New Methodology for the Organocatalysed α-Amination Reaction

By

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Abstract

Research into organocatalysed asymmetric reactions has been a rapidly growing and competitive field in recent times, wherein aminocatalysis is widely used for the asymmetric functionalisation of carbonyl compounds. Since its simultaneous publication by List and Jørgensen, the organocatalysed α-amination reaction has become a key method for asymmetric heteroatom functionalisation of carbonyl compounds. Herein we report the first application of this methodology to acetals, with the ultimate goal of applying the methodology to the asymmetric desymmetrisation of bis-acetals as a novel contribution to this growing field.

Following extensive optimisation, acidic reaction conditions for the reaction were established in which dibenzyl azodicarboxylate (DBAD) was used as the aminating agent and (*S*)-(-)-5-(2-pyrrolidinyl)-1*H*-tetrazole as the preferred organocatalyst. The desired aminated products were obtained in high yields and enantioselectivities. The reaction showed broad substrate scope in its application to ketals, dioxolanes and lactols.

A hydrazide N-N bond cleavage methodology was also developed for the aminated products in oxazolidinone form. This methodology is based on Magnus' alkylation / E_1CB strategy. The novel contribution here is using ditheyl bromoacetate as an alkylating agent and as a better elimination partner.

A range of bis-acetals were synthesised via three synthetic routes using malonate-, sulfone- and cyclopentene-based synthesis strategies. The acetal reaction was used for the desymmetrisation of two of these bisacetals as a proof of concept. This is a feat not achieved with the more reactive dicarbonyl analogue.

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Abbreviations

Ar	aromatic
Bn	benzyl
Boc	*N-tert*-butoxycarbonyl
Bu	butyl
J	coupling constant
Cbz	carboxybenzyl
DBAD	dibenzyl azodicarbxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DPPA	diphenylphosphoryl azide
D*t*BAD	di-*tert*-butyl azodicarboxylate
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddt	doublet of doublet of triplets
eq	equivalent(s)
HRMS	High-resolution Mass Spectroscopy
hr(s)	hour(s)
Hz	hertz
i	iso
i-Ar	*ipso*-aromatic resonance
m	multiplet
m/z	mass-to-charge ratio
MBA	monobromoacetic acid
Me	methyl
MCA	monochloroacetic acid
MHz	megahertz
MsCl	methanesulfonyl chloride
min	minute(s)
n	normal
NMR	nuclear magnetic resonance
oct	octet

p	para
p	pentet
Pr	propyl
RT	room temperature
s	singlet
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
TLC	thin layer chromatography
Ts	4-toluenesulfonyl
t	tert
t	triplet

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Chapter 1: Organo(Amino)catalysis in Asymmetric Synthesis

1.1 Introduction

Chirality is a symmetry property of objects in three-dimensional space in which an object is referred to as “chiral” if it cannot be superimposed on its mirror image. Chemically speaking, compounds can be found in two forms where they are constitutionally equivalent but the three-dimensional arrangement of atoms differs. In such a case the two molecules are termed “stereoisomers”. If these two stereoisomers are mirror images that cannot be superimposed on one another, then the compounds are both chiral and they are related as “enantiomers”. The cause of non-superimposability (chirality) is the lack of molecular S_N symmetry (improper axis of rotation/reflection symmetry), and there are three stereogenic structural elements that can cause this referred to as chiral centre, axis or plane. In each case a universal system to distinguish stereogenicity as either left-handed or right-handed has been developed called the Cahn-Ingold-Prelog nomenclature after three doyens in the field of stereochemistry, and in each case a stereodescriptor “*R*” or “*S*” is then used to distinguish handedness between the two enantiomers. Figure 1.1 below depicts the two enantiomers of alanine, a chiral amino acid, as an example. Enantiomers have identical chemical and physical properties bar one, except in the presence of an external chiral influence (for example a chiral stationary phase in chromatographic separation). The one property in which two enantiomers differ is optical activity in which they differ in the direction in which they rotate the plane of plane-polarised light. If the enantiomer rotates the plane of polarised light in a clockwise direction it is denoted as “(+)”, while “(-)” corresponds to an anti-clockwise direction. Net rotations of a mixture of enantiomers are additive and so the net measured rotation is used as a guide to determine enantiomeric composition.[1]

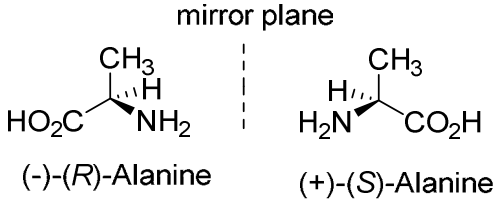


Figure 1.1: The two enantiomers of alanine.

However, the significance of chemical chirality goes beyond just optical activity. Indeed the world around us is chiral and most of the building blocks of biological macromolecules occur as single enantiomers. Thus, when a biologically active chiral molecule (perhaps a drug) interacts with its chiral receptor site, each enantiomer may react differently and lead to different effects. A classic (and tragic) example of this is the drug thalidomide, Figure 1.2,

which was administered as a mixture of both enantiomers. Both enantiomers led to the desired sedative effect but the (-)-enantiomer resulted in foetal deformities. Furthermore, even if the pure (+)-enantiomer had been used there still would have been issues since the two enantiomers interconvert (racemise) under physiological conditions.

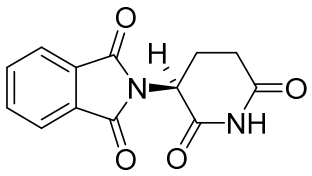


Figure 1.2: (-)-Thalidomide

For a compound with more than one chiral carbon (stereogenic centre), there are more than two stereoisomeric forms. In this case a maximum of 2^n stereoisomers are possible (where *n* is the number of stereogenic centres), and such isomers are called diastereoisomers or diastereomers for short. These are defined as stereoisomers that are not mirror images. In contrast to enantiomers, diastereomers have different chemical and physical properties and thus can be separated in a simpler manner (via crystallisation or chromatography using the usual achiral stationary phase). An example of diastereomers is the artificial sweetener aspartame (shown in Figure 1.3), which has two stereogenic centres and thus four stereoisomers since there are no simple mirror planes. Analysis of (a)-(d) stereochemically leads to the conclusion that there are two diastereomers which each have an enantiomer. However, each stereoisomer has two diastereomeric relationships with other compounds and one enantiomeric relationship. In this case, only diastereomer (a) is sweet whilst the other diastereomers are slightly bitter and must be avoided in the synthetic process. This example highlights the importance of synthesising chiral compounds in a stereoselective manner, not only to obtain stereoisomers with the desired effects, but also to prevent wastage in the synthetic procedure and improve atom-efficiency.

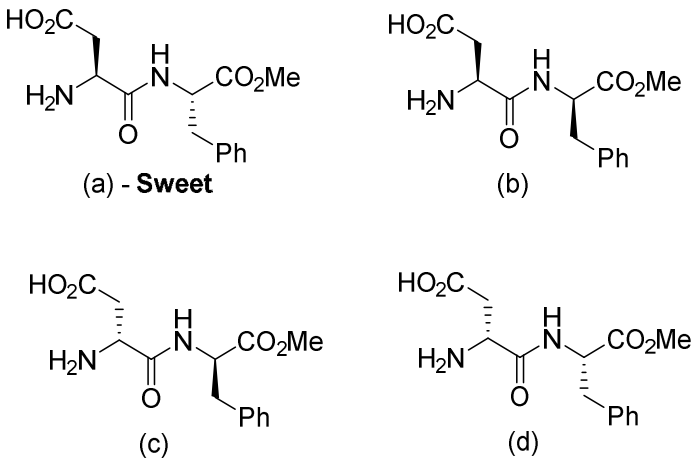


Figure 1.3: The four stereoisomers of aspartame.

Since the concept of chirality was recognised and its significance was discovered, organic chemists have become increasingly interested in asymmetric synthesis, defined as the assembly of simple and readily available starting materials into asymmetric products selectively, and is one of the ultimate goals of modern organic chemistry.[2] The broad value of homochiral (i.e. single enantiomer) molecules as pharmaceuticals, as probes of biological function, as polymer components with novel properties, and in electronic and optical devices has spearheaded the prominence of asymmetric synthesis.[3] Thus the influence of asymmetric synthesis has gone beyond the academic environment. This is illustrated by the role it has played in the pharmaceutical industry, since chiral drugs represent close to one third of all drug sales worldwide, and where regulatory considerations demand that great care and attention is paid to generating and evaluating drugs as pure enantiomers.[4]

Asymmetric synthesis methodology can be classified into two main groups: 1) diastereoselective substrate-controlled processes, and 2) enantioselective reagent-controlled processes. The objective is to produce enantioenriched products with defined relative stereochemistry if there are more than two stereogenic elements.

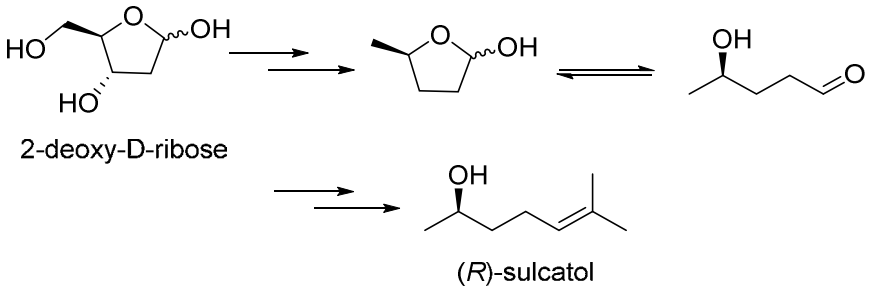
1.1.1 Diastereoselective Substrate-Controlled Methodology

These approaches involve the reaction of a chiral substrate. The reaction occurs at a prochiral site near the controlling chiral centre to produce one predominant diastereomer as a single enantiomer.

a) Chiral pool synthesis

Chiral pool synthesis involves an enantiomerically pure natural source functioning as the chiral source. The “chiral pool” is thus a group of readily available, chiral natural sources or

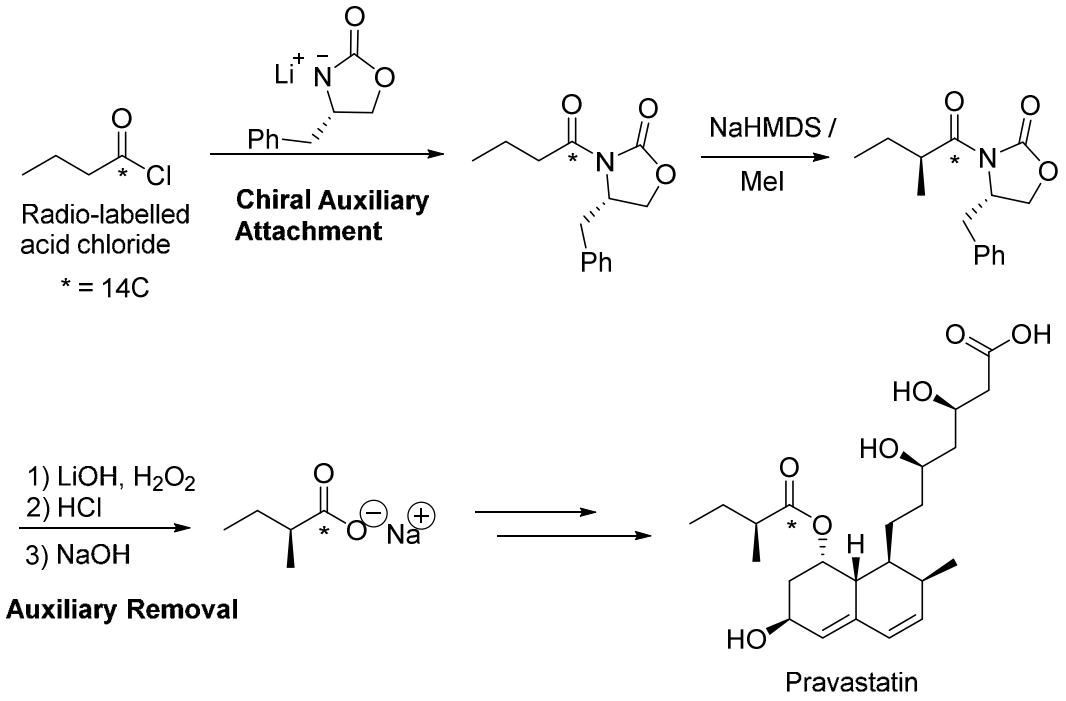
products in which amino acids and sugars dominate. Scheme 1.1 illustrates how the naturally occurring sugar 2-deoxy-D-ribose can be used to synthesise (*R*)-sulcatol, a beetle pheromone, as a pure enantiomer.[5] In chiral pool synthesis chirality may be added or removed to make the chiral target.



Scheme 1.1: Chiral pool synthesis of (*R*)-sulcatol.

b) Auxiliary-controlled methods

Auxiliary-controlled reactions are similar to chiral pool ones in that the controlling chirality originates from the substrate in a diastereoselective process. However, here the chirality in the substrate is deliberately introduced and is removed after serving its purpose. Successful methodologies demand a high diastereoselectivity and if a single diastereomer can be isolated, a single enantiomer product is ultimately obtained following auxiliary removal. Between the 1970's and 1990's most of the asymmetric synthesis methodologies reported fell into this category. Although highly useful, the need for additional attachment and removal steps is the major drawback of this asymmetric synthesis strategy. Scheme 1.2 illustrates an example in the synthesis of carbon-14 labelled Pravastatin based on one of the most famous and reliable auxiliary-controlled methodologies, David Evans' oxazolidinone enolate chemistry.[6]

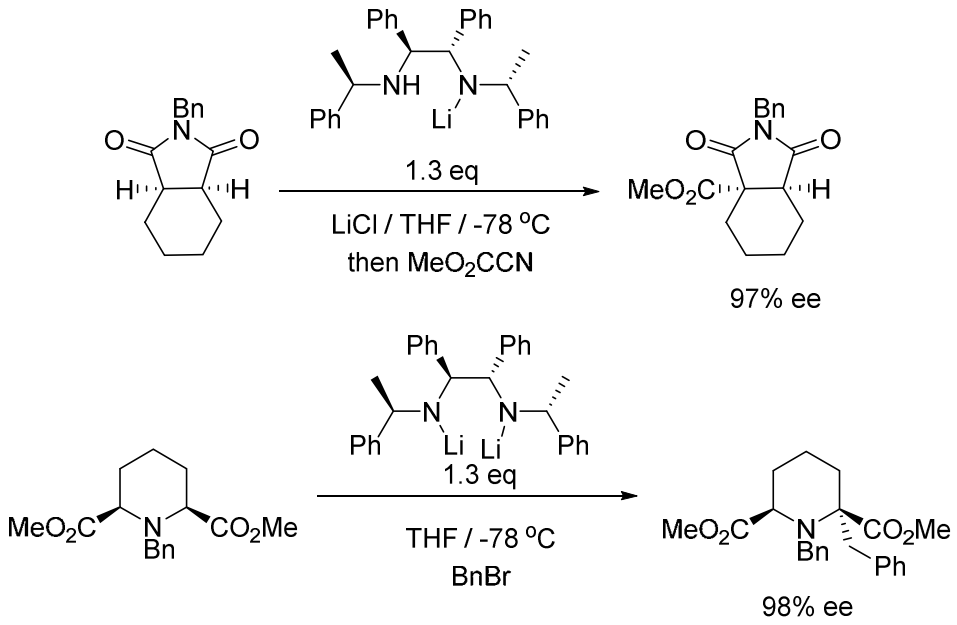


Scheme 1.2: Synthesis of carbon-14 labelled Pravastatin using a chiral auxiliary.

1.1.2 Reagent-Controlled Methods

a) Stoichiometric methods

In these methods an achiral substrate is converted to a chiral, non-racemic product by use of a stoichiometric amount of chiral reagent. Reactions involve an intermolecular control of the asymmetric induction. An example of this is enantioselective deprotonations using a chiral amide base, Scheme 1.3.[7] The major advantage of this methodology is the wider choice of starting materials possible as well as not having to attach and remove an auxiliary. However, stoichiometric amounts of the chiral reagent are required.



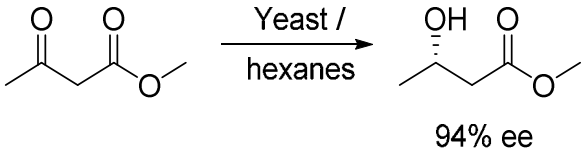
Scheme 1.3: Enantioselective deprotonation using chiral lithium amide bases.

b) Enantioselective Catalyst-controlled methods

In contrast to the above reaction, in this category an achiral substrate containing one or more prochiral centres reacts with the reagent in the presence of a chiral catalyst in sub-stoichiometric amounts. This results in enantioselective production of a chiral product via catalyst turnover. Peter Dalko et al. put it best: "Undoubtedly, the more elegant and economically most attractive way to introduce chirality into a molecule is by using a catalytic amount of a chiral controller to induce the chiral transformation…".[4] As such, these methods have become the most popular ways to synthesise chiral compounds. The three main types of enantioselective catalysis are biocatalysis, transition-metal catalysis and organocatalysis.

Biocatalysis

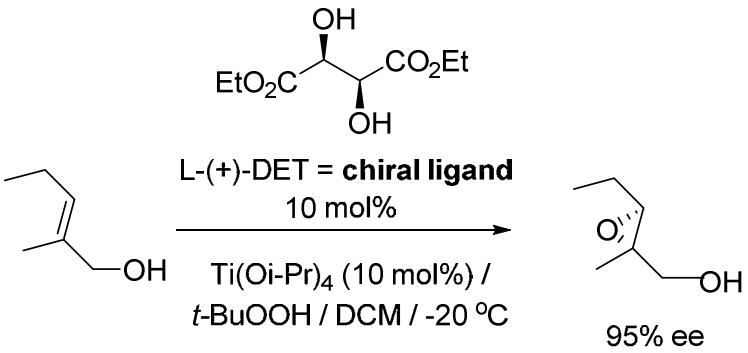
Biocatalysed asymmetric synthesis involves introduction of chirality into an achiral substrate through the influence of an enzyme.[8] These enzymes are sourced from animal and plant cells either by extracting or recovering them from cell exudates using protein and genetic engineering techniques. Enzymes act as chiral catalysts since almost all of them are peptides comprising chiral amino acid building blocks. Scheme 1.4 shows how yeast can be used as a catalyst for the enantioselective reduction of a ketone. In fact, enzymes are more than just highly evolved catalysts – catalytic efficiency, selectivity, and high turnover form only part of their sophisticated systems, which comprise built-in feedback mechanisms and subtle intra- and intermolecular cooperation.[9] One drawback, though, can be substrate specificity ie finding the right enzyme for a particular substrate.



Scheme 1.4: Biocatalysed enantioselective ketone reduction.

Transition-Metal Catalysis

The emergence of homogeneous enantioselective organometallic catalysis has had a pivotal impact on the development of enantioselective reactions. The development of the first potent organic ligands for rhodium complexes served as the foundation for the expansion of enantioselective catalytic hydrogenation reactions. Thus asymmetric catalysis has become almost synonymous with the use of metals in a chiral environment.[4] An important example is the Nobel Prize winning Sharpless epoxidation (Scheme 1.5), where a titanium Lewis acid catalyst is used in the presence of L-(+)-diethyl tartrate (L-(+)-DET) as a chiral ligand.[4,10,11]



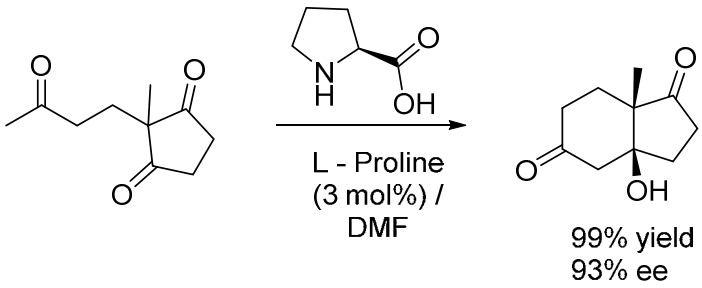
Scheme 1.5: Metal-catalysed asymmetric Sharpless epoxidation.

Metal complexes undoubtedly have considerable advantages: molecular and structural diversity due to higher coordination numbers and oxidation states, and a large array of reactivity patterns tuned by varying ligands. However, these tremendous advantages are coupled with challenging disadvantages such as high price, toxicity, pollution, waste treatment, product contamination and the depletion of our planet's natural metal reserves.[4,12] Therefore these days, in view of the Green Chemistry revolution, there is also an increasing tendency to develop methodologies that are sustainable, ie allow for regeneration of the chiral reagents. Also, functions that are typically associated with metals (for example, as Lewis acids / bases and as redox agents) can also be carried out efficiently by organic compounds.[4,13,14] Thus, methods based exclusively on metal-free chiral organic catalysts have become in vogue.

Organocatalysis

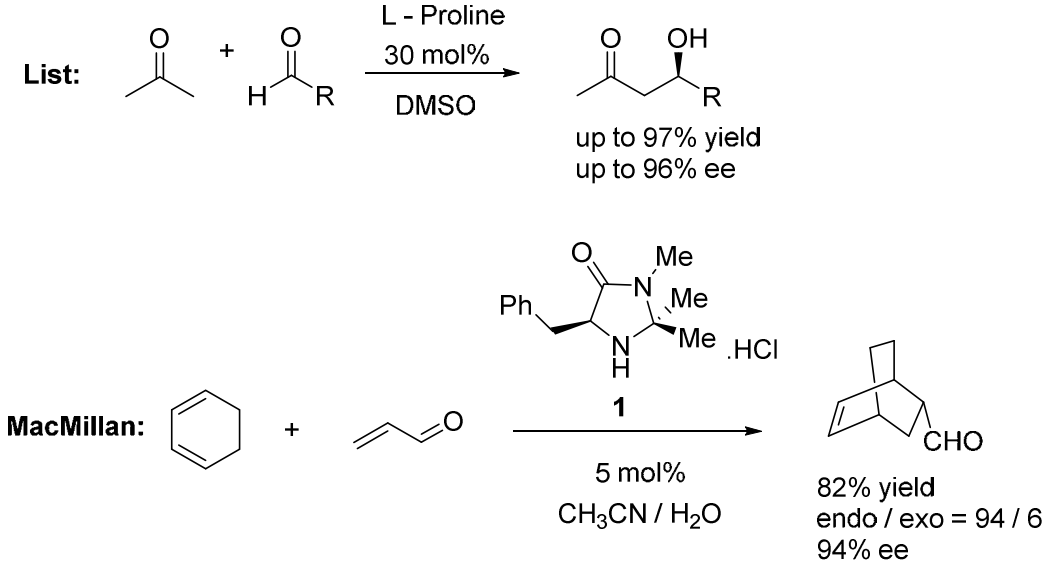
Organocatalysis is the use of small organic molecules (as opposed to protein enzymes) to catalyse organic transformations.[15] The preparative advantages of using organic molecules are impressive since: the reactions can often be performed under an aerobic atmosphere with wet solvents; catalysts are inexpensive and they are often more stable than bioorganic catalysts; these relatively small organic molecules can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues; the organic molecules have shown adaptability to high-throughput screening and process chemistry; and lastly, organocatalytic procedures are easier and result in reduction of chemical waste.[4] These advantages arise from the following simple facts, as David MacMillan puts it:[15] 1) organic molecules are generally insensitive to oxygen and moisture in the atmosphere, and therefore don't need special reaction vessels, storage containers and experimental techniques, or ultra-dry reagents and solvents; 2) a wide variety of organic reagents such as amino acids, carbohydrates and hydroxy acids, are naturally available as single enantiomers, and thus simple organocatalysts are usually cheap to prepare and readily accessible in a quantity suitable for either small-scale reactions or industrial-scale reactions; 3) small organic molecules are typically non-toxic and environmentally friendly thus increasing the safety of catalysis in research across all research settings. This combination of factors has substantially lowered the entry costs for researchers interested in developing asymmetric organocatalytic reactions and has led to the recent tremendous innovation of new organocatalytic systems.

Although chemical transformations utilising organocatalysts have been documented intermittently over the past century (for example the benzoin condensation reaction catalysed by cyanide anion, first described in the late 1830s),[16,17] it was not until the late 1990s that this field truly took shape, coalescing around a small number of articles that inspired an explosion of research. MacMillan considers three factors that were crucial to the sudden and rapid development of the field of organocatalysis: [15] first, the conceptualisation of the field; second, the advantages of organocatalytic research; and third, the discovery of generic modes of catalyst activation, induction and reactivity. Between 1968 and 1997, there were only a few reports of the use of organic molecules as catalysts for asymmetric reactions and these studies were viewed more as unique chemical reactions than as integral parts of a larger, interconnected field. In the early 1970s Hajos[18] and Wiechert[19] published the first and highly enantioselective catalytic aldol reactions using the simple amino acid proline as the catalyst (Scheme 1.6). However in these early publications, there was no suggestion by the authors that the use of organocatalysts could be a principal concept in organic synthesis.



Scheme 1.6: The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

This began to change in the late 1990s when the groups of Yian Shi[20] Scott Denmark[21] and Dan Yang[22] independently demonstrated that enantiomerically pure ketones could catalyse the enantioselective epoxidation of alkenes. Thereafter, Eric Jacobsen[23] and Elias J. Corey,[24] described the first examples of hydrogen bonding catalysis, in an asymmetric Strecker reaction, while Scott Miller[25] introduced the concept of using peptides for the enantioselective kinetic resolution of alcohols. All these contributions demonstrated for the first time that small organocatalysts could be used to solve important problems in chemical synthesis. However, it was not until 2000 that the field of organocatalysis was effectively launched by two almost simultaneous publications: one from Carlos Barbas, Richard Lerner and Benjamin List[26] on proline-catalysed aldol reactions; and the other from David MacMillan,[27] on an enantioselective Diels-Alder reaction catalysed by (2*S*)-imidazolidinone **1** as his first-generation catalyst (Scheme 1.7).



Scheme 1.7: The two reactions that launched the field of organocatalysis.

Barbas, Lerner and List's work was very important since it showed that the underlying mechanism of the Hajos–Parrish reaction could be extended and applied to transformations

of broader applicability. Moreover, it showed that small organic molecules (such as proline) could be as effective as enzymes in catalysing the same chemical reactions through similar mechanisms. During this period, MacMillan states that his work conceptualised "organocatalysis" in three important ways: by outlining how organocatalysts could provide economic, environmental and scientific benefits; by describing a general activation strategy that could be applied to a broad range of reaction classes; and by introducing the term organocatalysis to the chemical literature.[15]

Perhaps most crucial to the success of organocatalysis in the past decade has been the invention or identification of generic modes of catalyst activation, induction and reactivity.[15] Generic activation modes identify reactive species that can participate in many reaction types with consistently high enantioselectivity (as opposed to one or two unique transformations). Such reactive species arise from the interaction of the chiral catalyst with a simple functional group (aldehyde, ketone, alkene or imine) in a highly organised and predictable manner. Thus once these activation modes were established they became a platform for designing new enantioselective reactions. As a result, most of the organocatalytic reactions that have been reported since 1998 are founded directly on only a handful of activation modes.[15] Iminium catalysis (first reported in 2000) is one such case,[27] together with enamine catalysis (which was demonstrated to be a generic activation mode by its application to the Mannich reaction in 2000).[28] Similarly, Jacobsen and Wenzel[29] were the first to demonstrate that hydrogen bonding catalysis had multiple reaction utility, in 2002. Iminium and enamine activation modes are the leaders in aminocatalysis (to be discussed in Section 1.2), whilst hydrogen bonding is prominent in the realm of cinchona-alkaloid and thiourea-based catalysis (Figure 1.4).

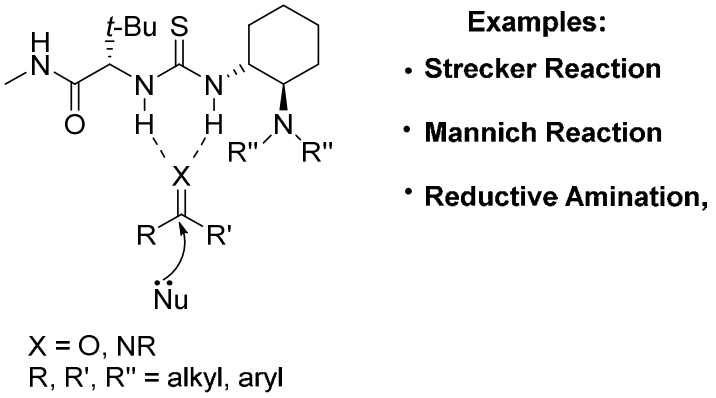


Figure 1.4: Hydrogen bond activation with a thiourea catalyst.

Organocatalysts can be derived naturally or synthetically. For the former, relatively few alkaloids possess a naturally occurring antipode that allows their convenient use in enantioselective synthesis. Cinchona alkaloids are the exception, as they are available in pseudoenantiomeric forms, both of which produce impressive results in enantioselective reactions. Cinchona alkaloids were the first chiral amines to be used in asymmetric catalysis, in the pioneering work of Pracejus from the 1960s on disubstituted ketene alcoholysis.[30] The cinchona alkaloid family consists of two pairs of diastereomers, namely, cinchonine/cinchonidine and quinidine/quinine (Figure 1.5) while all four are readily available in large quantities from chemical suppliers, albeit they are expensive. In such cases the hydroxyamine portions of the molecules are responsible for imparting selectivity. The past few years have witnessed an explosion of interest in the development of other classes of amine-based catalysts from the cinchona alkaloid chiral scaffold. Furthermore, chiral versions of common amines, such as DMAP derivatives and non-cinchona derivatives of quinuclidine have been successfully developed for use in asymmetric synthesis.

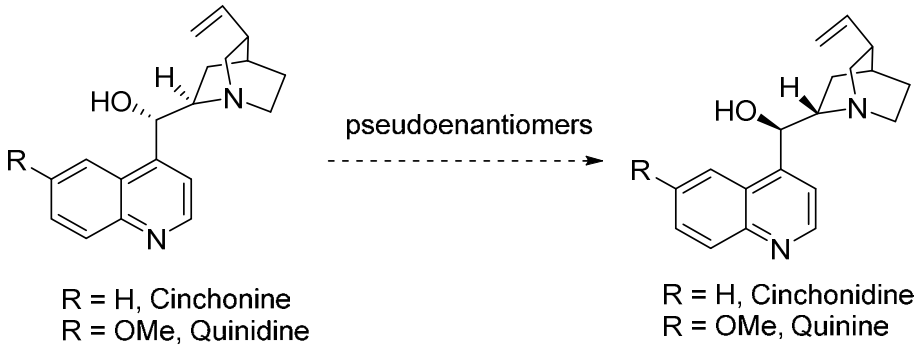


Figure 1.5: Cinchona alkaloid pseudoisomers.

Amino acids have been used as organocatalysts for a long time in asymmetric synthesis, with proline as the champion. In proline catalysis,[31] this simple natural amino acid efficiently imitates the concept of enzymatic catalysis and is often referred to as the "simplest enzyme" in nature.[32,33] However, there are several other reasons why proline has assumed such a prominent role in organocatalysis.[31] Firstly, it is an abundant, cheap and readily available chiral molecule. Secondly, mechanistically, proline is bifunctional (with a carboxylic acid and an amine portion) and these functionalities can act both as acid or base facilitating chemical reactions in concert similar to enzymes. Whilst all these criteria clearly apply to all amino acids, proline is a secondary, cyclic, pyrrolidine-based amino acid, which results in an elevated pK_b value in its amine portion. It has unique nucleophilicity due to this portion, which allows the formation of iminium ions and enamines more readily than other amino acids and amines (including cyclic piperidine). In addition, the carboxylic acid portion aids organocatalysis by acting as a Bronsted acid cocatalyst. Thus proline has not only acted as

a fantastic organocatalyst, but its structure has formed the basis of other new organocatalysts with varying reactivities and applications. Oligopeptides have also been used in organocatalysis. This is primarily because their reactivity can be tuned by varying the nature of the amino acids via combinatorial synthetic methods. Furthermore, their structural simplicity contrasts the complexity of enzymes and thus renders easier mechanistic investigations. Finally, they afford greater flexibility since it is easy to prepare the peptide sequence that can produce the opposite enantiomer or its epimer. Figure 1.6 displays various organocatalysts developed from amino acids and peptides. Many of the other synthetic molecules known to be efficient organocatalysts originate from ligand chemistry. This class of catalyst may include phosphorus-containing compounds, where phosphorus has the advantage of being able to act as both a Lewis base and a nucleophile, as well as providing a stereogenic centre.

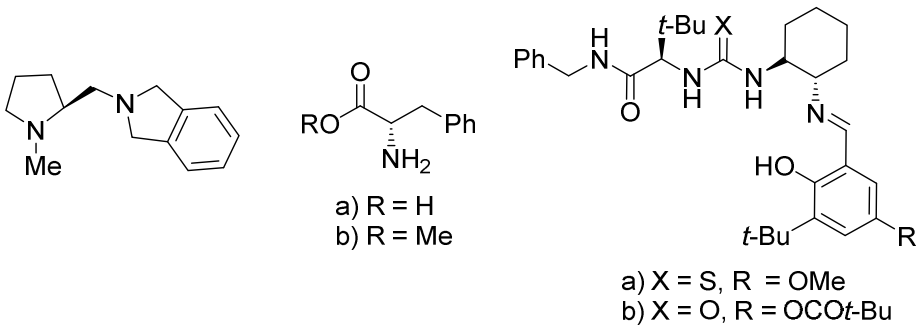


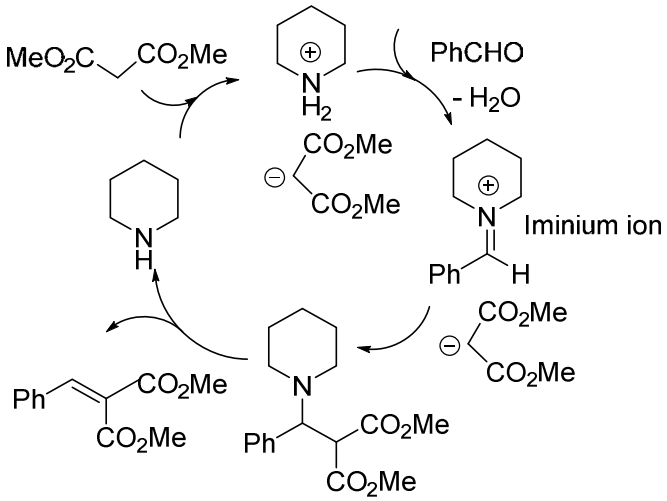
Figure 1.6: Catalysts derived from amino acids and peptides.

As a final point, organocatalytic reactions are of great use to medicinal chemists and this has led to their applications in industry. Medicinal chemists are the largest body of industrial synthetic chemists and they need to find rapid, broadly applicable ways of constructing new candidate drugs for testing. Thus the most important considerations for a catalyst are its generality, convenience and robustness. Organocatalysts meet all of these criteria and they have already been taken up by some medicinal chemists in the pursuit of therapeutic agents targeting a single enantiomer.[34] As the realisation grows that organocatalysts are highly efficient, easily manipulated and have important “green” advantages, asymmetric organocatalysis may catch up with or even surpass the remarkable advances in enantioselective transition-metal catalysis.[3] Furthermore, Dalko et al. have pointed out an interesting dichotomy between organic and organometallic/bioorganic catalysis with respect to their reactivity and applications. On the one hand, organocatalytic reactions have evolved essentially from the ligand chemistry of organometallic reactions (many of these ligands have shown activity in these reactions in the absence of a metal).[35] On the other hand, organocatalytic reactions can be more closely related to enzyme-catalysed reactions since

these molecules often act as artificial enzymes[36] or enzyme mimetics and show some characteristic features of bioorganic reactions. However, this apparent similarity hides major differences in the mode of action. Enzymes act essentially by stabilising the transition-state of the reaction by the subtle orchestration of a number of functions, whereas organic molecules promote the reactions as simple reagents. Thus it would be naive to promote organocatalysts as competitors of organometallic or bioorganic catalysts. Rather, they complement current methods, and offer conceptually novel ideas that open new horizons in synthesis.[4]

1.2 Aminocatalysis

The vast majority of organocatalytic reactions are amine-based. The term ‘‘aminocatalysis’’ was first coined in 2001 by List,[37] which he defined as the asymmetric catalysis of carbonyl transformations using chiral amines as organocatalysts.[38] Aminocatalysis comprises reactions catalysed by secondary and primary amine functionalities of organic molecules via enamine and iminium ion intermediates.[37–39] In this form of asymmetric catalysis, amino acids, peptides, alkaloids and synthetic nitrogen-containing molecules have been used as chiral catalysts.[3] In particular, the application of chiral **secondary** amines as catalysts in transformations of carbonyl compounds has seen an incredible development in recent years.[40] In these reactions the amine catalyst initiates proceedings by first acting as a nucleophile. Once incorporated into the substrate, it provides chirality for the reaction either as a nucleophilic chiral enamine or an electrophilic chiral iminium ion.[13,14,30] These intermediate species are involved in biomimetic strategies common to class I aldolase and ketoacid decarboxylase enzymes, and the proline-catalysed intramolecular Hajos–Parrish–Eder–Sauer–Wiechert reaction involving a chiral enamine was the first example in organic synthesis (see earlier in Scheme 1.6).[18,19,41] Westheimer, in his studies of amine catalysis in biology (which paved the way for the formulation of the class I aldolase mechanism), led to the conclusion that it involves iminium ion and enamine intermediates.[39,42] His ideas stemmed from Emil Knoevenagel who earlier found that primary and secondary amines, as well as their salts, catalyse the aldol condensation of β-ketoesters or malonates with aldehydes or ketones. Knoevenagel realised that his amines were truly catalytic (“Contactsubstanz”), and he achieved remarkably high turnover numbers; see Scheme 1.8 for his reaction. More importantly, in the case of imines - and in the case of β-ketoesters also with enamines—he suggested the same intermediates that Westheimer later proposed in his retro-aldolisation studies.[43,44] Benjamin List accordingly commented: “Thus Knoevenagel’s discovery and mechanistic interpretation of his reaction over 100 years ago laid the historical foundation for the development of modern aminocatalysis”.,[26,27,39]



Scheme 1.8: Knoevenagel's reaction depicted as a modern catalytic cycle.[39]

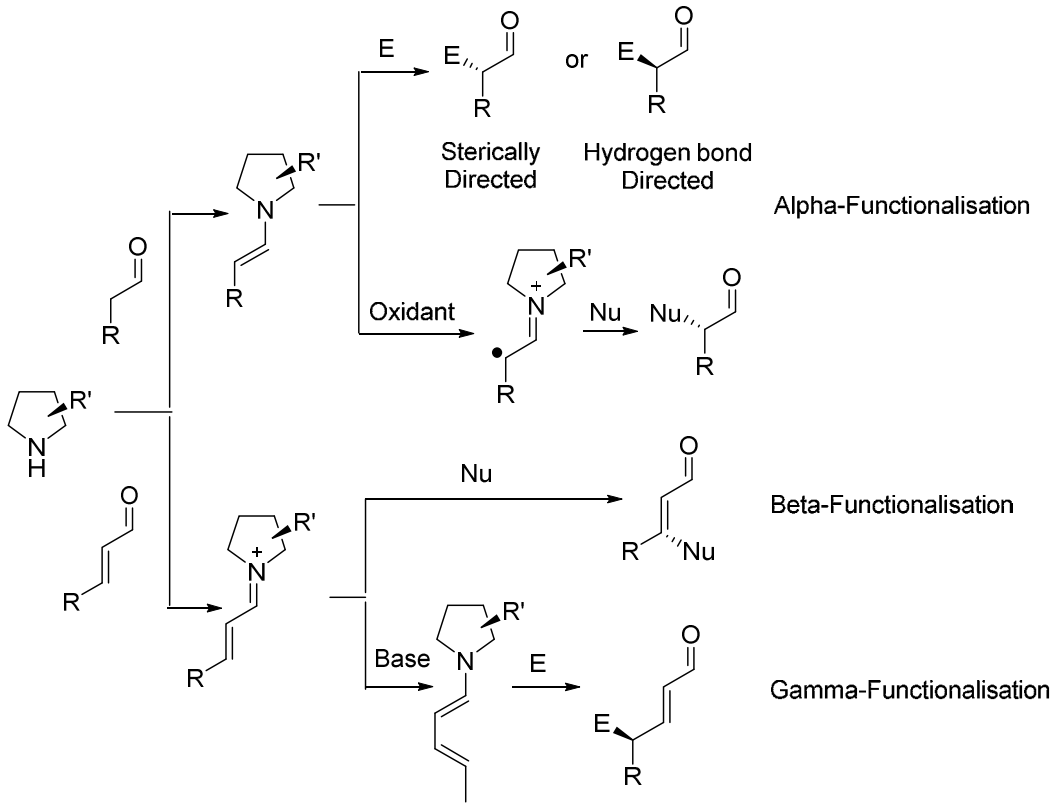
Knoevenagel's work set the stage for the Hajos and Wiechert's aldolisations in which their "catalyst design" is apparent: piperidinium and pyrrolidinium salts were established achiral catalysts of inter- and intramolecular aldolisations[45] and amino acids had already shown their potential,[46–48] thus proline was an obvious choice as an abundantly available chiral secondary amino acid catalyst. However, it is striking to consider (as List points out) [39] that in contrast to Knoevenagel more than 70 years earlier, Hajos and Parrish never discussed any mechanism nor realised or at least mentioned that their process was an early example of asymmetric catalysis. In fact, an enamine mechanism was rejected by Hajos. He opted for a mechanism involving the reaction of a weakly nucleophilic enol with a weakly electrophilic and sterically hindered hemiaminal (with retention of configuration!). Thus it's fair to say that real progress in a mechanistic understanding and generalisation of aminocatalysis was not made during these years. List poses possible reasons why:[39] 1) the Hajos-Parrish reaction was developed in an industrial setting, where the "academics" of a discovery are rarely fully explored; 2) the suggested mechanism by Hajos was counterintuitive and could not easily be generalised; 3) the scope of highly enantioselective aldol variants appeared to be very narrow; and finally 4) the trends of the time were different and the like of Sharpless' studies on transition-metal catalysis led to a whole new era of asymmetric synthesis research - a field that has inspired and fascinated organic chemists deeply to the extent that catalysis with "their own" purely organic molecules may have appeared less exciting for a few decades. In his rationlistion of why the Hajos-Parrish mechanism remained an enigma for decades, Carlos Barbas III suggests that the compartmentalisation of chemist and biochemist ideas as separate may be another reason. As such, chemists like Hajos and his

counterparts never turned to the teachings of Westheimer to elucidate the mechanism of their reaction.[49]

List and Macmillan's independent and deeper investigation of the Hajos-Parrish mechanism and seminal work in 2000 led the way for the generalisation of aminocatalysis and perhaps the explosion of asymmetric organocatalysis as a research field. How did this come about? The research group of Lerner and Barbas III (of which List was a member) was involved in the design of catalysts from aldolase antibodies that were able to promote intermolecular aldol reactions – thus combining organic chemistry ideas with biochemistry.[50–52] These enzyme catalysts use an enamine-based mechanism to catalyse the aldolisation of two carbonyl compounds.[53] Their findings highlighted a close mechanistic analogy between proline- and enzyme-catalysed aldol reactions, as enamine activation was central to both strategies. They thus suggested the potential employment of proline as a catalyst for the direct asymmetric intermolecular aldolisation of unmodified carbonyl compounds. Since then, asymmetric aminocatalysis has become a well-established and powerful synthetic tool for the chemo- and enantioselective functionalisation of carbonyl compounds. This research area has grown at such an extraordinary pace that it is now recognised as an independent area of synthetic chemistry, where the goal is the preparation of any chiral molecule in an efficient, rapid, and stereoselective manner.[33] The large number of concepts developed independently (and almost simultaneously) by different research groups has generated tremendous scientific competition which has guided asymmetric aminocatalysis towards amazing levels of development, and opened up new synthetic opportunities that were previously considered inaccessible. This "aminocatalytic gold rush", as Melchiorre coined it, emphasises an important aspect of scientific research and discovery: "progress depends on human effort".[33]

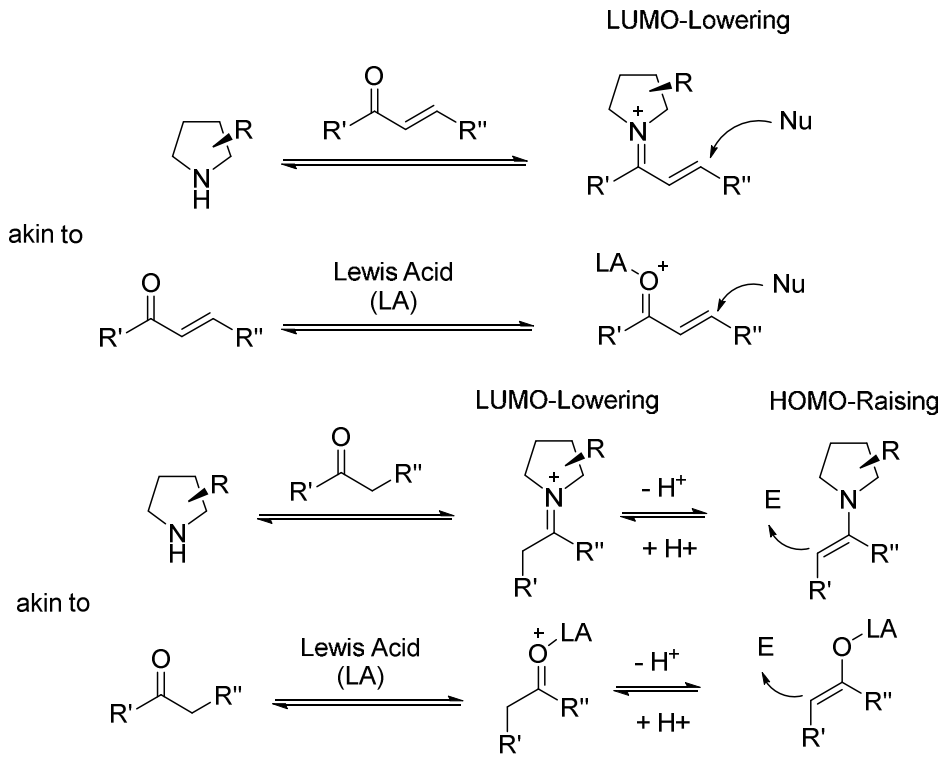
1.2.1 Secondary Amines

Although primary amine catalysis has its place in asymmetric organocatalysis, most experts in the field define aminocatalysis as organocatalysis with secondary amine compounds.[38,40] Jørgensen elegantly described four distinct outcomes based on aminocatalysed carbonyl functionalisations, two applying aldehydes and two using α,β-unsaturated aldehydes (Scheme 1.9).



Scheme 1.9: Diagram taken from Jørgensen's review on aminocatalysis mechanisms.[40]

The above activation modes are based on active intermediates generated by the condensation of chiral cyclic amines with a carbonyl group. Thus in Melchiorre's view, the principle for aminocatalytic activation emulates the mechanism of the activation of carbonyl compounds by Lewis acids, Scheme 1.10. This well-established strategy for enantioselective catalysis involves rate acceleration through the reversible binding of the Lewis acid to π-systems. This in turn results in a redistribution of the electronic density toward the positively charged metal centre. The reversible condensation of a chiral secondary amine with carbonyl compounds to form positively charged iminium ion intermediates mimics the electronic situation of the π-orbitals in Lewis acid catalysis, where the energy of the lowest unoccupied molecular orbital (LUMO) is effectively lowered. For conjugated π-systems, the electronic redistribution prompted by the iminium intermediates allows nucleophilic additions, including conjugate additions and pericyclic reactions (LUMO activation). In the case of isolated π-systems, the lowering of the LUMO energy increases the acidity of the α-proton, which prompts a fast deprotonation and leads to the generation of the enamine - a nucleophilic enolate equivalent (highest occupied molecular orbital (HOMO) activation). Here too, the raising of the energy of the HOMO leads to activation of the carbonyl compounds, similar to the generation of activated nucleophiles by Lewis acids.[33]



Scheme 1.10: Melchiorre's comparison of the activation of carbonyl compounds by a Lewis acid and by aminocatalysis.[33] E = electrophile, Nu = nucleophile.

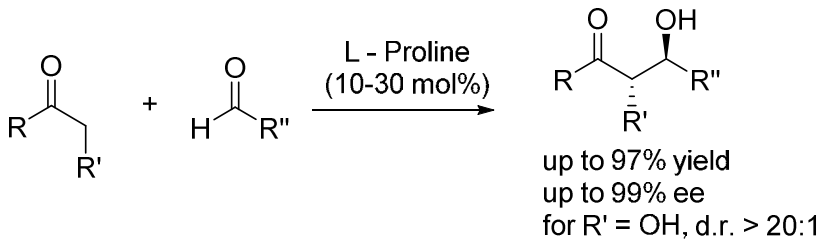
Viewing this, one might say that aminocatalysis follows basic mechanistic principles from introductory organic chemistry. Yet, closer mechanistic study of the aminocatalytic functionalisations of aldehydes and α,β-unsaturated aldehydes shows that the reaction mechanisms are often more complex than anticipated (often including subtle intra- and intermolecular bonding interactions), and their study reveals new, fascinating aspects of the reaction sequences.

It is clear that enamine and iminium aminocatalysis are based on the same origin, i.e. iminium-ion formation. This is what List has coined as the "ying and yang" of aminocatalysis where the two catalytic intermediates are opposites, yet interdependent, and they consume and support each other.[38] The understanding of this principle has given rise to the asymmetric functionalisation of a broad range of carbonyl compounds at different positions, which certainly has spurred on the exponential growth of this field. Therefore, the different activation modes of aminocatalysis will now be discussed.

α–Functionalisation

MacMillan's aminocatalysed (imidazolidinone **1**) Diels-Alder reaction (see Scheme 1.7) reported in 2000 was the first demonstration of the effectiveness of his well-designed

imidazolidinone catalyst **1** in the activation of α,β-unsaturated aldehydes. In the same year, following studies on the Hajos-Parrish reaction, Barbas, List and co-workers showed that the proline-catalysed asymmetric intermolecular aldol reaction with aldehyde acceptors could be successfully extended to different types of unmodified ketone donors, including cyclic substrates (Scheme 1.11). An excess of the ketone allows the isolation of the cross-aldol products in good yields and high enantiomeric excess. The enantioselectivity depends on the nature of aldehyde substituents, in which aliphatic aldehydes produce ees of approximately 90%, and aromatic aldehydes give ees of approximately 70%. When hydroxyacetone was used as the donor a highly diastereo- and enantioselective product was obtained. This powerful procedure affords access to synthetically useful *anti*-1,2-diols, which complements the Sharpless *syn*-dihydroxylation of these important building blocks.[54–56]

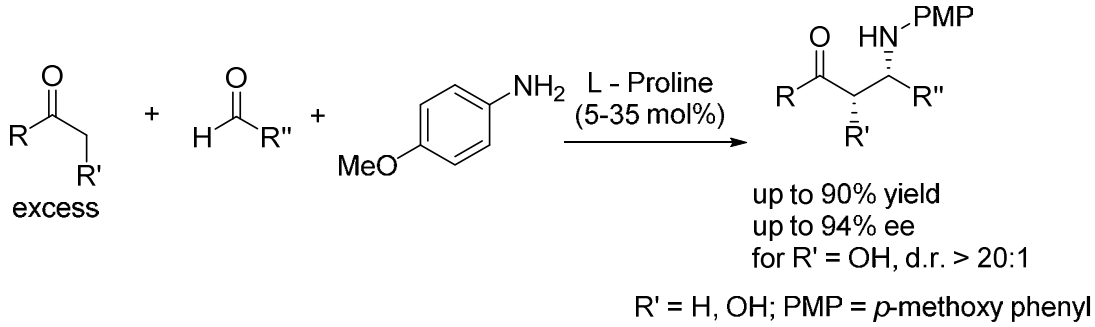


Scheme 1.11: Proline-catalysed intermolecular aldol reaction of unmodified aldehydes and ketones.

Subsequently, Northrup and MacMillan reported the first direct enantioselective proline-catalysed cross-aldol reaction of two aldehydes as another powerful transformation.[57] Using DMF as solvent and a slow addition (syringe pump) of the aldehyde donor, they supressed the formation of by-products arising from product dehydration or self-aldolisation. Thus in the presence of proline (10 mol%) chemo- and diastereoselective aldol cross-coupling of α-alkyl aldehydes furnished highly enantioenriched *anti*-aldol products.

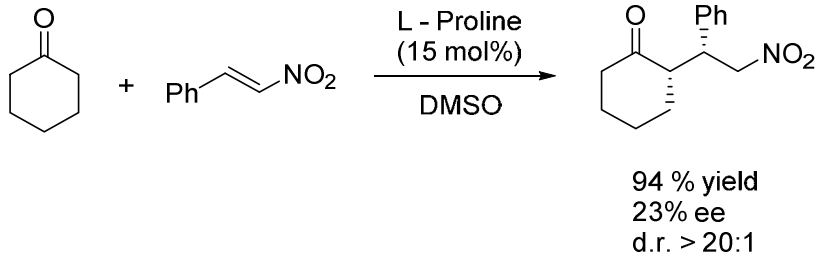
List applied the enamine activation strategy to achieve the first, direct, catalytic and asymmetric Mannich reaction between an aldehyde and a ketone, without prior formation of an enolate or imine (Scheme 1.12). The Mannich reaction constitutes one of the most powerful organic transformations for the construction of chiral nitrogen-containing molecules. This organocatalytic approach first established the possibility of indirectly using electrophiles other than aldehydes, and thus represents a cornerstone in the area of proline catalysis. Under mild conditions of proline catalysis, which allows the *in situ* generation of the imine, the direct three-component Mannich reaction of various ketones has been accomplished to furnish the desired products in high yield and enantioselectivity; the aldol derivatives were

not detected. Notably, the use of α-oxygenated ketones results in complete regioselectivity for the hydroxy-substituted alkyl chain, and allows the highly chemo-, diastereo-, and enantioselective synthesis of *syn*-1,2-amino alcohols.[28,58]



Scheme 1.12: The proline-catalysed Mannich reaction.

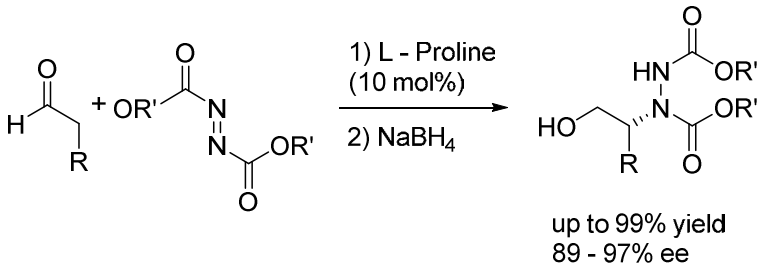
List et al.,[59] as well as Barbas and co-workers,[56] independently demonstrated that Michael acceptors such as nitro olefins react with ketones under proline catalysis (Scheme 1.13). Enantioselectivities were poor, although the reaction paved the way for future optimisations using proline[60] or different secondary amine catalysts.[61–64] Furthermore, these studies highlighted the necessity for the hydrogen bonding interaction between the electrophilic components and the carboxylic moiety of proline to enforce excellent stereocontrol. The interaction is not optimal in the case of Michael acceptors, resulting in very modest enantioselectivity.[33]



Scheme 1.13: The first aminocatalysed Michael reaction using a ketone as the nucleophile.

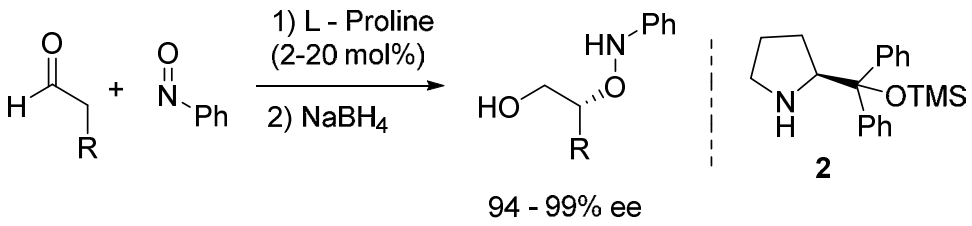
In 2002 Barbas and co-workers described the proline-catalysed direct self-aldolisation of acetaldehyde to afford (*S,E*)-5-hydroxy-2-hexenal in 90% ee.[65] From that point on, the involvement of aldehyde donors in proline catalysis had a profound impact on asymmetric aminocatalysis, encouraging the development of new aldehyde-based methodologies with a wide range of electrophiles. Thus aldehydes gained a central role in organocatalysis due to their high reactivity in reactions catalysed by enamines and iminium ions and because of their great versatility as building blocks.[33]

In nearly all areas of organic chemistry, an essential role is played by chiral molecules containing a stereogenic carbon atom attached to a heteroatom adjacent to a carbonyl moiety. In 2002, Jørgensen[66] and List[67] independently and almost simultaneously reported an efficient and simple method for the highly enantioselective α-amination of aldehydes and ketones using an azodicarboxylate as the electrophilic nitrogen source with 10 mol% proline (Scheme 1.14). This is the main reaction of this PhD thesis and will be reviewed in detail in Section 1.3.



Scheme 1.14: The proline-catalysed α-amination reaction.

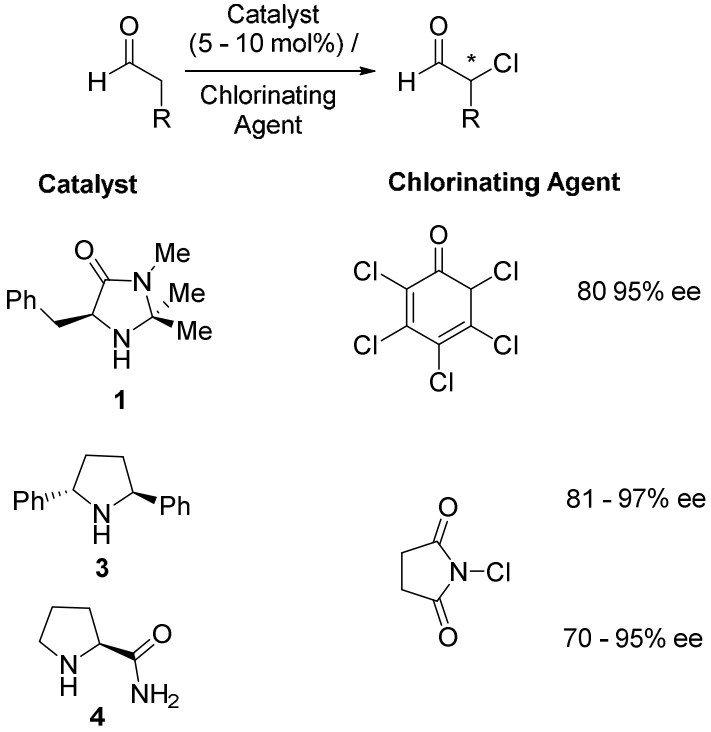
Subsequently in 2003 the direct asymmetric α-oxygenation of aldehydes (Scheme 1.15) was achieved with nitrosobenzene as the electrophilic oxygen source. Here a hydrogen bond in the transition-state is formed between the basic nitrogen atom of nitrosobenzene and the carboxyl hydroxyl-group hydrogen of proline. This accounts for the high regio-control of the reaction. Three different research groups separately exploited the possibility of controlling both the O/N selectivity and enantioselectivity of the direct α-oxygenation of aldehydes.[68–70] An analogous α-aminoxylation was developed using a different secondary amine catalyst, Jørgensen's TMS-protected diphenylprolinol catalyst **2**, which precludes an acid-base interaction between the nitroso nitrogen, since no carboxylic acid functionality is present in the catalyst.[71,72] However, oxygenation can be achieved when catalyst **2** is used in the presence of a Bronsted acid.



Scheme 1.15: The α-oxygenation of aldehydes.

Optically active halogen compounds are also important in various scientific fields for use in further manipulations or because the stereogenic C–halogen centre has a unique property that is of specific importance for a given molecule. The increasing importance of these

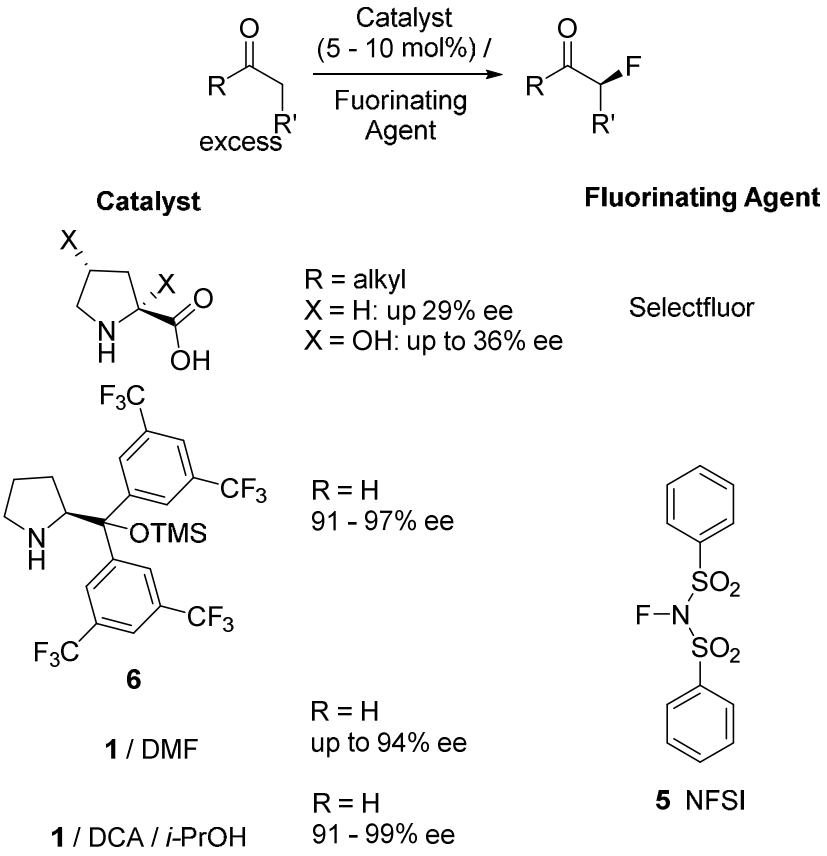
functional groups in medicinal chemistry and materials science has led to an increased search for catalytic asymmetric C–halogen bond-forming reactions.[73] The first aminocatalysed α-chlorination reaction made an impact in three ways: firstly, the reaction expanded the scope of enamine catalysis to intermolecular nucleophilic substitution reactions, secondly, it conclusively demonstrated that enamine catalysis is not limited to proline,[33] and finally, the reaction provided easy access to a large number of simple but extremely versatile building blocks and has since led to the synthesis of naturally occurring compounds.[74] Scheme 1.16 shows the excellent results obtained with the MacMillan catalyst **1** in combination with a perchlorinated quinone,[75] and with 2,5-diphenylpyrrolidine **3** when *N*-chlorosuccinimide is the chlorine source. Interestingly, the simple prolinamide **4** also shows very good reactivity and good enantioselectivity.[76] The authors showed that the products could easily be converted into terminal epoxides (via carbonyl reduction and ring closure), as well as amino acids, or amino alcohols, while maintaining a high enantiomeric excess. These successful α-chlorinations became the inspiration for, and the beginning of, a series of enantioselective α-halogenations of both aldehydes and ketones.



Scheme 1.16: The influential α-chlorination of aldehydes with catalysts other than proline.

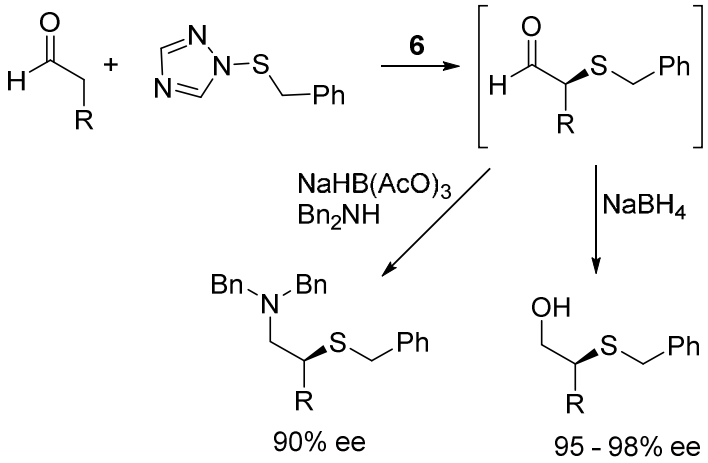
For α-bromination, the easily synthesised and air-stable 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone turned out to be the best reagent for aldehydes (enantioselectivities range between 68% and 96%) and for preparation of chiral α-bromoketones (73–94% ee).[77] This culminated in the successful α-fluorination of aldehydes.

Fluorination is a particularly challenging (and therefore intriguing) transformation since the large electronegativity and small van der Waals radius of the fluorine atom clearly differentiates it from the other halogens. Another strong incentive for achieving aminocatalysed asymmetric α-fluorination is the potential application of the fluorinated products, since fluorine substituents usually affect the overall physicochemical properties of a molecule (e.g. the addition of a fluorine atom to a biologically active compound can significantly improve its metabolic stability).[33,78] Direct enantioselective α-fluorination of aldehydes was presented within a few weeks in 2005 by four different research groups. Enders and Huttl,[79] Jørgensen and co-workers,[80] Barbas and co-workers[81] and Beeson and MacMillan.[82] Enders and Huttl described how different chiral amines catalysed the α-functionalisation of carbonyl compounds by using selectfluor as the electrophilic fluorine source with moderate enantioselectivity. The three other approaches - using *N*-fluorobenzenesulfonimide (NFSI, **5**) as the fluorination reagent - were more successful, with Jørgensen utilising (*S*)-2-[bis(3,5-bistrifluoromethylphenyl) trimethylsilanyloxymethyl]pyrrolidine **6** as a catalyst, Barbas using MacMillan's imidizolidinone catalyst **1** and MacMillan using the same catalyst in the presence of 10 mol% of dichloroacetic acid (DCA) and *iso*-propanol (Scheme 1.17).



Scheme 1.17: The first asymmetric aminocatalysed α-fluorinations of carbonyls.

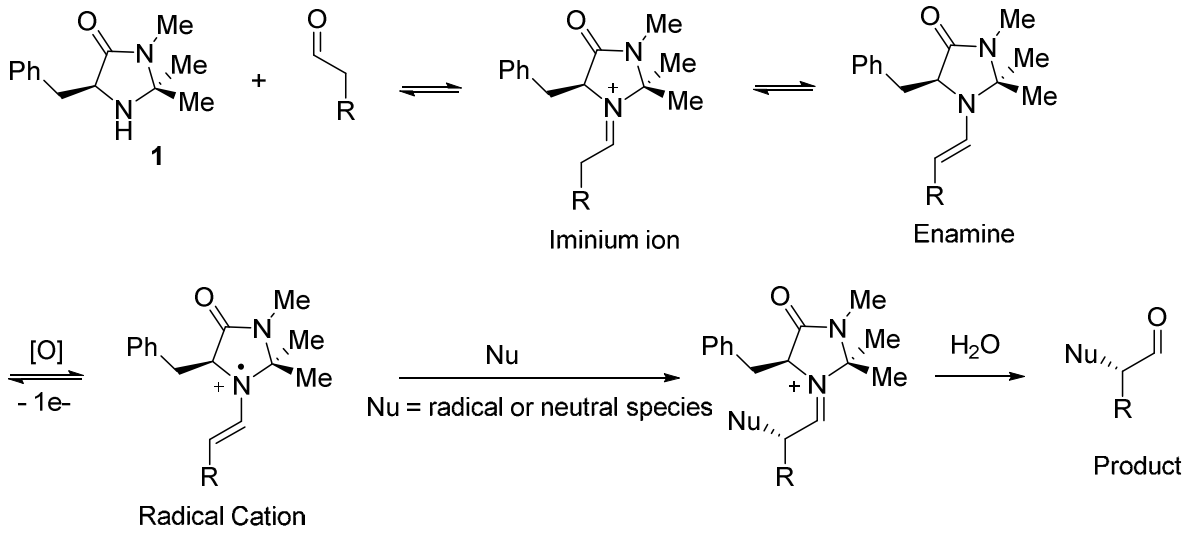
Chiral compounds having a free thiol functionality are very interesting as potent inhibitors of zinc-containing enzymes.[83,84] In 2005 Jørgensen extended the list of existing sulfenylating agents by preparing 1-benzylsulfanyl-1,2,4-triazole. Application of this reagent with his prolinol catalyst **6** to aldehydes resulted in a highly enantioselective process, Scheme 1.18.[85] Product racemisation was avoided by simple and quantitative *in situ* derivatisations (reductive amination and reduction).



Scheme 1.18: The α-sulfenylation of aldehydes.

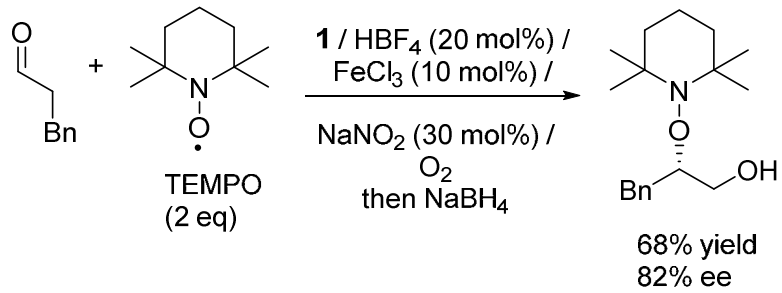
α-Functionalisation by Singly Occupied Molecular Orbital (SOMO) Catalysis

MacMillan[86,87] and Sibi[88] almost simultaneously introduced a new aminocatalytic activation concept in 2007, termed singly occupied molecular orbital (SOMO) catalysis in which activation is based on radical intermediates. Importantly, it links the distant research areas of organocatalysis and radical chemistry. Thus, this approach allows a shift from processes involving charged intermediates to those involving radical catalysis by exploiting the susceptibility of the transient enamine to undergoing selective oxidation relative to other reaction components. This generates a radical cation with three π-electrons and a SOMO, which is activated toward subsequent nucleophilic attack.[33,40] Scheme 1.19 diagrammatically explains this interesting concept.



Scheme 1.19: The principle of SOMO activation in aminocatalysis.

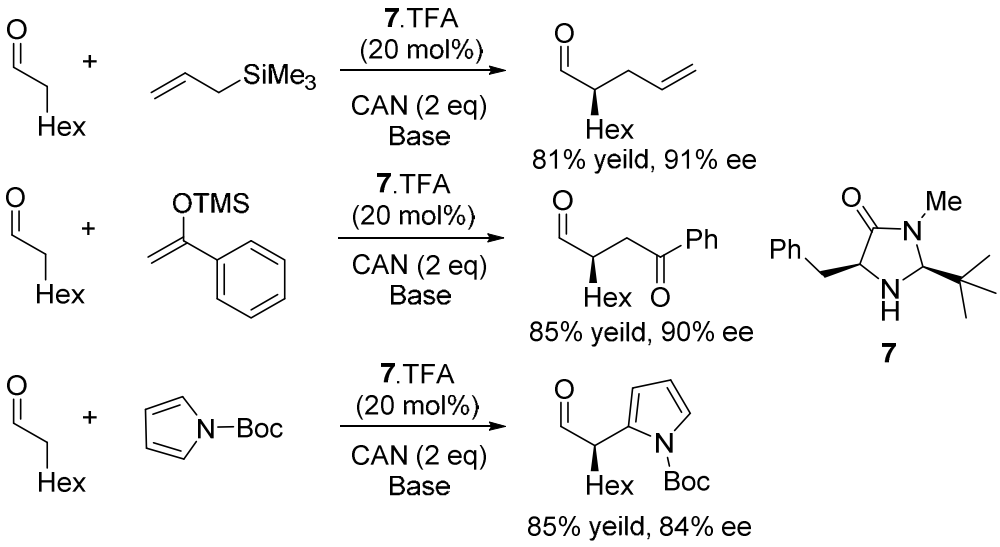
Sibi and Hasegawa exploited aminocatalytic SOMO activation for the stereoselective α-oxygenation of aldehydes with TEMPO, a reliable radical reagent, to intercept the radical cationic species thus generating an oxygenated adduct in moderate to high enantioselectivity (Scheme 1.20). They used the MacMillan imidazolidinone catalyst **1** and a catalytic amount of $FeCl_3$ as a cheap single-electron transfer (SET) reagent in the presence of a $NaNO_2$ / O_2 mixture as a cooxidant in order to avoid having to use a stoichiometric amounts of $FeCl_3$.[88] This method is based on studies by Liang et al. who showed that the $NaNO_2$ / O_2 combination activates $FeCl_3$ by oxidising the Fe^{2+} back to the reactive Fe^{3+}, which in turn oxidises the enamine to a radical cation.[89] Although the similar oxygenated products are accessible via the highly stereoselective proline-catalysed addition of aldehydes to nitrosobenzene or molecular oxygen, [90,91,92] this study represented a significant proof of concept for SOMO catalysis.[33]



Scheme 1.20: SOMO catalysis for aldehyde oxygenation.

MacMillan and co-workers demonstrated the real value of this novel SOMO activation strategy by applying it to the highly enantioselective α-alkylation of aldehydes.[86,87] Here, a

radical cation is generated by oxidation of the enamine with cerium ammonium nitrate (CAN), which is followed by reaction with an allylsilane as a π-electron-rich allyl nucleophile. A second oxidation by CAN (present as 2 equivalents) then removes the silyl group as a cation (Scheme 1.21). These reactions display high enantioselectivities with MacMillan's second-generation imidazolidinone catalyst **7**, the development of which will be discussed in the next section. In these transformations it should be noted that the α-carbon atom of the aldehyde reacts as if it is the electrophile. Thus this activation mode formally reverses (umpolung) the normal polarity of enamine intermediates, and in so doing introduces new reactions previously not possible with established catalysis concepts.[33]



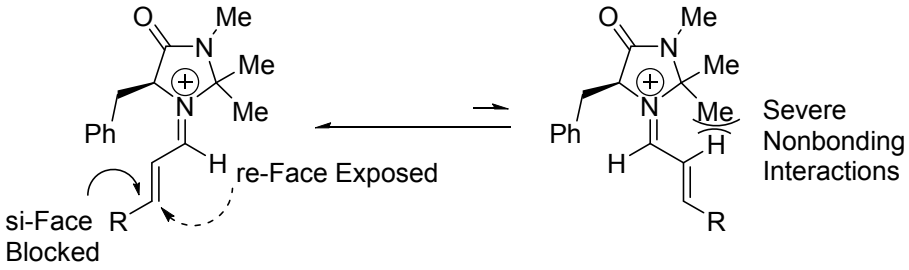
Scheme 1.21: SOMO-catalysed α-functionalisations using MacMillan's second –generation catalyst **7**.

Another important SOMO transformation is MacMillan's first asymmetric catalytic α-vinylation of aldehydes using vinyl trifluoroborate salts as coupling reagents for radical-based processes.[93] They also reported the α-amination of aldehydes with a nitrogen radical in 2013 – the first α-amination through SOMO acticvation.[94]

β-Functionalisation

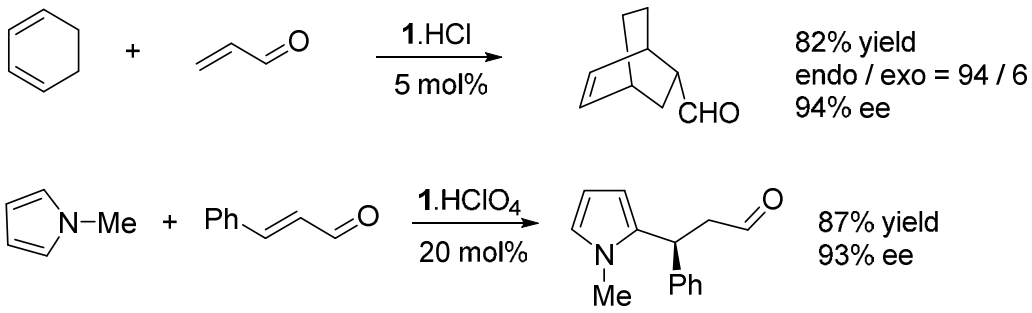
As previously mentioned, α,β-unsaturated carbonyl compounds are activated by lowering the LUMO energy of the system, making them more electrophilic, acidic, and prone to certain pericyclic reactions[38] This organocatalytic activation mode exploits the reversible condensation of a chiral amine catalyst, such as **1**, with an unsaturated aldehyde to form an iminium ion intermediate, which lowers the LUMO energy of the π-system and enhances its susceptibility toward nucleophilic attack. Central to the success of MacMillan's

imidazolidinone **1** as a stereoselective iminium activator is its ability to effectively and reversibly form the reactive iminium ion with high levels of both configurational control and π-facial discrimination (Scheme 1.22). The activated iminium predominantly exists in the $E_{iminium}$-geometry to minimise nonbonding interactions between the iminium double bond C-substituents and the gem-dimethyl groups on the catalyst (although reaction temperature, solvent, catalyst and the iminium counter-ion may affect the *E*:*Z* ratio).[95,96] The selective π-facial blocking by the imidazolidinone benzyl group leaves the re face of the iminium ion exposed for nucleophilic attack, resulting in a highly enantioselective bond formation.[33]



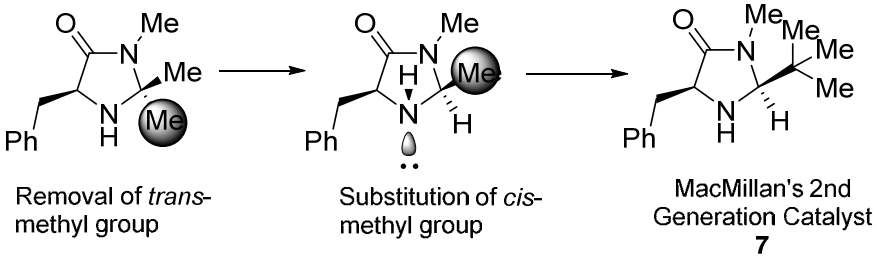
Scheme 1.22: The control of configuration of the iminium ion by imidazolidinone catalyst **1**.[33]

In this regard, MacMillan's asymmetric Diels–Alder reaction between α,β-unsaturated aldehydes and various dienes catalysed by catalyst **1** represents a milestone for asymmetric organocatalysis, since it introduced the novel catalytic activation concept termed iminium catalysis, which in turn led to the development of a wide range of asymmetric transformations involving unsaturated carbonyl compounds. Furthermore, studies on LUMO-lowering organocatalysis by MacMillan and co-workers established the effectiveness of the readily available chiral imidazolidinone **1** to promote mechanistically distinct transformations of α,β-unsaturated aldehydes in a highly enantioselective fashion. Scheme 1.23 shows examples of MacMillan's impressive methodologies: the seminal Diels-Alder reaction[27] and the Friedel-Crafts alkylation of pyrroles.[97] It is also important to note that the nature of the anion of the catalytically active salt is essential for modulating both the reactivity as well as the stereoselectivity of these reactions (although there is precedence of effectively using the imidazolidinone catalyst alone as a neutral species).



