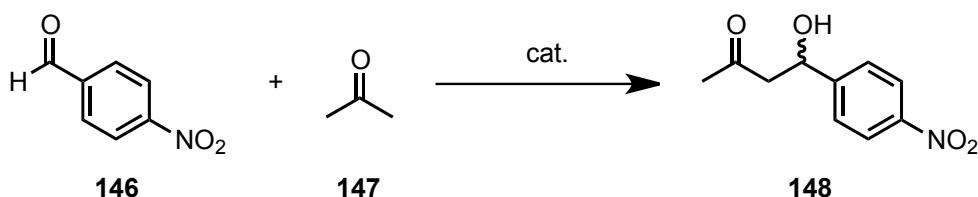


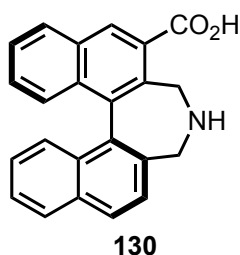
Figure 18 Proposed transition state in the reaction between a ketone and aldehyde catalyzed by L-Proline

Preliminary reactions using literature procedures for the condensation of acetone and p-nitrobenzaldehyde (Scheme **114**) were not met with success as no conversion to the desired product was seen even after several days at room temperature.



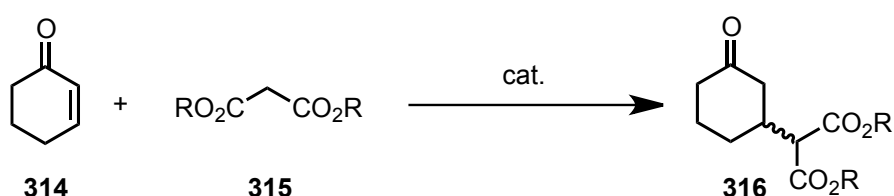
Scheme 114 Aldol condensation of acetone and p-nitrobenzaldehyde

Only after a benzoic acid co-catalyst was added was a small conversion seen, albeit at an extremely slow rate compared with other known catalysts such as that of Maruoka. His binaphthyl catalyst **130** that is mentioned above contains what essentially amounts to a benzoic acid (pKa ~4.2) derivative whereas ours contains something more like acetic acid (pKa ~4.76).

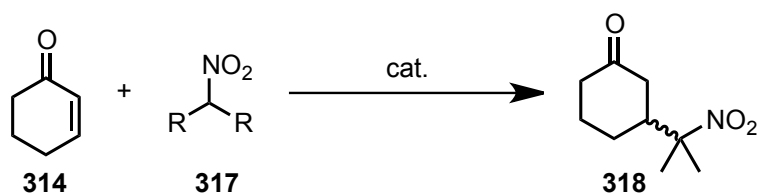


It may be that the lack of reactivity observed in our case is due to the differences in pKa between these two types of carboxylic acid, which is quite large considering the logarithmic nature of this scale.

We next turned our attention to the use of **311** in iminium-based organocatalysis. As discussed in the introduction, there are many variants of reactions based on this mode of catalytic activation. However, we desired something that utilized cheap, readily available and stable starting materials and formed stable products that were easily characterized. This led us to selecting two reactions that have been reported by numerous groups, the conjugate addition of malonates (Scheme **115**) and nitroalkanes (Scheme **116**) to α,β -unsaturated ketones.



Scheme 115 Malonate addition to an α,β -unsaturated enone



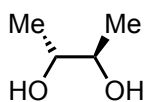
Scheme 116 Nitroalkane addition to an α,β -unsaturated enone

There are a wide range of enones, nitroalkanes and malonates that are commercially available which meant that a wide range of catalyst tests could be carried out without the need to synthesize any of the substrates. Enones are also generally more stable compared to the related enals, which would perhaps mean that side reactions would be kept to a minimum. The conversion from starting material to product could be easily monitored qualitatively by TLC and quantitatively by ^1H NMR spectroscopy and the enantiomeric excess could easily be calculated using either chiral HPLC or, as in our case, by further derivatization of the products.

6.2.2 Determination of enantiomeric excess

From study of the literature, it became apparent that if we were to test a wide variety of malonate and nitroalkane additions, we would require a wide range of chiral HPLC columns in order to satisfactorily separate the enantiomers of each of the products. This led us to search the literature for an alternative to this type of analysis. Fortunately, a paper by Wynberg and Hiemstra was found.²¹⁴ Before the use of chiral HPLC columns was widespread, they published an accurate method for determining the enantiomeric excess of chiral ketones using ^{13}C NMR spectroscopy. The method revolved around acetal formation using an enantiopure 1,2-diol. This would give a pair of diastereoisomeric acetals, each one corresponding to one of the two enantiomers of the initial product. It was then possible to obtain the ee by integrating the peaks of the ^{13}C NMR spectrum of this pair of diastereoisomers. The assumption was made initially that no kinetic resolution or racemization occurs when the acetal is formed. However, this was shown to be correct by analysing a sample of known enantiomeric excess. The data obtained showed the ee to be correct to $\pm 2\%$ in all cases.

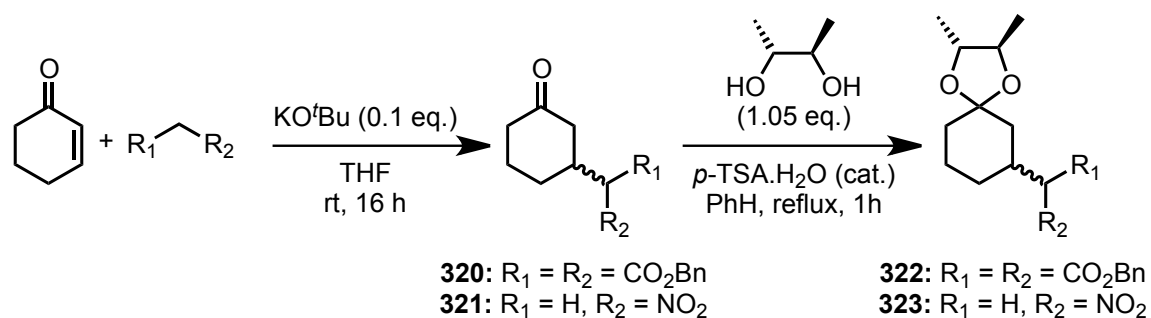
In this initial paper, it was found that using (*R*)-(-)-2,3-butanediol **319** gave the best separation between the diastereoisomeric pairs. Accurate measurements were only obtained when the separation between peaks was > 2 ppm, which was the case when **319** was used.



319

The authors of the original paper also pointed out that it could be argued that integrating ^{13}C peaks was not a valid method for obtaining ee because it is known that both nOe effects and differences in relaxation times can and do cause changes in the peak heights of carbon atoms depending on the environment they are in within a molecule. Wynberg argued that this effect was minimized due to the two diastereoisomers being so similar to one another.

To check that our potential products would be amenable to this type of further derivatization, we isolated **rac-321** and **rac-322** using a previously published method using catalytic potassium tert-butoxide in THF, which furnished the desired compounds in reasonable yield.²¹⁵ Using the aforementioned method acetals **322** and **323** were then formed in quantitative yield (Scheme 117).



Scheme 117 Synthesis of racemates

Gratifyingly, ¹³C NMR spectroscopy of both compounds gave acceptable separation of peaks in the two diastereoisomers. A portion of the spectrum of **rac-322** is shown in figure 19 showing the splitting of the peaks in the two diastereoisomeric acetals. By selecting one of the pairs of peaks and integrating them, it is also possible to confirm the racemic nature of the compound.

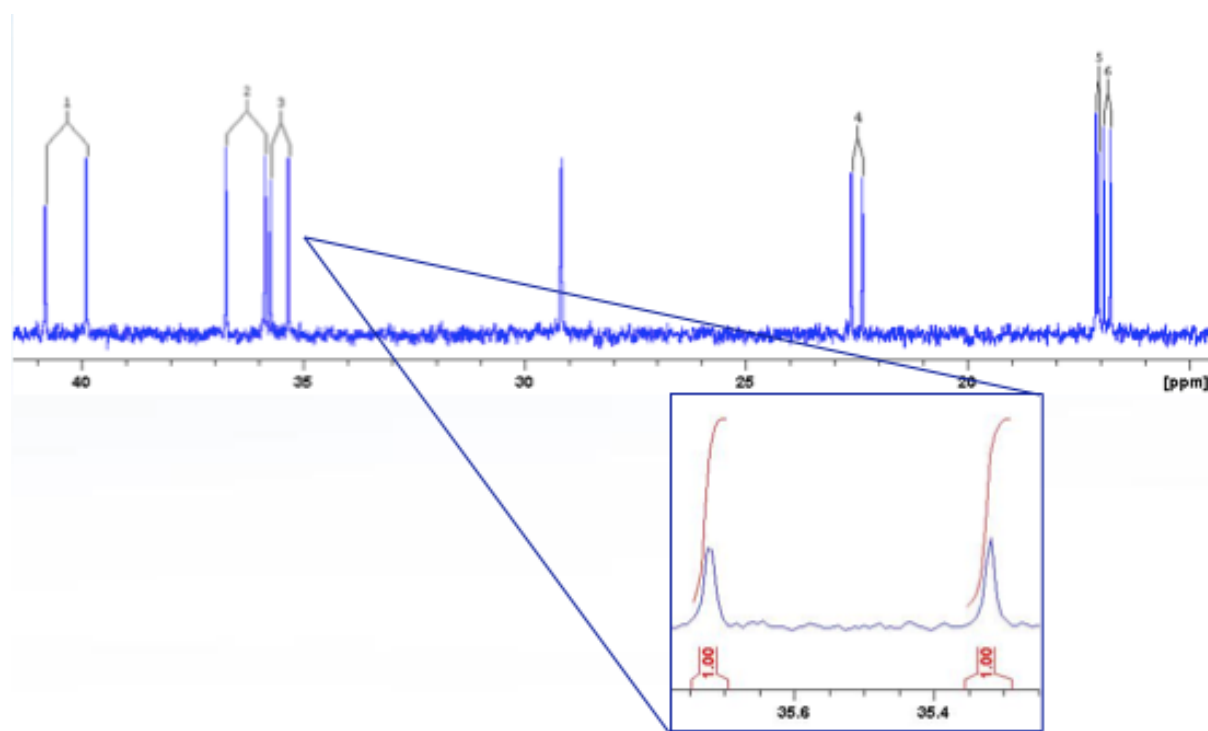


Figure 19 Part of the ¹³C NMR spectroscopy of acetal **322**

showing its racemic nature

6.2.3 Initial Testing – Malonate Addition

Our initial testing utilized cyclohexenone and dibenzyl malonate as substrates along with a variety of stoichiometric bases that were shown to be necessary in publications by Ley¹⁹⁷ and Hanessian²¹⁶ in order to deprotonate the malonate and facilitate the conjugate addition process. Hanessian reported the results they obtained using chloroform as solvent and L-proline as catalyst along with a wide variety of bases. We tested a variety of these bases as part of our own optimization using compound **311** as catalyst and chloroform as the solvent (Table 7).

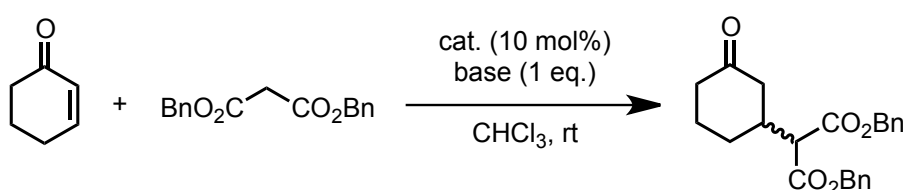


Table 7 Initial testing of catalyst **310**^(a)

Base	Time (h)	Conversion (%)	ee (%)
<i>trans</i> -2,5-Dimethylpiperazine	144	0	n/a
CsF	144	<10	n/d
LiOH.H ₂ O	48	100	17
NaOH	16	100	racemic
KOH	16	100	racemic
CsOH.H ₂ O	16	100	racemic
Hünig's base	96	0	n/a
DMAP	96	0	n/a
TMEDA	96	0	n/a

(a) Reactions were carried out on 0.25 mmol scale with magnetic stirring in Biotage microwave vials (2-5 mL size) using undistilled CHCl₃ (2 mL). Conversion from starting material to product was calculated via ¹H NMR using the integrations of diagnostic peaks. Enantiomeric excess was determined by integrating peaks in the ¹³C NMR of the diastereoisomeric acetals formed between the product and (*R*)-(-)-2,3-butanediol.

Of the bases tested by Ley and Hanessian caesium fluoride and trans-2,5-dimethylpiperazine were among the most selective. Unfortunately in our hands this proved not to be the case, with little to no conversion to the desired product isolated in either case. The use of other amine bases (TMEDA, DMAP etc.) also met with failure, with no conversion seen in either case. To our delight, however, using alkali metal hydroxides as the base under these conditions resulted in clean conversion to the desired addition product. Whereas NaOH, KOH and CsOH.H₂O yielded only racemic product, the use of LiOH.H₂O gave a small but encouraging enantiomeric excess in the region of 17%. Clearly, further optimization was required.

The choice of solvent is well known to have a large effect on the selectivity of organocatalytic reactions. Thus, using LiOH.H₂O as base and 10 mol% **310** we tested a number of solvents. Our results are shown in Table 8.

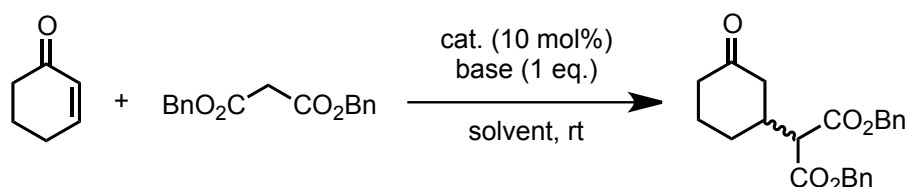


Table 8 Initial testing of catalyst **310**^(a)

Solvent	Base	Time (h)	Conversion (%)	ee (%)
Neat	None	144	0	n/a
Et ₂ O	LiOH.H ₂ O	168	100	14
Toluene	LiOH.H ₂ O	16	100	19
DMF	LiOH.H ₂ O	168	0	n/a
DMSO	LiOH.H ₂ O	168	0	n/a
Benzene	LiOH.H ₂ O	48	85	16
DCM	LiOH.H ₂ O	96	100	23
DCM	LiOH	144	100	21

(a) Reactions were carried out on 0.25 mmol scale with magnetic stirring in Biotage microwave vials (2-5 mL size) using undistilled solvents (2 mL). Conversion from starting material to product was calculated via ¹H NMR using the integrations of diagnostic peaks. Enantiomeric excess was determined by integrating peaks in the ¹³C NMR of the diastereoisomeric acetals formed between the product and (*R*)-(-)-2,3-butanediol.

There are a few interesting results in table 8. Running the reaction with no solvent or base resulted in no conversion, which shows that the base is necessary for the reaction to proceed. Use of ethereal solvent both increased reaction time and decreased selectivity. Use of toluene on the other hand caused a notable increase in reaction rate as well as an increase in ee. Polar aprotic solvents (i.e. N,N-dimethylformamide and dimethyl sulfoxide) killed catalytic activity completely, with no conversion seen after a week at room temperature in either case. The most promising entry, however, was that of dichloromethane. While the rate of reaction was lower (four days at room temperature was required for the reaction to reach completion), the ee increased to 23% which was the highest seen thus far. Finally, when considering the final two entries in table 8, it can be seen that the reaction proceeded at an increased rate using the hydrated base compared with the anhydrous one. This increase in rate is presumably due to the equivalent of water present in the reaction mixture, which may increase the rate of hydrolysis of the iminium intermediate and as a result increase catalyst turnover. A drop in selectivity did not accompany this rate increase. This confirmed our hypothesis that anhydrous conditions were not required for these catalyst runs and that an equivalent of water in the reaction was in fact beneficial.

Our next task was to test the effect of temperature on this system. Thus, four of the test reactions that are mentioned above were repeated, this time at 0 °C (Table 9).

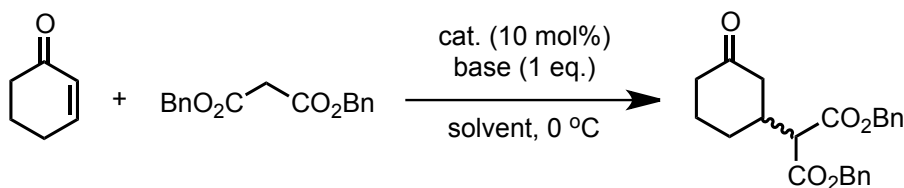


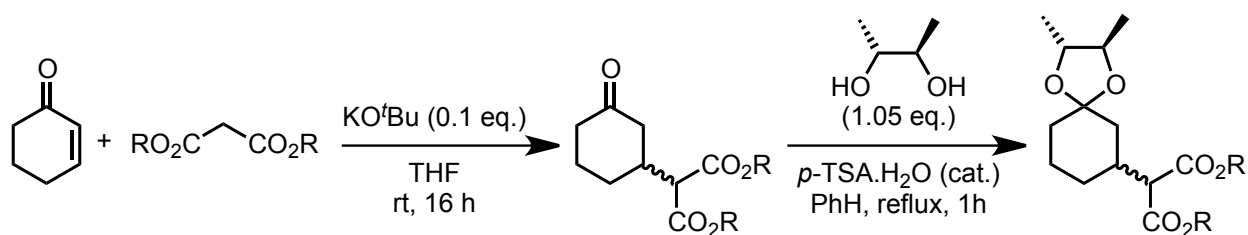
Table 9 Initial testing of catalyst **310**^(a)

Solvent	Base	Time (h)	Conversion (%)	ee (%)
CHCl ₃	LiOH.H ₂ O	240	100	19
CHCl ₃	NaOH	48	100	9
Toluene	LiOH.H ₂ O	48	100	14
Toluene	NaOH	48	100	7

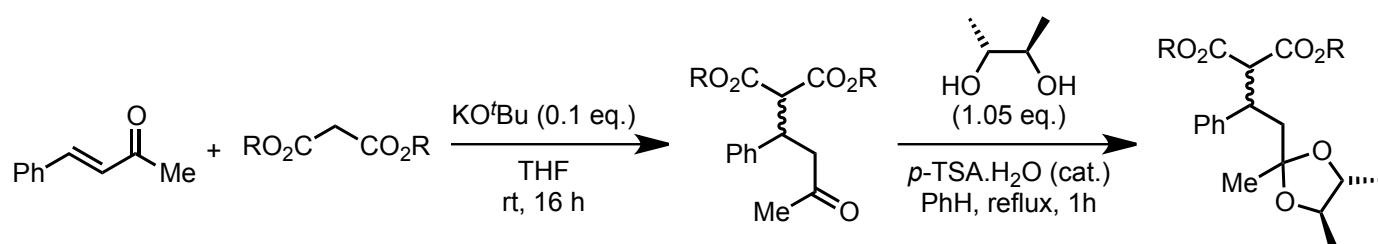
(a) Reactions were carried out on 0.25 mmol scale with magnetic stirring in Biotage microwave vials (2-5 mL size) using undistilled solvents (2 mL). Conversion from starting material to product was calculated via ¹H NMR using the integrations of diagnostic peaks. Enantiomeric excess was determined by integrating peaks in the ¹³C NMR of the diastereoisomeric acetals formed between the product and (*R*)-(-)-2,3-butanediol.

While there was a small increase in selectivity (e.g. 19% ee cf. 17%), this was deemed insignificant due to an associated massive increase in reaction times. Ten days at 0 °C was required for complete conversion in the first entry using CHCl₃ and LiOH.H₂O. While the same conditions were not tested using dichloromethane as solvent, we envisaged that the reaction would take an unacceptable period of time to reach completion.

With these preliminary results now in hand, a selection of different malonates were tested in the conjugate addition to cyclohexenone and an acyclic analogue, benzylideneacetone. While the addition of dibenzyl malonate to cyclohexenone has been shown to be a generally selective reaction compared with other similar examples, we believed it necessary to carry out these reactions in the interests of completeness. The racemates for these reactions were synthesized as before using KO^tBu in dry THF (Scheme **118** & **119**). These compounds were then converted into their respective acetals without issue and all in quantitative yields.



Scheme 118 Racemic malonate additions to cyclohexenone



Scheme 119 Racemic malonate additions to benzylideneacetone

Finally for this chapter, the enantioselective variants of these reactions were carried out using our previously optimized conditions. These results are presented in table 10.

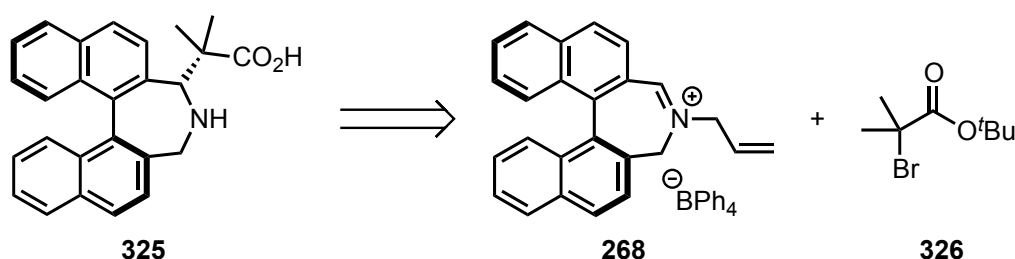
Table 10 Substrate testing using **310**^(a)

Enone	R	Time (h)	Conversion (%)	ee (%)
Benzylideneacetone	Me	96	40	8
Benzylideneacetone	Et	96	91	racemic
Benzylideneacetone	iPr	96	78	10
Benzylideneacetone	Bn	96	87	13
Cyclohexenone	Me	48	100	14
Cyclohexenone	Et	48	100	14
Cyclohexenone	iPr	96	100	17
Cyclohexenone	Bn	96	100	23

(a) Reactions were carried out on 0.25 mmol scale with magnetic stirring in Biotage microwave vials (2-5 mL size) using undistilled CHCl_3 (2 mL). Conversion from starting material to product was calculated via ^1H NMR using the integrations of diagnostic peaks. Enantiomeric excess was determined by integrating peaks in the ^{13}C NMR of the diastereoisomeric acetals formed between the product and (*R*)-(-)-2,3-butanediol.

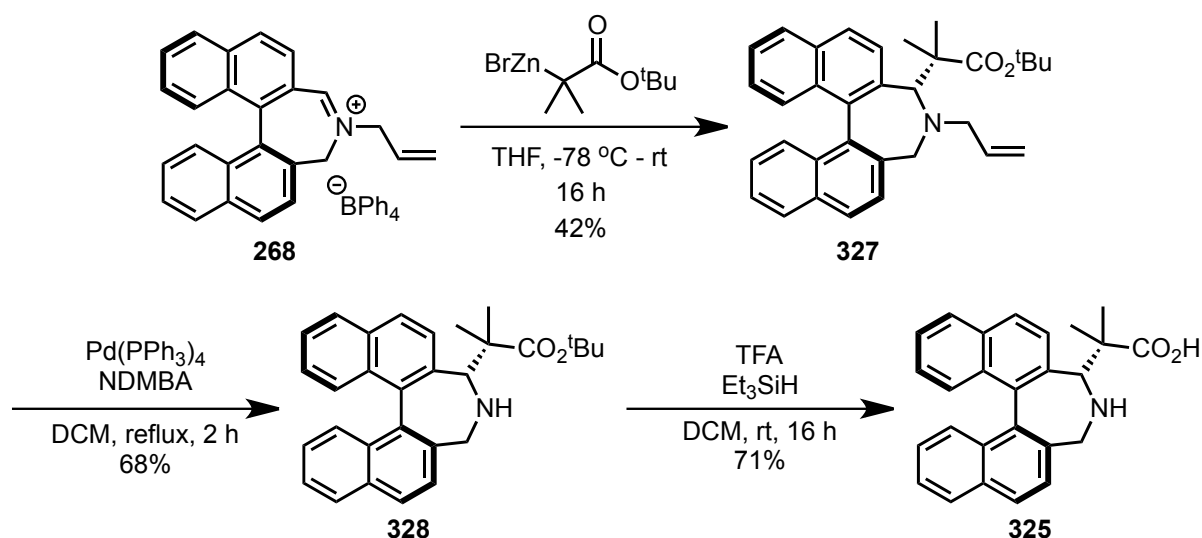
Benzylideneacetone is clearly not a good substrate for this type of reaction, with uniformly very low enantioselectivity and reactivity seen across the board even in comparison to cyclohexenone. Unfortunately, our initial test substrates also unsurprisingly gave our best results (perhaps due to the steric bulk of the benzyl groups compared with methyl or ethyl).

Following this initial work, we set about optimizing the structure of our organocatalyst **310**. We envisaged that altering the bromoacetate used in our pivotal Reformatsky reaction should impart different properties to our catalysts. While there are very few t-butyl bromoacetates commercially available with substituents at the α -position, one that is available is t-butyl α -bromoisobutyrate **326**. The retrosynthesis of potential catalyst **325** is shown in Scheme 120.



Scheme 120 Retrosynthesis of compound **325**

While catalyst **325** would be slightly less acidic than **310** due to the electron donating nature of the two methyl groups (similar comparisons can be made between acetic acid and pivalic acid), we also envisaged that steric hindrance could play some role in organizing the potential transition state in an organocatalytic reaction. In order to test this, organocatalyst **325** was synthesized using the route shown in scheme 121.



Scheme 121 Synthesis of catalyst **325**

While we were able to successfully synthesize **325**, the yields were lower across the board compared with compound **310**. Nevertheless, we were able to access **325** on a scale that was more than reasonable for catalyst tests to be run. For a direct comparison with compound **310**, we used our initial test reaction i.e. the reaction between dibenzyl malonate and cyclohexenone. The results are shown in table **11** (the testing of **310** is repeated here for clarity).

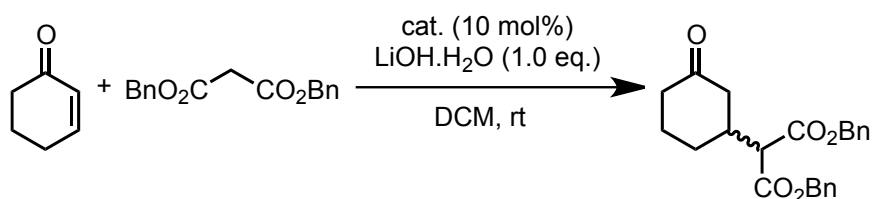


Table 11 Testing of catalyst **325**

Catalyst	Time	Conversion (%)	ee (%)
310	96	100	23
325	36	100	9

As can be seen, **325** is a much more active catalyst than **310**. The reaction time was reduced by over half from 96 hours to around 36 hours. However, the selectivity also decreased, with only 9% ee seen using **325**.

6.2.4 – Catalyst Testing – Nitroalkane additions

The other reaction that we proposed when testing catalyst **325** was the addition of nitroalkanes to the same enones as discussed above. Hanessian and co-workers have reported this reaction, catalysed by L-proline.²¹⁶ Due to the electron-withdrawing nature of the nitro group, nitroalkanes contain highly acidic protons, even more so in fact than malonates (nitromethane pKa 10.2 cf. diethyl malonate pKa 13.0) so we reasoned that they would be acceptable nucleophiles in this type of reaction. This suggested that it would be more easily deprotonated than any of the malonates used and should therefore add to our activated enone substrates. Our initial studies using nitromethane and 2-nitropropane are shown in tables **12** & **13**.

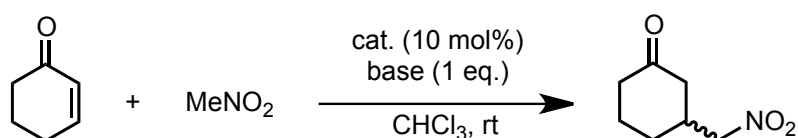


Table 12 Nitromethane addition to cyclohexenone

Base	Time (h)	Conversion (%)	ee (%)
LiOH.H ₂ O	144	0	-
CsF	144	0	-
<i>trans</i> -2,5-dimethylpiperazine	144	0	-

Reactions were carried out on 0.25 mmol scale with magnetic stirring in Biotage microwave vials (2-5 mL size) using undistilled CHCl₃ (2 mL). Conversion from starting material to product was calculated via ¹H NMR using the integrations of diagnostic peaks.

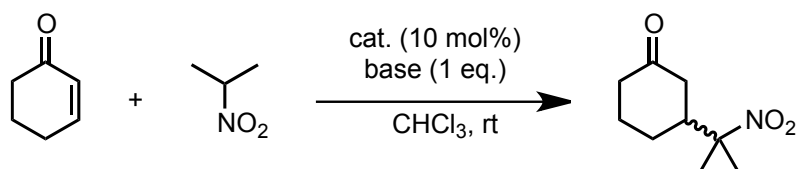


Table 13 2-nitropropane addition to cyclohexenone^(a)

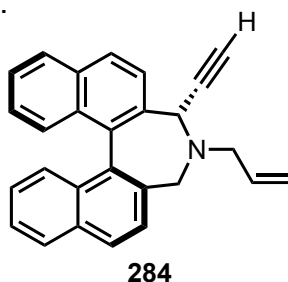
Base	Time (h)	Conversion (%)	ee (%)
LiOH.H ₂ O	144	0	-
CsF	144	0	-
<i>trans</i> -2,5-dimethylpiperazine	144	0	-

(a) Reactions were carried out on 0.25 mmol scale with magnetic stirring in Biotage microwave vials (2-5 mL size) using undistilled CHCl₃ (2 mL). Conversion from starting material to product was calculated via ¹H NMR using the integrations of diagnostic peaks.

Unfortunately, for unknown reasons, no reaction whatsoever took place using any of the bases tested.

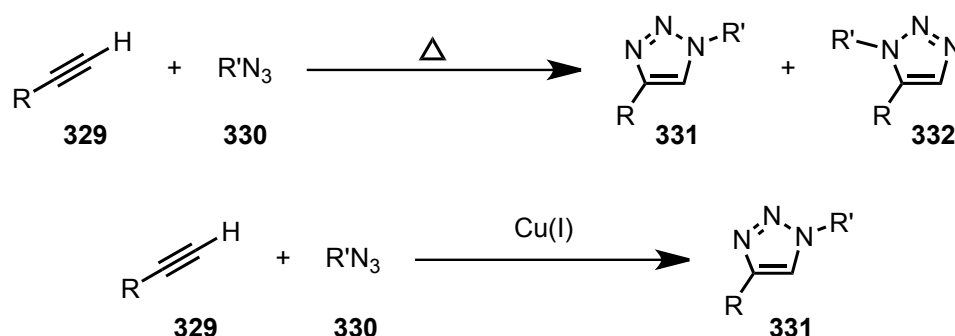
6.3.1 – Triazole sidechains

In our attempts to synthesize α -amino acid **273**, we made large quantities of the alkyne **284** using methods already previously described. As this route was not successful, we were left with a quantity of **284** that we decided to further functionalize in a different way.



The now ubiquitous Cu-catalysed Huisgen [3+2] cycloaddition between an alkyne and an azide is an extremely common reaction that has found uses in many different aspects of the chemical sciences since its publication by Sharpless. Whereas Huisgen required elevated temperatures to obtain the desired triazoles in his seminal paper,²¹⁷ Sharpless and Fokin observed that a source of copper (I) in the reaction allowed the reaction to proceed at far lower temperatures and at the same time selectively form only the 1,4-triazole regioisomer **331** (Scheme **122**).²⁰⁴ This is due to

the formation of organocopper intermediates that are described in the same publication.



Scheme 122 Uncatalysed and catalysed cycloadditions between alkynes and azides

The wide applicability and need for only mild reaction conditions have led this type of reaction to be classed by Sharpless as a ‘click’ reaction i.e. a reaction where two reagents react rapidly together with near-perfect atom economy.²¹⁸ We envisioned that if this could be applied to our system, it would be possible to obtain a wide variety of potential triazole-containing organocatalysts by merely altering the azide in the reaction mixture. For our initial purposes, benzyl azide **335** was deemed to be a safe, commonly used azide that could be synthesized from commercially available starting materials (Scheme **123**). It was synthesized according to the procedure of Hackenberger using benzyl bromide and sodium azide in DMSO.²¹⁹



Scheme 123 Synthesis of benzyl azide

With **284** and **335** in hand, some commonly used ‘click’ reaction conditions were tested. These results are shown in table **14**.

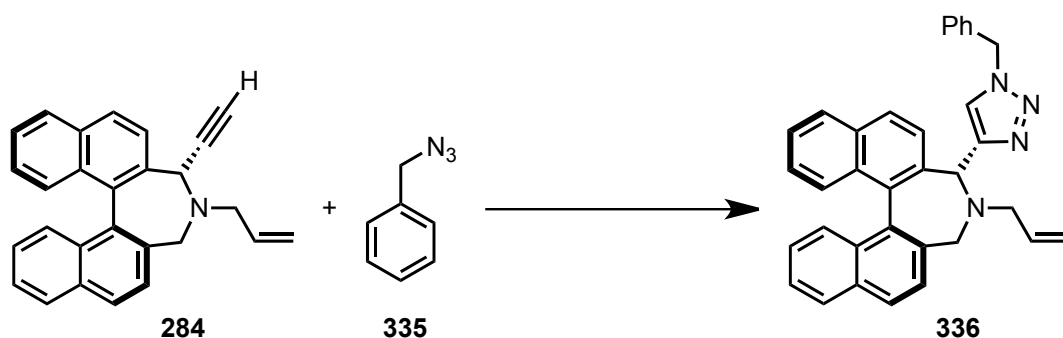
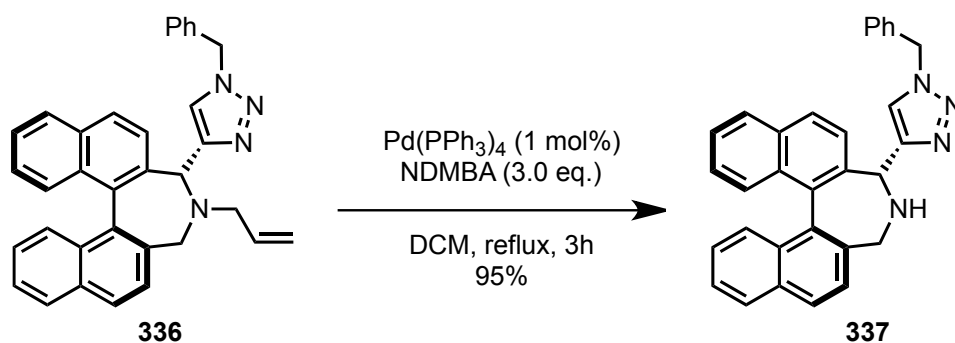


Table 14 Synthesis of triazole **336**

Solvent	Cu source (eq.)	Additive (eq.)	Temperature (°C)	Time (h)	Yield (%)
<i>t</i> BuOH/H ₂ O	CuSO ₄ (0.1)	Na ascorbate (0.15)	rt	48	<10
MeCN	CuI (0.1)	None	rt	1	23
THF/H ₂ O	CuSO ₄ (0.1)	Na ascorbate (0.15)	50	3	83

The first reaction shown in the table utilized the optimized conditions published by Sharpless using a catalyst system comprised of copper (II) sulfate and sodium ascorbate in a *t*BuOH/H₂O solvent mixture. The ascorbate in this case acts as a reducing agent for the copper (II) and maintains it in the desired oxidation state for the duration of the reaction. In our hands, no conversion was seen using this system, presumably due to the complete insolubility of **284** in the solvents used. Use of a copper (I) salt directly without the ascorbate (entry 2) did lead to the desired compound, albeit as the minor product out of two which were isolated. The structure of the other compound that was formed was not obvious and has not been characterized at this point. Finally, the use of the Sharpless catalyst system in THF/H₂O proved to be far more fruitful, yielding the desired compound **336** in 83% yield. This compound was then deallylated using the standard method described above in near quantitative yield to give catalyst **337** (Scheme 124).



Scheme 124 Deallylation of compound **336** to give **337**

We then tested compound **337** as a catalyst for the malonate additions that have been discussed above. The results are presented in table **15**.

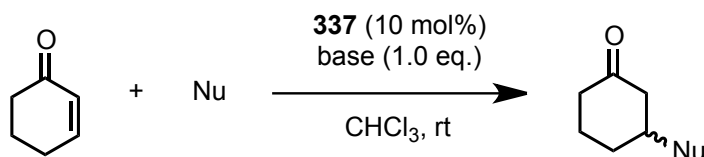


Table 15 Initial testing of catalyst **337**^(a)

Nucleophile	Base	Time (h)	Conversion (%)	ee (%)
dibenzyl malonate	CsF	144	0	-
dibenzyl malonate	<i>trans</i> -2,5-dimethylpiperazine	144	60	racemic
dibenzyl malonate	LiOH.H ₂ O	16	100	racemic
2-nitropropane	CsF	144	0	-
2-nitropropane	<i>trans</i> -2,5-dimethylpiperazine	144	0	-
2-nitropropane	LiOH.H ₂ O	144	0	-

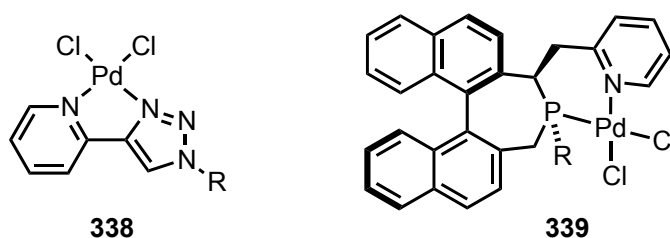
(a) Reactions were carried out on 0.25 mmol scale with magnetic stirring in Biotage microwave vials (2-5 mL size) using undistilled solvents (2 mL). Conversion from starting material to product was calculated via ¹H NMR using the integrations of diagnostic peaks. Enantiomeric excess was determined by integrating peaks in the ¹³C NMR of the diastereoisomeric acetals formed between the product and (R)-(-)-2,3-butanediol.

Unfortunately, while triazole **337** did effectively catalyse the addition of dibenzyl malonate to cyclohexenone, it did not give any enantiomeric excess. This is a disappointing result, but does show that it is probably necessary for a functionalized side chain with H-bonding capabilities like **310** or **325** to be present in the catalyst for it to give any enantioselectivity in this type of reaction. Also, no conversion was seen under any of the conditions when testing the addition of nitropropane to cyclohexenone. This is in keeping with the poor results shown before with catalyst **310**.

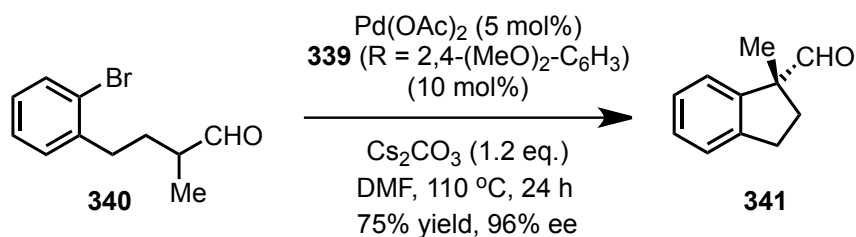
6.3.2 Metal Complexes

The first time **284** was synthesized, we noticed in the crude ^1H NMR spectrum that there was a large amount of peak broadening. While this can sometimes be put down to impaired rotation due to steric hindrance,²²⁰ we hypothesized that the broadening in this case was down to the presence of a paramagnetic copper complex being present in the crude material. Paramagnetic complexes, due to their unpaired electrons, are well known to distort NMR experiments.²²¹ These complexes are known to be effectively destroyed by adding other ligands such as EDTA to the crude reaction mixture. In our hands, however, we found that adding 1M ammonium hydroxide solution effectively removed copper from the reaction, forming water-soluble copper (II) amine complexes in the process.²²²

While compound **337** was shown to be an ineffective organocatalyst, we were also interested in its ability to chelate metals and form novel organometallic complexes. There are examples of similar ligands being used to chelate palladium in the literature, forming complexes such as **338**²²³ and **339**.²²⁴

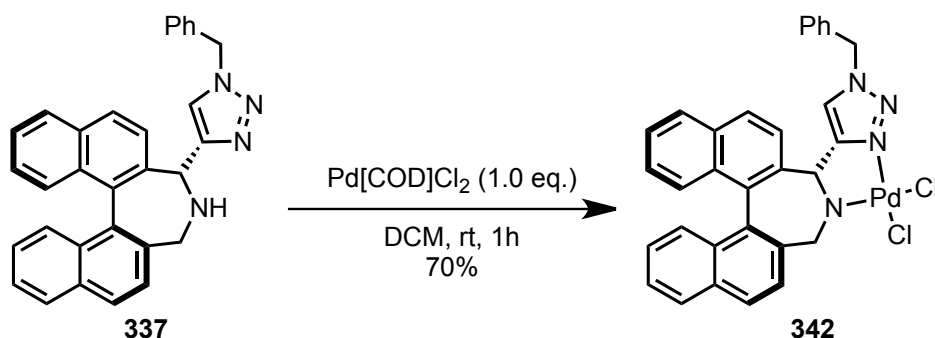


Amino phosphine complex **339**, based on an extremely similar system to ours (containing a dihydrophosphepine motif as opposed to our dihydroazepines), has also recently been shown to highly selectively catalyse the intramolecular α -arylation of α -branched aldehydes such as **340** (Scheme 125).



Scheme 125 α -Arylation of branched aldehydes catalysed by Pd complex **339**

We envisaged that **337** should effectively chelate palladium and as such we subjected it to the same conditions as reported by Sarkar. To our delight, stirring **337** for one hour with a dichloromethane solution of Pd[COD]Cl₂ yielded, after precipitation with petroleum ether, the novel complex **342** in a respectable 70% yield (Scheme 126).



Scheme 126 Synthesis of Pd complex **342**

This proposed structure was confirmed by X-ray analysis of crystals grown from a dichloromethane/diethyl ether solution of the complex (Figure 20). The square planar nature of this complex can be easily seen in this case.

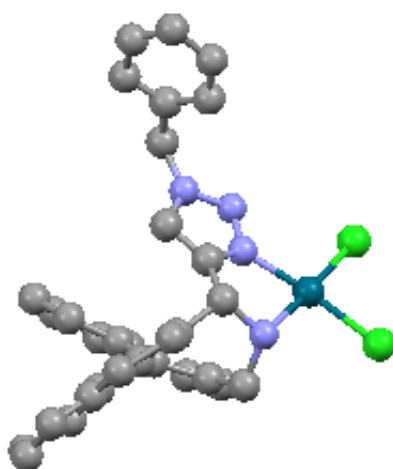


Figure 20 Crystal structures of compound **342**

Repetition of this reaction with **343**, which was synthesized using the same method as for **336**, yielded a similar Pd-complex **344** (Scheme 127). This complex exhibited some interesting peaks in the ¹H NMR spectrum, with several of the aromatic peaks exhibiting a pronounced downfield shift (Figure 21). We believe this could be due to a potential interaction between the aromatic protons in the PMB group and the dz² orbital of the Pd atom that lies perpendicular to the plane of the square planar complex. This is the opposite effect to the one responsible for the upfield shift

experienced by the pseudoaxial α -substituents of the azepines that are discussed at length in section 6.1 above.

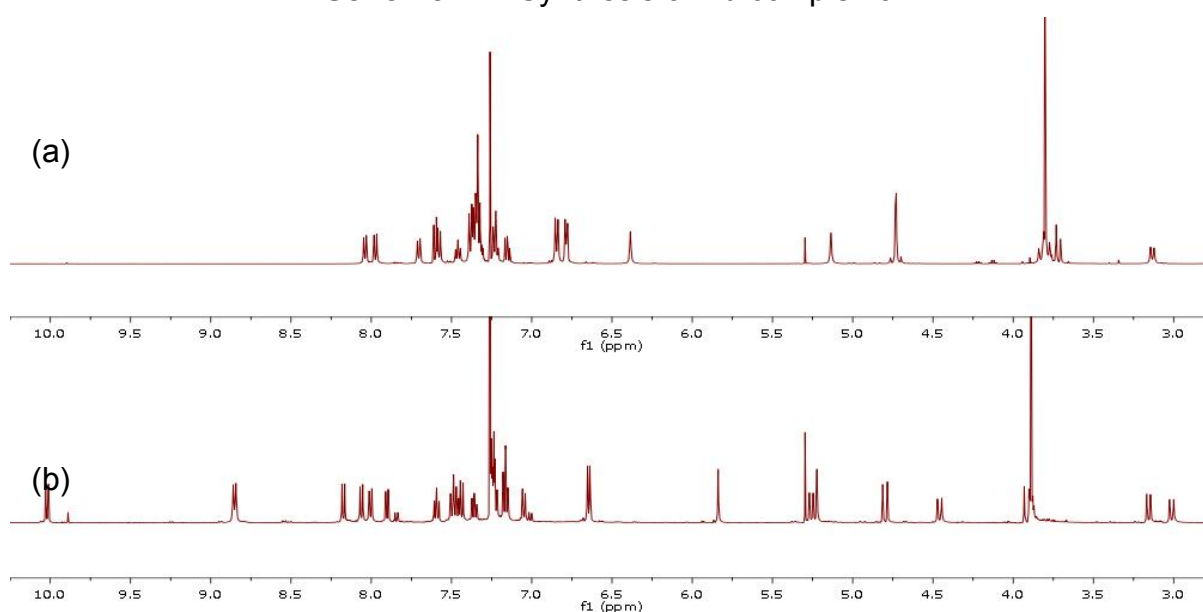
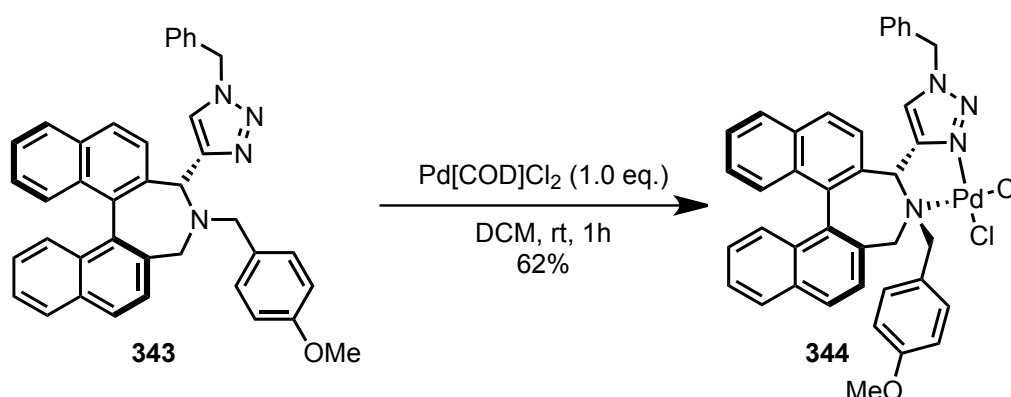


Figure 21 ^1H NMR spectra of (a) ligand **343** in CDCl_3 and
(b) after addition of 1.0 eq. of $\text{Pd}[\text{COD}]\text{Cl}_2$

There are few examples of these sorts of Pd (II) complexes being used for catalysis due to the need for the presence of Pd(0) in most catalytic cycles. There are, however, many examples of Cu diamine complexes being used in asymmetric catalysis. This is exemplified by the bisoxazoline (Box) type ligands, which have found a multitude of uses in asymmetric catalysis as previously discussed in section 4.1.4.²²⁵

In order to determine if a diamagnetic copper (I) complex containing **337** could be synthesized, we ran an NMR experiment. After running a ^1H spectrum of **337** in CD_3CN , we introduced 1.1 equivalents of CuI to the NMR tube, which resulted in an instant colour change. Subsequent analysis showed that a new complex had indeed formed quantitatively (Figure 22). However, attempts to isolate it were met with difficulties due to its unstable nature. This does show, however, that **337** is capable of forming diamagnetic complexes with copper. It is our hope that said complexes can be potentially used for catalytic processes. Our ideas about this are presented in section 3.1.

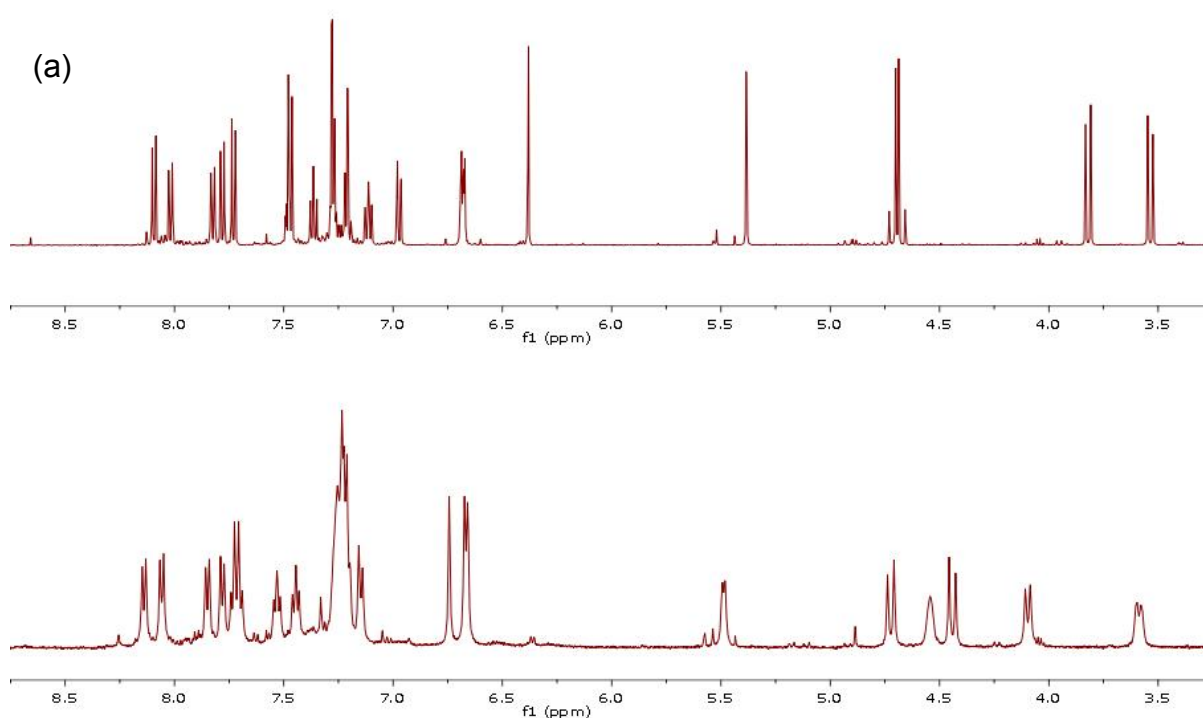
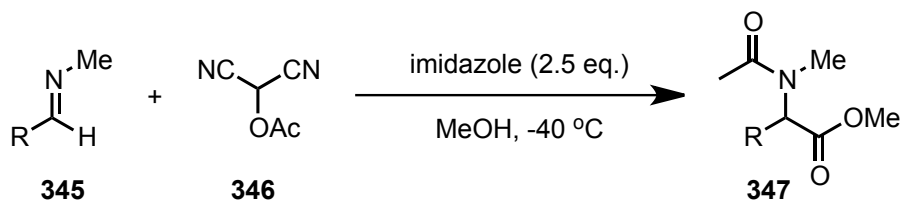


Figure 22 ^1H NMR spectra of (a) ligand **337** in CD_3CN and
(b) ligand **337** after addition of 1.1 eq. CuI

7.1 Future Work

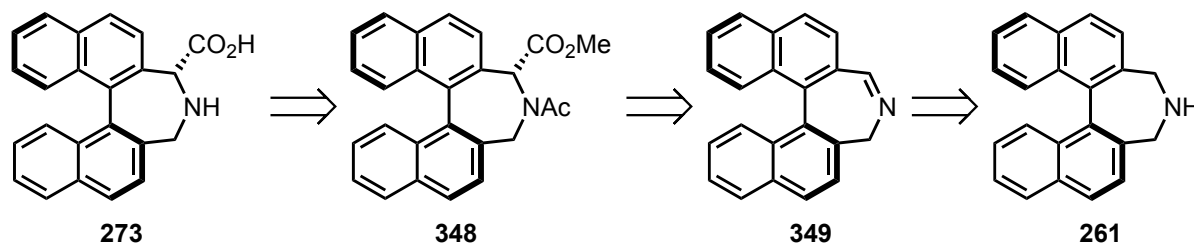
This thesis reports a new area of research within the Page group. Preliminary work on a range of topics has taken place and as such, there are several routes that this project could now take in the future. They are presented in this section.