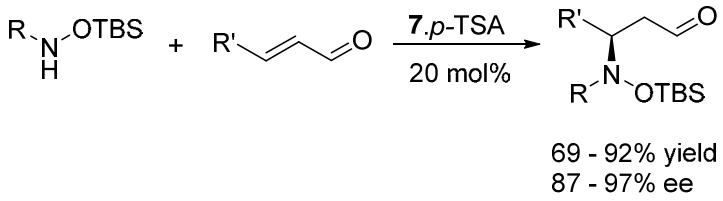
Scheme 1.23: MacMillan's important methodologies using iminium ion activation

The organocatalytic Friedel–Crafts strategy was extended to heteroaromatic indole and furan derivatives (less-activated π-nucleophiles compared to pyrrole) with less impressive results in terms of both yield and ee.[98,99] This highlighted the need for a new, more reactive, and versatile amine catalyst for iminium activation, which would allow for the enantioselective catalytic addition of less reactive nucleophiles. Kinetic studies on the reaction with imidazolidinone catalyst **1** suggested that the rate of formation of the iminium ion as well as that of the C-C bond-forming step both influenced the reaction rate. On this basis, it was theorised that the reaction rate and tendency to form an iminium ion could be improved by replacement of the trans-methyl group (with respect to the benzyl moiety) with a hydrogen atom in order to reduce steric hindrance on the participating free lone pair of electrons on the nitrogen atom (Scheme 1.24). Furthermore, replacement of the *cis*-methyl group with a larger *tert*-butyl moiety provided increased control over the geometry of the iminium ion and better coverage of the blocked *si*-enantioface. The removal of the methyl group also allowed the nucleophile to approach the re face of the formed chiral iminium ion without steric hindrance.[100] Since its introduction in 2002, the imidazolidinone catalyst **7** has been applied successfully to the catalysis of a wide range of asymmetric transformations of unsaturated aldehydes including conjugate additions with different nucleophiles,[101,102] [4+3] cycloadditions[103] and intramolecular Diels-Alder reactions[104,105].[33]



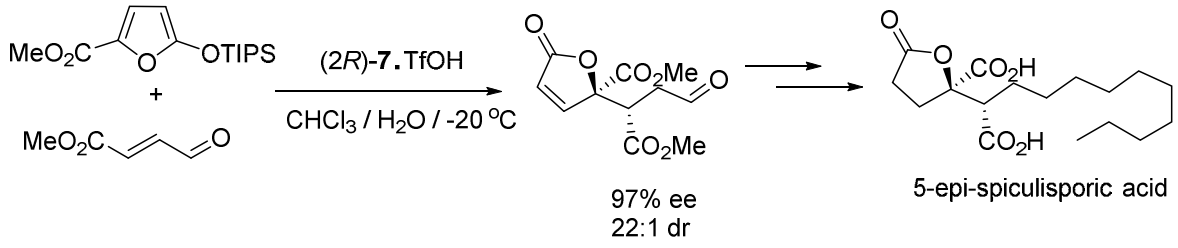
Scheme 1.24: The development of MacMillan's second-generation imidazolidinone catalyst **7**.[33]

The catalytic aza-Michael addition reaction is also important within synthetic organic chemistry, given the significance of the biologically and synthetically interesting products (such as β-amino acids and β-lactams) that result. Since the first example published by Jørgensen et al. in 1996,[106] a number of chiral catalyst systems (including metal-based catalysts) have been developed for this reaction. The first organocatalysed asymmetric aza-Michael addition was reported in 2006 by MacMillan and co-workers (Scheme 1.25).[102] *N*-silyloxycarbamates were applied as nitrogen nucleophiles, as they possess enhanced nucleophilicity due to the neighbouring silyloxy group via an α-effect. The non-basic carbamate N-H moiety enables the permanent loss of the nucleophile proton after the 1,4-addition, thus limiting the reverse reaction. The reaction produces β-amino-aldehydes in good to excellent yields and excellent enantioselectivities, thereby providing a simple, direct and highly stereoselective way to access both cyclic and acyclic, chiral, nitrogen-containing compounds under mild reaction conditions.[107]



Scheme 1.25: MacMillan's maiden organocatalysed aza-Michael addition.

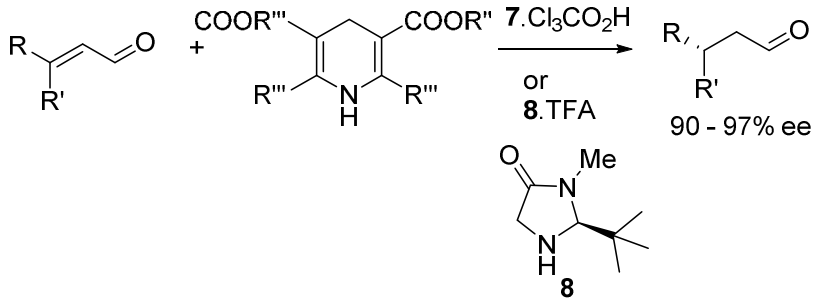
Iminium catalysis can deliver unique, orthogonal, or complementary selectivities compared to metal-catalysed transformations. This is exemplified by the synthesis of butenolides by the Mukaiyama–Michael addition of silyloxyfurans to enals using the (2*R*)-enantiomer of MacMillan's second-generation catalyst **7** (Scheme 1.26).[108]



Scheme 1.26: Synthesis of butenolides by the Mukaiyama–Michael addition.

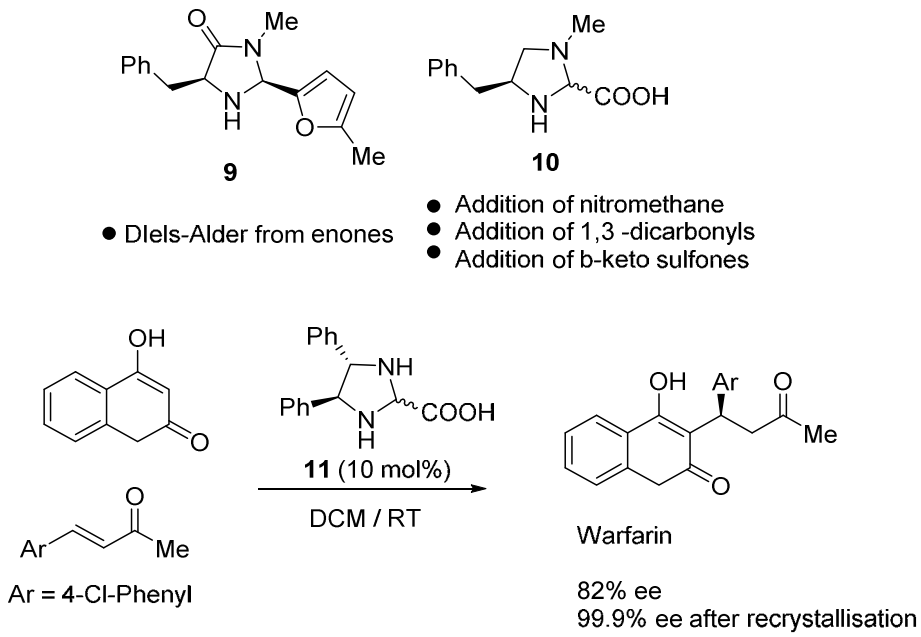
Perhaps the most impressive validation of this concept has been the organocatalytic asymmetric transfer hydrogenation of α,β-unsaturated aldehydes, since the metal-catalysed hydrogenations of double bonds are by far the most predominant metal-based asymmetric transformations applied in industry. In fact, their usefulness was recognised with the award of the Nobel Prize in Chemistry to Knowles and Noyori in 2001 (who jointly shared half of the

prize with Barry Sharpless). The development of organocatalytic hydrogenations would thus be useful to solve toxicity concerns associated with metal-catalysed processes. The research groups of MacMillan and List demonstrated that iminium catalysis is a suitable strategy for accomplishing the highly enantioselective reduction of enals by using synthetic Hantzsch dihydropyridines as hydride donors (Scheme 1.27).[109,110] List and co-workers employed MacMillan's second-generation imidazolidinone **7** as the catalyst, whereas MacMillan and co-workers designed the even newer organocatalyst **8**.[33]



Scheme 1.27: Aminocatalysed transfer hydrogenation.

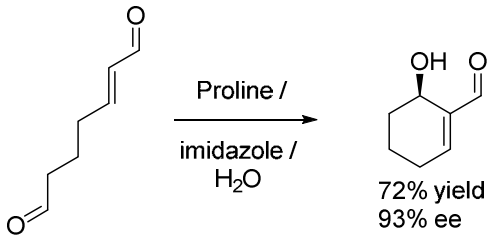
Similarly, stereoselective reactions of α,β-unsaturated ketones tend to be very challenging in organocatalysis. This is due to inherent problems of forming highly substituted iminium ions from ketones, as well as the more difficult aspect of controlling the configuration of the iminium ion. These factors have thus complicated the development of an efficient chiral organocatalyst for them.[33] The first advance in this area came from MacMillan's research group, with the development of a new imidazolidinone catalyst **9** that allowed the first catalytic Diels–Alder reaction with simple α,β-unsaturated ketones.[111] This catalyst allowed enantioselective access to substituted cyclohexenyl ketones, although it did not demonstrate a wide generality as a ketone activator.[112] An important contribution to this challenging field came from Jørgensen and co-workers, who introduced chiral secondary amine catalysts **10** and **11**.[113] These readily available organocatalysts have broad applicability, as they promote the highly enantioselective addition of different carbogenic nucleophiles such as nitroalkanes,[113] malonates,[114] and β-keto-esters[115] as well as sulfones to the unsaturated ketone,[116] thus providing access to useful chiral building blocks. The catalysts' utility as iminium activators has been further verified by the one-pot direct synthesis of enantioenriched biologically active compounds, such as the anticoagulant warfarin.[117] Scheme 1.28 displays these new catalysts and the warfarin synthesis with catalyst **11**.



Scheme 1.28: New catalysts for the activation of α,β-unsaturated ketones.

Phosphorus has also been effectively used as a nucleophile in the aminocatalysed Michael addition reaction of α,β-unsaturated aldehydes. For example, Cordova's hydrophosphination with diphenylphosphine, catalysed by Jørgensen's prolinol catalyst **2**, was achieved in good to excellent yields and enantioselectivities (76-99% ee).[118]

The imidazole-assisted, proline-catalysed intramolecular Baylis–Hillman reaction of an α,β-unsaturated aldehyde has also been achieved in good yield and excellent enantioselectivity. The high ee was attributed to hydrogen bonding between the carboxylic acid, a water molecule, and the aldehyde (Scheme 1.29).[119,120]

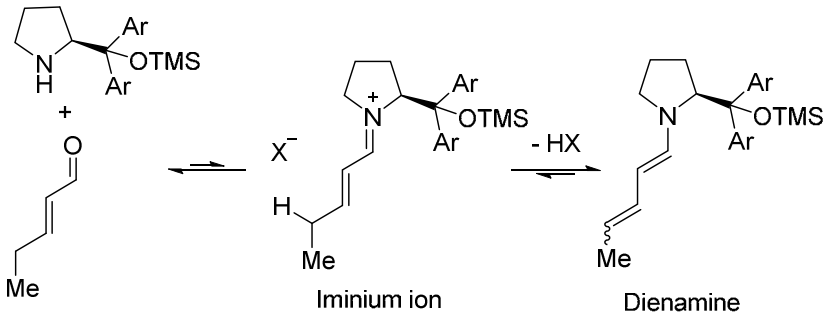


Scheme 1.29: The aminocatalysed, imidazole assisted Baylis-Hillman reaction.

γ-Functionalisation

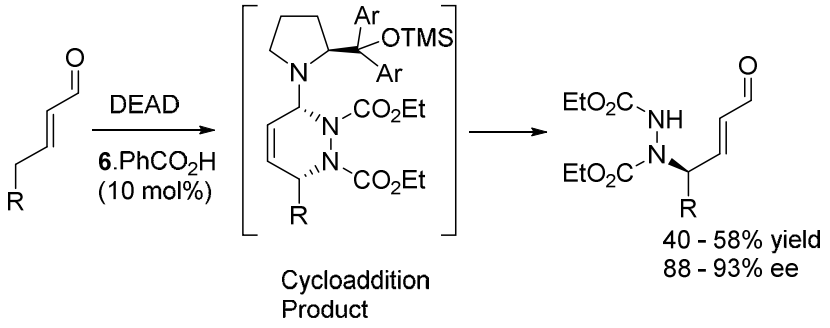
Jørgensen and co-workers[121] reported that under conditions generally used for 1,4-additions, the concentration of the iminium ion formed in the reaction between prolinol catalyst **6** and (*E*)-pent-2-enal was so low that it could not be detected by ^{1}H NMR spectroscopy. This was because the negatively charged counterion could easily abstract the γ-proton of the iminium

ion such that the electron-rich dienamine was the most abundant species in solution (Scheme 1.30).



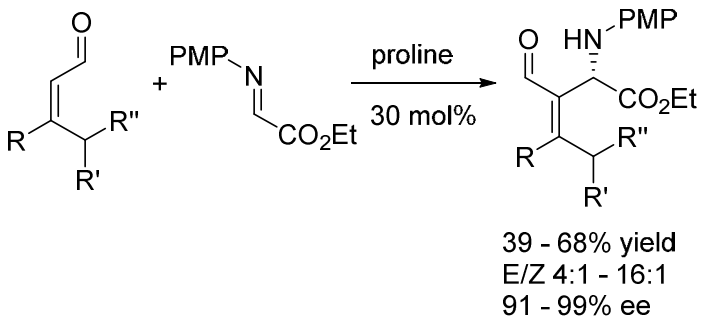
Scheme 1.30: The activation of α,β-unsaturated aldehydes to form dienamines.

Based on the above observations, Jørgensen and co-workers developed the first γ-amination of α,β-unsaturated aldehydes (Scheme 1.31).[121] Prolinol **6** catalyses the γ-functionalisation of α,β-unsaturated aldehydes with diethyl azodicarboxylate (DEAD). The products were obtained in moderate yield and with high enantioselectivity (88–93% ee). On the basis of the experimental evidence and computational investigations, the authors proposed that this outcome was the result of a Diels-Alder reaction between the (*E*-s-*cis*,*E*)-dienamine conformer and DEAD. Hydrolysis of the cyclic intermediate resulted in the release of the catalyst and the chiral γ-aminated product.



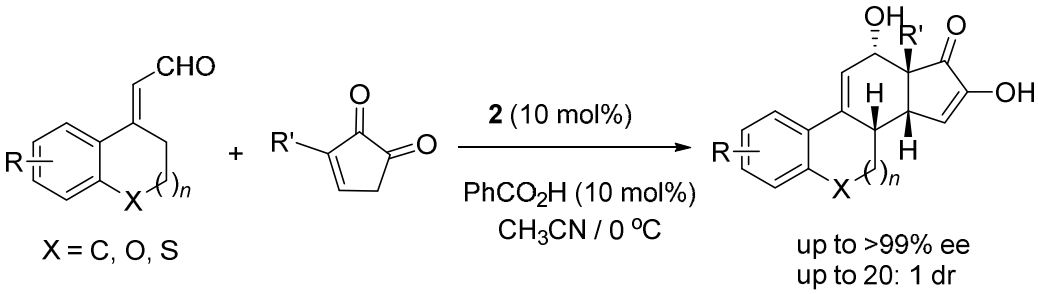
Scheme 1.31: The γ-amination of α,β-unsaturated aldehydes.

Subsequently, Barbas and co-workers demonstrated regioselectivity control with the dienamine [122,123] in its reaction with imines, which gave the α–product exclusively instead of adding the electrophile at the γ-carbon atom (Scheme 1.32). The product obtained equated with that from an aza-Morita–Baylis–Hillman (MBH) reaction, albeit formed via a different mechanism, and was formed in moderate yields but with excellent enantioselectivities (up to 99% ee).



Scheme 1.32: The proline-catalysed aza-Morita–Baylis–Hillman (MBH) reaction

Similarly, in 2014 Jørgensen et al. reported the use of prolinol catalyst **2** for generating a dienamine from the exocyclic enal shown in Scheme 1.33. This then reacted with an enone dienophile to effect a Diels-Alder route to the synthesis of 14β-steroids in high diastereoselectivity (up to 20:1 dr) and high enantioselectivity (up to >99% ee). There is also a chemoselective aspect to this reaction since the catalyst undergoes faster condensation with the enal compared to the enone. This new reaction has the attraction of allowing for several substituents in the A ring in a simple one-step approach (Scheme 1.33).[124]

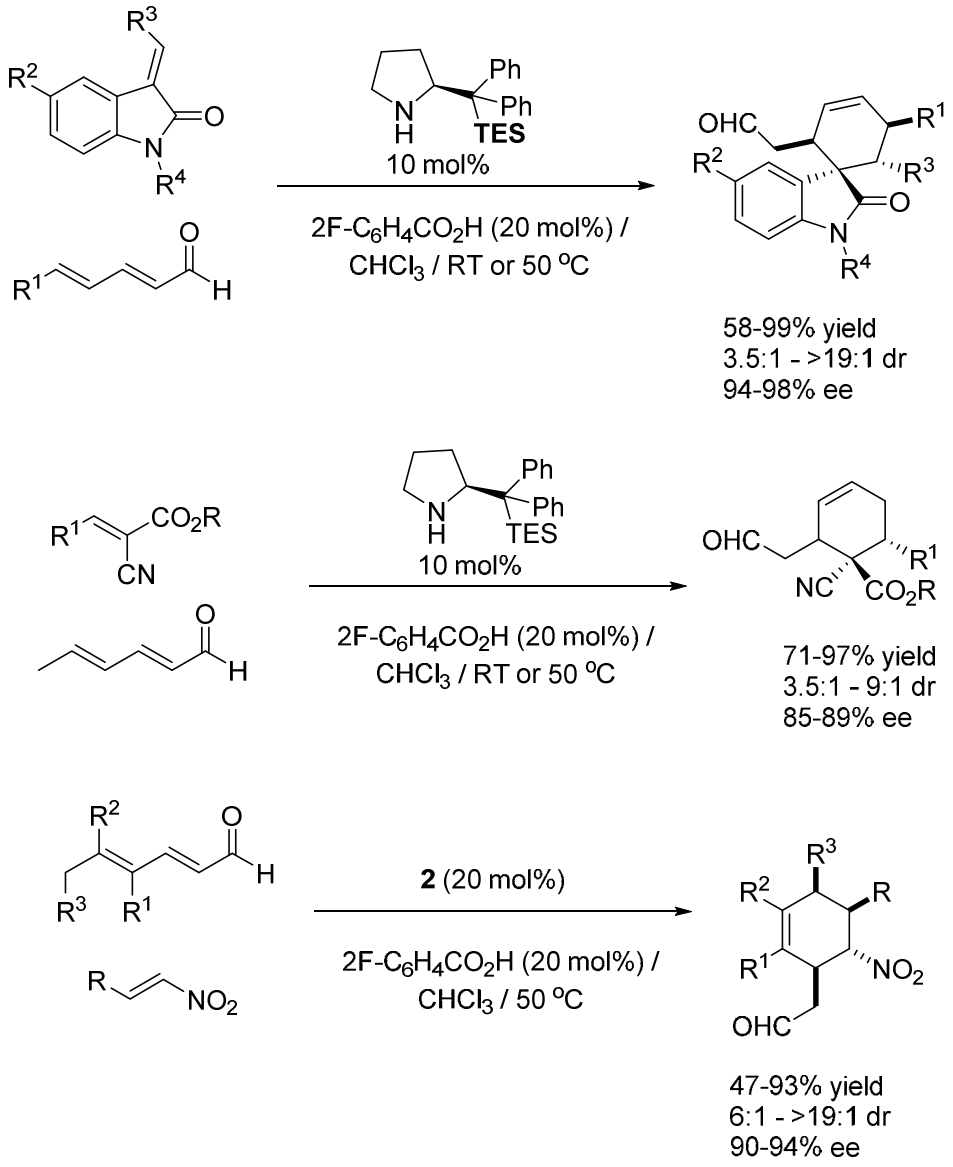


Scheme 1.33: The use of γ-functionalisation to synthesise 14β-steroids.

Thus the high reactivity of these conjugated enamines can be controlled by a careful choice of catalyst, reagents, and conditions. The few examples reported in this review show that the highly enantioselective γ-functionalisation of α,β-unsaturated carbonyl compounds can be achieved via a [4+2] cycloaddition or as a result of a direct nucleophilic γ-addition.

Aminocatalysis activation has also been extended to trienamines to give ε-functionalisation.[125] A collaboration between the Jørgensen and Chen research groups first established this HOMO-raising strategy.[126] The condensation of **2** or its triethylsilyl analogue with 2,4-heptadienal leads to the transient formation of an iminium ion, which rapidly equilibrates to the trienamine intermediate. Calculations have found the all-trans trienamine as the lowest energy isomer. Such trienes undergo highly stereoselective Diels–Alder processes at the β- and ε-carbons with olefinic dienophiles, such as methyleneindolinones or olefinic cyanoacetates (Scheme 1.34) with impressive control over the regio-, diastereo-, and

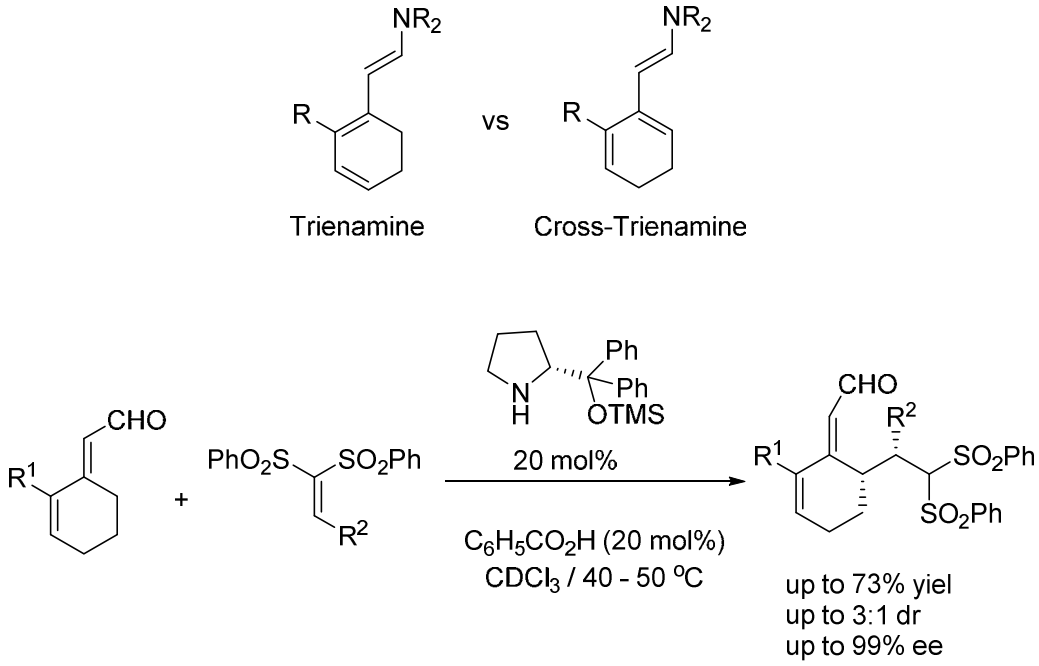
enantioselectivity. The cycloaddition's regio- and endo-selectivities were controlled by orbital factors and secondary orbital interactions, while the enantioselectivity was governed by the ability of chiral secondary amines to ensure effective π-facial discrimination through steric control. The scope of this Diels–Alder reaction was then successfully extended to include nitroalkenes with an *exo*-selectivity (Scheme 1.34).[127]



Scheme 1.34: Trienamine Diels-Alder transformations.

Soon afterwards, Jørgensen and co-workers introduced the concept of cross-trienamines generated from cyclic enals.[128] Thus, asymmetric Diels–Alder reactions proceed through a cross-trienamine intermediate in preference to the more stabilised linear trienamine intermediate. Jørgensen was able to show that cross-trienamine activation can also be applied to Michael additions. Thus cyclic 2,4-dienals form the cross-trienamine which then

undergoes a Michael addition with a vinyl bis-sulfone to give products in high yield and excellent enantioselectivities (up to 99% ee), Scheme 1.35.



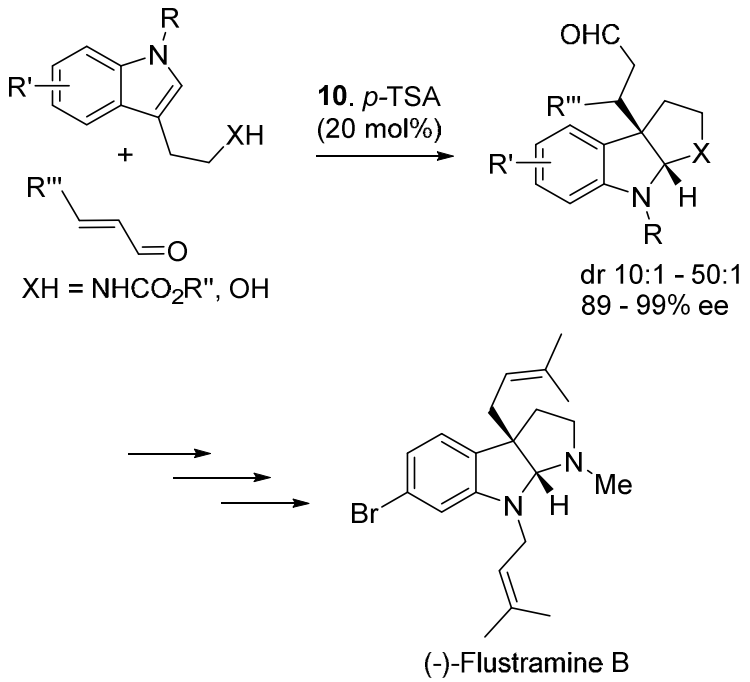
Scheme 1.35: Cross-trienamine aminocatalysis used in a Michael addition.

These results illustrate how asymmetric aminocatalysis still, remains a highly active area of chemical research, providing innovative strategies to successfully overcome difficult challenges related to the synthesis of complex chiral molecules.[129]

Tandem Reactions

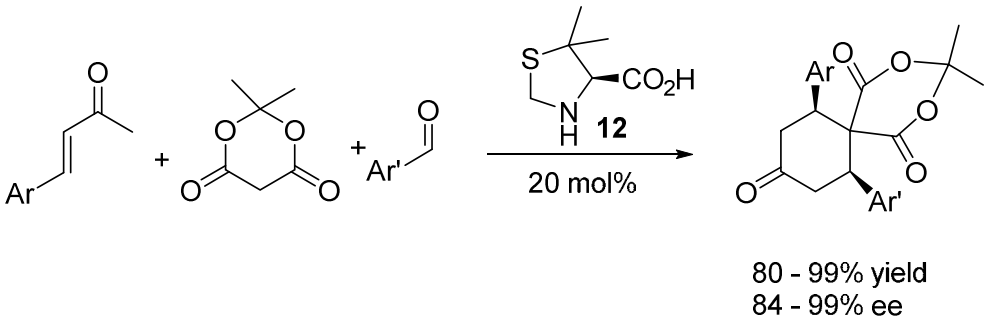
Combining the "ying and yang" aminocatalysis principles in tandem sequences is an attractive prospect in organocatalysis.[38] Multi-step sequences involving the synthesis, isolation and purification of intermediates are usually required to synthesise complex chiral molecules. In contrast, the biosynthesis of complex natural products is achieved by highly regulated catalytic domino reactions that do not require time-consuming and costly operations. Thus, with the efficiency of nature as inspiration, the design of catalytic enantioselective domino transformations has become an essential goal. Another big operational and economic advantage of organocatalytic cascade reactions is that they don't need protecting groups. The knowledge accumulated on the mechanism of enamine and iminium catalysis has allowed the integration of these activation modes into more elaborate reaction sequences. Such tandem sequences can be very powerful for the generation of molecular complexity in a simple one-flask operation, particularly if they are combined into double, triple, and even multiple cascades.

While Robinson annulations (following the Hajos-Parrish reaction) are well known with enones, the first example of a domino reaction involving α,β-unsaturated aldehydes was presented in 2004 by the MacMillan research group[130] in which indole C-3 addition to an enal-derived iminium ion using chiral imidazolidinone **1** (Scheme 1.36) resulted in a highly enantioselective formation of a quaternary stereocentre. The intermediate indolinium ion then underwent trapping by the appended alcohol or protected amino moiety to form an optically active pyrroloindoline, which could be accessed in high yield and in excellent diastereomeric and enantiomeric ratio in a single and simple operation. Many analogues of naturally occurring compounds were then accessed using this transformation. (-)-Flustramine B is an example, as it was synthesised in just five steps starting from the product of an organocatalytic reaction.



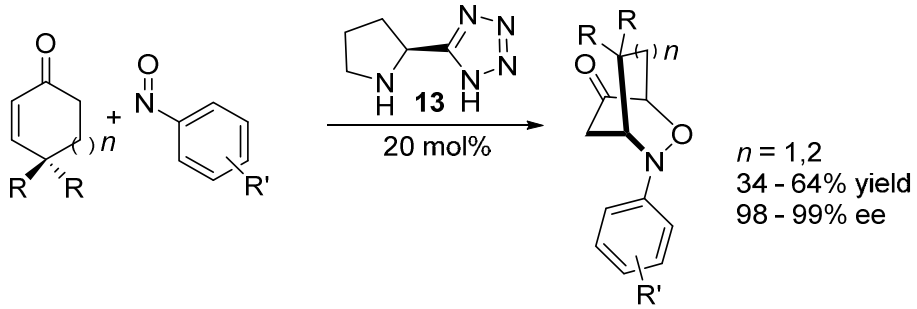
Scheme 1.36: Domino conjugate addition / cyclisation reaction leading to the synthesis of (-)-Flustramine B.

Around about the same time, Barbas and co-workers started investigating the coupling of three components through sequential Knoevenagel and Diels–Alder reactions.[131–134] Scheme 1.37 shows their approach[132] involving first a Knoevenagel condensation between the aldehyde and Meldrum's acid to form a dienophile, which reacts with the chiral dienamine intermediate formed by condensation of 5,5-dimethyl-thiazolidinium-4-carboxylate **12** with the enone. The chiral product of the resultant Diels–Alder reaction was obtained in excellent yield and up to 99% ee after hydrolysis of the catalyst.



Scheme 1.37: Asymmetric Knoevenagel / Diels-Alder reaction.

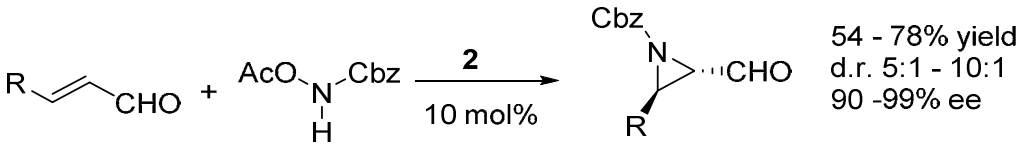
Another important example of an organocatalysed domino reaction involving unsaturated ketones was reported by Yamamoto et al., Scheme 1.38.[135,136] Here, a dien-2-amine was formed due to the presence of a quaternary centre at C-4 of the enone, which underwent a regioselective Diels-Alder reaction with nitrosobenzene. The authors suggest this to be a stepwise sequence involving α-addition to the oxygen of the nitroso group followed by ring closure of nitrogen onto the resultant α,β-unsaturated iminium ion, although it is feasible that cycloadduct formation involves a concerted process. This is one of the first examples of tetrazole catalyst **13** being used. This catalyst was developed and introduced on separate occasions by Yamamoto,[137] Arvidsson[138] and Ley[139] as an improvement on proline due to greater reactivity and broader solvent scope.



Scheme 1.38: A domino enamine/iminium ion reaction catalysed by tetrazole catalyst **13**.

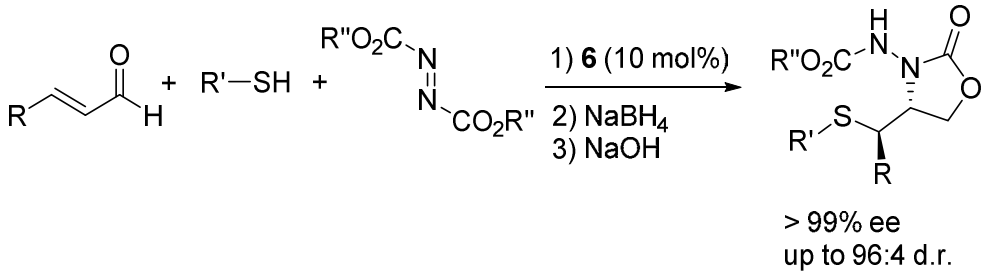
Similarly, in 2005 MacMillan and Kunz developed an organocatalysed cyclopropanation as a novel domino reaction.[140] Shortly after, Jørgensen and co-workers demonstrated that the prolinol catalyst **6** can catalyse the direct epoxidation of β-mono-substituted or α,β-di-substituted α,β-unsaturated aldehydes under very mild conditions.[141] Mixtures of *E*- and *Z*-olefins are transformed with very good stereoselectivity in a stereoconvergent manner. Approximately two years after these ground-breaking discoveries, the Cordova research group reported the asymmetric aziridination of α,β-unsaturated aldehydes (Scheme 1.39).[142] Key to the success of this reaction was the choice of a Cbz carbamate protecting group on

the hydroxylamine nitrogen source. Thus, valuable aziridines with easily removable protecting groups were obtained directly and in high enantiomeric excess (90–99% ee) using prolinol catalyst **2**. Using a similar mechanistic principle, in 2015 Hayashi et al. reported an aminocatalysed asymmetric epoxidation of 2-oxoindoline-3-ylidene acetaldehydes with hydrogen peroxide in good yield and up to 99% ee.[143]



Scheme 1.39: Organocatalysed aziridination.

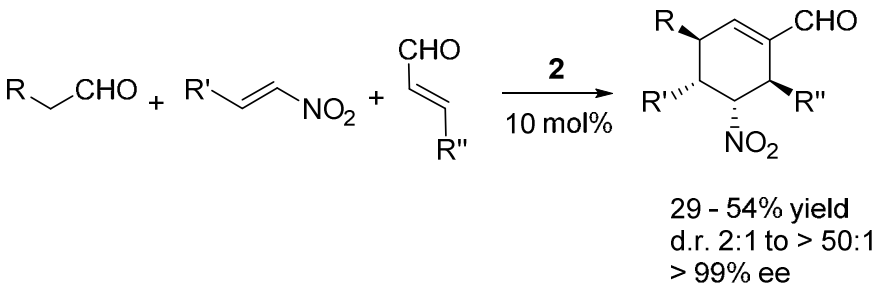
Jørgensen et al. have shown that asymmetric organocatalytic multi-component reactions (MCR) can lead to simpler procedures for the formation of multiple stereocentres and thus more environmentally-friendly processes.[144] They demonstrated the potential of the organocatalytic asymmetric MCR by presenting a domino-conjugated thiol addition / amination reaction. The soft sulfur nucleophile first reacts with the iminium ion intermediate to form an enamine, which then adds to the nitrogen electrophile, giving essentially enantiopure products when prolinol **6** was used as the catalyst (Scheme 1.40). Thus a simple approach to the synthesis of highly functionalised molecules having two adjacent stereocentres with ees mostly >99% was developed.



Scheme 1.40: Jørgensen's MCR catalysed by prolinol **6**.

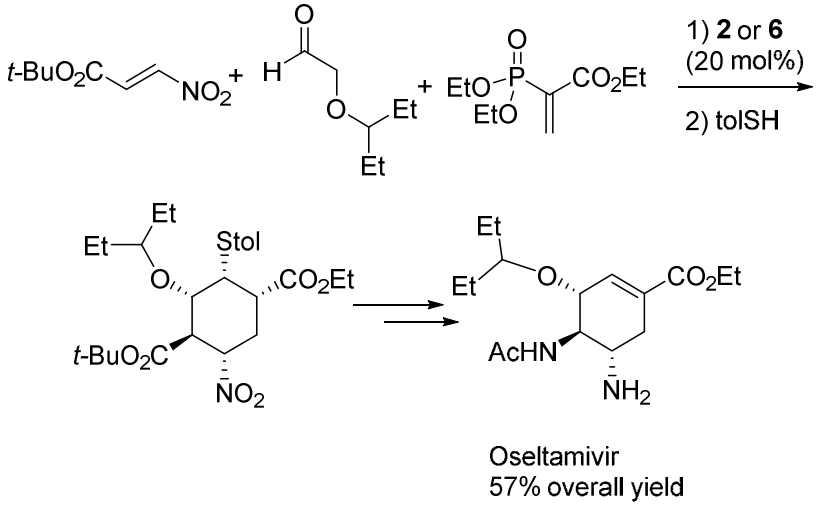
Remarkably, Enders and co-workers found success in the even more ambitious synthetic task of controlling four stereocentres in a triple domino reaction involving an exceptional sequential enamine/iminium/enamine activation sequence (Scheme 1.41).[145–147] The diphenylprolinol catalyst **2** first controls a Michael addition of the aldehyde to the nitrostyrene derivative, which adds in a second Michael reaction to a chiral enal-derived iminium ion to form an enamine. Finally an intramolecular aldol reaction leads to the cyclic six-membered product in which the carbonyl group from the original aldehyde acts as the acceptor. In such

a way highly functionalised cyclic products are obtained in essentially enantiopure (>99% ee) form in a simple single operation.[145]



Scheme 1.41: Aminocatalysed enamine/iminium/enamine domino reaction.

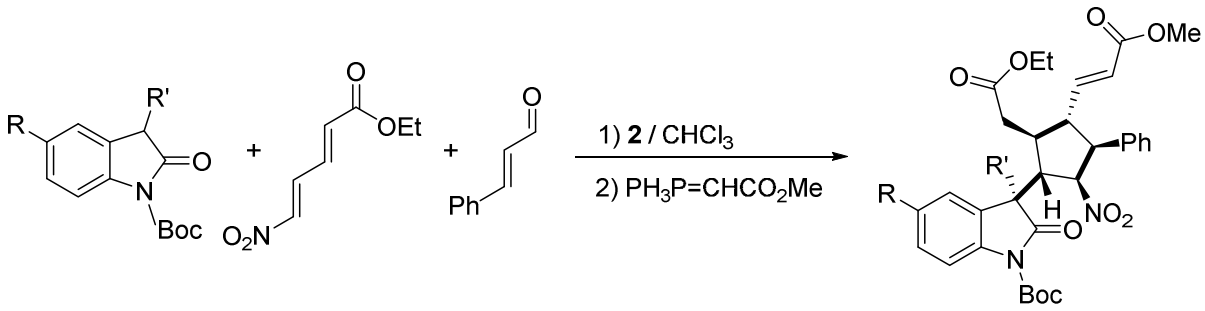
This cascade provided the inspiration for Hayashi's elegant organocatalytic asymmetric synthesis of (-)-Oseltamivir (Tamiflu) in 2009, Scheme 1.42.[148] The synthesis is based on 3 simple starting materials: an alkoxyaldehyde, a nitroalkene and a diethyl vinylphosphonate derivative. As before, addition of the chiral enamine (derived from the aldehyde with prolinol **2**) to the nitroalkene gave a Michael adduct, which underwent a second Michael addition to the vinyl phosphonate to generate an ylide that ring closed in a Wittig reaction. Finally, a thio-Michael reaction followed by nitro group reduction, and then restoration of the double bond rendered enantiopure Oseltamivir in 57% overall yield and an 87% ee. The thio-Michael step protects the double bond during the nitro-group reduction. The complete synthesis involved only three separate one-pot operations and a single chromatographic purification.



Scheme 1.42: Domino approach to the synthesis of (-)-Oseltamivir.

In 2014 Constantieux et al. described a new enantioselective three-component reaction between β-keto esters, enals and *N*-(2-aminoethyl)pyrroles to afford novel, fused tricyclic piperazines.[149] In the same year Enders and co-workers reported the organocatalysed

synthesis in one pot of functionalised cyclopentanes bearing an oxindole moiety together with several other functional groups. Their reaction involved a triple Michael domino reaction catalysed by Jørgensen's prolinol catalyst **2**, followed by a Wittig olefination to form three C-C bonds and 6-stereocentres, including a quaternary one (Scheme 1.43). The catalyst initiates the first Michael addition of the oxindole to the nitro ester at C-4 (C-1 as the ester carbon) by acting as a Bronsted base. This intermediate then undergoes a second Michael addition with a catalyst-activated cinnamaldehyde iminium ion and finally, the resulting enamine initiates the third Michael addition to the α,β-unsaturated ester at C-3. A Wittig olefination of the free aldehyde then completes the sequence.



up to 99% ee, 15:1 dr

Scheme 1.43: Multicomponent synthesis of cyclopentane-oxindoles.

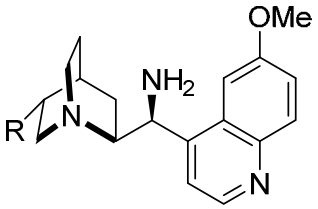
Predicting how extensive the application of organocatalysed domino reactions will be in organic synthesis in the future is almost impossible to predict, since new reports seem to be expanding the possibilities of this methodology all the time. As Jørgensen stated: "We believe and hope that the future will bring an increased use of organocatalysis in total synthesis, as well as in standard transformations. As the toolbox of organocatalytic reactions grows, it will bring new transformations that will short-cut established routes to interesting molecules."[150] In this view, advances made in tandem organocatalysed reactions are surely steps in the right direction.

1.2.2 Primary Amines

Until 2004 comparatively little attention had been paid to the development of chiral primary amine catalysts, even though primary amine catalysis is effectively exploited by natural enzymes such as Type I aldolases and decarboxylases.[53] The notion of unfavourable imine–enamine equilibria may have played a role in this,[151–153] although it was probably also due to the excitement generated by the advent of proline as an organocatalyst resulting in great emphasis being placed on cyclic secondary amines as organocatalysts. Even though the focus of this thesis is on secondary amine-catalysed reactions, it is still worth mentioning the

salient features of this class of organocatalysts since they often compensate for the weaknesses of aminocatalysts, especially with hindered or less reactive substrates.

Chiral primary amine derivatives have recently been employed to activate challenging classes of unsaturated carbonyl compounds by overcoming the steric restrictions associated with the more congested secondary amine catalysis. For instance, the efficient activation of α-substituted α,β-unsaturated aldehydes by imidazolidinone catalysts or by prolinol catalysts is generally not possible because of steric constraints. The β-functionalisation of unsaturated ketones is also hampered by sluggish reaction rates when using secondary chiral amine catalysis, probably because of the generation of only small amounts of the catalytically active adducts. Primary amines can overcome these limitations. In particular, it was demonstrated that the salts of 9-amino-9-deoxyepiquinine (**14**) and 9-amino-9-deoxyepihydroquinine (**15**) from the Cinchona class (Figure 1.7) are effective catalysts for the activation of enones.[154–158] By choosing the appropriate counteranions (such as from TFA), it was possible to tune the reactivity and the selectivity of the catalyst system, resulting in a highly enantioselective conjugate addition of a series of different nucleophiles (C, O and S nucleophiles).



R = vinyl - **14**
R = ethyl - **15**

Figure 1.7: The primary amine catalysed β-functionalisation of unsaturated ketones.

In addition to their generality as activators in iminium catalysis, primary amine catalysts have also been successfully employed for the asymmetric α-functionalisation of ketones via enamine intermediates.[159–161]

Primary amine catalysis therefore allows for the expansion of the range of possible electrophiles or nucleophiles that can be stereoselectively introduced into carbonyls, and comes close to the excellent levels of efficiency already reached in the secondary amine catalysed functionalisation of aldehydes. However, α-functionalisation reactions of α-substituted α,β-unsaturated carbonyl compounds still represent an important challenge.

1.2.3 ACDC

In 2006, List and co-workers introduced a novel strategy for enantioselective synthesis coined asymmetric counterion-directed catalysis (ACDC).[162,163] This approach exploits the fact that most chemical transformations proceed via charged intermediates or transition-states. Thus chiral catalysts capable of forming ion pairs can induce high stereocontrol. The List research group applied this concept to iminium catalysis. Initially, the asymmetric transfer hydrogenation (by a Hantzch ester) of α,β-unsaturated aldehydes was studied, [162] in which it was found that a catalytic amount of the ammonium salt **16** with an axially chiral phosphoric acid, TRIP, could function as a highly enantioselective iminium catalyst in the conjugate reduction of enals (Figure 1.8). The ACDC approach was later extended to the asymmetric transfer hydrogenation of α,β-unsaturated ketones with a Hantzch ester, involving[163] the salt derived from an L-Valine derivative **17** with TRIP, which resulted in an improved enantioselectivity. In this enone case, efficient activation relies on the ability of primary amines to form iminium ion intermediates from ketones, together with the benefits of asymmetric counteranion-directed catalysis.

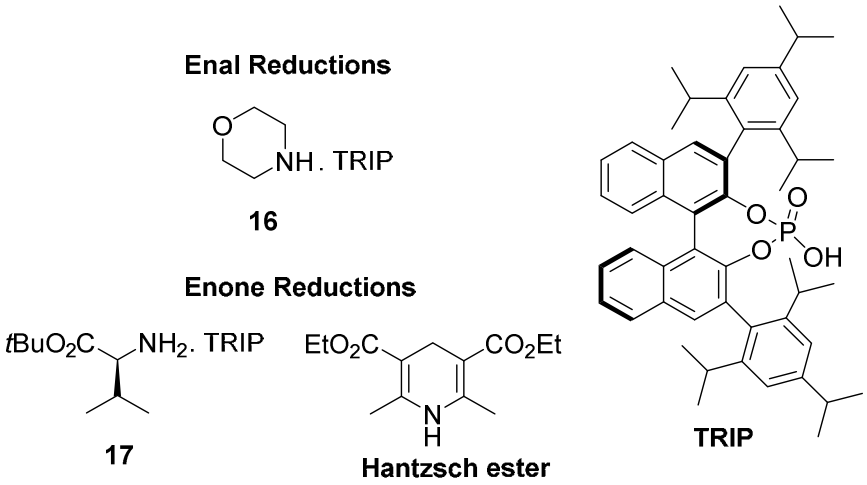
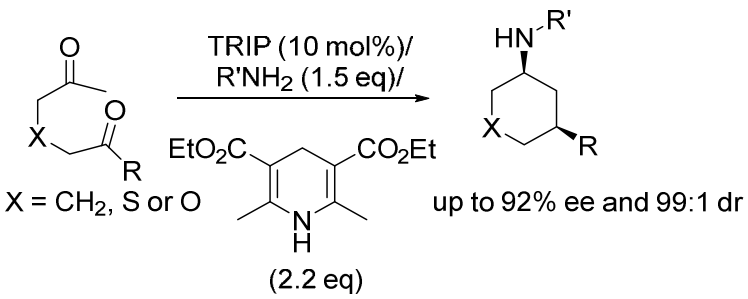


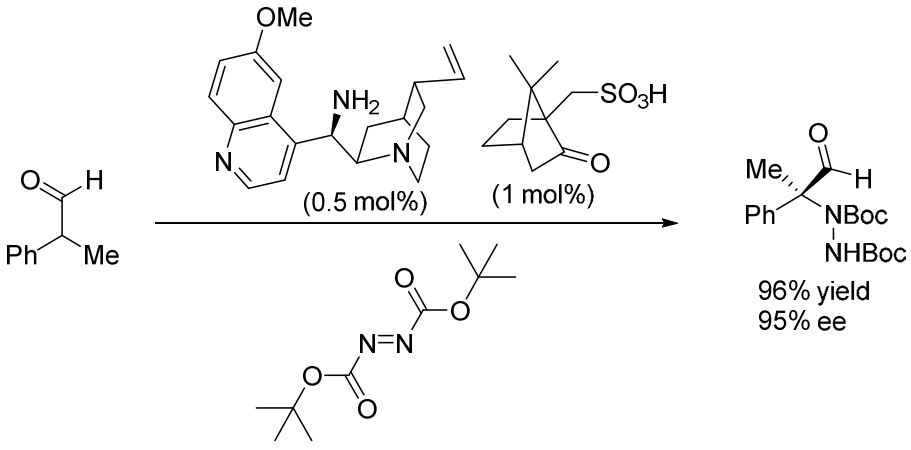
Figure 1.8: ACDC hydrogenation organocatalysts. TRIP = 3,3'-bis(2,4,6-triisopropylphenyl)1,1'-diylhydrogen phosphate.

Zhou and List combined ACDC and Bronsted acid activation in a new triple organocascade sequence to give pharmaceutically relevant substituted cyclohexylamines.[164] Starting from a 2,6-diketone or derivative (see Scheme 1.44) and the Hantzsch ester, the combination of an achiral primary amine with a catalytic amount of TRIP promoted an aldolisation/dehydration reaction via enamine activation. This was followed by an asymmetric conjugate reduction proceeding through ACDC, and finally a Bronsted acid catalysed reductive amination to give the product. Noteworthy is the fact that both the amine and the phosphoric acid are essential for promoting the first two reaction steps. List has also applied ACDC principles to the asymmetric epoxidation of enals.[165]



Scheme 1.44: Triple organocascade to synthesise chiral cyclohexylamines.

The power of ACDC was displayed when Lu et al. designed novel ion pair catalysts containing a chiral counter-anion for enamine catalysis for the first time. Such catalysts can be easily derived by mixing a cinchona alkaloid-derived primary amine catalyst with chiral camphorsulfonic acid (CSA), Scheme 1.45.[166] These ion-pair catalysts were found to be very effective in promoting the direct amination reactions (to be discussed later in subsection 1.3) of branched aldehydes with a catalyst loading of as little as 0.5 mol% and forming products in up to 95% ee. A gram-scale asymmetric synthesis of biologically-active (*R*)-methylphenylglycine was thereafter realised, displaying the great potential of chiral ion-pair catalysts for industrial applications.



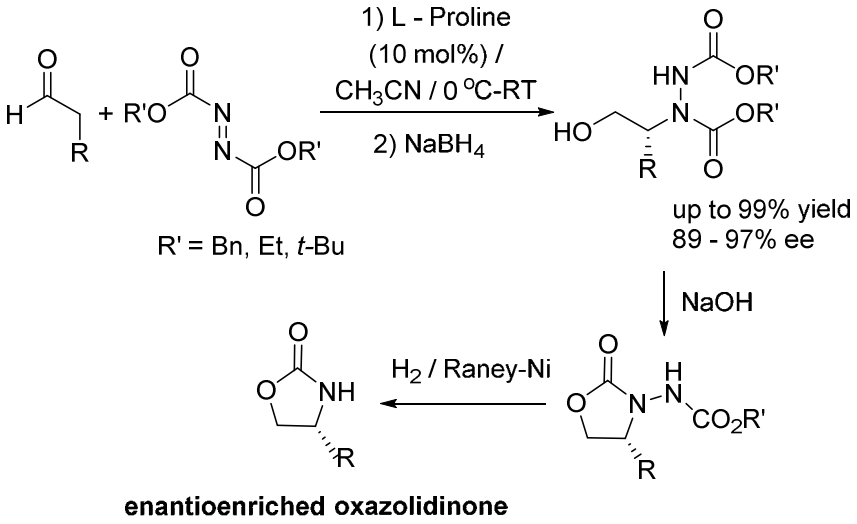
Scheme 1.45: Primary-amine-chiral-acid catalyst system for α-amination via ACDC.

It is not clear why the potential role of the counterion in aminocatalysis was underrated for so long. Notably, it has also been demonstrated how the ACDC strategy can be applied not only to purely organic catalysts, but also to organometallic systems, thus providing new opportunities for asymmetric catalysis.[167–169] This illustrates how organocatalysis is positively influencing other established synthetic areas.

1.3 The α-Amination Reaction

The amino functionality is ubiquitous and an essential component of building blocks in organic synthesis. Since most nitrogen-containing natural products possess an aza-stereogenic centre, it is vital to develop stereoselective transformations for their preparation in an enantioselective manner.[170] Therefore, the organocatalysed asymmetric α-amination reaction will now be discussed with a particular focus on aminocatalysis.

Since its simultaneous publication by List[67] and Jørgensen in 2002,[171] the proline-catalysed enantioselective α-amination reaction using an azodicarboxylate as the electrophile (aminating agent) has become a key methodology for the asymmetric α-heteroatom functionalisation of aldehydes.[172–176] Importantly, their reactions furnish α-hydrazino aldehydes in good yield and high enantioselectivity (Scheme 1.46). Given the tendency of the α-aminated aldehyde products to slowly racemize, *in situ* reduction with $NaBH_4$ is carried out leading to configurationally stable 2-hydrazino alcohols. The authors also showed how these α-hydrazino compounds can be transformed to useful optically pure compounds such as oxazolidinones.



Scheme 1.46: List's seminal proline-catalysed α-amination reaction.

However, the rather poor solubility of proline in many solvents, which effectively reduces the turnover number, resulted in high catalyst loadings (up to 30 mol%).[177] This emphasised the need for the development of novel organocatalysts with better solubility properties. Thus a wide range of secondary amine catalysts have been developed for this reaction. For example, Aldolfsson introduced a novel series of (*S*)-*N*-arenesulfonyl-2-aminomethylpyrrolidines, Figure 1.9.[177] These were synthesised from proline in a simple manner and his procedure allows for introduction of different aryl sulfonyl groups with

varying electronic and steric properties. Unfortunately, the enantioselectivities of these catalysts did not surpass those of proline.

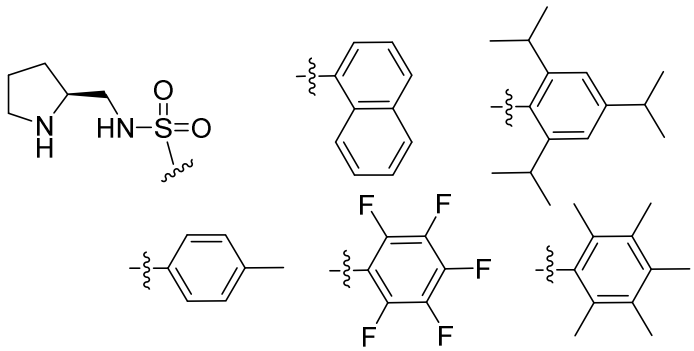
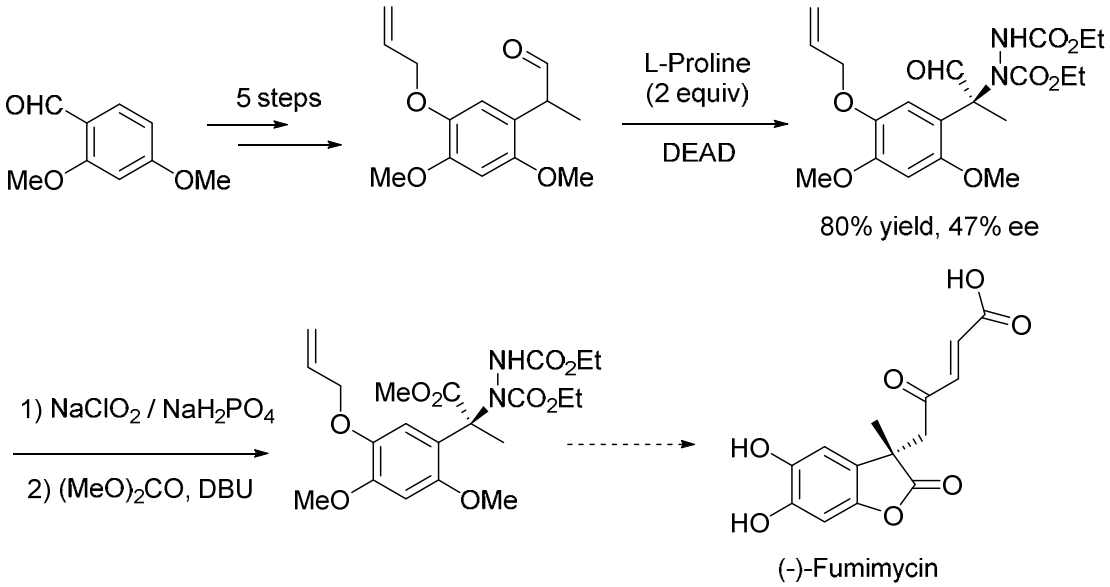


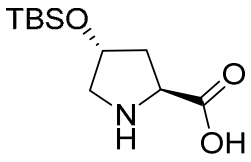
Figure 1.9: Adolfsson's novel series of α-amination catalysts

A year after the List and Jørgensen discoveries, Brase et al. showed that quaternary centres in chiral, non-racemic form could be accessed using this methodology. Thus α,α-disubstituted α-amino aldehydes and oxazolidinones were synthesised (with enantioselectivities up to 86% ee) starting from racemic aldehydes, using L-proline or L-azetidine carboxylic acid as catalysts. However, even though up to an 86% ee could be obtained, these reactions required a very high catalyst loading (50 mol%). Nevertheless, Brase applied his methodology towards an asymmetric synthesis of the bacterial peptide deformylase (PDF) inhibitor fumimycin using his methodology as a key step (Scheme 1.47).[178] Later, they developed the thermally accelerated organocatalytic α-amination of disubstituted aldehydes under microwave conditions. Compared to the results previously obtained at room temperature, both the yield and enantioselectivity could be significantly increased and reaction times were significantly reduced. Therefore, this improved protocol allowed the fast and efficient synthesis of α,α-disubstituted amino aldehydes, which provided the best results for the α-amination of disubstituted aldehydes.[170,179]



Scheme 1.47: α-Amination used towards the total synthesis of fumimycin.

In the same year as the publication of the original aminocatalysed aldehyde α-amination reaction, Jørgensen accomplished the same success with ketones.[66] This reaction is highly regioselective at the more substituted α-carbon atom. It was also found that increasing the length of the R'-substituent from methyl to ethyl and benzyl increased the enantioselectivity. However, cyclic ketones such as cyclohexanone and its derivatives generally gave poor results with proline as a catalyst. The α-amination of cyclohexanone with DEAD or dibenzyl azodicarboxylate (DBAD) using Greck's L-azetidine-2-carboxylic acid as catalyst showed improved enantioselectivities of 88–90%.[180] Similarly, Hayashi's 4-silyloxyproline catalyst **18** (Figure 1.10) proved to be quite a general catalyst for the α-amination of ketones. In addition to cyclohexanone derivatives, the catalyst was effective with acyclic ketones and α-branched aldehydes as substrates (64–73% yield, 78–96% ee).[181]

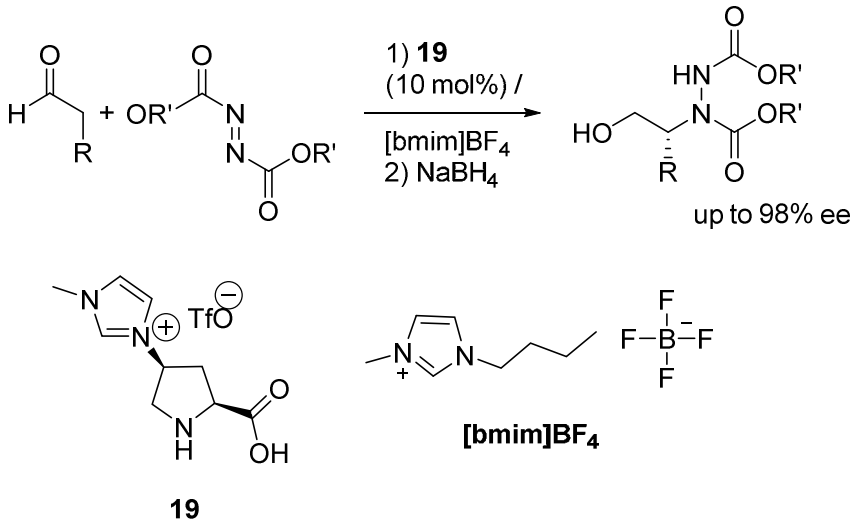


18

Figure 1.10: Hayashi's proline-based catalyst **18** for the α-amination of cyclic ketones.

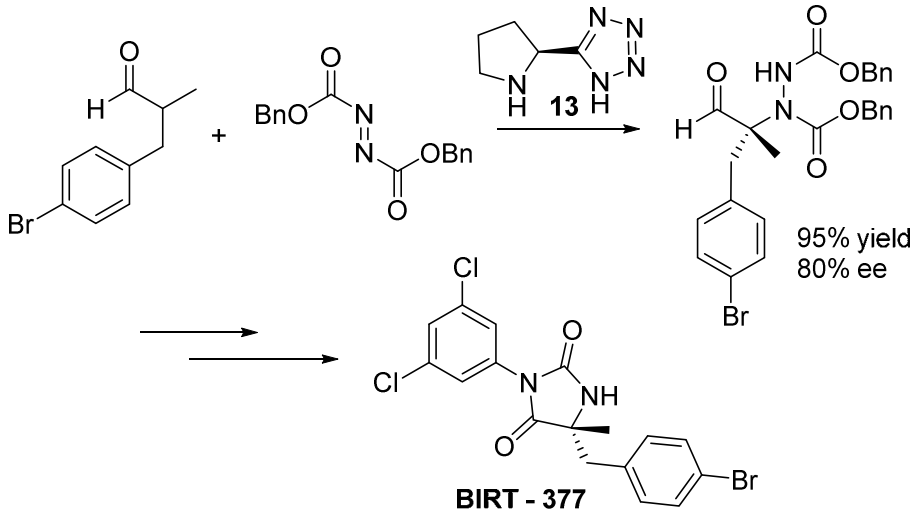
To aid catalyst solubility and make the reaction more environmentally favourable, Toma et al. probed the potential of ionic liquids as solvents.[182] For instance, the α-amination of aldehydes (and to a lesser extent, ketones) by DEAD in [bmim]BF_4 as an ionic liquid gave an ee of up to 94% with 4-hydroxyproline as the catalyst. In general the enantioselectivity was

comparable though often a bit lower than that achieved in traditional solvents. Similarly, Zhu et al. showed that the α-amination of aldehydes in ionic liquids and in the presence of imidazolium ion-tagged L-proline (**19**) gives excellent enantioselectivities (up to 98% ee) and high chemical yields (Scheme 1.48).[183] Impressively, their catalyst/[bmim]BF_4 system could be easily recycled, and retained similar reactivity as well as enantioselectivity after four recycles with the ionic solvent. Although showing promise, the success and generality of this procedure was hampered by reaction of the ionic liquid with the aminating agent. Later, North and co-workers showed that cyclic carbonates could be successfully used as an alternative green solvent, in which more favourable results were obtained with ketones, although not to the level of success obtained using the usual organic solvents.[174]



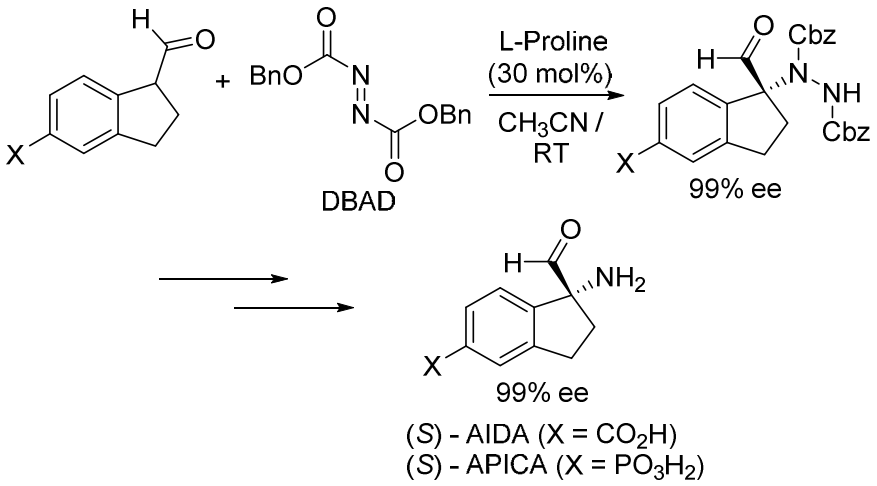
Scheme 1.48: α-Amination in ionic liquids.

The utility of the α-amination reaction is illustrated by its application to the synthesis of more complicated and useful chiral compounds and natural products. Barbas et al. developed the first catalytic asymmetric route to the total synthesis of BIRT-377 (a cell-adhesion inhibitor), Scheme 1.49, [184] in which a quaternary α-amino aldehyde was constructed from readily available precursors via organocatalysis. Proline gave disappointing results in terms of reaction times and enantioselectivity (44% ee), while the more reactive and soluble tetrazole catalyst **13** turned out to be a good choice for this enantioselective α-amination reaction, forming the desired optically active product in a 95% ee. This method allowed access to both enantiomers of BIRT-377.



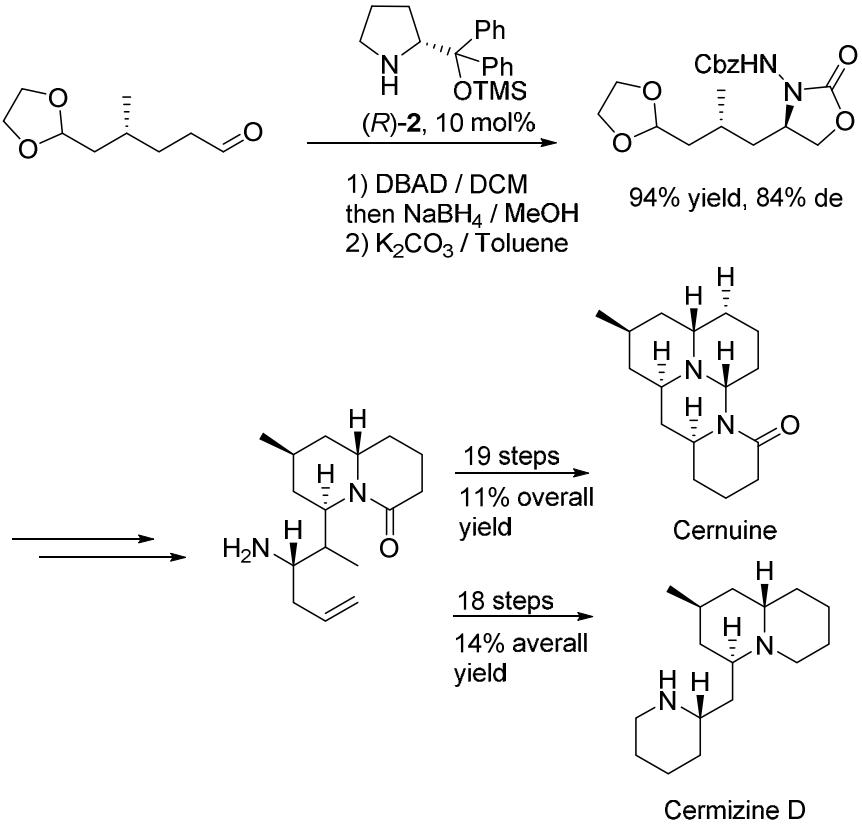
Scheme 1.49: Application of the aminocatalysed α-amination to the total synthesis of BIRT-377.

AIDA and APICA (structures given in Scheme 1.51) are known antagonists of metabotropic glutamate receptors and G-protein-coupled receptors associated with various neurodegenerative diseases. Barbas found organocatalysis to be an effective strategy for the enantioselective preparation of (*S*)-AIDA and (*S*)-APICA in >99% ee, Scheme 1.50.[185] This is impressive since the amination substrate is essentially a branched aldehyde and enantioselectivities this high for this type of substrate hadn't yet been obtained using proline (or any other secondary amine organocatalyst) in the absence of microwave irradiation, which had been the key to Barbas' success with branched aldehydes. The synthetic route is general and should allow for the preparation of other analogues. Also, the organocatalytic route could be readily scaled up, and either (*R*)- or (*S*)-products could be obtained using (*S*)- or (*R*)-proline respectively.



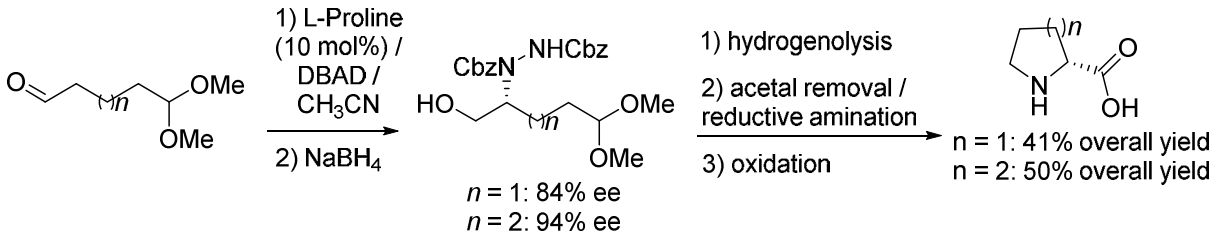
Scheme 1.50: The total synthesis of (*S*)-AIDA and (*S*)-APICA. DBAD = dibenzyl azodicarboxylate.

Takayama et al. reported the first total syntheses of two cernuine-type Lycopodium alkaloids, (-)-cernuine and (+)-cermizine D.[186] One of the key steps involved organocatalytic α-amination using Jørgensen's prolinol catalyst **2** to afford an oxazolidinone following *in situ* cyclisation (Scheme 1.51).



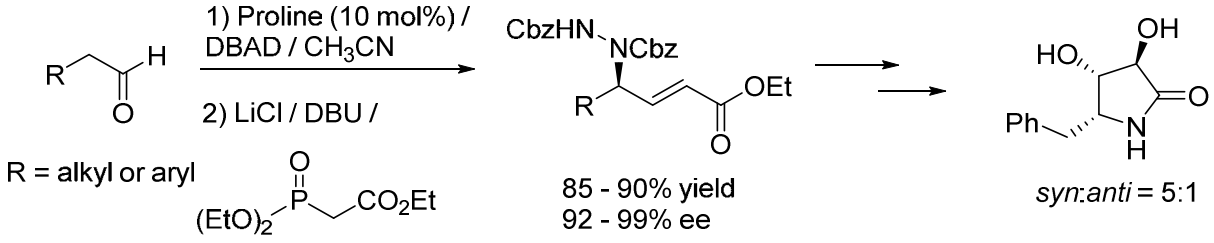
Scheme 1.51: The total synthesis of (-)-cernuine and (+)-cermizine D.

Interestingly, Greck et al. developed a straightforward protocol for synthesising unnatural cyclic amino acids using proline in stereoselective formation of the C–N bond, Scheme 1.52.[187] It is noteworthy that (*S*)-proline was used to synthesise its own enantiomer. (*R*)-Pipecolic acid and (*R*)-proline were obtained, in 50% yield and 94% ee from 6,6-dimethoxyhexanal, and in 41% yield and 84% ee from 5,5-dimethoxypentanal respectively.



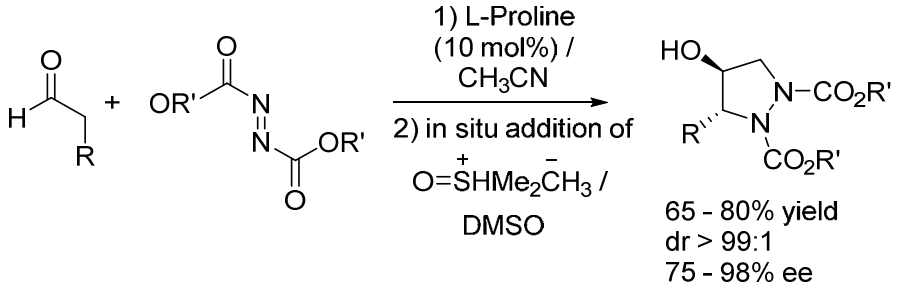
Scheme 1.52: Synthesis of (*R*)-proline and (*R*)-pipecolic acid.

As far as tandem reactions are concerned, Sudalai developed a novel, one-pot procedure involving sequential α-amination / Horner−Wadsworth−Emmons(HWE) olefination of an aldehyde leading to the enantioselective synthesis of γ-amino-α,β-unsaturated esters in excellent yields and high enantioselectivities (Scheme 1.53).[188] The resultant products were then transformed to 5-substituted 2-pyrrolidinone derivatives in good yields and great substrate generality.



Scheme 1.53: The proline catalysed tandem α-amination/HWE olefination of aldehydes.

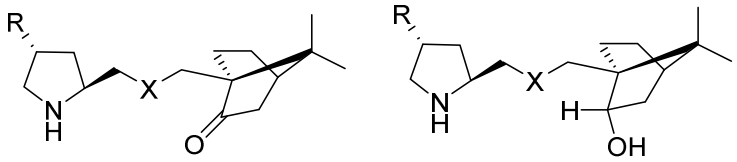
Another expression of tandem reactions appeared in 2012 when Sudalai developed an organocatalytic α-amination/Corey-Chaykovsky sequence of aldehydes with dimethyloxosulfonium methylide, Scheme 1.54.[189] The sequence ultimately afforded 4-hydroxypyrazolidine derivatives in high yields with excellent enantio- and diastereoselectivities via a 5-*endo*-tet epoxide opening as the final step.



Scheme 1.54: Proline-catalysed α-amination/Corey-Chaykovsky sequence

Aminocatalysts, however, have limitations in reactions with ketones, branched aldehydes and β-ketoesters.[175] To this end, Pihko et al.[190] showed the importance of cinchonine and cinchonidine alkaloids in the α-amination of β-ketoesters and β-ketolactones. Later, Jørgensen et al.[191] reported the first quinidine-derived catalyst allowing the amination of substituted α-cyanoacetates and β-dicarbonyl compounds, in very high enantioselectivity. It has also been shown[192] that cinchona alkaloids derived from either quinine and quinidine provide easy access to the formation of an aza-quaternary centre by electrophilic amination of α-cyanoacetates. Terada rationally developed a family of axially chiral guanidine bases

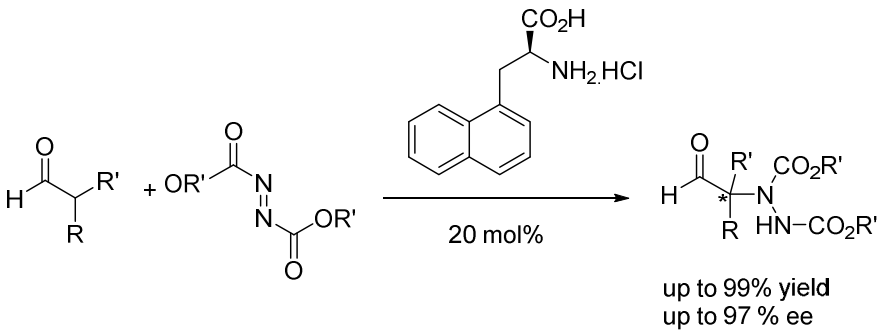
that, through hydrogen bonding, facilitate the highly enantioselective α-amination of unsymmetrically substituted 1,3-dicarbonyl compounds with high optical purity (up to 97% ee).[193] Chen et al. designed and synthesised a series of novel pyrrolidinyl camphor-based organocatalysts for asymmetric organocatalysis, Figure 1.11.[194] These act as efficient bifunctional (both iminium and hydrogen bonding activation modes) organocatalysts in asymmetric synthesis as they allow for much lower catalyst loading, faster reaction times and excellent enantioselectivity (up to >99% ee). These catalysts could also be applied to branched aldehydes although ees dropped to a high of only 76%. Xu has also developed secondary amine–thiourea bifunctional catalysts for the α-amination of aldehydes to produce products in excellent yields (up to 99%) and enantioselectivities (up to 99% ee).[195]



R = H, X = S
R = OH, X = S
R = OTBDPS, X = S
R = OTBDPS, X = SO_2
R = H, X = NH - SO_2

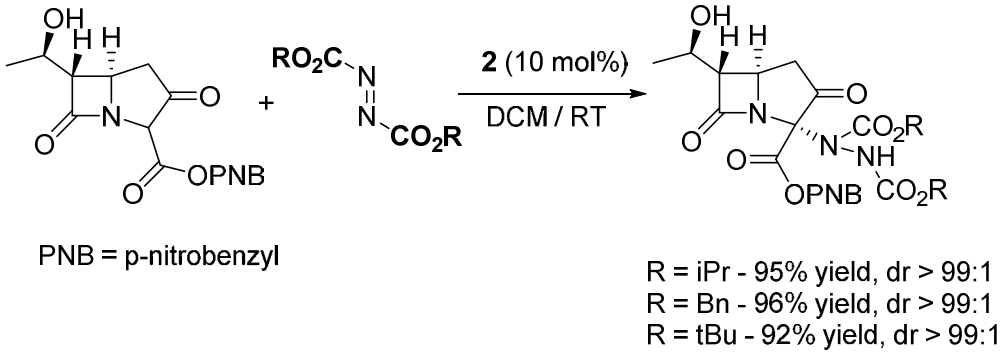
Figure 1.11: Chen's range of bifunctional pyrrolidinylcamphor catalysts.

Greck et al. used cinchona-derived primary amine catalysts for the amination of branched aldehydes with high levels of success (up to 99% ee).[196] Wang et al. developed a simple, cheap and commercially available chiral primary amino acid, 3-(1-naphthyl) alanine hydrochloride. This primary amino acid is a highly efficient and enantioselective catalyst for the direct asymmetric α-amination of branched and hindered aldehydes (Scheme 1.55) in excellent yields (up to 99%) and enantioselectivities (up to 97% ee).[197] Furthermore, Chen et al. found 9-amino-9-deoxyepicinchona alkaloids (primary amine catalysts) to be excellent enamine organocatalysts for the α-amination of aryl ketones.[160] Their catalysts showed impressive scope and excellent enantioselectivities (88-99% ee).



Scheme 1.55: Primary amino acid catalysed α–amination for aza-quaternary centres.

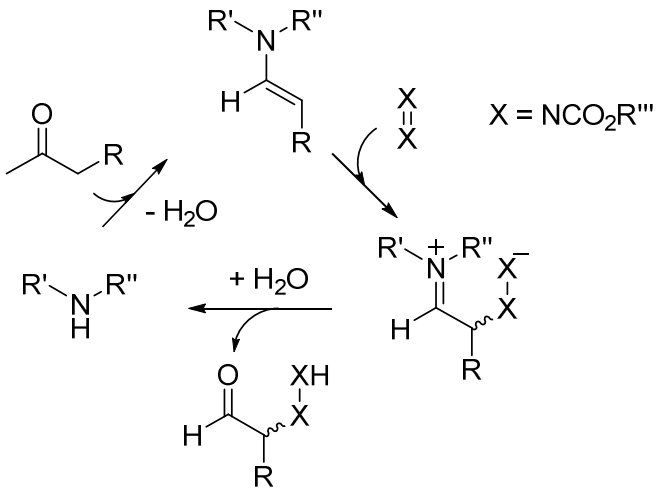
Finally, in 2015 Arvidsson et al. reported the α-amination (as well as α-hydroxylation, α-sulfenylation and α-selenylation) of a carbapenem core (Scheme 1.56). This reaction is a rare example of an aminocatalyst effectively aminating a hindered carbonyl in high stereoselectivity under mild conditions, with a catalyst loading of only 10 mol% (as opposed to the high loadings usually required).[198]



Scheme 1.56: The α-amination of carbapenem.

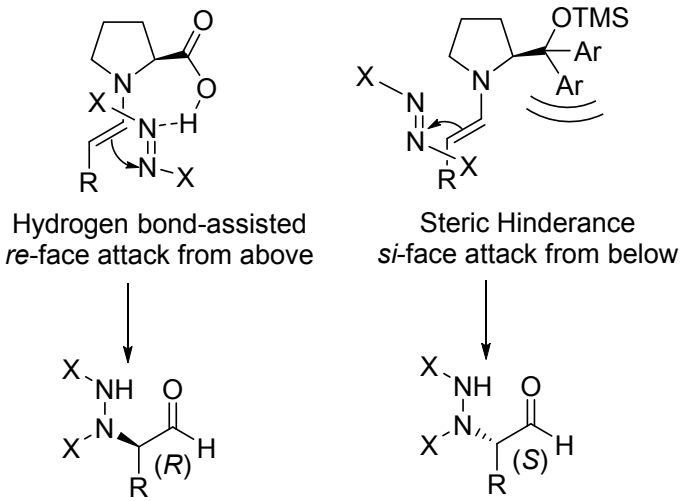
Mechanistic Considerations

The generally accepted catalytic cycle of the secondary-amine-catalysed α-amination reaction is shown below (Scheme 1.57), courtesy of List.[67]



Scheme 1.57: The catalytic cycle for the α-amination reaction.

When Jørgensen applied his diarylprolinol catalysts to the α-amination reaction, he was able to mirror proline's success in terms of yield and enantioselectivity (90 to 97% ee). However, despite the same absolute configuration of Jørgensen's catalysts as that of proline (*S*), the reactions produced the same products as enantiomers. The researchers reasoned that these differences could be explained by two different transition-state models, Scheme 1.58. Proline is suggested as operating through the dual activation of both the aldehyde (by forming a more nucleophilic enamine) and the electrophile (by hydrogen bonding).[199] On the other hand, Jørgensen's diarylprolinol catalysts resulted in high enantioselectivities despite the absence of functional groups that could participate in hydrogen bonding with the aminating agent. It was therefore reasoned that the enantioselectivities observed with these catalysts originated from controlling the geometry of the enamine in the same way as with proline but now with introduction of steric bias of the two enamine faces by the large substituent on the pyrrolidine ring of the catalyst. [40,172,200] However, Seebach, Eschenmoser and Blackmond have revealed alternative and more complex mechanistic explanations. Chapter 3 will elaborate on all these proposals and how they were applied to the acetal case in this thesis.



Scheme 1.58: The two catalyst-dependent transition-state models for the aminocatalysed α-amination reaction.[172]

In spite of all these advances, one aspect of enamine organocatalysis that currently requires developing is that of finding more chemotypes as starting materials. Following the waning of the organocatalysis "Gold Rush" (with all the aminocatalysis activation pathways therein discovered) many leaders in the field, particularly Jørgensen, are now focusing on using organocatalysis in target-oriented synthesis of biologically relevant compounds (especially heterocycles).[124] We therefore believe that the expansion of aminocatalysis chemotypes will be a useful complement to this trend, thus cementing the future of organocatalysis. The work presented in this thesis speaks to this very issue by reporting the first usage of acetals as masked carbonyl equivalents in the aminocatalysed enantioselective α-amination reaction. This methodology is then applied to a model asymmetric desymmetrisation of prochiral substrates. The following Chapters thus discuss these contributions to asymmetric organocatalysis.

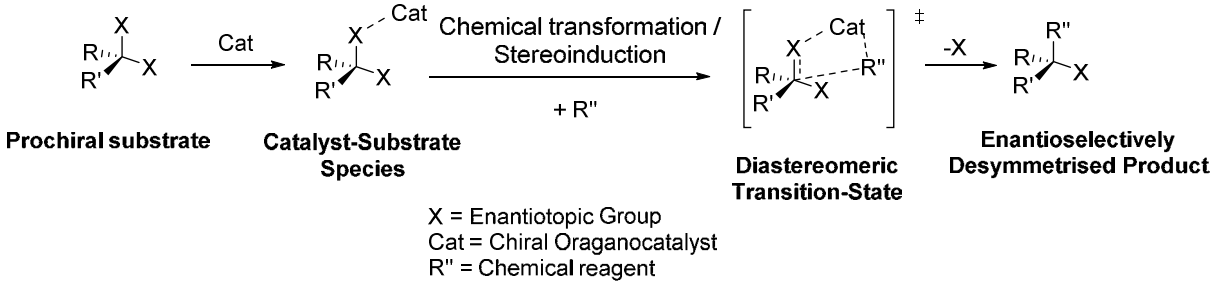
Chapter 2: Asymmetric Desymmetrisation Hypothesis and Substrate Synthesis

2.1 Catalytic Asymmetric Desymmetrisation

Catalytic desymmetrisation of a prochiral substrate via selective chemical modification so as to remove the symmetry element has emerged[1] as a powerful, efficient and economical procedure to create chirality in the substrate in a single step.[201,202] A selective modification of one of the enantiotopic groups at a prochiral centre results in enantiomers, the efficiency of which determines the degree of enantioenrichment in the product. Biocatalysts,[203] metal-based catalysts[204,205] and organocatalysts can all be used as the catalytic agent, but In view of the topic of this thesis only examples of organocatalysts will be reviewed in the following section.

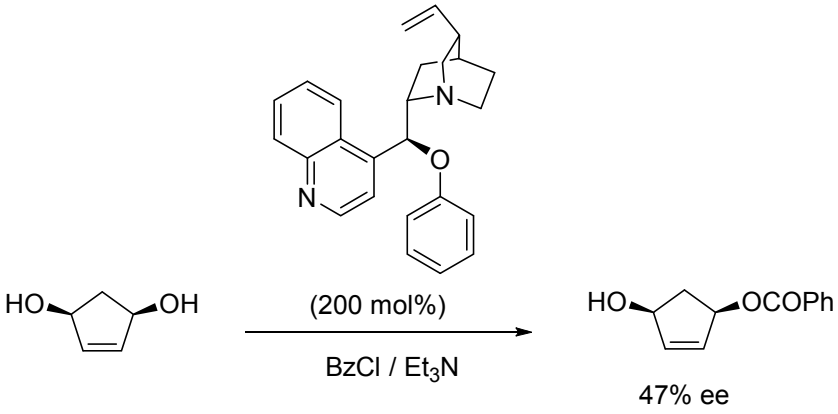
2.1.1 Organocatalysed Asymmetric Desymmetrisation

At the heart of the organocatalysed desymmetrisation reaction of a prochiral motif is the idea that a catalysed reaction takes place faster at one of the enantiotopic groups (or faces) of the prochiral substrate thus affording the two enantiomers of the product in unequal amounts.[203] In other words, as shown in Scheme 2.1, when a chiral organocatalyst associates (covalently or otherwise) with a prochiral symmetric substrate, the catalyst-substrate species formed distinguishes between the two enantiotopic groups because of the asymmetric environment provided by the catalyst which dictates the sense of stereoinduction of the now diastereotopic catalyst-substrate species (Scheme 2.1). This results in transition-states in the asymmetric induction step of unequal energy. Detachment of the catalyst thus gives the reaction product as two enantiomers, formed at different reaction rates.[206] Furthermore, if the catalytic reaction results in the creation of another stereogenic centre, desymmetrised products can be synthesised in a diastereoselective manner.



Scheme 2.1: An illustration of the process of asymmetric organocatalysed desymmetrisation.

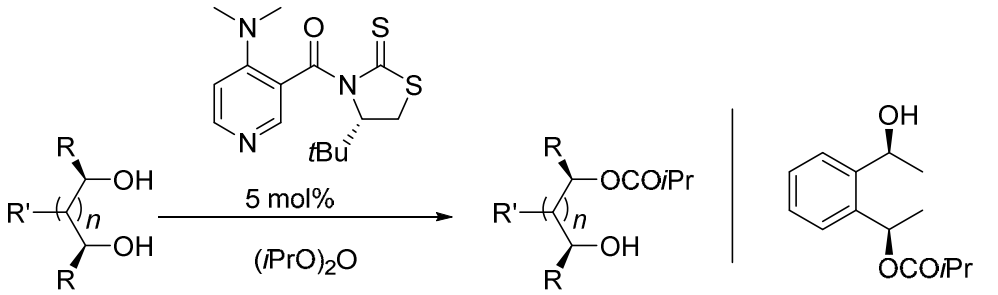
The desymmetrisation of *meso*-diols is probably the most common theme in organocatalysed asymmetric desymmetrisations. The very first desymmetrisation reported of a *meso*-diol mediated by a chiral organic compound using Lewis base catalysis was described in 1985 by Duhamel et al.[207] In his reaction *cis*-2-cyclopent-en-1,4-diol was enantioselectively benzoylated in the presence of different chiral tertiary amines giving a maximum ee of 47% when 200 mol% of *O*-phenylquinidine was used. Here, acyl transfer from the quinoline nitrogen takes place.



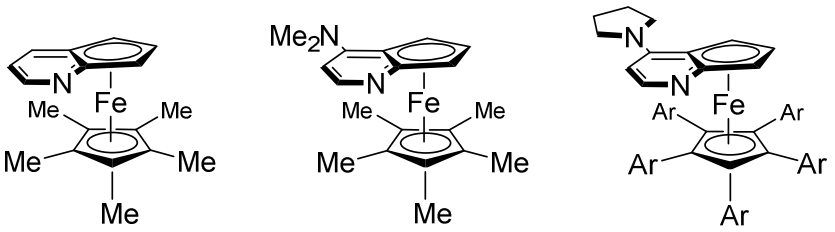
Scheme 2.2: Duhamel's Lewis-base-promoted desymmetrisation of a *meso*-1,4-diol.

Eleven years later Vedejs et al. reported the use of chiral phosphines in catalytic amounts for the monoacylation of meso-1,2-diols.[208] However, their results were also disappointing, owing to low conversion, diacylation and racemization under the reaction conditions. Since then and with the simultaneous organocatalysis "gold rush",[33] increasing research has being devoted to the development of efficient organocatalytic methods to perform this transformation as a powerful methodology for the preparation of chiral building blocks.[209] An example of this reaction class is shown in Scheme 2.3 where asymmetric desymmetrisation of meso-1,n-diols (n = 2–6) is achieved by acylation in the presence of 5 mol% of a chiral DMAP-derived catalyst.[210] The DMAP derivative functions as an acyl-transfer catalyst, and π-π-interactions between the catalyst pyridinium ring and the thiocarbonyl results in a chiral environment in the acyl transfer step, allowing it to distinguish between the two enantiotopic alcohol groups. This gave a range of ees (59–97%) depending on the distance and spatial disposition of the hydroxyl groups, with the phenyl-1,4-diol below giving the best result. The good result obtained with this and other phenyl-containing diols suggests that the phenyl moiety offers additional stabilising π-interactions with the catalyst, resulting in a more efficient chiral environment for the enantiogroup differentiation step with a lower energy transition-state. Other chiral DMAP derivatives that desymmetrise via chiral Lewis base catalysis involving other stereogenic types, such as planar chirality in the catalyst, have also

been developed with great success wherein Fu's catalysts lead the pack (Scheme 2.3 shows examples).[211,212]

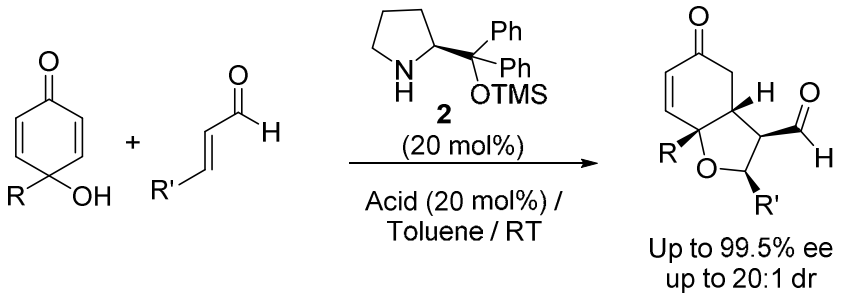


Examples of Fu's DMAP Catalysts



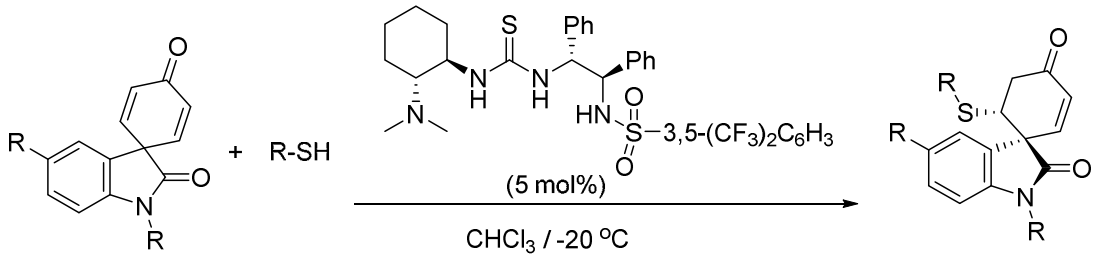
Scheme 2.3: The enantioselective desymmetrisation of a 1,n-diols.

Another important class of organocatalytic desymmetrisation substrates is a prochiral dienone. These contain unsaturated functional groups that may be directly transformed into more complex structures.[213] In 2013, Johnson and Corbett reported a tandem oxa-Michael / Michael desymmetrisation of a dienone with Jørgensen's catalyst **2** to make tetrahydrofuran derivatives enantioselectively (Scheme 2.4).[214] The mechanism involves the hydroxyl group of the dienone nucleophilically adding to the iminium ion formed between **2** and the Michael acceptor. The resulting enamine then undergoes Michael addition cyclisation on one side of the dienone, also activated as a chiral iminium ion, in a stereocontrolled manner due to the steric bulk and facial discrimination afforded by the chiral catalyst. Up to a 99.5% ee and 20:1 dr was obtained depending on the nature of the R-group, thus displaying how aminocatalysis can effectively be applied to desymmetrisations.



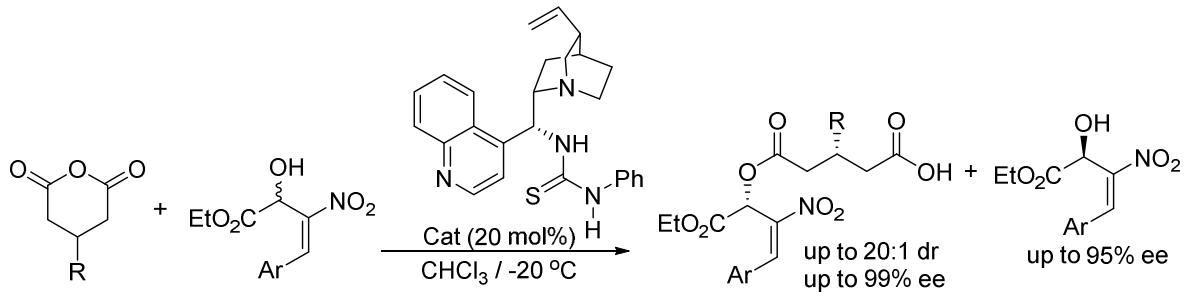
Scheme 2.4: The aminocatalysed desymmetrisation of a dienone.

In the same year Wang et al. reported the first catalytic asymmetric synthesis of spirocyclic oxindoles via organocatalysed desymmetrisation (Scheme 2.5).[201] The resulting products contain an all-carbon quaternary centre with an adjacent tertiary stereogenic centre. For this Michael addition stereoinduction occurred due to the chiral environment created by the bifunctional tertiary amine / thiourea catalytic system which exhibited high reactivity, excellent diastereoselectivity (dr > 20:1) and enantioselectivity (up to 95% ee), and broad substrate scope.



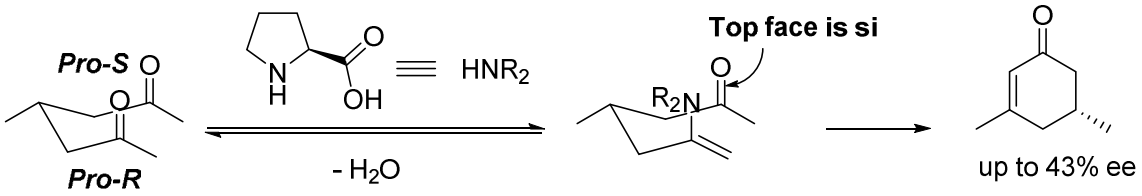
Scheme 2.5: The asymmetric desymmetrisation of spirocyclic oxindoles.

Meso-anhydrides represent another useful organocatalysed desymmetrisation substrate. Roy et al. have recently (2014) achieved the organocatalytic kinetic resolution of racemic secondary nitroallylic alcohols with simultaneous desymmetrisation of a prochiral cyclic anhydride (Scheme 2.6).[215] The enantioselective alcoholysis by one of the enantiomers of the racemic allylic alcohol of 3-substituted glutaric anhydrides afforded hemiesters with high enantioselectivities (up to 99% ee) in the presence of a cinchonidine-derived thiourea catalyst. The high optical enrichment (up to 95% ee) of (*S*)-nitroallylic alcohols was also achieved. They propose that the bifunctional organocatalyst simultaneously activates the nucleophile (hydroxyl group) and electrophile (symmetrical anhydride). The tertiary amine of the organocatalyst activates the hydroxyl, whilst the appropriately positioned thiourea group activates the cyclic anhydride through hydrogen bonding. This results in concomitant kinetic resolution of the nucleophile and desymmetrisation of the electrophilic component in a stereocontrolled manner.



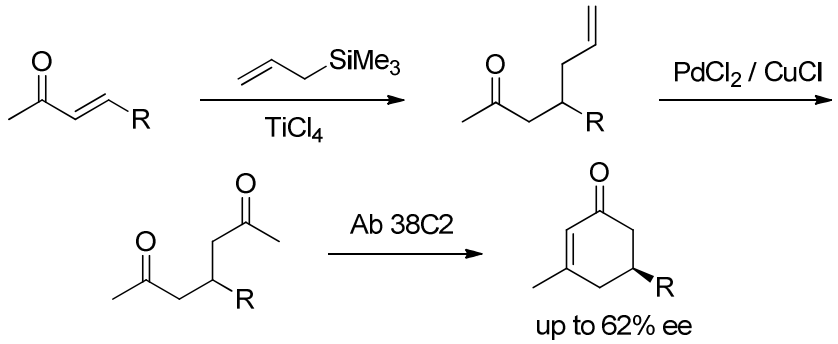
Scheme 2.6: The organocatalytic kinetic resolution of racemic secondary nitroallylic alcohols and simultaneous desymmetrisation of prochiral cyclic anhydrides

Besides the popular diols, dienones and *meso*-anhydrides, a variety of other prochiral substrates have been reported to undergo organocatalytic asymmetric desymmetrisations. A few interesting examples will now be discussed. One of the earliest examples of organocatalysed desymmetrisation was published in 1984 when Agami et al presented the proline-catalysed enantioselective desymmetrisation of a prochiral 1,5-diketone in their application of the classic Hajos-Parrish reaction (Scheme 2.7).[216] ThisHowever, since then aminocatalysis has been superseded by the use of tertiary amine catalysts (e.g. cinchona alkaloids and DMAP) and chiral phosphines in desymmetrisation reactions. This is primarily due to the more efficient asymmetric induction offered by these systems. Nevertheless, the mechanism of Agami's cyclodehydration deserves mentioning since it involves selective reaction of one of the enamines formed between proline and an enantiotopic ketone carbonyl group. The enamine nucleophilically adds to the carbonyl of the second ketone in an aldol fashion followed by dehydration and iminium ion hydrolysis, thus releasing the proline catalyst to give the enantioenriched reaction product in 75% yield. Stereocontrol occurs through enamine attack on the *si*-face of the *pro-S* ketone arm due to hydrogen bonding interactions, giving a 43% ee.



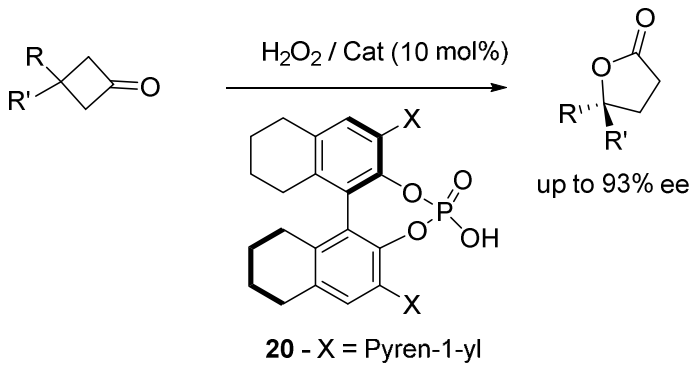
Scheme 2.7: The desymmetrisation of a 1,5-diketone by the Hajos-Parrish reaction

Agami's desymmetrisation didn't receive much attention until 15 years later in 1999 when Barbas and List catalysed the same reaction with antibodies instead of proline (Scheme 2.8).[217] In fact, List (a key figure in the development of organocatalysis) states that their study of Agami's reaction introduced him to proline catalysis.[39] The prochiral 1,5-diketone substrates were synthesised following a route developed by Sakurai et al.[218] involving a Lewis acid-mediated conjugate addition of allyltrimethylsilane to an α,β-unsaturated ketone. The resultant olefin underwent Wacker oxidation to give the desired substrate in modest to good overall yields. The biocatalyst gave up to 62% ee, which was an improvement on the original Agami result.



Scheme 2.8: Barbas' synthesis of prochiral 1,5-diketones and antibody-catalysed desymmetrisation.

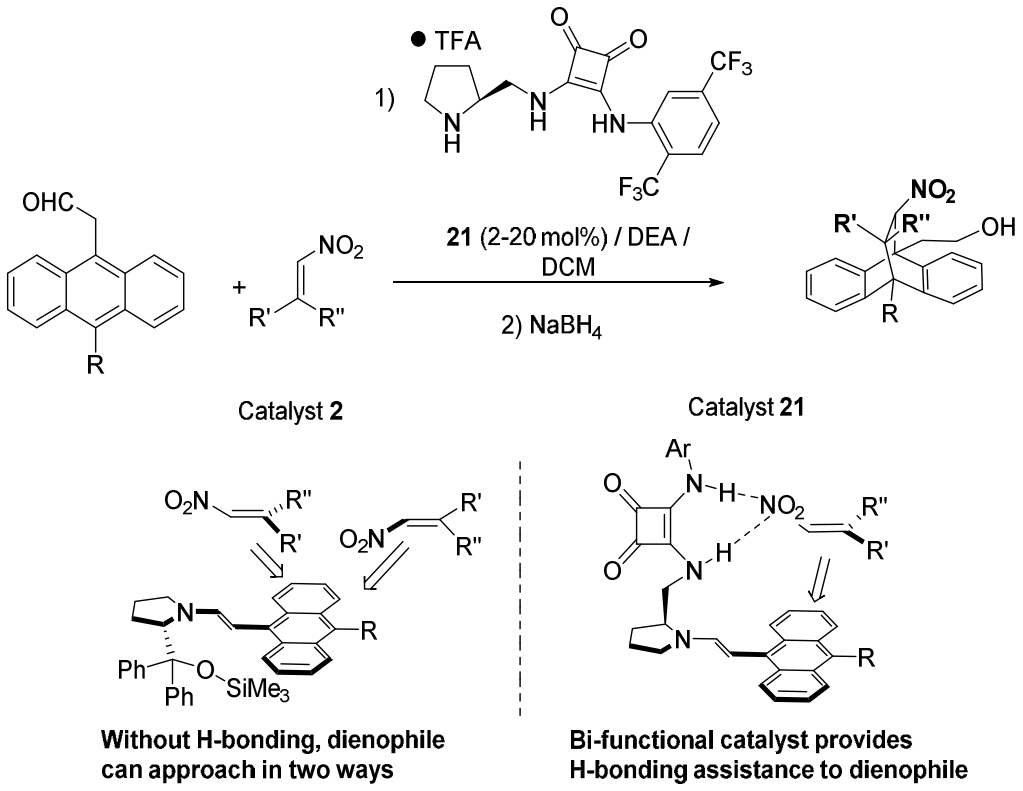
In 2008 Ding and co-workers demonstrated the use of a chiral phosphoric acid **20** (a strong chiral Brønsted acid catalyst) in the asymmetric Baeyer-Villiger oxidation of 3-substituted cyclobutanones with aqueous H_2O_2.[219] This oxidation reaction resulted in the asymmetric desymmetrisation of the cyclobutanone to the corresponding γ-lactone in excellent yields and up to 93% ee (Scheme 2.9). It is proposed that the asymmetric induction is provided by the chiral environment in the Criegee intermediate due to the catalyst bound to the substrate covalently and through hydrogen bonding.



Scheme 2.9: The asymmetric desymmetrisation of cyclobutanone

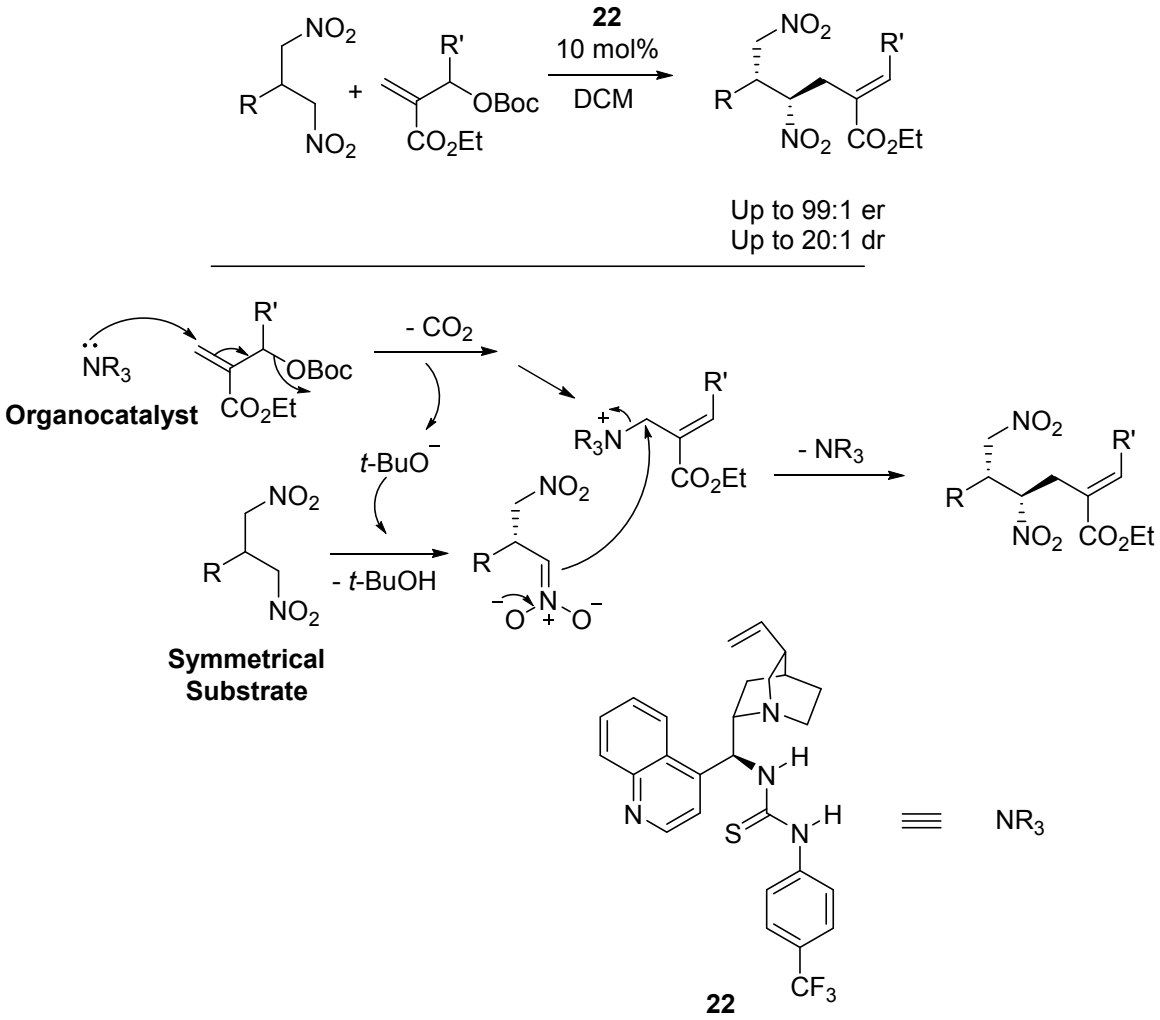
Prior to Jørgensen and co-worker's report in 2012 on the topic, the successful [4+2] cycloaddtion involving anthracenes as the 4π-component by direct HOMO-activation of the anthracene π-system using an organocatalyst had not yet been achieved. In order to overcome the dearomatisation energy barrier, available catalytic methods focused on achieving activation of the dienophile (LUMO-lowering).[220] However, using a unique bifunctional aminocatalyst, **21**, the Jørgensen group achieved an aromaticity-breaking desymmetrisation of anthracenes in a thermal Diels-Alder reaction (Scheme 2.10) to secure products in high yield and excellent enantioselectivity, and at very low catalyst loadings (2 mol%). Using his original prolinol catalyst **2** gave lower ees, up to 62%. High

enantiodiscrimination with **21** was achieved via shielding of one of the anthracene faces by the catalyst-substrate complex, leaving the other face unshielded for the approach of the dienophile. Mechanistically, the bifunctional catalyst works in the following manner: the secondary amine promotes HOMO-raising activation of the anthracene moiety by the formation of an enamine involving the aldehyde of the side chain; simultaneously, the squaramide directs the attack of the dienophile through hydrogen bonding between the enamine and the nitro group of the dienophile, thereby ensuring up to a 98% ee.



Scheme 2.10: The desymmetrisation of anthracenes.

As a final example, Mukherjee et al. have developed a catalytic enantioselective desymmetrisation of prochiral 1,3-dinitropropanes via an allylic alkylation reaction (Scheme 2.11).[221] Functionalised allylic carbonates were used as the allyl source, and the highly functionalised products consisting of two vicinal stereocentres were obtained in up to 20:1 dr and up to 99:1 er. The catalyst system used was a bifunctional tertiary amine / thiourea cinchona-based catalyst **22**. The reaction mechanism is shown below in Scheme 2.10. Enantiotopic group differentiation during the nucleophilic attack by the deprotonated 1,3-dinitropropane is the origin of the stereoinduction, which is as a result of non-bonded interactions between the 1,3-dinitropropane and the chiral catalyst.

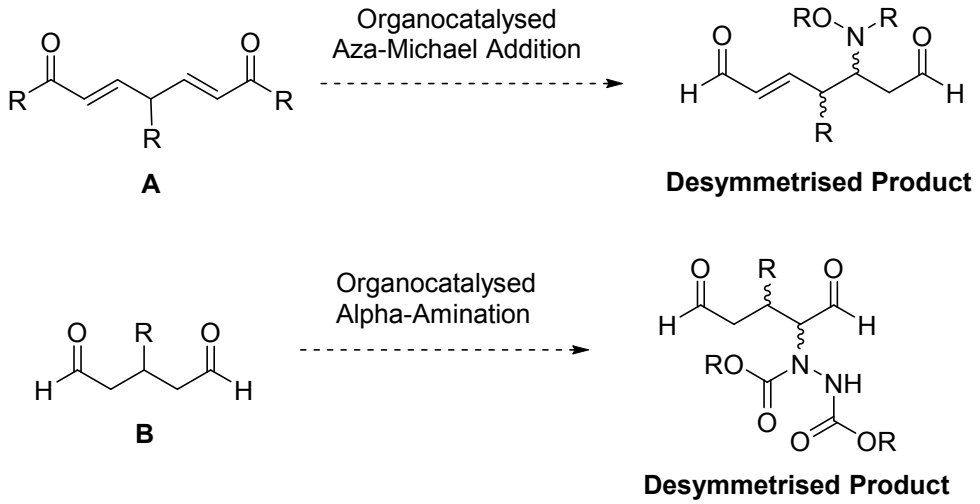


Scheme 2.11: The enantioselective desymmetrisation of 1,3-dinitropropanes.

As previously mentioned, aminocatalysis only features sporadically in the field of organocatalysed asymmetric desymmetrisations. Furthermore, to the best of our knowledge, the aminocatalysed α-amination and β-aza-Michael reactions have never been used in desymmetrisation reactions. Therefore the aim of this project was to develop conditions for such transformations as a novel contribution to this exciting field of research.

2.2 The Asymmetric Desymmetrisation Strategy of this Project

The desymmetrisation strategy concerned desymmetrising a symmetrical bis-enone **A** or bis-aldehyde **B**, each bearing a prochiral centre with two enantiotopic "arms" (Scheme 2.12). The reactions intended to achieve this were an organocatalysed enantioselective aza-Michael addition for **A** and an enantioselective α-amination substitution for **B**. The β-functionalisation option will be discussed first.

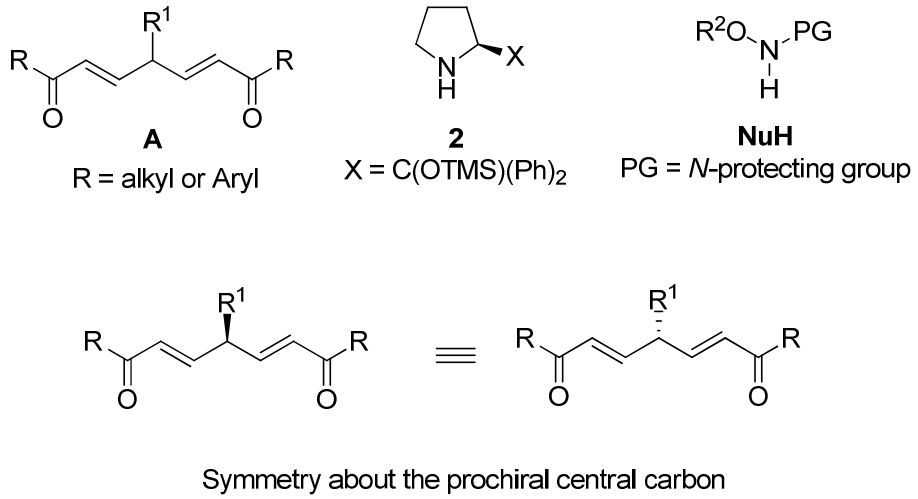


Scheme 2.12: The envisioned desymmetrisation of symmetrical substrates **A** and **B**.

2.2.1 β-Functionalisation Strategy

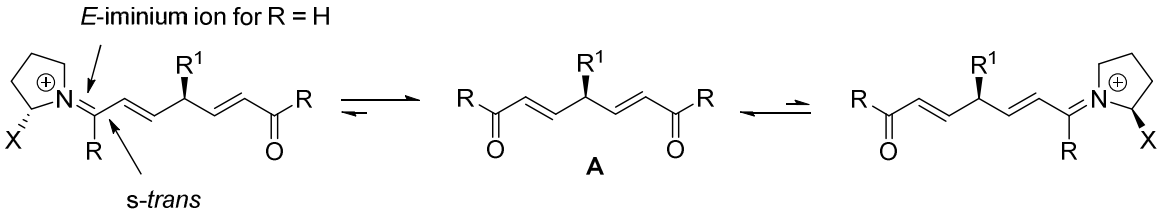
The first strategy considered was an organocatalysed aza-Michael addition as an example of a β-functionalisation reaction. As discussed in Chapter 1, this reaction involves stereoselective 1,4-addition of a nitrogen nucleophile to a chiral iminium ion generated from an α,β-unsaturated carbonyl compound. The reaction is useful because of the importance of the chiral aminated products it generates (such as β-amino acids and β-lactams).[107] Therefore, our hypothesis was to synthesise a symmetrical prochiral substrate **A** (most likely a bis-enone) that could be successfully desymmetrised via this reaction in an enantio- and diastereoselective manner. The following design aspects were considered as key:

- The reaction involves three components as: 1) A symmetrical bis-enone (shown in Scheme 2.13) assumed to have a zig-zag conformation as its lowest energy form; 2) Jørgensen's prolinol catalyst **2** which had shown excellent enantioselectivities in aza-Michael additions as mentioned in the review, Chapter 1; 3) a hydroxylamine-based nucleophile based on the principle, as applied in the literature,[102,222] of raising the nucleophilicity of the nitrogen via a HOMO-raising α-effect from the hydroxylamine oxygen to increase nitrogen softness in conjunction with the LUMO-lowering formation of the electrophilic iminium ion from the substrate and organocatalyst.[40]



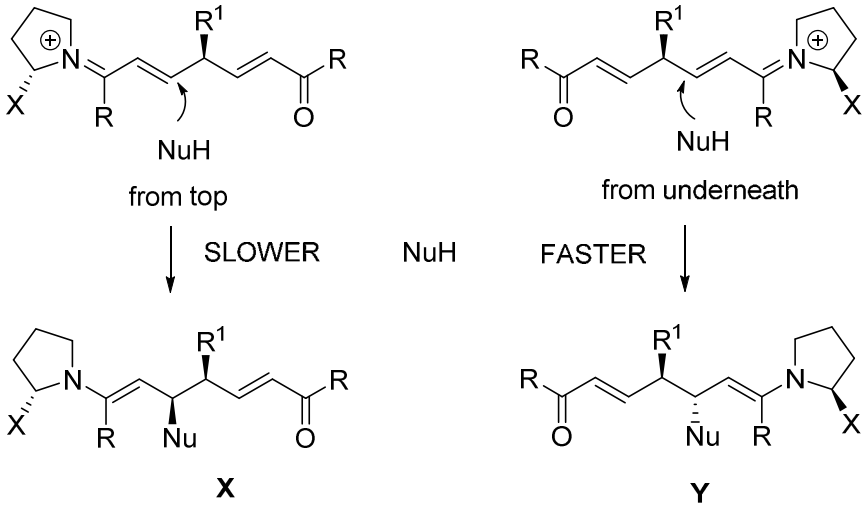
Scheme 2.13: The components of the envisioned aza-Michael desymmetrisation.

- In the iminium-ion activation step, since the catalyst is present in catalytic amounts with an excess of symmetrical **A** with respect to the nucleophile, it was reasonable to expect that formation of a mono- rather than a bis-iminium ion would dominate. For simplicity's sake in order to reveal enantio-discrimination, we will only consider one of the substrate forms (with the R^1-group at the prochiral centre wedged) and illustrate the generation of two mono-iminium ions formed on the left or the right enantiotopic arms of the symmetrical substrate (as shown in Scheme 2.14). From the outset the conformational preferences of the vinyl-iminium ion portion of the electrophilic intermediate were appreciated as being paramount for success in view of facial selectivity in the addition step. According to the literature,[40] the dominant species when R = H (aldehyde) as shown in Scheme 2.14 would be the mono-iminium ion with an *E*-geometry and the adjacent C-C single bond in an s-*trans* conformation due to fewer steric repulsions with the substrate chain.[223] However, if R is an alkyl group (which would be synthetically easier to access, as will be shown later), the mono-iminium according to literature is predicted to be an *E*:*Z* mixture. However, as Seebach has shown, this is dependent on the substrate as well as the iminium counterion, reaction solvent and temperature, so it was hoped that reaction conditions could be established for achieving a dominant conformer leading to high stereoselectivity.[95,96] Alternatively, a less hindered primary amine catalyst might be more effective in controlling the iminium geometry[224] although the tetrazole proline analogue **13** has also been shown by Ley and co-workers[225–227] to catalyse the enone aza-Michael reaction in high enantioselectivity. Thus, in view of literature precedent it was thought that generation of a dominant iminium-ion geometry would be realised for the bis-enal and likely to be realised in the bis-enone case as well. Scheme 2.14 below summarises these ideas.



Scheme 2.14: The iminium ions formed from **A**.

- The next part concerning the stereoselectivity of addition is shown in Scheme 2.15. The two mono-iminium ions generated are not equivalent in energy but they are close and thus would both be present in approximately equal amounts. Then comes the addition. According to the literature, when using Jørgensen's catalyst, the approach of the nucleophile, in this case as a substituted hydroxylamine, would be *anti* to the face bearing the large diphenylsilyloxymethyl substituent. Applying this steric principle to the two additions as shown in Scheme 2.15 below leads to the conclusion that addition to the right-hand enantiotopic arm to give **Y** with *anti*-relative stereochemistry would be kinetically favoured over that involving the left to give **X** with *syn* relative stereochemistry. This conclusion is based on the anticipated lower non-bonded interactions between the incoming nucleophile and the R-group at the prochiral centre for the right-hand arm, again based on an *anti*-steric principle operating during the addition. Scheme 2.15 depicts these ideas:

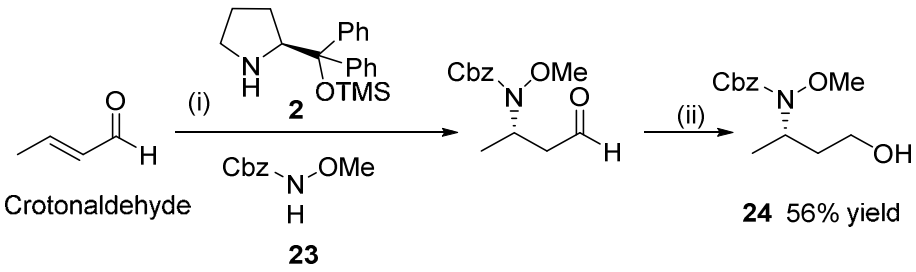


Scheme 2.15: Kinetic evaluation of the enantioselectivity in the aza-Michael addition.

Thus, the upshot would be to desymmetrise in an enantioselective fashion regarding the discrimination of the enantiotopic arms, as well as to control the diastereoselectivity to be *anti* in the customary zig-zag conformation.

With the desymmetrisation hypothesis established, a model study was carried out on the organocatalysed aza-Michael reaction to crotonaldehyde, using Jørgensen's catalyst **2**. The purpose of this study was to test out the literature conditions and to determine the best nucleophile in terms of yield and enantioselectivity.

Scheme 2.16 shows how the aza-Michael reaction was conducted using hydroxylamine-based nucleophile **23**, based on Cordova's work.[102,222] The resulting β-aminated aldehyde was reduced *in situ* by $NaBH_4$ (to simplify chromotagraphic separation) to give aminoalcohol **24**. As shown in Scheme 2.16, the nucleophile was the limiting reagent against 3 equivalents of crotonaldehyde and the reaction gave a moderate 56% yield. This was lower than the yield by Cordova et al. for the same reaction (86%), although our moderate yield agreed with yields for other aldehyde substrates in their study.[222] A possible reason for the moderate yield was thought to be a lack of nucleophilicity in the catalyst (which is solvent dependent, as suggested in the literature)[228] as well as difficulties encountered in following the hydroxylamine nucleophile as the limiting reagent on TLC as a result of the crotonaldehyde-associated by-products.



Scheme 2.16: Our model asymmetric aza-Michael reaction. *Reagents and conditions:* (i) Nucleophile **23** (1 eq), aldehyde (3 eq), **2** (20 mol%), $CHCl_3$, 24 hrs, -22 °C; (ii) $NaBH_4$ (1 eq), EtOH, 0 °C to RT

Figure 2.1 shows the ^1H NMR spectrum of aminoalcohol **24**. All the expected resonances were observed including the aromatic and benzyl Cbz resonances, the relatively downfield H-2 and H-4 (diastereotopic) resonances (due to deshielding by the adjacent heteroatoms), the methoxy singlet and the broad hydroxyl singlet.

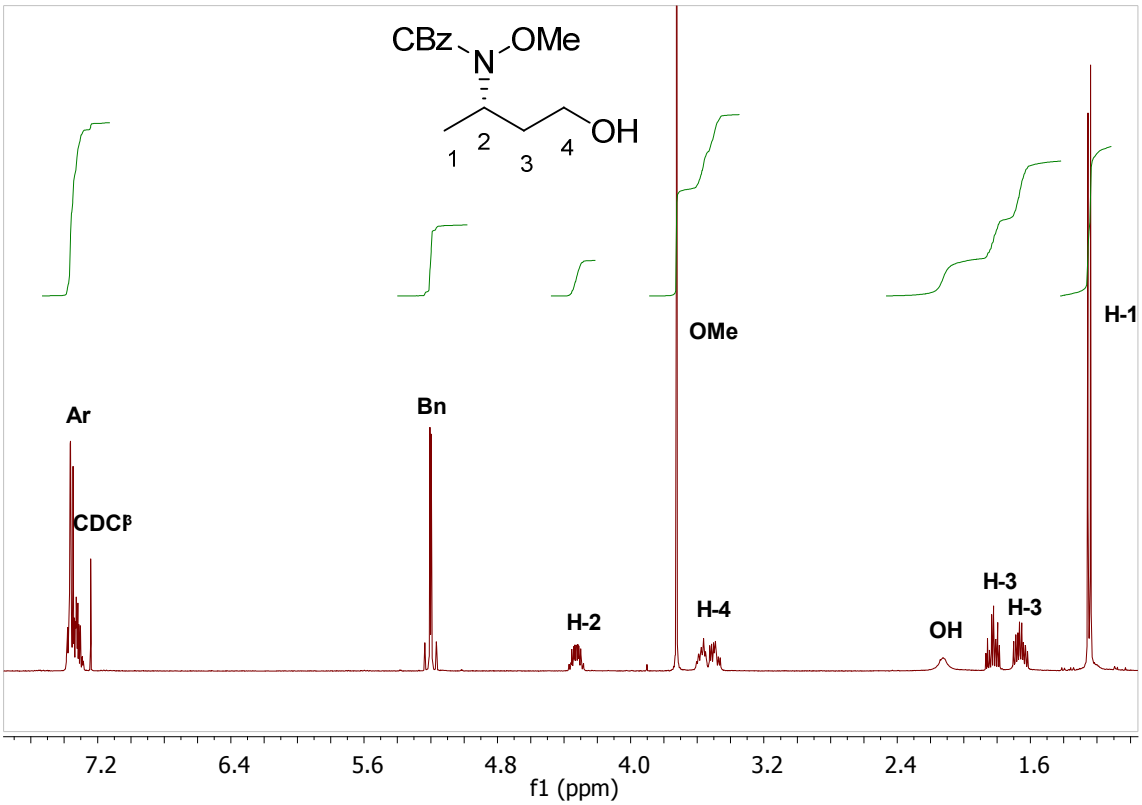


Figure 2.1: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **24**.

Table 2.1 shows the results obtained from the model study when the R-groups of the nucleophile were varied. The Cbz-based nucleophiles (**23** and **25**) are popular in the literature, while the tosyl-protected nucleophile **26** is a novel addition synthesised for this project. Moderate yields were obtained (34 – 56%), with **26** giving the lowest yield. Ees were determined via HPLC analysis of the aminoalcohols using a Chiralpak AD column. The Cbz-based nucleophiles promoted an excellent enantioselectivity (94% ee), while the sulfonamide nucleophile **26** gave a much lower enantioselectivity of 44% ee. Thus this aza-Michael model study was successful in demonstrating that nucleophiles **23** and **25** would be the best candidates for the desymmetrisation of substrate **A**, although yield optimisation studies would need to be conducted.

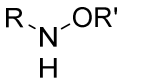
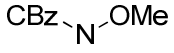
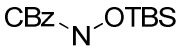
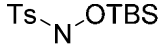
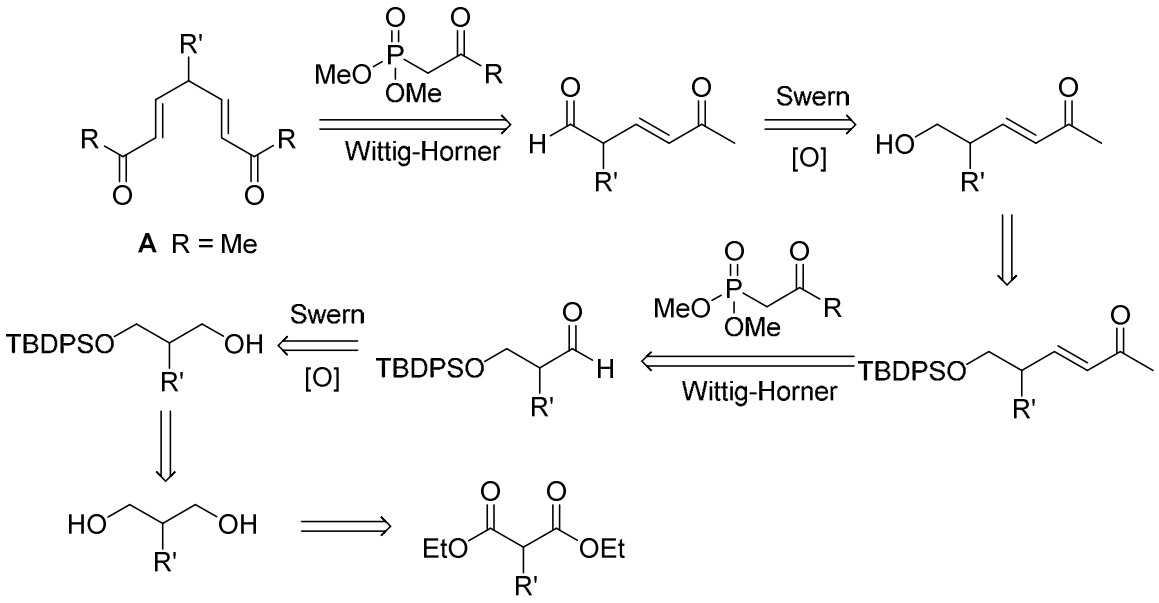
R-Groups	Nucleophile 	Yield (%)	ee (%)
R = Cbz, R' = OMe	 **23**	57	94
R = Cbz, R' = OTBS	 **25**	56	94
R = Ts, R' = OTBS	 **26**	34	44

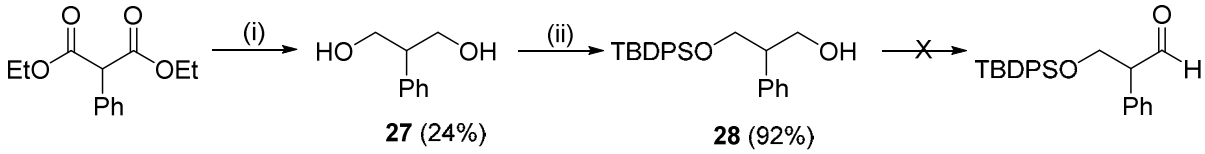
Table 2.1: Aza-Michael results for different hydroxylamine nucleophiles.

Attention was then turned to the synthesis of symmetrical substrate **A**, which was conceived to be accessible via the retrosynthetic analysis shown in Scheme 2.17. Even though a bis-enal was a better candidate for the aza-Michael reaction, its bis-enone analogue (with R = Me) was considered to be easier to synthesise. Thus in the forward direction the synthesis strategy planned on starting with a substituted malonate which, following reduction to the diol, could in principle be oxidised and extended iteratively using Wittig methodology.



Scheme 2.17: Retrosynthetic analysis of substrate **A**.

In the event (Scheme 2.18), using diethyl phenylmalonate as the starting material (R = Ph), double reduction with $LiAlH_4$ afforded the 1,3-diol **27** in a low yield of 24%, believed to be due to difficulties encountered during the reaction work-up and product isolation step, since the diol was difficult to separate from the lithium by-product salts (despite several work-up procedures attempted). The resulting diol was mono-protected with TBDPSCl using 1.1 eq of NaH to yield alcohol **28** in an excellent 92% yield following column chromatography. Regioselectivity is secured because of the large difference in nucleophilicity between the alkoxide ion (mono-deprotonation due to low base equivalents) and the other neutral hydroxyl group.



27 (24%) **28** (92%)

Scheme 2.18: *Reagents and Conditions*: (i) $LiAlH_4$ (2.5 eq), THF, 18 hrs, 0 °C to reflux; (ii) a) NaH (1.1 eq), THF, 1 hr, 0 °C to RT, b) TBDPSCl (1.2 eq), 5 hrs, 0 °C to RT.

Figure 2.2 shows the ^1H NMR spectrum of **28**, which displayed all the expected resonances, including the 10 aromatic protons, the downfield H-1 and H-3 resonances (deshielded by the adjacent oxygens) and the upfield *t*-Bu singlet.

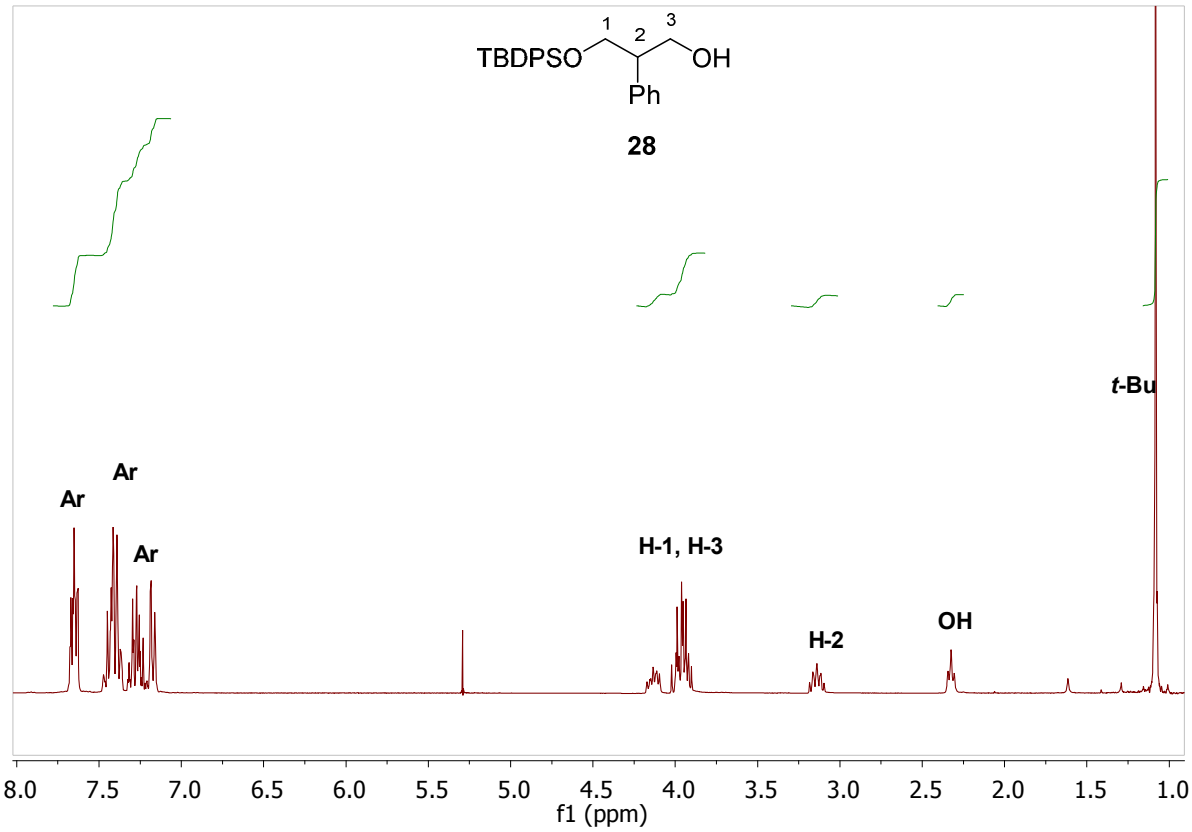
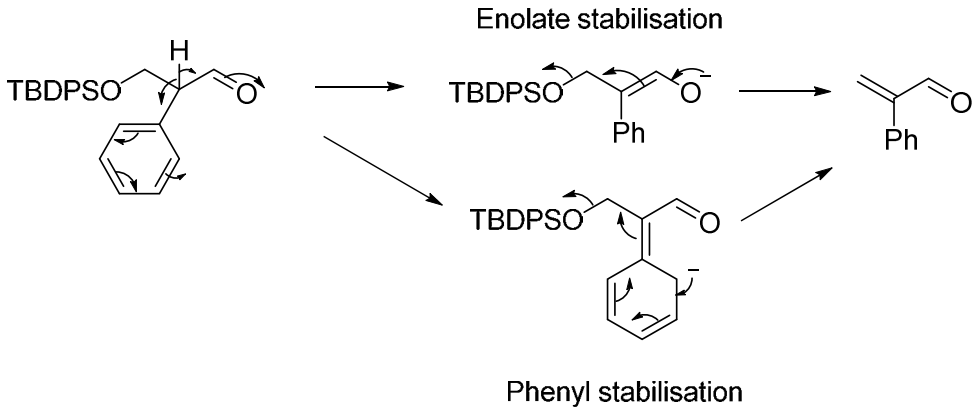


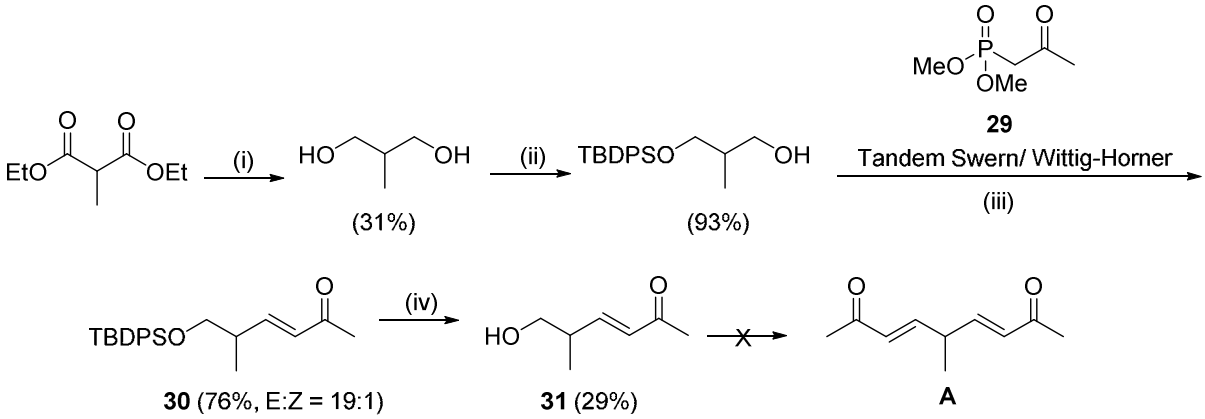
Figure 2.2: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **28**.

The Swern oxidation to alcohol **28** proved unsuccessful owing to elimination of the OTBDPS group during column chromatography purification, although the reaction TLC showed promising results. This was attributed to the natural tendency for the β-silyloxyaldehyde to β-eliminate enhanced by the stabilising nature of the phenyl substituent, helping to increase the acidity of the attached benzylic hydrogen (see the mechanism in Scheme 2.19). However, even though another purification method could have been attempted, this result led to questions about the stability of products further down in the synthetic sequence with a phenyl central substituent. It was thus decided that the central substituent should not be an electron-withdrawing functional group.



Scheme 2.19: β--Elimination of the β-silyloxyaldehyde.

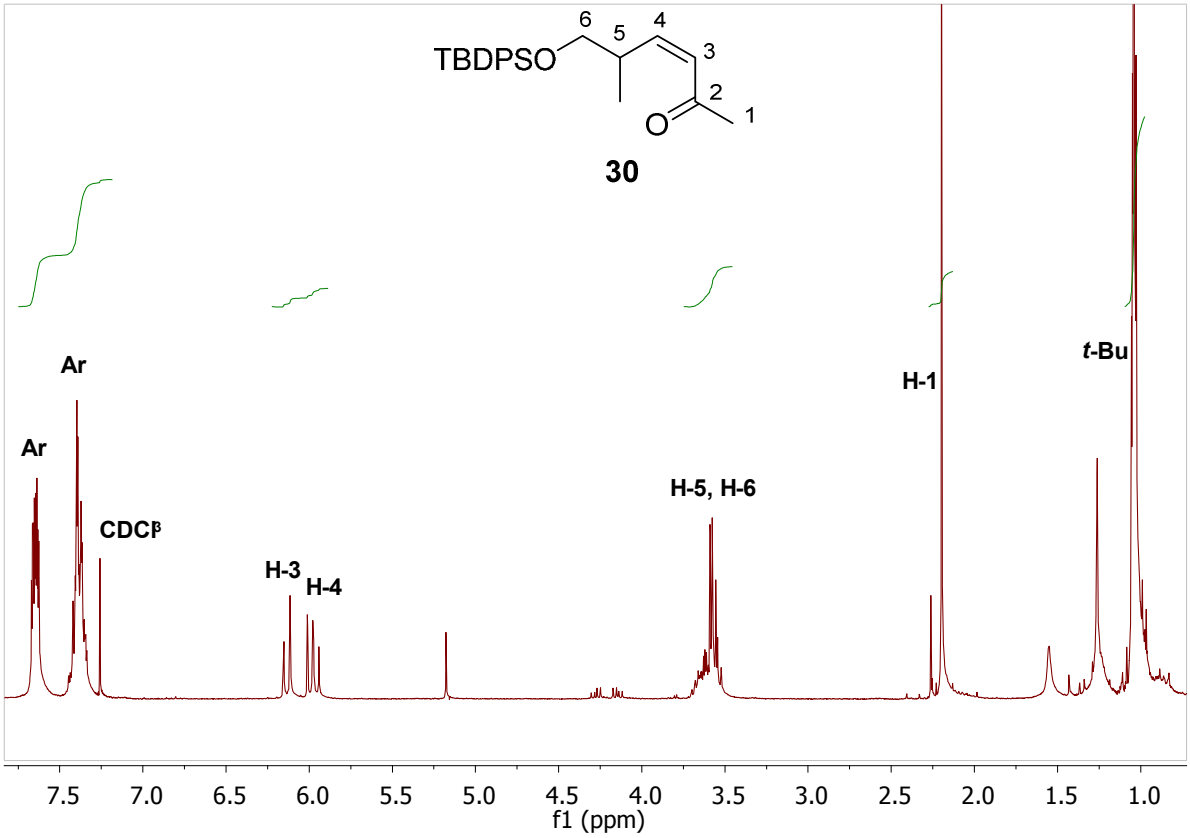
Therefore the starting material was changed to diethyl α-methyl malonate (as shown in Scheme 2.20) believing that elimination would be less likely with the methyl group at the prochiral position. The resulting 2-methyl-1,3-diol underwent reduction and TBDPS mono-protection with similar results to its phenyl counterpart as shown in Scheme 2.16. Once again, the yield of the 1,3-diol was low.



Scheme 2.20: *Reagents and Conditions*: (i) $LiAlH_4$ (1.5 eq), THF, 4 d, 0 °C to reflux; (ii) a) NaH (1.1 eq), THF, 1 hr, 0 °C to RT, b) TBDPSCl (1 eq), 24 hrs, RT; (iii) a) DMSO (3 eq), oxalyl chloride (2 eq), TEA (8 eq), DCM, 2 hrs, -78 °C to RT, b) phosphonate **29** (1.3 eq), NaH (1.2), THF, 0 °C; iv) a) NaH (1.2 eq), **29** (1.3 eq), THF, 30 min, 0 °C, b) aldehyde (1eq), 3 hrs, 0 °C to RT; v) TBAF (2 eq), AcOH (2eq), THF, 18 hrs, 0 °C to RT.

This time, a tandem Swern oxidation/Wittig-Horner (Horner-Wadsworth-Emmons) olefination strategy was chosen for accessing the enone. Inspiration for this came from work by Taylor and co-workers in their review on tandem oxidation / olefination strategies.[229] The Swern oxidation was performed as in the previous attempt (Scheme 2.12) but immediately after the reaction work-up, a Horner-Wittig-Wadsworth-Emmons olefination was performed with the ketone-based phosphonate **29** to give enone **30** in an excellent overall yield (76% over two

steps) following column chromatography. The known Swern and Wittig-Horner mechanisms are thought to apply here. Happily, the stabilised ylide was not affected by residues from the Swern oxidation still present after the work-up. The geometric isomers of **30** were separable by column chromatography so the *E*:*Z* ratio was determined by product weights, which gave an excellent 19:1 *E/Z*-ratio (as expected from this type of olefination in which the *E*-isomer is dominant). Assignment of the isomers was given by ^{1}H NMR spectral analysis (Figure 2.3), which displayed the predicted differences in the vinyl proton resonances.



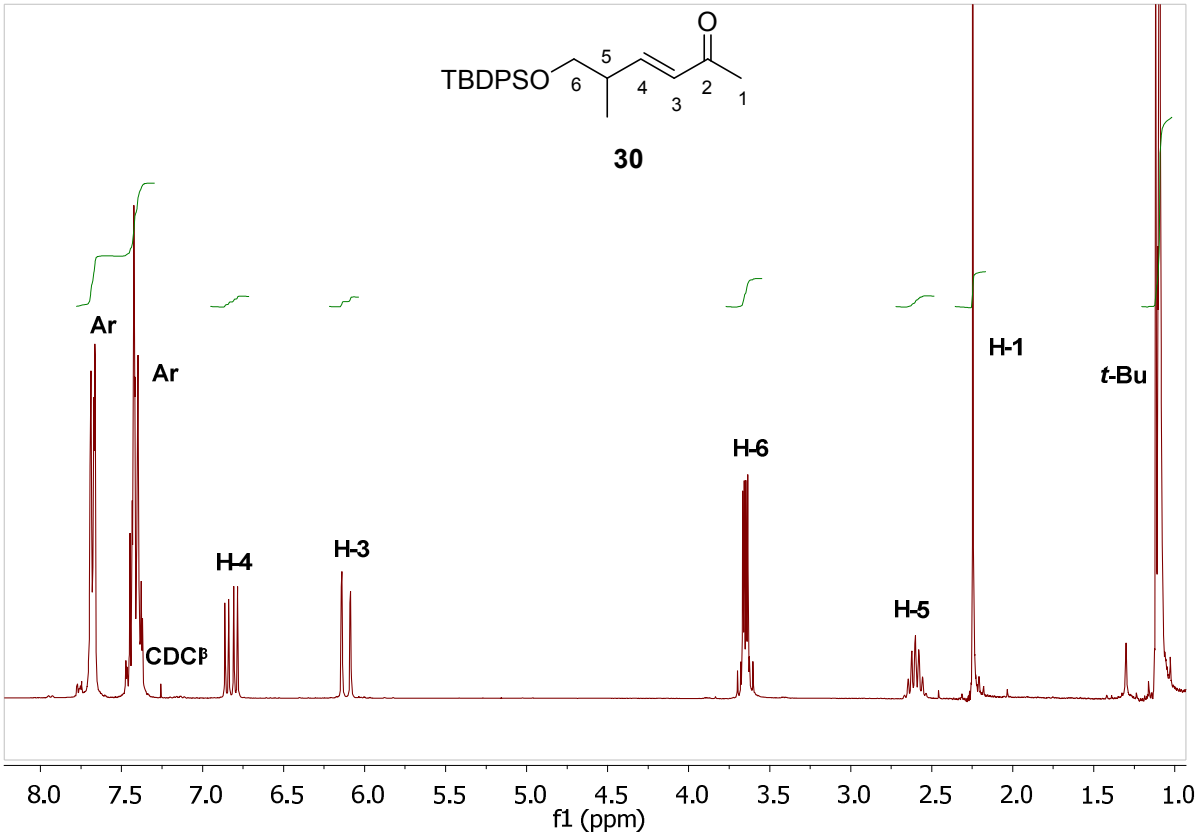


Figure 2.3: The ^{1}H NMR ($CDCl_3$, 300 MHz) spectra of both *E*- and *Z*-isomers of **30**.

Enone **30** was then deprotected with TBAF. This gave the deprotected hydroxyenone **31** in a modest 29% yield following column chromatography due to by-products formed under the acidic literature conditions.[230] Figure 2.3 depicts the ^{1}H NMR spectrum for **31**, which displayed the expected absence of TBDPS-related resonances, and the presence of the hydroxyl broad singlet and downfield vinyl resonances.

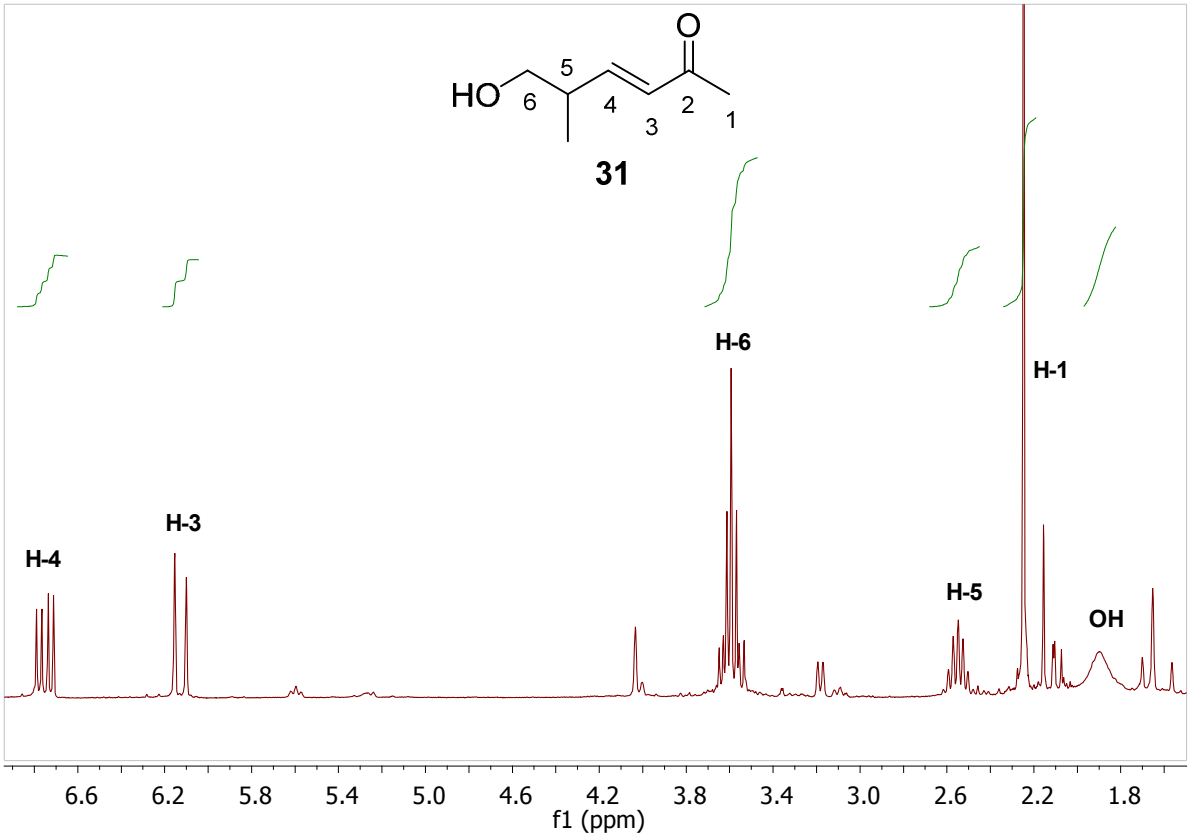
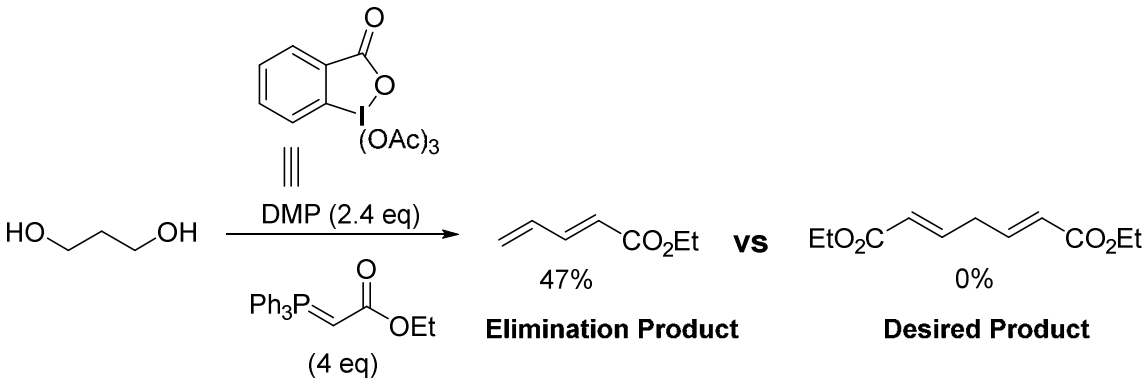


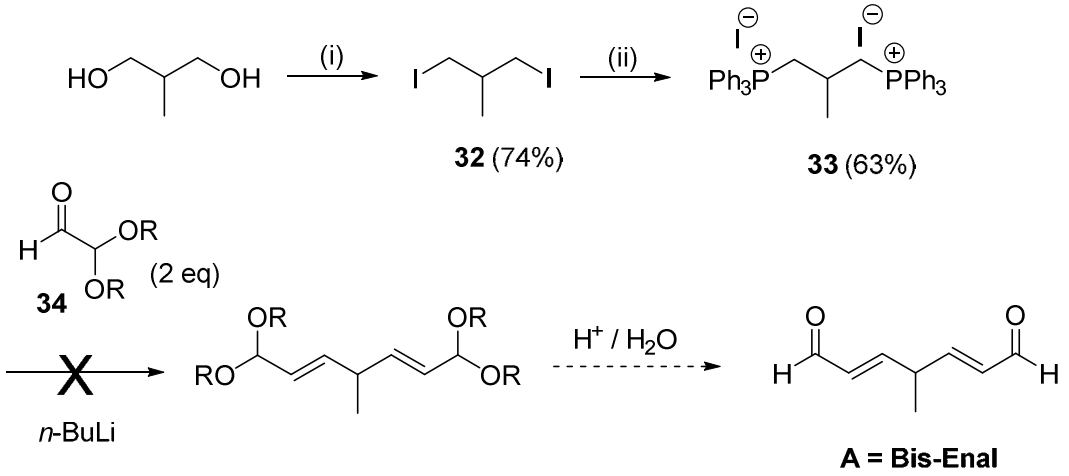
Figure 2.4: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **31**.

Thereafter, the tandem oxidation/olefination strategy was attempted again but this time was unsuccessful. ^{1}H NMR evidence of elimination to a 3,5-dienone (ie, extra vinyl resonances due to a diene in the downfield aliphatic region) during the oxidation step was observed. Once again, elimination was likely driven by the high conjugation of the elimination product. A similar elimination problem was observed by Barrett et al. in their attempted dioxidation/di-Wittig strategy using Dess-Martin periodinane (DMP) starting with 1,3-dipropandiol (Scheme 2.21).[231]



Scheme 2.21: Barrett's failed diolefination strategy.