First and foremost, the synthesis of α -amino acid **273** is still one of our main targets. There are two methods that we believe could still give access to this compound that has thus far evaded us. Firstly, Nemoto has published a methodology for the synthesis of amino acids directly from unactivated imines using masked acyl cyanide (MAC) reagents that were developed in his group.²²⁶ By reacting dicyanomethyl acetate **346** with imines of the type **345** in the presence of a mild base, it was possible to isolate cleanly and effectively products of the type **347** (Scheme 128).



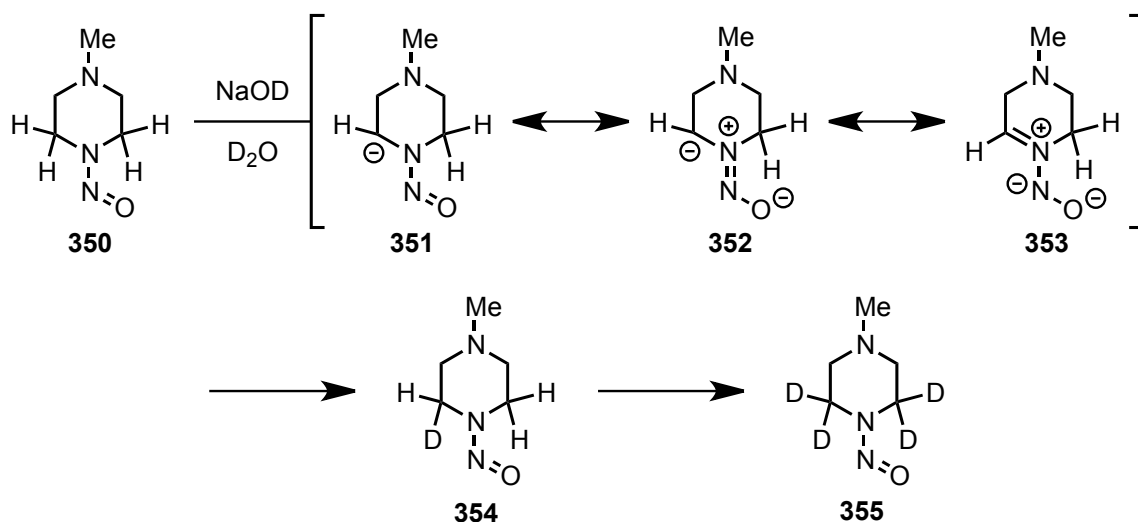
Scheme 128 Synthesis of α -amino esters using MAC reagents

The reaction is believed to proceed by nucleophilic attack of the deprotonated dicyanomethyl acetate followed by acetate migration to the newly formed secondary amine. The unstable acyl cyanide formed as a result then reacts with the methanol solvent resulting in the formation of methyl ester **347**. The loss of two equivalents of gaseous hydrogen cyanide drives the reaction forward and also explains the lack of side reactions that occur. We believe that methyl ester **348** could be accessed in this way from the known compound **349**, itself formed by oxidation of secondary amine **261** (Scheme 129).



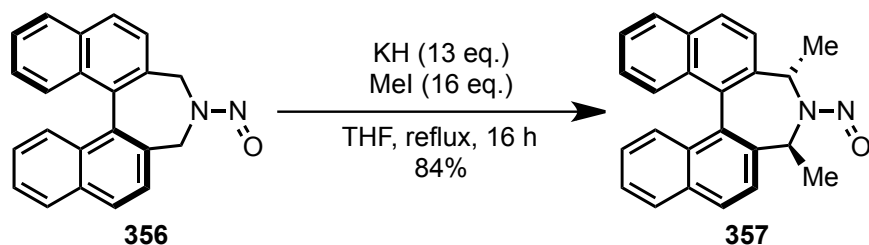
Scheme 129 Retrosynthesis of α -amino acid **273** based on Nemoto's MAC methodology

Secondly, it is possible that lithiation at the α -position of the azepine is possible if the correct protecting group is used. For example, nitrosamine **350** was shown by Keefer and Fodor to easily undergo ready H/D exchange in basic D₂O solution at elevated temperatures, suggesting that the α -carbanion **351** is stabilized by tautomers **352** and **353** (Scheme 130).²²⁷



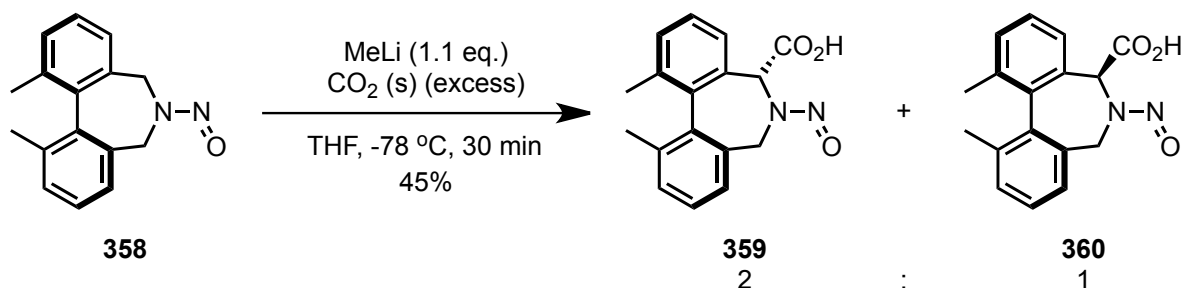
Scheme 130 H/D exchange in *N*-nitroso-*N'*-methylpiperazine

Superchi and co-workers have utilized this methodology for the synthesis of dimethylated **357** from parent nitrosamine **356**.²²⁸ Using an excess of KH and MeI in refluxing THF, the desired compound was isolated in high yield. This reaction proceeds *via* a dianion and yields the desired compound diastereoselectively, showing that the more reactive pseudoaxial proton is removed by the base used (Scheme 131).



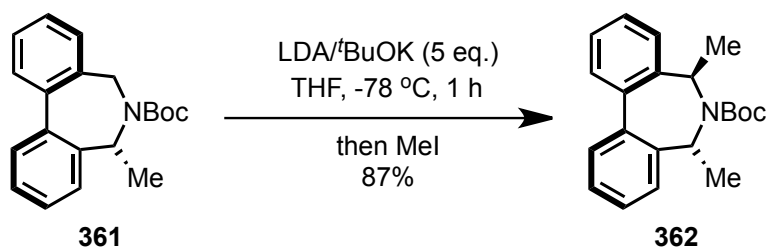
Scheme 131 Methylation of nitrosamine **356**

Wigfield has even shown that compounds such as acid **359** can be accessed using this methodology.²²⁹ Deprotonation of **358** and subsequent quenching of the anion with dry carbon dioxide gas yielded **359**, albeit as a mixture with **360** (Scheme 132). It is hoped that this sort of chemistry could be applied to the binaphthyl system utilized in our work.



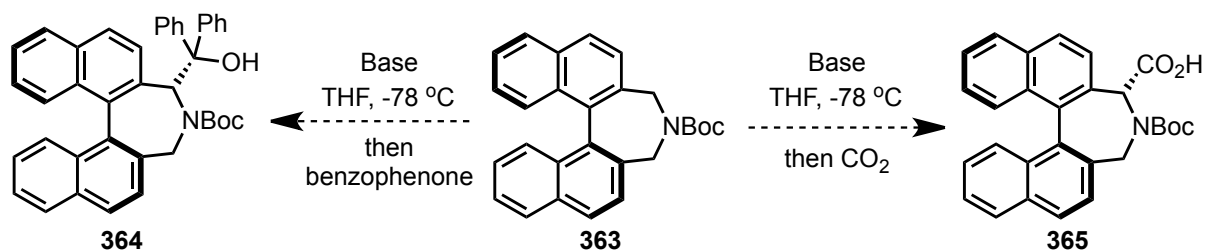
Scheme 132 Carbon dioxide addition to nitrosamine **358**

N-Boc azepine **361** is also known, and it was shown by Wallace²¹¹ that the α -protons in that case are also acidic enough to be removed by a strong base such as the Schlosser superbase derived from *n*-butyl lithium and KO^{*t*}Bu.²³⁰ Compound **362** was accessed in this way in excellent yield (Scheme 133).



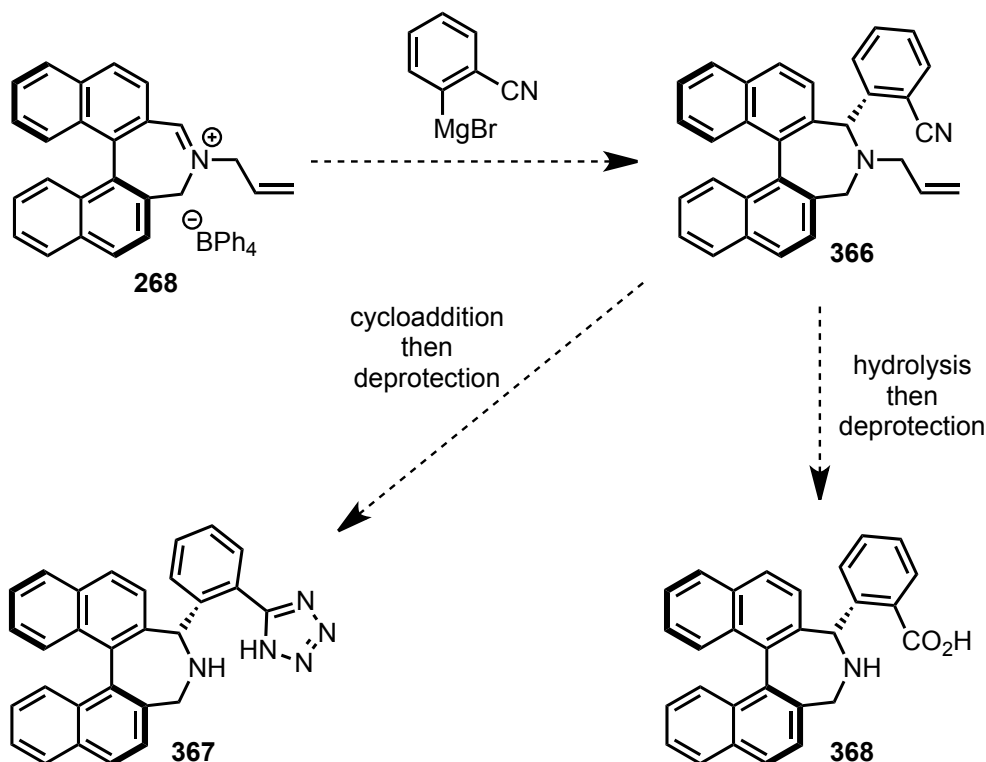
Scheme 133 Methylation of *N*-Boc azepine **361**

This, we believe, is definitely a potential method for the synthesis of α -amino acid **365** and also for related compounds such as tertiary alcohol **364** (an analogue of the popular Jørgensen-type catalyst) that could be accessed merely by altering the electrophile used (Scheme 134). This could itself also prove to be an effective organocatalyst.



Scheme 134 Potential routes to organocatalysts based on lithiation of azepine
363

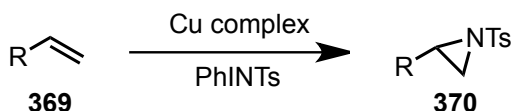
Another potential route to new organocatalysts using our original method of nucleophilic addition to iminium salt **268** is the use of functionalized Grignard reagents that have been developed by Knochel.²³¹ He has shown that functionalized Grignard reagents are accessible using his methodology, and behave in the same way as other Grignard reagents. As such, we believe that adding nucleophiles of this type to iminium salt **268** could yield compounds such as **366**. From there, benzoic acid derivative **367** or tetrazole **368** would hopefully be accessible by known literature procedures (Scheme 135).



Scheme 135 Potential routes to organocatalysts using functionalized Grignard reagents

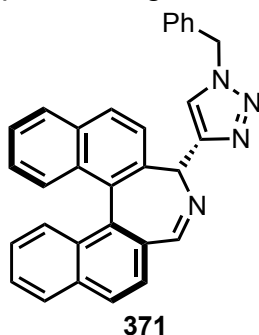
The pKa of this aromatic acid **368** would be lower than for β -amino acids **310** and **325** that are discussed above. We hope that this increase in acidity could also lead to an increase in reactivity, both in enamine and iminium-based organocatalytic processes.

Finally, the work on **337** and its metal complexes needs to be expanded upon. As indicated above, there are several asymmetric copper-catalysed reactions that utilize ligands similar to those described above. One of the most well-known is the asymmetric aziridination of olefin substrates using (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane in conjunction with a copper catalyst.²³² This forms a copper nitrene *in situ*, which can then add to the alkene substrate (Scheme 136). Our new ligand **337** will perhaps perform well in this type of asymmetric process.



Scheme 136 Copper-catalysed aziridination

Having shown that compounds such as **337** also form complexes with palladium, it would be interesting to see what effect different *N*-substituents on both the azepine and the triazole have on the properties of the metal complexes formed and also to see if complexes can be formed which contain other metals. This should be a relatively facile process due to the highly modular nature of the synthesis of these compounds. Also, it could be possible to oxidize **337** to yield imine **371**, which could have different properties still as a potential ligand.



In conclusion, there are still many routes that this project could take in the future. This thesis has barely scratched the surface in terms of the potential uses of compounds derived from these axially chiral amines. It will be interesting to see what the future holds for this type of compound within the Page group.

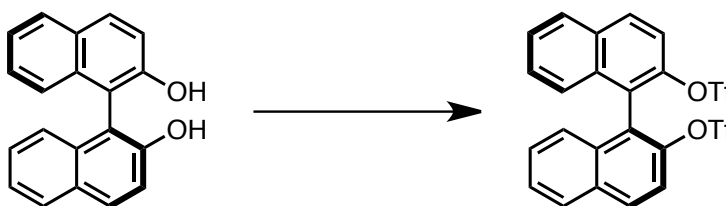
8.1 General Experimental

Unless otherwise stated, all starting materials were bought from commercial suppliers and were used without further purification. If necessary, solvents were dried in the usual manner; THF and Et₂O were distilled from sodium benzophenone ketyl radical, and toluene, DCM, MeCN, and DMF were distilled from CaH₂. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C. Commercial samples were distilled in the lab prior to use to remove any fractions with a boiling point higher than this. Solvents were removed using a Büchi rotary evaporator (water bath temperature approx. 40 °C) or a high vacuum pump between room temperature and 60 °C. In the case of anhydrous reactions glassware and needles were either flame-dried or dried in an oven (150 °C) for at least 2 hours and then allowed to cool under a stream of nitrogen immediately prior to use. All reactions were carried out under an atmosphere of nitrogen or argon. All liquid reagents and solvents were added to reaction vessels by means of syringes through rubber septa.

TLC analysis was carried out on commercially available Kieselgel aluminium backed plates. Visualisation was either by UV fluorescence, basic KMnO₄ solution and heat, or phosphomolybdic acid and heat. Column chromatography was carried out on Davisil® chromatographic silica media LC60Å 40-63 µm using standard methods. Melting points were obtained using a Büchi Melting Point B-545 apparatus and are uncorrected. Optical rotations were obtained using a Bellingham and Stanley ADP440 polarimeter using the solvent described in each case with concentrations quoted in grams per 100 mL. IR spectra were recorded in the range 4000-400 cm⁻¹ on a Perkin-Elmer 1720X FT-IR spectrophotometer as thin films on KBr plates or as solid samples on diamond windows. NMR spectra were recorded on a Bruker 500 MHz Spectrometer. Chemical shifts were recorded in parts per million (ppm) and are referenced to either tetramethylsilane or the residual protons of the deuterated solvents used. Abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet) and br (broad). Mass spectra were determined at the EPSRC Mass Spectrometry Unit, Swansea. Chiral HPLC was obtained using a VWR Hitachi Elite LaChrom HPLC system fitted with a Chiralcel OD column using the racemate as a standard.

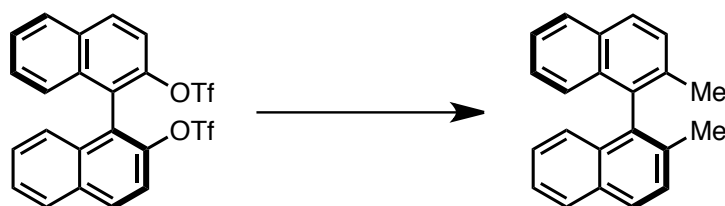
8.2 Experimental data

(S)-[1,1']-binaphthalene-2,2'-diol *bis*-trifluoromethanesulfonate 238²³³



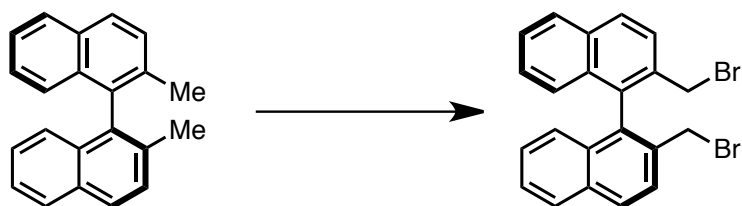
(S)-[1,1']-Binaphthalene-2,2'-diol (10.0 g, 34.8 mmol, 1.0 eq) and 4-dimethylaminopyridine (1.75 g, 14.2 mmol, 0.4 eq) were dissolved in dry dichloromethane (240 mL) and cooled to -78 °C. To the resulting yellow solution was added 2,6-lutidine (12.2 mL, 104 mmol, 3.0 eq) and triflic anhydride (18.00 mL, 104 mmol, 3.0 eq). The resulting pink solution was allowed to reach room temperature and stirred for 20 hours. Silica gel was added to the reaction mixture and the solvent removed *in vacuo*. The compound adsorbed onto silica was transferred to a glass sinter and washed with petroleum ether/EtOAc (99:1) until the title compound had eluted. Solvents were removed *in vacuo* to give the title compound as a colourless solid (18.65 g, 33.9 mmol, 97%), m.p. 94-96 °C (lit. 93-95 °C¹⁷³), $[\alpha]_D^{20} +148$ (c 1.00, CHCl₃) (lit. +145 (c. 1.00, CHCl₃¹⁷³), $\nu_{\text{max}}(\text{solid})/\text{cm}^{-1}$ 2927, 2363, 1621, 1582, 1508, δ_{H} (400 MHz; CDCl₃) 7.25-7.27 (2H, m), 7.39-7.43 (2H, m), 7.57-7.63 (4H, m), 8.00-8.02 (2H, m), 8.13-8.15 (2H, m), δ_{C} (75 MHz; CDCl₃) 53.3, 119.3, 123.5, 126.8, 127.4, 128.0, 128.4, 132.0, 132.4, 133.2, 145.4.

(S)-2,2'-Dimethyl-[1,1']binaphthalene 239²³³



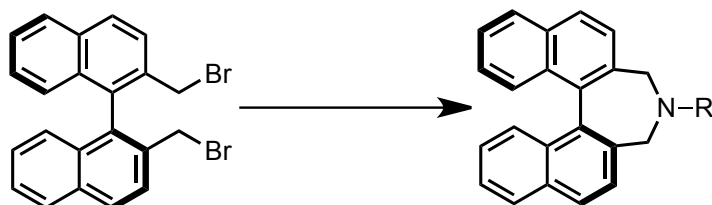
(S)-[1,1']-binaphthalene-2,2'-diol *bis*-trifluoromethanesulfonate (8.20 g, 14.9 mmol, 1.0 eq) and 1,3-bis(diphenylphosphino)propane nickel (II) chloride (0.70 g, 1.04 mmol, 0.07 eq) were dissolved in anhydrous diethyl ether (80 mL). The reaction was cooled to -78 °C before methylmagnesium bromide (3M in diethyl ether, 19.9 mL, 59.52 mmol, 4.0 eq) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature and the reaction mixture stirred for 60 hours. The dark brown solution was diluted with diethyl ether (50 mL) and Celite was added. The mixture was cooled to 0 °C, and the excess Grignard reagent was gradually quenched with water. The reaction mixture was then filtered through a plug of Celite (washing the solid residue with diethyl ether) to give a clear orange solution. This was transferred to a separating funnel and washed sequentially with concentrated aqueous HCl solution, water, and brine. The organic phase was dried (MgSO₄), filtered, and concentrated *in vacuo* to give a colourless oil which could be used without further purification (3.95 g, 14.0 mmol, 94 %). An analytically pure sample could be obtained by recrystallization from MeOH; m.p. 84-85 °C (lit. 72-74 °C¹⁷³), $[\alpha]_D^{20} + 45.8$ (c 1.00, CHCl₃) (lit. +38 (c. 1.00, CHCl₃¹⁷³), $\nu_{\max}(\text{solid})/\text{cm}^{-1}$ 3042, 2916, 1906, 1617, 1593, 1565, 1504, 1443, 1419, 1377, 1351, δ_{H} (400 MHz; CDCl₃) 2.01 (6H, s), 7.05 (2H, d, J= 8.5 Hz), 7.13-7.15 (2H, m), 7.32-7.34 (4H, m), 7.46 (2H, d, J= 8.4 Hz), 7.82-7.86 (4H, m); δ_{C} (75 MHz; CDCl₃) 19.9, 125.0, 125.7, 126.1, 127.5, 128.0, 128.8, 132.3, 132.8, 134.4, 135.2.

(S)-2,2'-Bis-bromomethyl-[1,1']binaphthalene 240²³³



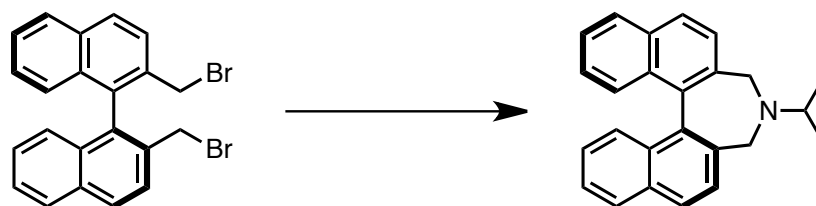
(S)-2,2'-Dimethyl-[1,1']binaphthalene (3.50 g, 12.40 mmol, 1.0 eq) was dissolved in cyclohexane (28 mL). *N*-bromosuccinimide (4.66 g, 24.8 mmol, 2.0 eq) and azobisisobutyronitrile (0.21 g, 0.13 mmol, 0.1 eq) were added and the mixture refluxed for 3 h (TLC showed disappearance of starting material). Ethyl acetate (10 mL) and water (50 mL) were added to dissolve byproducts and excess NBS. The resulting suspension was stirred for 1 hour resulting in precipitation of the title compound as a colourless powder (2.70 g, 6.13 mmol, 49%), m.p. 171-174 °C (lit. 180-182 °C¹⁷³), $[\alpha]_{20}^D$ -163.7 (c 1.30, CHCl₃) (lit. -158 (c. 1.00, CHCl₃¹⁷³), $\nu_{\max}(\text{solid})$ /cm⁻¹, 3044, 2916, 1909, 1722, 1593, 1505, 1432, 1211, 817, 759, δ_H (400 MHz; CDCl₃) 4.25 (4H, s), 7.07 (2H, d, *J*= 8.5 Hz), 7.25-7.29 (2H, m), 7.47-7.51 (2H, m), 7.75 (2H, d, *J*= 8.5 Hz), 7.92 (2H, d, *J*= 8.1 Hz), 8.02 (2H, d, *J*= 8.6 Hz), δ_C (75 MHz; CDCl₃) 32.5, 126.85, 126.87, 126.90, 127.80, 128.1, 129.4, 132.6, 133.3, 134.2, 134.3.

General procedure for the synthesis of binaphthalene-derived azepines from (S)-2,2'-bis(bromomethyl)-[1,1']binaphthalene and primary amines²³³



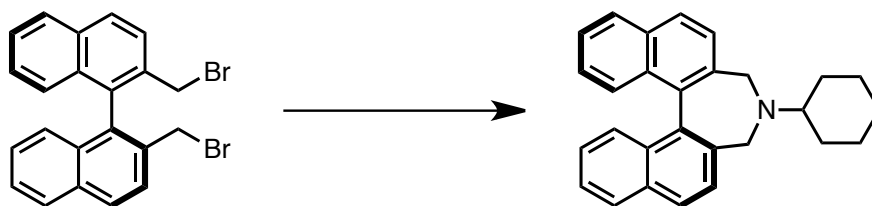
The primary amine (1.1 eq.) was added to a nitrogen purged, stirred solution of (S)-2,2'-bis(bromomethyl)-[1,1']binaphthalene (1.0 eq.) and potassium carbonate (3.0 eq.) in acetonitrile (10 mL per gram of dibromide) at room temperature. The reaction mixture was heated to reflux and stirred overnight or until the disappearance of starting material was seen by TLC. The mixture was diluted with dichloromethane (40 mL per gram of dibromide) and washed with water (2 x 30 mL per gram of dibromide) and brine (2 x 30 mL per gram of dibromide). The organic phase was separated, dried (MgSO_4) and the solvent removed *in vacuo* to give the desired products.

(S)-N-Isopropyl-2,7-dihydro-dinaphtho[2,1-c;1',2'-e]azepine 244



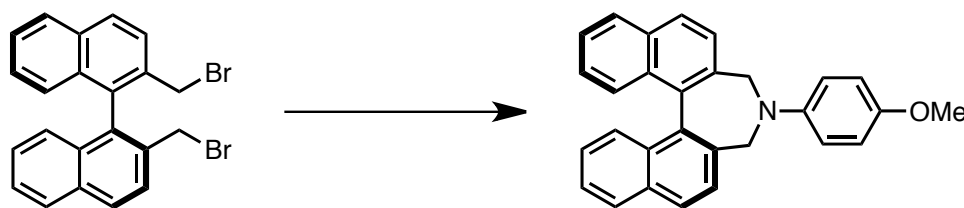
Prepared according to the general procedure using isopropylamine (0.15 g, 2.27 mmol, 1.1 eq.). Trituration of the crude product in acetone (5 mL) gave the analytically pure *title compound 5* as colourless powder (0.65 g, 1.92 mmol, 85%), m.p. 159-160 °C, $[\alpha]_D^{20} +336.4$ (c 1.00, acetone), $\nu_{\max}(\text{solid})/\text{cm}^{-1}$ 3044, 2965, 2802, 1590, 1505, 1459, 1372, 1348, 1238, 1158, δ_{H} (400 MHz; CDCl_3) 1.15 (3H, d, $J = 6$ Hz), 1.29 (3H, d, $J = 6$ Hz), 2.76 (1H, septet, $J = 6$ Hz), 3.26 (2H, d, $J = 12$ Hz), 3.93 (2H, d, $J = 12$ Hz), 7.24-7.28 (2H, m), 7.44-7.48 (4H, m), 7.59 (2H, d, $J = 8$ Hz), 7.94 (4H, d, $J = 8$ Hz), δ_{C} (75 MHz; CDCl_3) 19.4, 20.0, 50.4, 51.0, 123.5, 124.0, 125.7, 126.2, 126.4, 126.5, 129.6, 131.3, 132.6, 133.2, HRMS (CI⁺): calc. for $\text{C}_{25}\text{H}_{23}\text{N}$ (MH⁺) 337.1831, found 337.1826.

(S)-N-Cyclohexyl-2,7-dihydro-dinaphtho[2,1-c;1',2'-e]azepine 245



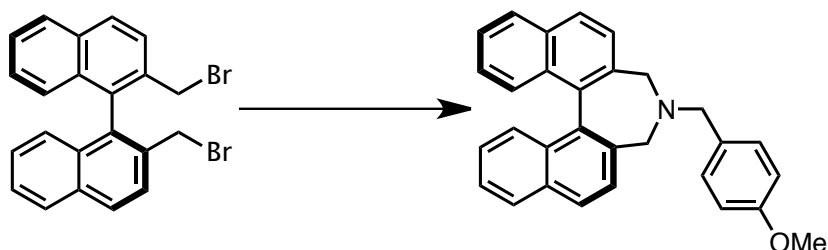
Prepared according to the general procedure from cyclohexylamine (0.29 mL, 2.50 mmol, 1.1 eq). The title compound **19** was isolated as a colourless foam which solidified upon drying (0.81 g, 2.15 mmol, 95%), m.p. 81-82 °C , $[\alpha]^{20}_{\text{D}} +252$ (c 1.00, CHCl_3), $\nu_{\text{max}}(\text{solid}) / \text{cm}^{-1}$, 3046, 2922, 2850, 1593, 1506, 1447, 1361, 1343, 1236, 1113, 1092, δ_{H} (400 MHz; CDCl_3) 1.18-1.40 (5H, m), 1.64 (1H, m), 1.76-1.97 (1H, m), 2.22 (1H, d, $J = 12.2$ Hz), 2.40-2.42 (1H, m), 3.29 (2H, d, $J = 13$ Hz), 3.97 (2H, d, $J = 12$ Hz), 7.23-7.28 (2H, m), 7.44-7.46 (4H, m), 7.60 (2H, d, $J = 8$ Hz), 7.94-7.96 (4H, m), δ_{C} (75 MHz; CDCl_3) 25.6, 26.0, 30.5, 31.1, 31.6, 51.9, 61.7, 125.3, 125.7, 127.5, 128.0, 128.3, 128.4, 131.4, 133.1, 134.5, 135.1, HRMS (CI⁺): calc. for $\text{C}_{28}\text{H}_{27}\text{N}$ (MH⁺) 377.2144, found 377.2138.

(S)-N-(4-methoxyphenyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 249



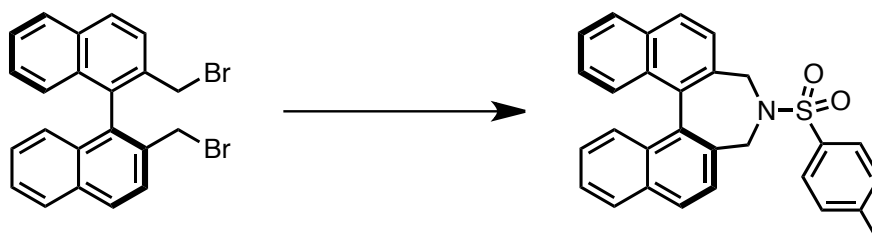
Prepared according to the general procedure from *p*-anisidine (0.15 g, 1.14 mmol). The crude product was isolated as a pale yellow foam which was purified by column chromatography (1:1 petrol : EtOAc) to give the *title compound* **22** as yellow powder (380 mg, 0.94 mmol, 83%) m.p. 91-92 °C, $[\alpha]_{\text{D}}^{20}$ -259.6 (c 1.00, CHCl₃), $\nu_{\text{max}}(\text{solid})$ /cm⁻¹ 3388, 3049, 2995, 2948, 2907, 2831, 2348, 2047, 1915, 1830, 1734, 1615, 1594, 1580, δ_{H} (300 MHz; CDCl₃) 3.76 (s, 3H), 3.78 (d, 2H, J = 12 Hz), 4.32 (d, 2H, J = 12 Hz), 6.80-6.92 (m, 4H), 7.24-7.31 (m, 2H), 7.43-7.53 (m, 6H), 7.91 (t, J = 8 Hz), δ_{C} (75 MHz; CDCl₃) 53.7, 55.5, 114.4, 117.9, 125.6, 125.9, 127.5, 127.6, 128.4, 128.8, 131.4, 133.3, 133.6, 134.8, 144.4, 153.1, HRMS (CI⁺): calc. for C₂₉H₂₃NO (MH⁺) 402.1844, found 402.1847.

(S)-4-(4-methoxybenzyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 259



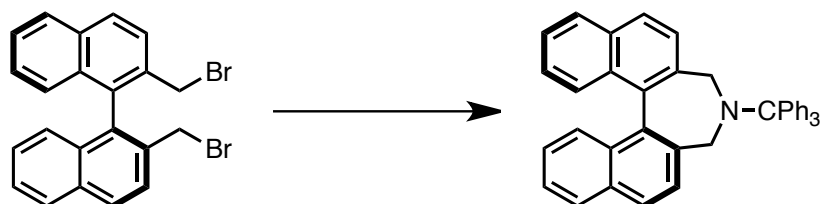
Prepared according to the general route from p-methoxybenzylamine (247 mg, 1.80 mmol, 1.05 eq.). The title compound was isolated as a colourless foam which was used without further purification (580 mg, 1.40 mmol, 82 %). An analytically pure sample was obtained by column chromatography (5:1 petrol:EtOAc → 2:1); $[\alpha]_D^{20}$ +135 (c 0.98, CHCl₃); ν_{\max} (solid) /cm⁻¹ 3420, 3051, 3009, 2934, 2833, 1707, 1611, 1510, 1441, 1246; δ_H (500 MHz; CDCl₃) 3.19 (d, 2H, J = 12.4 Hz), 3.52 (d, 1H, J = 12.8 Hz), 3.63 (d, 1H, J = 12.7 Hz), 3.67 (d, 2H, J = 12.4 Hz), 3.83 (s, 3H), 6.91 (d, 2H, J = 8.7 Hz), 7.25-7.28 (m, 2H), 7.35 (d, 2H, J = 8.6 Hz), 7.45-7.49 (m, 4H), 7.54 (d, 2H, J = 8.3 Hz), 7.96 (d, 4H, J = 8.2 Hz); δ_C (125 MHz; CDCl₃) 55.06, 55.30, 59.07, 113.80, 125.39, 125.73, 127.50, 127.89, 128.26, 128.31, 130.41, 131.14, 131.45, 133.15, 133.15, 133.67, 135.12, 158.81; HRMS (CI⁺): calc. for C₃₀H₂₆NO (MH⁺) 416.2009, found 416.2010

(S)-4-(tosyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 264



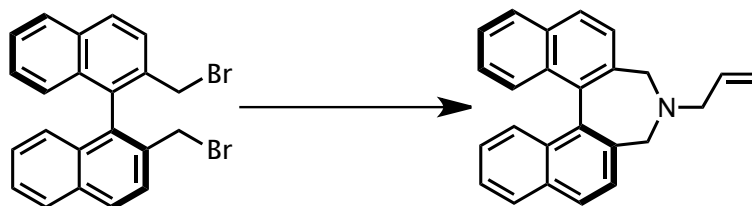
Prepared according to the general route using *p*-toluenesulfonamide (383 mg, 2.45 mmol, 1.1 eq.). The reaction was complete within 2 hours in refluxing MeCN. After work-up, careful column chromatography of the crude material (20:1 petrol:EtOAc) gave the title compound as a colourless foam (680 mg, 1.52 mmol, 68%); $[\alpha]_D^{20} +98$ (c 1.06, CHCl₃); $\nu_{\text{max}}(\text{solid})/\text{cm}^{-1}$ 3052, 2923, 2866, 1919, 1596, 1508, 1493, 1462; δ_{H} (500 MHz, CDCl₃) δ 2.39 (s, 3H), 3.68 (d, $J = 13.0$ Hz, 2H), 4.75 (d, $J = 13.0$ Hz, 2H), 7.22 – 7.27 (m, 4H), 7.34 – 7.38 (m, 3H), 7.47 (ddd, $J = 8.1, 6.7, 1.2$ Hz, 2H), 7.71 (d, $J = 8.2$ Hz, 2H), 7.85 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), δ_{C} (125 MHz; CDCl₃) 21.52, 49.24, 126.04, 126.13, 127.25, 127.37, 127.41, 128.34, 129.08, 129.62, 130.99, 131.20, 133.35, 135.03, 136.77, 143.30; HRMS (CI⁺): calc. for C₂₉H₂₄NO₂S (MH⁺) 450.1522, found 450.1522

(S)-4-trityl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 266



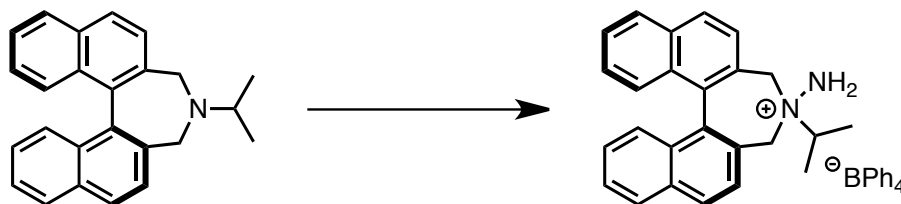
Prepared according to the general route using tritylamine (190 mg, 0.72 mmol). The product was isolated as a colourless foam (240 mg, 0.68 mmol, 95%); $[\alpha]_D^{20} +304$ (c 1.02, CHCl_3); ν_{max} (solid) $/\text{cm}^{-1}$ 3046, 2928, 2850, 1678, 1643, 1458, 1465, 1361; ^1H NMR (500 MHz, CDCl_3) δ 3.34 (d, 2H, $J = 12.5$ Hz), 4.07 (d, 2H, $J = 12.5$ Hz), 7.00 – 7.18 (m, 13H), 7.23 – 7.32 (m, 4H), 7.46 (d, 6H, $J = 7.4$ Hz), 7.59 (d, 2H, $J = 8.6$ Hz), 7.72 (d, 2H, $J = 8.1$ Hz); δ_{C} (125 MHz; CDCl_3) 50.8, 78.1, 125.2, 125.4, 126.1, 127.6, 127.8, 128.0, 128.1, 128.2, 129.8, 131.2, 132.7, 134.7, 135.0, 144.7; HRMS (Cl^+): calc. for $\text{C}_{41}\text{H}_{31}\text{N}$ (MH^+) 537.2456, found 537.2452

(S)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine 267



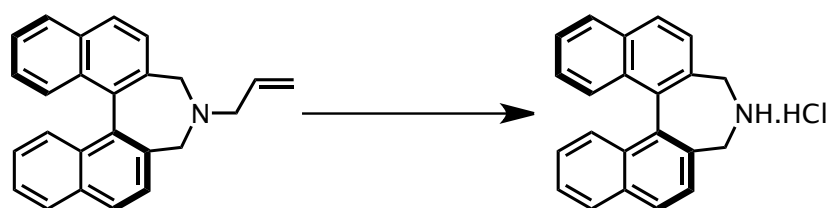
(S)-2,2'-bis(bromomethyl)-[1,1']binaphthalene (5.0 g, 11.26 mmol, 1.0 eq.), allylamine (1.26 mL, 16.89 mmol, 1.5 eq.) and Et₃N (4.70 mL, 33.8 mmol, 3.0 eq.) were dissolved in MeCN (50 mL) and stirred at 50 °C for 4 h (TLC indicated disappearance of starting material). The solvent was removed in vacuo, leaving a pale yellow solid residue. DCM and water were added and the organic phase was separated, washed with water (2 x 50 mL) and brine (50 mL), dried (MgSO₄) then concentrated *in vacuo* to give a brown solid. This mixture was triturated with cold acetone resulting in the precipitation of the title compound as a colourless solid (3.201 g, 9.46 mmol, 84 %); m.p. 175 – 178 °C; $[\alpha]_D^{20} +361$ (c 1.01, CHCl₃); $\nu_{\max}(\text{solid})/\text{cm}^{-1}$ 3048, 2935, 2801, 2363, 1593, 1507, 1461, 1367, 1335; δ_{H} (400 MHz; CDCl₃) 3.07-3.13 (m, 2H, -NCH₂CH=CH₂), 3.16 (d, 2H, J= 16 Hz, ArCH₂N), 3.75 (d, 2H, J= 16 Hz, ArCH₂N), 5.22-5.31 (m, 2H, NCH₂CH=CH₂), 5.94-6.06 (m, 1H, -NCH₂CH=CH₂), 7.26-7.29 (m, 2H, 2 x CH *arom.*), 7.46-7.49 (m, 4H, 4 x CH *arom.*), 7.55 (d, 2H, J= 12 Hz, 2 x CH *arom.*), 7.95 (d, 4H, J= 12 Hz, 4 x CH *arom.*); δ_{C} (75 MHz; CDCl₃) 54.78, 58.47, 118.04, 125.49, 125.83, 127.55, 127.55, 127.88, 128.39, 131.50, 133.21, 133.53, 135.14, 136.42.

(11bS)-4-amino-4-isopropyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium tetraphenylborate 253²³⁴



(S)-N-Isopropyl-2,7-dihydro-dinaphtho[2,1-c:1',2'-e]azepine (1.0 g, 2.96 mmol) was dissolved in DCM (30 mL). DppONH₂ (758 mg, 3.25 mmol) was added as a solid in a single portion and the resulting white slurry was stirred overnight at room temperature (TLC indicated complete consumption of the starting material). The mixture was filtered through a pad of Celite and concentrated *in vacuo* to give the hydrazinium diphenylphosphinate as a hygroscopic yellow foam. The crude compound was redissolved in a minimum amount of DCM and a saturated solution of sodium tetraphenylborate (1.11 g, 3.25 mmol) in MeCN was added. Copious precipitation of a colourless solid ensued. The *title compound* was isolated via filtration as a colourless powder (1.53g, 2.28 mmol, 77%), $[\alpha]^{20}_{\text{D}} +160.8$ (c 0.99, CHCl₃), m.p. 217-219 °C (decomp.); ν_{max} (DCM) /cm⁻¹ 3326, 3255, 3054, 3000, 2984, 1595, 1579, 1478, 1427, 1265; δ_{H} (500 MHz; CD₂Cl₂) 1.09 (d, 3H, J = 6 Hz), 1.24 (d, 3H, J = 6 Hz), 2.98 (br s, 2H), 3.18 (d, 1H, J = 13 Hz), 3.30 (septet, 1H, J = 6 Hz), 3.56 (d, 1H, J = 12 Hz), 3.72 (d, 1H, J = 12 Hz), 4.05 (d, 1H, J = 13 Hz), 6.79 (t, 4H, J = 7 Hz), 6.93 (t, 8H, J = 7 Hz), 7.28-7.38 (m, 9H), 7.39-7.53 (m, 5H), 7.61-7.72 (m, 2H), 8.02-8.20 (m, 4H); δ_{C} (125 MHz; CD₂Cl₂) 16.6, 16.8, 65.3, 65.6, 66.5, 122.1 (4C, para in ⁻BPh₄), 125.3, 125.9 (8C, m, meta in ⁻BPh₄), 126.2, 126.4, 127.38, 127.41, 127.5, 127.7, 127.8, 127.9, 128.0, 128.0, 128.6, 128.8, 130.4, 130.7, 131.3, 131.4, 134.6, 134.8, 134.8, 136.0 (8C, s, ortho in ⁻BPh₄), 136.3, 138.6, 163.9 (q, 4C, J = 49 Hz, ipso in ⁻BPh₄), HRMS (CI⁺): calc. for C₂₅H₂₅N₂⁺ 353.2012, found 353.2014.

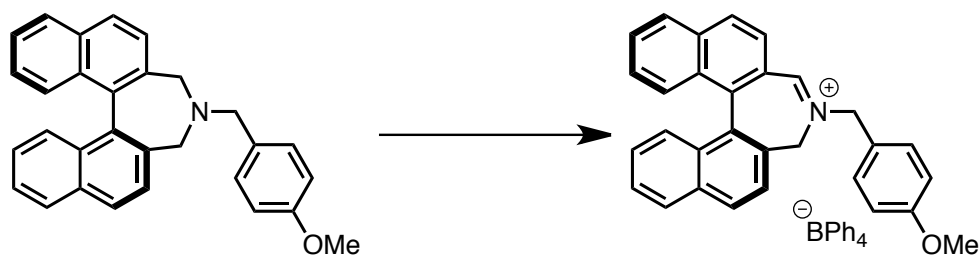
(S)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine hydrochloride 261.HCl



To a flame-dried 50 mL flask was added (S)-N-allyl-2,7-dihydro-dinaphtho[2,1-c:1',2'-e]azepine (1.00 g, 2.99 mmol, 1.0 eq.) and dry DCM (30 mL). N,N'-dimethylbarbituric acid (702 mg, 4.5 mmol, 1.5 eq.), Pd(OAc)₂ (14 mg, 0.06 mmol, 0.02 eq.) and PPh₃ (79 mg, 0.3 mmol, 0.1 eq.) were added in that order and the resulting yellow solution was heated to reflux overnight. The reaction mixture was cooled to room temperature and filtered through Celite before being washed sequentially with 1M NaOH, water and brine. Concentrated HCl (0.1 mL) was added and the solvent was then removed *in vacuo* to give an amorphous solid that was redissolved in hot CHCl₃. After 5 minutes, copious precipitation of the title compound ensued. The solid was filtered and isolated as a colourless powder (846 mg, 2.54 mmol, 85%); m.p. 217 – 220 °C; $[\alpha]_D^{20}$ +329 (c 0.98, MeOH); ν_{\max} (solid) /cm⁻¹ 3415, 2933, 2737, 2588, 1677, 1592, 1507, 1446, 1364, 1336; ¹H NMR (500 MHz, CD₃OD) δ 3.72 (d, *J* = 13.0 Hz, 2H), 4.38 (d, *J* = 13.1 Hz, 2H), 7.42 – 7.25 (m, 4H), 7.42 – 7.25 (m, 4H), 7.42 – 7.25 (m, 4H), 7.66 – 7.48 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.90 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H); δ_C (125 MHz; CD₃OD) 47.1, 127.9, 128.1, 128.2, 128.3, 129.3, 129.8, 131.2, 132.6, 135.7, 135.8.

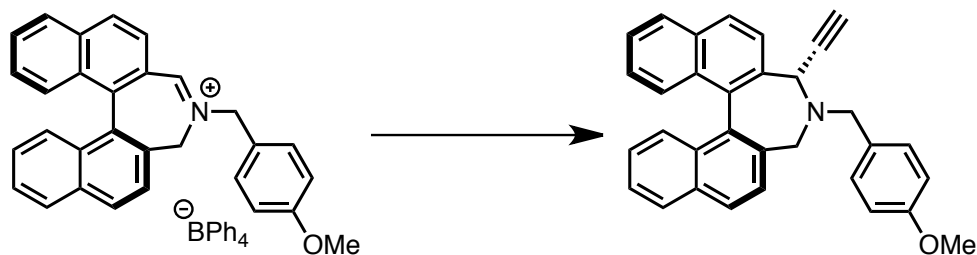
The amine hydrochloride was easily converted to the secondary amine by stirring a DCM solution of the amine hydrochloride with saturated aqueous NaHCO₃ solution for 30 minutes. Separation of the organic layer, drying and removing the solvent *in vacuo* gave the secondary amine as a yellow foam in quantitative yield.

**(S)-4-(4-methoxybenzyl)-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium
tetraphenylborate 260**



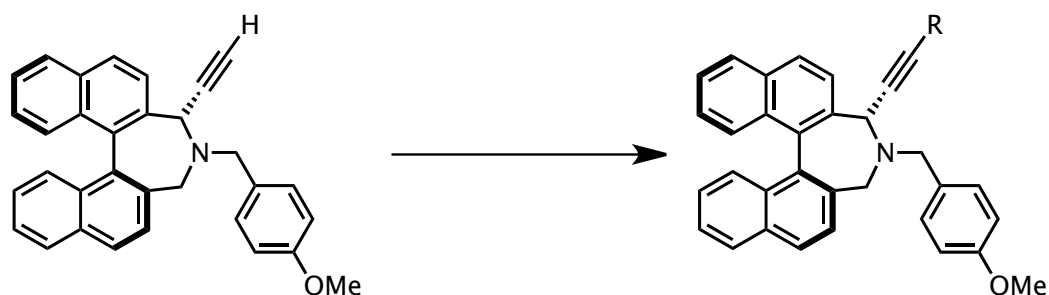
To a stirred solution of (S)-*N*-(4-methoxybenzyl)-2,7-dihydro-dinaphtho[2,1-*c*:1',2'-*e*]azepine (3.301 g, 7.95 mmol, 1.0 eq.) in DCM (50 mL) was added *N*-bromosuccinimide (1.485 g, 8.34 mmol, 1.05 eq.). The bright yellow solution was stirred for 1 h at room temperature and 30 minutes at reflux (TLC indicated complete consumption of starting material). Water (30 mL) was added and the organic layer was separated then washed sequentially with water (2 x 30 mL) and brine (30 mL). Drying (MgSO₄) and concentration *in vacuo* yielded the crude iminium bromide as a yellow foam. This was dissolved in the minimum amount of EtOH before NaBPh₄ (2.852 g, 8.34 mmol, 1.05 eq.) dissolved in a minimum amount of MeCN was added *via* pipette. After stirring for 5 minutes, the solvent was removed *in vacuo* and the crude solid was triturated in hot EtOH to give the *title compound* as a bright yellow solid which was dried *in vacuo* at 60 °C for 12 h to remove residual EtOH (5.341 g, 7.28 mmol, 92%); m.p. 111 – 113 °C (decomp.); [α]_D²⁰ +350 (c 1.08, CHCl₃); ν_{max}(solid) /cm⁻¹ 3449, 3054, 2999, 1639, 1610, 1548, 1513; ¹H NMR (500 MHz, acetone-d₆) δ 3.88 (s, 3H), 4.85 (dd, *J* = 13.5, 1.5 Hz, 1H), 5.27 (dd, *J* = 13.5, 1.5 Hz, 1H), 5.53 (d, *J* = 13.8 Hz, 1H), 5.56 (d, *J* = 13.8 Hz, 1H), 6.79 (t, *J* = 7.2 Hz, 4H), 6.94 (t, *J* = 7.4 Hz, 8H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.09 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.29-7.35 (m, 2H), 7.35-7.42 (m, 8H), 7.47-7.56 (m, 4H), 7.59 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.84 (ddd, *J* = 8.1, 6.3, 1.7 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.3 Hz, 1H), 8.39 (d, *J* = 8.6 Hz, 1H), 9.75 (s, 1H); ¹³C NMR (125 MHz, acetone-d₆) δ 55.0, 56.1, 65.1, 114.6, 121.6, 123.1, 125.4 (q, *J* = 2.7 Hz), 125.51, 126.01, 126.8, 126.9, 127.0, 127.1, 127.7, 128.7, 129.40, 129.43, 130.3, 130.96, 131.03, 131.65, 131.71, 131.74, 133.2, 135.4, 136.25, 136.7 (d, *J* = 1.8 Hz), 141.6, 161.0, 164.1 (q, *J* = 49.4 Hz), 168.4, 205.6; HRMS (CI⁺): calc. for C₃₀H₂₄NO (MH⁺) 414.1852, found 414.1853.