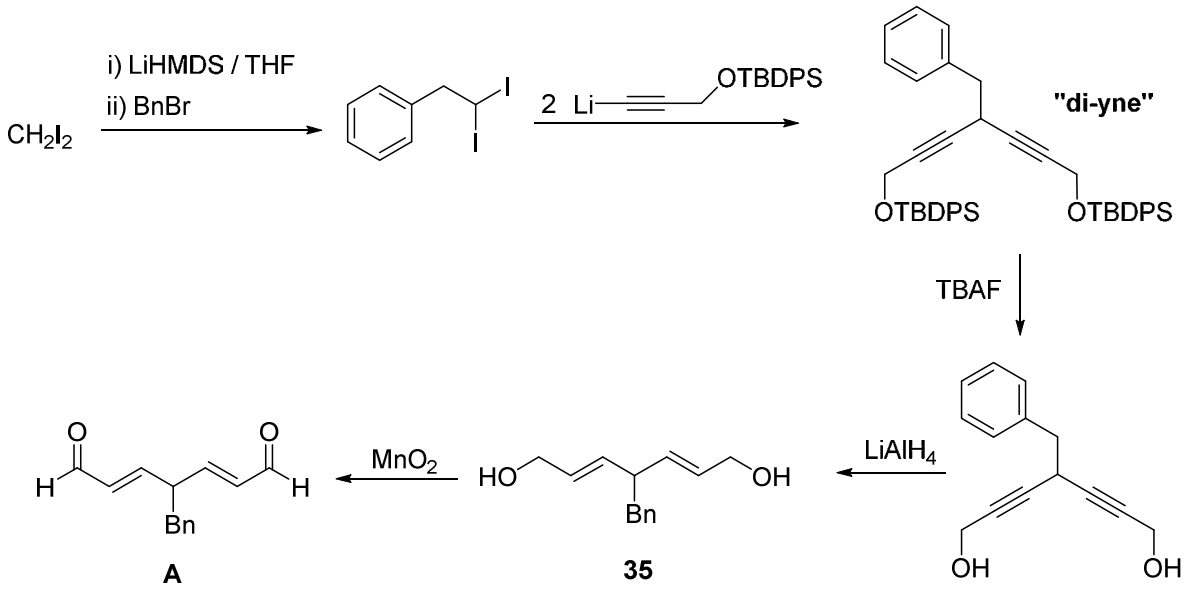
In order to avoid the problematic oxidation step, a new strategy was formulated that would reverse the sense of the Wittig-Horner disconnection by converting the 1,3-diol into a bis-iodophosphonium salt (Scheme 2.22). In this case the 1,3-diol was converted to a 1,3-diiodo **32** in 74% yield using iodine and PPh_3 in the presence of imidazole. Thereafter, **32** was successfully transformed into Wittig bis-phosphonium salt **33** in a respectable yield of 63% using a 2.4 equivalent excess of PPh_3 under reflux for four days, and aided by tricky TLC monitoring in a DCM / methanol / acetic acid solvent system. The product was purified by recrystallisation from a methanol / DCM mixture. Aldehyde **34** (which is commercially available) was chosen as the reagent for the double Wittig reaction. This is because the dialdehyde and mixed aldehyde-ketone analogues were either difficult to synthesise, or their commercially sourced forms were stored in incompatible protic solvents. Thus this strategy would allow access to the coveted, more reactive bis-enal. Unfortunately, when the Wittig reaction was attempted using **33** with *n*-BuLi and the ethyl acetal of **34**, it proved unsuccessful in which solubility issues with the salt were believed to be the cause of the failure.



Scheme 2.22: *Reagents and Conditions*: (i) a) PPh_3 (2.2 eq), I_2 (2.2 eq), imidazole (2.3 eq), CH_3CN/Et_2O (1/3), 3hrs, 0 °C to RT, b) 1,3-diol (1 eq), 40 min, 0 °C to RT; (ii) PPh_3 (2.4 eq), CH_3CN, 4 days, 85 °C.

As a final attempt at the synthesis of **A**, a new synthetic strategy was devised (Scheme 2.23), with the hope that all issues encountered in previous attempts would be avoided. Based on the known reaction that reduction of a substituted alkynol with $LiAlH_4$ gives exclusively an *E*-allylic alcohol, a strategy was devised to gain rapid access to the bis-allylic alcohol **35**, since allylic alcohols are known to be good precursors for MnO_2 oxidation.[229,232] Except for the first step, this strategy also relies on simple, established organic reactions. The first step involves benzylation of the anion of diiodomethane formed using LiHMDS using Charette's procedure for synthesising *gem*-diiodoalkanes.[233] Thereafter, the iodide is

used in a di-alkylation with an acetylide anion to give a di-yne (shown in the Scheme), which, following silyl group deprotection, stereoselective reduction with $LiAlH_4$ and finally double oxidation with MnO_2, on paper at least, should furnish the desired bis-enal. However, a change in the focus of this project to the synthesis of **B** (and the resulting new methodologies this led to) unfortunately prevented the testing of this strategy.

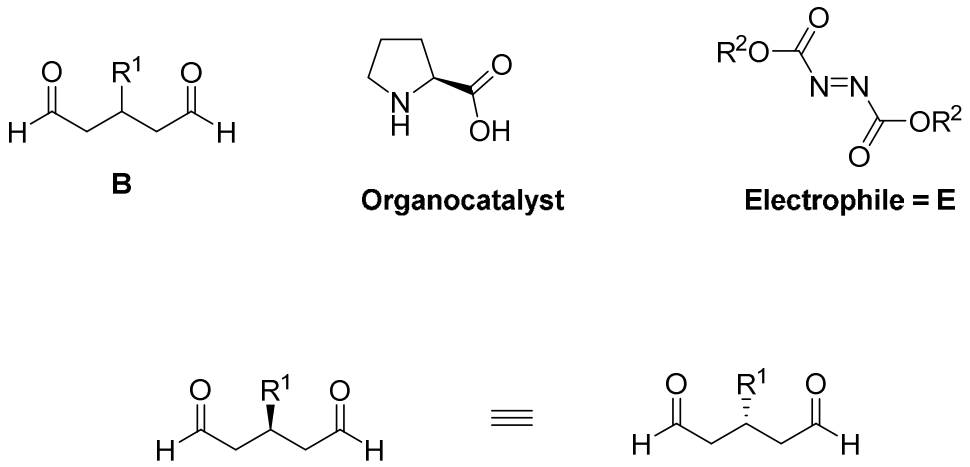


Scheme 2.23: Final envisioned route to **A** to be pursued in the future.

2.2.2 α-Functionalisation Strategy

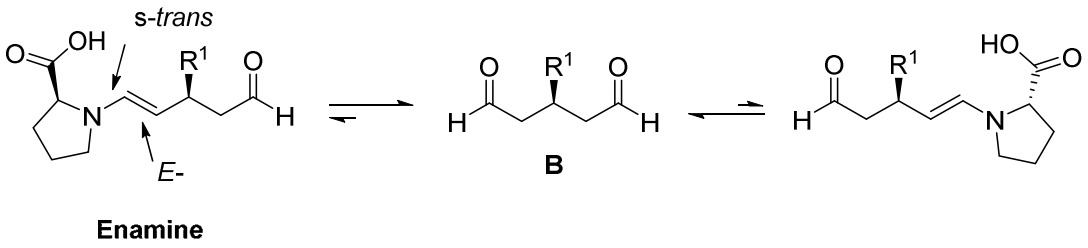
The desymmetrisation of **B** was envisioned to take place using an organocatalysed α-amination reaction. This reaction was chosen as it is a reliable method for introducing both nitrogen and chirality into to carbonyl compounds in high yield and enantioselectivity, as discussed in Chapter 1.[73] To this end, as with the aza-Michael strategy, the objective involved synthesising a symmetrical prochiral substrate **B** (a bis-aldehyde) that could be successfully desymmetrised via α-amination in an enantio- and diastereoselective manner. Also, as in the β-functionalisation case, the key design aspects were:

- The reaction would involve three components as (shown in Scheme 2.24): 1) A symmetrical bis-aldehyde substrate represented in its zig-zag conformation; 2) L-proline as the organocatalyst which had shown excellent enantioselectivities in List's work;[67] 3) an azodicarboxylate Mitsunobu electrophile.



Scheme 2.24: The components of the envisioned α-amination desymmetrisation.

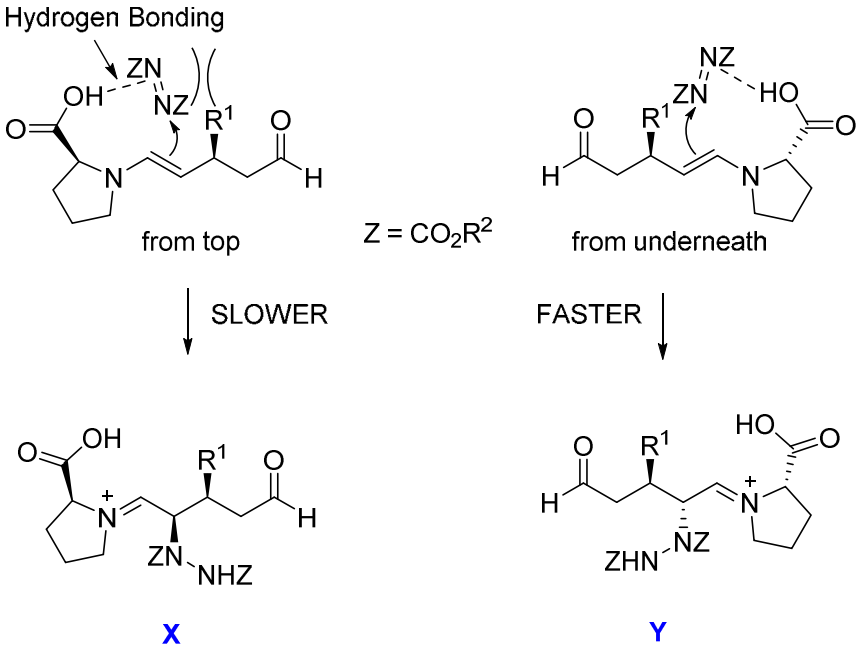
- An excess of bis-aldehyde and the addition of a catalytic amount of proline would ensure dominance of a mono-enamine in the enamine activation step. As before, for simplicity's sake in order to reveal enantio-discrimination, we will only consider one of the substrate forms (with the R^1-group at the prochiral centre wedged) and illustrate the generation of two enamines formed on the left or the right enantiotopic arms of the symmetrical substrate (as shown in Scheme 2.25). According to the literature,[40] the dominant species would be the mono-enamine with an (*E*-s-*trans*)-geometry due to fewer steric repulsions with the substrate chain, Scheme 2.25.



Scheme 2.25: The enamines formed from **B**.

- With regards to the stereoselectivity, the two enamines generated are not exactly equivalent in energy but were considered close enough so they would both be present in approximately equal amounts. According to the literature when using proline as the catalyst,[40] the amination process involves a *syn*-addition of the electrophile with respect to the proline carboxylate, due to hydrogen bonding between the proline carboxylate and one of the azo nitrogens. Implementing this to each iminium ion leads to the conclusion that addition to the right-hand enantiotopic arm to give **Y** with *anti*-relative

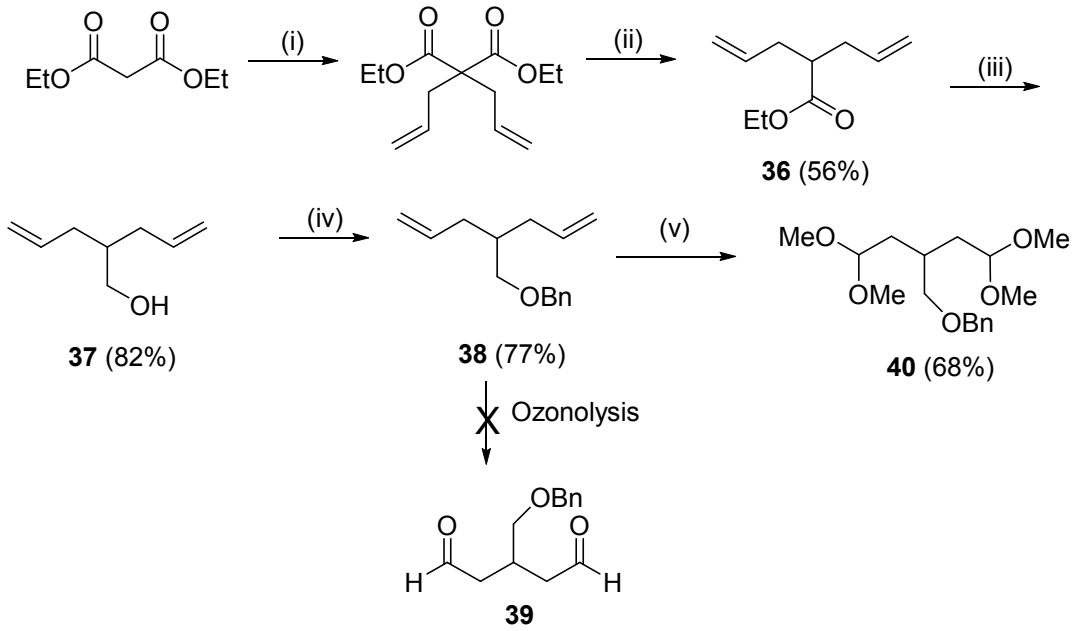
stereochemistry would be kinetically favoured over that involving the left to give **X** with *syn*-relative stereochemistry. As with the bis-enone case (Scheme 2.15), this is based on the anticipated lower non-bonded interactions between the approaching hydrogen-bonded electrophile and the R^1 group at the prochiral centre, based on the *anti*-steric principle. Scheme 2.26 depicts these ideas:



Scheme 2.26: Kinetic evaluation of the stereoselectivity in the α-amination.

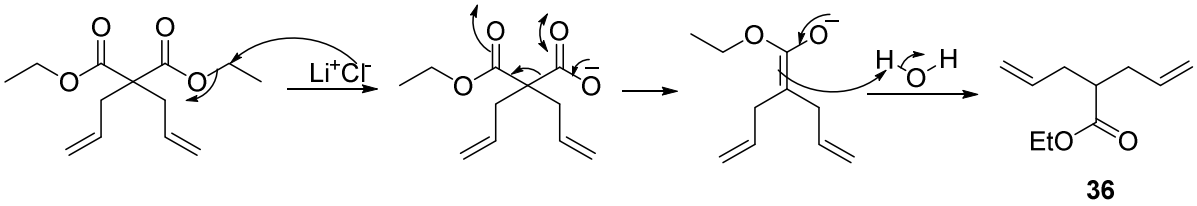
Thus, desymmetrisation would be achieved in an enantioselective fashion regarding the discrimination of the enantiotopic arms, as well as to control the diastereoselectivity to be *anti*- in the customary zig-zag conformation.

In contrast to substrate **A**, the synthesis of bis-aldehyde **B** was pursued with more promising results. The overall achievement is shown in Scheme 2.27.



Scheme 2.27: *Reagents and Conditions*: (i) a) NaH (2.5 eq), THF, 45 min, 0 °C to RT, b) allyl bromide (2 eq), 26 hrs, 70 °C; (ii) LiCl (2.2 eq), DMSO (with a little H_2O), 21 hrs, 180 °C; (iii) $LiAlH_4$ (1.6 eq), THF, 4 hrs, 0 °C to RT; (iv) a) NaH (1.2 eq), THF, 1.25 hrs, 0 °C to RT, b) BnBr (1.5 eq), TBAI (10 mol%), 18 hrs, RT; (v) a) O_3, MeOH, 2 hrs, -78 °C to 0 °C, b) PPh_3 (2.2 eq), 2 hrs, 0 °C to RT, c) Tosic acid (20 mol%), 18 hrs, RT.

Thus, diethyl malonate was diallylated with an excess of allyl bromide in the presence of NaH as base (2.5 eq) and after the reaction work-up, the crude product was reduced via the Krapcho decarboxylation. The suggested mechanism for the decarboxylation is shown in Scheme 2.28.



Scheme 2.28: The suggested mechanism for the Krapcho decarboxylation.

Column chromatography gave the desired diallyl ester **36** in a 56% yield (over the two steps). For this known compound, the ^1H NMR resonances (Figure 2.5) agreed with the literature.[234] The most significant resonances were the downfield vinyl resonances and the ethyl triplet and quartet resonances (which are characteristically quite deshielded by the ester functionality).

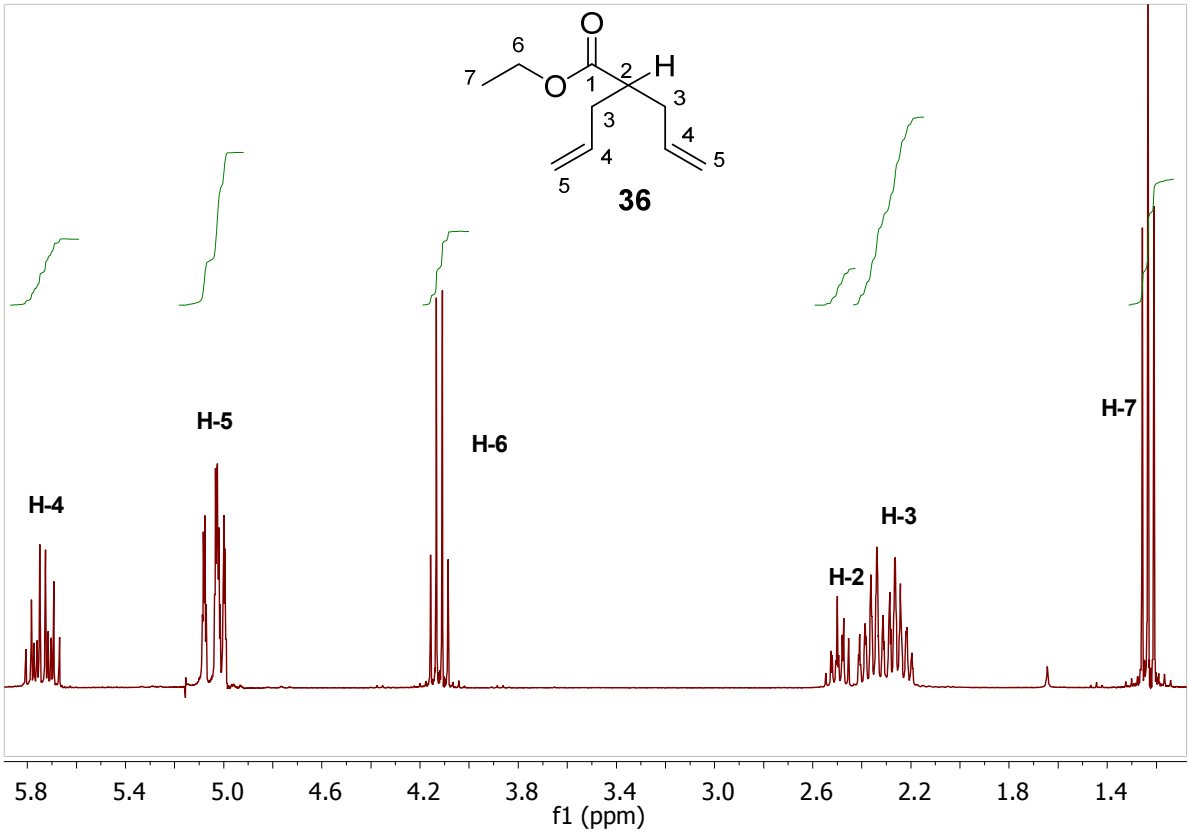


Figure 2.5: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **36**.

Ester **36** then underwent reduction with $LiAlH_4$ to give alcohol **37** in excellent yield (82%) following column chromatography. Thereafter, **37** was protected with benzyl bromide using sodium hydride as base to give **38** in 77% yield. This is also a known compound with its ^{1}H NMR resonances (Figure 2.6) agreeing with the literature.[235] The aromatic and methylene resonances of the added benzyl group were most significant in confirming the structure of **38**.

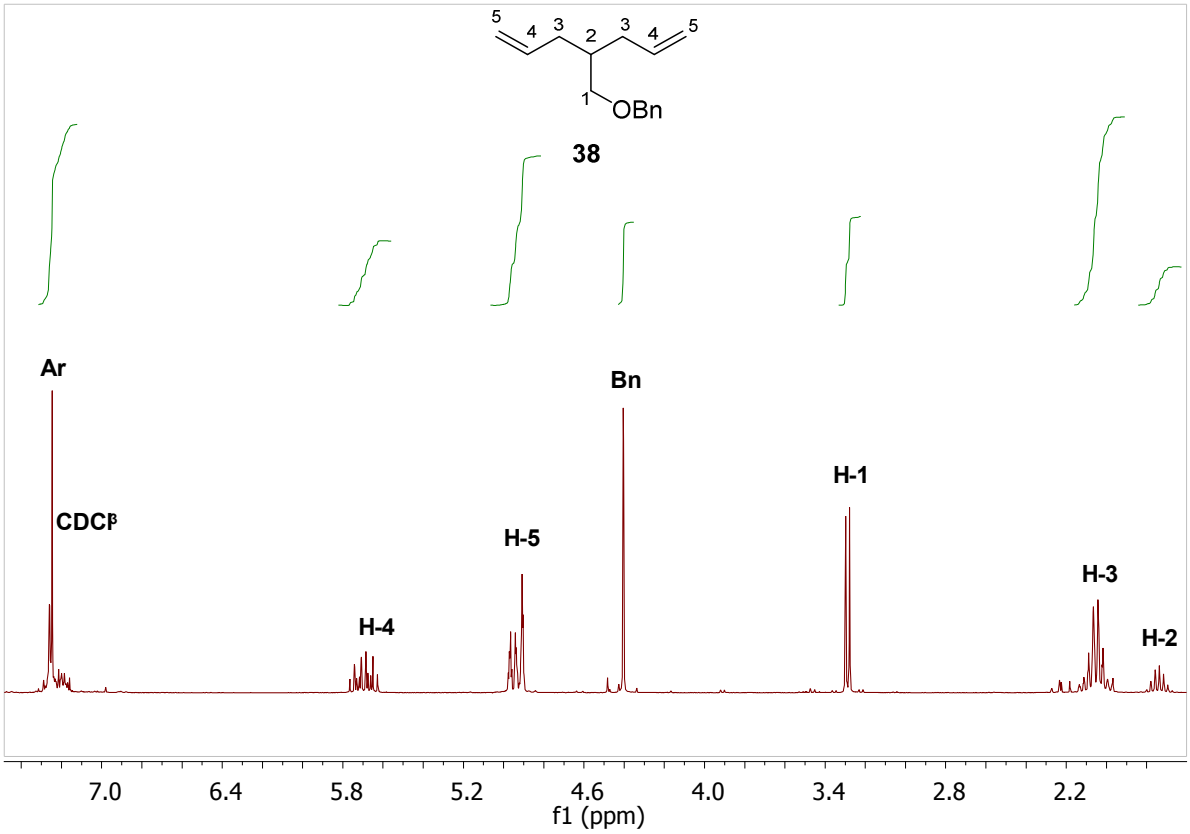
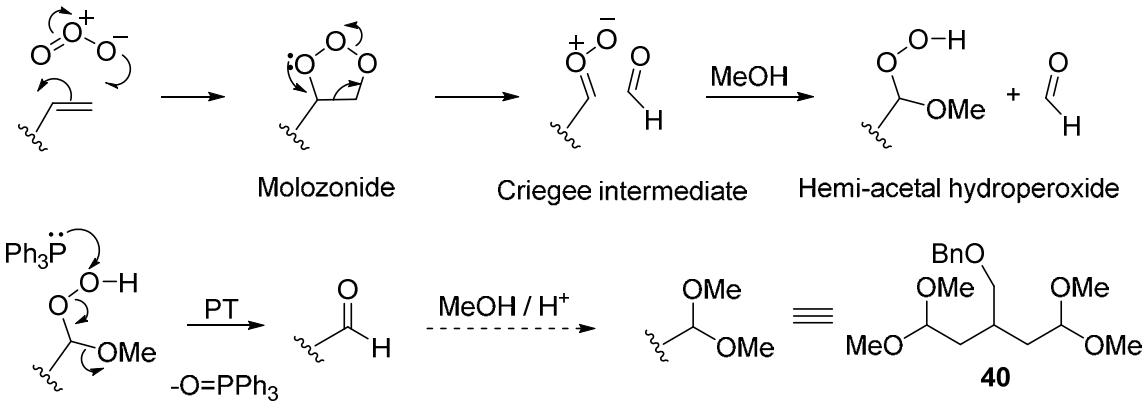


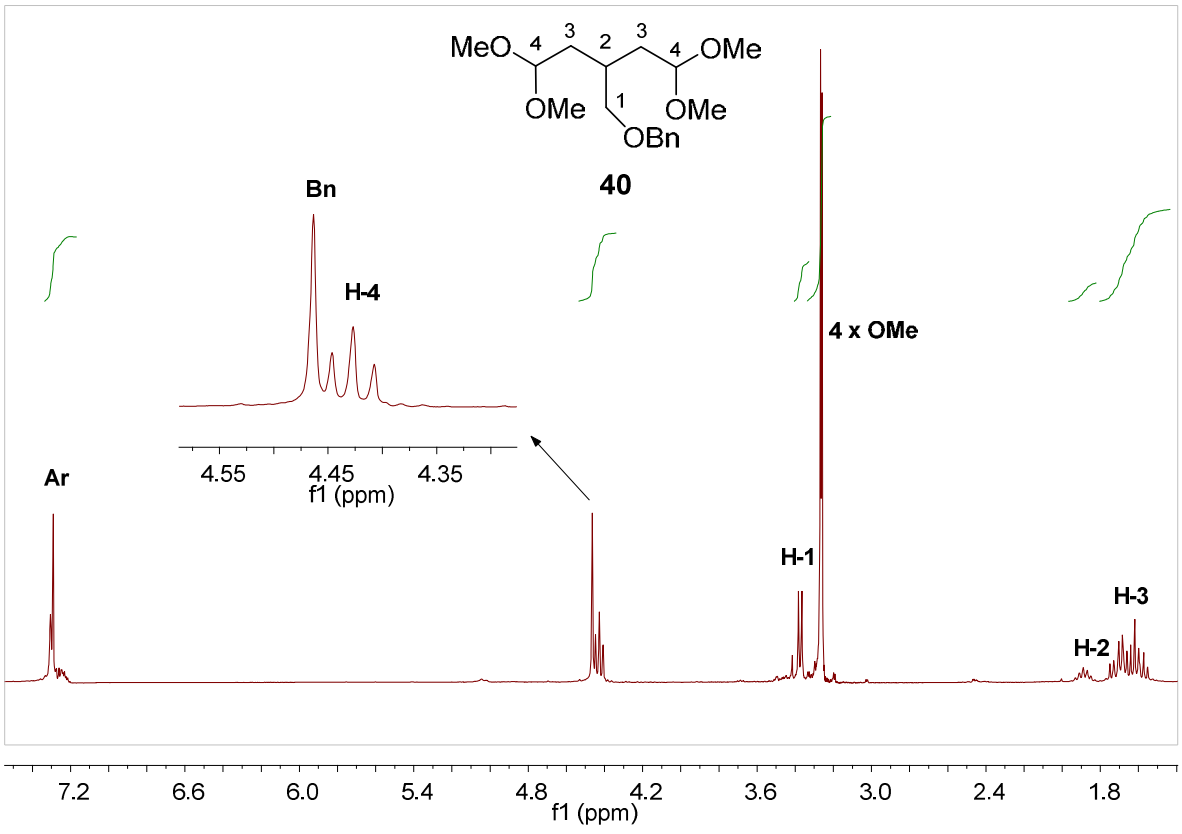
Figure 2.6: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **38**.

Product **38** was then subjected to a double ozonolysis in an attempt to produce the bis-enal, using PPh_3 as the reducing agent. However, even though reaction TLCs were initially promising, the ^{1}H NMR spectrum of the product after column chromatography did not show the expected resonances. Indeed, TLCs of the columned product showed streaks of a second, more polar product (or a mixture of products). This suggested that bis-aldehyde **39** was prone to self-condensation (due to enolisation-type reactions) when adsorbed onto the relatively acidic and hygroscopic silica gel. Although other purification methods could have been explored, this was taken as a warning of the final product being unstable and difficult to handle. Therefore, it was decided to isolate the final symmetrical substrate as a bis-acetal - a masked aldehyde, which was expected to be far more stable and not prone to self-condensation. This was achieved via a one-pot tandem ozonolysis / acetalisation procedure. The mechanism of this transformation is shown in Scheme 2.29, involving a 1,3-cycloaddition to the double bond to form a molozonide, followed by a retro-1,3-cycloaddition (regioselectivity unknown) to a Criegee intermediate (an aldehyde and an aldehyde oxide). Because methanol is present, the carbonyl oxide is intercepted to form a hemi-acetal hydroperoxide. Thereafter, triphenylphosphine reduces this to a second molecule of aldehyde. On addition of the *p*-tosic acid the aldehydes are converted into their acetals, forming bis-acetal **40** ultimately, Scheme 2.29.



Scheme 2.29: The mechanism for the tandem ozonolysis / acetalisation step.

The one-pot tandem ozonolysis/acetalisation gave the desired bis-acetal **40** in 68% yield as an oil. Since this was a new compound, its structure was elucidated using a range of analytical techniques (infrared spectroscopy and high-resolution mass spectrometry) in addition to ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR and ^{13}C NMR spectra of **40** are shown in Figure 2.7. The ^{1}H spectrum showed the benzyl, methoxy (diastereotopic) and H-4 resonances in their expected places and with the correct integration.



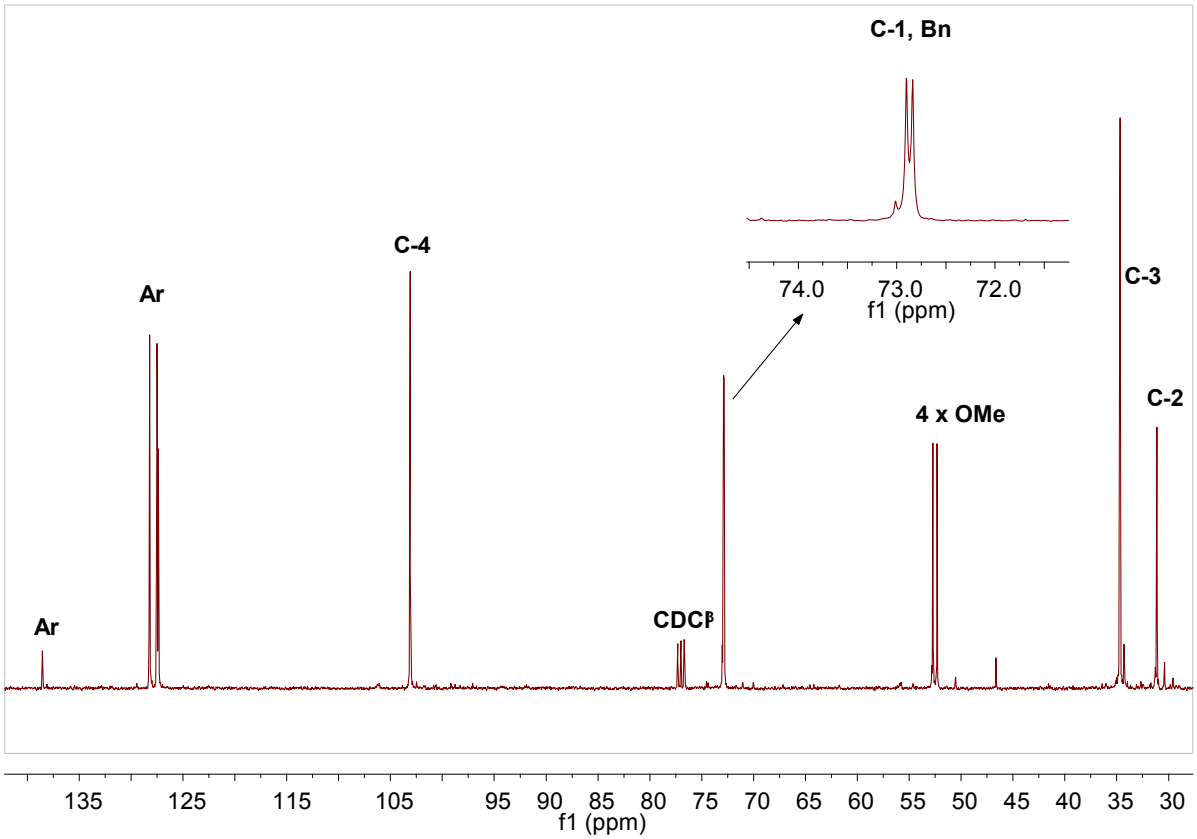
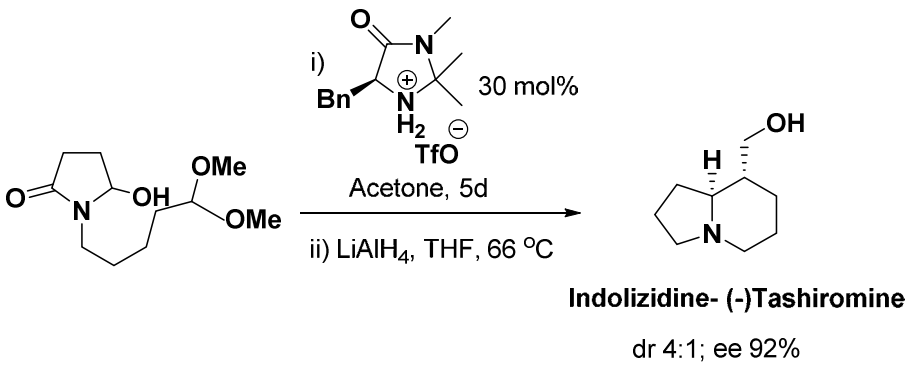


Figure 2.7: The ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75.5 MHz) spectra of bis-acetal **40**.

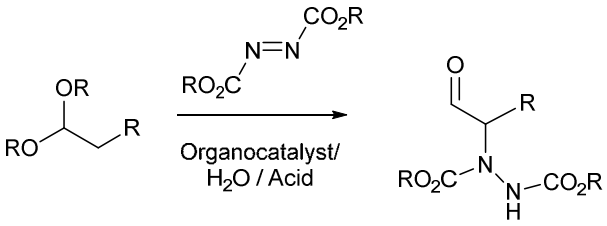
The relative ease of this synthesis encouraged focus to be directed solely to the α-amination of bis-acetal substrates. Furthermore, a deeper search into the literature revealed that the conditions for an organocatalysed α-amination of an acetal had never been reported. In fact, outside of our work, the only other use of acetals to generate an enamine intermediate in organocatalysis reactions was Koley and co-worker's organocatalysed Mannich cyclisation (Scheme 2.30) involving a hemiaminal as an *N*-acyliminium ion precursor being intercepted by an acetal-derived enamine (this was published in September 2014, 8 months after the publication of our work). Thus a model study was undertaken in order to develop optimal conditions for the α-amination of an acetal for taking forward into desymmetrisation. The next Chapter describes the results of this study.



Scheme 2.30: The use of an acetal in an organocatalysed Mannich reaction.

Chapter 3: The Acetal Model Study

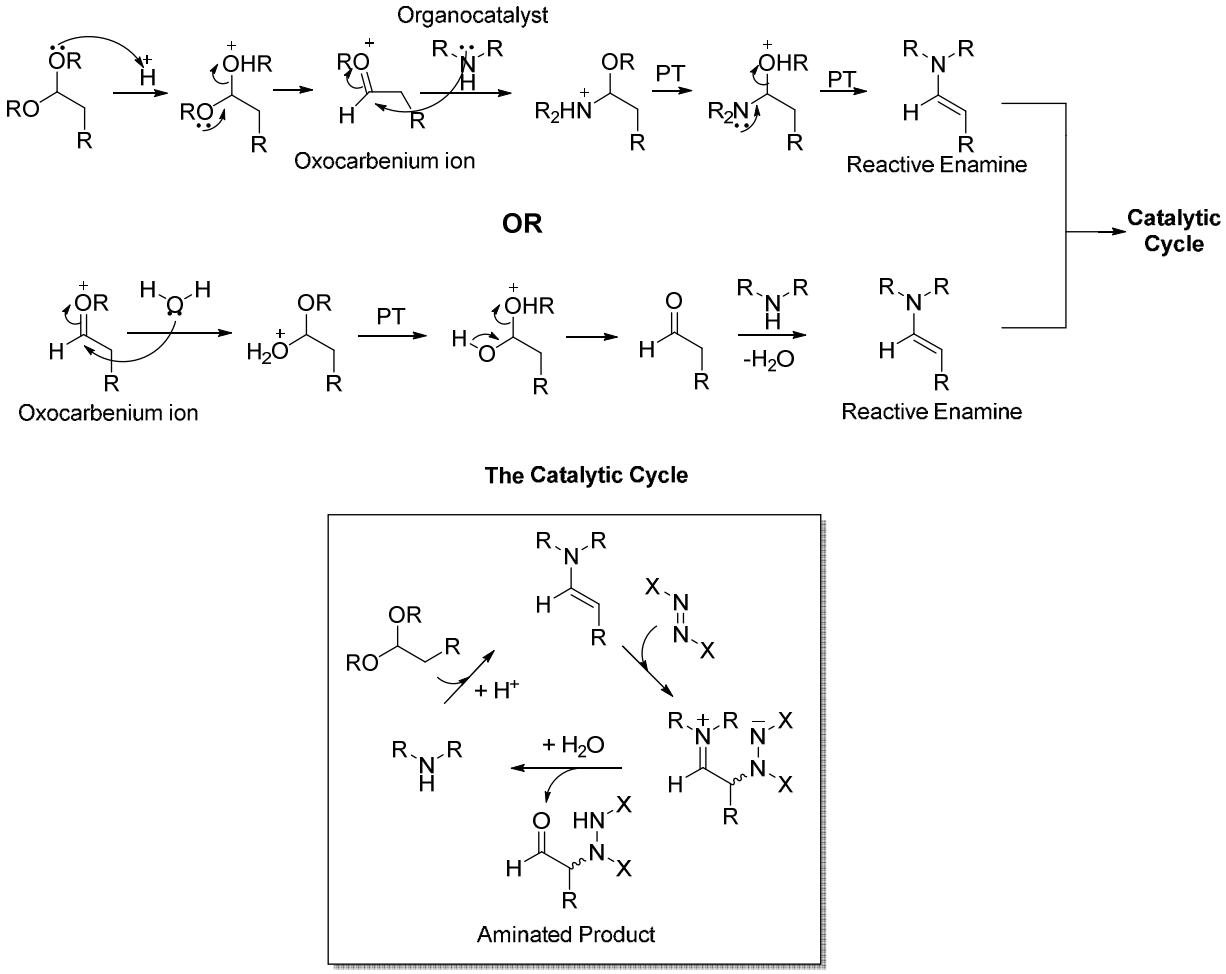
As discussed in the previous Chapter, the objective of the PhD developed into establishing optimal conditions for the usage of acetals as masked carbonyl equivalents in the organocatalysed enantioselective α-amination reaction, Scheme 3.1. The methodology intended was new although ketals had been shown to undergo non-stereoselective, Lewis-acid catalysed α-amination to form α-hydrazino ketals.[236]



Scheme 3.1: The envisioned acetal α-amination.

3.1 Mechanistic Considerations – Finding an Appropriate Acid

From the outset the mechanistic challenges involved in developing such a reaction were clear. As shown in Scheme 3.2, first was the need to use Lewis or Bronsted catalysis[237–242] in order to generate an oxocarbenium ion[243,244] that could react with the organocatalyst to generate the key enamine intermediate. Additionally, water would need to be added to ensure catalyst turnover. However the presence of both these necessary components suggested the possibility of product racemization via acid-catalysed enol formation. Also, the enamine could in principle be generated directly from the oxocarbenium ion or from the aldehyde following complete hydrolysis of the oxocarbenium ion. Since the organocatalyst was more nucleophilic than water it was hoped that the first pathway would apply since this seemed likely to ensure a greater chance of chemoselectivity as well as retain one of the acetal groupings in the bis-acetal desymmetrisation.



Scheme 3.2: The suggested pathway for acetal α-amination.

The initial pilot study was conducted on 1,1-dimethoxydecane (DMD) in order to avoid volatility issues with lower molecular weight substrates. The reaction conditions were chosen to be similar to those of List's initial reaction[67] using an excess of acetal (1.5 equivalents), DBAD (or DIAD) as the limiting reagent and 10 mol% of L-Proline at room temperature. However, whereas he had used acetonitrile, in our case acetic acid was added as both solvent and as a weak Bronsted acid catalyst (pKa = 4.8, 1 ml = 10.2 equivalents).[245] Moreover, at least one equivalent of water was included to ensure catalyst turnover (see Scheme 3.2), which subsequently was studied as a reaction parameter. When one equivalent of water was used (Table 3.1, entry 5), following borohydride reduction of the primary product to minimise racemization, hydrazino alcohol **41** was obtained after 2 days as an amorphous white solid, following column chromatography in 37% yield and 12% ee. Thus this initial result showed that the acetal was 45 hours slower and far less stereoselective than the List protocol with aldehydes. Importantly however, no hydrazino alcohol was observed in the absence of proline. Figure 3.1 shows the ^{1}H NMR spectrum of **41**. Except for

the H-10 upfield triplet, all of the other resonances occurred as unresolved peaks. This was attributed to the presence of a population of conformers involving the hydrazide functionality that slowly equilibrated on the NMR timescale together with s-*cis* and s-*trans* conformers around the N-CO bond involving the tertiary nitrogen of the hydrazide (similar spectra are observed for all compounds in List's and other similar work). Nonetheless, the expected resonances were observed in the downfield aliphatic and aromatic regions as assigned in Figure 3.1. Owing to deshielding by adjacent heteroatoms, H-1 and H-2 appeared as multiplets in the same region as the OH resonance. The benzyl methylene resonances appeared as a multiplet in the 5.00 - 5.50 ppm range due to deshielding from the carbamate oxygen. Finally, the NH resonance appeared as a broad singlet very close to the benzyl aromatic multiplets. These diagnostic signals (H-1, H-2, OH, Bn and NH) were used to elucidate the structures of similar molecules synthesised later in the acetal model study. In view of the difficulties with the ^{1}H NMR assignments just mentioned and also since this was a new compound, additional analysis techniques were used in order to confirm the structure (^{13}C NMR, infrared spectroscopy and high-resolution mass spectrometry) ^{13}C NMR spectroscopy was particularly useful in assigning the C-1, C-2, benzyl resonances in the 55-70 ppm region as well as the two carbonyl resonances in the 150–160 ppm region, which were common to all hydrazino alcohols in this model study.

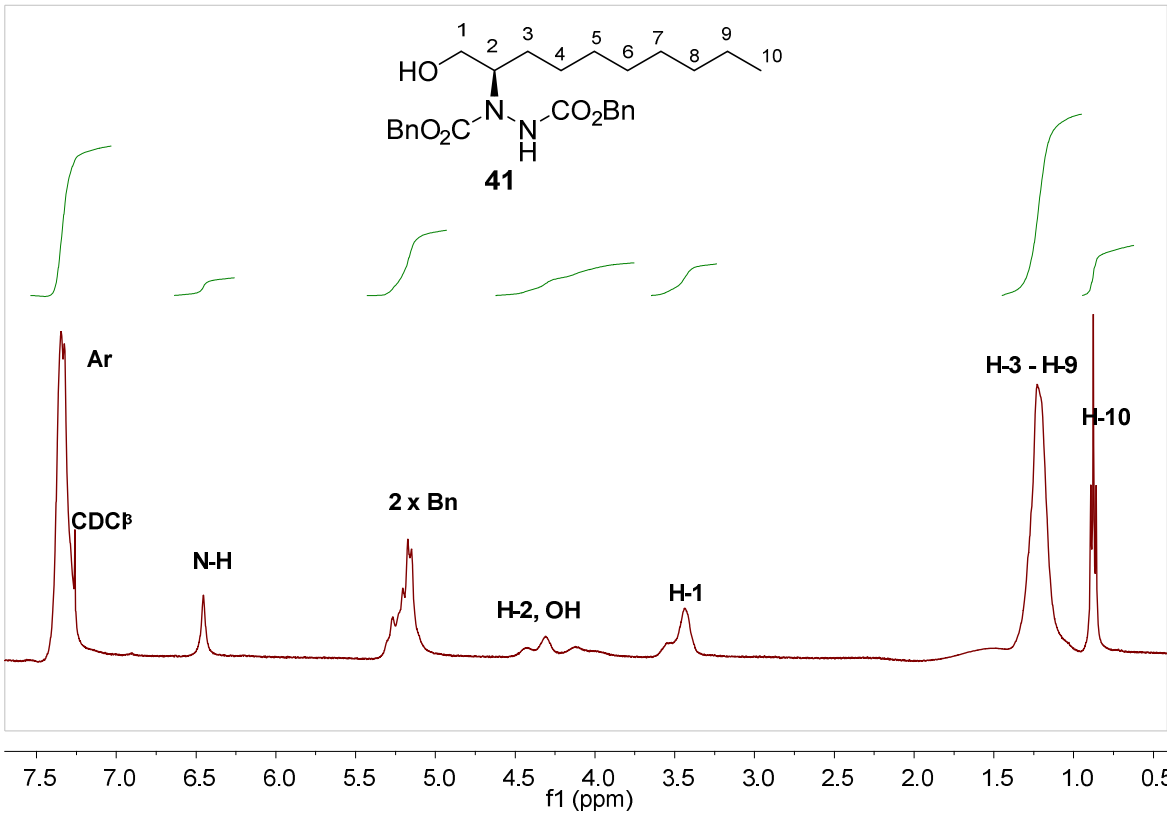
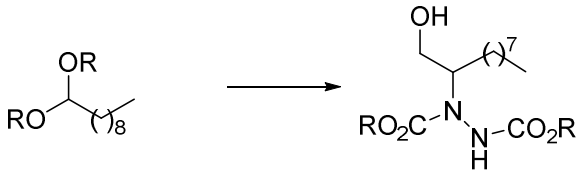


Figure 3.1: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **41**.

With the correct product in hand, the reaction model study was conducted at room temperature in acetic acid varying the water content and aminating agent (DBAD or DIAD). The results are shown in Table 3.1.



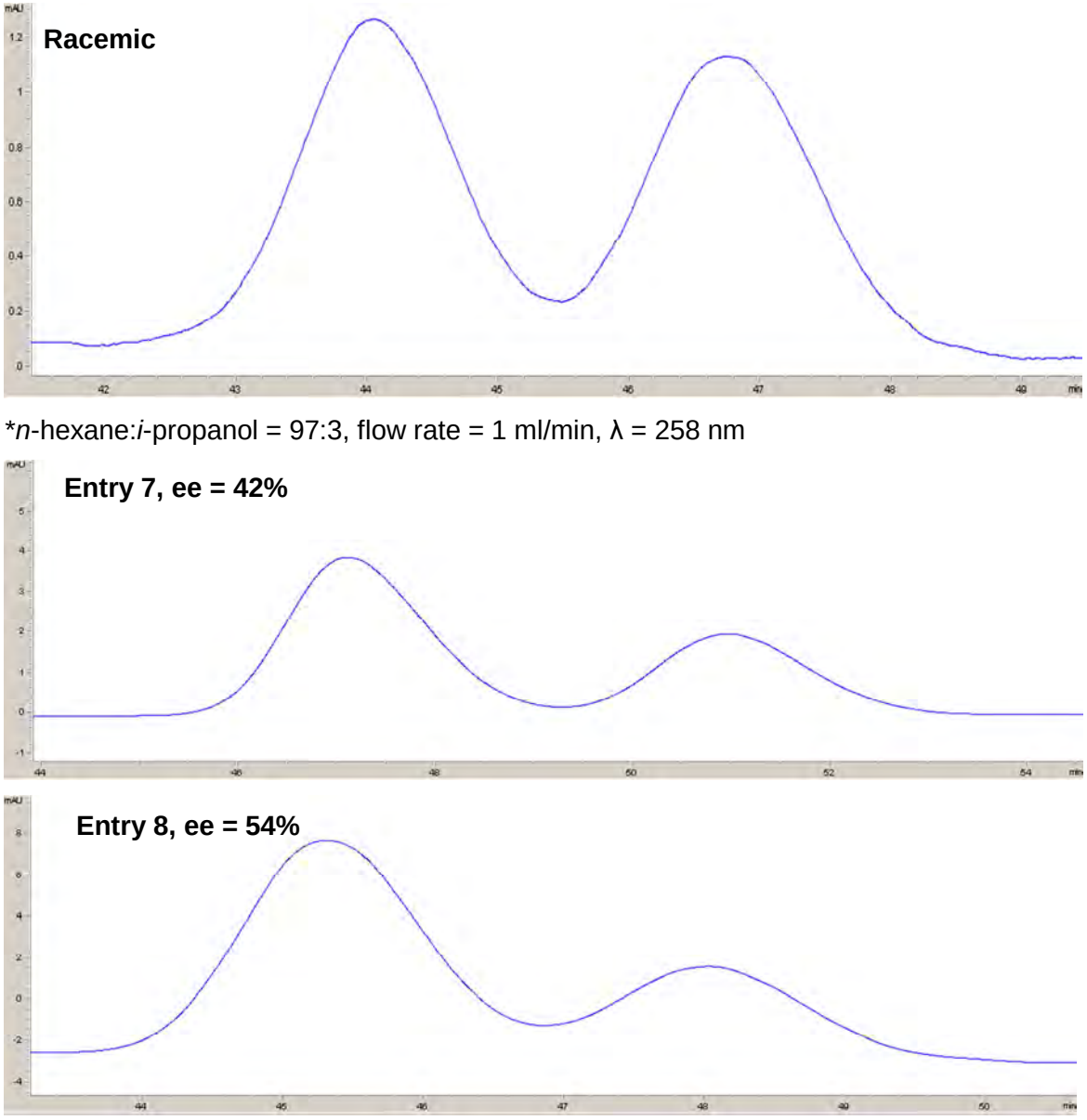
R = *i*-Pr
R = Bn, **41**

Entry	Substrate (1.5eq)	Electrophile (1 eq)	Proline (mol %)	Acid (eq)	H_2O (eq)	Time	Temp (°C)	Yield (%)	ee (%)
1	DMD	DIAD	10	AcOH (10.2)	1	5.5 d	RT	69	2
2	DMD	DIAD	10	AcOH (10.2)	5	3 d	RT	84	30
3	DMD	DIAD	10	AcOH (10.2)	10	2 d	RT	80	42
4	Decanal	DIAD	10	AcOH (10.2)	10	24 hrs	RT	84	46
5	DMD	DBAD	10	AcOH (10.2)	1	2 d	RT	37	12
6	DMD	DBAD	10	AcOH (10.2)	5	40 hrs	RT	37	36
7	DMD	DBAD	10	AcOH (10.2)	10	16 hrs	RT	38	42
8	Decanal	DBAD	10	AcOH (10.2)	10	2.5 hrs	RT	41	54

Table 3.1: The Initial acetal experiments with acetic acid.

The results indicated that DBAD reacted about twice as fast as DIAD, likely for steric reasons, but gave about half the yield suggesting that it was less stable in the medium compared to DIAD. In each reaction the aminating agent was used as limiting, and reactions were run to complete conversion of the aminating agent by TLC. Similarly, the rate of each reaction in both series increased with increasing water content as did the ee. The reaction ees were determined by chiral HPLC (Chiralpak AD or OD columns) with a UV-detector. Thus the DBAD products proved more convenient because they contained a UV-active chromophore, whereas the DIAD-derived hydrazino alcohols needed to be benzoylated prior to HPLC analysis. Nevertheless, both aminating agents gave similar ee's under identical conditions, with a maximum of 42% in both cases (entries 3 and 7); see Figure 3.2 for the HPLC chromatograms of entries 7 and 8. As a control, both the DIAD and DBAD reactions were carried out using decanal at 10 equivalents of water (the amount of water which gave the fastest reaction and the highest ee). Interestingly, the aldehyde reacted much faster (two times for DIAD and about six for DBAD) but ees were comparable (entries 3/4 and 7/8) to

those for the acetal. This supported the view from the literature[243] that the rate-limiting step for the acetal is the formation of the oxocarbenium ion, since thereafter the steps are virtually identical for each substrate. Moreover, an HPLC chromatogram of the decanal product shown in Figure 3.2 revealed the same sense of stereogenicity in the product (known to be *R*- for aldehydes), which indicated that they operate via the same enamine as expected, with possibly a similar transition-state model. Despite its lower yields, DBAD was picked as the aminating agent of choice for further studies in view of its considerably faster reaction times and its operational simplicity due to UV-activity from the benzyl groups for ee evaluation via HPLC.



*n-hexane:*i*-propanol = 97:3, flow rate = 1 ml/min, λ = 258 nm

Figure 3.2: The HPLC chromatogram of entries 7 and 8.

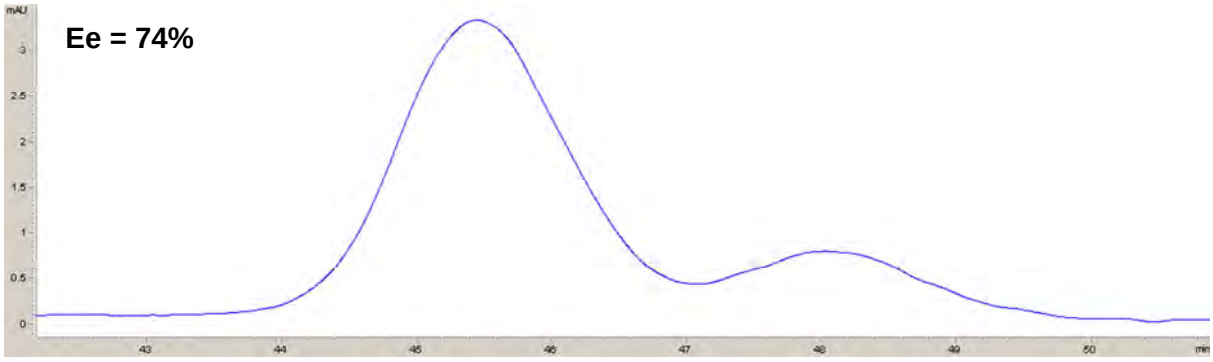
The acetic acid results were encouraging but the ees were too low, and this was attributed to acid-catalysed enolisation post-amination leading to a degree of racemization. However, the low ee was also thought to be associated with long reaction times, which in turn were determined by the acid strength and water content. It was thus decided to carry out a study varying the strength of the acid in which TFA, *p*-tosic acid (*p*-TSA), MBA (monobromoacetic acid) and MCA (monoochloroacetic acid) were chosen as acids. Perhaps one of these acids (with the optimal amount of water) would give the desired ee improvement by minimising the reaction time and post-catalytic-cycle racemization. Blackmond had already shown that α-amination reaction rates could be increased by the addition of a protic additive (such as AcOH or methanol) in which[246] a level of 1% of acid (v/v) was found to be effective in their study – this translated to 2.6 equivalents (in 1 ml of solvent) of the stronger acid TFA (pKa = -0.28). DCM (a very common solvent in organocatalysis)[66,247] was chosen as the reaction solvent at the same concentration as in the acetic acid study (1 ml, 0.5 M). Table 3.2 shows initial results focusing on TFA.

Entry	Electrophile (1 eq)	Proline (mol %)	Acid (eq)	H_2O (eq)	Solvent (0.5 M)	Time	Temp (°C)	Yield (%)	ee (%)
1	DBAD	-	TFA (2.6)	1	DCM	2 d	RT	11	0
2	DBAD	10	TFA (2.6)	1	DCM	24 hrs	RT	22	74
3	DBAD	10	TFA (2.6)	10	DCM	30 hrs	RT	14	16
4	DIAD	20	TFA (2.6)	1	DCM	6 d	RT	28	26
5	DBAD	20	TFA (2.6)	1	DCM	70 hrs	4	30	80
6	DBAD	20	*p*-TSA (0.2)	1	DCM	9 d	4	20	76
7	DBAD	20	MBA (2.6)	1	DCM	3 d	4	50	66
8	DBAD	20	MCA (2.6)	1	DCM	3 d	4	48	72

Table 3.2: Selected results from the comparison of different acids for the acetal α-amination.

Entry 1 shows the blank reaction (no proline) for TFA at RT with 1 equivalent of water where disappointingly a product, albeit only a small amount (11%), was obtained in the absence of the organocatalyst. This implied that with TFA the substrate was completely hydrolysing to decanal, which then aminated via an enol nucleophile (or vinyl ether) from acid-catalysed enolisation. Naturally, in the absence of a chiral catalyst, this reaction gave 0% ee. However, in the presence of proline at 10 mol% (entry 2), also with one equivalent of water, the TFA reaction gave an impressive 74% ee (see Figure 3.3 for the HPLC chromatogram) in an improved 22% yield in half the time compared to the blank. Thus reaction time as determined by water content and acid strength seemed to be the important parameter to follow. An

attempt to improve the yield by increasing the water equivalents to 10 only resulted in a decrease in both yield and ee (entry 3), presumably because of an increased ionicity of the medium for promoting racemization via enol formation. The time factor was then confirmed by using DIAD (we knew reactions with this were slower) as the aminating agent (entry 4), which even at 20 mol% of catalyst and still with 1 equivalent of water resulted in a much longer reaction time (6 days) and a drastic decrease in ee to 26%. Returning to DBAD (at 20 mol% of catalyst) and trying to improve on the 74% ee result in entry 2 led to choosing a decrease in reaction temperature (to 4 °C), which as expected retarded the reaction to 6 days for full conversion, but pleasingly increased the ee to 80% as well as the yield from 22% (entry 2) to 30% (entry 5), It was clear that DBAD was fairly unstable in the acid medium and with this in mind it was decided to test other (weaker) acids with different pKas (entries 6-8) including: *p*-toluenesulfonic acid (pKa = -1.34), MBA (pKa = 2.89) and MCA (pKa = 2.86). Similar to TFA, the even more acidic toluenesulfonic acid gave a high 80% ee although still at low yield. Only 0.2 equivalents of this acid were added as higher equivalents led to no reaction due to DBAD decomposition. Conversely, the weaker acids MBA and MCA gave an improved yield while still retaining a decent ee so in the next stage of optimisation MCA was chosen over MBA on the basis of results (entries 7/8) and chemical corrosiveness.



*Chiralpak AD column, 3% *i*-Pr in *n*-hexane, 258 nm and 1 ml/min

Figure 3.3: The HPLC chromatogram of entry 2.

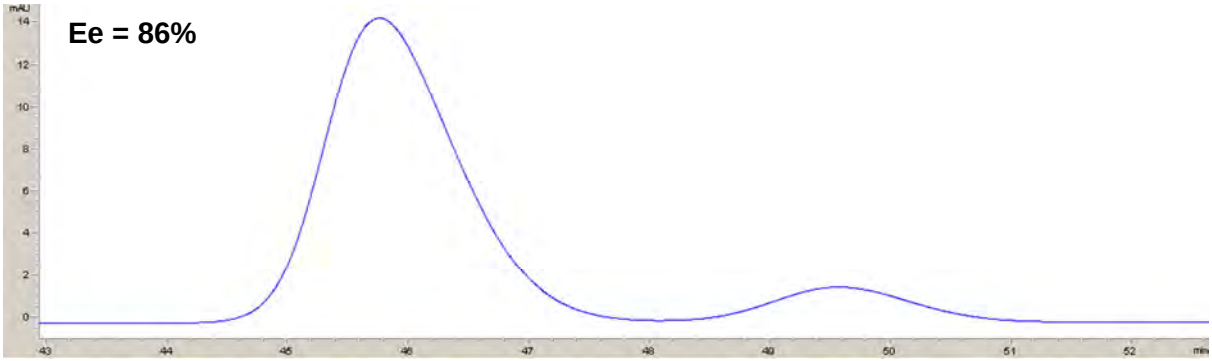
3.2 Optimisation Using MCA

With the appropriate acid (MCA) and aminating agent (DBAD) chosen, the reaction conditions were further studied to optimise reaction time, yield and ee. Of particular interest was the influence of the amount of MCA on reaction rate and hence yield and ee. Significant results are shown in Table 3.3.

Entry	DMD (eq)	DBAD (eq)	Cat (mol %)	DCM (M)	H_2O (eq)	MCA (eq)	Time	Temp (°C)	Yield (%)	ee (%)
1	1.5	1	20	0.5	1	2.6	3 d	4	48	72
2	1	4	20	0.5	1	4	18 d	4	83	32
3	1	4	20	0.5	1	4	2 d	4	35	68
4	1	4	20	0.5	1	10.4	49 hrs	4	81	74
5	1	4	20	0.5	5	10.4	41 hrs	4	78	78
6	1	4	20	0.1	5	10.4	5 d	4	72	84
7	1	4	20	0.1	5	10.4 + TFA (0.1 eq)	4 d	4	61	86

Table 3.3: The MCA optimisation study.

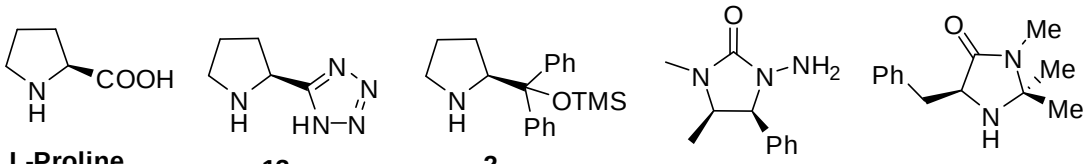
With entry 1 representing the baseline case from before using 2.6 equivalents of MCA, 20 mol% of L-proline and 1 equivalent of water at RT, it was decided to increase the equivalents of DBAD (in view of its instability) and make the acetal (DMD) limiting. This (entry 2) resulted in the hoped for yield improvement to a high 83%, though significantly, with a much lower ee (32%), probably as a result of the much longer reaction time (18 days for full starting material conversion). Evidence for the latter (entry 3) came from stopping this reaction much earlier (at 2 days), which as expected gave a much lower yield (35%) but with a much higher ee of 68%. Thus previous speculation about time-dependent acid-catalysed racemization was more or less confirmed. We were intrigued by the drop in rate on increasing the DBAD equivalents and then we realised that the high ee in entry 1 had been achieved with a ratio of DBAD:MCA equal to 1:2.6. Applying this ratio (as 4:10.4, entry 4) with the 4 equivalents of DBAD gratifyingly lowered the time from 18 days to 49 hours with a pleasing increase in yield to 81%, and importantly, an increase in ee to 74%. This suggested that the reaction requires a protonated transition-state in order to maximise stereocontrol. This will be discussed later in Section 3.4. Increasing the water to 5 equivalents (entry 5) marginally improved both time (41 hrs) and ee (78%), while diluting the solution (entry 6) from 0.5 M to List's original reaction concentration of 0.1 M slowed the reaction down to 5 days but improved the ee further to 84% without compromising yield to any great extent (72%). This increased reaction time was somewhat reduced to 4 days by the addition of a catalytic amount of TFA (0.1 equivalents) which also resulted in an increased ee (86%), though at lower yield (61%), (entry 7). The HPLC chromatogram of this reaction is shown in Figure 3.4.



*Chiralpak AD column, 3% *i*-Pr in *n*-hexane, 258 nm and 1 ml/min

Figure 3.4: The HPLC chromatogram of Entry 7.

From here, attention was turned to catalyst variation in which five organocatalysts were screened (Table 3.4): proline, the proline-tetrazole catalyst **13** (same numbering as in Chapter 1), Jørgensen's diphenylsilyloxyprolinol **2**, a new imidazolidinone primary amine catalyst (**39**) developed in our laboratories and McMillan's first-generation imidazolidinone organocatalyst **1**.



L-Proline

13

2

42

1

Cat	DMD (eq)	DBAD (eq)	Cat (mol %)	DCM (M)	H_2O (eq)	MCA (eq)	Time	Temp (°C)	Yield (%)	ee (%)
Proline	1	4	20	0.5	5	10.4	2 d	4	78	78
13	1	4	20	0.5	5	10.4	23 hrs	4	86	74
2	1	4	20	0.5	5	10.4	5 d	4 to RT	20	36
42	1	4	20	0.5	5	10.4	7 d	4 to RT	44	16
1	1	4	20	0.5	5	10.4	>7 d	4 to RT	trace	-

Table 3.4: The comparison of different organocatalysts.

These catalysts were studied under the 0.5 M optimised conditions from entry 5 in Table 3.3. While the McMillan catalyst **1** was ineffective (trace amount of product after several days), and catalysts **2** and **42** returned a low ee (36% and 16 %, respectively) due to long reaction times, the tetrazole catalyst **13** promoted the fastest reaction (23 hours) and gave the highest yield (86%). Although the ee from **13** was slightly lower compared to that of using

proline at 74%, its faster reaction time and higher yield were enough of an encouragement to continue using it in further optimisations. Overall, the results show that the usually high rate with aldehydes using all of these catalysts is reduced and is catalyst-dependent. Presumably this reflects that the addition step involving catalyst and the acetal-derived (alkylated) oxocarbenium ion (see the mechanism in Scheme 3.1) is now more responsive towards steric effects in the catalyst structure compared to the case for addition to the sterically less congested aldehyde. Figure 3.5 shows the chromatograms from chiral HPLC obtained using proline, **13** and **2**. Importantly, Jørgensen's catalyst **2** gave a major enantiomer of opposite configuration. This result is in accordance with the literature's view on the transition-state of these aminations, and its mechanistic implications will be discussed further in Section 3.4.

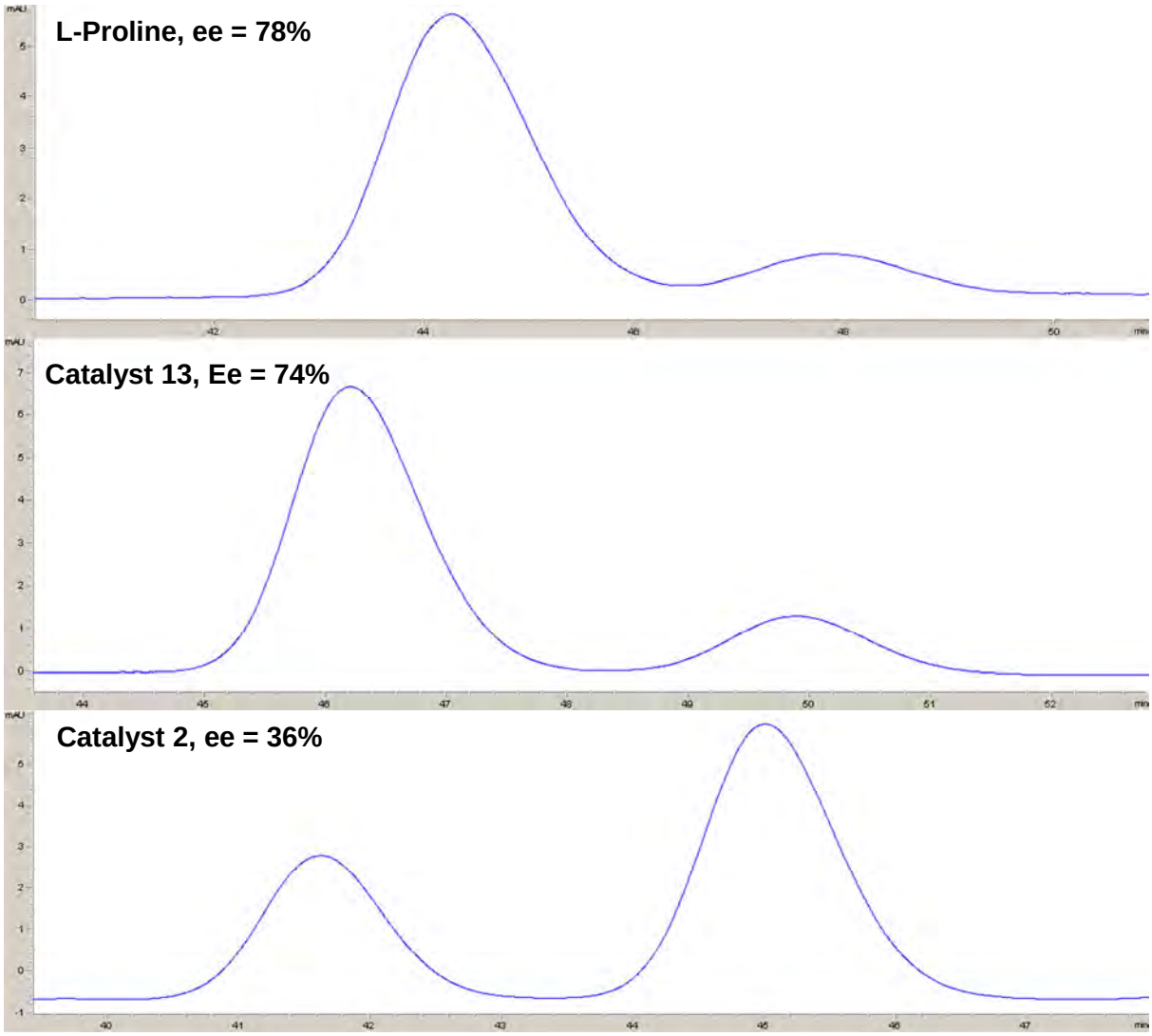


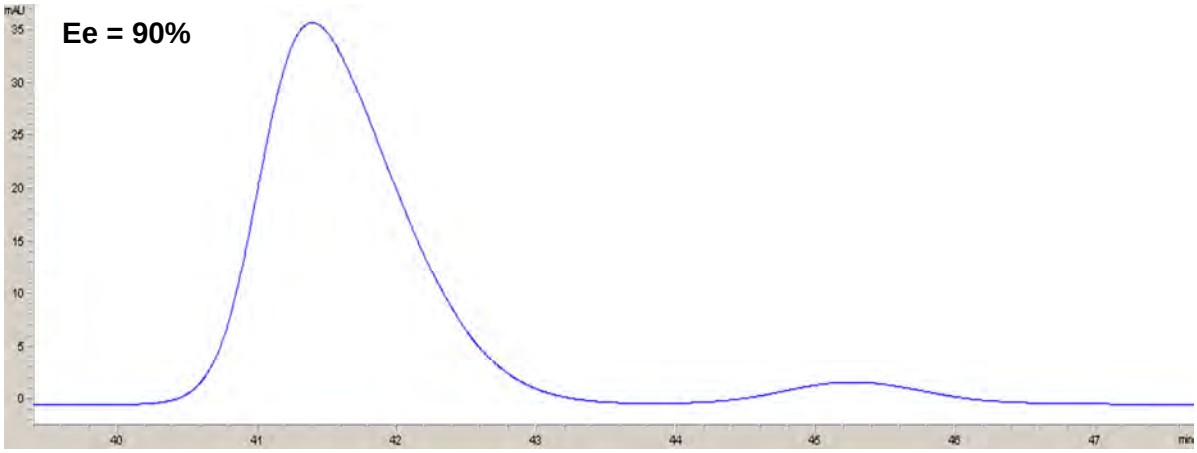
Figure 3.5: The HPLC chromatograms of products from **proline**, **13**, and **2**.

Table 3.5 below shows the results from a direct comparison of proline with tetrazole catalyst **13** using different amounts of DBAD in order to minimise cost and at the 2.6 ratio (DBAD:MCA), as well as varying the concentration as either 0.1 M or 0.5 M, while maintaining the water content at 5 equivalents, and the temperature at 4 °C. In entries 4 and 5 a small amount of TFA was introduced.

Entry	Reaction Conditions	L-Proline (20 mol %)			Tetrazole Catalyst 13 (20 mol%)		
		Time	Yield (%)	ee (%)	Time	Yield (%)	ee (%)
1	DMD (1 eq), DBAD (4 eq), MCA (10.4 eq), H_2O (5 eq), DCM (0.5 M)	41 hrs	78	78	23 hrs	86	74
2	2 eq DBAD, 5.2 eq MCA	52 hrs	73	84	3 d	79	42
3	2 eq DBAD, 5.2 eq MCA, 0.1 M DCM	5 d	72	84	5 d	70	56
4	2 eq DBAD, 5.2 eq MCA, 0.1 eq TFA, 0.1 M DCM	4 d	61	86	17 hrs	83	90
5	2 eq DBAD, 5.2 eq MCA, 0.1 eq TFA, 0.5 M DCM				9hrs	79	90

Table 3.5: A comparison of the proline results with those of catalyst **13**.

The results show that the tetrazole-catalysed reaction fared worse regarding ee when reducing the amount of DBAD with yields about the same (entries 1-3). However, pleasingly, with a small amount of TFA reaction rates improved to something experimentally attractive (< I day) with a concomitant increase of the ee up to 90%, which was only a few percent lower than the prototype reaction by List using the aldehyde. Hence, after many long months of arduous optimisation a set of experimental conditions in a multi-parameter reaction was arrived at in which a relatively low reaction time (for organocatalysis) was important to avoid racemization as was the acid strength of the medium and the ratio of acid:DBAD. By using a medium-strength acid at high concentration of reagent a high ee could be realised. The chromatogram in Figure 3.6 shows the 90% ee result from entry 5.



*Chiralpak AD column, 5% *i*-Pr in *n*-hexane, 258 nm and 1 ml/min

Figure 3.6: The HPLC chromatogram of entry 5.

The final step in the acetal reaction optimisation was a solvent study (Table 3.6). Using a 2 equivalent excess of DBAD, 20 mol% of **13**, 5.2 equivalents of MCA and 0.1 equivalents of TFA at a constant reaction temperature (4 °C) and time (9 hours), DCM (Entry 1) showed superiority in terms of yield and ee, with acetonitrile as close runner-up (entry 3). Chloroform, toluene and ethyl acetate also gave good ee's, although in lower yields (18 – 66%).The Lewis basic solvents THF and DMSO gave no reaction product, suggesting that they interfere with the acid-base transformations and hydrogen bonding critical to the success of the reaction.

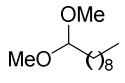
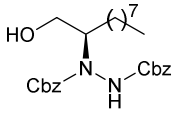
Entry	DMD	DBAD	13 (mol %)	Solvent (0.5 M)	H_2O (eq)	MCA (eq)	Time	Yield (%)	ee (%)
1	1	2	20	DCM	5	5.2 + TFA (0.1 eq)	9 hrs	79	90
2	1	2	20	$CHCl_3$	5	5.2 + TFA (0.1 eq)	9 hrs	66	86
3	1	2	20	CH_3CN	5	5.2 + TFA (0.1 eq)	9 hrs	75	90
4	1	2	20	Toluene	5	5.2 + TFA (0.1 eq)	9 hrs	57	80
5	1	2	20	EtOAc	5	5.2 + TFA (0.1 eq)	9 hrs	18	78
6	1	2	20	THF	5	5.2 + TFA (0.1 eq)	9 hrs	Trace (TLC)	-
7	1	2	20	DMSO	5	5.2 + TFA (0.1 eq)	9 hrs	-	-

Table 3.6: The solvent study.

Thus this exhaustive optimisation study made it clear that enantioselective α-amination of acetals can successfully be achieved in high yields and ees, and in acceptable reaction times.

3.3 Application to Different Acetal Substrates

Regarding scope, Table 3.7 displays the results of applying the optimised conditions to a range of acetals. Changing the acetal from dimethoxy to diethoxy (entries 1 and 2) increased the reaction rate, presumably due to an increase in stability of the intermediate oxocarbenium ion as well as the greater basicity of the ethoxy group, making it a better leaving group.[248] Importantly, in view of the faster reaction the yield rose to 93% reflecting the instability of DBAD in an acid medium over long periods. As with the model (entry 1) ee values were both very good (>85%). The highest ee of all was obtained with isovaleraldehyde diethylacetal, which gave an exceptional 94% ee (entry 3). Entry 4 reveals that quaternised stereocentres could also be accessed, albeit with a drop in ee to 56%. This nevertheless compares reasonably with other reports on the corresponding aldehyde[170,249] using proline-based catalysts at sub-stoichiometric amounts. Product **45** was isolated as an aldehyde without reduction to the hydrazino alcohol since the enolisable α-proton is absent in the aminated product. For ketals (entries 5-9), as expected, rates depended on the ketal OR-groups in the order cyclic > acyclic for the same OR-group and dimethoxy > dioxolane, which is in agreement with known hydrolysis rates[248] and the stability of the intermediate oxocarbenium ion based on inductive and hyperconjugative effects. As indicated in Table 3.7, in all ketal cases excess substrate was used (to 1 equiv of DBAD) to drive the reaction to completion as well as to avoid disubstitution. For slower reactions (entries 5 and 8) a large excess of ketal (20 equivalents) was used which also resulted in ee improvements (entries 6 and 9). For ketals the α-aminated ketone was isolated without carbonyl reduction to avoid the introduction of an extra stereocentre into the product. This work was published in Tetrahedron Letters in 2014.[250]

Entry	Substrate	Product	Acetal (eq)	DBAD (eq)	Cat mol%	DCM (M)	H_2O (eq)	MCA (eq)	Time	T (°C)	Yield (%)	ee (%)
1		 **41**	1	2	20	0.5	5	5.2 + TFA (0.1 eq)	9 hrs	4	79	90

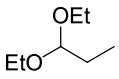
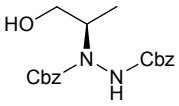
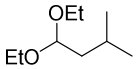
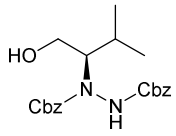
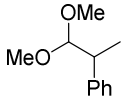
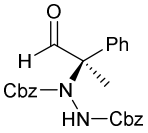
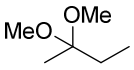
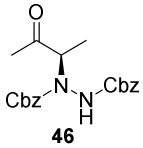
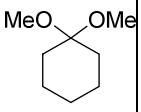
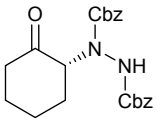
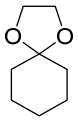
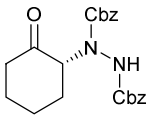
2		 **43**	1	2	20	0.5	5	5.2 + TFA (0.1 eq)	4 hrs	4	93	86
3		 **44**	1	2	20	0.5	5	5.2 + TFA (0.1 eq)	9 hrs	4	73	94
4		 **45**	1	4	20	0.5	5	10.4 + TFA (0.1 eq)	3 d	4	51	66
5		 **46**	5	1	20	0.5	5	5.2 + TFA (0.1 eq)	5 d	RT	22	82
6			20	1	20	1	5	10.4 + TFA (0.1 eq)	2 d	4	33	86
7		 **47**	5	1	20	0.5	5	5.2 + TFA (0.1 eq)	9 hrs	4	71	62
8		 **47**	5	1	20	0.5	5	5.2 + TFA (0.1 eq)	8 d	4	61	40
9			20	1	20	0.5	5	10.4 + TFA (0.1 eq)	2 d	4	66	64

Table 3.7: Different acetals and ketals.