(3*S*,11*cS*)-3-ethynyl-4-(4-methoxybenzyl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine 291



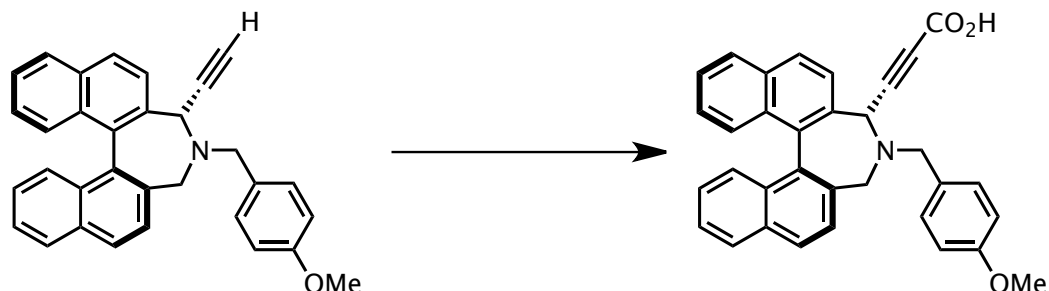
In a flame dried 100 mL round-bottomed flask, the iminium salt (1.0 g, 1.36 mmol, 1.0 eq.) was dissolved in dry THF (20 mL). The yellow solution was cooled to -78 °C before ethynylmagnesium bromide (27.2 mL of a 0.5 M solution in THF, 13.6 mmol, 10 eq.) was added in three portions over 5 minutes. The orange solution was allowed to reach room temperature and stirred overnight. Celite and MgSO₄ were added to the reaction mixture and water was cautiously added over 20 minutes to quench any excess Grignard reagent. The mixture was then filtered through a pad of Celite and concentrated in vacuo. The residue was redissolved in CHCl₃ resulting in precipitation of a solid that was removed by a 2nd filtration through Celite. Column chromatography of the resulting residue (DCM elution) gave the title compound as a yellow foam (449 mg, 1.02 mmol, 75%), [α]_D²⁰ +102 (c 1.21, CHCl₃); $\nu_{\text{max}}(\text{solid})/\text{cm}^{-1}$ 3289, 3053, 2933, 2835, 1776, 1682, 1602, 1510; δ_{H} (400 MHz; CDCl₃) 1.25 (d, J= 2.6 Hz, 1H), 3.28 (d, J= 12.2 Hz, 1H), 3.67 (d, J= 13.2 Hz, 1H), 3.70 (d, J= 12.3 Hz, 1H), 3.79 (d, J= 13.1 Hz, 1H), 3.82 (s, 3H), 4.74 (d, J= 2.6 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.23 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.29 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.36-7.45 (m, 4H), 7.48-7.51 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.57 (d, J= 8.2 Hz, 1H), 7.58 (d, J= 8.5 Hz, 1H), 7.92 (d, J= 8.5 Hz, 1H), 7.94 – 7.97 (m, 3H); HRMS (CI⁺): calc. for C₃₂H₂₆NO (MH⁺) 440.2009, found 440.2008

General procedure for functionalization of the terminal alkyne



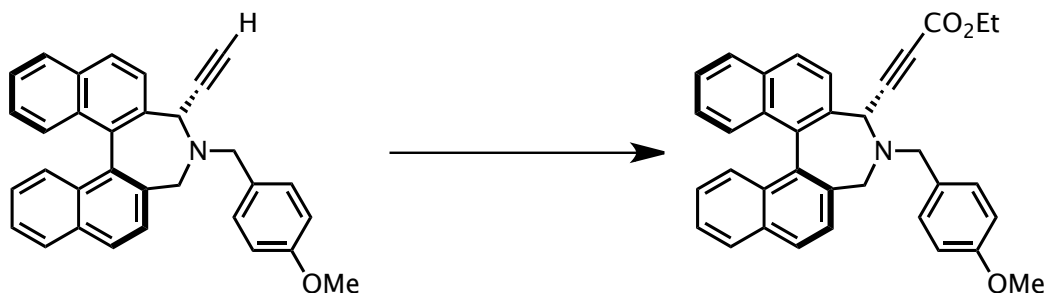
The terminal alkyne (1.0 eq.) was dissolved in dry THF (20 mL per gram of alkyne) and cooled to -78°C . $n\text{-BuLi}$ (1.5 eq. of a 2.5 M solution in hexane) was then added causing a colour change from yellow to dark blue. After stirring at -78°C for 1 hour, the required electrophile (1.5 eq.) was added in a single portion and the cooling bath was removed. The reaction mixture was then stirred until complete consumption of the starting material was seen by TLC (typically 1-2 hours). Et_2O and saturated NH_4Cl solution were added to quench the reaction. The organic phase was then separated and washed sequentially with water and brine. The solution was then dried (MgSO_4) and concentrated *in vacuo* to give the crude compound.

3-((3S,11cS)-4-(4-methoxybenzyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)propionic acid 295



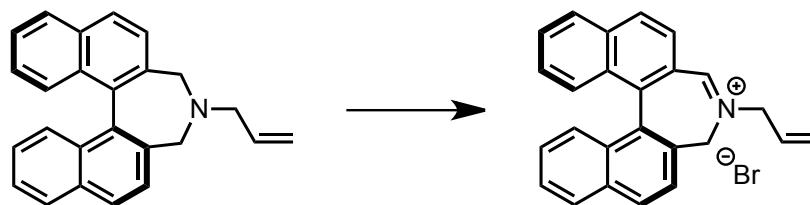
The terminal alkyne (400 mg, 0.82 mmol, 1.0 eq.) was dissolved in dry THF (12 mL) and cooled to -78 °C. n-BuLi (496 μ L of a 2.5 M solution in hexane, 1.24 mmol, 1.5 eq.) was then added causing a colour change from yellow to dark blue. The solution was allowed to reach room temperature for 1 hour. After cooling again to -78 °C, the cooling bath was removed and CO₂ gas was bubbled through the solution for 1h. Et₂O and saturated NH₄Cl solution were added to quench the reaction. The organic phase was then separated and washed sequentially with water and brine. The solution was then dried (MgSO₄) and concentrated *in vacuo* to give the crude compound. Recrystallization from hot EtOH gave the *title compound* as a pale brown powder (308 mg, 0.64 mmol, 70 %); ν_{max} (KBr) /cm⁻¹ 3054, 2987, 2685, 2411, 2305, 1655, 1512, 1441, 1422, 1264; δ_{H} (400 MHz; DMSO-d₆) 2.98 (d, *J* = 12.0 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.69 (d, *J* = 11.8 Hz, 1H), 3.74 (s, 3H), 4.97 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 7.15 – 7.28 (m, 2H), 7.32 – 7.35 (m, 3H), 7.38 – 7.43 (m, 2H), 7.52 – 7.59 (m, 3H), 7.95 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 12.28 (br s, 1H); δ_{C} (125 MHz; CDCl₃) 54.5, 55.4, 55.5, 57.9, 114.3, 125.9, 126.4, 126.7, 126.9, 127.1, 127.8, 128.2, 128.7, 128.9, 129.2, 129.6, 130.6, 130.7, 131.5, 131.9, 132.7, 133.4, 133.5, 134.7, 134.8, 135.0, 158.9; HRMS (CI⁺): calc. for C₃₃H₂₄NO₃ (MH⁺) 482.1762, found 482.1767.

Ethyl 3-((3*S*,11*cS*)-4-(4-methoxybenzyl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-3-yl)propiolate 294



Prepared according to the general route for functionalization of the terminal alkyne. The lithiated species was quenched with ethyl chloroformate (138 μ L, 1.38 mmol, 1.5 eq.) and stirred overnight. After normal work-up the crude material was purified by column chromatography (DCM eluent) to give the title compound as a yellow oil (392 mg, 0.16 mmol, 69 %); $[\alpha]_D^{20}$ +65 (c 0.92, CHCl_3); ν_{max} (solid) / cm^{-1} 3051, 2981, 2957, 2935, 2834, 2231, 1704; δ_{H} (500 MHz; CDCl_3) 0.95 (t, J = 7.1 Hz, 3H), 3.30 (d, J = 12.3 Hz, 1H), 3.62 – 3.70 (m, 2H), 3.70 (d, J = 13.7 Hz, 1H), 3.72 (d, J = 12.4 Hz, 1H), 3.81 (d, J = 13.3 Hz, 1H), 3.82 (d, J = 12.4 Hz, 1H), 3.83 (s, 3H), 4.77 (s, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.26 (ddd, J = 8.1, 6.7, 1.1 Hz, 1H), 7.31 (ddd, J = 8.1, 6.7, 1.1 Hz, 1H), 7.37-7.45 (m, 5H), 7.51 (ddd, J = 8.1, 6.7, 1.1 Hz, 1H), 7.61 (t, J = 8.3 Hz, 2H), 7.61 (t, J = 8.8 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.2 Hz, 1H); δ_{C} (125 MHz; CDCl_3) 13.79, 54.98, 55.31, 55.36, 57.82, 60.97, 75.03, 77.60, 86.37, 113.97, 125.44, 125.93, 126.14, 127.13, 127.32, 127.55, 127.79, 128.12, 128.25, 128.70, 129.35, 130.29, 130.39, 131.76, 132.15, 132.39, 133.43, 133.59, 134.57, 135.20, 135.33, 152.80, 159.01; HRMS (CI⁺): calc. for $\text{C}_{35}\text{H}_{30}\text{NO}_3$ (MH⁺) 512.2220, found 512.2217.

(S)-4-allyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate 268

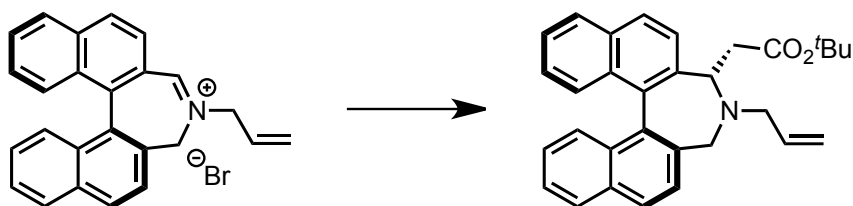


To a solution of 4-allyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (1.77 g, 5.28 mmol, 1.0 eq.) in DCM (200 mL) was added solid NBS (1.034 g, 5.81 mmol, 1.1 eq.) portionwise over 5 minutes so as not to increase the reaction temperature. After 2 h at room temperature (TLC indicated complete consumption of starting material) water (100 mL) was added. The organic phase was separated and washed with water (2 x 50 mL) and brine (50 mL) then dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a bright yellow foam (2.051 g, 4.95 mmol, 94%); ν_{max} (solid) /cm⁻¹ 3404, 3053, 2955, 2734, 2544, 2406, 1932, 1708, 1687, 1650, 1614, 1595, δ_{H} (500 MHz; CDCl₃) 4.55 (dd, 1H, *J* = 13.2, 1.3 Hz, ArCH₂N), 4.96 (dd, 1H, *J* = 13.3, 0.7 Hz), 5.22 (dd, 1H, *J* = 14.2, 7.4 Hz), 5.35 (dd, 1H, *J* = 14.3, 5.3 Hz), 5.59 (d, 1H, *J* = 10.4 Hz), 5.70 (d, 1H, *J* = 16.4 Hz), 5.90 – 5.93 (m, 1H), 7.06 (d, 1H, *J* = 10.0 Hz), 7.26 (ddd, 1H, *J* = 8.4, 6.8, 1.3 Hz), 7.37 (ddd, 1H, *J* = 8.5, 6.8, 1.3 Hz), 7.50 (d, 1H, *J* = 9.2 Hz), 7.53 (ddd, 1H, *J* = 8.0, 6.8, 1.0 Hz), 7.58 (d, 1H, *J* = 8.4 Hz), 7.71 (ddd, 1H, *J* = 8.1, 6.8, 1.1 Hz), 7.96 (d, 1H, *J* = 8.2 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 8.10 (d, 1H, *J* = 8.4 Hz), 8.16 (d, 1H, *J* = 8.5 Hz), 8.52 (d, 1H, *J* = 8.6 Hz), 10.90 (s, 1H),

The iminium bromide could be easily converted to the iminium tetraphenylborate by addition of a solution of sodium tetraphenylborate (1.1 eq.) in a minimum amount of acetonitrile to a stirred DCM solution of the iminium bromide. After 5 minutes, the reaction mixture was concentrated *in vacuo* and redissolved in chloroform. Insoluble impurities were removed by filtration through Celite. The filtrate was concentrated *in vacuo*, redissolved in acetone and once more filtered through Celite to remove residual sodium tetraphenylborate. The clear filtrate was concentrated *in vacuo* a final time and dried under high vacuum for several hours giving the title compound as a yellow foam (2.413 g, 3.696 mmol, 70 %).

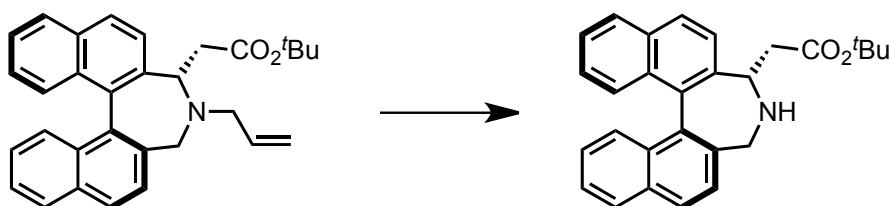
δ_{H} (500 MHz; acetone- d_6) 4.87 (d, 1H, $J = 13.5$ Hz), 5.02 (d, 2H, $J = 6.2$ Hz), 5.29 (d, 1H, $J = 13.5$ Hz), 5.63 (d, 1H, $J = 10.1$ Hz), 5.76 (d, 1H, $J = 17.1$ Hz), 6.03 – 6.09 (m, 1H), 6.74 (t, 4H, $J = 7.2$ Hz), 6.91 (t, 8H, $J = 7.4$ Hz), 7.08 (d, 1H, $J = 8.7$ Hz), 7.30 (ddd, 1H, $J = 8.3, 6.8, 1.3$ Hz), 7.31 (m, 8H), 7.50 (ddd, 1H, $J = 7.9, 6.6, 1.0$ Hz), 7.55 (d, 1H, $J = 8.4$ Hz), 7.58 (ddd, 1H, $J = 8.0, 6.9, 1.1$ Hz), 7.82 (ddd, 1H, $J = 8.1, 6.7, 1.2$ Hz), 7.88 (d, 1H, $J = 8.4$ Hz), 8.07 (d, 1H, $J = 8.8$ Hz), 8.10 (d, 1H, $J = 8.2$ Hz), 8.24 (d, 1H, $J = 8.2$ Hz), 8.27 (d, 1H, $J = 8.5$ Hz), 8.36 (d, 1H, $J = 8.6$ Hz), 9.47 (s, 1H).

***tert*-butyl 2-((3*S*,11*cS*)-4-allyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-3-yl)acetate 312**



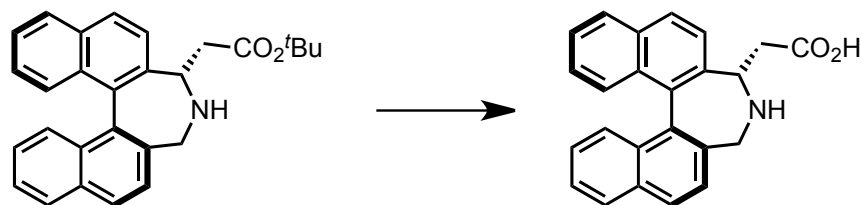
Zn powder (276 mg, 4.32 mmol, 6.0 eq.) was suspended in dry THF (20 mL) in a flame-dried 100 mL 3-necked round-bottomed flask. 1,2-Dibromoethane (60 μ L, 0.72 mmol, 1.0 eq.) and chlorotrimethylsilane (91 μ L, 0.72 mmol, 1.0 eq.) were then added and the reaction mixture was heated to reflux for 1 h. Whilst maintaining reflux, *t*-butyl bromoacetate (529 μ L, 3.60 mmol, 5.0 eq.) was then added in portions over 5 minutes. Reflux was maintained for a further hour, giving rise to a pale yellow solution. In a separate dry flask, (*S*)-4-allyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (0.72 mmol) was suspended in dry toluene (20 mL) and cooled to -78 $^{\circ}$ C. The Reformatsky reagent was cooled to room temperature and then added to the iminium salt solution in a single portion *via* syringe. The mixture was allowed to reach room temperature and stirred overnight before being quenched with water. DCM (50 mL) was added. The organic phase was separated and washed with water (2 x 50 mL) and brine (50 mL) then dried (MgSO_4) and concentrated *in vacuo* to give a pale yellow oil. Column chromatography (9:1 petrol : EtOAc) yielded the *title compound* as a colourless foam (183 mg, 0.41 mmol, 57%); $[\alpha]_D^{20} +188$ (c 0.85, CHCl_3); ν_{max} (solid) / cm^{-1} 3051, 3005, 2977, 2933, 2807, 1724; δ_{H} (500 MHz; CDCl_3) 1.16 (s, 9H, *t*Bu), 1.51 (dd, 1H, $J = 15.1, 7.1$ Hz), 1.73 (dd, 1H, $J = 15.1, 7.1$ Hz), 3.09 (d, 1H, $J = 11$ Hz), 3.24 – 3.33 (m, 2H), 3.71 (d, 1H, $J = 11$ Hz), 4.42 (t, 1H, $J = 8.0$ Hz), 5.19 (dd, 1H, $J = 10.0, 1.5$ Hz), 5.25 (dd, 1H, $J = 10.0, 1.5$ Hz), 5.93 – 5.99 (m, 1H), 7.24 – 7.27 (m, 2H), 7.37 (d, 1H, $J = 8.5$ Hz), 7.43 – 7.48 (m, 4H), 7.63 (d, 1H, $J = 8.5$ Hz), 7.93 – 7.97 (m, 4H); δ_{C} (125 MHz; CDCl_3) 28.0, 42.6, 56.1, 61.4, 64.11, 79.8, 117.8, 125.5, 125.6, 125.7, 125.8, 127.4, 127.6, 128.0, 128.1, 128.2, 128.3, 129.0, 129.9, 131.8, 131.9, 133.0, 133.2, 133.5, 135.1, 135.2, 135.4, 136.2, 171.3; HRMS (CI⁺): calc. for $\text{C}_{31}\text{H}_{31}\text{NO}_2$ (MH⁺) 450.2428, found 450.2424.

***tert*-butyl 2-((3*S*,11*cS*)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-3-yl)acetate 313**



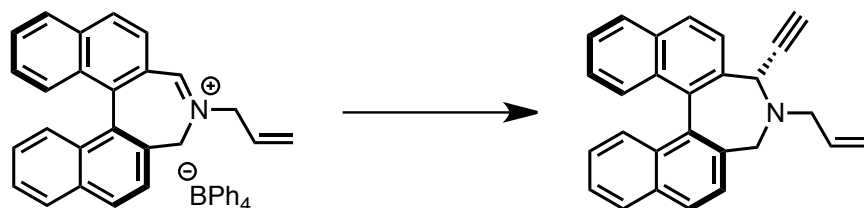
tert-Butyl 2-((3*S*,11*cS*)-4-allyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-3-yl)acetate (178 mg, 0.40 mmol, 1.0 eq.) and *N,N*'-dimethylbarbituric acid (187 mg, 1.2 mmol, 3.0 eq.) were dissolved in dry DCM (10 mL) and stirred under N₂. Pd(PPh₃)₄ (9.2 mg, 0.008 mmol, 0.02 eq.) was added as a solid and the resulting orange mixture was stirred at 35 °C for 16 h. Further Pd(PPh₃)₄ (9.2 mg, 0.008 mmol, 0.02 eq.) was added and the reaction was heated for a further 1 h (50 °C external temperature). TLC indicated complete consumption of starting material at this point. The reaction mixture was extracted with saturated NaHCO₃ solution (3 x 10 mL) and the combined aqueous phases were re-extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil. Column chromatography (EtOAc eluent) removed a strongly coloured impurity and yielded the *title compound* as a pale brown foam (154 mg, 0.38 mmol, 95%); [α]_D²⁰ +299 (c 1.27, CHCl₃); ν_{max}(solid) /cm⁻¹ 3337, 3050, 3004, 2977, 2930, 1912, 1720; δ_H (500 MHz; CDCl₃) 1.18 (s, 9H), 1.73 (qd, 2H, J = 15.8, 7.6 Hz), 2.35 (br s, 1H), 3.71 (d, 1H, J = 12.1 Hz), 3.79 (d, 1H, J = 12.1 Hz), 4.62 (t, 1H, J = 7.6 Hz), 7.23 (ddd, 1H, J = 8.0, 6.7, 1.3 Hz), 7.24 – 7.26 (m, 1H), 7.34 (d, 1H, J = 8.2 Hz), 7.40 (d, 1H, J = 8.4 Hz), 7.44 – 7.48 (m, 2H), 7.52 (d, J = 8.4 Hz), 7.58 (d, J = 8.2 Hz), 7.94 (t, 3H, J = 7.2 Hz), 7.97 (d, 1H, J = 8.3 Hz); δ_C (125 MHz; CDCl₃) 28.0, 43.0, 48.8, 59.1, 80.2, 125.5, 125.6, 125.7, 125.9, 127.0, 127.4, 127.5, 128.1, 128.3, 128.8, 129.1, 129.3, 132.1, 133.1, 133.2, 133.8, 135.0, 136.7, 137.4, 171.4; HRMS (CI⁺): calc. for C₂₈H₂₇NO₂ (MH⁺) 410.2115, found 410.2114.

2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetic acid 311



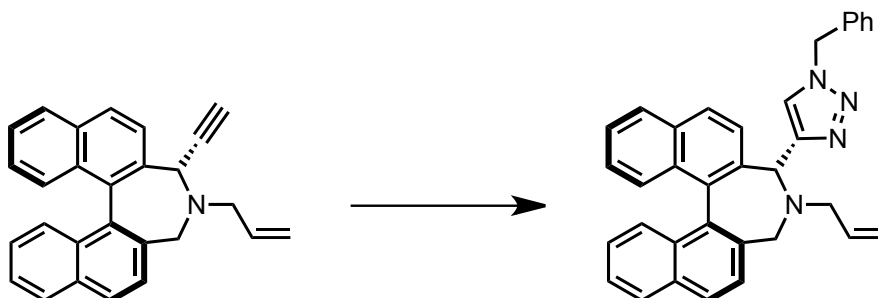
tert-Butyl 2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)acetate (150 mg, 0.37 mmol, 1.0 eq.) was dissolved in DCM (10 mL) and stirred under N₂ atmosphere. Et₃SiH (177 μ L, 1.11 mmol, 3.0 eq.) and TFA (1 mL) were added *via* syringe and the clear solution was stirred overnight. The mixture was filtered through Celite and concentrated *in vacuo*. The reaction mixture was azeotroped with CHCl₃ (3 x 10 mL) and toluene (3 x 10 mL) to remove volatile impurities. The colourless oil was dissolved in a minimum amount of DCM and petrol was added resulting in precipitation of the *title compound* as a colourless solid. Repetition of this step resulted in a second crop of similar purity (total 108 mg, 0.31 mmol, 83%); m.p. 228 – 230 °C (dec.); $[\alpha]_D^{20}$ +211 (c 0.91, CHCl₃); ν_{\max} (solid) /cm⁻¹ 3399, 3053, 2961, 2628, 1596; δ_H (500 MHz; CDCl₃) 1.63 (dd, 1H, J = 16.7, 12.5 Hz), 2.10 (dd, 1H, J = 16.8, 2.7 Hz), 3.85 (d, 1H, J = 12.9 Hz), 4.28 (d, 1H, J = 12.9 Hz), 5.33 (d, 1H, J = 11.4 Hz), 7.22 (ddd, 1H, J = 8.0, 6.7, 1.0 Hz), 7.26 – 7.33 (m, 3H), 7.40 (d, 1H, J = 8.4 Hz), 7.46 (ddd, 1H, J = 7.7, 6.6, 0.8 Hz), 7.53 (t, 1H, J = 7.4 Hz), 7.72 (d, 1H, J = 8.3 Hz), 7.79 (d, 1H, J = 8.4 Hz), 7.90 (d, 1H, J = 8.3 Hz), 7.95 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 8.2 Hz); δ_C (125 MHz; DMSO-d₆) 38.2, 46.8, 57.1, 126.5, 126.6, 126.8, 126.88, 126.91, 128.0, 128.8, 129.1, 129.3, 129.6, 129.7, 131.7, 131.8, 133.2, 133.3, 133.4, 134.3, 135.2, 136.5, 173.1; HRMS (CI⁺): calc. for C₂₄H₂₀NO₂ (MH⁺) 354.1489, found 354.1487.