All of the above α-amination products (except **41**, as discussed earlier) were known compounds whose ^{1}H and ^{13}C NMR resonances agreed with the literature.[67,174,180,251] Figure 3.7 shows the ^{1}H NMR spectrum of **43**, entry 2. The diagnostic downfield H-1, H-2, OH and Bn methylene resonances were in the expected 3.00–5.50 ppm region. As expected, the resonances were not very well resolved due to conformational interconversion. Furthermore, the upfield CH_3 doublet (H-3), confirmed the presence of the propyl chain.

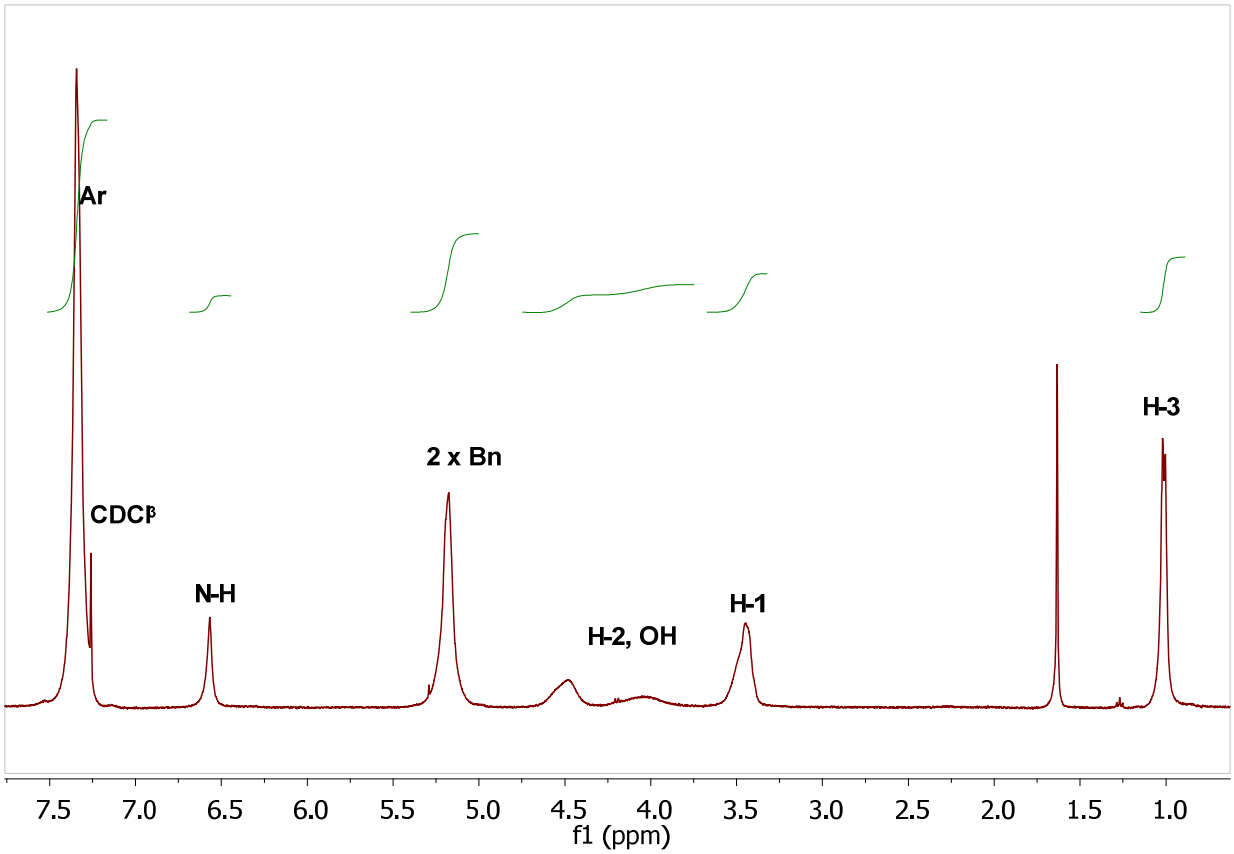
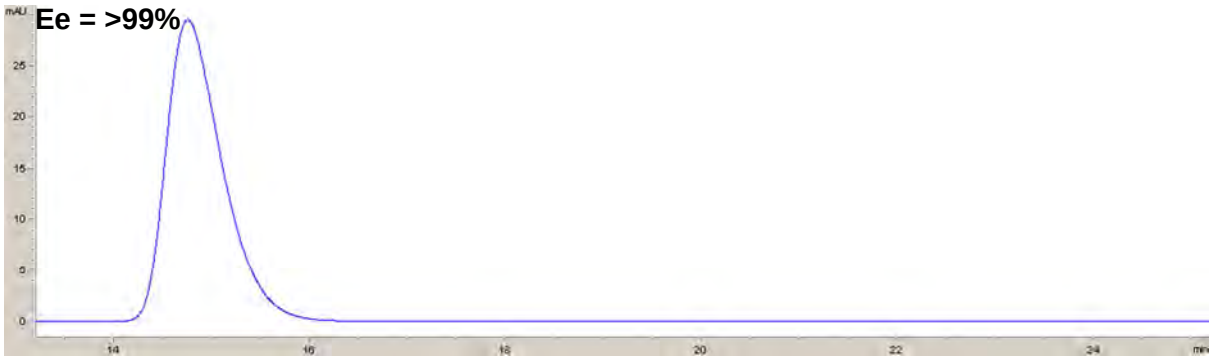


Figure 3.7: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **43**.

Both **43** and **44** were synthesised as crystalline solids in which it was observed that repeated recrystallisations (DCM / hexane mixtures) resulted in enantioenrichment. In fact, in the case of compound **44** (HPLC chromatograms shown in Figure 3.8), the already excellent 94% ee was improved to >99%. This demonstrates how the organocatalysed α-amination reaction can result in optically pure chiral building blocks.



*Chiralpak AD column, 10% *i*-Pr in *n*-hexane, 258 nm and 1 ml/min

Figure 3.8: The HPLC chromatograms of **44** before and after recrystallisation.

The ^{1}H NMR spectrum of quaternary product **45** is displayed in Figure 3.9. In this case there is evidence of the product existing as a 3:1 mixture of rotamers. This is reflected in the NH and aldehyde protons each appearing as two resonances. The origin of the rotamers is the partial double bond created by nitrogen electron donation of the tertiary nitrogen into the carbonyl of the Cbz carbamate. This results in restricted rotation of the N-carbonyl bond.

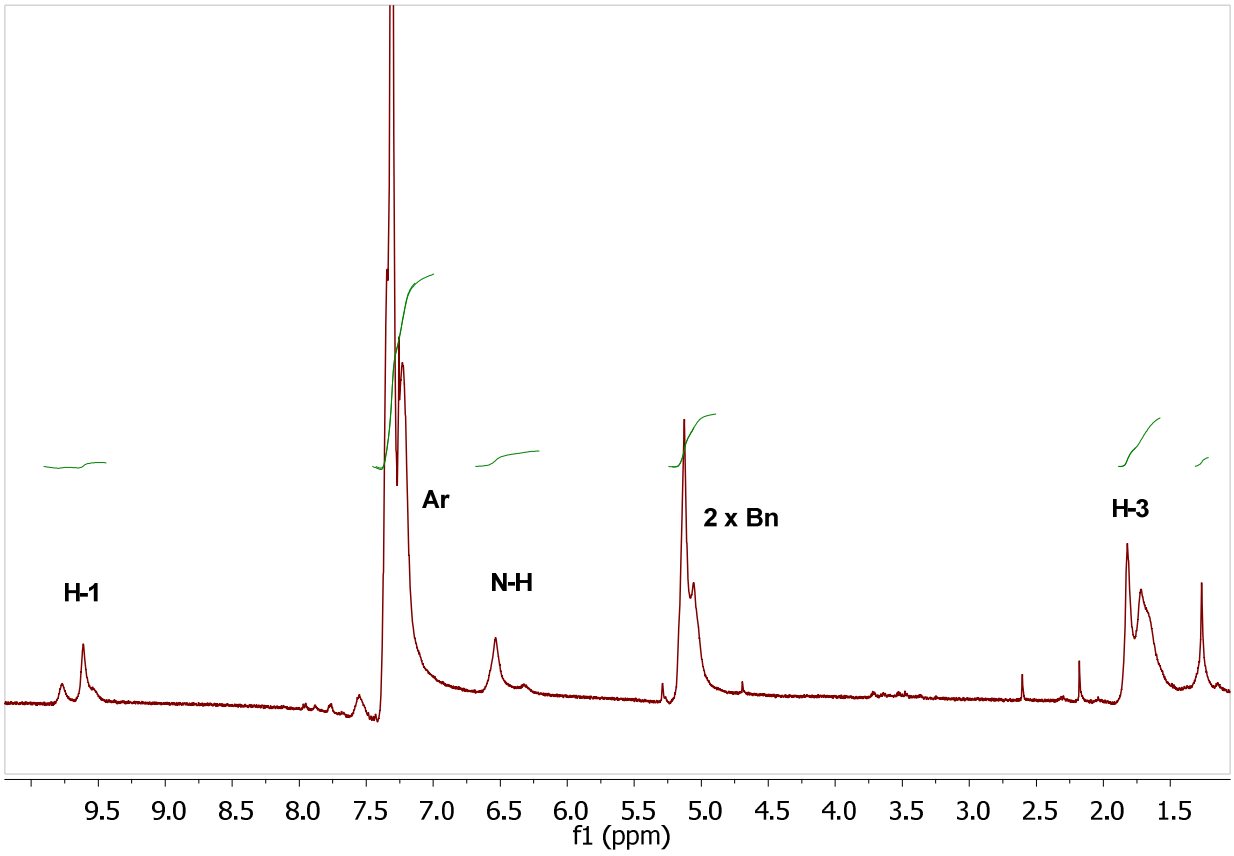
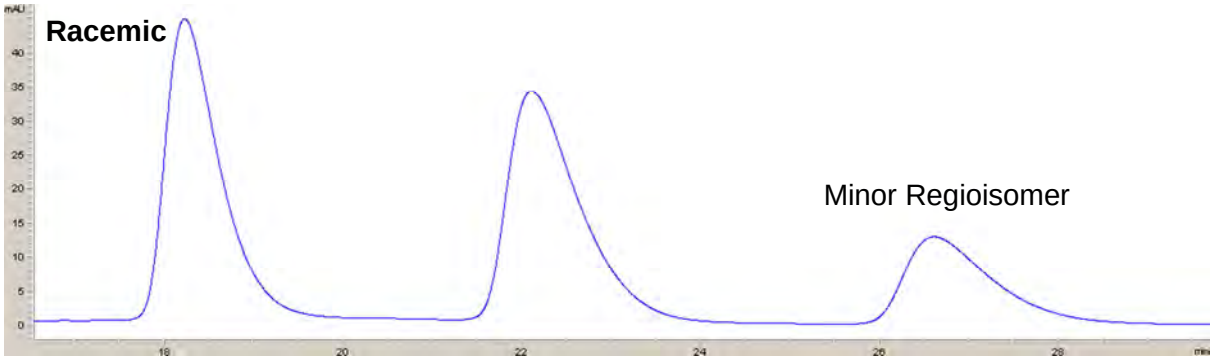


Figure 3.9: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **45**.

For product **46** from the ketal of 2-butanone (entry 6), there was the possibility of obtaining two regioisomeric products depending on whether the amination occurred on C-2 or C-4 (see numbering in Figure 3.10). The racemic version of this reaction was carried out using the corresponding ketone, 2-butanone, under Jørgensen's conditions[66] with DL-Proline as the catalyst. As shown in the chromatogram in Figure 3.10, with Jørgensen's reaction conditions the two regioisomers were seen as a 4:1 mixture (two enantiomer peak areas:regioismer peak area) with the desired C-2-aminated product (as a racemate) dominating, in accordance with intermediacy of the more stable enamine. However, in our ketal version of this reaction (with the corresponding ketal and tetrazole catalyst **13**), the regioisomeric ratio was improved to an impressive 96:4. It is also worth mentioning that these two regioisomers can be distinguished by ^{1}H and ^{13}C NMR spectroscopy, but they cannot be separated by flash column chromatography.



*Chiralpak OD column, 10% *i*-Pr in *n*-hexane, 258 nm and 1 ml/min

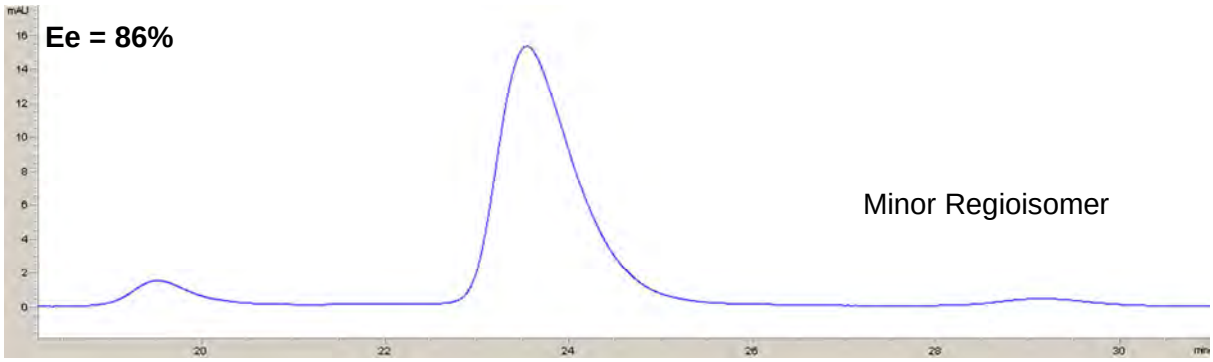


Figure 3.10: The racemic and chiral HPLC chromatograms of **46**.

Figure 3.11 shows the ^{13}C NMR spectrum of product **47** from cyclohexanone ketal. This product also appears as a mixture of rotamers which is suggested by the ketone carbonyl

resonances appearing in duplicate. This conclusion is also supported by NH and H-1 resonances in the ^{1}H NMR spectrum each appearing in a 3:1 ratio.

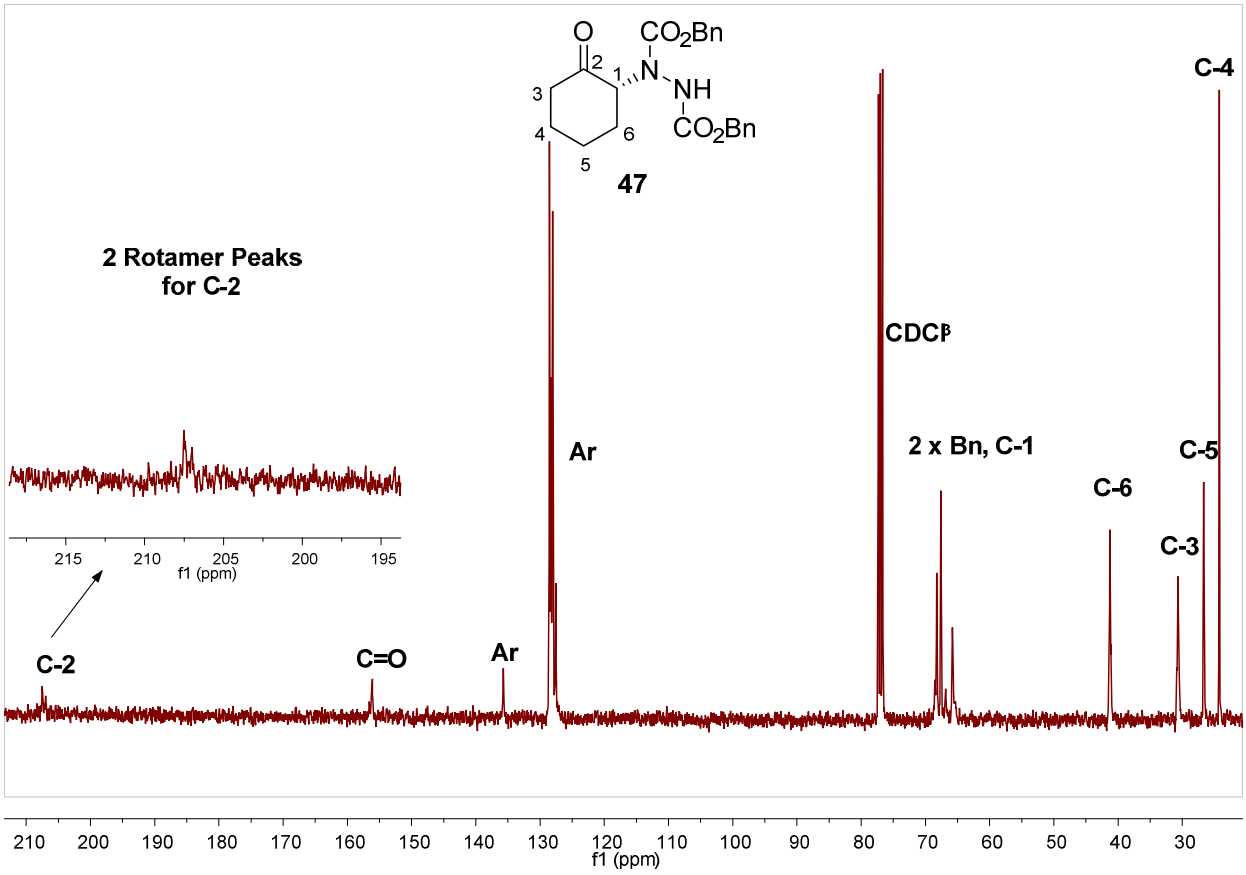


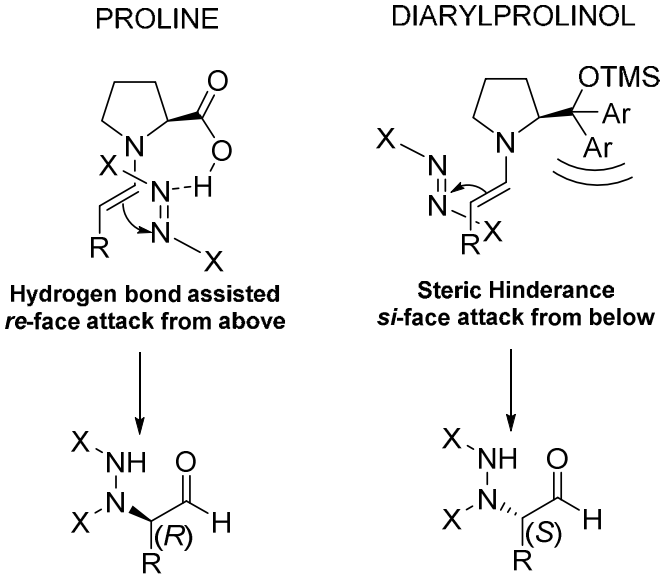
Figure 3.11: The ^{13}C NMR spectrum ($CDCl_3$, 75.5 MHz) of **47**.

3.4 Mechanistic Considerations and the Proposed Transition-State

Before the acetal reaction mechanism and enantioselectivity is discussed, a brief discussion on the literature view of the α-amination mechanism is necessary.

The aldehyde α-amination reaction was discovered simultaneously by List and Jørgensen,[66,67,252] in which L-proline was used (Jorgensen and List)[66,67] as well as a diarylprolinol catalyst **2** (Jorgensen only).[252] Despite the same absolute (*S*)-configuration of prolinol catalyst **2** as that of proline, the reactions produced the same products with opposite enantioselectivity. This was probably the most important clue in uncovering the mechanism of asymmetric induction in the α-amination reaction. Thus researchers reasoned that these differences could be explained by two different transition-state models involving a single enamine configuration, Scheme 3.2. In this, proline is posited as operating through the activation of both the aldehyde (by forming a more nucleophilic enamine) and the electrophile (by hydrogen bonding) in which the enantioselectivity indicates the approach of

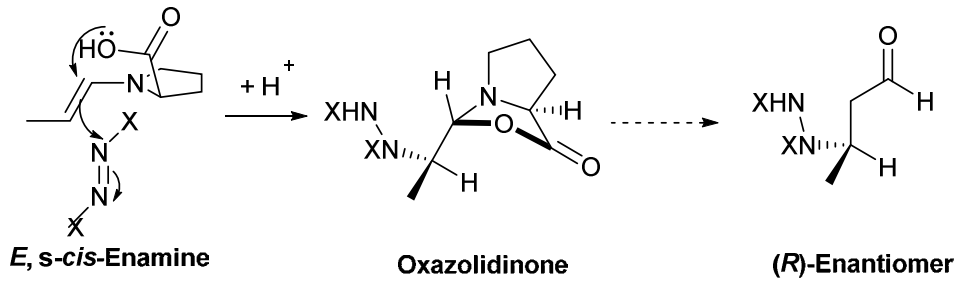
the electrophile (azodicarboxylate ester in this case) to be controlled by hydrogen bonding with the carboxyl group of the catalyst, resulting in *re*-face attack of the (*E*, s-*trans*)-enamine leading to the (*R*)-enantiomer.[173] This transition-state model is referred to as the Houk-List model and involves a favourable six-membered transition-state.[199] On the other hand, Jørgensen's diarylprolinol catalyst resulted in high enantioselectivity despite the absence of functional groups that could participate in hydrogen bonding with the aminating agent. It was therefore reasoned that the enantioselectivity observed originated from the same enamine as that of proline (*E*, s-*trans*-) but now via introduction of steric bias onto one of the two enamine faces by the large diphenylsilyloxy substituent at the chiral centre This results in electrophile approach *anti* to this group, i.e. onto the *si*-face of the enamine, which explains the formation of the observed (*S*)-enantiomer, Scheme 3.3.[40,172,200]



Scheme 3.3: The two catalyst-dependent transition-state models for the aminocatalysed α-amination reaction.[172]

Seebach and Eschenmoser have proposed a different model for depicting the stereochemical outcome using proline (Scheme 3.4). [253,254] Their model invokes *anti*-attack by the electrophile on the (*E*,s-*cis*)-enamine involving the intermediacy of an oxazolidinone. Seebach particularly suggested *anti*-addition to the *syn*-enamine rotamer, which leads directly to the exo-isomer of the product oxazolidinone, which later hydrolyses to the aldehyde with catalyst turnover.[255] The Seebach-Eschenmoser hypothesis is consistent with the observed stereochemical outcome (*R*-), yet also accommodates Blackmond's observation that the stereoselectivity can be reversed to afford predominantly (*S*-) in the presence of a base such as DBU.[255] Interesting experimental evidence (such as NMR, IR and kinetic measurements) support the presence of the oxazolidinone intermediate.

However, ESI-MS, NMR spectroscopy and crystal structures of enamine intermediates by the List group have led them to present structural characterisations of a series of proline enamines. This provides substantial motivation for accepting their enamine mechanism in proline catalysis involving the s-*trans* rotamer.[200,254]



Scheme 3.4: The Seebach-Eschenmoser transition-state model.[255]

In accordance with the Houk-List hydrogen-bond-assisted model, Düthaler has proposed a chair conformation for L-proline-catalysed enamine reactions of ketones and aldehydes. In this model a six-membered chair is formed comprising the enamine double bond and nitrogen atom, the H of the proline carboxyl group and the two nitrogens of the diazo group, which is held together by hydrogen bonding (Figure 3.12).[176]

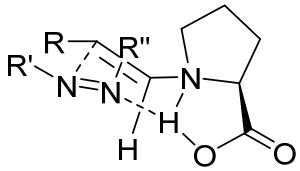
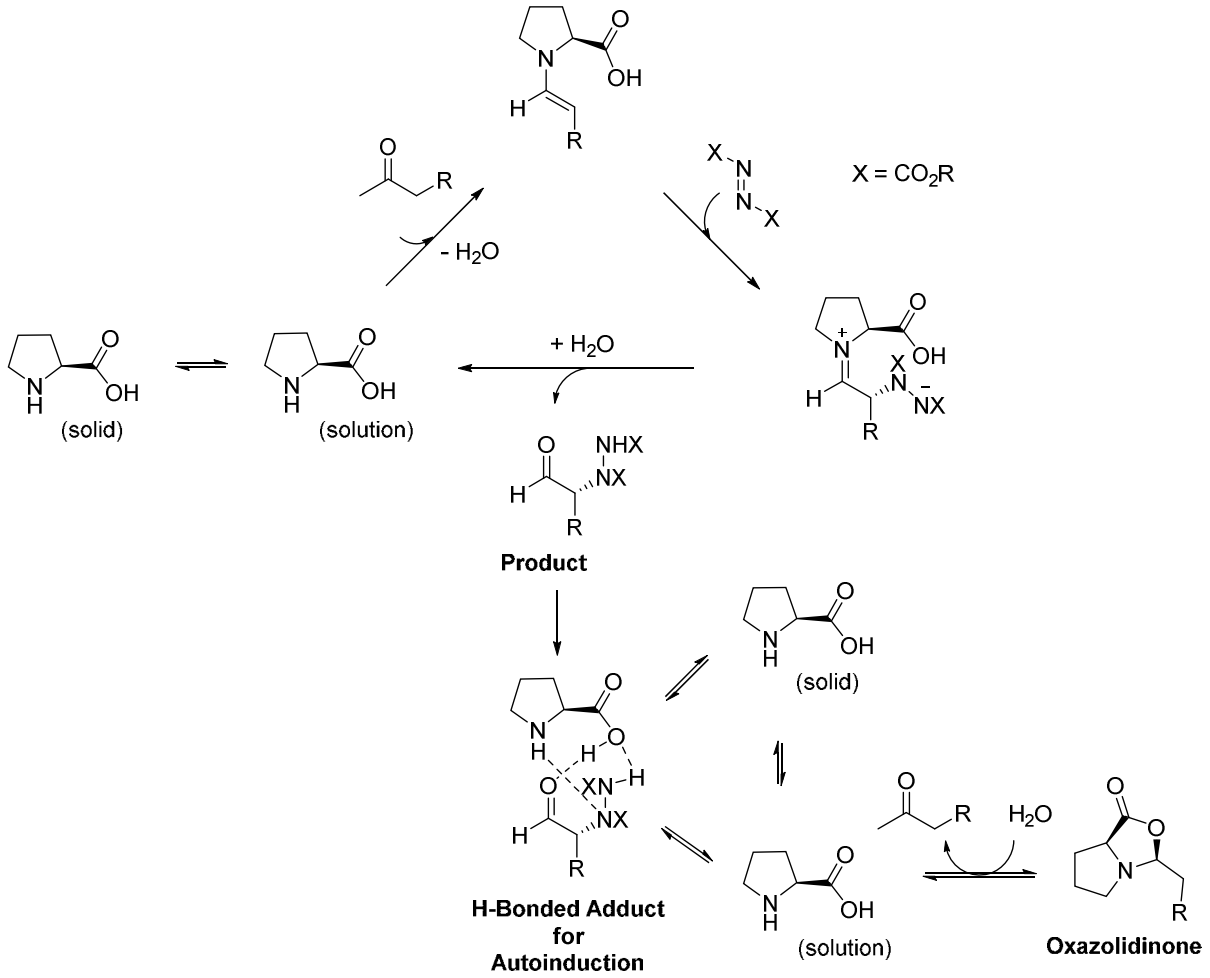


Figure 3.12: The Düthaler proposed chair-conformation transition-state.

Blackmond has also demonstrated that protic additives such as AcOH and MeOH increase the rate of the α-amination reaction (a point mentioned in Section 3.1), as well as the α-aminoxylation, but not the aldol reaction.[246] Additionally, kinetic studies based on these observations led her to the conclusion that the rate-determining step in the case of the amination reaction is enamine formation. As mentioned previously another Blackmond study revealed that the proline-catalysed amination reaction shows an inversion in the enantioselectivity when bases, such as DBU, are added to the reaction mixture.[255] The authors suggested two explanations for this observation: 1) the proline carboxylate (along with its counter-cation) acts as a shielding group as with the TMS-protected diarylprolinol-catalysts or; 2) the proline carboxylate assists the nucleophilic attack in accordance with the Seebach-Eschenmoser oxazolidinone model,[253] although in this case to account for the observed stereochemistry, the resulting oxazolidinone would have to be formed through a

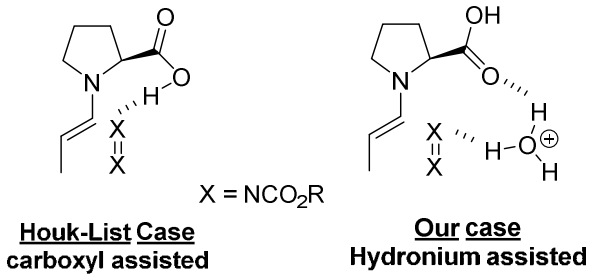
stable stereoelectronically favoured (*E*, s-*trans*)-enamine and the determining factor would no longer be the stability of the oxazolidinone products, as originally suggested by Seebach et al. Advanced kinetic studies of the α-amination reaction have also led Blackmond et al. to propose an autoinductive reaction mechanism where the product species accelerates the reaction.[256,257] The hydrogen-bonded adduct of proline and the amination product was isolated and found to be more reactive than proline itself. Their experimental observation was therefore attributed to a specific hydrogen bonding interaction of the product aldehyde with proline in which the proline conformation is such that the nitrogen atom lone pair electrons are exposed, thus increasing its reactivity. The presence of the hydrogen-bonded adduct also increases the amount of proline (often insoluble in organic solvents) in solution, which in turn also increases the reaction rate.[256,258] Thus, the reaction product has a role in increasing the concentration of active catalyst species (and therefore rate). Furthermore, proline can be channelled into the cycle in three different ways: as pure solid proline; as proline in solution; or in the form of an enamine (or oxazolidinone) produced by its reaction with the aldehyde starting material. Lastly, Blackmond and co-workers also suggest a transition-state similar to the Houk-List model even though they don't reject the participation of an oxazolidinone in the catalytic cycle. This catalytic cycle may therefore be the best current explanation of all of the existing evidence mentioned earlier, based on both oxazolidinone and enamine species being detected in the α-amination reaction. Scheme 3.5 illustrates the more complex catalytic cycle proposed by the Blackmond team involving autoinduction and an oxazolidinone.



Scheme 3.5: The catalytic cycle proposed by Blackmond.

As far as the mechanism in our study is concerned, first of all the absolute configuration of the acetal products had to be determined. The HPLC traces comparing the acetal / proline product with that using Jørgensen's catalyst as shown in Figure 3.5 earlier strongly indicated the *R*-configuration for proline. This was corroborated by measuring the optical rotation ($[\alpha]_D$) for product **43** (Table 3.7) from propionaldehyde diethyl acetal, which was established as -22.6, comparing in sign with the literature value for the (*R*)-product of -32.0.[174] These results indicate that the reaction proceeds via an assisted transition-state according to the Houk-List model, assuming, as is reasonable, that the acetal reaction proceeds through the same (*E*, s-*trans*)-enamine intermediate as that of the aldehyde form of the reaction. However, this still leaves the intriguing question as to why the ratio of MCA: DBAD needed to be greater than 2 in order to secure a high product ee. Our rationale is that in this case the carboxyl group of the enamine intermediate is heavily H-bonded to a hydronium ion / water conglomerate, the concentration of hydronium ion as a powerful H-bond donor depending on the strength of acid. Such H-bonding is a sterically more severe environment than that in List and Jørgensen's case pertaining to the reaction of aldehydes, which involves the production of

only one mol. of water per mol. of substrate from the condensation reaction to generate the enamine, and in which there is no acid. Indeed, in their model it is assumed that this water plays no important role in the assisted transition-state involving direct hydrogen bonding between the proline carboxyl group and one of the diazo nitrogens. In the acetal reaction, at high acid concentrations assistance might be promoted in two possible ways. Either protonation of the DBAD occurs, rendering it an excellent hydrogen bond donor to the carboxyl group carbonyl oxygen, or high hydronium ion concentration around the carboxyl group promotes general acid catalysis towards the electrophile. In either case, direct hydrogen bonding between the carboxyl OH and the DBAD as in the Houk-List model is not considered to be operating in view of the fluctuation in ee's as a function of acid concentration (observed in Table 3.3). Reducing the acid strength (e.g. to AcOH) shifts the assisted model to a steric one leading to an increase in the (*S*)-enantiomer. Importantly, leaving the tetrazole **13**-catalysed reaction for 48h, only marginally reduced the ee (90 to 84%), indicating that racemization wasn't a major event within this timeframe. Presumably the tetrazole catalyst promotes the fastest reaction because of the superior H-bonding acceptor attributes of the aza-amidine functionality. Scheme 3.6 below illustrates the proposed transition-state.

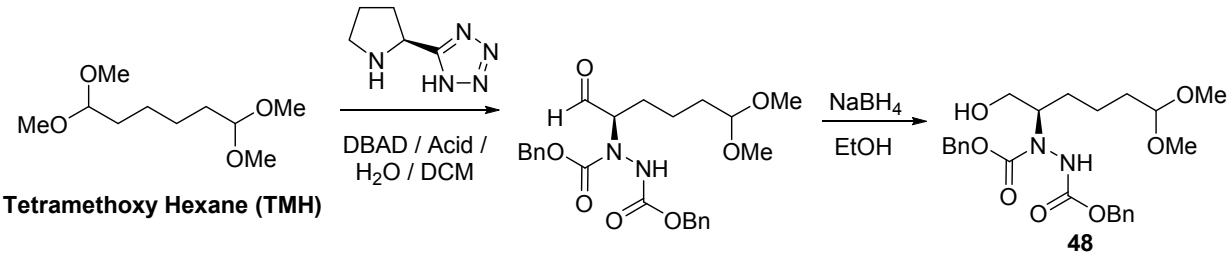


Scheme 3.6: A comparison of our proposed transition-state with the Houk-List model.

In answering the question of enamine formation regarding whether it proceeds from the aldehyde (from hydrolysis) or via the oxocarbenium ion, control experiments were conducted. Firstly, reacting the acetal with 10.4 equivalents of MCA and 5 equivalents of water (as in the optimised reaction) for 48 hours did not lead to acetal hydrolysis as judged by TLC. Secondly, unreacted DMD acetal could be recovered (as it is in excess) by column chromatography after the reaction, although trace amounts of decanol, formed by reduction of unreacted aldehyde originating form complete hydrolysis, was visible on TLC. Thus it was concluded that the enamine is mainly generated directly from the oxocarbenium ion of the acetal and not via hydrolysis to the aldehyde first.

3.5 Bis-Acetal Model Study

Another demonstration of the scope of the acetal α-amination reaction came in the chemo-differentiation of a bis-acetal, 1,1,6,6-tetramethoxy hexane (TMH), as a prototype for the desymmetrisation discussed in Chapter 2. This furnished the same product in comparable ee to that reported by Greck et al.,[187] when they used L-proline on the corresponding half acetal/aldehyde substrate obtained from a Wittig sequence. In their case alcohol **48** was then transformed into (*R*)-proline.



Tetramethoxy Hexane (TMH)

48

Entry	TMH (eq)	DBAD (eq)	Cat (mol %)	DCM (M)	H_2O (eq)	MCA (eq)	Time	Temp (°C)	Yield (%)	ee (%)
1	5	1	**Proline** (20)	0.1	5	2.6 + TFA (0.1 eq)	5 d	4	70	84
2	5	1	**13** (20)	0.1	5	2.6 + TFA (0.1 eq)	2 d	4	78	66
3	5	1	**13** (20)	0.1	5	5.2 + TFA (0.1 eq)	22 hrs	4	78	90
4	5	1	**13** (20)	0.5	5	5.2 + TFA (0.1 eq)	6.5 hrs	4	70	88

Table 3.8: Bis-acetal optimisation.

In an initial trial reaction, applying the optimised acetal conditions and using TMH as the limiting reagent resulted in a low yield (22%) and a diamination product in 18% yield. However, as shown in entry 1 of Table 3.8, using an excess (5 equivalents) of the substrate resulted in a good yield and ee of the mono-aminated product **48**, with proline as the catalyst. However, maintaining the DBAD:MCA ratio of 1:2.6 compromised the catalyst **13** ee result (entry 2) to give only 66% ee. Thus it was necessary to increase the ratio of MCA to DBAD to 5.2 to account for the increased basicity of the additional acetal grouping on the TMH substrate. This improved the reaction rate (22 hours) and ee to 90%, entry 3. Finally, concentrating the medium to 0.5 M gave an even faster reaction (6.5 hours) whilst maintaining a high yield (70%) and ee (88%), entry 4. Figure 3.13 shows the ^{1}H NMR spectrum of **48**. The important methoxy and H-6 resonances are visible as well as the characteristic α-hydrazino alcohol resonances. The ^{1}H NMR and ^{13}C NMR data of this known compound agreed with the literature.[187] It was also established that this product had the

same stereogenicity as that of the corresponding aldehyde reaction by Greck ($[\alpha]_D^{20}$ +5.2, lit +3.8).

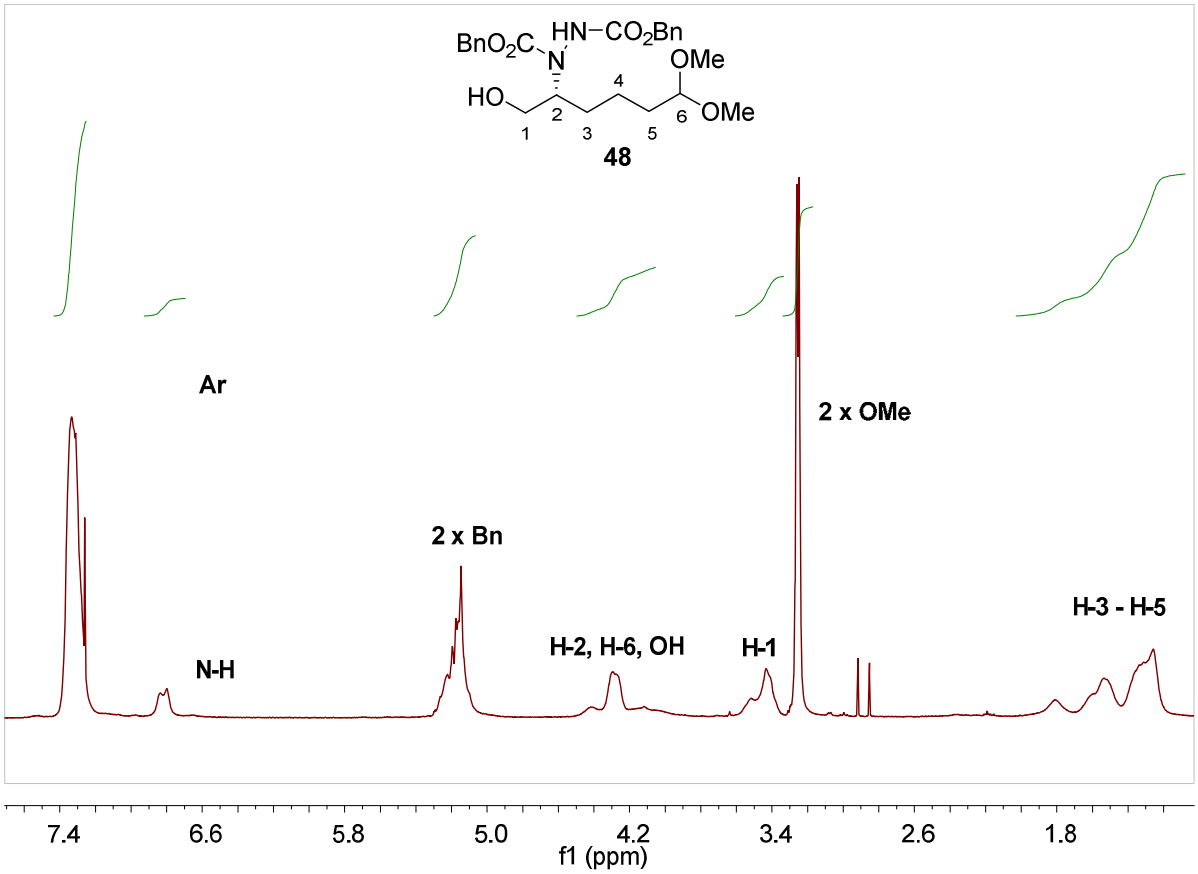
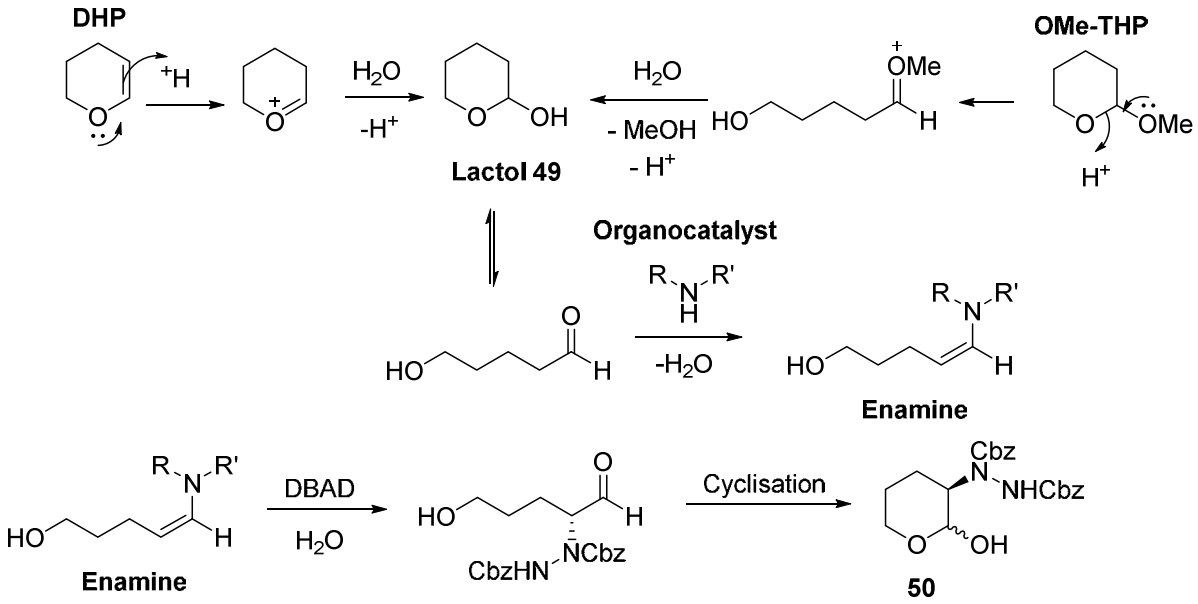


Figure 3.13: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **48**.

This result opens up the possibility of desymmetrising prochiral bis-acetals into useful functionalised homochiral synthons in a rapid and benign manner, as discussed in Chapter 2.

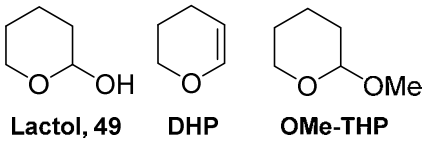
3.6 Application to Other Masked Carbonyl Functionalities

Finally, in view of an obvious application to carbohydrate α-amination, it was then decided to study the enantioselective α-amination of α-lactols containing masked aldehyde functionality. Thus lactol **49** as well as its relatives 3,4-dihydro-2*H*-pyran (DHP) and 2-methoxytetrahydropyran (OMe-THP) were studied. The suggested mechanism for these transformations is shown in Scheme 3.7. Most important is the fact that, through acid-catalysed hydrolysis equilibria, all three masked carbonyls lead to the same product **50**.



Scheme 3.7: The suggested mechanism for cyclic masked carbonyl α-amination.

Table 3.9 below shows the results of this final study.



Entry	Substrate (eq)	DBAD (eq)	Catalyst (mol %)	Acid (eq)	H_2O (eq)	CH_3CN (M)	Time	Temp (°C)	Yield (%)	ee (%)	dr
1	Lactol (10)	1	**Proline** 20	-	-	0.5	4.5 hrs	RT	90	60	60:40
2	Lactol (10)	1	**Proline** 20	MCA (0.1)	10	0.5	40 min	RT	85	74	59:41
3	Lactol (10)	1	**13** 20	MCA (0.1) and TFA (0.1)	10	0.5	9 hrs	0	80	93	61:39
4	DHP (10)	1	**Proline** 20	TFA (0.2)	10	0.5	9 hrs	RT	55	76	62:38
5	OMe-THP (10)	1	**Proline** 20	1 M HCl (0.2)	10	0.5	3 d	RT	28	74	55:45 65:35

Table 3.9: Lactol-related masked carbonyls.

As expected, in view of its ability to open directly to an aldehyde form, lactol **49** was quite reactive, forming the α-aminated product as a 3:2 ratio of diastereomers in high yield with proline as organocatalyst, within a few hours at room temperature and importantly without the need to include a Bronsted activator (entry 1). However, interestingly, the ee was quite low (60%), which was likely due to the free hydroxyl in the acyclic hydroxy-enamine

intermediate interfering with the hydrogen bond assisted transition-state. Introduction of MCA at low equivalents (0.1 eq, entry 2) and water (10 eq) to promote an even faster reaction and higher ee resulted in the desired reaction time (40 min) and ee improvement (74%), endorsing the idea of promoting transition-state assistance through a protonated environment. A combination of changing to the tetrazole catalyst, adding 0.1 equivalents of TFA and decreasing the temperature to 0 °C returned a much higher and pleasing ee of 93% in high yield (entry 3). Both DHP and OMe-THP had slower rates since formation of the lactol intermediate (which is visible on TLC) was slower. Hence, more acidic conditions had to be employed (entries 4 and 5) which together with the longer reaction times resulted in lower yields due to decomposition of the limiting reagent (DBAD), and elimination of H_2O from product **50** to form an aminated glycal, (this by-product was isolated via column chromatography and characterised by ^{1}H NMR). Figure 3.14 below shows the racemic and chiral chromatograms of entry 3. HPLC data aided not only in determining the ee, but also in distinguishing between the two diastereomers, thereby determining the dr, which was always about 1:1 (since the diastereomers could equilibrate via the hemi-aminal).

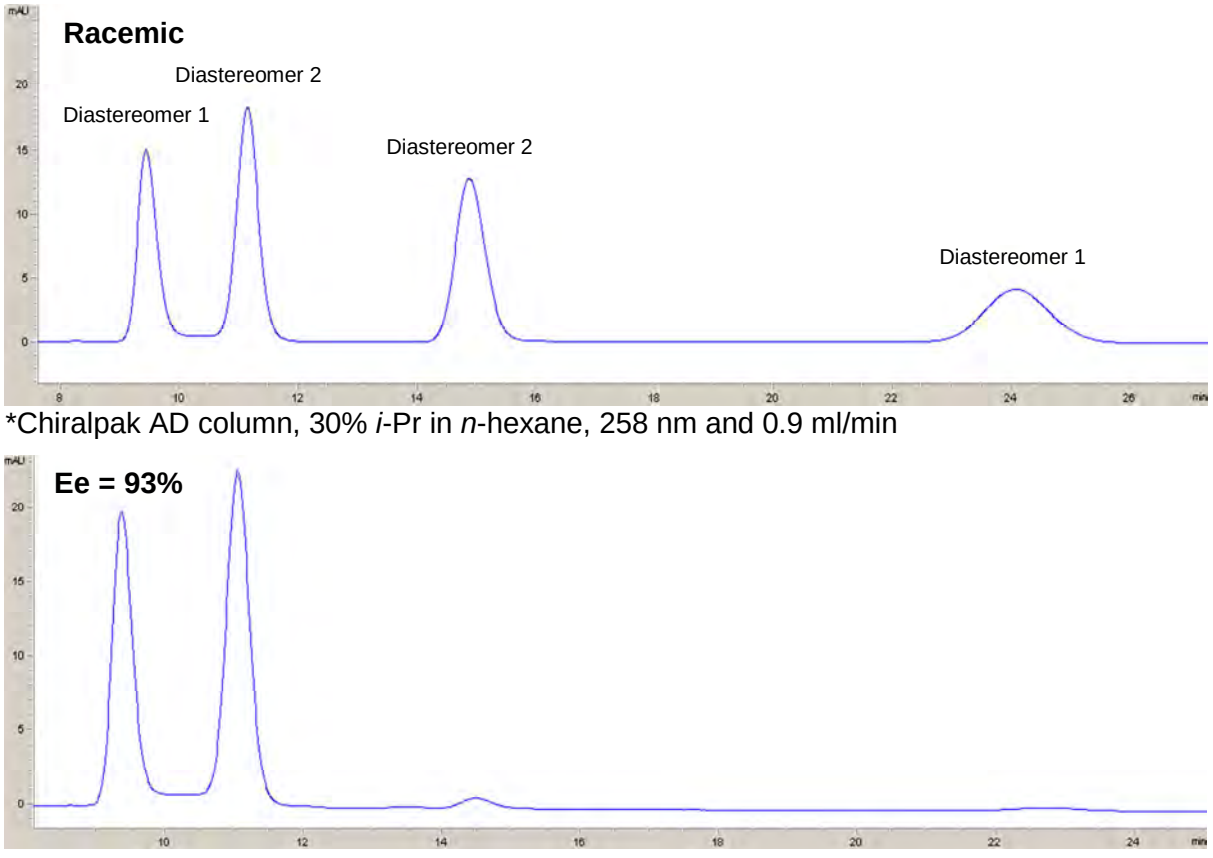
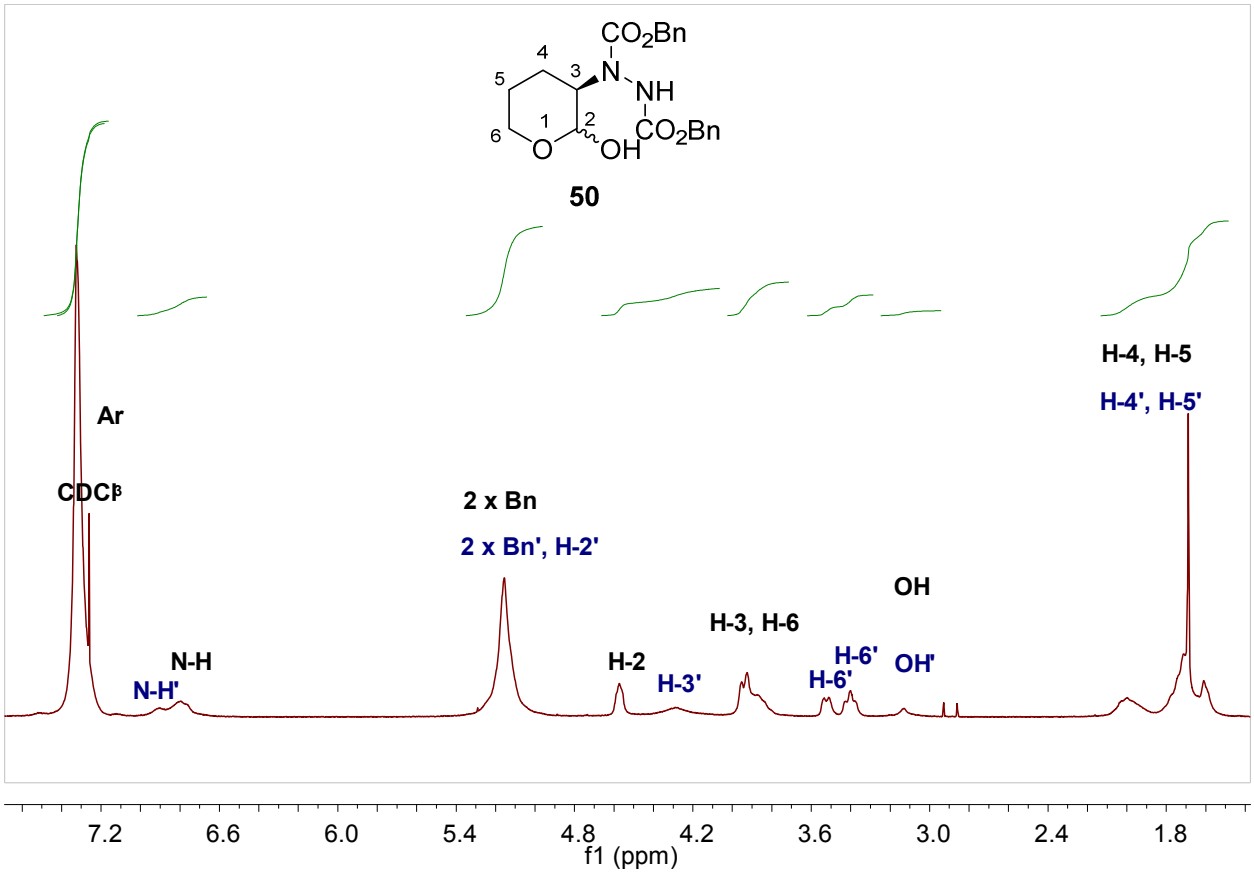


Figure 3.14: The racemic and chiral HPLC chromatograms of entry 3.

Figure 3.15 shows the ^{1}H NMR and ^{13}C NMR spectra of **50** as a mixture of diastereomers, which could not be separated by flash column chromatography. The H-2 and H-3 resonances appear in the typical region, together with the deshielded H-6 resonances in the same downfield region. Notably, in the ^{13}C NMR spectrum the hemiacetal C-2 and C-2' resonances for the two diastereomers are deshielded by the two adjacent oxygens, resulting in a very downfield signal for an sp^{3} carbon to approximately 100 ppm. As this is a new compound, additional analysis techniques were used in order to confirm its structure (infrared spectroscopy and high-resolution mass spectrometry). Particularly helpful was the 2-D HSQC NMR data which helped to confirm the NMR assignments and distinguish between the two diastereomers (**50** and **50'**).



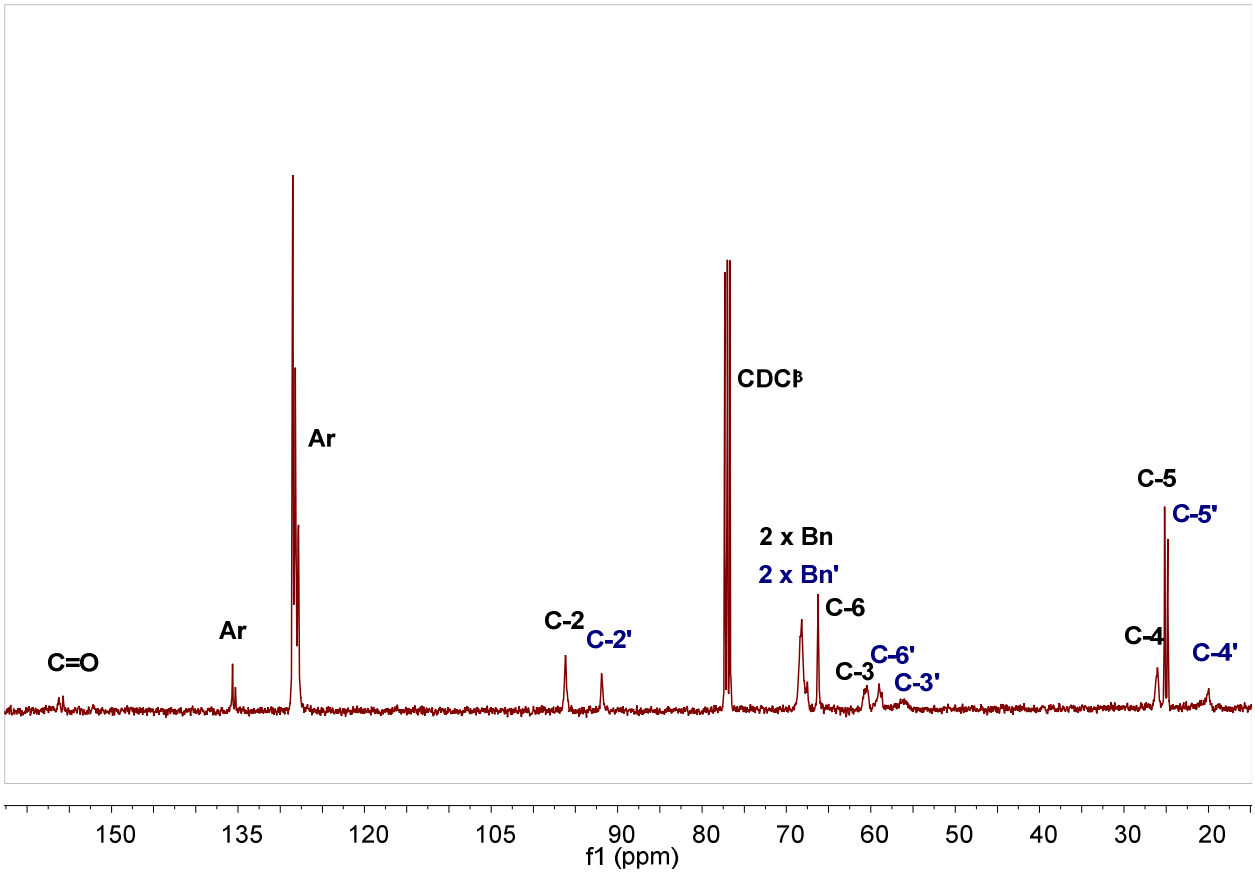


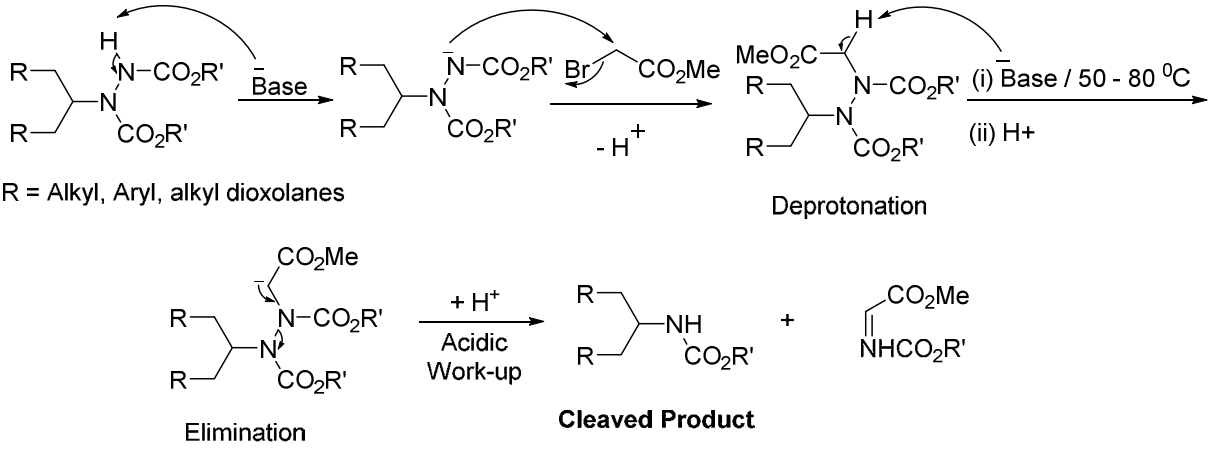
Figure 3.15: The ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75.5 MHz) spectra of the two diastereomers – **50** and **50'**.

In conclusion, conditions were successfully established for using acetals and associated masked functionalities as carbonyl equivalents in enantioselective α-amination reactions.

However, the utility of the derived α-aminated products is only truly harnessed after cleavage of the hydrazine N-N bond. This results in chiral α–amino products, which are important building blocks for a variety of organic compounds. Although there are known methods for achieving this they are unchemoselective. Before discussion of efforts to apply the new acetal amination to desymmetrisation, the following Chapter discusses a new methodology that was developed for hydrazide N-N bond cleavage.

Chapter 4: Hydrazide N-N Bond Cleavage

The traditional methods used to cleave the N-N bond in hydrazides derived from α-amination with Mitsunobu reagents involve classical reductive methods (Raney nickel,[67] zinc / acetic acid,[247] trifluoroacetic anhydride / samarium iodide[185] and $NaNO_2$ / HCl).[249] Other reagents that are less commonly used include: Al amalgam,[259] Li / NH_3,[260] B_2H_6,[261] $NiCl_2$[262], polymethylhydrosiloxane,[263] *m*-CPBA or magnesium monoperoxyphthalene.[264] In general, these procedures involve harsh conditions and are not compatible with highly functionalised substrates containing, for instance, double bonds, triple bonds, benzyl ethers or acetals. Recently, following sporadic reports of eliminative N-N cleavage,[265–269] Magnus reported N-N bond reductive cleavage of hydrazides with attached alkyl or aryl groups, as well as hydrazino dioxolanes derived from an achiral Lewis-acid catalysed α-amination reaction (mentioned in Chapter 3), via an $E1_CB$ protocol mechanism.[236,270] Their method involved *N*-alkylation of the secondary nitrogen of the hydrazide with ethyl (or methyl) bromoacetate followed by base-promoted elimination (NaH or Cs_2CO_3). The latter was postulated by Magnus to involve an $E1_CB$ mechanism involving the acidic methylene hydrogen of the newly introduced alkoxycarbonylmethylene group, and the two-step sequence could be carried out either sequentially (with purification of the *N*-alkylated intermediate) or as a one-pot procedure, particularly when NaH was used (Scheme 4.1).

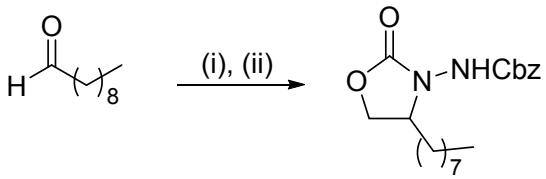


Scheme 4.1: The recent Magnus methodology for hydrazide N-N bond reductive cleavage.

It was envisaged that this would be an appropriate, benign procedure for the N-N bond cleavage of bis-acetal-derived products. However since this method had never been applied to α-hydrazino alcohols derived from the organocatalytic α-amination reaction, it was decided that a model study would be conducted first in order to test the applicability of this procedure, particularly in the context of acetal-containing substrates.

4.1 The Magnus Protocol Study

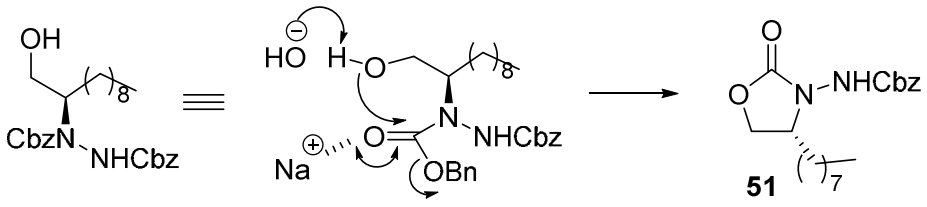
The model substrate chosen was the α-hydrazino alcohol from decanal. However, from the outset it was noted that any attempt to cleave the N-N bond of this substrate using Magnus' procedure would inevitably lead to base-catalysed cyclisation to the *N*-substituted oxazolidinone so the α–amination product was first converted to its oxazolidinone using NaOH. The procedure is shown below (Scheme 4.2) in which the overall sequence of three chemical steps could be realised in 86% overall yield and a 92% ee to afford oxazolidinone-hydrazide product **51** in accordance with List and Jørgensen's original findings. Decanal was chosen instead of its acetal form (from Chapter 3), since (for decanal and similar simple aldehydes) the classic List[67] version of the amination was faster and operationally simpler than the current acetal protocol, while the conditions for the cyclisation were chosen from Jørgensen's work on the α-amination of ketones.[66]



51 86% yield
92% ee

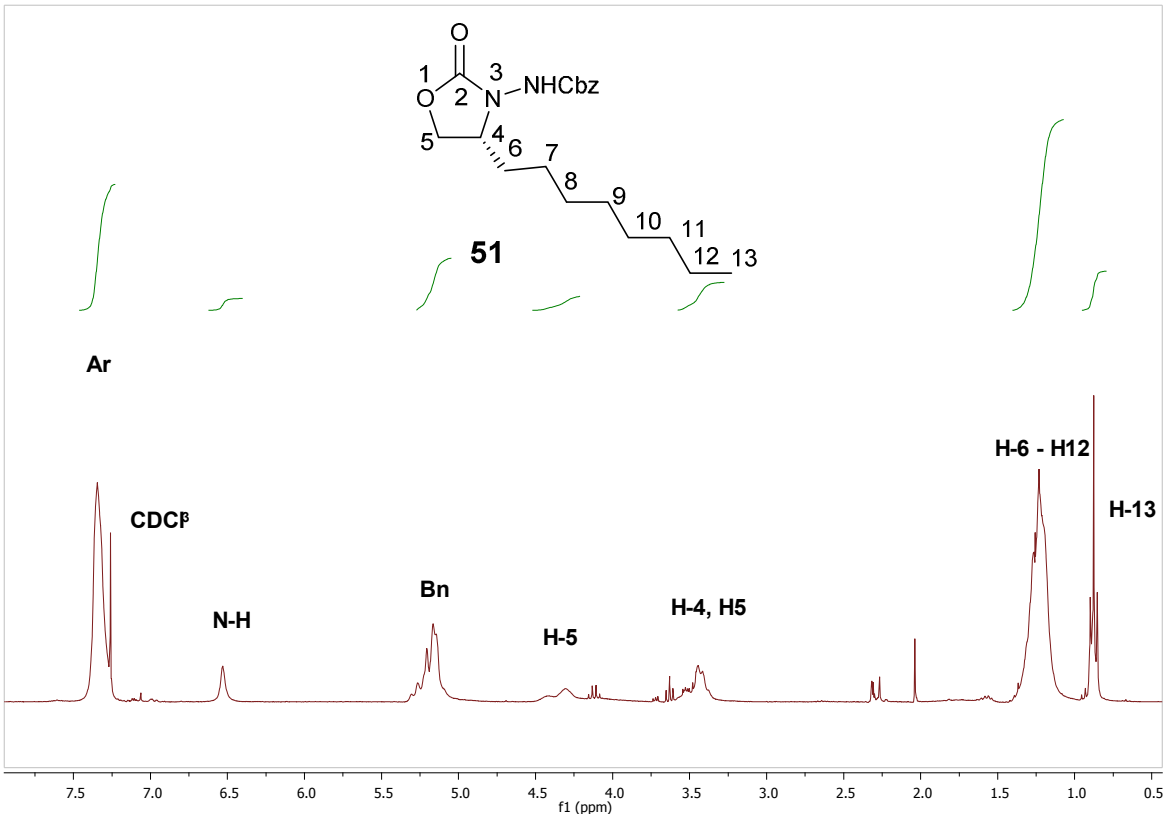
Scheme 4.2: Oxazolidinone-hydrazide synthesis from decanal in a three-step, one-pot procedure. *Reagents and Conditions*: (i) a) decanal (1.5 eq), DBAD (1 eq), L-proline (10 mol%), CH_3CN, 0 °C to RT, 2 hrs, b) $NaBH_4$ (1 eq), MeOH, 0 °C, 15 min; (ii) 1 M NaOH (3 eq), RT, 2 hrs.

The mechanism for this transformation is shown in Scheme 4.3. Regioselectivity is observed in the cyclisation in terms of kinetically favouring the 5-exo-trig product over the 6-exo-trig possibility in agreement with Baldwin's rules. Chemoselectivity is also displayed in that the secondary nitrogen (NH) of the hydrazide doesn't compete with the hydroxyl group as nucleophile in spite of its hydrogen being more acidic (due to resonance stabilisation of the *N*-anion), because of the unfavourable formation of a three-membered ring.



Scheme 4.3: A suggested mechanism for oxazolidinone formation.

The ^{1}H NMR and ^{13}C NMR spectra of **51** are shown in Figure 4.1. The most important diagnostic ^{1}H NMR signals, which were used in the characterisation of similar products in the study, were the H-4 and diastereotopic H-5 protons which came in the range of 3.50 – 4.50 ppm in the chemical shift order $H5_1 \geq H4 \geq H5_2$ (the big chemical shift difference between the H5 protons being due to alkyl shielding); as well as the benzyl signals integrating for only one benzyl group. As in the hydrazino alcohol cases, the broad resonances suggested sluggish conformational interconversion on the NMR time-scale. The ^{13}C NMR spectrum revealed a more marked difference between the C-5 and the less deshielded C-4 due to O being more electronegative and deshielding than N, while the oxazolidinone carbonyl resonance was in a similar range as the now single Cbz carbonyl resonance (150.0 – 160.0 ppm). The ^{13}C NMR spectrum also clearly showed all of the required singlets compared to the hydrazino alcohols in Chapter 3 where certain resonances were significantly relaxed and tied up with conformers.



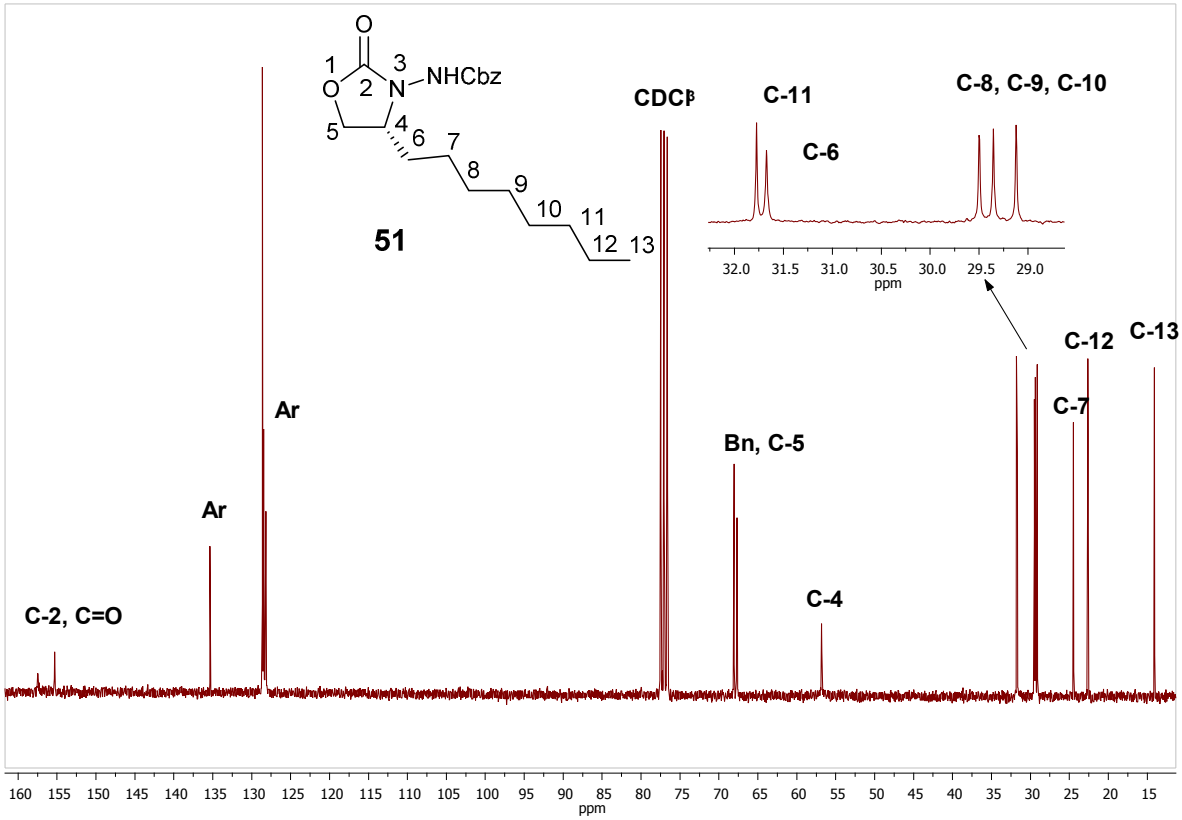
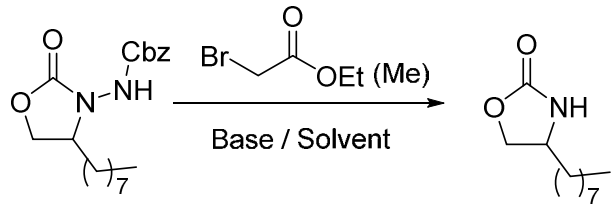


Figure 4.1: The ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75.5 MHz) spectra of **51**.

Before studying Magnus' methodology in context it was decided to first apply other standard methodologies in which hydrogenolysis with Raney Ni gave an unimpressive yield of 53%, while the sequential one-pot Pd-C hydrogenolysis of the Cbz benzyl followed by Zn / acetic acid N-N reduction gave an even worse one of only 24% overall yield. This was despite the fact that both reactions showed a complete conversion of the starting material on TLC. We were also aware of the fact that such methods would have chemoselectivity issues with substrates containing unsaturated functional groups. Thus Magnus' procedure using ethyl bromoacetate and NaH or Cs_2CO_3 appeared as very attractive by comparison. Table 4.1 below shows the results of various attempts using the Magnus conditions varying the base and solvent.



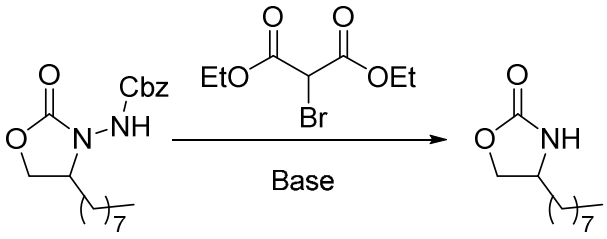
51 **52**

Entry	Procedure	Base (2.5 eq)	Alkylating agent (2eq)	Solvent (0.25 M)	Temp (°C)	Time	Yield
1	**Magnus-1**	Cs_2CO_3	Methyl bromoacetate	CH_3CN	80	>2 d	-
2		Cs_2CO_3	Ethyl bromoacetate	CH_3CN	80	>2 d	-
3	**Magnus-2**	NaH	Ethyl bromoacetate	Diglyme	50	17 hrs	16%
4		NaH	Ethyl bromoacetate	CH_3CN	50-80	2 d	-
5		NaH	Ethyl bromoacetate	THF	50-80	2 d	-
6		NaH	Ethyl bromoacetate	DMF	50	24 hrs	46

Table 4.1: Testing the original Magnus conditions.

Magnus-1 refers to the use of methyl bromoacetate and Cs_2CO_3 in CH_3CN as a one-pot procedure as described by Magnus,[270] while Magnus-2 refers to his later usage of ethyl bromoacetate as the alkylating agent and NaH with diglyme as the solvent in a one-pot procedure.[236] The results show that the Magnus-1 conditions were completely unsuccessful (entries 1 and 2). No conversion of starting material was observed on reaction TLCs even after prolonged heating for more than two days. By comparison, the Magnus-2 procedure did give a level of success in diglyme (Magnus' solvent in his original publication), using sodium hydride as base giving a low isolated yield of 16% (full conversion of substrate) after heating at 50 °C for 17 hours (entry 3). However, this protocol involved a difficult isolation due to the tendency of diglyme to remain associated with the product in trace amounts even after water washings and column chromatography. Moreover, the excessively long reaction times at 50 °C that were needed to achieve a full substrate conversion eventually led to alkylation of the cleaved product, as the bromoacetate alkylating agent was in excess. Owing to the heterogeneous nature of this reaction, it was then decided that other solvents should be tested in the hope of improving solubility and, hence, the reaction yield, but both THF and acetonitrile gave absolutely no starting material conversion (entries 4 and 5). However, DMF did afford a modest improvement as the best result (46% yield) and made for an easier purification compared to that from the diglyme reaction. This highlighted the solvent

dependency of the Magnus reaction. It was therefore speculated that the Magnus protocol failed due to steric and stereoelectronic factors introduced by having the oxazolidinone ring, compared to Magnus' alkyl and aryl substrates in an open hydrazide system. In the hope of addressing these issues it was decided to try another readily available ester-based alkylating agent in the form of diethyl bromomalonate. The expectation here was that both steps would be accelerated, the alkylation step because of the enhanced electrophilicity and the E1cB step because of enhanced acidity based on comparing malonate against acetate in the respective steps. Table 4.2 below shows the initial results using diethyl bromomalonate and varying the base from NaH to Cs_2CO_3.



51 **52**

Entry	Diethyl bromomalonate (eq)	Base (eq)	Solvent (0.25 M)	Time	Temp (°C)	Yield (%)
1	2	NaH (3)	THF	24 hrs	50	48
2	2	Cs_2CO_3 (2.5)	CH_3CN	2 d	RT	64
3	2	Cs_2CO_3 (2.5)	CH_3CN	4 hrs	50	64
4	5	Cs_2CO_3 (2.5)	CH_3CN	5 hrs	50	66
5	2	Cs_2CO_3 (5)	CH_3CN	5 hrs	50	68
6	5	Cs_2CO_3 (5)	CH_3CN	5 hrs	50	80

Table 4.2: Initial optimisation study for N-N bond cleavage using diethyl bromomalonate.

Entry 1 shows that NaH (3 equivalents added to ensure complete starting material conversion) in THF gave only a moderate 48% yield, despite complete hydrazide consumption. Attempts to improve this by lowering the temperature (longer reaction time), and changing the reaction solvent (to DMF or acetonitrile) led to even lower yields (29% and 0%, respectively). However, it was good to see that the bromomalonate system was compatible with a more volatile organic solvent other than DMF or diglyme. Cs_2CO_3 was then tested under a range of different conditions. With 2 equivalents of bromomalonate and 2.5 equivalents of base at room temperature and 50 °C the same 64% yield could be achieved (entries 2 and 3), although the reaction time was far longer at room temperature.

Besides the eliminated imine (see Scheme 4.1), another important reaction by-product was the malonate dimer (Figure 4.2) which was characterised by ^{1}H NMR spectroscopy, and it was thought that its formation was contributing to the moderate yields.

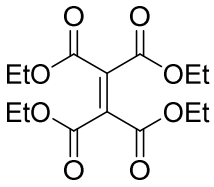
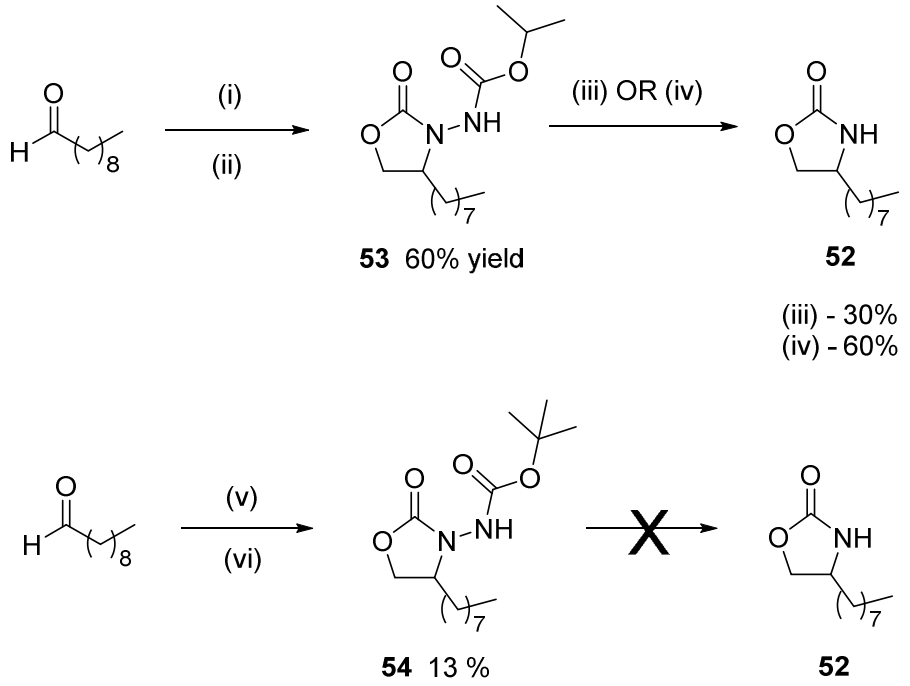


Figure 4.2: The diethyl bromomalonate dimer.

Secondary alkylation of product **52** was not observed in this case, e.g. extending the time for the 4 hr reaction in entry 3 to 20 hours at a higher 80 °C did not result in a yield decline (although refluxing at 80 °C for longer than two days did result in a yield depreciation). Reaction TLCs revealed that some of the cleaved product was formed within a few minutes, while the alkylated intermediate was never observed. These observations together with the long reaction times indicated that the alkylation step was rate-determining (k_1), with a fast elimination step (k_2). These conclusions supported our idea of malonate being a better $E1_CB$ partner than the acetate. Attempts to improve the moderate yields were made by increasing the equivalents of bromomalonate to 5 equivalents (to compensate for reagent loss due to dimerisation), while keeping the base at 2.5 equivalents but this led to an increase in product yield of only 2% (entry 4). Similarly, increasing the equivalents of only the base to 5 while keeping the reagent at 2 equivalents also only led to a modest 4% yield improvement (entry 5). However, increasing both the bromomalonate and base equivalents to 5 (entry 6) gave the best result, a high 80 % yield. In view of excessive cost it was decided to continue the study with conditions from entry 2 using room temperature with 2 equivalents of reagent and 2.5 of base. Nevertheless it was pleasing to see that reactions could be carried out in acetonitrile making product isolation much easier than before with the Magnus-2 original procedure.

It was also appropriate to determine whether the identity of the aminating agent had any effect on the reaction. Thus oxazolidinone-hydrazides **53** and **54** were synthesised from DIAD and di-*tert*-butyl azodicarboxylate (DTBAD) reagents, respectively. However yields were much lower (60% and 13% respectively) for formation of the cyclic hydrazides compared to the yield for DBAD (Scheme 4.4). Furthermore, while the cleavage reaction worked in moderate yield for the DIAD case (up to 60% with conditions (iv) in Scheme 4.4), the reaction failed completely in the DTBAD case, again vindicating our notion that steric

effects do come into play. Thus it was concluded that DBAD was the best aminating reagent for our strategy.



Scheme 4.4: *Reagents and Conditions*: (i) a) decanal (1.5 eq), DIAD (1 eq), L-proline (10 mol%), CH_3CN, 0 °C to RT, 2 hrs, b) $NaBH_4$ (1 eq), MeOH, 0 °C, 15 min; (ii) 1 M NaOH (3 eq), RT, 2 hrs; (iii) oxazolidinone (1 eq), Cs_2CO_3 (2.5 eq), diethyl bromomalonate (2 eq), CH_3CN, 80 °C, 24 hrs; (iv) oxazolidinone (1 eq), Cs_2CO_3 (5 eq), diethyl bromomalonate (5 eq), CH_3CN, 80 °C, 6 hrs (v) a) decanal (1.5 eq), DTBAD (1 eq), L-proline (10 mol%), CH_3CN, 0 °C to RT, 3 hrs, b) $NaBH_4$ (1 eq), MeOH, 0 °C, 15 min; (vi) 1 M NaOH (3 eq), 60 °C, 24 hrs.

Although oxazolidinone-hydrazides **53** and **54** weren't pursued any further, their structures were confirmed using ^{1}H and ^{13}C NMR spectroscopy. Figure 4.3 below shows the ^{1}H NMR spectrum for **53** derived from DIAD. This showed similar characteristics to those in the spectrum for the equivalent DBAD-derived **51** with the key difference being that benzyl resonances were replaced by *iso*-propyl resonances. Again, rotamers could be observed (NH resonance).

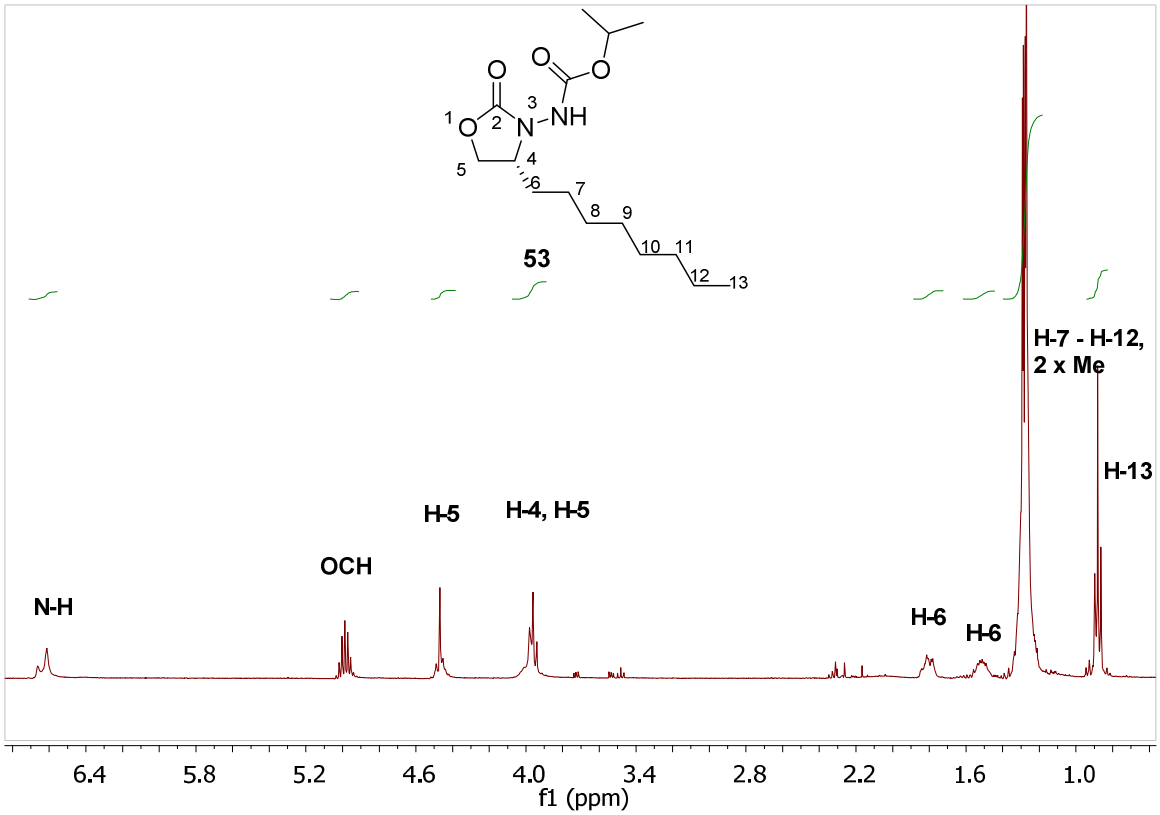
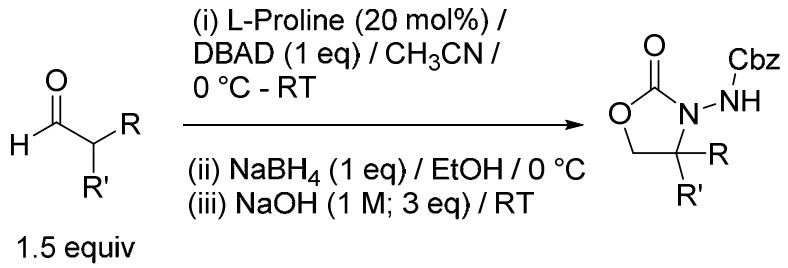


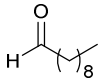
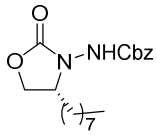
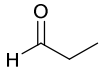
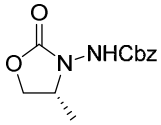
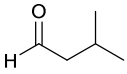
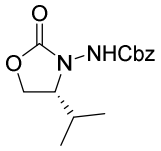
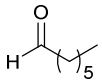
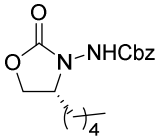
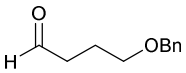
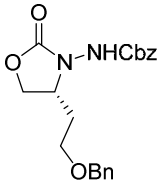
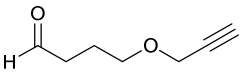
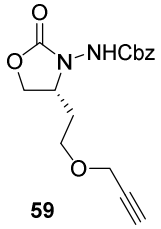
Figure 4.3: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **53**.

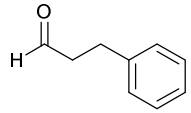
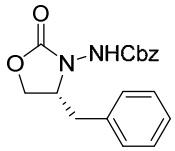
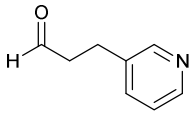
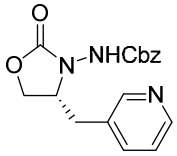
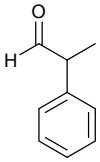
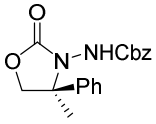
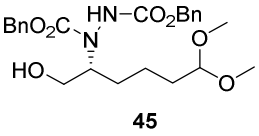
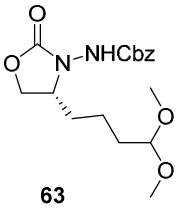
4.2 The Scope of the Bromomalonate Reaction

Chiral 2-oxazolidinones have the advantage of being important chemical building blocks (e.g. for the synthesis of natural products[186] and antibiotics) and reagents (e.g. as chiral auxiliaries – Evans' auxiliary).[271] Thus, the scope of the bromomalonate methodology was tested using a range of oxazolidinone-hydrazides varying the C-4 substituents, chosen to address aspects of chemoselectivity (Table 4.3). Substrates **55** to **62** were prepared using the three-step sequence used to synthesise **51**, which successfully yielded high yields (80-91%) - this included the functionalised oxazolidinone-hydrazides (**58** to **62**) containing OBn, propargyl ether, aromatic, heteroaromatic or a quaternary C-4 moiety. It is also worth noting that oxazolidinone-hydrazide **63** (a prototype for the desymmetrisation of a bis-acetal) was obtained via cyclisation of α-hydrazino alcohol **48** (synthesised from the acetal methodology described in Chapter 3) to give the acetal-containing oxazolidinone-hydrazide in a slightly lower yield (72%). The ees were determined by chiral HPLC. As expected for the simple aldehyde cases **55** to **57** based on published cases by List and Jørgensen the ees were high (>90%). The more funtionalised oxazolidinone-hydrazides also gave very high ees with the exception of **62** (46%) due to the low enantioselectivity of the proline-catalysed α-amination of branched aldehydes (as mentioned in Chapter 3). Unfortunately the enantiomers of the bis-acetal-derived **63** were not separable by all three of the chiral columns we had available

(Chiralpak AD, OD and IC) even after trying several *iso*-propyl / *n*-hexane mobile phase mixtures. Therefore its ee was inferred from hydrazino alcohol **48** (90% ee).



Entry	Starting Material	Product	Yield	ee
1		 **51**	92	90
2		 **55**	88	90
3		 **56**	91	91
4		 **57**	89	93
5		 **58**	86	92
6		 **59**	87	90

7		 **60**	91	86
8		 **61**	87	94
9		 **62**	80[a]	46
10	 **45**	 **63**	72	90[b]

[a]5 eq of aldehyde used to improve reaction rate and conversion

[b]nferred from **48**.

Table 4.3: Asymmetric synthesis of oxazolidinone-hydrazides from the corresponding aldehydes.

All of the new compounds were fully characterised by NMR spectroscopy, infrared spectroscopy and high-resolution mass spectrometry, the latter in view of them being oils. The ^{1}H NMR spectrum of **63** (the desymmetrisation prototype) is shown in Figure 4.4. It clearly shows the acetal-associated resonances – two diastereotopic methoxy singlets as well as a downfield H-4' triplet. The oxazolidinone resonances appear as multiplets in the expected chemical shift order $H5_1 > H4 = H5_2$.

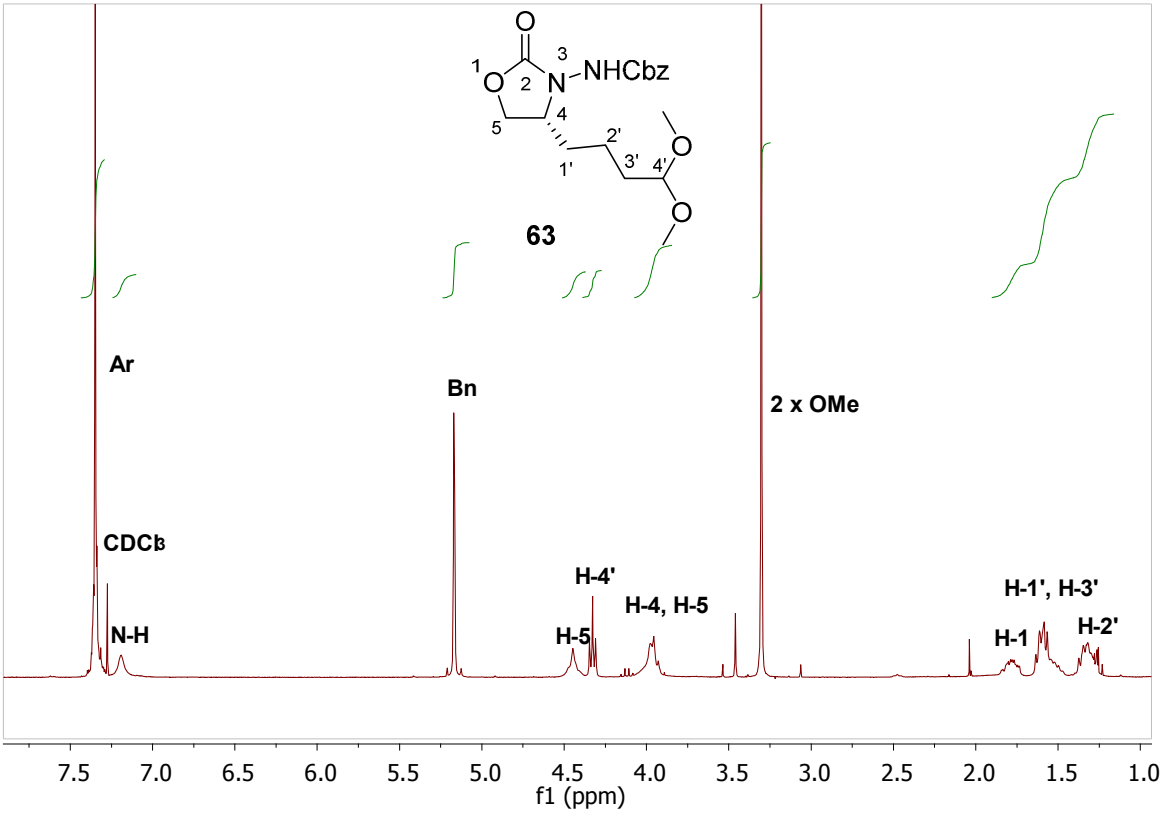
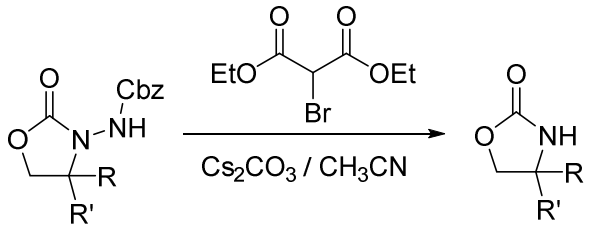
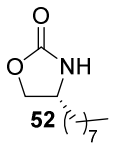
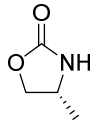
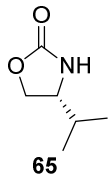
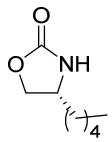
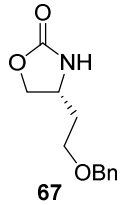
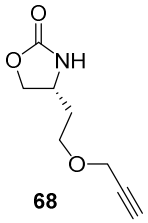
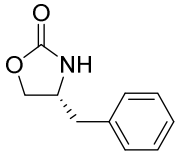
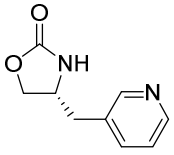
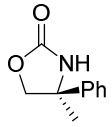


Figure 4.4: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **63**.

The Cs_2CO_3 / bromomalonate strategy was then tested on the wide range of oxazolidinone-hydrazides using the aforementioned conditions. The results are shown in Table 4.4. In general, the reaction was conducted at room temperature; however, the temperature was increased to 50 °C for lower yielding or slower-converting cases (entries 7 and 14). The switch to room temperature was made in order to discourage side-reactions, including the formation of a malonate dimer and the possibility of alkylating the cleaved product.



Entry	Product	Diethyl bromomalonate(eq)	Cs_2CO_3 (eq)	Temp (°C)	Time (hrs)	Yield
1		2	2.5	RT	48	64
2		2	2.5	50	4	64
3		5	5	50	5	80

4	 **64**	2	2.5	RT	20	88
5	 **65**	2	2.5	RT	20	96
6	 **66**	2	2.5	RT	48	63 (58% conv)
7		2	2.5	50	48	65 (58% conv)
8	 **67**	2	2.5	RT	5	84
9	 **68**	2	2.5	RT	4	81
10	 **69**	2	2.5	RT	3	82
11	 **70**	2	2.5	RT	2	90
12	 **71**	2	2.5	RT	48	-

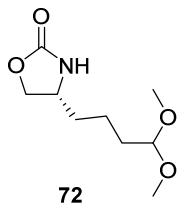
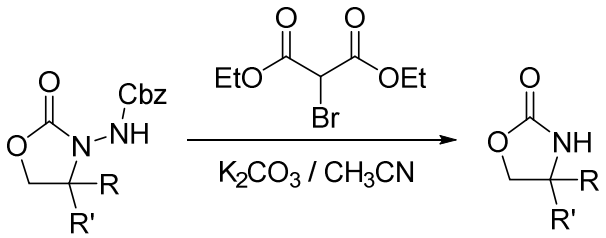
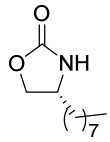
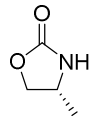
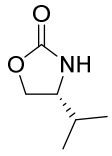
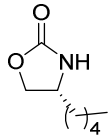
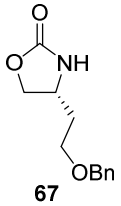
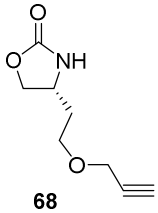
13	 **72**	2	2.5	RT	48	57 (89% conv)
14		2	2.5	50	48	59

Table 4.4: N-N Cleavage using bromomalonate with caesium carbonate as base.

Generally the cleaved products were obtained in very high yields (80 – 96%) following column chromatography, which was higher than that for the model case (**52**, 64%). Reaction times were also faster than that of the model (as low as two hours for **70**, entry 11), and notably improved with polarity in the C-4 substituent (**67 - 70**). Oxazolidinones **66** and **72** were obtained in only moderate yields (63% and 57%, respectively) and for some reason that couldn't be ascertained struggled to go to full conversion even at 50 °C (entries 6/7 and 13/14). Entry 12 shows how the quaternary case failed to give a reaction product (**71**). Indeed, even though reaction TLCs showed some (though not complete) conversion of the starting material, what was believed to be product **71** co-eluted with reaction by-products (which were not quite visible on TLCs) during column chromatographic purification. Nevertheless this Table clearly shows that our methodology can successfully be applied to a wide range of azatertiary substrates at room temperature, and without the need for a large excess of malonate or base (2 and 2.5 equivalents, respectively) for high yields.

In view of the high cost of Cs_2CO_3, K_2CO_3 was also tested as a cheaper alternative. Table 4.5 shows the results of this study.



Entry	Product	Diethyl Bromomalonate (eq)	K_2CO_3 (eq)	Temp (°C)	Time (hrs)	Yield
1	 **52**	2	2.5	RT	23	90
2	 **64**	2	2.5	RT	48	61
3		2	2.5	50	40	30
4	 **65**	2	2.5	RT	48	62
5		2	2.5	50	40	42
6	 **66**	2	2.5	RT	48	76 (85% conv)
7		2	2.5	50	48	68 (59% conv)
8	 **67**	2	2.5	RT	24	82
9	 **68**	2	2.5	RT	24	80

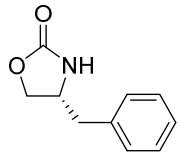
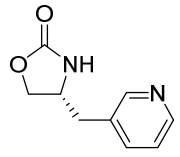
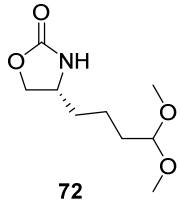
10	 **69**	2	2.5	RT	20	84
11	 **70**	2	2.5	RT	24	75
12	 **72**	2	2.5	RT	48	86 (70% conv)

Table 4.5: Potassium carbonate study.

Here reactions needed longer times, and yields were generally a little lower except for the model **52** (entry 1) which went from 64 to 90%. Starting material conversion and yields were also improved for **66** (76%, entry 6) and **72** (86%, entry 12) compared to using Cs_2CO_3. Products **64** and **65** were obtained in significantly lower yield (61% and 62%, respectively) than when using Cs_2CO_3, and increasing the reaction temperature to 50 °C led to a substantial drop in yield for both products (entries 3 and 5). However, the results of this study showed that both Cs_2CO_3 and K_2CO_3 are suitable bases for this reaction although reactions with them are substrate-dependent. Moreover, apart from a few cases, room temperature was far superior to 50 °C for this modified-strategy giving very high yields. Finally, the chemoselectivity profile was attractive in that many of the functional groups certainly wouldn't have survived Raney-Nickel conditions.

Another aspect to note was that the cleaved oxazolidinones gave much better resolved ^{1}H NMR spectra due to the absence of conformers and rotamers associated with the Cbz-hydrazide. This is exemplified by the ^{1}H NMR spectrum for **72** shown in Figure 4.5 in which resonances are pleasingly resolved.

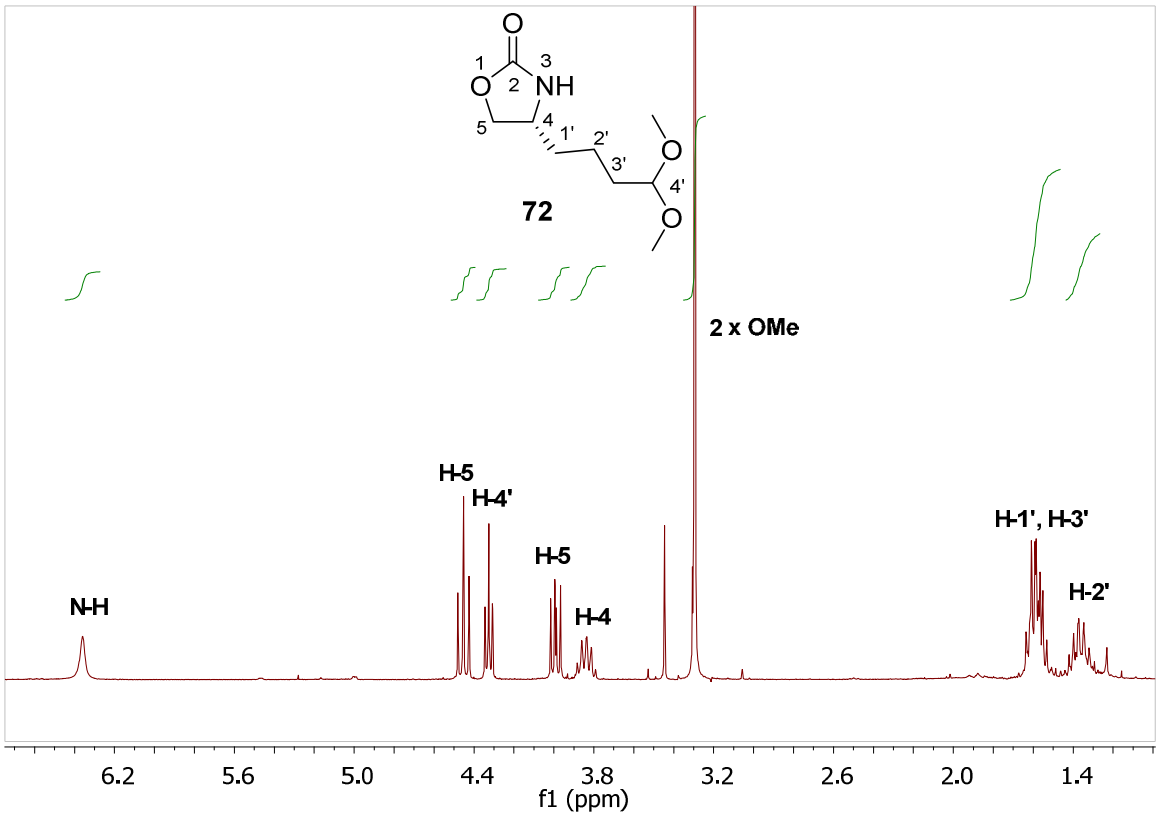
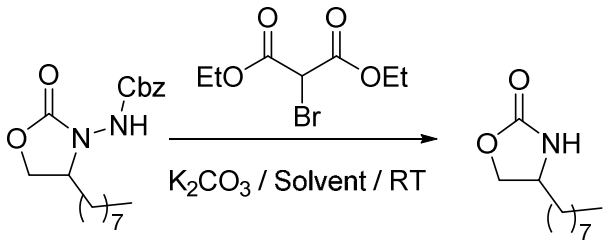


Figure 4.5: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **72**.

In order to test the solvent dependency observed in Magnus' original protocols (Table 4.2), a solvent study was conducted using potassium carbonate as base. The results are shown in Table 4.6 below using oxazolidinone-hydrazide **51** as the substrate. As seen in entry 1 acetonitrile was the best solvent, giving a 90% yield. DMF (entry 3) did not perform as well as it did under Magnus-2 conditions, only returning a 30% yield. Toluene gave a moderate 44% yield (entry 3) and methanol (entry 4) gave no reaction due to destruction of the bromomalonate as seen on reaction TLCs (the starting material was recovered and analysed by ^{1}H NMR to confirm this conclusion). Reaction times were also considerably longer with solvents other than acetonitrile.

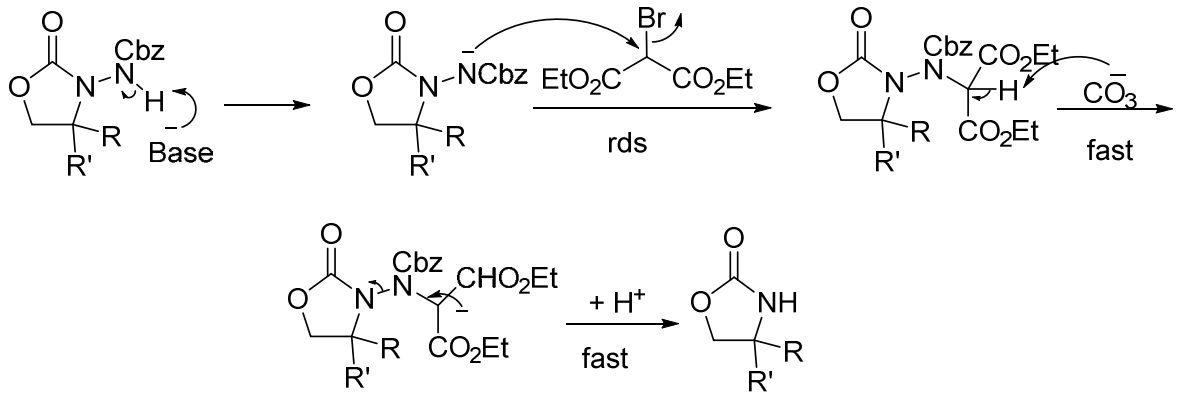


51 **52**

Entry	Hydrizide (eq)	Diethyl bromomalonate (eq)	K_2CO_3 (eq)	Solvent (ml)	Time (hrs)	Temp (°C)	Yield (%)
1	1	2.5	2	CH_3CN	23	RT	90
2	1	2.5	2	DMF	72	RT	30
3	1	2.5	2	Toluene	72	RT	44
4	1	2.5	2	Methanol	43	RT	0

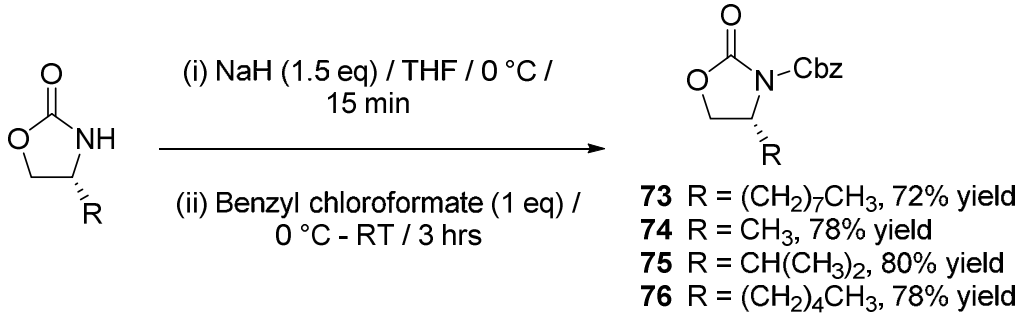
Table 4.6: Solvent study.

Mechanistic considerations suggest that our modified Magnus methodology follows the same E1cB pathway (Scheme 4.5). As discussed earlier, the TLC results indicate that the rate-determining step is the S_N2 alkylation step. This suggests that the improved results compared to using Magnus' conditions are due to rate improvements in the alkylation and elimination steps as mentioned previously due to the superior characteristics of bromomalonate compared to bromoacetate. We also wondered whether our conditions for the reaction owed their success to having a cyclic template as the leaving group in the E1cB step. To address this possibility, the hydroxyl group of hydrazino alcohol **41** (synthesised from decanal) was TBDPS-protected and the product was reacted under our new conditions. However, no reaction occurred with either K_2CO_3 or Cs_2CO_3 as base, with only starting material (which was isolated from the reaction mixture and whose structure was confirmed by NMR spectroscopy) visible on TLC together with the bromomalonate and its dimer. These results suggest that our conditions do profit from something in the cyclic template, possibly to do with pre-organisation (stereoelectronics) in the elimination. However it doesn't explain why Magnus' conditions were pretty ineffective in our (cyclic) system.



Scheme 4.5: Likely E1cB mechanism for this modified Magnus strategy.

Since no racemisation is possible during the N-N bond cleavage procedure due to low likelihood of carbanion formation at the chiral centre, the ees of the cleaved products were expected to remain unchanged from their original values (Table 4.1). However, chiral HPLC was once again utilised in order to confirm this. Owing to the absence of a UV-active chromophore in their structures, products **52**, **64**, **65** and **66** were Cbz-derivatised in reasonable yields (72-80%) to give UV-active products for HPLC analysis (Scheme 4.6). Unfortunately the Cbz protection of **68** and the acetal **72** couldn't be performed because the substrates decomposed, even though they had been stored at -22 °C.



Scheme 4.6: The Cbz-derivatisation of cleaved products.

All these derivatives were new compounds and thus their structures were elucidated using the full gamut of ^{1}H NMR, ^{13}C NMR and infrared spectroscopies in addition to high-resolution mass spectrometry. As an example, Figure 4.6 depicts the ^{1}H NMR spectrum of **74**. As expected, the downfield NH resonance was replaced by benzyl resonances in the aliphatic and aromatic regions.

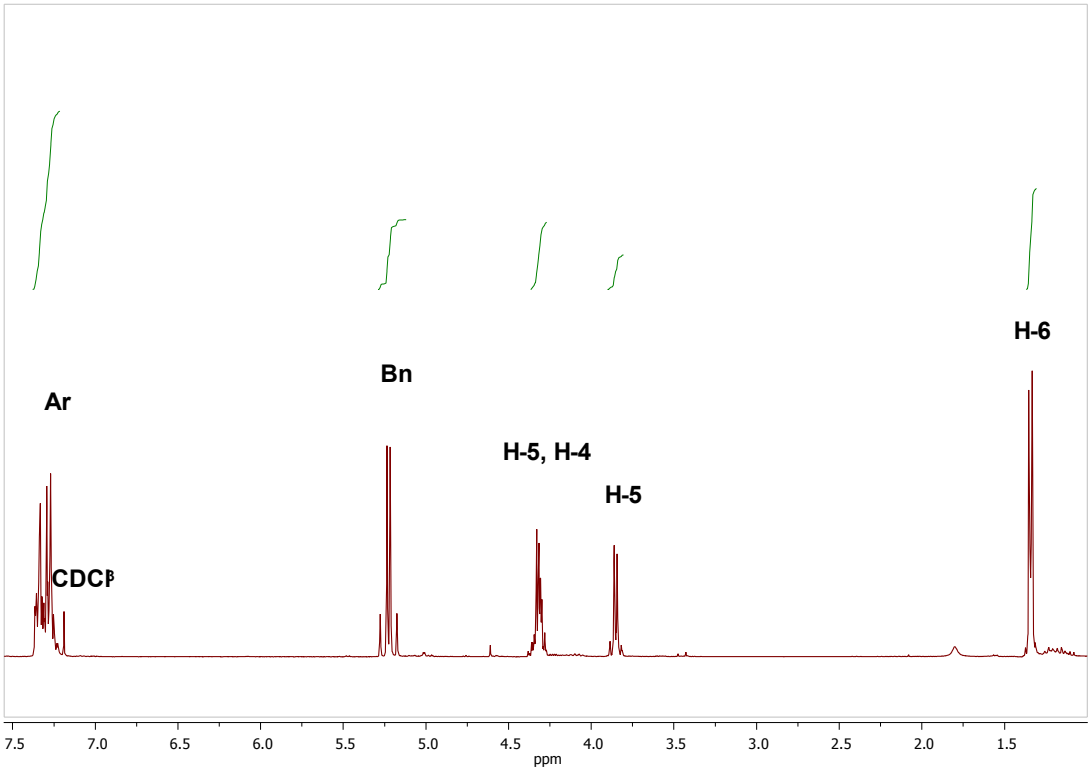
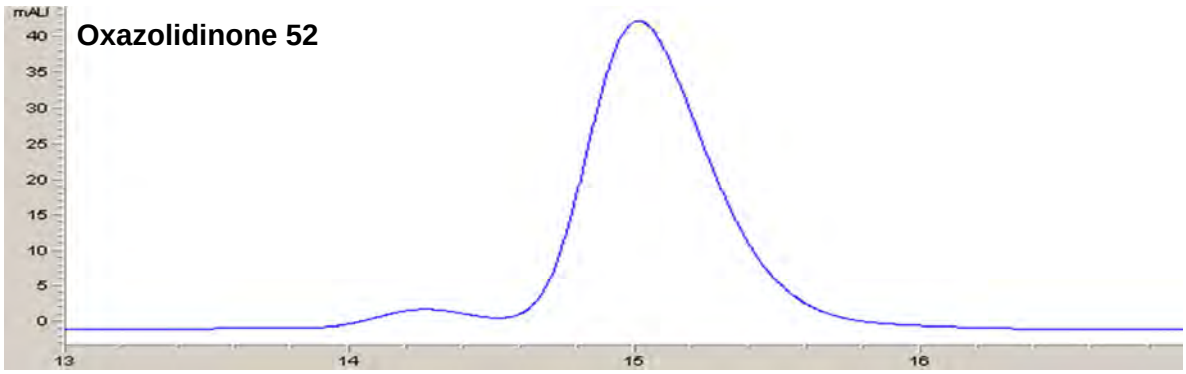


Figure 4.6: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **74**.

The HPLC data from these compounds confirmed that the N-N bond cleavage step had not led to racemisation at C-4. Figure 4.7 compares HPLC chromatograms for the decanal-derived oxazolidinone hydrazide **52** and its N-N cleaved and Cbz-protected analogue **73**, which show a consistently high enantiomeric ratio of 95:5 for **52** and 92:8 for **73** (the slight differences in er for this and all other cases are a result of how well the chiral columns were able to separate the enantiomers).

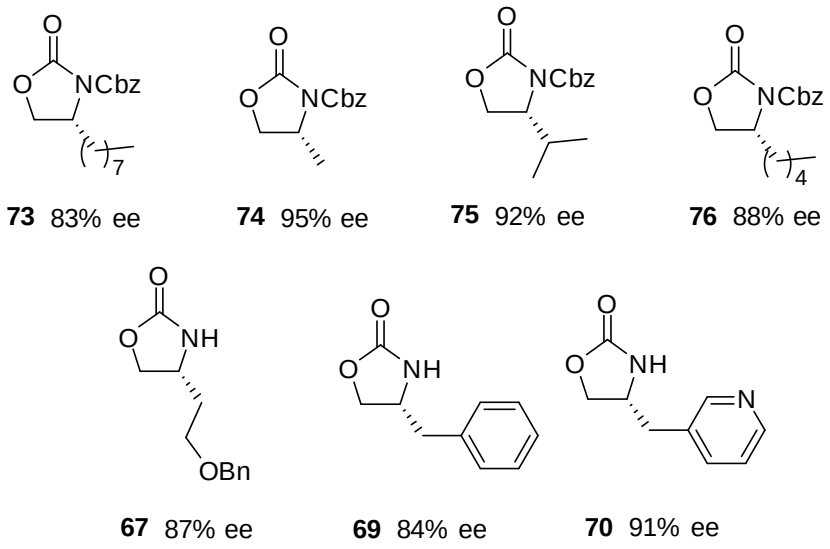


Chiralpak OD 10% *i*-Pr in *n*-Hexane, 258 nm and 0.3ml/min

Chiralpak OD 10% *i*-Pr in *n*-Hexane, 258 nm and 0.3ml/min

Figure 4.7: A comparison of the HPLC chromatograms of product **52** and **73** showing a consistent enantiomeric ratio between the two products.

Figure 4.8 shows the HPLC determined ees of the range of cleaved oxazolidinones produced.



73 83% ee **74** 95% ee **75** 92% ee **76** 88% ee

67 87% ee **69** 84% ee **70** 91% ee

Figure 4.8: The ees of the final oxazolidinone products.

In conclusion, a modified Magnus protocol was developed for the N-N bond cleavage of enantioenriched oxazolidinone-hydrazides. Its successful application to the acetal-containing oxazolidinone-hydrazide **63** opened up the way forward for bis-acetal desymmetrisation transformations. However, the decomposition of the cleaved oxazolidinone containing the acetal in the chain (**72**) was worrying and we hoped that this wouldn't be a general trend for other bis-acetal hydrazide-cleaved products.

Chapter 5: The Desymmetrisation

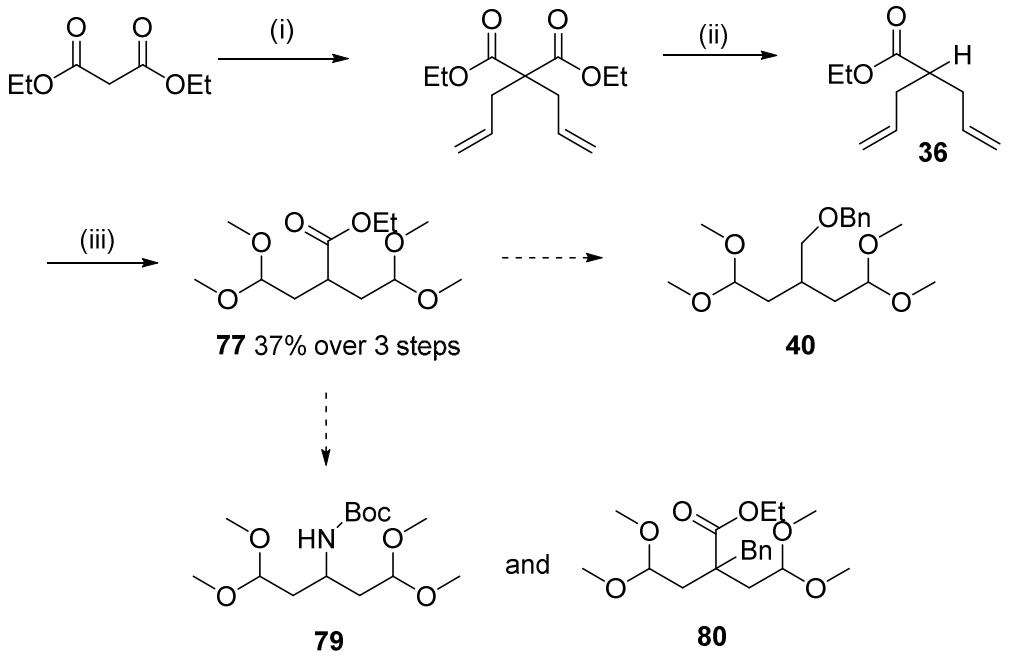
With new acetal α-amination and N-N bond cleavage methodologies developed and optimised, it was time to apply them to the desymmetrisation of bis-acetals.

5.1 Synthesis of the Symmetrical Substrates

Following the work presented in Chapter 2, a range of symmetrical, prochiral bis-acetal substrates needed to be synthesised. Thus three appropriate pathways were envisioned: 1) a divergent malonate-based strategy; 2) a divergent sulfone-based strategy; and 3) a far shorter 3-cyclopentene-based strategy. The chief goal was to develop a representative library of substrates containing a prochiral centre varying the A-value of the central substituent.

5.1.1 The Divergent Malonate Strategy

Allyl ester **36**, whose synthesis was described in Chapter 2 using a malonate diallylation / decarboxylation sequence, was converted into bis-acetal ester **77** en route to the final benzyl ether derivative (Chapter 2), and this bisacetal ester **77** was identified as the starting material for two other derivatives, **79** and **80**, varying the prochiral groups (Scheme 5.1).



Scheme 5.1: *Reagents and Conditions*: (i) a) NaH (2.5 eq), THF, 45 min, 0 °C to RT, b) allyl bromide (2 eq), 26 hrs, reflux; (ii) LiCl (2.2 eq), DMSO (with a little H_2O), 21 hrs, 180 °C; (iii) a) O_3, MeOH, 30 min, -78 °C to 0 °C, b) PPh_3 (2.2 eq), 2 hrs, 0 °C to RT, c) *p*-TSA (20 mol%), 18 hrs, reflux.

Thus, through the tandem ozonolysis / acetalisation procedure described in Chapter 2, bis-acetal **77** was synthesised from **36** over three steps and in a modest 37% yield after column chromatography. This lower yield was attributed to the fact that complete conversion of the bis-aldehyde (as judged by TLC) required refluxing for 26 hours. This in turn led to additional by-products related to the acetalisation intermediates. Figure 5.1 below shows the ^{1}H NMR spectrum of bis-acetal **77**, which displayed characteristic acetal-related resonances (two methoxy singlets and an H-4 triplet) as well as a set of ethyl ester resonances (an upfield triplet and downfield quartet). In this case the symmetrical H-3 protons of the chain resolved into a doublet of doublet of doublets (ddd) due to geminal coupling between the two diastereotopic H-3 protons (J = 13.7 Hz), coupling with H-2 (J = 7.5 Hz) and coupling with H-4 (J = 5.3 Hz). This new compound was characterised with the use of ^{1}H, ^{13}C NMR and infrared spectroscopies as well as high-resolution mass spectrometry.

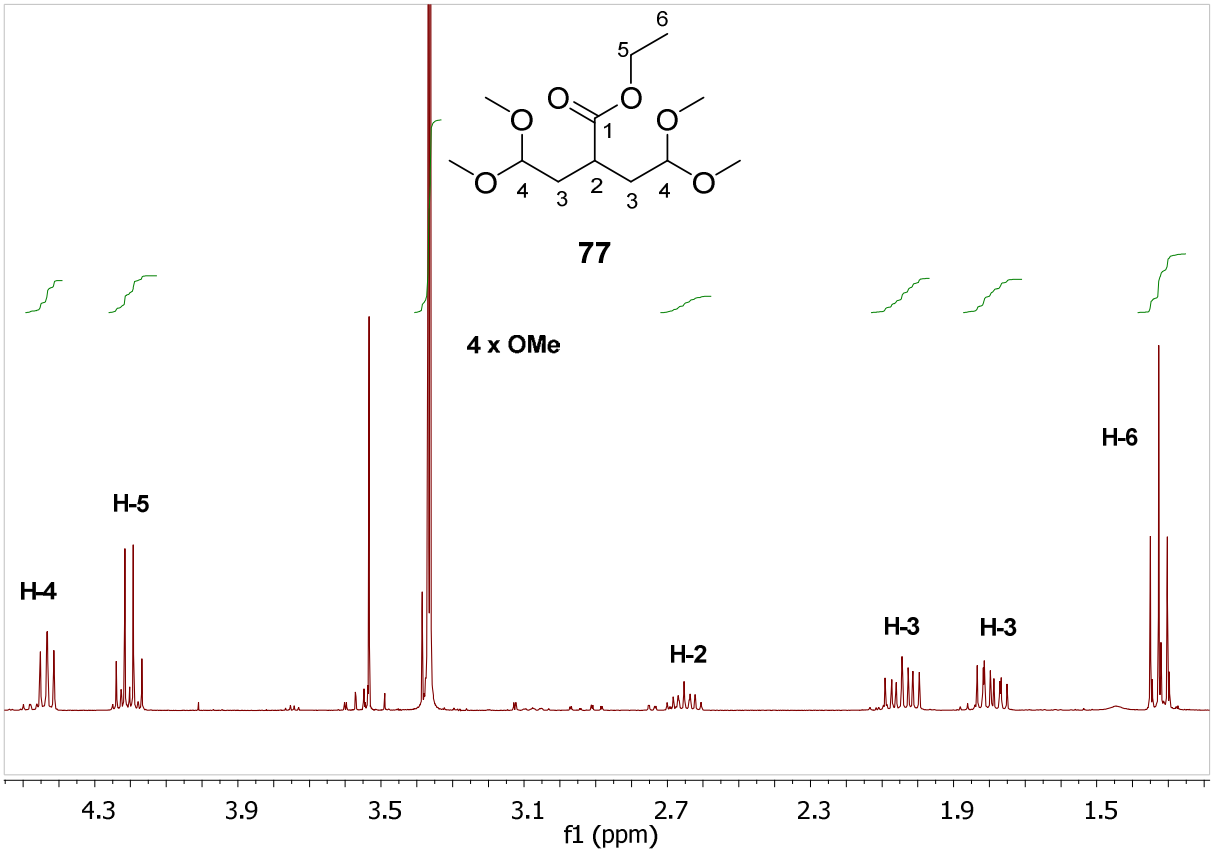
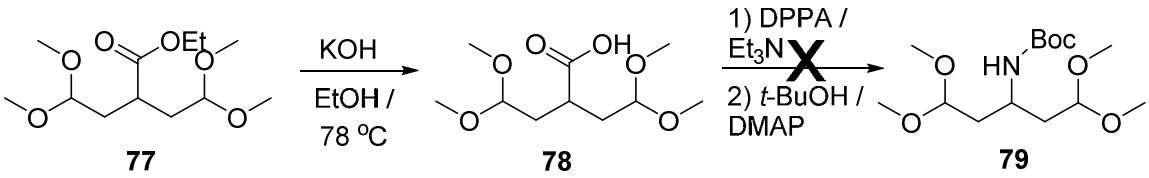


Figure 5.1: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **77**.

Bis-acetal **77** was then used to attempt the preparation of the other two targets **79** and **80**. The first one, amine **79,** protected as a Boc carbamate, was envisaged as being accessible via transposition of the ester group to an amine using the well-known Curtius rearrangement via an acyl azide. To this end, **77** was hydrolysed with KOH under ethanol reflux for 2 hours,

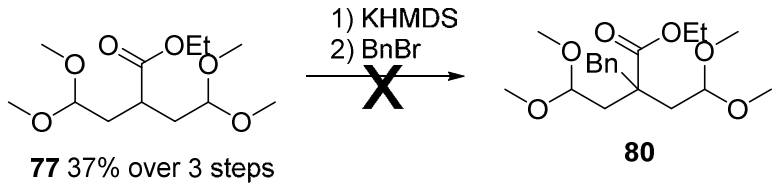
to give acid **78** as a crude product. The success of this transformation was judged by TLC analysis which showed the complete conversion of **77** to a more polar product that streaked on the TLC plate. This was expected because of greater hydrogen bonding interactions of the more polar carboxylic acid with the silica stationary phase. A Curtius rearrangement of **78** was then attempted. This involved reaction with diphenylphosphoryl azide (DPPA) and triethylamine (one equivalent each) in order to generate an acyl azide. After four hours of refluxing in toluene, reaction TLCs showed complete conversion of the acid to two non-polar products, one of which appeared as a major spot hypothesised to be the rearranged isocyanate. Addition of four equivalents of butanol to the reaction in the hope of effecting an addition to the said isocyanate to furnish the corresponding Boc-carbamate followed by a further heating of 18 hours unfortunately gave a very complicated TLC reaction profile with no real major product. Scheme 5.2 summarises the chemistry. At this point an alternative target was pursued.



77 **78** **79**

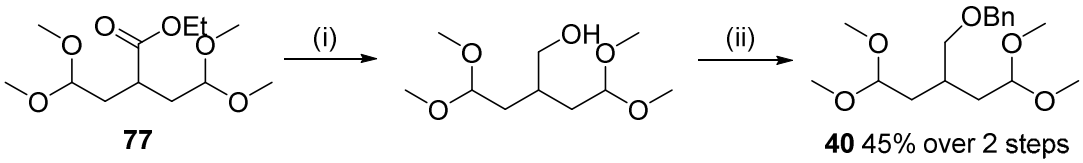
Scheme 5.2: The attempted Curtius rearrangement.

For the second derivative **80**, the idea was to α-alkylate ester **77** to generate a quaternary centre at the prochiral carbon. To this end, **77** was treated with KHMDS at -78 °C in order to generate the ester enolate, always keeping the temperature low to avoid side-reactions (such as elimination to the ketene). The reaction was then warmed up after addition of benzyl bromide (intended to provide some bulk at the prochiral centre and as a reactive S_N2 electrophile). However, no conversion of starting material was observed by TLC. Thinking that the problem was in the deprotonation step, the enolate generation was allowed to warm to room temperature before cooling and adding the electrophile. The solution was then allowed to warm to RT after adding the electrophile as before, but still no product was produced after 24 hours, with only starting material and benzyl bromide showing on TLC. The starting material was isolated after the reaction work-up and analysed by ^{1}H NMR spectroscopy to confirm this conclusion. In retrospect, alkylation with a smaller electrophile should have been carried out, but this route was also not pursued any further. Scheme 5.3 summarises the relevant chemistry.



Scheme 5.3: The attempted alkylation of **77**.

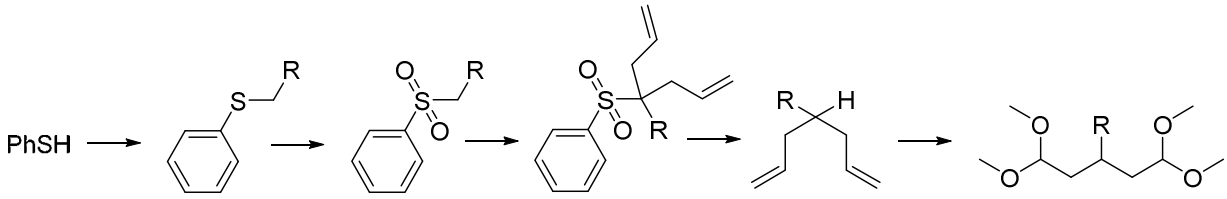
Bis-acetal **77** was nevertheless successfully transformed via reduction and subsequent benzylation as described previously to produce **40** bearing a benzyloxymethyl substituent in a 46% yield over two steps, following column chromatography (Scheme 5.4). The product gave satisfactory spectroscopic and analytical (HRMS) data.



Scheme 5.4: *Reagents and Conditions*: (i) $LiAlH_4$ (1.6 eq), THF, 4 hrs, 0 °C to RT; (ii) a) NaH (1.2 eq), THF, 1.25 hrs, 0 °C to RT, b) benzyl bromide (1.5 eq), TBAI (10 mol%), 18 hrs, RT.

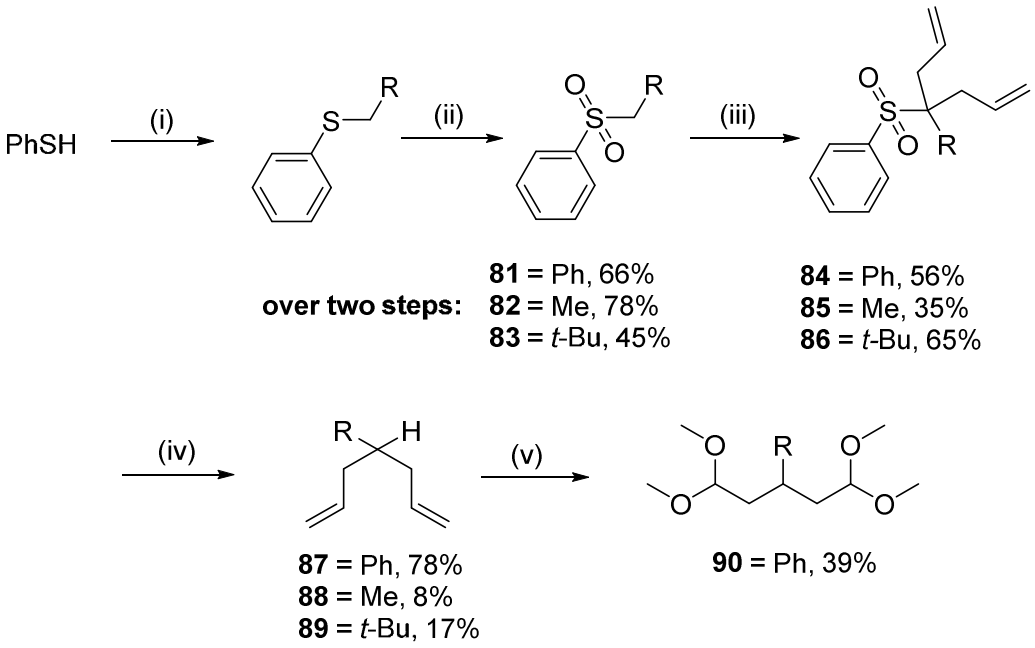
5.1.2 The Divergent Sulfone Strategy

In view of the problems just described in generating a range of derivatives bearing different substituents at the all-important central prochiral carbon, it was decided to invest time into an alternative alkylation strategy based on the α-carbanionic and reductive chemistry of sulfones. Thus, as shown in Scheme 5.5, using sulfone functionality as the pivot a divergent sequence was pursued involving thiophenol alkylation, oxidation, double allylation, reductive cleavage and ozonolysis / acetalisation. In such a way an R-group could be introduced at the prochiral carbon from an alkyl or benzyl halide, the latter providing a phenyl group at the said centre ultimately. This relatively straightforward 5-step procedure was cheap and relatively simple to carry out from readily available starting materials (thiophenol and alkyl- or benzyl halides). Three R-substituents were targeted as phenyl, methyl and *t*-butyl. Scheme 5.5 summarises the overall sequence:



Scheme 5.5: An overview of the sulfone synthetic strategy.

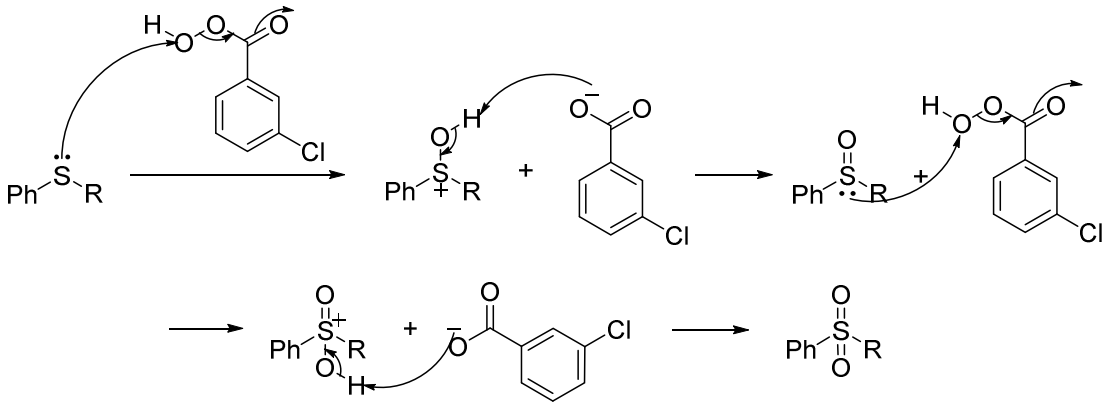
The full details are given in Scheme 5.6:



Scheme 5.6: *Reagents and Conditions*: (i) Thiophenol (1 eq), K_2CO_3 (1.1 eq), RCH_2X (X = Br or I, 1 eq), DMF, 18 hrs, RT (100 °C for R = *t*-Bu); (ii) sulfide (1 eq), *m*-CPBA (3.5 eq), DCM,18 hrs, 0 °C to RT (or CH_3CN, 50 °C); (iii) a) sulfone (1 eq), *n*-BuLi (1.1 eq), THF, 30 min, 0 °C to 66 °C, b) allyl bromide (1 eq), 1 hr, RT to 66 °C, c) *n*-BuLi (1.1 eq), 30 min, 0 °C to 66 °C, d) allyl bromide (1 eq), 1 hr, RT to reflux; (iv) diallyl sulfone (1 eq), Mg (36 eq), MeOH, 3 hrs, 50 °C; (v) O_3, MeOH, 30 min, -78 °C to RT, b) PPh_3 (2.2 eq), 2 hrs, 0 °C to RT, c) *p*-Tosic acid (20 mol%), 21 hrs, 65 °C.

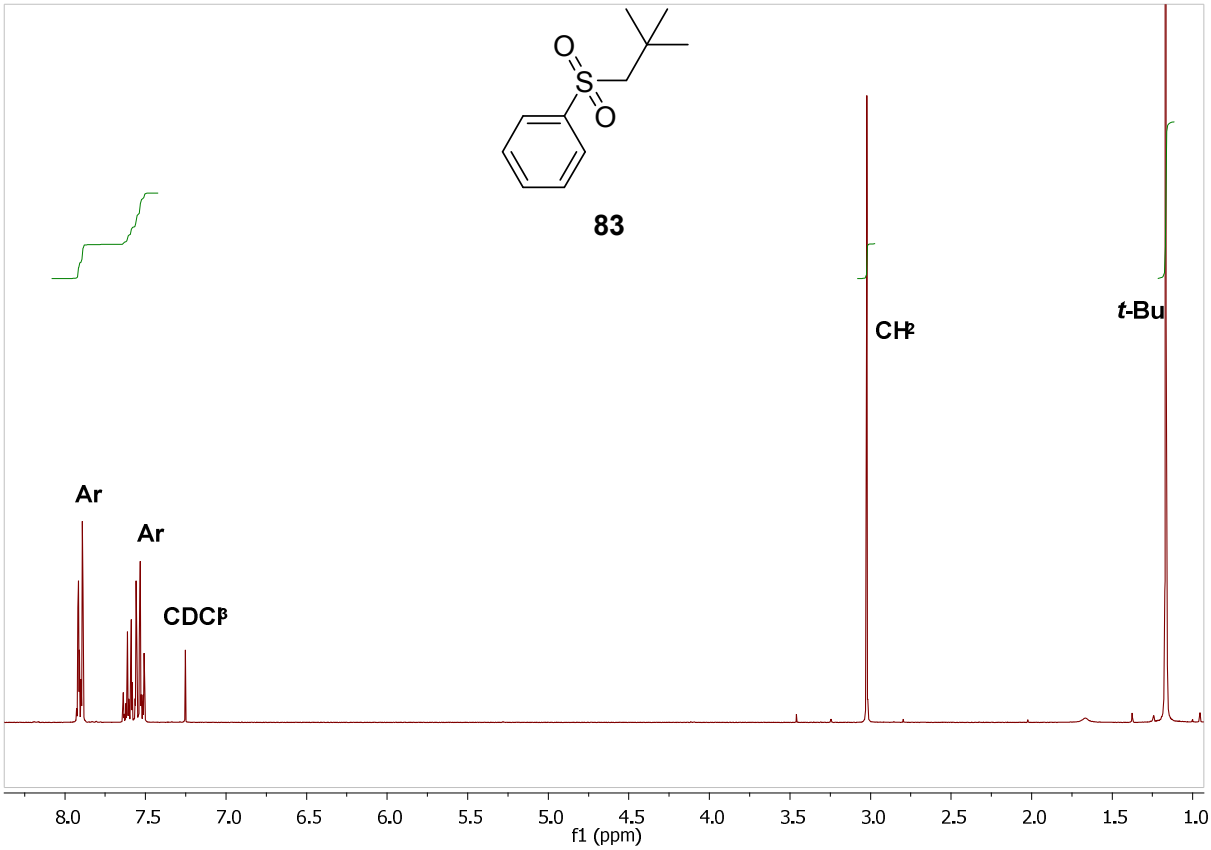
Thus, in the first step, thiophenol was alkylated with either an alkyl or benzyl halide in the presence of K_2CO_3 according to the Zhang procedure[272] to generate derivatives **81**-**83**. Reaction TLCs showed the *tert*-butyl alkylation to be particularly sluggish (due to steric hindrance), which required heating to 100 °C to achieve complete starting material conversion. The crude product in each case was then oxidised with an excess of *m*-CPBA. The reactions could be followed by TLC in which the non-polar sulfide converted first to a relatively more polar sulfoxide and then to the slightly less polar sulfone. In the case of the methyl and *t*-butyl products full conversion of the sulfoxide required overnight heating at 50 °C in acetonitrile. Column chromatographic purification gave the desired sulfones in moderate to good yields, with the methyl sulfone **82** giving the highest yield (78% over two steps). The suggested mechanism for the oxidation is illustrated in Scheme 5.7. The nucleophilic thiol attacks the more electrophilic peracid oxygen, with the resonance-stabilised carboxylate ion acting as the leaving group. Deprotonation of the

hydroxysulfonium cation yields the sulfoxide intermediate, which is followed by a second oxidation in a similar fashion.



Scheme 5.7: The suggested mechanism for sulfide oxidation to a sulfone.

Sulfones **81** and **82** are known compounds whose ^{1}H NMR data agreed with the literature.[273,274] Additional analysis techniques (^{13}C NMR and infrared spectroscopy as well as high-resolution mass spectrometry) were utilised to elucidate the structure of **83** as a new compound. Figure 5.2 shows its ^{1}H NMR and ^{13}C NMR spectra, which revealed a singlet for the methylene hydrogens confirming a sulfone since for a sulfoxide an AB pair of doublets would have been expected due to a pair of diastereotopic methylene hydrogens as a result of chirality at sulfur. Similarly, a methylene carbon resonance at 67.7 ppm was consistent with the more electron-withdrawing sulfone functionality rather than sulfoxide. Finally, the *tert*-butyl group was clearly discernible in both sets of spectra.



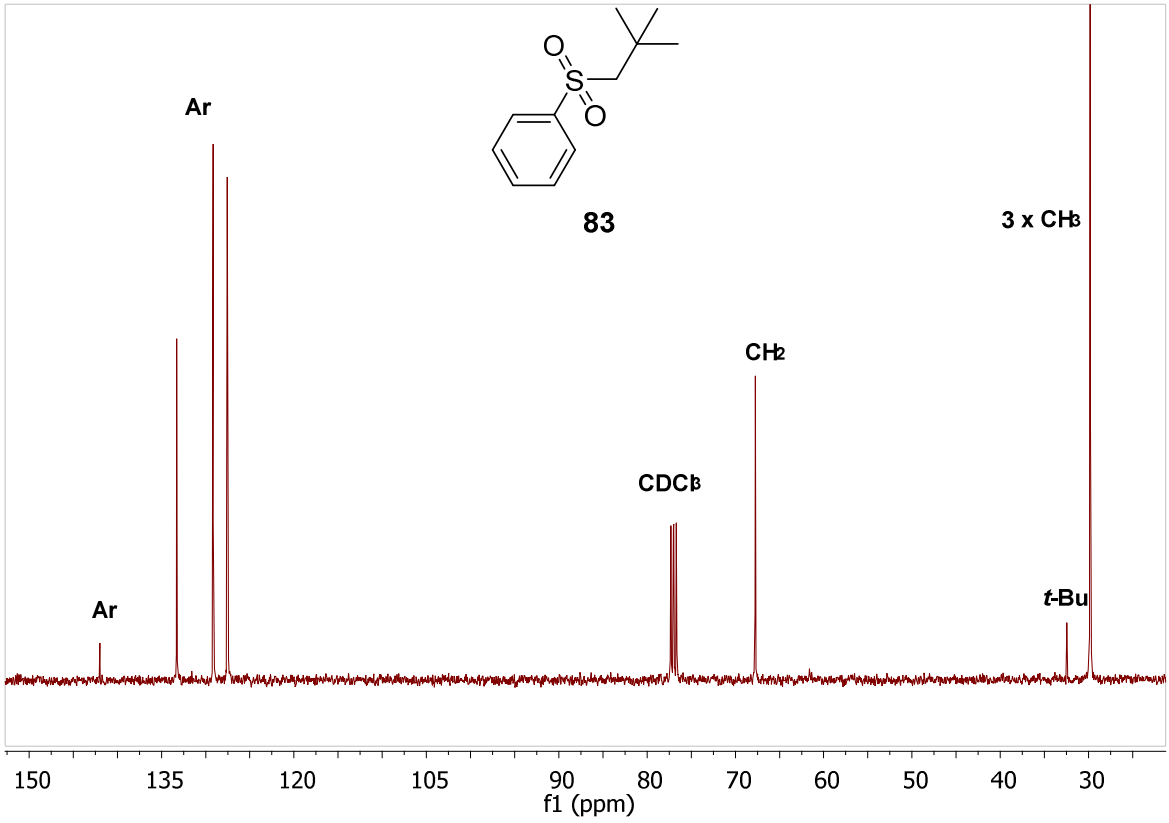


Figure 5.2: The ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75.5 MHz) spectra of **83**.

Next in this synthetic strategy was the diallylation step. Initially, phenylated derivative **81** was chosen to take through. Refluxing **81** in THF with an excess of NaH and allyl bromide (3.5 equivalents each, similar to the malonate diallylation in Scheme 5.1), unfortunately gave a very low product yield (25%) due to low starting material conversion. It was therefore postulated that the heterogeneity of the NaH medium was hampering the sulfone deprotonation, thus NaH was replaced by *n*-BuLi (1.4 M in toluene). This modification, however, didn't result in any yield improvement either, and was rationalised as due to *n*-BuLi reacting with the allyl bromide *in situ*. In order to address this, it was decided to perform the deprotonation and allylation steps separately with a minimum amount of base and allyl bromide. This involved first adding one equivalent of *n*-BuLi at 0 °C and warming the reaction to 66 °C in THF for 30 minutes in order to achieve complete deprotonation of the first acidic proton, followed by addition of one equivalent of allyl bromide at room temperature and heating to 66 °C over an hour at which time complete conversion of the sulfone to a less polar product was observed by TLC. The second allylation was achieved in the same way, with the same temperatures and times, which resulted in diallylated product **84** being isolated in an improved 56% yield following column chromatography.

The formation of highly non-polar by-products as observed on reaction TLCs during both allylation steps suggests that high yields (>75%) here were unobtainable. Application of this sequential one-pot diallylation sequence to the methyl and *t*-butyl sulfones **82** and **83** respectively resulted in yields of 35% for **85** and 65% for **86**. A highly speculative explanation for the higher *t*-butyl yield is the greater inductive electron releasing effect of the *t*-butyl, which gives rise to a more reactive carbanion (higher energy HOMO for this soft nucleophile). All three allyl sulfones are unknown compounds and were thus fully characterised using ^{1}H NMR, ^{13}C NMR and infrared spectroscopy as well as high-resolution mass spectrometry. Figure 5.3 shows the ^{1}H and ^{13}C NMR spectra obtained for **85** bearing a methyl group at the prochiral carbon. The most interesting resonances of the ^{1}H NMR spectrum are the doublet of doublet of triplets seen for the symmetrical and diastereotopic H-3/5 nuclei. This complicated multiplicity can be explained by virtue of geminal coupling with the other H-3/5 proton (J = 14.4 Hz), vicinal coupling with the H-2/6 proton (J = 6.9 Hz) and allylic coupling with the two H-1/7 protons (J = 1.2 Hz). The mirror-plane symmetry of this compound resulted in a very simple ^{13}C NMR spectrum, which displayed a deshielded quaternary C-4 at 65.2 ppm due to the sulfone inductive electron-withdrawing effect.

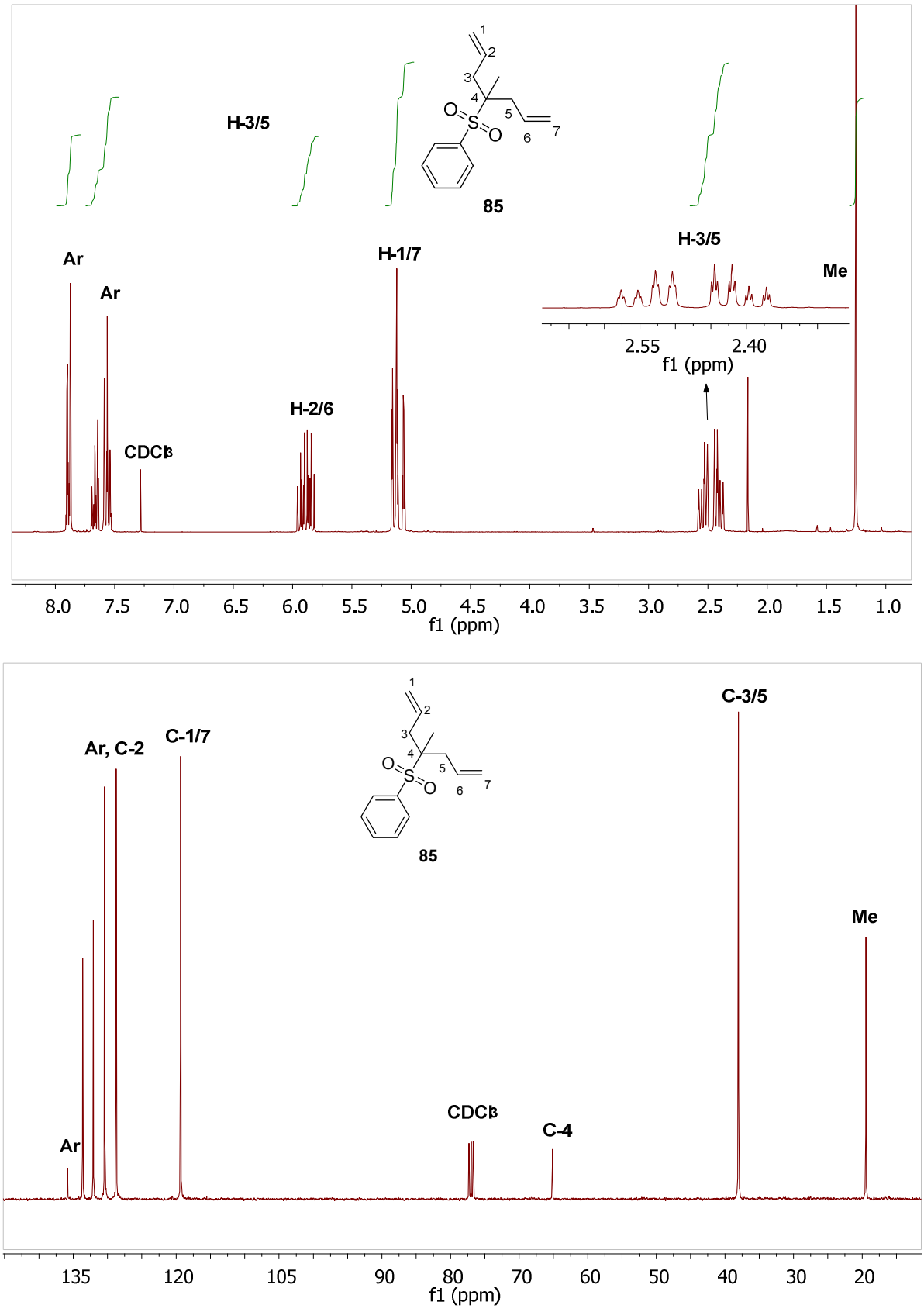
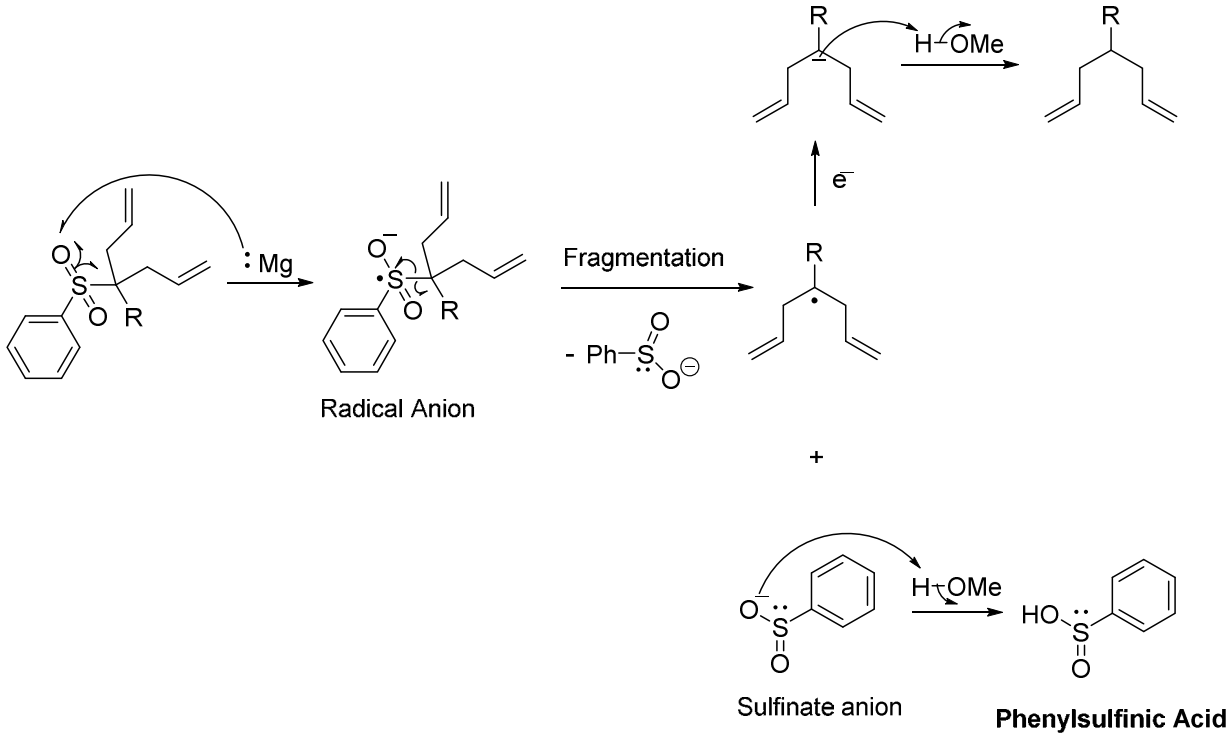


Figure 5.3: The ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75.5 MHz) spectra of bis-acetal **85**.