(3*S*,11*cS*)-4-allyl-3-ethynyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine 284



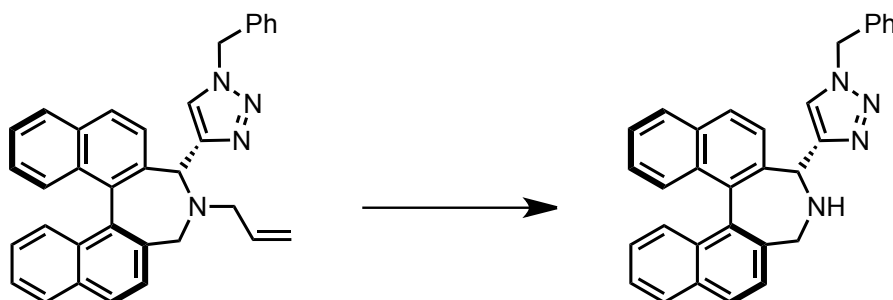
A stirred solution of (*S*)-4-allyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (1.00 g, 2.41 mmol, 1.0 eq.) in dry THF (20 mL) was cooled to -78 °C. Ethynylmagnesium bromide (0.5 M in THF, 48.2 mL, 24.1 mmol, 10 eq.) was then added over 10 minutes. The cooling bath was removed and the reaction was stirred at room temperature overnight. Saturated aqueous NH₄Cl solution was added. The quenched reaction mixture was extracted repeatedly with DCM. The combined organic phases were combined, washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude product as a brown foam. Column chromatography of the residue (6:1 petrol:EtOAc) yielded the *title compound* as a yellow foam (648 mg, 1.81 mmol, 75%); [α]_D²⁰ +252 (c 0.98, CHCl₃); ν_{max} (solid) /cm⁻¹ 3297, 3050, 2962, 2932, 2875, 2816, 2303, 2114, 1910, 1843, 1675; δ_{H} (500 MHz; CDCl₃) 1.27 (d, 1H, *J* = 2.6 Hz), 3.18 (d, 1H, *J* = 12.0 Hz), 3.20 (dd, 1H, *J* = 14.0, 7.2 Hz), 3.31 (dd, 1H, *J* = 14.0, 7.2 Hz), 3.76 (d, 1H, *J* = 12.0 Hz), 4.86 (d, 1H, *J* = 2.5 Hz), 5.27 (d, 1H, *J* = 10.2 Hz), 5.35 (dd, 1H, *J* = 16.5, 0.7 Hz), 6.00 – 6.08 (m, 1H), 7.25 (ddd, 1H, *J* = 8.2, 6.6, 1.4 Hz), 7.30 (ddd, 1H, *J* = 8.3, 6.8, 1.3 Hz), 7.41 – 7.45 (m, 3H), 7.50 (ddd, 1H, *J* = 8.0, 6.8, 1.1 Hz), 7.58 (d, 1H, *J* = 8.6 Hz), 7.59 (d, 1H, *J* = 8.3 Hz), 7.92 (d, 1H, *J* = 8.2 Hz), 7.96 (t, 2H, *J* = 7.9 Hz), 7.97 (d, 1H, *J* = 8.3 Hz); δ_{C} (125 MHz; CDCl₃) 55.0, 55.4, 58.1, 70.5, 81.9, 118.8, 125.3, 125.8, 125.98, 126.02, 127.4, 127.47, 127.53, 127.8, 128.2, 128.2, 128.6, 128.8, 131.8, 132.3, 132.7, 133.29, 133.33, 134.6, 134.8, 135.7, 135.9; HRMS (CI⁺): calc. for C₂₇H₂₂N (MH⁺) 360.1747, found 360.1750.

(3*R*,11*cS*)-4-allyl-3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine 336



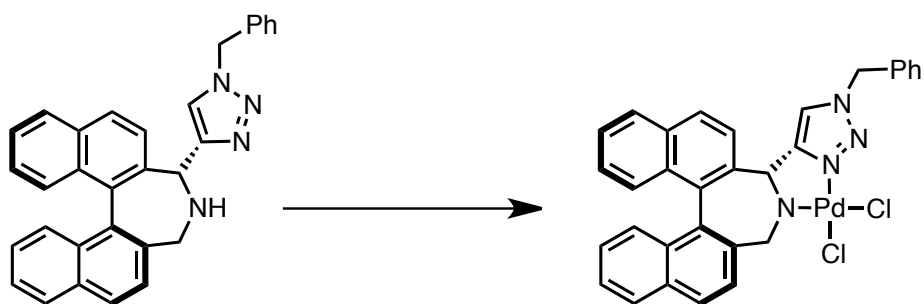
(3*S*,11*cS*)-4-allyl-3-ethynyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (860 mg, 1.96 mmol, 1.0 eq.) and benzyl azide (384 mg, 2.35 mmol, 1.2 eq.) were dissolved in THF (10 mL). With stirring, a solution of sodium ascorbate (40 mg, 0.4 mmol, 0.2 eq.) in distilled water (5 mL) was added followed by a solution of CuSO₄·5H₂O (50 mg, 0.2 mmol, 0.1 eq.) in distilled water (5 mL). The reaction mixture was warmed to 50 °C and stirred for 3 h (TLC showed complete consumption of starting material). DCM (50 mL) was added and 1M NH₄OH (10 mL) was added to destroy any residual Cu complexes present in the reaction mixture. The yellow organic phase was separated, washed with water and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (2:1:0.02 petrol:EtOAc:Et₃N) which gave the title compound as a colourless foam (782 mg, 1.59 mmol, 81%); $[\alpha]_D^{20} +84$ (c 1.06, CHCl₃); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3152, 3050, 2935, 2810, 1771, 1720, 1668; δ_{H} (500 MHz; CDCl₃) 3.13 (d, 1H, *J* = 10.9 Hz), 3.24 (dd, 1H, *J* = 13.9, 7.7 Hz), 3.37 (dd, 1H, *J* = 13.9, 5.1 Hz), 3.76 (d, 1H, *J* = 10.9 Hz), 4.66 (d, 2H, *J* = 2.5 Hz), 5.21 (d, 1H, *J* = 9.7 Hz), 5.28 (s, 1H), 5.34 (dq, 1H, *J* = 17.1, 1.5 Hz), 5.94 – 6.02 (m, 1H), 6.19 (s, 1H), 6.78 – 6.80 (m, 2H), 7.14 – 7.17 (m, 1H), 7.20 – 7.24 (m, 2H), 7.28 – 7.32 (m, 3H), 7.35 – 7.39 (m, 2H), 7.44 (d, 1H, *J* = 8.3 Hz), 7.46 (ddd, 1H, *J* = 8.0, 6.7, 1.1 Hz), 7.60 (d, 1H, *J* = 8.3 Hz), 7.65 (d, 1H, *J* = 8.3 Hz), 7.74 (d, 1H, *J* = 8.2 Hz), 7.97 (d, 1H, *J* = 8.2 Hz), 8.03 (d, 1H, *J* = 8.2 Hz), δ_{C} (125 MHz; CDCl₃) 53.1, 56.5, 60.1, 62.2, 118.3, 120.1, 125.5, 125.7, 125.78, 125.80, 127.1, 127.46, 127.48, 127.6, 128.17, 128.23, 128.3, 128.7, 128.8, 129.2, 131.4, 132.0, 132.5, 133.3, 134.0, 134.3, 134.7, 134.9, 135.8, 136.1, 152.2; HRMS (CI⁺): calc. for C₃₄H₂₉N₄ (MH⁺) 493.2387, found 493.2374

(3*R*,11*cS*)-3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine 337



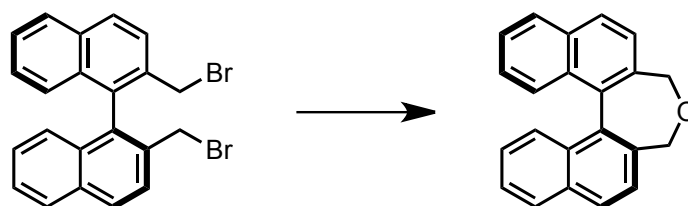
(3*R*,11*cS*)-4-allyl-3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (665 mg, 1.35 mmol, 1.0 eq) was dissolved in dry DCM (10 mL) and stirred under N₂. NDMBA (631 mg, 4.05 mmol, 3.0 eq.) and Pd(PPh₃)₄ (31 mg, 0.027 mmol, 0.02 eq.) were then added sequentially. The resulting orange solution was heated to reflux for 3 h (TLC indicated complete consumption of starting material). The reaction mixture was cooled then washed with 1M NaOH, water and brine before being dried (MgSO₄), filtered and concentrated *in vacuo* to give an orange oil. Column chromatography of the crude product (EtOAc) yielded the title compound as a colourless foam (579 mg, 1.28 mmol, 95%); δ_{H} (500 MHz; CDCl₃) 2.74 (br s, 1H, NH), 3.74 (d, 1H, *J* = 12.6 Hz, Ar-CH₂-N), 3.87 (d, 1H, *J* = 12.6 Hz, Ar-CH₂-N), 4.39 (d, 1H, *J* = 14.7 Hz, N-CH₂-Ph), 4.70 (d, 1H, *J* = 14.7 Hz, N-CH₂-Ph), 5.47 (s, 1H, Ar-CH-triazole), 6.06 (s, 1H (triazole CH)), 6.76 (dd, 2H, *J* = 1.4, 7.9 Hz, ArH), 7.15 (d, 1H, *J* = 8.0 Hz, ArH), 7.18 (dd, 1H, *J* = 1.2, 6.5 Hz, ArH), 7.20 – 7.25 (m, 4H, ArH), 7.36 (d, 1H, *J* = 8.5 Hz, ArH), 7.38 (ddd, 1H, *J* = 1.4, 6.4, 8.0 Hz, ArH), 7.46 (d, 1H, *J* = 8.4 Hz, ArH), 7.47 (ddd, 1H, *J* = 1.1, 6.7, 8.0 Hz, ArH), 7.70 (d, 1H, *J* = 8.3 Hz, ArH), 7.74 (d, 1H, *J* = 8.3 Hz, ArH), 7.80 (d, 1H, *J* = 8.2 Hz, ArH), 7.96 (d, 1H, *J* = 8.2 Hz, ArH), 8.02 (d, 1H, *J* = 8.2 Hz, ArH); δ_{C} (125 MHz; CDCl₃) 48.6, 53.1, 57.7, 119.1, 125.2, 125.8, 125.9, 126.9, 127.1, 128.1, 128.2, 128.4, 128.6, 128.8, 129.2, 131.5, 132.1, 133.4, 134.1, 134.6, 134.8, 136.7, 136.8, 136.9, 151.8; HRMS (CI⁺): calc. for C₃₁H₂₅N₄ (MH⁺) 453.2074, found 453.2081.

Palladium Complex 342



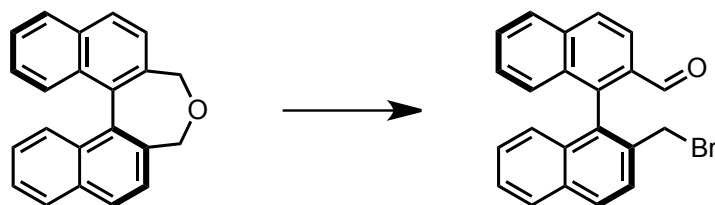
(3*R*,11*cS*)-3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (250 mg, 0.55 mmol, 1.0 eq.) was dissolved in dry DCM (5 mL) and stirred under nitrogen. Dichloro(1,5-cyclooctadiene)palladium(II) (158 mg, 0.55 mmol, 1.0 eq.) was then added as a solid in a single portion and the resulting solution was stirred at room temperature for 1 hour. Most of the DCM was removed in vacuo, petroleum ether was added and the *title compound* precipitated as a pale yellow powder (242 mg, 0.385 mmol, 70%); δ_{H} (500 MHz; CDCl_3) 3.56 (dd, 1H, $J = 12.7, 4.1$ Hz), 4.12 (d, 1H, $J = 14.7$ Hz), 4.64 (d, 1H, $J = 12.4$ Hz), 4.96 (d, 1H, $J = 14.7$ Hz), 6.13 (d, 1H, $J = 0.8$ Hz), 6.69 – 6.71 (m, 2H), 6.85 (d, 1H, $J = 6.5$ Hz), 7.17 (d, 1H, $J = 8.8$ Hz), 7.19 – 7.22 (m, 2H), 7.25 – 7.29 (m, 2H), 7.37 (d, 1H, $J = 9.2$ Hz), 7.49 – 7.54 (m, 2H), 7.60 (br t, 1H, $J = 4.9$ Hz), 7.89 (d, 1H, $J = 8.1$ Hz), 7.97 (d, 1H, $J = 8.2$ Hz), 8.06 (d, 2H, $J = 8.3$ Hz), 8.15 (d, 1H, $J = 8.5$ Hz), 8.58 (d, 1H, $J = 8.3$ Hz).

(S)-3,5-dihydrodinaphtho[2,1-c:1',2'-e]oxepine 269²³³



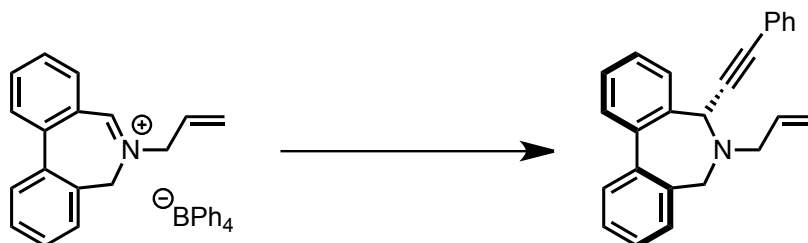
(S)-2,2'-Bis(bromomethyl)-1,1'-binaphthalene (2.20 g, 5.0 mmol, 1.0 eq.) was dissolved in 1,4-dioxane (60 mL) and saturated Na₂CO₃ solution (60 mL) was added. The mixture was heated to reflux for 24 hours (TLC indicated consumption of starting material). The reaction mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed with brine (50 mL) then dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil. Column chromatography (50:1 petrol:EtOAc) yielded the title compound as a colourless solid (947 mg, 3.2 mmol, 64%); m.p 184-186 °C (lit. 184-186 °C¹⁷³); [α]_D²⁰ +571 (c 1.00, CHCl₃) (lit. +571 (c 1.00, CHCl₃)¹⁷³); ν_{max} (solid) /cm⁻¹ 3049, 2959, 2923, 1594, 1507, 1463, 1367, 1237, 1195, 1057, 909, 828; δ_{H} (500 MHz; CDCl₃) 4.20 (d, 2H, J = 11.3 Hz, ArCH₂O), 4.64 (d, 2H, J = 11.3 Hz, ArCH₂O), 7.29 (t, 2H, J = 7.7 Hz, ArH), 7.50 (t, 2H, J = 7.5 Hz, ArH), 7.53 (d, 2H, J = 8.6 Hz, ArH), 7.62 (d, 2H, J = 8.2 Hz, ArH), 7.97 (d, 2H, J = 8.2 Hz, ArH), 8.00 (d, 2H, J = 8.2 Hz, ArH); δ_{C} (125 MHz; CDCl₃) 67.5, 125.95, 125.98, 127.4, 127.6, 128.4, 129.2, 131.2, 133.56, 133.64, 135.5.

(S)-2'-(bromomethyl)-[1,1'-binaphthalene]-2-carbaldehyde 270²³³



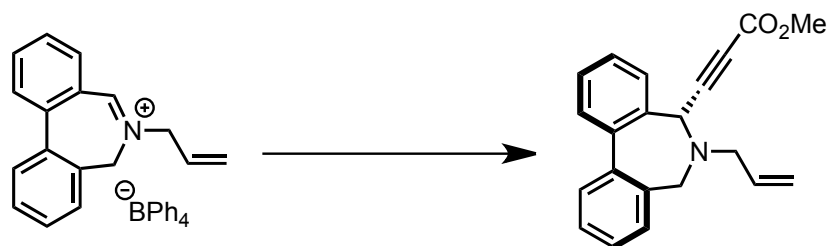
(S)-3,5-dihydrodinaphtho[2,1-c:1',2'-e]oxepine (800 mg, 2.70 mmol, 1.0 eq.) was dissolved in warm cyclohexane (30 mL). Bromine (1.1 eq.) dissolved in cyclohexane (10 mL) was then added slowly. The reaction mixture was heated to reflux until the colour of the bromine had dissipated (approximately 1 h). The solvent was removed *in vacuo* and the residue was redissolved in diethyl ether (20 mL) which was subsequently washed with saturated aqueous sodium bicarbonate, water and brine. The combined organic phases were dried (MgSO₄), filtered and concentrated in *vacuo* to give the crude product as a yellow oil. Column chromatography (99:1 petrol:EtOAc) yielded the title compound as a colourless solid (531 mg, 1.42 mmol, 53%); m.p 152-154 °C (lit. 150-152 °C¹⁷³) ; $[\alpha]_D^{20}$ -143 (c 1.00, CHCl₃) (lit. -143 (c 1.00, CHCl₃¹⁷³); ν_{\max} (solid) /cm⁻¹ 3057, 2845, 2357, 1688, 1616, 1593, 1509, 1429, 1324, 1240, 1223, 1027, 909, 870, 821, 750, 730; δ_H (500 MHz; CDCl₃) 4.09 (dd, 1H, J = 10.1, 1.0 Hz), 4.34 (dd, 1H, J = 10.1, 1.0 Hz), 7.02 (d, 1H, J = 8.5 Hz, ArH), 7.24 (d, 1H, J = 8.5 Hz, ArH), 7.29 (ddt, 1H, J = 8.2, 6.8, 1.3 Hz, ArH), 7.35 (ddt, 1H, J = 8.2, 6.8, 1.3 Hz, ArH), 7.51 (ddt, 1H, J = 8.2, 6.8, 1.3 Hz, ArH), 7.63 (ddt, 1H, J = 8.2, 6.8, 1.3 Hz, ArH), 7.73 (dd, 1H, J = 8.5, 1.0 Hz, ArH), 7.95 (d, 1H, J = 1H, J = 8.2 Hz, ArH), 7.99 (d, 1H, J = 8.6 Hz, ArH), 8.05 (d, 1H, J = 8.6 Hz, ArH), 8.09 (d, 1H, J = 8.7 Hz, ArH), 8.22 (dd, 1H, J = 8.7, 1.2 Hz, ArH), 9.56 (s, 1H, ArCHO), δ_C (125 MHz; CDCl₃) 32.0, 122.4, 126.6, 127.0, 127.1, 127.42, 127.43, 127.44, 128.2, 128.5, 129.3, 129.4, 129.9, 132.40, 132.42, 132.5, 133.0, 133.6, 134.6, 134.6, 134.6, 136.3, 141.7, 191.9.

***rac*-6-allyl-5-(phenylethynyl)-6,7-dihydro-5*H*-dibenzo[*c,e*]azepine 304**



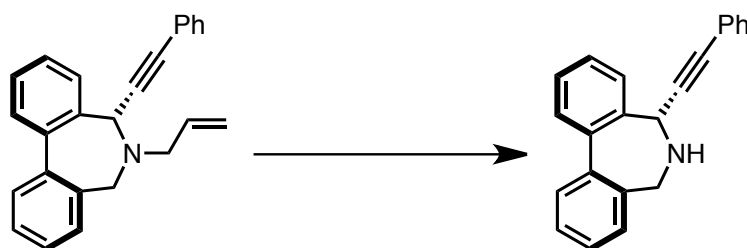
To a stirred solution of 6-allyl-5*H*-dibenzo[*c,e*]azepin-6-ium tetraphenylborate (250 mg, 0.45 mmol, 1.0 eq.) in MeCN (10 mL) was added CuI (8.5 mg, 0.045 mmol, 0.1 eq.), phenylacetylene (148 μ L, 1.35 mmol, 3.0 eq.) and Hünig's base (126 μ L, 0.675 mmol, 1.5 eq.). The cloudy yellow reaction mixture was stirred for 16 h at room temperature (TLC indicated consumption of starting material). The MeCN was removed in vacuo and the resulting residue was partitioned between DCM and water. The organic phase was separated then washed sequentially with water and brine before being dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude product as an orange oil. Column chromatography (25:1 petrol:EtOAc) yielded the *title compound* as a pale yellow oil (120 mg, 0.36 mmol, 80%); ν_{max} (KBr) /cm^{−1} 3054, 2986, 2685, 2410, 2305, 1598, 1442, 1421, 1265; δ_{H} (500 MHz; CDCl₃) 3.35 (d, 1H, *J* = 13.0 Hz), 3.41 (dd, 1H, *J* = 13.4, 7.7 Hz), 3.61 (dd, 1H, *J* = 13.3, 5.7 Hz), 3.71 (d, 1H, *J* = 13.0 Hz), 4.40 (s, 1H), 5.28 (d, 1H, *J* = 10.2 Hz), 5.35 (dd, 1H, *J* = 17.0, 1.4 Hz), 6.04 – 6.12 (m, 1H), 7.28–7.29 (m, 3H), 7.33 (d, 1H, *J* = 7.4 Hz), 7.37–7.42 (m, 3H), 7.44–7.49 (m, 4H), 7.55 (dd, 1H, *J* = 7.4, 1.1 Hz), 7.93 (d, 1H, *J* = 7.0 Hz); δ_{C} (125 MHz; CDCl₃) 52.6, 56.0, 56.3, 87.7, 118.4, 123.0, 127.6, 127.9, 128.0, 128.17, 128.19, 128.3, 128.5, 128.6, 129.6, 129.8, 131.8, 133.4, 134.6, 136.4, 140.4, 140.7; HRMS (CI⁺): calc. for C₂₅H₂₂N (MH⁺) 336.1747, found 336.1749.

***rac*-Methyl 3-(6-allyl-6,7-dihydro-5*H*-dibenzo[*c,e*]azepin-5-yl)propiolate**



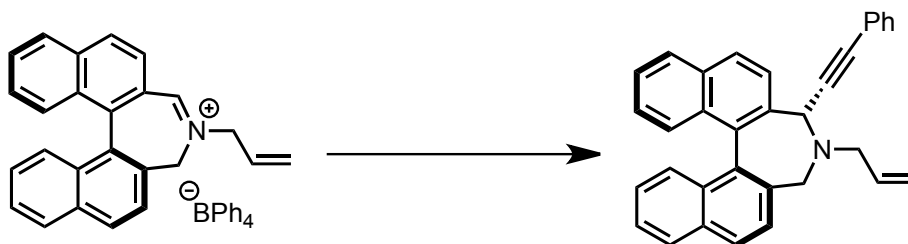
To a stirred solution of 6-allyl-5*H*-dibenzo[*c,e*]azepin-6-ium tetraphenylborate (250 mg, 0.45 mmol, 1.0 eq.) in MeCN (10 mL) was added CuI (8.5 mg, 0.045 mmol, 0.1 eq.), methyl propiolate (48 μ L, 0.54 mmol, 1.2 eq.) and Hünig's base (126 μ L, 0.675 mmol, 1.5 eq.). The orange reaction mixture was stirred for 16 h at room temperature (TLC indicated consumption of starting material). The MeCN was removed *in vacuo* and the resulting residue was partitioned between DCM and water. The organic phase was separated then washed sequentially with water and brine before being dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude product as an orange oil. Column chromatography (25:1 petrol:EtOAc \rightarrow 15:1) yielded the *title compound* as a pale yellow oil (112 mg, 0.353 mmol, 79%); ν_{max} (KBr) /cm^{−1} 3054, 2986, 2955, 2305, 2239, 1714, 1451, 1435, 1435, 1265; δ_{H} (500 MHz; CDCl₃) 3.30 (dd, 1H, *J* = 13.3, 6.0 Hz), 3.34 (d, 1H, *J* = 13.0 Hz), 3.46 (dd, 1H, *J* = 13.5, 5.8 Hz), 3.60 (d, 1H, *J* = 13.7 Hz), 3.72 (s, 3H), 4.33 (s, 1H), 5.28 (dd, 1H, *J* = 9.9, 1.4 Hz), 5.35 (dq, 1H, *J* = 17.1, 1.7 Hz), 5.96–6.04 (m, 1H), 7.30 (d, 1H, *J* = 7.4 Hz), 7.39 (dt, 1H, *J* = 7.4, 1.5 Hz), 7.42 – 7.48 (m, 4H), 7.50 (dt, 1H, *J* = 8.1, 1.3 Hz), 7.70 (d, 1H, *J* = 8.0 Hz); δ_{C} (125 MHz; CDCl₃) 52.6, 52.7, 55.8, 56.2, 86.5, 118.7, 127.7, 128.0, 128.17, 128.21, 128.49, 128.53, 129.0, 129.8, 132.8, 133.3, 135.8, 140.3, 153.8; HRMS (CI⁺): calc. for C₂₁H₂₀NO₂ (MH⁺) 318.1489, found 318.1491.