The penultimate step of this strategy involved cleavage of the sulfonyl moiety via reductive desulfonylation (replacement of a carbon-sulfur bond with a carbon-hydrogen bond). This was done according to Tunge's procedure[275] with activated Grignard magnesium in methanol at 50 °C. The suggested mechanism for the reaction is shown in Scheme 5.8. Single-electron transfer from magnesium to one of the sulfone oxygens generates a radical anion, which cleaves with expulsion of a stabilised phenylsulfinate ion generating the alkyl radical of the organic chain. Further electron transfer to the chain radical followed by carbanion protonation (MeOH) generates the reduced product. Of importance was the regioselective fragmentation to afford the alkyl radical in preference to the aryl radical alternative, presumably because of the partial double-bond character of the *S*-aryl bond (hence stronger) due to resonance between the ring and the sulfonyl group.



Scheme 5.8: The suggested mechanism for reductive desulfonylation.

Simple purification by filtration over a pad of silica gel gave the phenyl product **87** in a good 78% yield. The ^{1}H NMR spectrum of **87**, a known compound, agreed with the literature.[276] As Figure 5.4 shows, the expected allyl and aryl multiplets were observed with the correct integration.

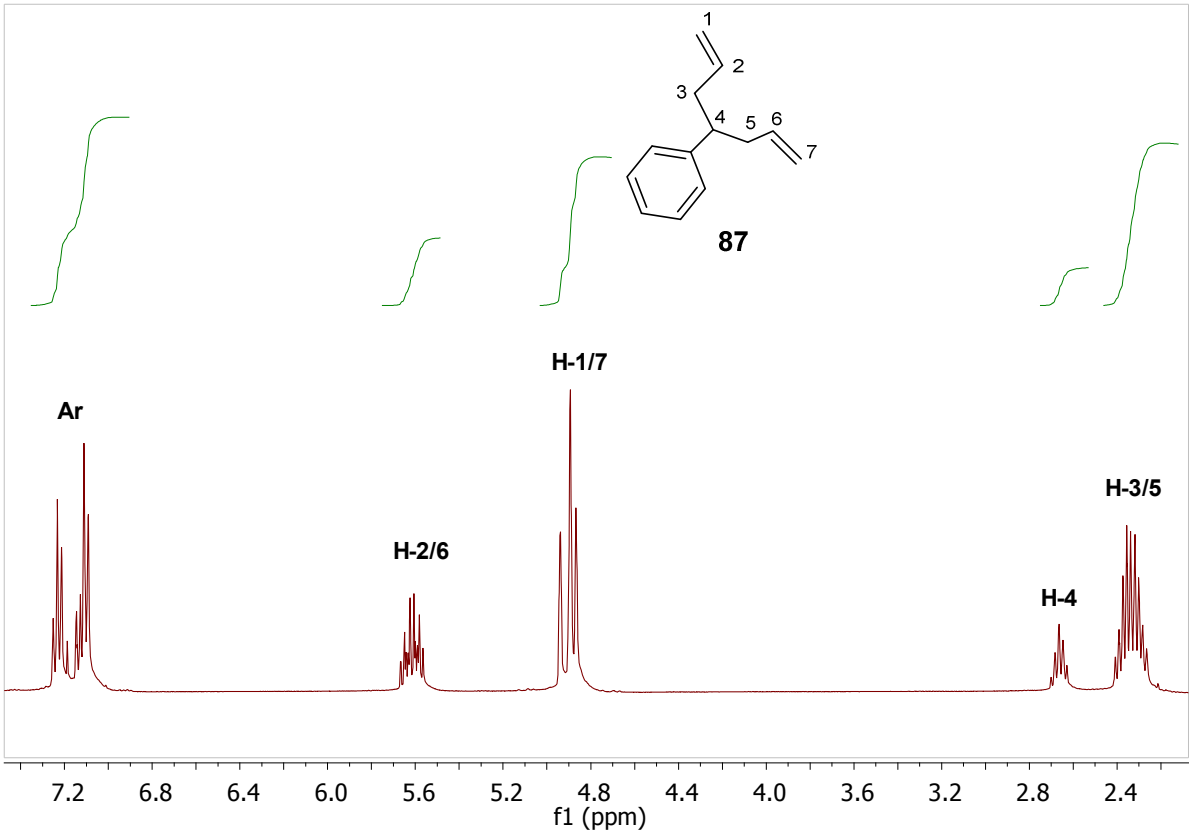


Figure 5.4: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **87**.

Unfortunately the cleavage of **85** (R = Me) and **86** (R = *t*-butyl) to give products **88** and **89** respectively gave less favourable results (8% and 18% yield, respectively). Both reactions did not give a clean reaction product and Figure 5.5 shows the *tert*-butyl case as an example. Reaction TLCs showed a number of very non-polar products which were difficult to separate from **89** (also a very nonpolar compound), even after column chromatography. The extra resonances in the downfield vinyl region suggest that the phenylsulfinic acid by-product of this reaction (Scheme 5.8) was promoting side-reactions such as allyl shifts. Thus an alternative sulfone cleavage method will need to be employed in the future in order to improve yields and purity for **88** and **89**.

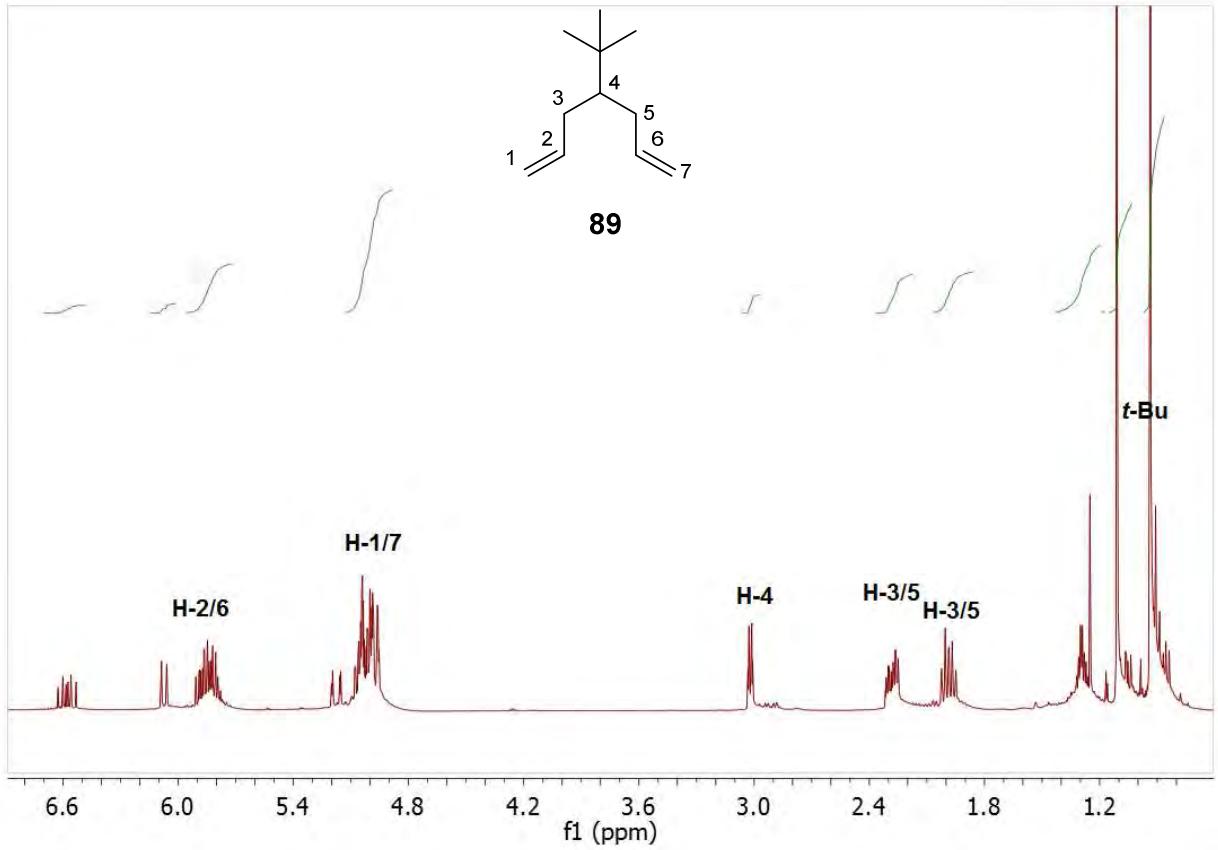


Figure 5.5: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **89**.

In spite of these issues we were gratified to have access to phenyl diallyl intermediate **87** for taking through for evaluation of the desymmetrisation methodology. Tandem ozonolysis / acetalisation of **87** yielded bis-acetal **90** in a modest 39% yield following column chromatography. Figure 5.6 displays its ^{13}C NMR spectrum, which was used, in addition to ^{1}H NMR and infrared spectroscopy together with high-resolution mass spectrometry, to characterise this new compound. The acetal methoxy and methine resonances as well as the downfield aromatic resonances provided diagnostic features in support of the assigned structure.

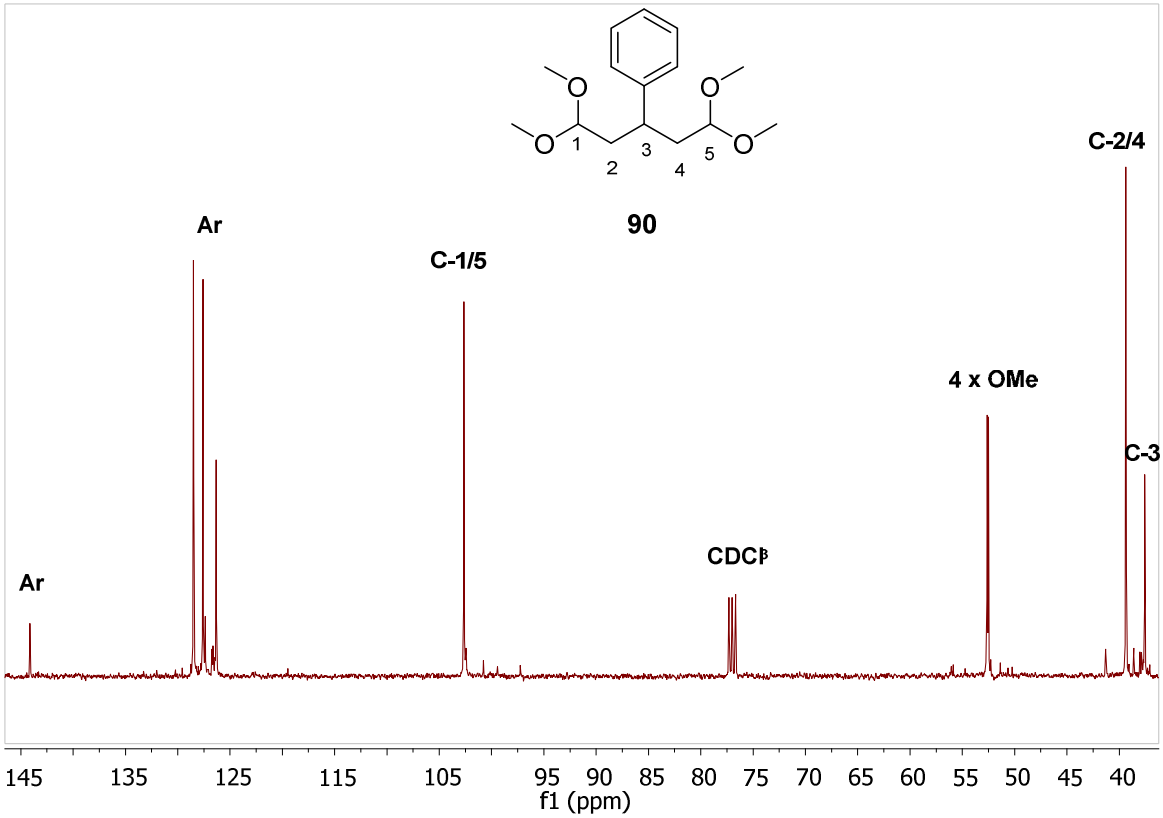
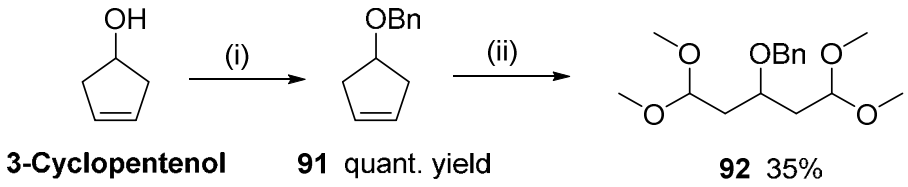


Figure 5.6: The ^{13}C NMR spectrum ($CDCl_3$, 75.5 MHz) of **90**.

5.1.3 The Cyclopentenyl Strategy

This was the simplest strategy of all since it involved direct tandem ozonolysis / acetalisation of a commercially available symmetrical 4-substituted cyclopentene. However, there wasn't a wide range of commercially available options, which were in any case expensive and in which 3-cyclopentenol turned out to be the cheapest one. The conversion of this to the desired bis-acetal **92** is shown in Scheme 5.9 below.



Scheme 5.9: *Reagents and Conditions*: (i) a) NaH (1.2 eq), THF, 1.25 hrs, 0 °C to RT, b) benzyl bromide (1.5 eq), TBAI (10 mol%), 19 hrs, 66 °C; (ii) a) O_3, MeOH, 30 min, -78 °C to 0 °C, b) PPh_3 (2.2 eq), 2 hrs, 0 °C to RT, c) *p*-Tosic acid (20 mol%), 43 hrs, 65 °C.

Benzyl protection of 3-cyclopentenol with benzyl bromide was conducted to prevent the hydroxyl group from competing as the nucleophile later in the envisaged bis-acetal α-

amination reaction. This benzylation reaction was conducted under the same conditions as in earlier reactions (e.g. Scheme 5.1) using a slight excess of NaH and benzyl bromide and a catalytic amount of TBAI to improve the electrophilicity of the benzyl bromide by converting it to benzyl iodide (C-I bond is longer and weaker). This gave **91** happily in quantitative yield. Figure 5.7 shows the ^{1}H NMR spectrum obtained for **91**, which agreed with the literature.[277] The most prominent resonances were the downfield H-1; benzyl methylene; and the vinyl H-3/4 resonances. This spectrum also clearly reflects the mirror-plane symmetry of this compound.

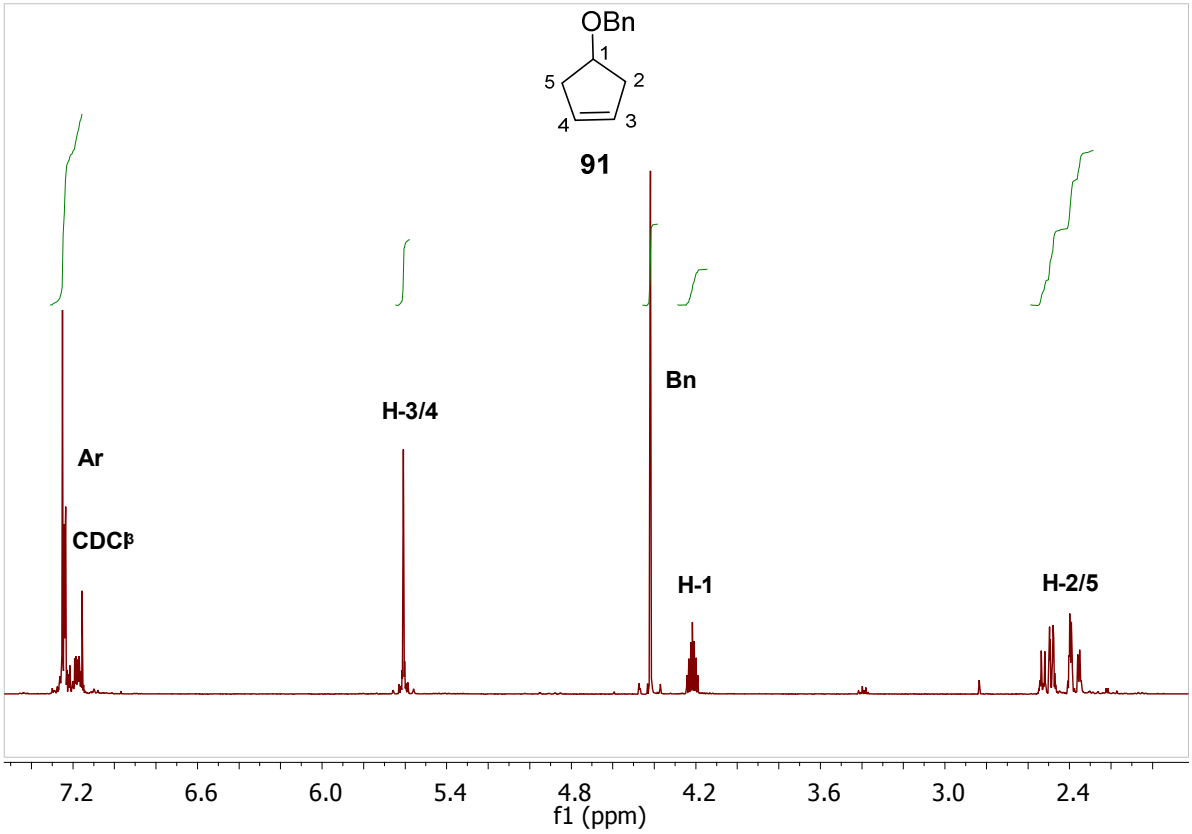


Figure 5.7: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **91**.

Tandem ozonolysis / acetalisation of **91** gave bis-acetal **92** in 35% yield following column chromatography, a yield similar to most of the other bis-acetals. The ^{13}C NMR spectrum of **92**, a new compound, is shown below in Figure 5.8. It clearly shows the acetal-related resonances (two methoxy resonances representing two sets of diastereotopic methoxy carbons, and the very downfield C-1/5 methine resonance) as well as OBn-related resonances in the aliphatic and aromatic regions. As expected, the central C-3 nucleus was deshielded by the adjacent oxygen and thus had a 71.4 ppm chemical shift.

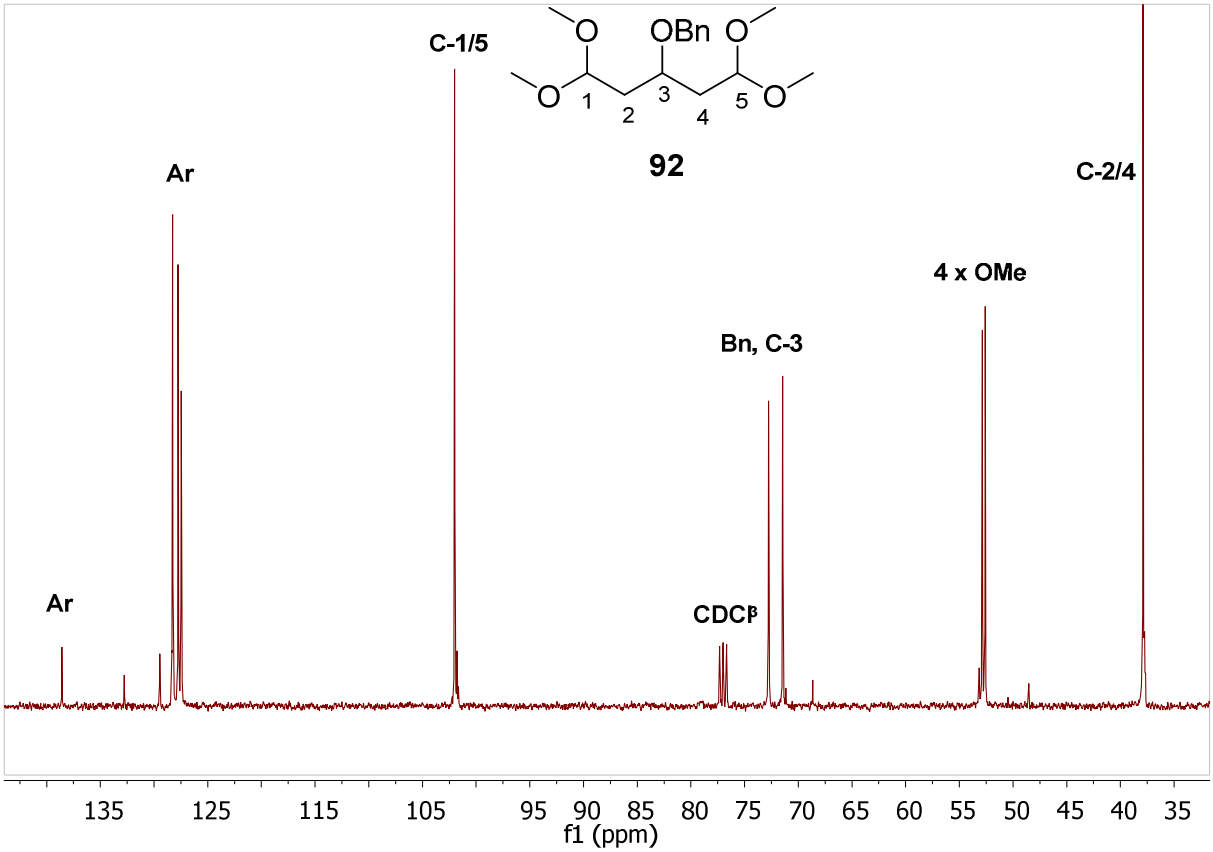
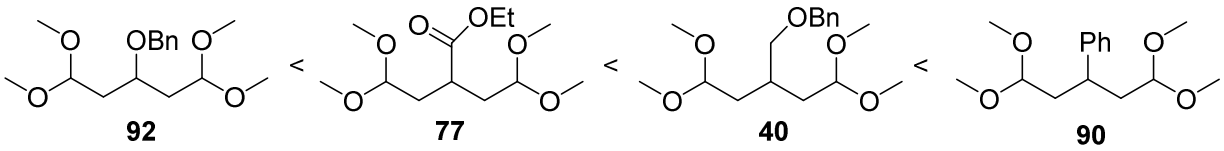


Figure 5.8: The ^{13}C NMR spectrum ($CDCl_3$, 75.5 MHz) of **92**.

Thus, four symmetrical bis-acetals were synthesised using three different strategies. Scheme 5.10 shows these compounds in order of increasing steric bulk on the central carbon according to R group A-values. This range of substrates was thus seen as suitable for testing our desymmetrisation hypothesis.

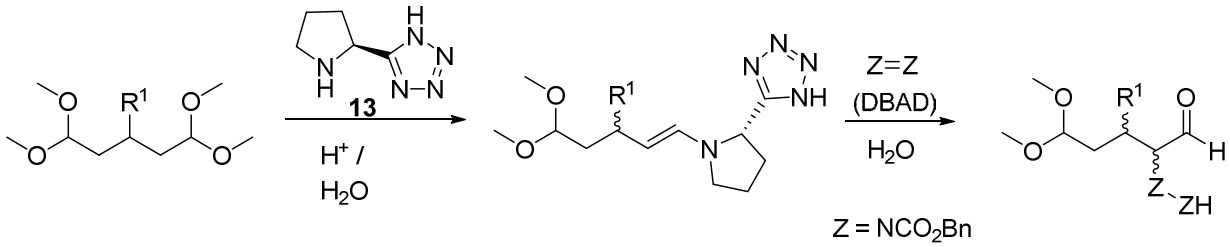


Scheme 5.10: The synthesised bis-acetals in order of increasing steric bulk on the central carbon.

5.2 The Desymmetrisation Reaction

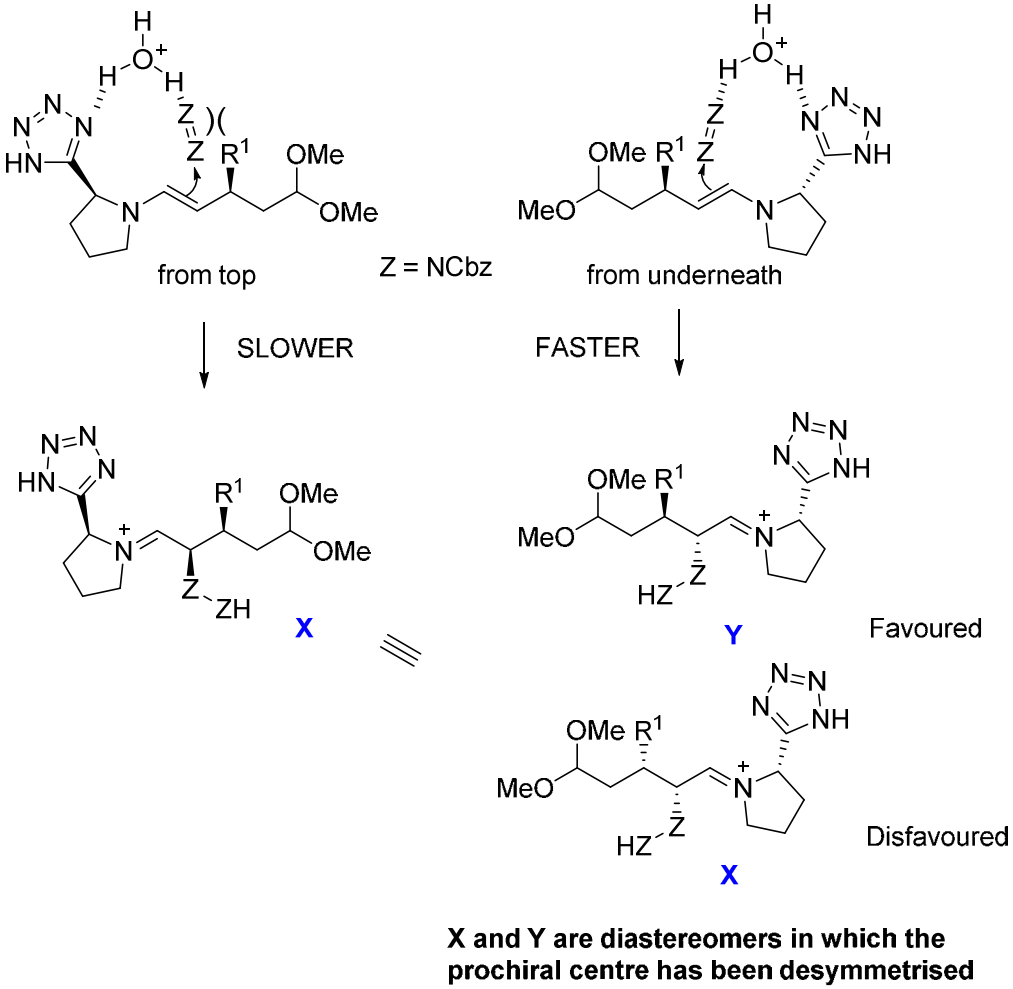
With a small library of bis-acetals in hand, it was finally time to perform the desymmetrisation reaction (Scheme 5.11). The reaction was hoped to proceed in the same way as in the acetal model study where an enamine generated from the bis-acetal and organocatalyst **13**

nucleophilically adds to DBAD to give the desymmetrised aminated product following enamine hydrolysis.



Scheme 5.11: The bis-acetal desymmetrisation

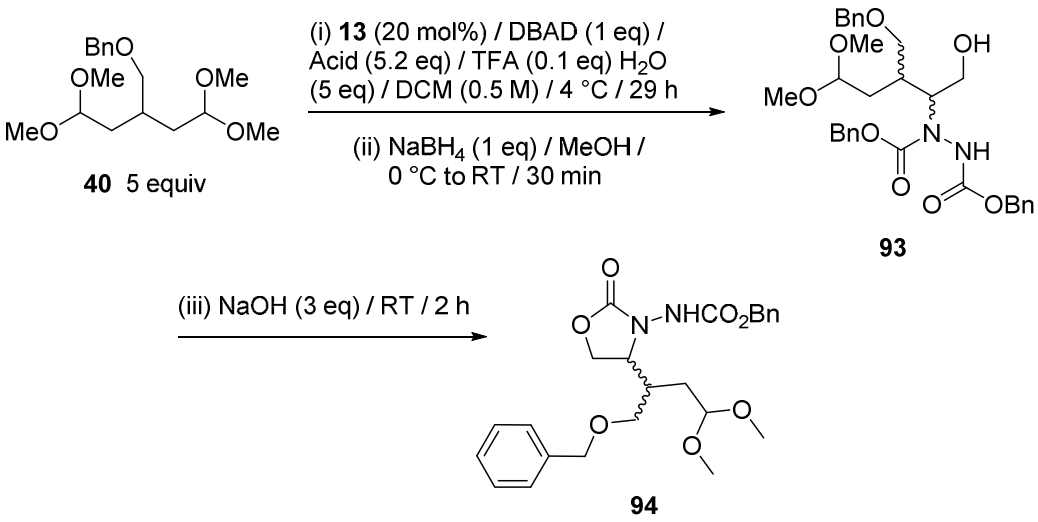
Once again, in developing a model to accommodate stereoselectivity aspects, for simplicity's sake only one of the (equivalent) substrate forms (with the R^1-group at the prochiral centre wedged) will be considered, in which the two enamines formed on the left or the right enantiotopic arms of the symmetrical substrate are illustrated (Scheme 5.12). The success of the 1,1,6,6-tetramethoxyhexane (TMH) amination in the model study confirmed that it was possible to generate a mono-enamine. Furthermore, the mechanistic discussions in Chapter 3 showed that the mono-enamine here would likely have an *E*-s-*trans* geometry. The two enamines generated are diastereomers (shown in Scheme 5.12) and expected to be very similar in energy (but not equal), and as such they would both be present in approximately equal amounts. Owing to the hydrogen bonding network on the enamine *re*-face (syn to the chiral centre), enamine addition to the electrophile would be favoured as *syn*. This leads to the conclusion that addition to the right-hand enantiotopic arm to give **Y** with *anti*- relative stereochemistry would be kinetically favoured over that involving the left to give **X** with *syn*-relative stereochemistry as a result of anticipated lower non-bonded interactions between the hydrogen-bonded electrophile and the R^1-group at the prochiral centre. Thus the bis-acetal desymmetrisation would be achieved in an enantioselective fashion regarding the discrimination of the enantiotopic arms, as well as with an *anti*-diastereoselectivity. A chemoselectivity was also anticipated (already shown in the model reaction with TMH) by using excess substrate in which α-amination was expected to occur on one acetal group whilst leaving the other intact. Thus a chemo-, and diastereoselective desymmetrisation to produce an enantioenriched product was hoped for.



Scheme 5.12: Kinetic evaluation of the stereoselectivity in the bis-acetal α-amination.

In testing this hypothesis in the laboratory, the knowledge gained from the extensive model study in Chapter 3 was expected to help considerably. Bis-acetal **40** was the first substrate chosen as it was available in good amount and also had reasonable steric bulk to test out the model. In carrying out the desymmetrisation reaction (as shown in Scheme 5.13) a few challenges were anticipated such as difficulties in isolating the product as separate diastereomers, as well as obtaining good ^{1}H and ^{13}C NMR spectra in view of the greater conformational complexity in the desymmetrised products. Nevertheless, reaction conditions were chosen based on the optimised conditions from the tetramethoxyhexane (TMH) model study (Scheme 5.13). As with TMH a reasonably large excess of substrate was used (5 equiv) to maximise mono-amination. The reaction was carried out in DCM (0.5 M) at 4 °C with tetrazole catalyst **13** (20 mol%), MCA and TFA (5.2 and 0.1 eq, respectively) and 5 equivalents of water. Thus a high DBAD:acid ratio was maintained in order to ensure good "enantioselectivity. The amination was complete as judged by consumption of DBAD on TLC within 29 hrs. This was 22 hours longer than the corresponding TMH reaction, and attributed to the greater steric hindrance due to the substituent at the prochiral centre close by.

Following column chromatography hydrazino alcohol **93** was isolated in 35% yield as a mixture of diastereomers (although TLC analysis did suggest that separation of the diastereomers was possible by preparative TLC). Subsequent careful HPLC studies revealed a dr of about 3:2. This low yield (40% lower than the TMH reaction) was attributed to minor by-products associated with bis-acetal hydrolysis however, it was possible to recover about 50% of the excess bis-acetal starting material through column chromatography. ^{1}H NMR analysis revealed that the hydrazino alcohol **93** (even after separation as a single diastereomer) gave a highly complex set of resonances due to hydrazide conformers, thus it was decided to characterise the desymmetrisation products as oxazolidinones, which was easily achieved at room temperature using NaOH in methanol, Scheme 5.13. Consequently, the 3-step sequence to oxazolidinone hydrazides was conducted in one pot (as in Chapter 4) in all future cases.



Scheme 5.13: The desymmetrisation of bis-acetal **40**.

Through careful flash column chromatography and preparative TLC it was possible to separate the diastereomers of oxazolidinone **94**. The ^{1}H NMR spectrum of the major diastereomer of **94** is shown below in Figure 5.9. Similar to the oxazolidinones described in Chapter 4, the spectrum was far more resolved than that of alcohol **93** and the oxazolidinone resonances followed the chemical shift order H-5_1 > H-4 ≥ H-5_2. The H-4' and the Cbz benzyl methylene resonances had a similar chemical shift, resulting in a complex 4.00 – 4.50 ppm region, although the AB system for the benzyl ether diastereotopic methylene protons could clearly be seen. Finally, the presence of only one acetal functionality was confirmed by two diastereotopic methoxy singlets (in very close proximity) integrating for 6H. In support of these assignments, the ^{13}C NMR spectrum displayed the oxazolidinone ring resonances, which appeared in the expected chemical shift order C-5 > C-4. In the same region, the

benzyl ether and Cbz benzyl resonances were also visible. The presence of an acetal group was confirmed by the highly deshielded acetal carbon resonance (105 ppm), as well as the two methoxy resonances (which in this case overlapped). This new compound was characterised using ^{1}H NMR, ^{13}C NMR and infrared spectroscopies in addition to high-resolution mass spectrometry as it was an oil. Furthermore the infrared spectrum was very helpful in confirming the presence of two carbonyl groups – C-2 and the Cbz carbonyl at 1775 and 1716 cm^{-1} respectively.

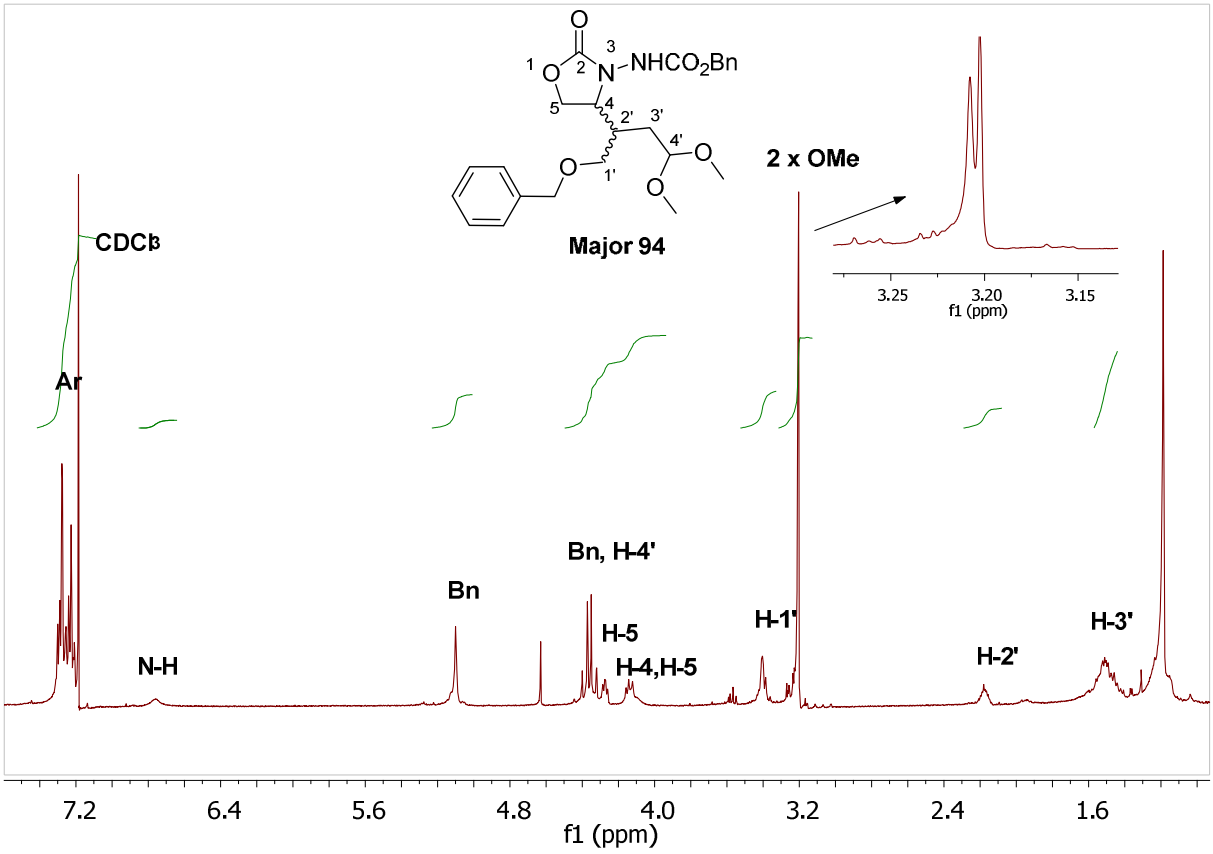
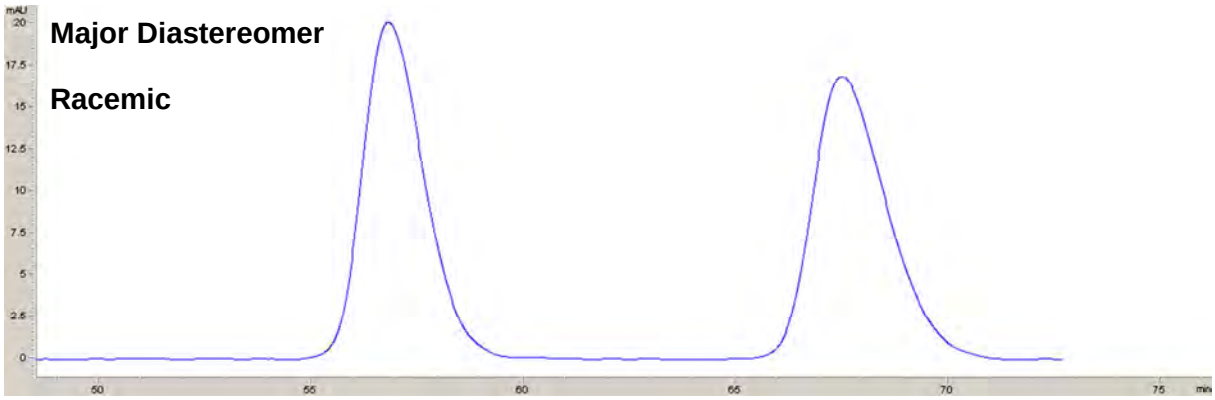


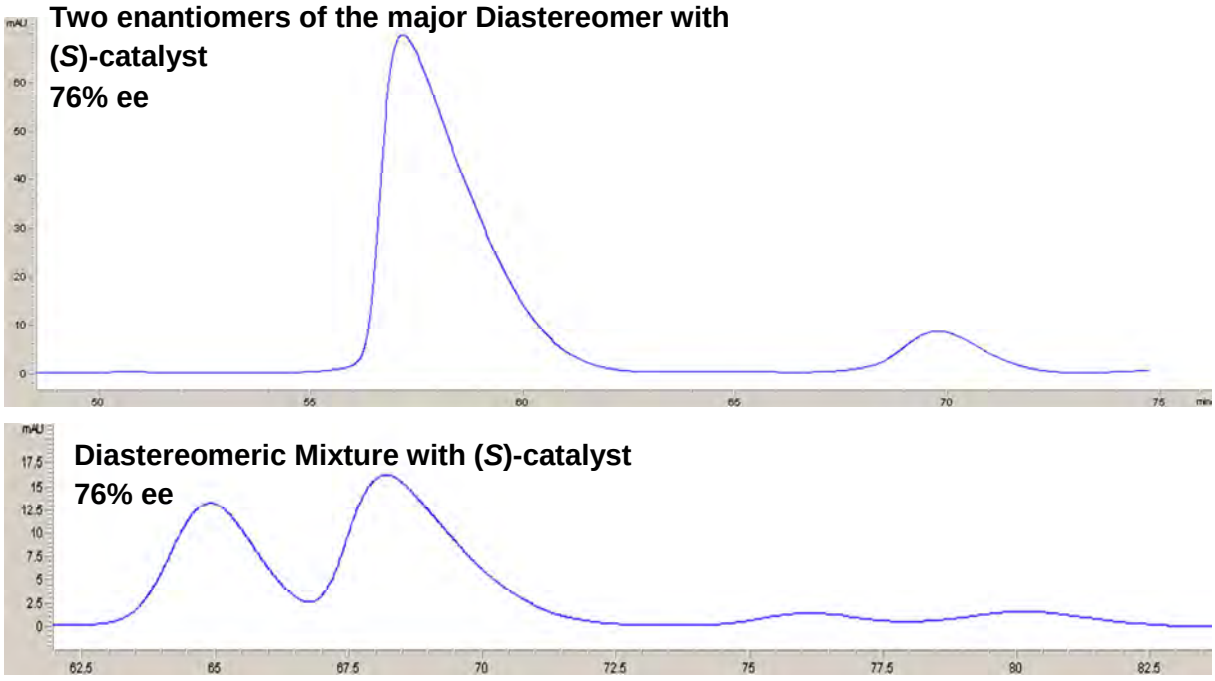
Figure 5.9: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **94**.

The ees and drs were once again determined using chiral HPLC. Figure 5.10 shows the HPLC results obtained when using a Chiralpak AD column. The chromatogram of the major diastereomer for the racemic reaction (carried out with DL-Proline) is shown first. This was compared with the chromatogram of the same diastereomer from the chiral reaction and the ee was determined to be 76% (88:12) based on the peak area ratio between the two peaks. HPLC analysis of the minor diastereomer also gave the same ee value of 76%. This ee was good, but lower than that from the TMH model reaction (88% as 94:6) under the same conditions which was attributed to the longer reaction time. Nevertheless, the good ee demonstrated that the bisacetal desymmetrisation could in fact be achieved with a fair

degree of enantioselectively. We expected the diastereomeric mixture of **94** to separate into four distinct peaks (representing the major and minor enantiomers from each diastereomer according to the 2^n stereogenicity rule). Unfortunately the AD column did not give good separation of the diastereomeric mix (Figure 5.10, third chromatogram). However, the Chiralpak OD column was more effective at separating the diastereomers (although the minor enantiomers of each diastereomer co-eluted, see later in Figure 5.11). Thus the dr was determined as 60:40 and happily, the ee values were consistent with those given by the AD column. This was certainly a lower dr than we had hoped given our desymmetrisation hypothesis thus an optimisation study was embarked on to try to improve both yield and diastereoselectivity.



* Chiralpak AD column, 10% *i*-Pr in *n*-hexane, 258 nm and 0.5 ml/min



* Chiralpak AD column, 10% *i*-Pr in *n*-hexane, 258 nm and 0.4 ml/min

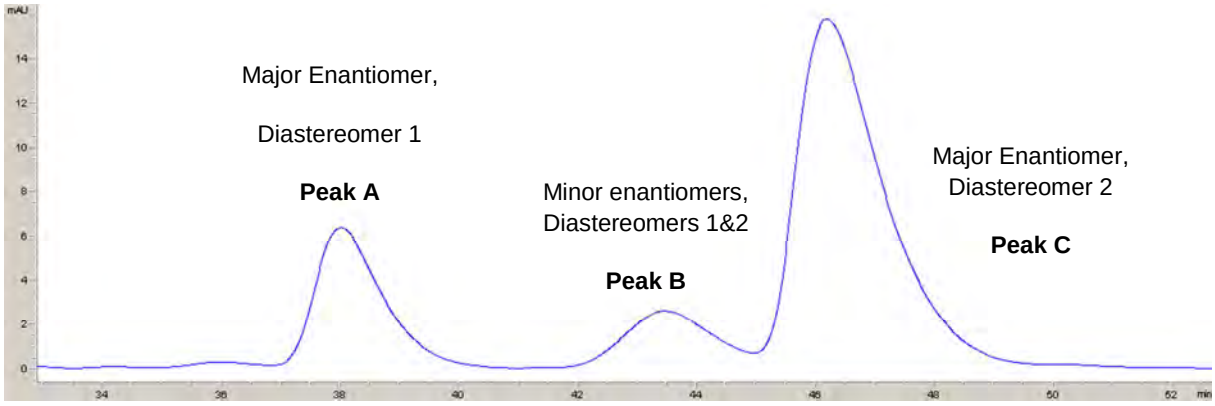
Figure 5.10: The racemic and chiral HPLC chromatograms of **94** given by the AD column.

In order to try to improve the modest yield and diastereoselectivity, the reaction conditions were revisited. Table 5.1 below shows the results obtained for oxazolidinone **94** in the brief optimisation study conducted. From the exhaustive studies presented in Chapter 3 it was known that the DBAD, acid and water equivalents were at optimal levels in order to ensure high enantioselectivity. Therefore, solvent amount (concentration) and temperature were the only remaining parameters that could be manipulated whilst minimising chances of compromising the enantioselectivity. The temperature could be lowered (perhaps to -22 °C as in the aza-Michael model in Chapter 2), however this would have increased the reaction time significantly with the risk of product racemisation. Thus dilution was judged as the best option to focus on, hoping that the more dilute medium would decrease the bis-acetal by-products and improve the reaction yield. Dilution had also been shown to improve enantioselectivity in Chapter 3 (Table 3.3). The results of this optimisation study are displayed in Table 5.1.

Entry	DCM (M)	H_2O (eq)	MCA (eq)	Time	Temp (^{0}C)	Yield (%)	ee (%)	dr
1	0.5	5	5.2 + 0.1 eq TFA	29 hrs	4	35	76	6:4
2	0.1	5	5.2 + 0.1 eq TFA	3 d	4	40	78	6:4
3	0.05	5	5.2 + 0.1 eq TFA	3 d	4	61	80	74:26

Table 5.1: Desymmetrisation of bis-acetal **40**.

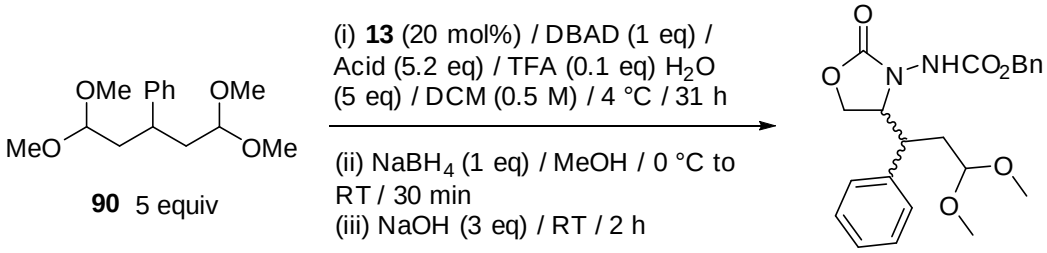
Entry 1 shows the baseline case with a 0.5 M concentration and 35% yield. Entries 2 and 3 show the positive effect of diluting the medium to 0.1 and 0.05 M, respectively. As expected, this led to a lower rate (3 days for both reactions). The best results were obtained at a 0.05 M concentration to give a 61% yield, 80% ee (for both separated diastereomers) and 7:3 dr. Figure 5.11 shows the HPLC chromatogram of a diastereomeric mixture from this 0.05 M reaction), using the Chiralpak OD column. With this data the enantioselectivity of the diastereomers could only be determined as an average based on the peak-area ratio between the sum of the major enantiomers and the minor enantiomer mixture [(A+C) : B]. This was calculated to be 90:10, to give an 80% ee. The dr was determined using the peak area ratio between the major enantiomer of each diastereomer (C : A) to give a dr of 74:26. Perhaps diluting the reaction even further would have yielded a better diastereoselectivity, however this would have slowed things down too much. The absolute configuration was not determined, but from the acetal model study results it was expected that the aminated centre would have an (*R*)- configuration. Therefore, an *anti*-diastereoselectivity would translate to an (*S*)- configuration in the major diastereomer at the prochiral centre C-3.



* Chiralpak OD column, 10% *i*-Pr in *n*-hexane, 258 nm and 0.4 ml/min

Figure 5.11: The HPLC chromatogram of the diastereomeric mixture of **94** using the OD column.

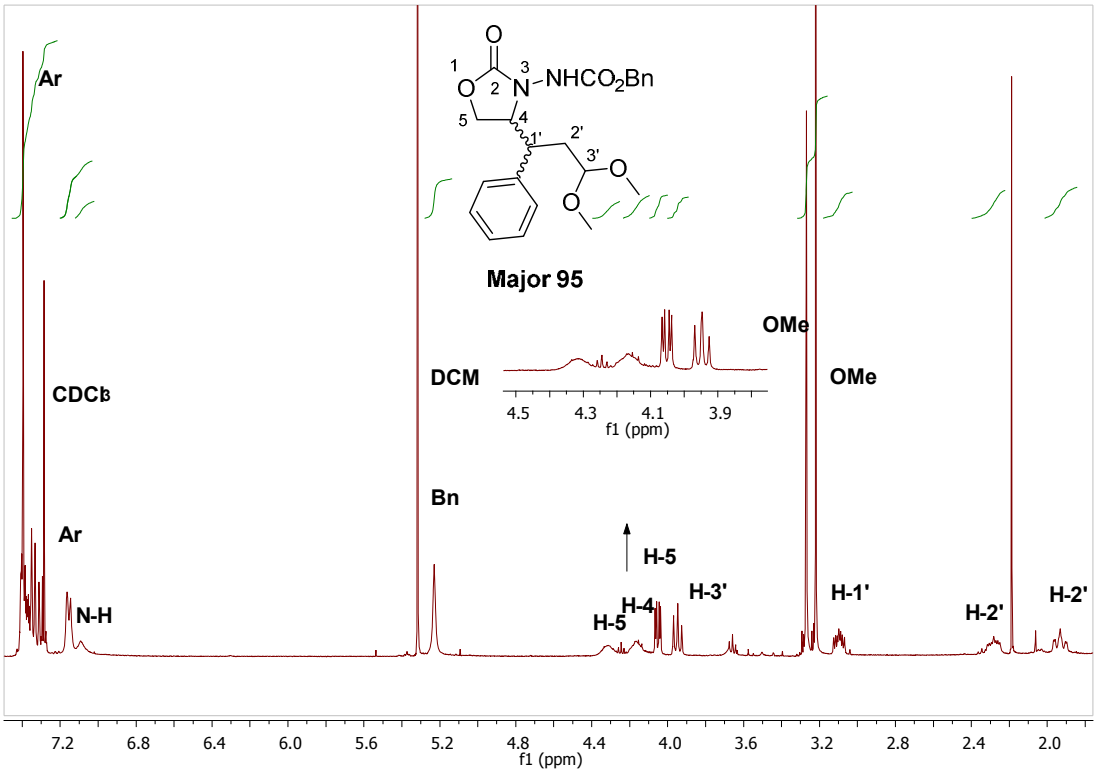
As further support of proof of concept, the desymmetrisation was also performed on bis-acetal **90** bearing a phenyl group at the prochiral centre. Because phenyl has a higher A-value than a benzyloxymethyl ether group, it was hoped this would improve the diastereoselectivity by ensuring better facial discrimination in the transition-state. As shown in Scheme 5.14, the reaction was first carried out according to the baseline conditions for **40** with the concentrated 0.5 M medium. The amination step was complete after 31 hours as judged by TLC, and following $NaBH_4$ reduction, NaOH cyclisation and column chromatography gave oxazolidinone **95** as a mixture of diastereomers in a good 70% yield. This higher yield (as well as the cleaner TLC reaction profile) suggested that this bis-acetal was more robust towards the acidic medium and thus less prone to side-reactions.



Scheme 5.14: The desymmetrisation of bis-acetal **90**.

Preparative TLC was used to separate the diastereomers of oxazolidinone **95**, although this proved more difficult than for **94**. Compound **95** was also a new compound, an oil, which was characterised using ^{1}H NMR, ^{13}C NMR and infrared spectroscopies together with high-resolution mass spectrometry. Once again, the infrared spectrum was helpful in confirming the structure by showing two carbonyl resonances at 1778 and 1718 cm^{-1}. Figure 5.12

shows the ^{1}H NMR and ^{13}C NMR spectra of the major diastereomer of **95**. Similar to the ^{1}H NMR spectrum for **94**, all the expected resonances were observed in which once again the oxazolidinone resonances appeared in the chemical shift order H-5_1 > H-4 > H-5_2 and in the same downfield region as the H-3' triplet. Notably, H-1' (H-2' in **94**) of the chain α-to the oxazolidinone ring was now more deshielded by the adjacent phenyl, appearing at 3.10 ppm compared to 2.26 ppm in **94** (Figure 5.9). Furthermore two separated diastereotopic methoxy singlets integrating for 6H could be readily observed. The oxazolidinone ^{13}C resonances in the ^{13}C NMR spectrum appeared in the chemical shift order C-5 > C-4 in the expected region. The two diastereotopic methoxy resonances, C-3' (as expected at 102.7 ppm) and aromatic resonances from the phenyl and benzyl functional groups were also observed. The deshielding of the phenyl group at C-1' (benzylic) was confirmed in the ^{13}C NMR spectrum by the higher chemical shift (44.8 ppm versus 31.2 ppm for C-2' in **94**).



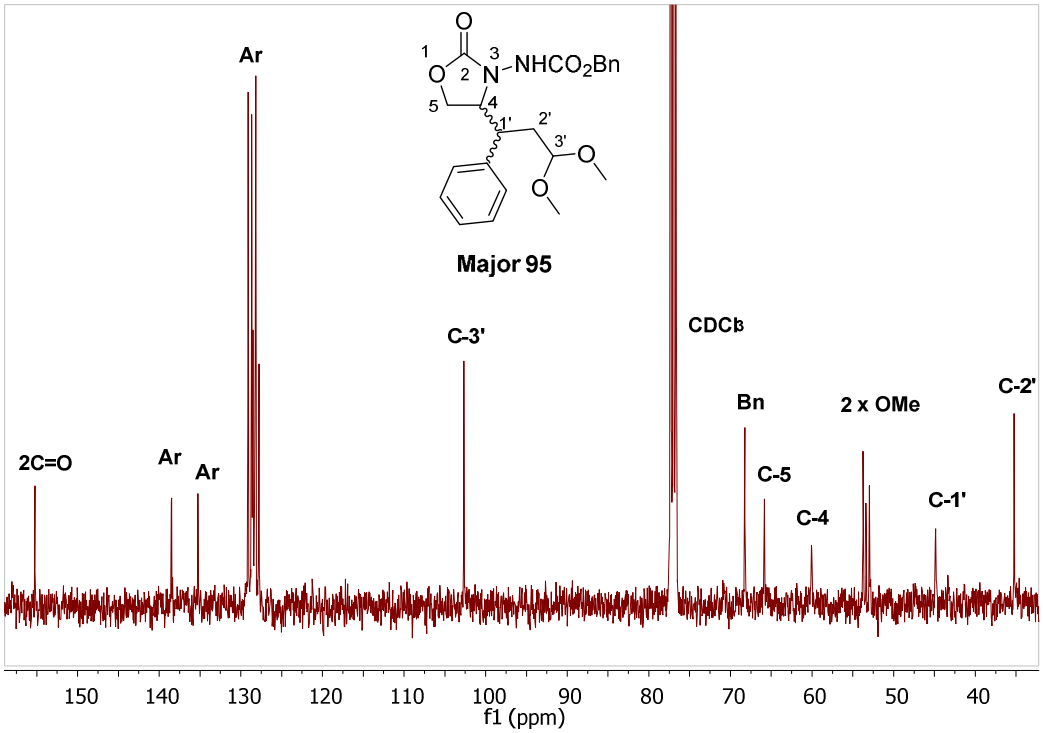
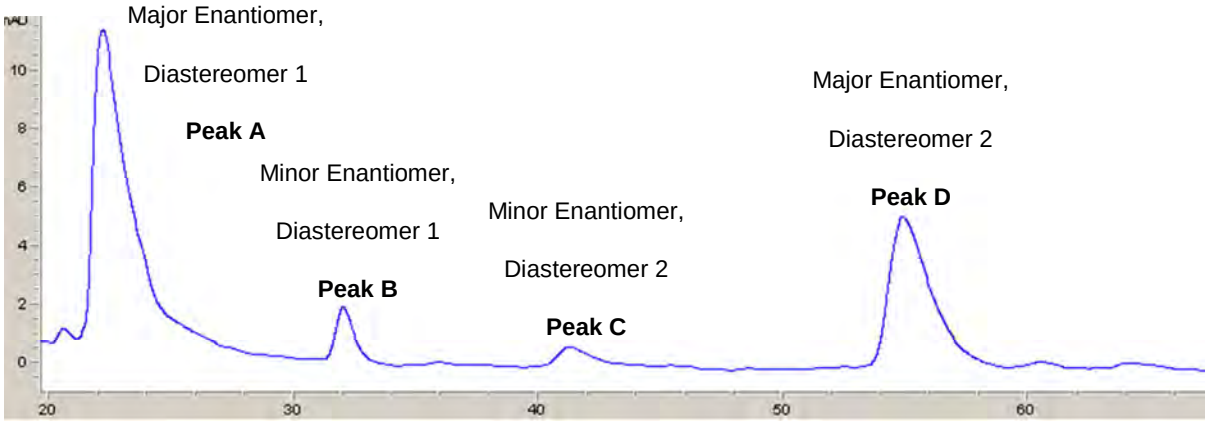


Figure 5.12: The ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75.5 MHz) spectra of **95**.

In order to determine the ee and dr of this reaction, HPLC analysis of the diastereomeric mixture of **95** was carried out using the same Chiralpak OD column as for **94**. Figure 5.13 displays the HPLC chromatogram obtained, which illustrates how well the OD column separated the diastereomers of **95,** with the four expected peaks appearing separately The enantioselectivity was determined by calculating the peak area ratio A : B giving 88 : 12 (76% ee) which was consistent with the value obtained from the second diastereomer (D : C). This was a good result, consistent with that of **94** and showed that phenyl substitution did not compromise enantioselectivity (although it didn't enhance it either). The diastereoselectivity was determined by calculating the ratio A : D which gave 68:32. This dr value was confirmed by calculating the ratio B : C, which gave a consistent value. This was only slightly better than the dr from **94** under the same reaction conditions. In other words, changing the benzyl ether to a more bulky phenyl substituent did not result in much of a diastereoselectivity improvement. Thus the next step was to see whether dilution of the reaction would improve the diastereoselectivity.



Chiralpak OD column, 10% *i*-Pr in *n*-hexane, 258 nm and 0.4 ml/min

Figure 5.13: The HPLC chromatogram of the diastereomeric mixture of **95**.

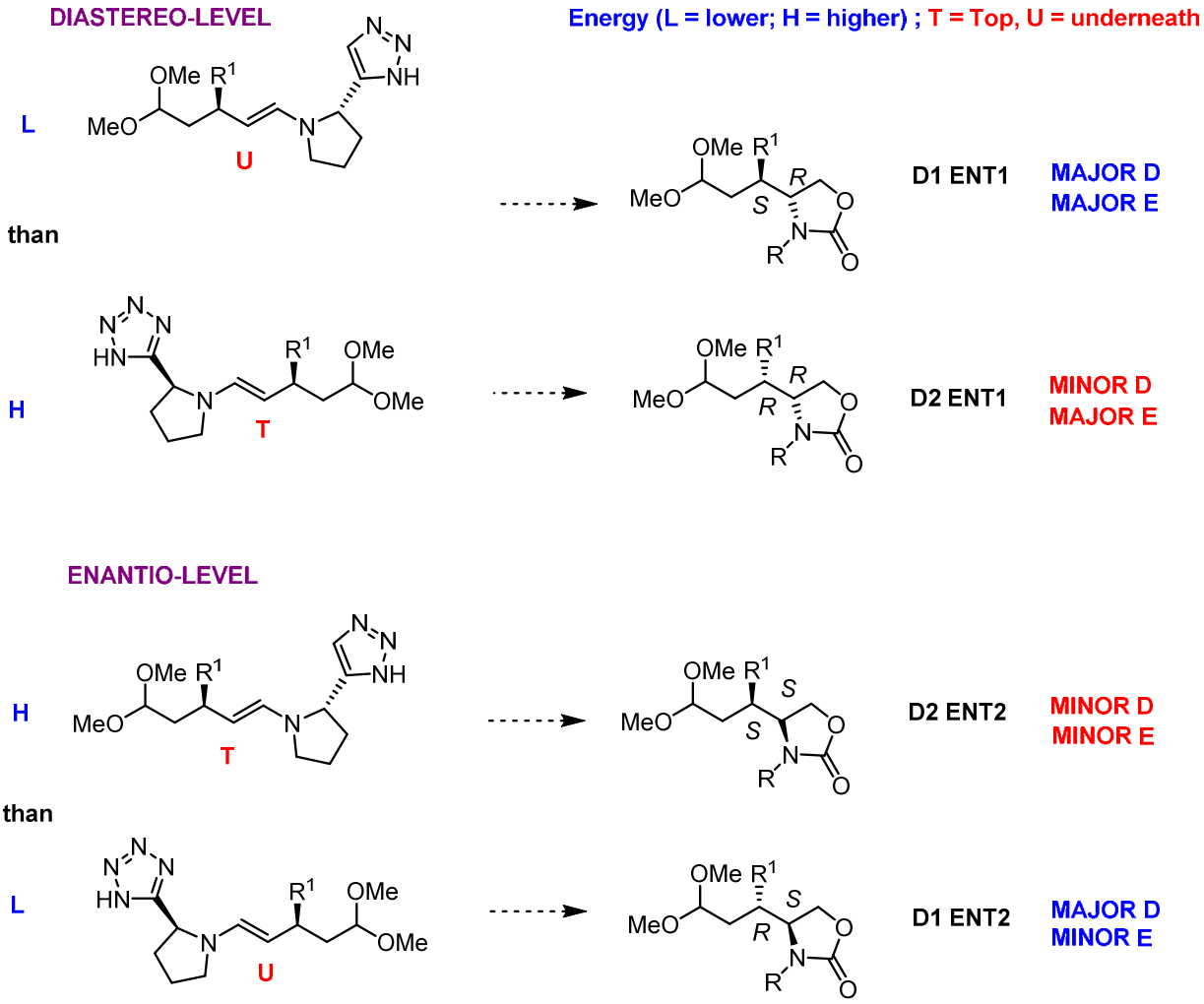
As discussed, the 0.5 M medium gave **95** in a good yield, high ee and low dr (Table 5.2, entry 1). In an effort to improve the diastereoselectivity the reaction medium was diluted to 0.1 M (entry 2). This dilution gave too long a reaction time - after 14 days approximately only a 50 % conversion (based on TLC) of **90** was achieved so no yield was ascertained. Thus the dr from the 0.5 M reaction suggests that the phenyl substituent exerted a modest steric influence in the stereoinduction step.

Entry	DCM (M)	H_2O (eq)	MCA (eq)	Time	Temp (^{0}C)	Yield (%)	ee (%)	dr
1	0.5	5	5.2 + 0.1 eq TFA	31 hrs	4	70	76	68:32
2	0.1	5	5.2 + 0.1 eq TFA	14 d	4	- (57% conv)	-	-

Table 5.2: Desymmetrisation of bis-acetal **90**.

In conclusion, this study has demonstrated a level of validity in a desymmetrisation hypothesis Enantioselective α-amination methodology has been applied in a chemoselective fashion to demonstrate desymmetrisation of a prochiral bis-acetal with modest diastereoselectivity (3:1 at best). To gain a more sophisticated understanding of the interplay of the various conformations involved in the transition-state, particularly regarding the assumption that zig-zag conformations of the chain are the major ones influencing stereoselectivity ultimately, one would need to resort to doing some conformational energy calculations using molecular mechanics. However, assuming the zig-zag conformation to be the dominant conformer throughout, a simple model accounting for the interplay between

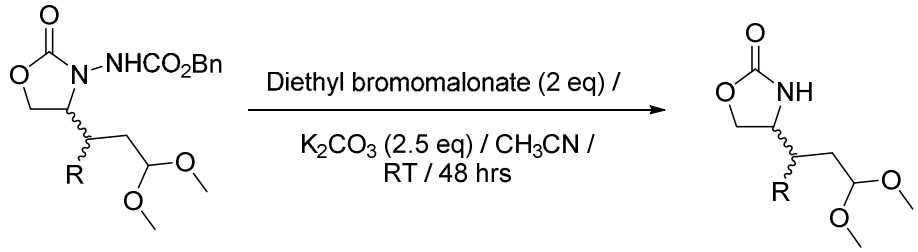
diastereo- and enantioselectivity features as observed in the work may be summarised in the following Scheme 5.15. Here *syn*-addition relative to the chiral directing group on the organocatalyst controls the enantioselectivity (major), while *anti*-addition with respect to the prochiral centre controls the diastereoselectivity, Further work would need to determine absolute configurations in order to validate the concept.



Scheme 5.15: A model explaining the observed stereochemical outcome.

5.3 Application of the N-N Bond Cleavage Methodology

The N-N bond cleavage methodology developed in Chapter 4 was applied to both oxazolidinones **94** and **95** (isolated as a mixture of diastereomers). Since the model oxazolidinone **63** showed better results under the K_2CO_3 reaction conditions, this was the base chosen for this transformation (Scheme 5.16). Thus each of the oxazolidinone hydrazides was reacted with 2 equivalents of bromomalonate and 2.5 equivalents of K_2CO_3 in acetonitrile at room temperature.



94 R = CH_2OBn
95 R = Ph

Scheme 5.16: N-N bond cleavage of the desymmetrisation products.

Reaction TLCs showed very promising results in terms of complete starting material conversion (after 48 hrs) and formation of a more polar product, as expected from the model study. The products were isolated successfully by column chromatography as a mixture of diastereomers in both cases. However, in the process of drying the products *in vacuo*, a change in appearance was observed – clear, colourless oils turned greyish brown. This was seen as a sign of product decomposition and ^{1}H NMR analysis of both products confirmed this suspicion. Figure 5.14 shows the ^{1}H NMR spectrum of the product obtained after the N-N bond cleavage of **95**. The spectrum is far more complicated than expected: e.g. multiple methoxy-like and aromatic resonances were observed, a more upfield N-H resonance was not observed and the oxazolidinone H-5 resonances did not resolve to the expected dd and triplet. Thus this spectrum could not be used to confirm the success of the N-N cleavage reaction initially (from the crude). Similar oxazolidinone decomposition had been observed with the cleaved acetal model substrate **72**, albeit at a slower rate since the cleaved product was stable long enough to be fully characterised (as discussed in Chapter 4).

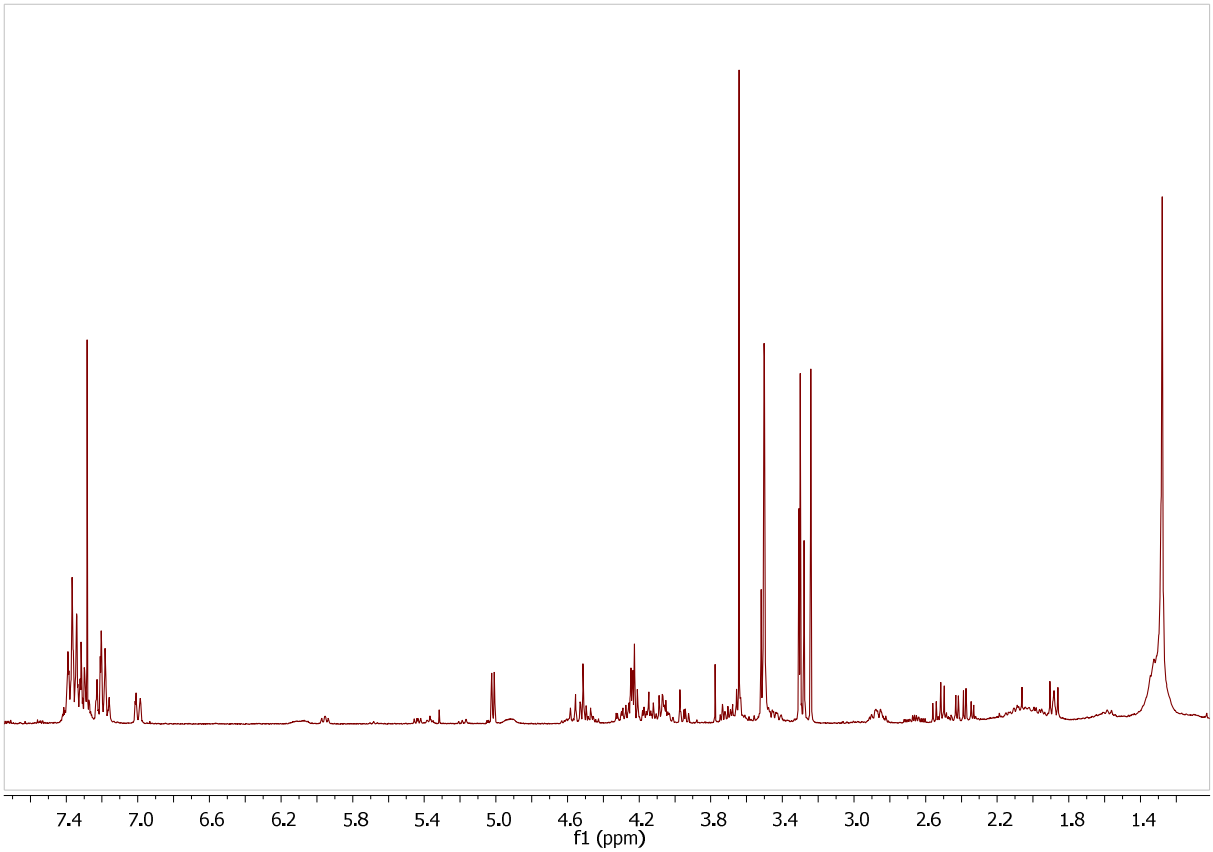


Figure 5.14: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) obtained after the N-N cleavage of **95**.

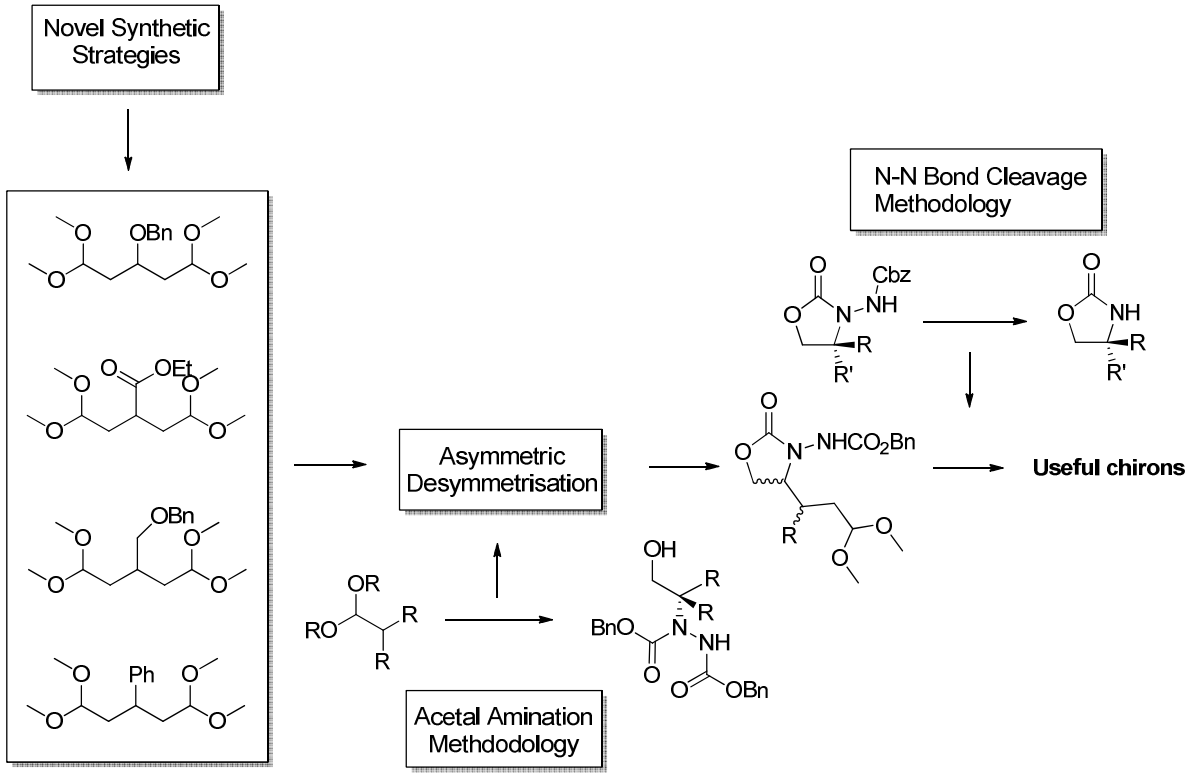
This disappointing result suggested that the methyl acetal was not robust enough for the cleavage reaction, even though acetals are generally stable under basic conditions at room temperature. Future work therefore needs to focus on the synthesis of more robust bis-acetals (e.g. ethyl acetals and dioxolanes, which were shown in the model study to undergo successful α-amination, Table 3.7, Chapter 3).

In closing, the two cases shown of successful chemo- and stereoselective desymmetrisation of bis-acetals served as a proof of concept, which justifies the possibility of developing this strategy in the future.

Chapter 6: Conclusions and Future Work

6.1 Conclusions

Scheme 6.1 illustrates a summary of the work achieved in this project. Novel methodologies and synthetic strategies were developed with the ultimate goal of achieving the asymmetric desymmetrisation of symmetrical prochiral bis-acetals via enantioselective α-amination. The final products were chiral oxazolidinones with two contiguous stereocentres.



Scheme 6.1: An overview of work achieved in this project.

6.2 Future Work

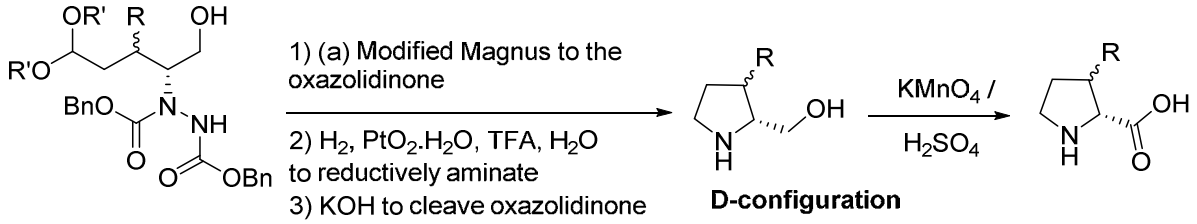
Future work will focus on developing the desymmetrisation methodology by exploring other substrates varying the prochiral R group. As mentioned, a change from dimethoxy to 1,3-dioxolane will be made for the acetals. Substrates will need to be prepared in quantity (e.g. by improving the yields of the sulfone strategy) so that the optimisation of reaction conditions can be pursued to maximise the yield, and the enantio- and diastereoselectivity. This will hopefully lead to a deeper understanding of the workings of the asymmetric induction step, through careful experimental work, notably regarding how the R-group at the prochiral centre influences the stereo-outcome. Finally, determination of the absolute configurations of the major diastereomer will also be addressed by preparing a crystalline derivative for an X-Ray determination so as to address ideas described herein.

6.2.1 Potential Application of Desymmetrised products

On paper the desymmetrised oxazolidinones have a number of potential options for further transformation into useful chirons. Some possibilities are shown in the following synopsis:

a) Proline mimics (Scheme 6.2):

As discussed earlier, Greck has used the half acetal/aldehyde analogue of 1,1,6,6-tetramethoxyhexane to synthesise D-proline.[187] In a similar manner, the synthesis of 3-substituted prolines from our desymmetrised hydrazino alcohols is envisioned.

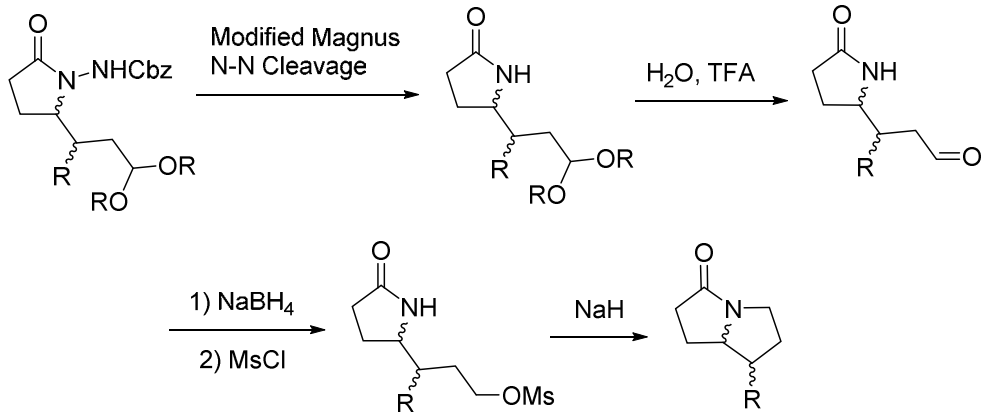


Scheme 6.2: Pyrrolidine amino acid synthesis.