***rac*-5-(phenylethynyl)-6,7-dihydro-5*H*-dibenzo[*c,e*]azepine 305**



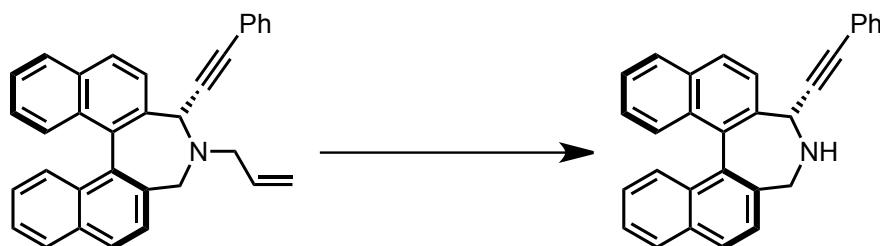
To a stirred solution of *rac*-6-allyl-5-(phenylethynyl)-6,7-dihydro-5*H*-dibenzo[*c,e*]azepine (100 mg, 0.30 mmol, 1.0 eq.) in dry DCM (10 mL) was added NDMBA (140 mg, 0.90 mmol, 3.0 eq.) and Pd(PPh₃)₄ (7 mg, 0.006 mmol, 0.02 eq.). The orange reaction mixture was heated to reflux for 2 hours (TLC indicated complete consumption of starting material). The reaction mixture was transferred to a separatory funnel and extracted sequentially with 1M NaOH, water, and brine. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to give the crude product as a dark orange oil. Column chromatography (3:1 petrol:EtOAc → 1:1) yielded the title compound as an orange oil (72 mg, 0.244 mmol, 81%); δ_{H} (500 MHz; CDCl₃) 3.50 (br s, 1H), 3.57 (d, 1H, *J* = 12.7 Hz), 3.80 (d, 1H, *J* = 12.7 Hz), 4.77 (s, 1H), 7.29-7.31 (m, 3H), 7.38-7.42 (m, 4H), 7.45-7.51 (m, 5H), 7.92-7.94 (m, 1H); HRMS (CI⁺): calc. for C₂₂H₁₆N (MH⁺) 296.1434, found 296.1436

(3*S*,11*cS*)-4-allyl-3-(phenylethynyl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine 287



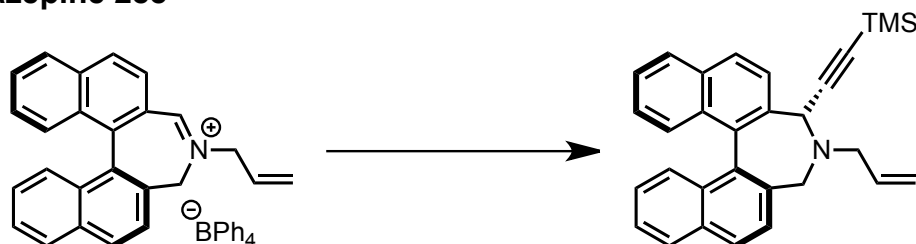
To a stirred solution of (*S*)-4-allyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (1.0 g, 1.53 mmol, 1.0 eq.) in MeCN (20 mL) was added CuI (29 mg, 0.15 mmol, 0.1 eq.), phenylacetylene (503 μ L, 4.59 mmol, 3.0 eq.) and Hünig's base (860 μ L, 4.59 mmol, 3.0 eq.). The cloudy reaction mixture was stirred overnight at room temperature (TLC indicated complete consumption of starting material). The reaction was concentrated in vacuo and the residue was dissolved in DCM. The organic phase was washed sequentially with water and brine before being dried (MgSO_4), filtered and concentrated in vacuo to give the crude product as an orange oil. Column chromatography (8:1 petrol:EtOAc) gave the *title compound* as a pale brown foam (492 mg, 1.13 mmol, 74%); $[\alpha]_{\text{D}}^{20} +126$ (c 1.11, CHCl_3); $\nu_{\text{max}}(\text{solid})/\text{cm}^{-1}$ 3055, 3010, 2927, 1686, 1594; ; δ_{H} (500 MHz; CDCl_3) 3.26 (dd, 1H, $J = 13.5, 7.8$ Hz), 3.27 (d, 1H, $J = 12.0$ Hz), 3.39 (ddt, 1H, $J = 13.4, 5.5, 1.4$ Hz), 3.80 (d, 1H, $J = 12.0$ Hz), 5.09 (s, 1H), 5.30 (d, 1H, $J = 9.8$ Hz), 5.38 (dq, 1H, $J = 17.1, 1.5$ Hz), 6.03 – 6.05 (m, 2H), 6.06 – 6.14 (m, 1H), 6.83 – 6.86 (m, 2H), 6.97 (ddt, 1H, $J = 8.7, 7.0, 1.3$ Hz), 7.27 (ddd, 1H, $J = 8.2, 6.8, 1.3$ Hz), 7.45 (ddd, 1H, $J = 8.3, 6.8, 1.3$ Hz), 7.48 – 7.52 (m, 3H), 7.61 (d, 1H, $J = 8.3$ Hz), 7.62 (d, 1H, $J = 8.5$ Hz), 7.89 (d, 2H, $J = 8.2$ Hz), 7.98 (t, 2H, $J = 8.0$ Hz); δ_{C} (125 MHz; CDCl_3) 55.1, 56.3, 58.1, 83.2, 118.8, 122.8, 125.4, 125.9, 125.93, 126.0, 127.0, 127.5, 127.6, 127.7, 127.9, 128.3, 128.4, 128.7, 128.9, 129.6, 131.3, 131.9, 132.4, 133.3, 133.6, 133.7, 134.6, 134.7, 134.8, 135.7, 136.1; HRMS (CI⁺): calc. for $\text{C}_{33}\text{H}_{26}\text{N}$ (MH^+) 436.2060, found 436.2061.

(3*S*,11*cS*)-3-(phenylethynyl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine 296



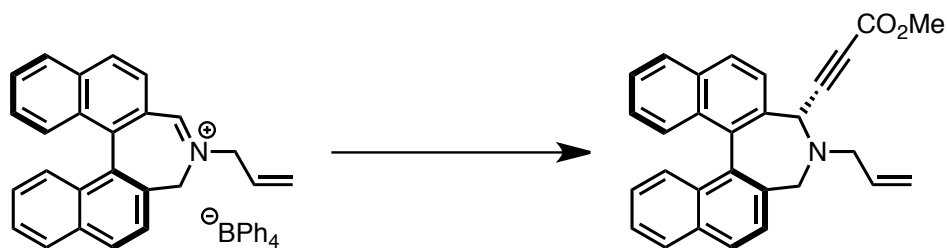
To a stirred solution of (3*S*,11*cS*)-4-allyl-3-(phenylethynyl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (164 mg, 0.37 mmol, 1.0 eq.) in dry DCM was added NDMBA (173 mg, 1.11 mmol, 3.0 eq.) and Pd(PPh₃)₄ (8.5 mg, 0.007 mmol, 0.02 eq.). The orange solution was refluxed for 3 hours (TLC indicated complete consumption of starting material). The reaction mixture was transferred to a separatory funnel and extracted sequentially with 1M NaOH, water, and brine. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to give the crude product as a dark orange oil. Column chromatography (3:1 petrol:EtOAc → 0:1) yielded the title compound as an orange oil (134 mg, 0.34 mmol, 92%); [α]_D²⁰ +204 (c 1.00, CHCl₃); ν_{max} (solid) /cm⁻¹ 3054, 2925, 2851, 1686, 1594; δ_{H} (500 MHz; CDCl₃) 3.69 (d, 1H, *J* = 13.0 Hz), 3.87 (d, 1H, *J* = 13.0 Hz), 5.24 (s, 1H), 6.03 – 6.05 (m, 2H), 6.84 – 6.87 (m, 2H), 6.98 (ddt, 1H, *J* = 8.8, 7.1, 1.3 Hz), 7.26 (ddd, 1H, *J* = 8.3, 6.7, 1.3 Hz), 7.30 (ddd, 1H, *J* = 8.3, 6.7, 1.3 Hz), 7.44 – 7.51 (m, 3H), 7.54 – 7.58 (m, 3H), 7.91 (t, 2H, *J* = 7.8 Hz), 7.96 (d, 1H, *J* = 8.2 Hz), 7.99 (d, 1H, *J* = 8.3 Hz), δ_{C} (125 MHz; CDCl₃) 48.4, 51.8, 82.5, 90.1, 122.6, 125.4, 126.0, 126.1, 127.0, 127.19, 127.22, 127.4, 127.5, 127.6, 128.29, 128.33, 129.2, 129.3, 131.2, 132.0, 132.6, 133.4, 133.5, 134.9, 135.0, 135.2, 136.3; HRMS (CI⁺): calc. for C₃₀H₂₂N (MH⁺) 396.1747, found 396.1747.

(3*R*,11*cS*)-4-allyl-3-((trimethylsilyl)ethynyl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine 288



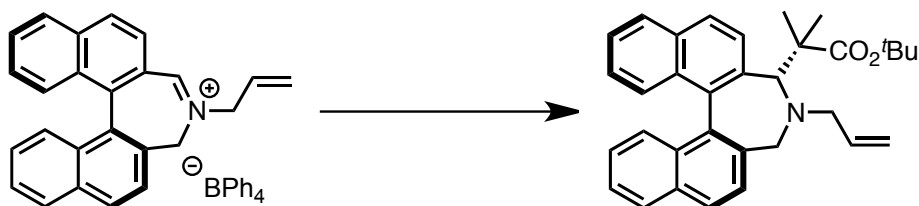
To a stirred solution of (*S*)-4-allyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (1.0 g, 1.531 mmol, 1.0 eq.) and CuI (29 mg, 0.153 mmol, 0.1 eq.) in MeCN (20 mL) was added trimethylsilylacetylene (1.087 mL, 7.66 mmol, 5.0 eq.) and Hünig's base (1.33 mL, 7.66 mmol, 5.0 eq.). The reaction was stirred for 16 hours (TLC showed complete consumption of starting material) then concentrated *in vacuo*. The residue was redissolved in DCM then washed sequentially with water and brine. The organic phase was dried (MgSO₄), filtered and concentrated in *vacuo* to give a crude orange oil. Column chromatography (20:1 petrol:EtOAc) yielded the title compound containing a small amount of an unidentified impurity. Crystallization of this product yielded colourless needles of the title compound (485 mg, 1.13 mmol, 74%); $[\alpha]_D^{20} +202$ (c 1.17, CHCl₃); ν_{\max} (solid) /cm⁻¹ 3414, 3050, 3008, 2956, 2897, 2812, 2162, 1641, 1507; δ_H (500 MHz; CDCl₃) -0.55 (s, 9H), 3.15 (d, 1H, *J* = 12.0 Hz), 3.17 (dd, 1H, *J* = 13.6, 7.8 Hz), 3.32 (dt, 1H, *J* = 13.3, 5.3, 1.3 Hz), 3.74 (d, 1H, *J* = 12.0 Hz), 4.90 (s, 1H), 5.27 (d, 1H, *J* = 10.2 Hz), 5.34 (dq, 1H, *J* = 17.2, 1.6 Hz), 6.02 – 6.09 (m, 1H), 7.23 – 7.27 (m, 1H), 7.28 (ddd, 1H, *J* = 8.3, 6.7, 1.3 Hz), 7.42 – 7.45 (m, 3H), 7.48 (ddd, 1H, *J* = 8.0, 6.7, 1.1 Hz), 7.54 (d, 1H, *J* = 8.6 Hz), 7.58 (d, 1H, *J* = 8.3 Hz), 7.91 – 7.97 (m, 4H); δ_C (125 MHz; CDCl₃) -0.6, 55.4, 56.3, 58.3, 87.2, 103.7, 118.8, 125.5, 125.8, 125.95, 125.98, 127.7, 127.8, 127.9, 128.3, 128.5, 128.6, 128.8, 132.0, 132.5, 133.41, 133.42, 133.6, 134.77, 134.81, 135.8, 136.3; HRMS (CI⁺): calc. for C₃₀H₃₀NSi (MH⁺) 432.2142, found 432.2150.

Methyl 3-((3*S*,11*cS*)-4-allyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-3-yl)propiolate 289



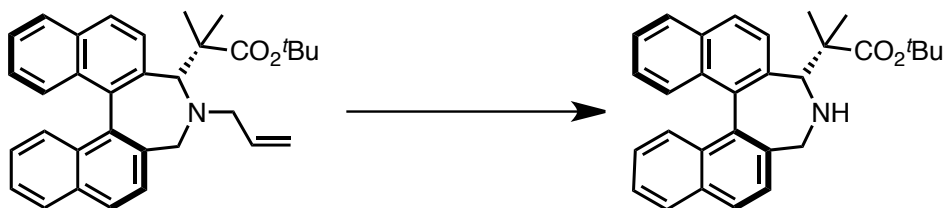
To a stirred solution of (*S*)-4-allyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (1.0 g, 1.531 mmol, 1.0 eq.) and CuI (29 mg, 0.153 mmol, 0.1 eq.) in MeCN (20 mL) was added methyl propiolate (142 mg, 1.68 mmol, 1.1 eq.) and Hünig's base (1.33 mL, 7.66 mmol, 5.0 eq.). The reaction was stirred for 2 hours (TLC showed complete consumption of starting material) then concentrated *in vacuo*. The residue was redissolved in DCM then washed sequentially with water and brine. The organic phase was dried (MgSO₄), filtered and concentrated in *vacuo* to give a crude orange oil. Column chromatography (20:1 petrol:EtOAc) yielded the title compound as a colourless foam (555 mg, 1.33 mmol, 87%) [α]_D²⁰ +71 (c 1.18, CHCl₃); ν_{max} (solid) /cm⁻¹ 3049, 2977, 2934, 2833, 2230, 1704, 1510; δ_{H} (500 MHz; CDCl₃) 3.19 (s, 3H), 3.21 – 3.25 (m, 2H), 3.31 (ddt, 1H, *J* = 13.5, 5.5, 1.4 Hz), 3.74 (d, 1H, *J* = 12.2 Hz), 4.90 (s, 1H), 5.27 – 5.29 (m, 1H), 5.36 (dq, 1H, *J* = 17.0, 1.3 Hz), 5.95 – 6.03 (m, 1H), 7.26 (ddd, 1H, *J* = 8.6, 6.7, 1.3 Hz), 7.33 (ddd, 1H, *J* = 8.6, 6.7, 1.3 Hz), 7.41 – 7.46 (m, 3H), 7.52 (ddd, 1H, *J* = 8.0, 6.8, 1.1 Hz), 7.58 (d, 1H, *J* = 8.3 Hz), 7.62 (d, 1H, *J* = 8.6 Hz), 7.90 – 7.92 (m, 1H), 7.96 – 7.98 (m, 3H); δ_{C} (125 MHz; CDCl₃) 31.0, 51.8, 54.6, 55.5, 57.6, 74.6, 86.7, 119.0, 125.5, 126.0, 126.2, 127.1, 127.3, 127.5, 127.7, 128.1, 128.3, 128.8, 129.4, 131.76, 131.81, 132.3, 133.5, 133.7, 134.3, 135.2, 135.3, 135.6, 153.1;

tert-Butyl 2-((3S,11cS)-4-allyl-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate 327



Zn dust (3.978 g, 61.2 mmol, 10 eq.) was suspended in dry THF (50 mL) in a dry 3-necked round-bottomed flask. Under a flow of nitrogen, 1,2-dibromoethane (524 μ L, 6.12 mmol, 1.0 eq.) and TMSCl (772 μ L, 6.12 mmol, 1.0 eq.) were added. The resulting suspension was heated to reflux for 1 h. While maintaining reflux, tert-butyl α -bromoisobutyrate (11.41 mL, 61.2 mmol, 10 eq.) was added dropwise via syringe at such a rate as to maintain steady reflux. The mixture was heated until no zinc dust remained then cooled to room temperature. This solution was then added to a pre-cooled (-78°C) solution of (S)-4-allyl-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium tetraphenylborate (4.0 g, 6.12 mmol, 1.0 eq.) in dry THF (50 mL). The resulting mixture was allowed to reach room temperature and stirred for 16 h (TLC indicated complete consumption of starting material) before being quenched with water. DCM (50 mL) was added. The organic phase was separated and washed with water (2 x 50 mL) and brine (50 mL) then dried (MgSO_4), filtered, and concentrated *in vacuo* to give a pale yellow oil. Column chromatography (99:1 petrol : EtOAc) yielded the *title compound* as a colourless oil (1.245 g, 2.61 mmol, 42%); $[\alpha]_D^{20} +191$ (c 0.92, CHCl_3); $\nu_{\text{max}}(\text{solid})/\text{cm}^{-1}$ 3050, 2976, 2934, 2808, 1764, 1718, 1597; δ_{H} (500 MHz; CDCl_3) 0.29 (s, 3H), 0.42 (s, 3H), 1.29 (s, 9H), 3.41 (d, 1H, $J = 11.4$ Hz), 3.47 – 3.49 (m, 2H), 3.65 (d, 1H, $J = 11.4$ Hz), 4.54 (s, 1H), 5.12 – 5.14 (m, 1H), 5.23 (dq, 1H, $J = 17.1, 1.6$ Hz), 5.89 – 5.97 (m, 1H), 7.18 (ddd, 1H, $J = 8.5, 6.9, 1.5$ Hz), 7.21 (ddd, 1H, $J = 8.4, 6.9, 1.4$ Hz), 7.31 (d, 1H, $J = 8.2$ Hz), 7.37 (d, 1H, $J = 8.6$ Hz), 7.40 – 7.45 (m, 3H), 7.55 (d, 1H, $J = 8.3$ Hz), 7.87 – 7.90 (m, 4H); δ_{C} (125 MHz; CDCl_3) 22.4, 22.6, 28.0, 51.0, 55.1, 64.6, 77.0, 79.8, 117.2, 125.2, 125.3, 125.6, 125.8, 127.6, 127.7, 128.0, 128.20, 128.24, 128.3, 128.7, 132.2, 132.8, 132.9, 133.0, 134.2, 135.8, 136.0, 136.1, 136.5, 176.9; HRMS (CI⁺): calc. for $\text{C}_{33}\text{H}_{36}\text{NO}_2$ (MH^+) 478.2741, found 478.2735.

***tert*-Butyl 2-((3*S*,11*cS*)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-3-yl)-2-methylpropanoate 328**



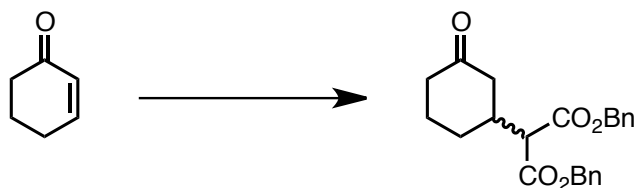
To a solution of *tert*-Butyl 2-((3*S*,11*cS*)-4-allyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-3-yl)-2-methylpropanoate (1.05 g, 2.20 mmol, 1.0 eq.) in degassed DCM (20 mL) was added NDMBA (1.029 g, 6.60 mmol, 3.0 eq.) and Pd(PPh₃)₄ (25 mg, 0.022 mmol, 0.01 eq.). The resulting orange reaction mixture was heated to reflux for 2 h (TLC indicated complete consumption of starting material). The organic phase was washed sequentially with 1M NaOH, water, and brine then dried (MgSO₄), filtered, and concentrated *in vacuo* to give an orange oil. Column chromatography (5:1 petrol : EtOAc) yielded the *title compound* as a colourless foam (654 mg, 1.49 mmol, 68%); [α]_D²⁰ +287 (c 0.99, CHCl₃); ν_{max} (solid) /cm⁻¹ 3343, 3050, 3009, 2976, 2929, 1720; δ_{H} (500 MHz; CDCl₃) 0.25 (s, 3H), 0.75 (s, 3H), 1.39 (s, 9H), 2.30 (br s, 1H), 3.74 (d, 1H, J = 12.7 Hz), 3.96 (d, 1H, J = 12.7 Hz), 4.90 (s, 1H), 7.15 (ddd, 1H, J = 8.3, 7.1, 1.6 Hz), 7.21 (ddd, 1H, J = 8.0, 6.6, 1.2 Hz), 7.26 – 7.28 (m, 1H), 7.39 – 7.44 (m, 2H), 7.46 (d, 1H, J = 8.6 Hz), 7.51 (d, 1H, J = 8.3 Hz), 7.88 – 7.91 (m, 4H); δ_{C} (125 MHz; CDCl₃) 19.6, 23.7, 28.0, 49.4, 50.8, 70.4, 80.1, 125.0, 125.4, 125.7, 125.8, 126.7, 127.5, 127.7, 127.9, 128.1, 128.4, 128.8, 132.4, 132.8, 132.9, 133.4, 134.7, 134.8, 136.1, 139.1, 176.8; HRMS (CI⁺): calc. for C₃₀H₃₂NO₂ (MH⁺) 438.2428, found 438.2424.

2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoic acid 325



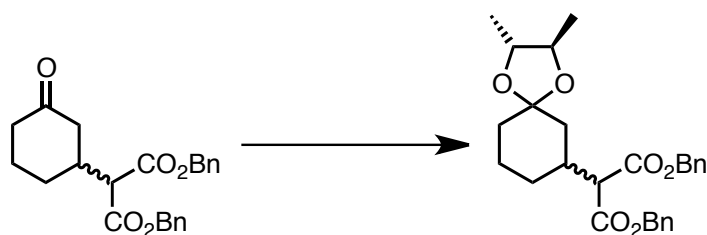
To a solution of *tert*-Butyl 2-((3S,11cS)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepin-3-yl)-2-methylpropanoate (520 mg, 1.19 mmol, 1.0 eq.) in DCM (10 mL) was added triethylsilane (568 μ L, 3.57 mmol, 3.0 eq.) and trifluoroacetic acid (5 mL). The green reaction mixture was stirred overnight at room temperature and then concentrated *in vacuo*. The reaction mixture was dissolved in toluene and again concentrated *in vacuo* in order to remove volatile impurities. Column chromatography (EtOAc \rightarrow 4:1 EtOAc:MeOH) of the residue gave the title compound as a colourless powder (322 mg, 0.85 mmol, 71%); $[\alpha]_D^{20} +132$ (c 0.91, CHCl₃); ν_{max} (solid) /cm⁻¹ 3383, 3053, 2966, 2715, 1688, 1598, 1578; δ_{H} (500 MHz; CDCl₃) - 0.01 (s, 3H), 1.15 (s, 3H), 4.04 (d, 1H, J = 13.1 Hz), 4.44 (d, 1H, J = 13.1 Hz), 5.30 (s, 1H), 7.18 – 7.24 (m, 2H), 7.30 – 7.32 (m, 2H), 7.48 – 7.53 (m, 2H), 7.61 – 7.63 (m, 2H), 7.79 (d, 1H, J = 8.3 Hz), 7.90 – 8.01 (m, 3H); δ_{C} (125 MHz; CDCl₃) 20.0, 26.4, 46.9, 48.1, 68.0, 126.1, 126.3, 126.6, 126.7, 127.2, 127.6, 127.98, 128.04, 128.6, 129.1, 129.5, 130.3, 131.7, 132.0, 132.4, 133.0, 133.5, 133.8, 133.9, 136.1, 181.8; HRMS (CI⁺): calc. for C₂₆H₂₄NO₂ (MH⁺) 382.1802, found 382.1803.

***rac*-Dibenzyl 2-(3-oxocyclohexyl)malonate**



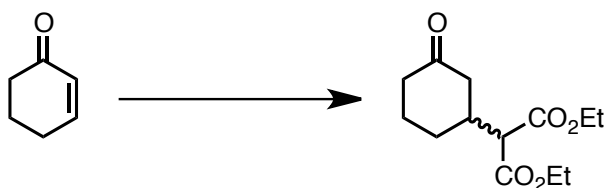
Cyclohexenone (250 μ L, 2.6 mmol, 1.0 eq.) and dibenzyl malonate (650 μ L, 2.60 mmol, 1.0 eq.) were dissolved in EtOH and stirred at room temperature. DBU (97 μ L, 0.65 mmol, 0.25 eq.) was slowly added via microsyringe and the colourless solution quickly became yellow. The mixture was stirred for 1 hour then the solvent was removed *in vacuo*. The residue was dissolved in DCM and sequentially washed with water and brine then dried (MgSO₄), filtered and concentrated *in vacuo*. Column chromatography (20:1 petrol:acetone \rightarrow 10:1) gave the title compound as a colourless solid (243 mg, 0.64 mmol, 25%); δ_{H} (500 MHz; CDCl₃) 1.43 – 1.51 (m, 1H), 1.59 – 1.68 (m, 1H), 1.89 – 1.92 (m, 1H), 1.99 – 2.05 (m, 1H), 2.17 – 2.27 (m, 2H), 2.35 – 2.39 (m, 1H), 2.42 – 2.46 (m, 1H), 2.52 – 2.60 (m, 1H), 3.41 (d, 1H, J = 7.7 Hz), 5.14 (s, 2H), 5.15 (s, 2H), 7.27 – 7.29 (m, 4H), 7.32 – 7.35 (m, 6H); δ_{C} (125 MHz; CDCl₃) 24.5, 28.7, 38.1, 40.1, 45.1, 56.8, 67.29, 67.31, 128.3, 128.5, 128.6, 135.12, 135.14, 167.5, 167.6, 209.4

Dibenzyl 2-((2*R*,3*R*)-2,3-dimethyl-1,4-dioxaspiro[4.5]decan-7-yl)malonate



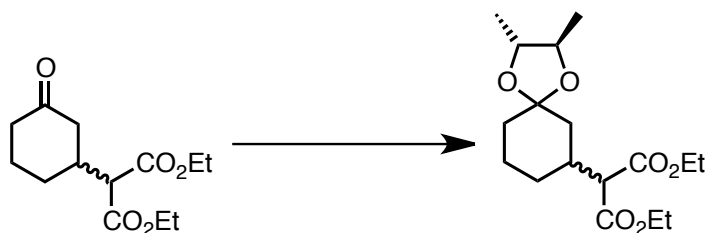
rac-Dibenzyl 2-(3-oxocyclohexyl)malonate (187 mg, 0.49 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol, 0.1 eq.) were dissolved in benzene. To the clear solution was then added (*R*)-(-)-2,3-butanediol (90 μ L, 0.98 mmol, 2.0 eq.). The reaction mixture was heated to reflux for 3 h (TLC indicated complete consumption of starting material). The solvent was removed in *vacuo* and the residue was redissolved in DCM. It was then washed sequentially with water and brine then dried (MgSO_4), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (221 mg, 0.49 mmol, quant.); δ_{H} (500 MHz; CDCl_3 , mixture of two diastereoisomers) 1.01 – 1.07 (m, 1H), 1.15 – 1.20 (m, 6H), 1.26 – 1.45 (m, 3H), 1.52 – 1.78 (m, 5H), 2.45 – 2.50 (m, 1H), 3.35 (t, 1H, $J = 16.3$ Hz), 3.43 – 3.58 (m, 2H), 5.08 – 5.20 (m, 4H), 7.28 – 7.34 (m, 10H); δ_{C} (125 MHz; CDCl_3 , mixture of two diastereoisomers) 16.8, 16.9, 17.0, 17.1, 22.4, 22.6, 29.1, 29.2, 35.3, 35.7, 35.8, 36.7, 39.9, 40.8, 57.4, 66.9, 67.0, 77.8, 78.0, 78.1, 78.2, 107.60, 107.63, 128.21, 128.24, 128.30, 128.33, 128.5, 135.4, 135.5, 168.1, 168.1, 168.24, 168.25

***rac*-Diethyl 2-(3-oxocyclohexyl)malonate**



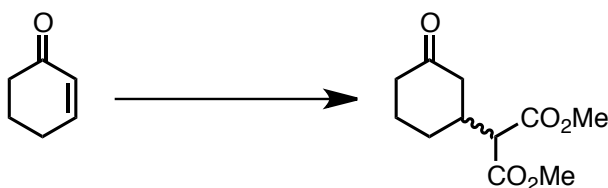
Cyclohexenone (250 μ L, 2.6 mmol, 1.0 eq.) and diethyl malonate (396 μ L, 2.60 mmol, 1.0 eq.) were dissolved in EtOH (5 mL) and stirred at room temperature. DBU (97 μ L, 0.65 mmol, 0.25 eq.) was slowly added via microsyringe and the colourless solution quickly became yellow. The mixture was stirred for 16 h then the solvent was removed *in vacuo*. The residue was dissolved in DCM and sequentially washed with water and brine then dried (MgSO₄), filtered and concentrated *in vacuo*. The crude brown oil was filtered through a plug of silica (DCM elution) to remove coloured impurities. After concentration *in vacuo*, the title compound was isolated as a colourless oil (624 mg, 2.44 mmol, 94%); δ_{H} (500 MHz; CDCl₃) 1.26 – 1.29 (m, 6H), 1.49 – 1.55 (m, 1H), 1.64 – 1.70 (m, 2H), 1.94 – 1.97 (m, 1H), 2.04 – 2.09 (m, 1H), 2.22 – 2.30 (m, 2H), 2.39 – 2.46 (m, 2H), 2.52 – 2.55 (m, 1H), 3.29 (d, 1H, J = 8.0 Hz), 4.18 – 4.23 (m, 4H); δ_{C} (125 MHz; CDCl₃) 14.11, 14.12, 24.6, 28.8, 38.1, 41.1, 45.1, 56.9, 61.6, 167.8, 167.9, 209.7

Diethyl 2-((2*R*,3*R*)-2,3-dimethyl-1,4-dioxaspiro[4.5]decan-7-yl)malonate



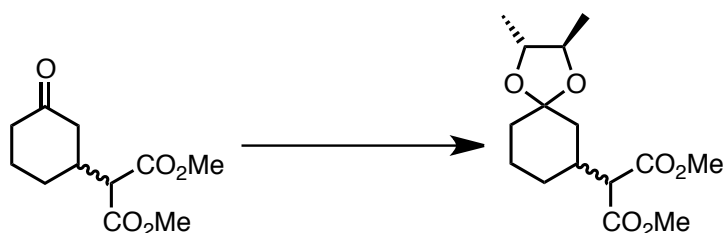
rac-Diethyl 2-(3-oxocyclohexyl)malonate (100 mg, 0.39 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol, 0.1 eq.) were dissolved in benzene. To the clear solution was then added (*R*)-(-)-2,3-butanediol (72 μ L, 0.78 mmol, 2.0 eq.). The reaction mixture was heated to reflux for 1 h (TLC indicated complete consumption of starting material). The solvent was removed *in vacuo* and the residue was redissolved in DCM. It was then washed sequentially with water and brine then dried (MgSO₄), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (128 mg, 0.39 mmol, quant.); δ_{H} (500 MHz; CDCl₃, mixture of two diastereoisomers) 1.04 – 1.07 (m, 2H), 1.20 – 1.27 (m, 12H), 1.31 – 1.34 (m, 1H), 1.36 – 1.38 (m, 1H), 1.43 – 1.82 (m, 5H), 2.39 – 2.46 (m, 1H), 3.21 (d, 1H, *J* = 8.5 Hz), 3.58 – 3.64 (m, 2H), 4.15 – 4.19 (m, 4H); δ_{C} (125 MHz; CDCl₃, mixture of two diastereoisomers) 14.2, 16.8, 17.0, 17.11, 17.13, 22.4, 22.7, 29.07, 29.13, 35.2, 25.6, 25.9, 36.8, 40.0, 40.1, 57.4, 57.5, 61.2, 77.9, 78.1, 78.3, 107.7, 107.8, 168.4, 168.5, 168.57, 168.60

***rac*-Dimethyl 2-(3-oxocyclohexyl)malonate**



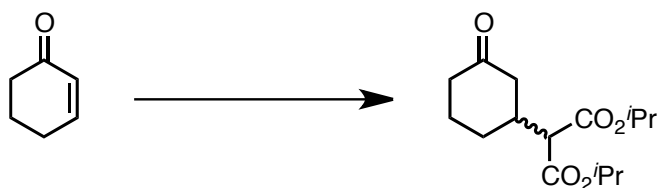
Cyclohexenone (250 μ L, 2.6 mmol, 1.0 eq.) and dimethyl malonate (297 μ L, 2.60 mmol, 1.0 eq.) were dissolved in EtOH (5 mL) and stirred at room temperature. DBU (97 μ L, 0.65 mmol, 0.25 eq.) was slowly added via microsyringe and the colourless solution quickly became yellow. The mixture was stirred for 16 h then the solvent was removed *in vacuo*. The residue was dissolved in DCM and sequentially washed with water and brine then dried (MgSO₄), filtered and concentrated *in vacuo*. The crude brown oil was filtered through a plug of silica (DCM elution) to remove coloured impurities. After concentration *in vacuo*, the title compound was isolated as a colourless oil (512 mg, 2.24 mmol, 86%); δ_{H} (500 MHz; CDCl₃) 1.45 – 1.53 (m, 1H), 1.63 – 1.72 (m, 2H), 1.92 – 1.95 (m, 1H), 2.05 – 2.09 (m, 1H), 2.22 – 2.29 (m, 2H), 2.38 – 2.44 (m, 2H), 2.49 – 2.56 (m, 1H), 3.34 (d, 1H, J = 8.0 Hz), 3.74 – 3.75 (m, 6H); δ_{C} (125 MHz; CDCl₃) 24.5, 28.8, 38.1, 41.0, 45.1, 52.7, 56.6, 168.2, 168.3, 209.6.

Dimethyl 2-((2*R*,3*R*)-2,3-dimethyl-1,4-dioxaspiro[4.5]decan-7-yl)malonate



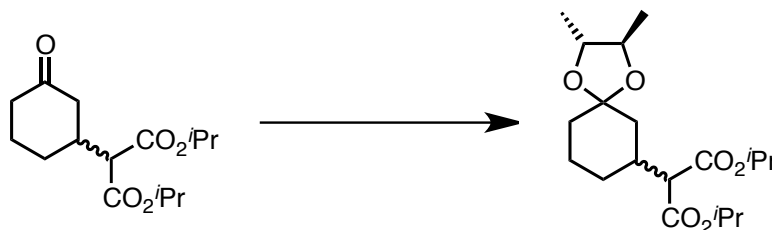
rac-Dimethyl 2-(3-oxocyclohexyl)malonate (70 mg, 0.30 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (6 mg, 0.03 mmol, 0.1 eq.) were dissolved in benzene. To the clear solution was then added (*R*)-(-)-2,3-butanediol (54 μ L, 0.60 mmol, 2.0 eq.). The reaction mixture was heated to reflux for 1 h (TLC indicated complete consumption of starting material). The solvent was removed *in vacuo* and the residue was redissolved in DCM. It was then washed sequentially with water and brine then dried (MgSO₄), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (90 mg, 0.30 mmol, quant.); δ_{H} (500 MHz; CDCl₃, mixture of two diastereoisomers) 0.99 – 1.04 (m, 2H), 1.14 – 1.22 (m, 12H), 1.30 – 1.37 (m, 2H), 1.40 – 1.49 (m, 2H), 1.53 – 1.69 (m, 10H), 2.39 – 2.45 (m, 2H), 3.26 (d, 2H, *J* = 8.5 Hz), 3.53 – 3.64 (m, 2H), 3.71 (s, 12H); δ_{C} (125 MHz; CDCl₃, mixture of two diastereoisomers) 16.8, 17.0, 17.06, 17.12, 22.4, 22.7, 29.1, 35.3, 35.7, 35.8, 36.7, 40.0, 40.1, 52.3, 52.4, 57.0, 57.1, 77.9, 78.1, 78.3, 107.6, 107.7, 168.8, 168.9, 168.95, 168.98.

Diisopropyl 2-(3-oxocyclohexyl)malonate



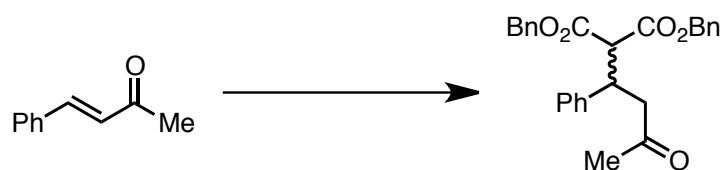
To a stirred solution of diisopropyl malonate (493 μ L, 2.6 mmol, 1.0 eq.) in dry THF (10 mL) was added potassium *tert*-butoxide (60 mg, 0.26 mmol, 0.1 eq.). After stirring for 5 minutes, cyclohexenone (250 μ L, 2.6 mmol, 1.0 eq.) was added dropwise over 5 minutes at room temperature. The resulting reaction mixture was stirred overnight at room temperature (TLC indicated complete consumption of starting material). The reaction mixture was diluted with DCM then washed sequentially with water and brine before being dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude product as an orange oil. Column chromatography (6:1 petrol:EtOAc) yielded the title compound as a colourless oil (439 mg, 1.54 mmol, 59%); δ_{H} (500 MHz; CDCl₃) 1.25 – 1.26 (m, 12 H), 1.49 – 1.55 (m, 1H), 1.66 – 1.70 (m, 1H), 1.95 – 1.98 (m, 1H), 2.04 – 2.09 (m, 1H), 2.22 – 2.30 (m, 2H), 2.38 – 2.53 (m, 3H), 3.22 (d, 1H, *J* = 7.8 Hz), 5.03 – 5.09 (m, 2H); δ_{C} (125 MHz; CDCl₃) 21.6, 21.71, 21.72, 24.6, 28.8, 37.9, 41.1, 45.2, 57.2, 69.16, 69.18, 167.4, 167.5, 209.9.

Diisopropyl 2-((2*R*,3*R*)-2,3-dimethyl-1,4-dioxaspiro[4.5]decan-7-yl)malonate



rac-Diisopropyl 2-(3-oxocyclohexyl)malonate (158 mg, 0.55 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (10.5 mg, 0.055 mmol, 0.1 eq.) were dissolved in benzene. To the clear solution was then added (*R*)-(-)-2,3-butanediol (98 μL , 1.10 mmol, 2.0 eq.). The reaction mixture was heated to reflux for 1 h (TLC indicated complete consumption of starting material). The solvent was removed *in vacuo* and the residue was redissolved in DCM. It was then washed sequentially with water and brine then dried (MgSO_4), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (195 mg, 0.55 mmol, quant.); δ_{H} (500 MHz; CDCl_3 , mixture of two diastereoisomers) 1.02 – 1.07 (m, 2H), 1.18 – 1.22 (m, 36H), 1.33 (q, 2H, $J = 12.3$ Hz), 1.37 – 1.46 (m, 2H), 1.54 – 1.58 (m, 2H), 1.65 – 1.73 (m, 6H), 1.79 – 1.82 (m, 2H), 2.37 – 2.40 (m, 2H), 3.11 (dd, 2H, $J = 8.7, 1.1$ Hz), 3.54 – 3.61 (m, 4H), 4.99 – 5.05 (m, 4H); δ_{C} (125 MHz; CDCl_3 , mixture of two diastereoisomers) 16.8, 16.9, 17.1, 17.2, 21.61, 21.63, 21.71, 22.5, 22.8, 29.0, 29.1, 35.0, 35.4, 35.9, 36.8, 40.0, 40.1, 57.8, 57.9, 68.55, 68.57, 68.59, 68.61, 77.8, 78.0, 78.2, 107.77, 107.79, 167.9, 168.0, 168.07, 168.10.

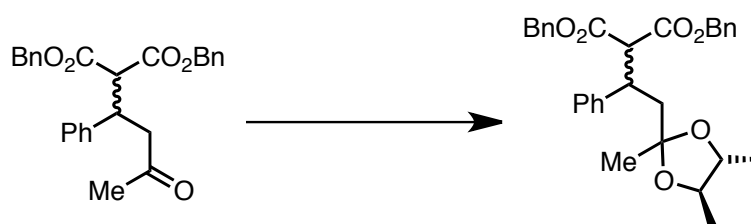
***rac*-Dibenzyl 2-(3-oxo-1-phenylbutyl)malonate**



To a stirred solution of dibenzyl malonate (655 μ L, 2.6 mmol, 1.0 eq.) and potassium *tert*-butoxide (29 mg, 0.26 mmol, 0.1 eq.) in dry THF (5 mL) was added benzylideneacetone (379 mg, 2.6 mmol, 1.0 eq.) as a solution in dry THF (5 mL). The orange reaction mixture was stirred at room temperature overnight then quenched with water. The organic phase was separated and washed sequentially with water and brine before being dried (MgSO₄), filtered and concentrated in vacuo to give the crude product as an orange oil. Column chromatography of the residue (10:1 petrol:EtOAc) yielded the title compound as a pale yellow oil which solidified on standing (941 mg, 2.19 mmol, 86%); δ_{H} (500 MHz; CDCl₃) 1.95 (s, 3H), 2.88 (d, 2H, J = 6.9 Hz), 3.82 (d, 1H, J = 9.9 Hz), 3.97 – 4.02 (m, 1H), 4.89 (s, 2H), 5.13 – 5.14 (m, 2H), 7.05 – 7.06 (m, 2H), 7.18 – 7.33 (m, 13H); δ_{C} (125 MHz; CDCl₃) 30.3, 40.5, 47.1, 57.4, 67.2, 67.3, 127.3, 128.1, 128.2, 128.27, 128.31, 128.4, 128.5, 128.57, 128.59, 135.0, 135.2, 140.2, 167.4, 167.9, 206.0.

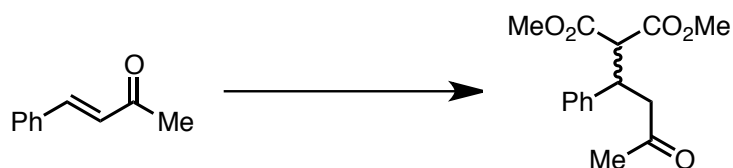
Dibenzyl 2-(1-phenyl-2-((4*R*,5*R*)-2,4,5-trimethyl-1,3-dioxolan-2-yl)ethyl)

malonate



rac-Dibenzyl 2-(3-oxo-1-phenylbutyl)malonate (55 mg, 0.13 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (3 mg, 0.013 mmol, 0.1 eq.) were dissolved in benzene. To the clear solution was then added (*R*)-(-)-2,3-butanediol (24 μ L, 0.26 mmol, 2.0 eq.). The reaction mixture was heated to reflux for 1 h (TLC indicated complete consumption of starting material). The solvent was removed *in vacuo* and the residue was redissolved in DCM. It was then washed sequentially with water and brine then dried (MgSO₄), filtered and concentrated *in vacuo* to give the title compound as a pale yellow oil (65 mg, 0.13 mmol, quant.); δ_{H} (500 MHz; CDCl₃, mixture of two diastereoisomers) 1.01 (d, 3H, *J* = 6.0 Hz), 1.04 (d, 3H, *J* = 6.2 Hz), 1.06 (d, 3H, *J* = 6.2 Hz), 1.10 (app t, 6H, *J* = 3.0 Hz), 1.14 (s, 3H), 2.03 – 2.23 (m, 4H), 3.27 – 3.33 (m, 2H), 3.47 – 3.55 (m, 2H), 3.70 – 3.81 (m, 4H), 4.87 (app q, 4H, *J* = 11.0 Hz), 5.15 (app d, 4H, *J* = 5.6 Hz), 7.03 – 7.05 (m, 4H), 7.16 – 7.34 (m, 26H); δ_{C} (125 MHz; CDCl₃, mixture of two diastereoisomers) 16.2, 16.4, 16.9, 17.0, 26.2, 26.3, 41.4, 41.5, 43.0, 43.1, 59.05, 59.09, 67.0, 67.18, 67.19, 78.09, 78.14, 78.2, 78.3, 108.2, 108.3, 126.76, 126.84, 128.1, 128.2, 128.28, 128.33, 128.34, 128.4, 128.6, 128.7, 135.17, 135.18, 135.35, 135.37, 141.4, 141.6, 167.58, 167.63, 168.0, 168.1

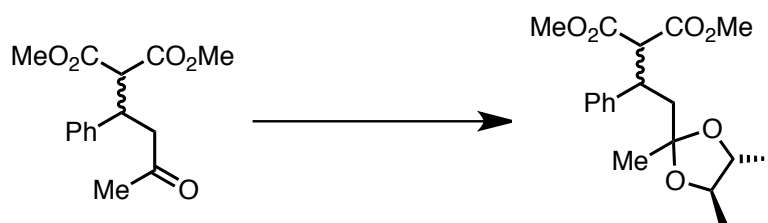
***rac*-Dimethyl 2-(3-oxo-1-phenylbutyl)malonate**



To a stirred solution of dimethyl malonate (297 μ L, 2.6 mmol, 1.0 eq.) and potassium *tert*-butoxide (29 mg, 0.26 mmol, 0.1 eq.) in dry THF (5 mL) was added benzylideneacetone (379 mg, 2.6 mmol, 1.0 eq.) as a solution in dry THF (5 mL). The orange reaction mixture was stirred at room temperature overnight then quenched with water. The organic phase was separated and washed sequentially with water and brine before being dried (MgSO₄), filtered and concentrated in vacuo to give the crude product as an orange oil. Column chromatography of the residue (4:1 petrol:EtOAc) yielded the title compound as a colourless oil (372 mg, 1.35 mmol, 52%); δ_{H} (500 MHz; CDCl₃) 2.03 (s, 3H), 2.88 – 2.99 (m, 2H), 3.50 (s, 3H), 3.72 (s, 3H), 3.73 (d, 1H, *J* = 9.6 Hz), 3.95 – 4.00 (m, 1H), 7.18 – 7.23 (m, 3H), 7.26 – 7.29 (m, 2H); δ_{C} (125 MHz; CDCl₃) 30.3, 40.5, 47.2, 52.4, 52.7, 57.1, 127.3, 128.0, 128.6, 140.37, 168.1, 168.6, 206.1.

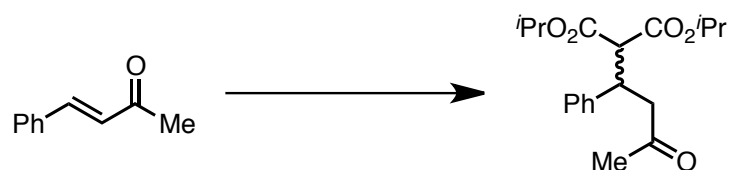
**Dimethyl
yl)ethyl)malonate**

2-(1-phenyl-2-((4*R*,5*R*)-2,4,5-trimethyl-1,3-dioxolan-2-



rac-Dimethyl 2-(3-oxo-1-phenylbutyl)malonate (100 mg, 0.359 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (8 mg, 0.035 mmol, 0.1 eq.) were dissolved in benzene. To the clear solution was then added (*R*)-(-)-2,3-butanediol (65 μ L, 0.7 mmol, 2.0 eq.). The reaction mixture was heated to reflux for 1 h (TLC indicated complete consumption of starting material). The solvent was removed *in vacuo* and the residue was redissolved in DCM. It was then washed sequentially with water and brine then dried (MgSO₄), filtered and concentrated *in vacuo* to give the title compound as a pale yellow oil (125 mg, 0.359 mmol, quant.); δ_{H} (500 MHz; CDCl₃, mixture of two diastereoisomers) 1.04 – 1.09 (m, 9H), 1.14 – 1.19 (m, 9H), 2.02 – 2.24 (m, 4H), 3.36 – 3.41 (m, 2H), 3.43 (d, 6H, *J* = 2.4 Hz), 3.50 – 3.56 (m, 2H), 3.64 – 3.70 (m, 4H), 3.72 (d, 6H, *J* = 5.8 Hz) 7.16 – 7.19 (m, 2H), 7.23 – 7.26 (m, 8H); δ_{C} (125 MHz; CDCl₃, mixture of two diastereoisomers) 16.3, 16.4, 16.8, 17.0, 26.2, 26.3, 41.4, 41.5, 43.0, 43.1, 52.18, 52.20, 52.5, 52.6, 58.85, 58.93, 7.81, 78.16, 78.23, 78.4, 108.3, 108.4, 126.75, 126.83, 128.11, 128.14, 128.5, 128.6, 141.5, 141.6, 168.2, 168.3, 168.7, 168.8.

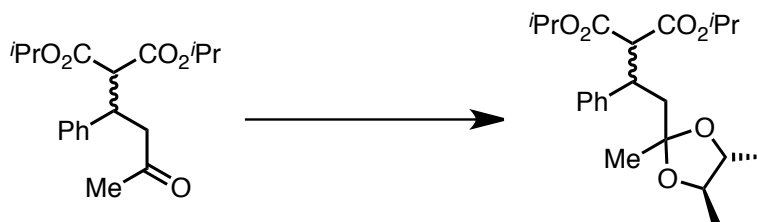
***rac*-Diisopropyl 2-(3-oxo-1-phenylbutyl)malonate**



To a stirred solution of diisopropyl malonate (493 μ L, 2.6 mmol, 1.0 eq.) and potassium *tert*-butoxide (29 mg, 0.26 mmol, 0.1 eq.) in dry THF (5 mL) was added benzylideneacetone (379 mg, 2.6 mmol, 1.0 eq.) as a solution in dry THF (5 mL). The orange reaction mixture was stirred at room temperature overnight then quenched with water. The organic phase was separated and washed sequentially with water and brine before being dried (MgSO_4), filtered and concentrated in vacuo to give the crude product as a yellow oil. Column chromatography of the residue (10:1 petrol:EtOAc) yielded the title compound as a colourless oil (666 mg, 1.77 mmol, 68%); δ_{H} (500 MHz; CDCl_3) 0.98 (d, 3H, $J = 6.3$ Hz), 1.05 (d, 3H, $J = 6.3$ Hz), 1.24 (d, 3H, $J = 6.3$ Hz), 1.25, d, 3H, $J = 6.3$ Hz), 2.03 (s, 3H), 2.87 – 2.93 (m, 2H), 3.65 (d, 1H, $J = 10.1$ Hz), 3.95 (td, 1H, $J = 14.5, 5.6$ Hz), 4.79 (septet, 1H, $J = 6.3$ Hz), 5.07 (septet, 1H, $J = 6.3$ Hz), 7.18 – 7.21 (m, 1H), 7.25 – 7.29 (m, 4H); δ_{C} (125 MHz; CDCl_3) 21.28, 21.32, 21.5, 21.7, 30.3, 40.4, 47.8, 57.7, 68.8, 69.3, 127.2, 128.3, 128.4, 140.5, 167.2, 167.8, 206.2.

**Diisopropyl
2-(1-phenyl-2-((4*R*,5*R*)-2,4,5-trimethyl-1,3-dioxolan-2-yl)ethyl)malonate**

2-(1-phenyl-2-((4*R*,5*R*)-2,4,5-trimethyl-1,3-dioxolan-2-yl)ethyl)malonate



rac-Diisopropyl 2-(3-oxo-1-phenylbutyl)malonate (130 mg, 0.39 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (7 mg, 0.04 mmol, 0.1 eq.) were dissolved in benzene. To the clear solution was then added (*R*)-(-)-2,3-butanediol (79 μ L, 0.78 mmol, 2.0 eq.). The reaction mixture was heated to reflux for 1 h (TLC indicated complete consumption of starting material). The solvent was removed *in vacuo* and the residue was redissolved in DCM. It was then washed sequentially with water and brine then dried (MgSO_4), filtered and concentrated *in vacuo* to give the title compound as a pale yellow oil (158 mg, 0.39 mmol, quant.); δ_{H} (500 MHz; CDCl_3 , mixture of two diastereoisomers) 0.85 – 0.87 (m, 6H), 1.01 – 1.05 (m, 15H), 1.11 – 1.13 (m, 6H), 1.17 – 1.24 (m, 15H), 2.01 – 2.19 (m, 4H), 3.30 – 3.43 (m, 2H), 3.45 – 3.64 (m, 6H), 4.66 – 4.73 (m, 2H), 5.00 – 5.09 (m, 2H), 7.12 – 7.15 (m, 2H), 7.20 – 7.26 (m, 8H); δ_{C} (125 MHz; CDCl_3 , mixture of two diastereoisomers) 16.3, 16.4, 16.7, 16.9, 21.20, 21.22, 21.4, 21.5, 21.6, 21.7, 26.2, 26.3, 41.2, 41.4, 43.4, 43.6, 59.37, 59.39, 68.5, 68.90, 69.92, 78.1, 78.15, 78.17, 108.3, 108.4, 126.56, 126.64, 127.9, 128.0, 128.85, 128.91, 141.6, 141.7, 167.3, 167.4, 167.9, 168.0.

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