R = Ph, (the *trans* diastereomer of 3-phenyl proline), is a known compound[278] with reported optical rotation values. Therefore this substrate is ideal for determining the absolute configuration of the desymmetrisation products, by comparing experimental and literature optical rotation values.

b) Hexahydro-1*H*-pyrrolizidines (Scheme 6.3):

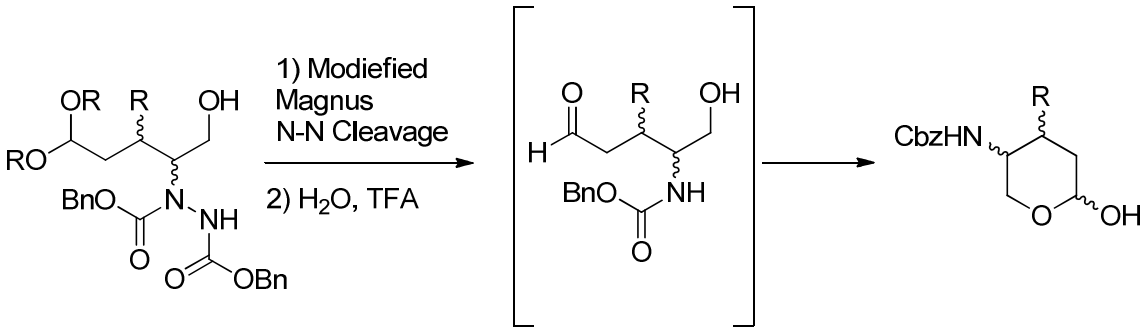
Chiral pyrrolizidine derivatives constitute a class of heterocyclic compounds that serve as promising scaffolds for anticancer drugs.[279] The conversion of our cleaved oxazolidinones to these valuable structural cores could in principle be achieved in four steps using mesylation and S_N2 substitution steps.



Scheme 6.3: Pyrrolizidine synthesis.

c) Lactol synthesis (Scheme 6.4):

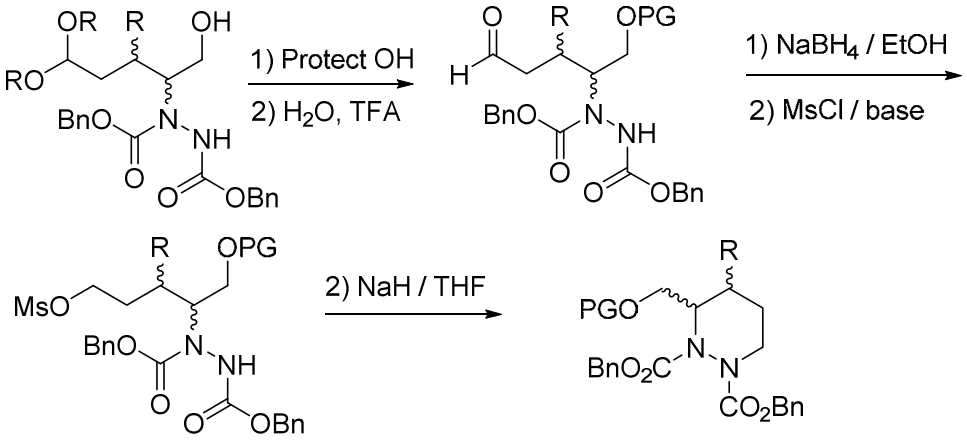
The three-step conversion of desymmetrised hydrazino alcohols into chiral aminolactols would give access to aminated sugar-like products:



Scheme 6.4: Lactol synthesis.

d) Pyridazine synthesis (Scheme 6.5):

The synthesis of chiral hexahydropyridazines is also envisioned. In this case cyclisation is unambiguous in view of only one NH in the hydrazide leading to a 6-membered chiral di-substituted pyridazine core. Other strategies, in principle, could be developed for chiral 2,3-disubstituted pyrrolidines.



Scheme 6.5: Pyridazine synthesis.

In conclusion, a package of methodologies lies in wait for extending the organocatalysed enantioselective α-amination reaction of acetals, with an asymmetric desymmetrisation of a prochiral bis-acetal as the highlight. The study bodes well for expanding the work towards obtaining a range of functionalised chirons for application to synthesis.

Chapter 7: Experimental

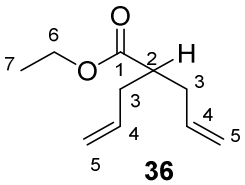
7.1 General Information

Column chromatography was performed using silica-gel 60 (Merck 7734). Thin layer chromatography was carried out on aluminium-backed Merck silica-gel 60 F_{254} plates. Compounds were visualised on TLC by using one or more of the following revealing techniques: UV lamp, iodine vapour or spraying with a 2.5% solution of anisaldehyde in a mixture of sulfuric acid and ethanol (1:10 v/v). Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 MHz (75.5 MHz for ^{13}C) or a Bruker 400 MHz (101 MHz for ^{13}C) instrument and were carried out in chloroform-d. Chemical shifts (δ) were recorded relative to residual chloroform (δ 7.26 in ^{1}H NMR and δ 77.0 in ^{13}C NMR). All chemical shifts are reported in ppm. Infra-Red (IR) absorptions were measured on a Perkin Elmer Spectrum 100 FT-IR Spectrometer. All mass spectra were recorded on a Waters Synapt G2 machine in ESI mode. Melting points were obtained using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHNS elemental analyser. The enantiomeric excess (ee) of the products were determined by HPLC on an Agilent 1220 Series using a Diacel Chiracel OD (250 $\times$ 4.6 mm) or Chiralpak AD (250 $\times$ 4.6 mm) column. Optical rotations were obtained using a Perkin Elmer 343 polarimeter at λ = 589 nm and 20 °C. The concentration *c* refers to g/100ml.

All solvents were freshly distilled. Dichloromethane was distilled from phosphorus pentoxide under nitrogen. Acetonitrile was distilled from calcium hydride under nitrogen. THF was distilled over sodium wire with benzophenone under nitrogen. All reagents were available by commercial sources (Sigma-Aldrich, Merck) and were used without further purification. Isovaleraldehyde diethyl acetal was synthesised from isovaleraldehyde and EtOH under *p*-TSA catalysis, whilst butanone dimethyl ketal was synthesised using trimethyl orthoformate.[280] Cyclohexanone ethylene ketal was synthesised by ketal exchange with ethylene glycol. Tetrahydro-2*H*-pyran-2-ol was synthesised from 3,4-dihydro-2*H*-pyran using Tamaru's procedure.[281]

7.2 Experimental Section

Ethyl 2-allylpent-4-enoate[234]



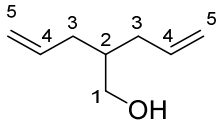
36

In a solution of diethyl malonate (7.12 ml, 48.8 mmol, 1 equiv) in THF (250 ml), was added NaH (60% in mineral oil, 4.60 g, 115 mmol, 2.5 equiv) and the mixture cooled to 0 °C. Allyl bromide (8.00 ml, 92.4 mmol, 2 equiv) was then added and the reaction was warmed to reflux for 26 hours, until complete consumption of the diethyl malonate was observed on TLC. The reaction was then cooled to room temperature and quenched with saturated NH_4Cl solution (80.0 ml) and extracted with EtOAc (3 x 80.0 ml). The organic layer was then dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude product was judged pure enough to continue to the next step.

To a solution of the crude α,α'-diallyl malonate in DMSO (82.0 ml) and H_2O (1.00 ml) was added LiCl (4.30 g, 101 mml, 2.20 equiv). The reaction mixture was then heated to 180 °C for 21 hours. The reaction was then cooled to room temperature and quenched with brine (70.0 ml), extracted with EtOAc (3 x 100 ml) and washed with water (3 x 50.0 ml). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (5% ethyl acetate / petroleum ether) to give **36** (4.31 g, 56% yield over two steps) as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82-5.66 (m, 2H, H-4), 5.12-4.99 (m, 4H, H-5), 4.11 (q, *J* = 7.7 Hz, 2H, H-6), 2.50 (m, 1H, H-2), 2.30 (m, 4H, H-3), 1.24 (t, *J* = 7.7 Hz, 3H, H-7).

2-Allylpent-4-en-1-ol[235]

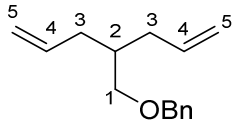


37

Product **36** (3.68 g, 21.9 mmol, 1 equiv) was dissolved in 35.0 ml THF and cooled to 0 °C. $LiAlH_4$ (1.33 g, 35.0 mmol, 1.6 equiv) was then added and the reaction warmed to reflux for 4 hours. The reaction mixture was then cooled to 0 °C and quenched with water (4.30 ml), 25.0 ml of NaOH (10% solution) and stirred at room temperature for 20 minutes. The resultant suspension was filtered over Celite and washed with ether (100 ml). The filtrate was dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (10% ethyl acetate / petroleum ether) to give **37** (2.26 g, 82% yield) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88-5.74 (m, 2H, H-4), 5.05 (m, 4H, H-5), 3.57 (d, *J* = 3.3 Hz, 2H, H-1), 2.10 (t, *J* = 6.9 Hz, 4H, H-3), 1.78-1.65 (m, 1H, H-2), 1.42 (s, 1H, OH).

(((2-Allylpent-4-en-1-yl)oxy)methyl)benzene[235]



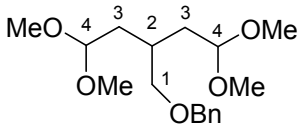
38

To as solution of alcohol **37** (3.10 g, 24.6 mmol, 1 equiv) in THF (125 ml) was added NaH (60% in mineral oil, 1.20 g, 29.5 mmol, 1.2 equiv) at 0 °C and the reaction mixture was warmed to room temperature and stirred for a further 1.25 hours. Benzyl bromide (4.40 ml, 36.8 mmol, 1.5 equiv) was added along with TBAI (907 mg, 2.45 mmol, 10 mol%) and the reaction mixture warmed to reflux for 18 hours. When complete consumption of **37** was observed on TLC the reaction was quenched with water (80.0 ml) and extracted with ethyl acetate (3 x 50.0 ml). The organic layers were dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (2% ethyl acetate / petroleum ether) to give **38** (4.09 g, 77% yield) as a colourless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 5H, Ar), 5.78-5.62 (m, 2H, H-4), 5.01-4.86 (m, 4H, H-5), 4.40 (s, 2H, Bn), 3.29 (d, *J* = 6.0 Hz, 2H, H-1), 2.14-1.98 (m, 4H, H-3), 1.78-1.69 (m, 1H, H-2).

General procedure 1: bis-acetal synthesis via ozonolysis

Into a solution of the diallyl substrate (10.0 mmol, 1 equiv) in methanol (50.0 ml) and DCM (10.0 ml) at -78 °C was bubbled O_3 gas for 30 minutes (or until the solution turned blue). The reaction mixture was then flushed with O_2 gas and warmed to 0 °C under an inert Ar atmosphere. PPh_3 (5.77 g, 22.0 mmol, 2.2 equiv) was then added and the reaction mixture warmed to room temperature over 2 hours. *p*-TSA (360 mg, 1.90 mmol, 20 mol%) was added and the reaction mixture was stirred at room temperature (or refluxed, if necessary) until complete consumption of the dially intermediate was observed on TLC (minimum of 18 hours). The reaction mixture was then quenched with saturated K_2CO_3 (25.0 ml) and extracted with ethyl acetate (4 x 50.0 ml). The organic layers were dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (5-10% ethyl acetate / petroleum ether) to yield the desired bisacetal.

((2-(2,2-Dimethoxyethyl)-4,4-dimethoxybutoxy)methyl)benzene



40

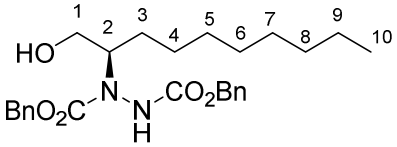
Synthesised using **General procedure 1** from **38** to give the product **40** (2.02 g, 65 % yield) as a colourless oil.

IR ($CHCl_3$) ν_{max}/cm^{-1} 1265 (C-O), 1112 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H, Ar), 4.46 (s, 2H, Bn), 4.43 (t, *J* = 5.9 Hz, 2H, H-4), 3.37 (d, *J* = 5.1 Hz, 2H, H-1), 3.27 (s, 6H, 2xOMe), 3.26 (s, 6H, 2xOMe), 1.89 (m, 1H, H-2), 1.75-1.55 (m, 4H, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (*i*-Ar), 128.2 (Ar), 127.5 (Ar), 127.4 (Ar), 103.1 (C-4), 72.9, 72.8, 52.7 (OMe), 52.3 (OMe), 34.7 (C-3), 31.1 (C-2); HRMS (ESI): *m/z* 335.1838 $[M + Na]^+$, $C_{17}H_{28}O_5Na$ requires 335.1834.

General procedure 2: α-amination of acetals

Dibenzyl azodicarboxylate (DBAD, 75.0 mg, 0.500 mmol, 2 equiv (1.00 mmol, 4 equiv for **45**)) was added to a mixture of acetal (0.250 mmol, 1 equiv), tetrazole catalyst (7.00 mg, 0.050 mmol, 20 mol%) monochloroacetic acid (MCA, 123 mg, 1.30 mmol, 5.2 equiv (246 mg, 2.60 mmol, 10.4 equiv for **45**)), trifluoroacetic acid (TFA, 2.0 µl, 0.025 mmol, 0.1 equiv) and water (22.5 mg, 1.25 mmol, 5 equiv) in DCM (0.50 ml). The reaction mixture was kept at 4 °C until complete consumption of the acetal was observed by TLC. On reaction completion, the reaction mixture was quenched with water (10.0 ml) and extracted with DCM (3 x 10 ml) and the organic extracts were washed with saturated $NaHCO_3$ (10.0 ml) and brine (10.0 ml). The organic layers were then dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. To the resultant residue was added EtOH (3.0 ml) and $NaBH_4$ (18.9 mg, 0.500 mmol, 2 equiv) at 0 °C and the mixture was allowed to warm up over 15 minutes. The reaction was quenched with saturated NH_4Cl (10.0 ml), extracted with DCM (3 x 10.0 ml) and the organic extracts were washed with brine (10.0 ml). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (ethyl acetate / petroleum ether) to give the desired product.

(*R*)-Dibenzyl 1-(1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate



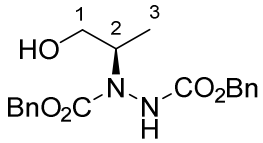
41

Synthesised from the corresponding acetal using **General procedure 2** to give **41** (79% yield) as a white amorphous solid and a 3:1 mixture of rotamers.

$[\alpha]_D^{20}$ -6.0 (*c* = 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 1714 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 10H, Ar), 6.45 (br s, 1H, NH), 5.20 (m, 4H, 2xBn), 4.49-3.93 (m, 2H, H-2, OH), 3.44 (3.55) (m, 2H, H-1), 1.23 (m, 14H, H-3-H-9), 0.88 (t, *J* = 6.9 Hz, 3H, H-10). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C=O), 135.8 (*i*-Ar), 135.09 (*i*-Ar), 128.7 (Ar), 128.5 (Ar), 128.3 (Ar), 127.9 (Ar), 69.6 (Bn), 62.2 (Bn), 61.1 (C-1), 60.0 (C-2), 31.8 (C-3), 29.4 (C-8), 29.2 (C-5), 27.8 (C-6), 26.0 (C-7), 22.6 (C-4,C-9), 14.0 (C-10); HRMS (ESI): *m/z* 457.2703 $[M + H]^+$, $C_{26}H_{37}N_2O_5$ requires 457.2702.

The ee (90%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol = 95:5, flow rate = 0.5 ml/min, λ = 258 nm); τ_{major} = 41.40 min, τ_{minor} = 45.25 min.

(*R*)-Dibenzyl 1-(1-hydroxypropan-2-yl)hydrazine-1,2-dicarboxylate[174]



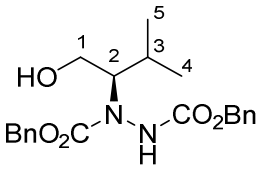
43

Synthesised from the corresponding acetal using **General procedure 2** to give **43** (93% yield) as colourless crystals.

$[\alpha]_D^{20}$ -22.5 (*c* = 0.4, $CHCl_3$), lit: $[\alpha]_D^{20}$ -32.0 (*c* = 0.4, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 10H, Ar), 6.57 (m, 1H, NH), 5.23 (m, 4H, 2xBn), 4.64-3.79 (m, 2H, OH, H-2), 3.45 (m, 2H, H-1), 1.01 (d, *J* = 6.1 Hz, 3H, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C=O), 135.8 (*i*-Ar), 135.1 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.2 (Ar), 127.9 (Ar), 68.5 (Bn), 63.2 (Bn), 56.4 (C-1), 55.4 (C-2), 13.7 (C-3).

The ee (86%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 18.00 min, τ_{minor} = 19.66 min.

(*R*)-Dibenzyl 1-(1-hydroxy-3-methylbutan-2-yl)hydrazine-1,2-dicarboxylate[174,67]



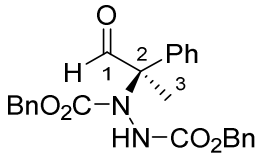
44

Synthesised from the corresponding acetal using **General procedure 2** to give **44** (73% yield) as colourless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 10H, Ar), 6.48 (br s, 1H, NH), 5.21 (m, 4H, 2xBn), 4.34-3.92 (m, 2H, OH, H-2), 3.73 (m, 1H, H-1), 3.46 (m, 1H, H-1), 1.62 (m, 1H, H-3), 0.88 (m, 6H, H-4, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (C=O), 135.8 (*i*-Ar), 135.1 (*i*-Ar), 128.7 (Ar), 128.5 (Ar), 128.3 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 68.5 (Bn), 68.3 (C-1), 67.2 (C-2), 60.4 (Bn), 27.5 (C-3), 20.1 (C-4/5), 19.4 (C-4/5).

The ee (94%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 15.81 min, τ_{minor} = 23.26 min.

(*R*)-Dibenzyl 1-(1-oxo-2-phenylpropan-2-yl)hydrazine-1,2-dicarboxylate[251]



45

Synthesised from the corresponding acetal using **General procedure 2** to give **45** (51% yield) as a colourless oil and a 2:1 mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$, minor rotamer cited in parentheses) δ 9.62 (9.69) (m, 1H, H-1), 7.29 (m, 15H, Ar), 6.54 (6.33) (br s, 1H, NH), 5.09 (m, 4H, 2xBn), 1.83-1.56 (m, 3H, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2 (194.1) (C-1), 156.3 (C=O), 156.2 (C=O), 135.3 (*i*-Ar), 135.1 (*i*-Ar), 135.1 (*i*-Ar), 129.0 (Ar), 128.9 (Ar), 128.8 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 126.8 (Ar), 73.4 (C-2), 68.9 (Bn), 68.0 (Bn), 17.6 (C-3).

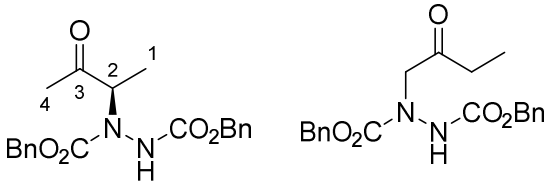
The ee (56%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol 88:12, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 69.56 min, τ_{minor} = 64.05 min.

General procedure 3: α-amination of ketals (Compounds **46** & **47**)

DBAD (75.0 mg, 0.250 mmol, 1 equiv) was added to a mixture of ketal (5.00 mmol, 20 equiv), tetrazole catalyst (7.00 mg, 0.05 mmol, 20 mol%), MCA (246 mg, 2.60 mmol), TFA (2.0 µl, 0.025 mmol, 0.1 equiv) and water (22.5 mg, 1.25 mmol, 5 equiv) in DCM (0.50 ml). The reaction mixture was kept at 4 °C until complete consumption of the DBAD was observed by TLC. On reaction completion, the reaction mixture was quenched with water

(10.0 ml) and extracted with DCM (3 x 10.0 ml) and the organic extracts were washed with saturated $NaHCO_3$ (10.0 ml) and brine (10.0 ml). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (ethyl acetate / petroleum ether) to give the desired product.

(*R*)-Dibenzyl 1-(3-oxobutan-2-yl)hydrazine-1,2-dicarboxylate / dibenzyl 1-(2-oxobutyl)hydrazine-1,2-dicarboxylate[174]



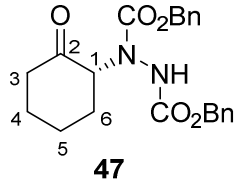
46 Major Minor

Synthesised from the corresponding acetal using **General procedure 3** to give **46** (33% yield) as a white solid and a mixture of regioisomers (major : minor = 96:4), each of which existing as a 3:1 mixture or rotamers.

For the major regioisomer (which corresponded to the reported literature data):[174] ^{1}H NMR (400 MHz, $CDCl_3$, minor rotamer cited in parentheses) δ 7.26 (m, 10H, Ar), 6.81 (6.59) (br s, 1H, NH), 5.14 (m, 4H, 2xBn), 4.92 (4.67) (m, 1H, H-2), 2.18 (m, 3H, H-4), 1.43 (m, 3H, H-1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1 (C-3), 156.2 (C=O), 135.7 (*i*-Ar), 135.5 (*i*-Ar), 128.6 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 127.8 (Ar), 127.6 (Ar), 68.3 (C-2), 67.9 (Bn), 67.7 (Bn), 26.5 (C-4), 13.1 (C-1).

The ee (86%) was determined by chiral HPLC using a Chiralcel OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 23.54 min; τ_{minor} = 19.52 min.

(*R*)-Dibenzyl 1-(2-oxocyclohexyl)hydrazine-1,2-dicarboxylate[174,180]



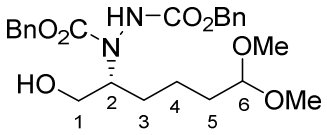
47

Synthesised from the corresponding acetal using **General procedure 3** to give **47** (71% yield) as a white solid and a 2:1 mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$, minor rotamer cited in parentheses) δ 7.28 (m, 10H Ar), 6.86 (6.60) (br s, 1H, NH), 5.15 (m, 4H, 2xBn), 4.92 (4.67) (m, 1H, H-1), 2.50-1.60 (m, 8H, H-3 - H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5 (207.0) (C-2), 156.3 (C=O), 156.1 (C=O), 135.7 (*i*-Ar), 128.5 (Ar), 128.3 (Ar), 128.0 (Ar), 127.5 (Ar), 68.2 (Bn), 67.6 (Bn), 65.8 (C-1), 41.3 (C-3), 30.7 (C-6), 26.7 (C-4), 24.3 (C-5).

The ee (64%) was determined by chiral HPLC using a Chiralcel OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.9 ml/min, λ = 258 nm); τ_{major} = 24.55 min, τ_{minor} = 17.50 min.

(*R*)-Dibenzyl 1-(1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate[187]



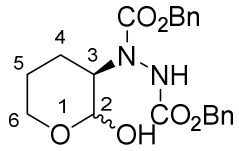
48

Dibenzyl azodicarboxylate (258 mg, 75.0 mg, 0.250 mmol, 1 equiv) was added to a mixture of 1,1,6,6-tetramethoxyhexane (1.25 mmol, 5 equiv), tetrazole catalyst (0.05 mmol, 20 mol%), MCA (123 mg, 1.3 mmol, 5.2 equiv), TFA (2.0 µl, 0.025 mmol, 0.1 equiv) and water (22.5 mg, 1.25 mmol, 5 equiv) in DCM (2.50 ml). The reaction mixture was kept at 4 °C until complete consumption of the DBAD was observed by TLC. On reaction completion, the reaction mixture was quenched with water (10.0 ml) and extracted with DCM (3 x 10.0 ml) and the organic extracts were washed with saturated $NaHCO_3$ (10.0 ml) and brine (10.0 ml). The organic layer was then dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. To the resultant residue was added EtOH (3 ml) and $NaBH_4$ (18.9 mg, 0.5 mmol, 2 equiv) at 0 °C and the mixture was allowed to warm up over 15 minutes. The reaction was quenched with saturated NH_4Cl (10.0 ml), extracted with DCM (3 x 10.0 ml) and the organic extracts were washed with brine (10.0 ml). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (30% ethyl acetate / petroleum ether) to give 90mg of **48** (78% yield) as a colourless solid.

$[\alpha]_D^{20}$ +5.2 (*c* = 1, MeOH), lit: $[\alpha]_D^{25}$ +3.8 (*c* = 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 10H, Ar), 6.82 (m, 1H, NH), 5.19 (m, 4H, 2xBn), 4.52-4.01 (m, 3H, OH, H-2, H-6), 3.58-3.35 (m, 2H, H-1), 3.26 (s, 3H, OMe), 3.25 (s, 3H, OMe), 1.92-1.20 (m, 6H, H-3-H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (C=O), 156.1 (C=O), 135.8 (*i*-Ar), 135.2 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.5 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 104.2 (C-6), 68.4 (Bn), 62.2 (Bn), 61.0 (C-1), 59.8 (C-2), 53.0 (OMe), 52.5 (OMe), 32.0 (C-3), 27.4 (C-5), 20.9 (C-4).

The ee (90%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.5 ml/min, λ = 258 nm); τ_{major} = 47.28 min, τ_{minor} = 43.68 min.

Dibenzyl 1-((3*R*)-2-hydroxytetrahydro-2*H*-pyran-3-yl)hydrazine-1,2-dicarboxylate



50

DBAD (75.0 mg, 0.25 mmol, 1 equiv) was added to a mixture of lactol **49** (255 mg, 2.50 mmol, 10 equiv), tetrazole catalyst (7.00 mg, 0.05 mmol, 20 mol%) MCA (2.36 mg, 0.025 mmol, 0.1 equiv), TFA (2.0 µl, 0.025 mmol, 0.1 equiv) and water (22.5 mg, 2.50 mmol, 5 equiv) in CH_3CN (0.50 ml). The reaction mixture was kept at 0 °C until complete consumption of the DBAD was observed by TLC. On reaction completion, the reaction mixture was quenched with water (10.0 ml) and extracted with DCM (3 x 10.0 ml) and the organic extracts were washed with saturated $NaHCO_3$ (10.0 ml) and brine (10.0 ml). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude residue was purified by flash column chromatography (30% ethyl acetate / petroleum ether) to give 80mg (80% yield) of **50** as a white amorphous solid and a 6:4 mixture of diastereomers.

$[\alpha]_D^{20}$ +7.4 (*c* = 0.5, MeOH); IR ($CHCl_3$) ν_{max}/cm^{-1} 1746 (C=O), 1688 (C=O); for the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 10H, Ar), 6.80 (br s, 1H, NH), 5.22 (m, 4H, 2xBn), 4.57 (m, 1H, H-2), 3.96-3.83 (m, 3H, H-3, H-6), 3.14 (br s, 1H, OH), 2.01-1.56 (m, 4H, H-4, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C=O), 155.8 (C=O), 135.6 (*i*-Ar), 135.3 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.2 (Ar), 127.8 (Ar), 96.2 (C-2), 68.4 (Bn), 68.2 (Bn), 66.3 (C-6), 60.7 (C-3), 26.0 (C-4), 25.2, (C-5); for the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 10H, Ar), 6.92 (br s, 1H, NH), 5.22 (m, 5H, 2xBn, H-2), 4.27 (m, 1H, H-3), 3.40 (s, 1H, H-6), 3.53 (s, 1H, H-6), 3.14 (br s, 1H, OH), 2.01-1.56 (m, 4H, H-4, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C=O), 155.8 (C=O), 135.6 (*i*-Ar), 135.3 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.2 (Ar), 127.8 (Ar), 91.9 (C-2), 68.4 (Bn), 68.2 (Bn), 59.0 (C-6), 56.0 (C-3), 24.8 (C-5), 20.0 (C-4); HRMS (ESI): *m/z* 383.1613 $[M - H_2O + H]^+$, $C_{21}H_{23}N_2O_5$ requires 383.1605; Analysis: found C 62.53%, H 6.10%, N 7.01%; $C_{21}H_{24}N_2O_6$ requires C 62.99%, H 6.04%, N 7.00%.

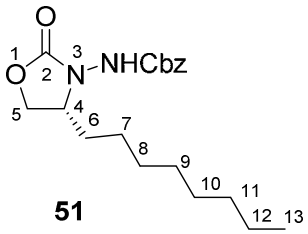
The ee (93%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol = 70:30, flow rate = 0.9 ml/min, λ = 258 nm); τ_{major} = 9.38 min, τ_{minor} = 22.72 min; τ_{major} = 11.05 min, τ_{minor} = 14.49 min.

General Procedure 4: synthesis of oxazolidinones

To a solution of the appropriate aldehyde (1.66 mmol, 1.5 equiv) and L-proline (13.0 mg, 0.11 mmol, 10 mol%) in CH_3CN (10 ml) at 0 °C was added dibenzyl azodicarboxylate (330

mg, 1.11 mmol, 1.0 equiv) and the reaction mixture was left to stir at 0 °C for 30 minutes and then warmed to room temperature until the complete consumption of DBAD (as determined by TLC). The reaction mixture was then cooled to 0 °C and diluted with methanol (20.0 ml) followed by addition of sodium borohydride (42 mg, 1.11 mmol, 1.0 equiv). After 15 minutes, 1M NaOH (3.3 ml, 3.32 mmol, 3.0 equiv) was added and after an additional 2 hours the resulting mixture was quenched with NH_4Cl (15.0 ml) and extracted with ethyl acetate (3 x 30.0 ml). The combined organic layers were washed with brine (20.0 ml) and dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was chromatographed on silica gel with an ethyl acetate / petroleum ether mixture to afford the oxazolidinone hydrazide.

Benzyl (*R*)-(4-octyl-2-oxooxazolidin-3-yl)carbamate



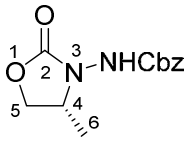
51

Synthesised from the corresponding aldehyde using **General procedure 4** to give **51** (92% yield) as a colourless oil.

$[\alpha]_D^{20}$ -12.9 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1740 (2 x C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H, Ar), 6.68 (br s, 1H, N-H), 5.12 (s, 2H, Bn), 4.39 (m, 1H, H-5), 3.90 (m, 2H, H-5, H-4), 1.73 (m, 1H, H-6), 1.44 (m, 1H, H-6), 1.19 (m, 12H, H-7-H-12), 0.81 (t, *J* = 6.0 Hz, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (C=O), 155.4 (C=O), 135.4 (*i*-Ar), 128.7 (Ar), 128.6 (Ar), 128.3 (Ar), 68.2 (Bn), 67.8 (C-5), 56.9 (C-4), 31.9 (C-6), 31.8 (C-11), 29.6 (C-8), 29.4 (C-9), 29.2 (C-10), 24.6 (C-7), 22.8 (C-12), 14.2 (C-13); HRMS (ESI): *m/z* 349.2131 $[M + H]^+$, $C_{19}H_{29}N_2O_4$ requires 349.2127.Chiralpak.

The ee (90%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 23.60 min, τ_{minor} = 15.37 min.

Benzyl (*R*)-(4-methyl-2-oxooxazolidin-3-yl)carbamate



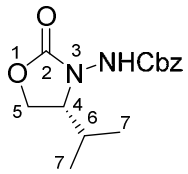
55

Synthesised from the corresponding aldehyde using **General procedure 4** to give **55** (88% yield) as a white solid.

$[\alpha]_D^{20}$ -12.7 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1772 (C=O), 1704 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H, Ar), 6.73 (br s, 1H, N-H), 5.11 (s, 2H, Bn), 4.41 (t, *J* = 5.3 Hz, 1H, H-5), 4.12–3.97 (m, 1H, H-4), 3.82 (t, *J* = 5.3 Hz, 1H, H-5), 1.21 (d, *J* = 6.0 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (C=O), 154.2 (C=O), 135.4 (*i*-Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 68.9 (Bn), 68.3 (C-5), 53.0 (C-4), 17.0 (C-6); HRMS (ESI): *m/z* 251.1036 $[M + H]^+$, $C_{12}H_{15}N_2O_4$ requires 251.1032.

The ee (90%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 31.62 min, τ_{minor} = 23.81 min.

Benzyl (*R*)-(4-isopropyl-2-oxooxazolidin-3-yl)carbamate



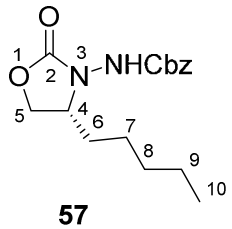
56

Synthesised from the corresponding aldehyde using **General procedure 4** to give **56** (91% yield) as a colourless oil.

$[\alpha]_D^{20}$ -12.5 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1764 (C=O), 1726 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.23 (m, 5H, Ar), 6.96 (br s, 1H, N-H), 5.09 (s, 2H, Bn), 4.28 (m, 1H, H-5), 4.09–3.80 (m, 1H, H-5, H-4), 2.03–1.85 (m, 1H, H-6), 0.91 (m, 6H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C=O), 155.1 (C=O), 135.3 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.2 (Ar), 68.1 (Bn), 64.1 (C-5), 60.9 (C-4), 28.5 (C-6), 17.8 (C-7), 15.9 (C-7); HRMS (ESI): *m/z* 279.1345 $[M + H]^+$, $C_{14}H_{19}N_2O_4$ requires 279.1345.

The ee (91%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 23.60 min, τ_{minor} = 15.37 min.

Benzyl (*R*)-(2-oxo-4-pentyloxazolidin-3-yl)carbamate



57

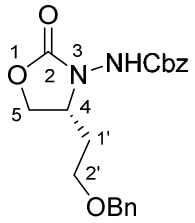
Synthesised from the corresponding aldehyde using **General procedure 4** to give **57** (89% yield) as a colourless oil.

$[\alpha]_D^{20}$ -12.8 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 3285 (N-H), 1770 (C=O), 1722 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H, Ar), 6.74 (br s, 1H, N-H), 5.10 (d, *J* = 2.0 Hz, 2H, Bn), 4.38 (m, 1H, H-5), 4.00–3.83 (m, 2H, H-5, H-4), 1.76–1.36 (m, 2H, H-6), 1.29–1.14

(m, 6H, H-7-H-9), 0.91 (t, *J* = 6.8 Hz, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C-2), 155.4 (C=O), 136.2 (*i*-Ar), 128.9 (Ar), 128.8 (Ar), 127.7 (Ar), 68.3 (Bn) 66.5 (C-5), 54.6 (C-4), 33.3 (C-6), 31.7 (C-8), 26.1 (C-7), 22.8 (C-9), 14.3 (C-10); HRMS (ESI): *m/z* 307.1657 $[M + H]^+$, $C_{16}H_{23}N_2O_4$ requires 307.1658.

The ee (93%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 26.03 min, τ_{minor} = 17.21 min.

Benzyl (*R*)-(4-(2-(benzyloxy)ethyl)-2-oxooxazolidin-3-yl)carbamate



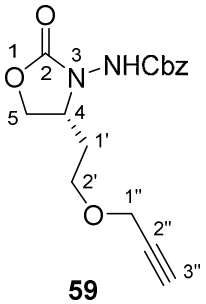
58

Synthesised from the corresponding aldehyde using **General procedure 4** to give **58** (86 % yield) as a colourless oil.

$[\alpha]_D^{20}$ -8.0 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 1774 (C=O), 1730 (C=O), 1221 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 10H, Ar), 6.94 (br s, 1H, NH), 5.19 (s, 2H, Bn), 4.51 (m, 1H, H-5), 4.45 (s, 2H, Bn), 4.12 (m, 2H, H-4, H-5), 3.50 (m, 2H, H-2'), 1.96 (m, 2H, H-1'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C=O), 155.3 (C=O), 137.6 (*i*-Ar), 135.4 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 127.9 (Ar), 127.7 (Ar), 73.5 (Bn), 68.0 (Bn), 68.0 (C-5), 66.3 (C-2'), 56.1 (C-4), 31.9 (C-1'); HRMS (ESI): *m/z* 371.1601 $[M + H]^+$, $C_{20}H_{23}N_2O_5$ requires 371.1607.

The ee (92%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol 50:50, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 25.92 min, τ_{minor} = 10.15 min.

Benzyl (*R*)-(2-oxo-4-(2-(prop-2-yn-1-yloxy)ethyl)oxazolidin-3-yl)carbamate



59

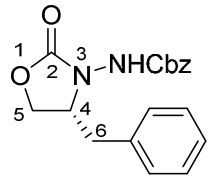
Synthesised from the corresponding aldehyde using **General procedure 4** to give **59** (87 % yield) as a yellow oil.

$[\alpha]_D^{20}$ -12.9 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 1771 (C=O), 1726 (C=O), 1222 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H, Ar), 6.80 (br s, 1H, NH), 5.18 (s, 2H, Bn), 4.55 (m,

1H, H-5), 4.09 (d, *J* = 2.4 Hz, 2H, H-1''), 4.08 (m, 2H, H-4, H-5), 3.66 (m, 1H, H-2'), 3.56 (m, 1H, H-2'), 2.42 (t, *J* = 2.4 Hz, 1H, H-3''), 1.99 (m, 2H, H-1'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (C=O), 155.3 (C=O), 135.3 (*i*-Ar), 128.7 (Ar), 128.5 (Ar), 128.3 (Ar), 79.1 (C-2''), 74.9 (C-3''), 68.2 (Bn), 68.0 (C-5), 66.0 (C-2'), 58.4 (C-1''), 56.1 (C-4), 31.7 (C-1'); HRMS (ESI): *m/z* 319.1281 $[M + H]^+$, $C_{16}H_{19}N_2O_5$ requires 319.1294.

The ee (90%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol 50:50, flow rate = 0.5 ml/min, λ = 258 nm); τ_{major} = 16.53 min, τ_{minor} = 15.64 min.

Benzyl (*R*)-(4-benzyl-2-oxooxazolidin-3-yl)carbamate



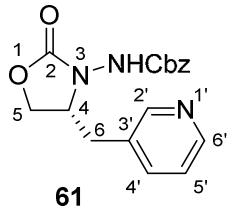
60

Synthesised from the corresponding aldehyde using **General procedure 4** to give **60** (91 % yield) as a colourless oil.

$[\alpha]_D^{20}$ -19.5 (*c* = 1.0, DCM); IR ($CHCl_3$) ν_{max}/cm^{-1} 1774 (C=O), 1728 (C=O), 1217 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, 1H, NH), 7.31 (m, 8H, Ar), 7.15 (m, 2H, Ar), 5.13 (s, 2H, Bn), 4.28 (m, 2H, H-4, H-5), 4.03 (m, 1H, H-5), 3.15 (dd, *J* = 10.2, 3.3 Hz, 1H, H-6), 2.81 (m, 1H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C=O), 155.3 (C=O), 135.3 (*i*-Ar), 135.3 (*i*-Ar), 128.8 (Ar), 128.7 (Ar), 128.4 (Ar), 128.2 (Ar), 128.0 (Ar), 127.0 (Ar), 67.8 (Bn), 67.0 (C-5), 57.6 (C-4), 37.6 (C-6); HRMS (ESI): *m/z* 327.1338 $[M + H]^+$, $C_{18}H_{19}N_2O_4$ requires 327.1345

The ee (86%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol 50:50, flow rate = 0.5 ml/min, λ = 258 nm); τ_{major} = 17.10 min, τ_{minor} = 15.69 min.

Benzyl (*R*)-(2-oxo-4-(pyridin-3-ylmethyl)oxazolidin-3-yl)carbamate



61

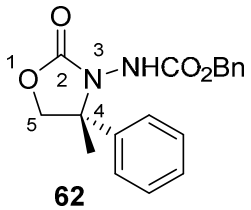
Synthesised from the corresponding aldehyde using **General procedure 4** to give **61** (87 % yield) as a colourless oil.

$[\alpha]_D^{20}$ -12.8 (*c* = 1.0, MeOH); IR ($CHCl_3$) ν_{max}/cm^{-1} 1777 (C=O), 1718 (C=O), 1215 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 3.3 Hz, 1H, H-6'), 8.41 (s, 1H, H-2'), 8.34 (br s, 1H, NH), 7.49 (m, 1H, H-4'), 7.31 (m, 5H, Ar), 7.19 (dd, *J* = 5.7, 3.3 Hz, 1H, H-5'), 5.12 (s, 2H,

Bn), 4.33 (m, 2H, H-5, H-4), 3.97 (m, 1H, H-5), 3.03 (dd, *J* = 10.5, 3.2 Hz, 1H, H-6), 2.87 (m, 1H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (C=O), 155.6 (C=O), 149.8 (Ar), 148.1 (Ar), 136.9 (Ar), 135.4 (Ar), 131.2 (*i*-Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 123.7 (Ar), 67.9 (Bn), 66.5 (C-5), 57.1 (C-4), 34.8 (C-6); HRMS (ESI): *m/z* 328.1298 $[M + H]^+$, $C_{17}H_{18}N_3O_4$ requires 328.1297.

The ee (94%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol 60:40, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 17.86 min, τ_{minor} = 8.95 min.

Benzyl (*R*)-(4-methyl-2-oxo-4-phenyloxazolidin-3-yl)carbamate[249]



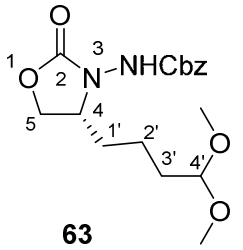
62

Synthesised from the corresponding aldehyde using **General procedure 4** (with the modification of using 5 eq of aldehyde) to give **62** (80 % yield) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.31 (m, 10H, Ar), 6.69 (br s, 1H, NH), 5.13 (s, 2H, Bn), 4.37 (d, *J* = 8.8 Hz, 1H, H-5), 4.34 (d, *J* = 8.8 Hz, 1H, H-5), 1.79 (br s, 3H, Me).

The ee (46%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol 88:12, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 57.65 min, τ_{minor} = 62.26 min.

Benzyl (*R*)-(4-(4,4-dimethoxybutyl)-2-oxooxazolidin-3-yl)carbamate



63

To a solution of hydrazine alcohol **48** (780 mg, 1.69 mmol, 1 equiv) in MeOH (15.0 ml) was added NaOH (5.10 ml, 1M, 5.10 mmol, 3 equiv) and the reaction was stirred for 1 hour at room temperature, when complete consumption of the hydrazine was observed on TLC. The reaction was quenched with saturated NH_4Cl solution (20.0 ml) and extracted with ethyl acetate (3 x 20.0 ml). The organic layers were dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (40% ethyl acetate / petroleum ether) to give **63** (430 mg, 72% yield) as a colourless gum.

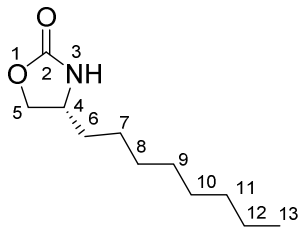
$[\alpha]_D^{20}$ -12.2 (*c* = 0.5, DCM); IR ($CHCl_3$) ν_{max}/cm^{-1} 1780 (C=O), 1740 (C=O), 1236 (C-O), 1125 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, Ar), 7.19 (br s, 1H, NH), 5.22 (s, 2H, Bn), 4.45 (m, 1H, H-5), 4.33 (t, *J* = 5.4 Hz, 1H, H-4'), 3.96 (m, 2H, H-4, H-5), 3.30 (s, 6H, 2xOMe),

1.78 (m, 1H, H-1'), 1.59 (m, 3H, H-1', H-3') 1.34 (m, 2H, H-2'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C=O), 155.3 (C=O), 135.3 (*i*-Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 104.1 (C-4'), 67.9, (Bn), 67.4 (C-5), 56.6 (C-4), 52.9 (OMe), 52.9 (OMe), 32.2 (C-1'), 31.3 (C-3'), 19.3 (C-2'); HRMS (ESI): *m/z* 375.1529 $[M + Na]^+$, $C_{17}H_{24}N_2O_6Na$ requires 375.1532.

General Procedure 5: N-N bond cleavage

To a solution of the oxazolidinone hydrazide (0.26 mmol, 1.0 equiv) in dry CH_3CN (1.00 ml) at room temperature under nitrogen, was added a base (K_2CO_3 or Cs_2CO_3, 0.65 mmol, 2.5 equiv) followed by addition of diethyl bromomalonate (0.09 ml, 0.52 mmol, 2.0 eq). The reaction mixture was left to stir at 20 °C until the starting material was consumed before being quenched with ammonium chloride (5.00 ml) and extracted with ethyl acetate (3 x 10.0 ml). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was chromatographed on silica gel with an ethyl acetace / petroleum ether mixture to afford the cleaved product.

(*R*)-4-Octyloxazolidin-2-one

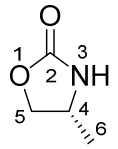


52

Synthesised using **General procedure 5** with oxazolidinone **51** and K_2CO_3 to give **52** (90% yield) as a colourless oil.

$[\alpha]_D^{20}$ +29.0 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1746 (C=O), 1239 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (br s, 1H, N-H), 4.41 (t, *J* = 5.3 Hz, 1H, H-5), 3.94 (dd, *J* = 6.2, 5.3 Hz, 1H, H-5), 3.77 (m, 1H, H-4), 1.70–1.39 (m, 2H, H-6), 1.30–1.12 (m, 12H, H-7-H-12), 0.81 (t, *J* = 6.0 Hz, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (C=O), 70.5 (C-5), 67.9 (C-4), 35.4 (C-6), 31.9 (C-11), 29.5 (C-8), 29.5 (C-9), 29.3 (C-10), 25.6 (C-7), 22.7 (C-12), 14.2 (C-13); HRMS (ESI): *m/z* 200.1652 $[M + H]^+$, $C_{11}H_{22}NO_2$ requires 200.1651.

(*R*)-4-Methyloxazolidin-2-one

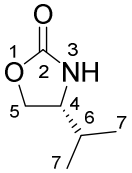


64

Synthesised using **General procedure 5** with oxazolidinone **55** and Cs_2CO_3 to give **64** (88% yield) as a white solid.

$[\alpha]_D^{20}$ +22.3 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1721 (C=O), 1238 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (br s, 1H, N-H), 4.42 (t, *J* = 7.9 Hz, 1H, H-5), 3.95 (m, 1H, H-4), 3.87 (dd, *J* = 7.9, 6.3 Hz, 1H, H-5), 1.22 (d, *J* = 6.0 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (C=O), 71.7 (C-5), 48.3 (C-4), 20.7 (C-6); HRMS (ESI): *m/z* 102.0541 $[M + H]^+$, $C_4H_8NO_2$ requires 102.0555.

(*R*)-4-Isopropyloxazolidin-2-one

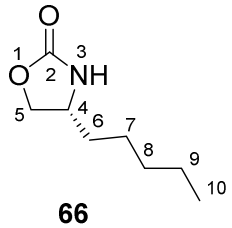


65

Synthesised using **General procedure 5** with oxazolidinone **56** and Cs_2CO_3 to give **65** (96% yield) as a colourless oil.

$[\alpha]_D^{20}$ +22.3 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1728 (C=O), 1224 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (br s, 1H, N-H), 4.36 (t, *J* = 6.0 Hz, 1H, H-5), 4.03 (dd, *J* = 6.0, 5.0, 1H, H-5), 3.54 (m, 1H, H-4), 1.65 (oct, *J* = 6.7 Hz, 1H, H-6), 0.88 (d, *J* = 6.9 Hz, 3H, H-7), 0.93 (d, *J* = 6.6 Hz, 3H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (C=O), 68.6 (C-5), 58.4 (C-4), 32.7 (C-6), 17.9 (C-7), 17.6 (C-7); HRMS (ESI): *m/z* 130.0873 $[M + H]^+$, $C_6H_{12}NO_2$ requires 130.0868.

(*R*)-4-Pentyloxazolidin-2-one

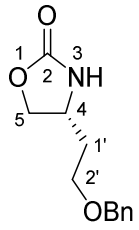


66

Synthesised using **General procedure 5** with oxazolidinone **57** and K_2CO_3 to give **66** (76% corrected yield based on a 85% conversion of **57**) as a colourless oil.

$[\alpha]_D^{20}$ +25.1 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1742 (C=O), 1233 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (br s, 1H, N-H), 4.41 (t, *J* = 6.3 Hz, 1H, H-5), 3.94 (dd, *J* = 6.3, 4.8 Hz, 1H, H-5), 3.78 (m, 1H, H-4), 1.50 (m, 2H, H-6), 1.34–1.14 (m, 6H, H-7-H-9), 0.82 (t, *J* = 5.8 Hz, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (C=O), 70.5 (C-5), 52.8 (C-4), 35.4 (C-6), 31.6 (C-8), 25.0 (C-7), 22.5 (C-9), 14.0 (C-10); HRMS (ESI): *m/z* 158.1183 $[M + H]^+$, $C_8H_{16}NO_2$ requires 158.1181.

(*R*)-4-(2-(Benzyloxy)ethyl)oxazolidin-2-one



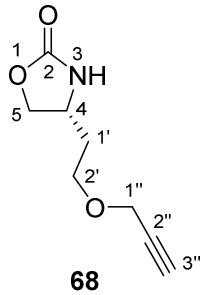
67

Synthesised using **General procedure 5** with oxazolidinone **58** and Cs_2CO_3 to give **67** (84% yield) as a colourless oil.

$[\alpha]_D^{20}$ +22.0 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 1738 (C=O), 1243 (C-O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, Ar), 6.33 (br s, 1H, NH), 4.50 (s, 2H, Bn), 4.46 (dd, *J* = 7.8, 5.7 Hz, 1H, H-5), 4.03 (m, 2H, H-4, H-5), 3.58 (t, *J* = 5.7 Hz, 2H, H-2'), 1.87 (m, 2H, H-1'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7 (C=O), 129.8 (*i*-Ar), 128.6 (Ar), 128.0 (Ar), 127.7 (Ar), 73.5 (Bn), 70.4 (C-5), 67.6 (C-2'), 52.0 (C-4), 35.1 (C-1'); HRMS (ESI): *m/z* 222.1119 $[M + H]^+$, $C_{12}H_{16}NO_3$ requires 222.1130.

The ee (88%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol 70:30, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 8.62 min, τ_{minor} = 9.71 min.

(*R*)-4-(2-(Prop-2-yn-1-yloxy)ethyl)oxazolidin-2-one



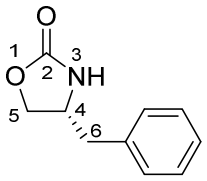
68

Synthesised using **General procedure 5** with oxazolidinone **59** and Cs_2CO_3 to give **68** (81% yield) as a colourless oil.

$[\alpha]_D^{20}$ +21.3 (*c* = 1.0, DCM); IR ($CHCl_3$) ν_{max}/cm^{-1} 1733 (C=O), 1243 (C-O); ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (br s, 1H, NH), 4.50 (m, 1H, H-5), 4.14 (d, *J* = 2.4 Hz, 2H, H-1''), 4.03 (m, 2H, H-4, H-5), 3.63 (t, *J* = 5.7 Hz, 2H, H-2'), 2.46 (t, *J* = 2.4 Hz, 1H, H-3''), 1.85 (m, 2H,

H-1'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (C=O), 79.3 (C-2''), 74.9 (C-3''), 70.4 (C-5), 67.1 (C-2'), 58.4 (C-1''), 51.6 (C-4), 34.9 (C-1'); HRMS (ESI): *m/z* 170.0809 $[M + H]^+$, $C_8H_{12}NO_3$ requires 170.0817.

(*R*)-4-Benzyloxazolidin-2-one



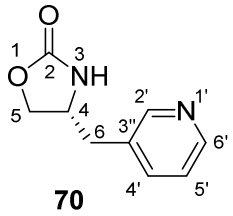
69

Synthesised using **General procedure 5** with oxazolidinone **60** and K_2CO_3 to give **69** (84% yield) as a colourless oil.

$[\alpha]_D^{20}$ +51.4 (*c* = 1.0, DCM); IR ($CHCl_3$) ν_{max}/cm^{-1} 1738 (C=O), 1246 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2H, Ar), 7.28 (m, 1H, Ar), 7.20 (m, 2H, Ar), 6.08 (br s, 1H, NH), 4.43 (t, *J* = 5.7 Hz, 1H, H-5), 4.11 (m, 2H, H-4, H-5), 2.93 (dd, *J* = 10.2, 4.8 Hz, 1H, H-6), 2.86 (dd, *J* = 10.2, 4.8 Hz, 1H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C=O), 135.9 (*i*-Ar), 129.0 (Ar), 128.9 (Ar), 127.1 (Ar), 69.5 (C-5), 53.7 (C-4), 41.3 (C-6); HRMS (ESI): *m/z* 178.0864 $[M + H]^+$, $C_{10}H_{12}NO_2$ requires 178.0868.

The ee (84%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol 50:50, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 6.71 min, τ_{minor} = 6.04 min.

(*R*)-4-(Pyridin-3-ylmethyl)oxazolidin-2-one



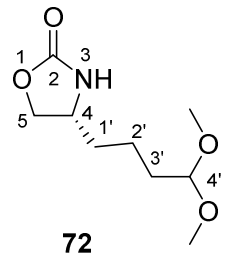
70

Synthesised using **General procedure 5** with oxazolidinone **61** and Cs_2CO_3 to give **70** (90% yield) as a colourless oil.

$[\alpha]_D^{20}$ +18.5 (*c* = 1.0, MeOH); IR ($CHCl_3$) ν_{max}/cm^{-1} 1771 (C=O), 1726 (C=O), 1222 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H, H-2'), 8.45 (d, *J* = 3.5 Hz, 1H, H-6'), 7.70 (m, 1H, H-4'), 7.30 (dd, *J* = 6.0, 3.5 Hz, 1H, H-5'), 6.79 (br s, 1H, NH), 4.42 (t, *J* = 6.3 Hz, 1H, H-5), 4.23 (m, 1H, H-4), 4.10 (dd, *J* = 6.3, 4.2 Hz, 1H, H-5), 2.96 (d, *J* = 4.5 Hz, 2H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (C=O), 151.6 (Ar), 149.1 (Ar), 137.8 (Ar), 133.6 (*i*-Ar), 124.5 (Ar), 69.8 (C-5), 53.9 (C-4), 39.0 (C-6); HRMS (ESI): *m/z* 179.0819 $[M + H]^+$, $C_9H_{11}N_2O_2$ requires 179.0821.

The ee (92%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol 60:40, flow rate = 1 ml/min, λ = 258 nm); τ_{major} = 14.92 min, τ_{minor} = 13.44 min.

(*R*)-4-(4,4-Dimethoxybutyl)oxazolidin-2-one



72

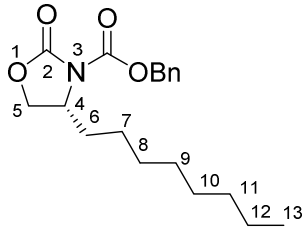
Synthesised using **General procedure 5** with oxazolidinone **63** and K_2CO_3 to give **72** (86% corrected yield based on a 70% conversion of **63**) as a colourless oil.

$[\alpha]_D^{20}$ -27.1 (*c* = 0.5, DCM); IR ($CHCl_3$) ν_{max}/cm^{-1} 1748 (C=O), 1263 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (br s, 1H, NH), 4.45 (t, *J* = 8.3 Hz, 1H, H-5), 4.33 (t, *J* = 5.4 Hz, 1H, H-4'), 3.99 (dd, *J* = 8.3, 6.0 Hz, 1H, H-5), 3.84 (m, 1H, H-4), 3.30 (s, 3H, OMe), 3.29 (s, 3H, OMe), 1.58 (m, 4H, H-1', H-3'), 1.37 (m, 2H, H-2'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (C=O), 104.2 (C-4'), 80.6 (C-5), 68.8 (C-4), 55.2 (OMe), 50.0 (OMe), 30.3 (C-1'), 29.4 (C-3'), 17.5 (C-2'); HRMS (ESI): *m/z* 226.1052 $[M + Na]^+$, $C_9H_{17}NO_4Na$ requires 226.1055.

General Procedure 6: Cbz-derivatisation of oxazolidinones

To a solution of oxazolidinone (4.00 mmol, 1.0 equiv) in THF (10.0 ml) at 0 °C, was added NaH (60% in mineral oil, 120 mg, 3.00 mmol, 1.5 equiv) and the reaction was stirred for 15 min at 0 °C. A solution of benzyl chloroformate (0.30 ml, 2.00 mmol, 1.0 equiv) in THF (10.0 ml) was then added dropwise and the reaction mixture was stirred for 3 hrs at room temperature before being quenched with NH_4Cl (10.0 ml) and extracted with EtOAc (3 x 20.0 ml). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was chromatographed on silica gel with ethyl acetate / petroleum ether mixtures.

Benzyl (*R*)-4-octyl-2-oxooxazolidine-3-carboxylate



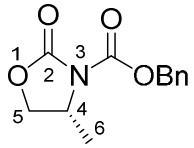
73

Synthesised from **52** using **General procedure 6** to give **73** (88% yield) as a white solid.

$[\alpha]_D^{20}$ -7.0 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1792 (C=O), 1725 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.19 (m, 5H, Ar), 4.58 (s, 2H, Bn), 4.20 (m, 2H, H-5, H-4), 3.95 (m, 1H, H-5), 2.01–1.53 (m, 2H, H-6), 1.19 (m, 12H, H-7–H-12), 0.80 (t, *J* = 6.0 Hz, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (C=O), 151.6 (C=O), 135.6 (*i*-Ar), 128.9 (Ar), 128.7 (Ar), 128.5 (Ar), 69.6 (C-5), 66.5 (Bn), 50.9 (C-4), 35.4 (C-6), 31.5 (C-11), 29.6 (C-8), 29.6 (C-9), 29.3 (C-10), 24.6 (C-7), 22.5 (C-12), 14.3 (C-13); HRMS (ESI): *m/z* 356.1831 $[M+Na]^+$, $C_{19}H_{27}NNaO_4$ requires 356.1838.

The ee (83%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.3 ml/min, λ = 258 nm); τ_{major} = 15.07 min, τ_{minor} = 14.25 min.

Benzyl (*R*)-4-methyl-2-oxooxazolidine-3-carboxylate



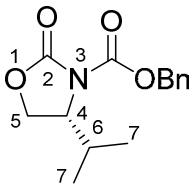
74

Synthesised from **64** using **General procedure 6** to give **74** (88% yield) as a white solid.

$[\alpha]_D^{20}$ -9.0 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1735 (C=O), 1718 (C=O), 1251 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H, Ar), 5.23 (s, 2H, Bn), 4.32 (m, 2H, H-5, H-4), 3.85 (m, 1H, H-5), 1.34 (d, *J* = 6.0 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (C=O), 150.8 (C=O), 135.0 (*i*-Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 68.6 (Bn), 68.6 (C-5), 51.3 (C-4), 19.6 (C-6); HRMS (ESI): *m/z* 251.1036 $[M + H]^+$, $C_{12}H_{15}N_2O_4$ requires 251.1032.

The ee (96%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.5 ml/min, λ = 258 nm); τ_{major} = 31.62 min, τ_{minor} = 23.81 min.

Benzyl (*R*)-4-isopropyl-2-oxooxazolidine-3-carboxylate



75

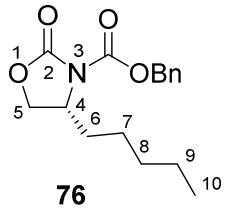
Synthesised from **65** using **General procedure 6** to give **75** (88% yield) as a white solid.

$[\alpha]_D^{20}$ -8.0 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1800 (C=O), 1714 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H, Ar), 5.25 (s, 2H, Bn), 4.15 (m, 3H, H-5, H-4), 2.33–2.21 (m, 1H, H-6), 0.91 (d, *J* = 4.5 Hz, 3H, H-7), 0.84 (d, *J* = 6.6 Hz, 3H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C=O), 155.1 (C=O), 136.1 (*i*-Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar),

67.1 (Bn), 65.2 (C-4), 60.7 (C-5), 28.5 (C-6), 17.2 (C-7), 16.9 (C-7); HRMS (ESI): *m/z* 286.1048 $[M+Na]^+$, $C_{14}H_{17}NNaO_4$ requires 286.1055.

The ee (92%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.5 ml/min, λ = 258 nm); τ_{major} = 26.70 min, τ_{minor} = 29.63 min.

Benzyl (*R*)-2-oxo-4-pentyloxazolidine-3-carboxylate



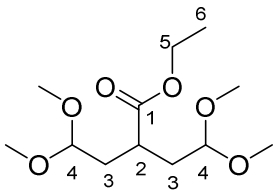
76

Synthesised from **66** using **General procedure 6** to give **76** (88% yield) as a white solid.

$[\alpha]_D^{20}$ -9.0 (*c* = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1737 (C=O), 1726 (C=O), 1251 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.22 (m, 5H, Ar), 5.25 (s, 2H, Bn) 5.20 (m, 2H, H-5, H-4), 4.02 (t, *J* = 6.0 Hz, 1H, H-5), 2.32 (m, 2H, H-6), 1.98 (m, 6H, H-7-H-9), 0.91 (t, *J* = 6.2 Hz, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (C=O), 151.7 (C=O), 135.5 (*i*-Ar), 128.7 (Ar), 128.7 (Ar), 128.5 (Ar), 69.5 (C-5), 66.2 (Bn), 51.8 (C-4), 35.6 (C-6), 31.8 (C-8), 23.0 (C-7), 22.4 (C-9), 14.0 (C-10); HRMS (ESI): *m/z* 292.1537 $[M + H]^+$, $C_{16}H_{22}NO_4$ requires 292.1549.

The ee (88%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.3 ml/min, λ = 258 nm); τ_{major} = 41.29 min, τ_{minor} = 44.52 min.

Ethyl 2-(2,2-dimethoxyethyl)-4,4-dimethoxybutanoate

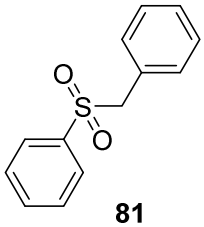


77

Synthesised from **36** using **General procedure 1** on a 5.6 mmol scale, to give **77** (950 mg, 64 % yield) as a colourless oil.

IR ($CHCl_3$) ν_{max}/cm^{-1} 1727 (C=O), 1265 (C-O), 1124 (C-O), 1093 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 4.46 (t, *J* = 5.4 Hz, 2H, H-4), 4.20 (q, *J* = 7.2 Hz, 2H, H-5), 3.37 (s, 6H, 2xOMe), 3.36 (s, 6H, 2xOMe), 2.65 (m, 1H, H-2), 2.04 (ddd, *J* = 13.7, 7.5, 5.4 Hz, 2H, H-3), 1.80 (ddd, *J* = 13.7, 7.5, 5.4 Hz, 2H, H-3), 1.37 (t, *J* = 7.2 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3 (C-1), 103.0 (C-4), 60.3 (C-5), 53.2 (OMe), 53.0 (OMe), 37.7 (C-2), 35.4 (C-3), 14.2 (C-6); HRMS (ESI): *m/z* 287.1476 $[M + Na]^+$, $C_{12}H_{24}O_6Na$ requires 287.1471.

(Benzylsulfonyl)benzene[273]



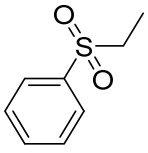
81

To a mixture of thiophenol (3.31 g, 30.0 mmol, 1 equiv) and K_2CO_3 (4.56 g, 30.0 mmol, 1.1 equiv) in DMF (25.0 ml) was added benzyl bromide (5.13 g, 30.0 mmol, 1 equiv). The reaction mixture was then stirred at room temperature for 18 hours, after which it was quenched with water (30.0 ml), extracted with ethyl acetate (3 x 50.0 ml) and washed with brine (3 x 50.0 ml). The organic layer was then dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude sulfide product was judged pure enough to continue to the next step.

To a solution of the crude sulfide in DCM (150 ml) was added *m*-CPBA (18.1 g, 105 mmol, 3.5 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred for a further 18 hrs. The reaction was then quenched with saturated $NaHCO_3$ (150 ml) and stirred for 2 hours. The reaction mixture was extracted with DCM (3 x 50.0 ml) the organic layer dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (20% ethyl acetate / petroleum ether) to give **81** (4.60 g, 66% yield over two steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.59 (m, 3H, Ar), 7.43-7.35 (m, 2H, Ar), 7.24-7.12 (m, 3H, Ar), 7.09-7.08 (m, 2H, Ar), 4.33 (s, 2H, CH_2).

(Ethylsulfonyl)benzene[274]



82

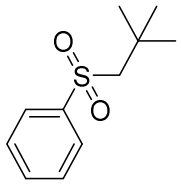
To a mixture of thiophenol (3.31 g, 30.0 mmol, 1 equiv) and K_2CO_3 (4.56 g, 30.0 mmol, 1.1 equiv) in DMF (25.0 ml) was added iodoethane (4.71 g, 30.2 mmol, 1 equiv). The reaction mixture was then stirred at room temperature for 18 hours, after which it was quenched with water (30.0 ml), extracted with ethyl acetate (3 x 50.0 ml) and washed with brine (3 x 50.0 ml). The organic layer was then dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude sulfide product was judged pure enough to continue to the next step.

To a solution of the crude sulfide in CH_3CN (150 ml) was added *m*-CPBA (18.1 g, 105 mmol, 3.5 equiv) at 0 °C. The reaction mixture was warmed to 50 °C and stirred for a further 18 hrs.

The reaction was then cooled to room temperature, quenched with saturated $NaHCO_3$ (150 ml) and stirred for 2 hours. The reaction mixture was extracted with DCM (3 x 50.0 ml), the organic layer dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (20% ethyl acetate / petroleum ether) to give **82** (4.00 g, 78% yield over two steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 2H, Ar), 7.65-7.49 (m, 3H, Ar), 3.10 (q, *J* = 5.4 Hz, 2H, CH_2) 1.24 (t, *J* = 5.4 Hz, 3H, CH_3).

((4-Methylhe(Neopentylsulfonyl)benzene



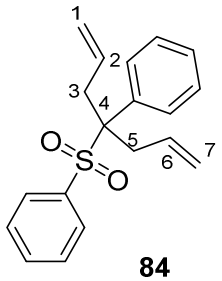
83

To a mixture of thiophenol (6.62 g, 60.0 mmol, 1 equiv) and K_2CO_3 (9.12 g, 60.0 mmol, 1.1 equiv) in DMF (50.0 ml) was added neopentyl bromide (5.13 g, 60.0 mmol, 1 equiv). The reaction mixture was warmed to 100 °C and then stirred for 18 hours, after which water (60.0 ml) was added and the organic material extracted into ethyl acetate (3 x 100 ml), and washed with brine (3 x 50.0 ml). The organic layer was then dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude sulfide product was judged pure enough (by TLC) to continue to the next step.

To a solution of the crude sulfide in CH_3CN (150 ml) was added *m*-CPBA (20.7 g, 120 mmol, 3.5 equiv) at 0 °C. The reaction mixture was warmed to 50 °C and stirred for a further 18 hrs. The reaction was then cooled to room temperature, quenched with saturated $NaHCO_3$ (150 ml) and stirred for 2 hours. The reaction mixture was then extracted with ethyl acetate (3 x 100 ml), the organic layer dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (20% ethyl acetate / petroleum ether) to give **83** (5.70 g, 45% yield over two steps) as colourless crystals.

M.p. 34-36 °C (from DCM / *n*-Hexane); IR ($CHCl_3$) ν_{max}/cm^{-1} 1314 (S=O), 1307 (S=O), 1151 (S=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 2H, Ar), 7.64-7.48 (m, 3H, Ar), 3.02 (s, 2H, CH_2), 1.17 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (*i*-Ar), 133.3 (Ar), 129.2 (Ar), 127.5 (Ar), 67.7 (CH_2), 32.5 (*t*-Bu), 29.8 (CH_3); HRMS (ESI): *m/z* 213.0953 $[M + H]^+$, $C_{11}H_{17}O_2S$ requires 213.0949.

((4-Phenylhepta-1,6-dien-4-yl)sulfonyl)benzene

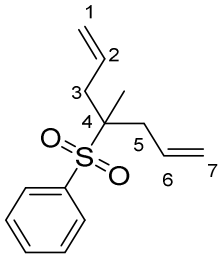


84

To a solution of sulfone **81** (2.33 g, 10.0 mmol, 1 equiv) in THF (30.0 ml) at 0 °C was added *n*-BuLi (7.90 ml, 1.4 M, 11.0 mmol, 1.1 equiv) in a dropwise fashion. The reaction mixture was then warmed to reflux for 30 minutes. Allyl bromide (0.870 ml, 10.0 mmol, 1 equiv) was then added at room temperature, after which the reaction mixture was heated to reflux for a further hour after which consumption of the starting material was observed on TLC. The reaction mixture was then cooled to 0 °C and a further aliquot of *n*-BuLi (7.90 ml, 1.4 M, 11.0 mmol, 1.1 equiv) was added in a dropwise fashion. The reaction mixture was then warmed to reflux for 30 minutes. Allyl bromide (0.870 ml, 10.0 mmol, 1 equiv) was then added at room temperature, after which the reaction mixture was heated to reflux for a further hour after which consumption of the monoallyl intermediate was observed on TLC. The reaction mixture was then quenched with saturated NH_4Cl solution (20.0 ml) and extracted with ethyl acetate (3 x 20.0 ml). The organic layer was dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (5% ethyl acetate / petroleum ether) to give **84** (1.75 g, 56% yield) as colourless crystals.

M.p. 88-91 °C (from DCM / *n*-Hexane); IR ($CHCl_3$) ν_{max}/cm^{-1} 1305 (S=O), 1295 (S=O), 1148 (S=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.52 (m, 2H, Ar), 7.36-7.25 (m, 8H, Ar), 6.02-5.84 (m, 2H, H-2/6), 5.29-5.14 (m, 4H, H-1/7), 3.35 (ddt, *J* = 15.0, 6.6, 1.9 Hz, 2H, H-3/5), 3.09 (ddt, *J* = 15.0, 6.6, 1.9 Hz, 2H, H-3/5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (*i*-Ar), 134.6 (*i*-Ar), 133.3, 132.0, 130.2, 129.6, 128.6, 128.1, 127.8, 119.4 (C-1/7), 70.7 (C-4), 35.1 (C-3/5); HRMS (ESI): *m/z* 305.1071 $[M + Na]^+$, $C_{19}H_{20}O_2NaS$ requires 305.1082.

((4-Methylhepta-1,6-dien-4-yl)sulfonyl)benzene

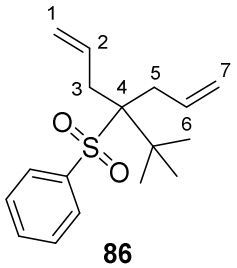


85

To a solution of sulfone **82** (2.00 g, 11.8 mmol, 1 equiv) in THF (40.0 ml) at 0 °C was added *n*-BuLi (9.20 ml, 1.4 M, 12.9 mmol, 1.1 equiv) in a dropwise fashion. The reaction mixture was then warmed to reflux for 30 minutes. Allyl bromide (1.02 ml, 11.75 mmol, 1 equiv) was then added at room temperature, after which the reaction mixture was heated to reflux for a further hour after which consumption of the starting material was observed on TLC. The reaction mixture was then cooled to 0 °C and a further aliquot of *n*-BuLi (9.20 ml, 1.4 M, 12.9 mmol, 1.1 equiv) was added in a dropwise fashion. The reaction mixture was then warmed to reflux for 30 minutes. Allyl bromide (1.02 ml, 11.75 mmol, 1 equiv) was then added at room temperature, after which the reaction mixture was heated to reflux for a further hour after which consumption of the monoallyl intermediate was observed on TLC. The reaction mixture was quenched with saturated NH_4Cl solution (20.0 ml) and extracted with ethyl acetate (3 x 20.0 ml). The organic layer was dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (5% ethyl acetate / petroleum ether) to give **85** (1.02 g, 35% yield) as colourless crystals.

M.p. 43-46 °C (from DCM / *n*-Hexane); IR ($CHCl_3$) ν_{max}/cm^{-1} 1302 (S=O), 1293 (S=O), 1146 (S=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 2H, Ar), 7.70-7.53 (m, 3H, Ar), 5.98-5.84 (m, 2H, H-2/6), 5.16-5.01 (m, 4H, H-1/7), 2.54 (ddt, *J* = 14.4, 6.9, 1.2 Hz, 2H, H-3/5), 2.41 (ddt, *J* = 14.4, 6.9, 1.2 Hz, 2H, H-3/5), 1.25 (s, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (*i*-Ar), 133.6, 132.1, 130.4, 128.7, 119.4 (C-1/7), 65.2 (C-4), 38.0 (C-3/5), 19.5 (Me); HRMS (ESI): *m/z* 251.1098 $[M + H]^+$, $C_{14}H_{19}O_2S$ requires 251.1106; Analysis: found C 66.45%, H 7.53%, S 11.98%; $C_{21}H_{24}N_2O_6$ requires C 67.17%, H 7.25%, N 12.81%.

((4-(*tert*-Butyl)hepta-1,6-dien-4-yl)sulfonyl)benzene

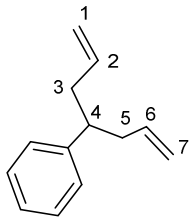


86

To a solution of sulfone **83** (4.25 g, 20.0 mmol, 1 equiv) and THF (60.0 ml) at 0 °C was added *n*-BuLi (15.7 ml, 1.4 M, 22.0 mmol, 1.1 equiv) in a dropwise fashion. The reaction mixture was then warmed to reflux for 30 minutes. Allyl bromide (1.73 ml, 20.0 mmol, 1 equiv) was then added at room temperature, after which the reaction mixture was heated to reflux for a further hour after which consumption of the starting material was observed on TLC. The reaction mixture was then cooled to 0 °C and a further aliquot of *n*-BuLi (15.7 ml, 1.4 M, 22.0 mmol, 1.1 equiv) was added in a dropwise fashion. The reaction mixture was then warmed to reflux for 30 minutes. Allyl iodide (1.83 ml, 20.0 mmol, 1 equiv) was then added at room temperature, after which the reaction mixture was heated to reflux for a further hour after which consumption of the monoallyl intermediate was observed on TLC. The reaction mixture was quenched with saturated NH_4Cl solution (40.0 ml) and extracted with ethyl acetate (3 x 40.0 ml). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (5% ethyl acetate / petroleum ether) to give **86** (3.75 g, 64% yield) as yellowish crystals.

M.p. 68-70 °C (from DCM / *n*-Hexane); IR ($CHCl_3$) IR ($CHCl_3$) ν_{max}/cm^{-1} 1301 (S=O), 1286 (S=O), 1134 (S=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 2H, Ar), 7.70-7.55 (m, 3H, Ar), 6.11-5.97 (m, 2H, H-2/6), 5.15-5.06 (m, 4H, H-1/7), 2.72 (ddt, *J* = 15.6, 6.9, 1.5 Hz, 2H, H-3/5), 2.59 (ddt, *J* = 15.6, 6.9, 1.5 Hz, 2H, H-3/5), 1.34 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (*i*-Ar), 134.4, 133.3, 130.6, 128.7, 118.2 (C-1/7), 75.5 (C-4), 39.4 (*t*-Bu), 38.0 (C-3/5), 28.8 (CH_3); HRMS (ESI): *m/z* 315.1071 $[M + Na]^+$, $C_{17}H_{24}O_2NaS$ requires 315.1380.

Hepta-1,6-dien-4-ylbenzene[276]

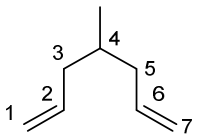


87

Sulfone **84** (2.50 g, 8.00 mmol, 1 equiv) was dissolved in dry MeOH (80.0 ml). Grignard magnesium (7.00 g, 288 mmol, 36 equiv) was added and the reaction was warmed to 50 °C and stirred for 3 hours, whilst carefully monitoring the exothermic reaction. When complete consumption of the sulfone was observed on TLC the reaction was quenched with 2 M HCl (150 ml) at 0 °C and allowed to warm up to room temperature. The reaction mixture was then extracted with ethyl acetate (3 x 50.0 ml) and washed with $NaHCO_3$ (100 ml) and finally with brine (100 ml). The organic layer was dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by filtering over a pad of silica (2% ethyl acetate / petroleum ether) to give **87** (1.07 g, 78% yield) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.07 (m, 5H, (Ar), 5.71-5.53 (m, 2H, H-2/6), 4.90 (m, 4H, H-1/7), 2.63 (m, 1H, H-4), 2.43-2.25 (m, 4H, H-3/5).

4-Methylhepta-1,6-diene[282]

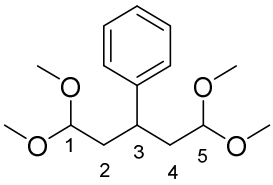


88

Sulfone **85** (1.20 g, 4.79 mmol, 1 equiv) was dissolved in dry MeOH (50.0 ml). Grignard magnesium (4.31 g, 177 mmol, 37 equiv) was added and the reaction was warmed to 50 °C and stirred for 3 hours, whilst carefully monitoring the exothermic reaction. When complete consumption of the sulfone was observed on TLC the reaction was quenched with 2 M HCl (200 ml) at 0 °C and allowed to warm up to room temperature. The reaction mixture was then extracted with ethyl acetate (3 x 30.0 ml) and washed with $NaHCO_3$ (50.0 ml), and finally with brine (50.0 ml). The organic layer was dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by filtering over a pad of silica (2% ethyl acetate / petroleum ether) to give **88** (40.0 mg, 8% yield) as a volatile colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01-5.82 (m, 2H, H-2/6), 5.07-4.97 (m, 4H, H-1/7), 2.19 (m, 4H, H-3/5), 1.97 (m, 1H, H-4), 0.89 (m, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (C-2/6), 116.4 (C-1/7), 42.4 (C-4), 40.9 (C-3/5), 20.9 (Me).

(1,1,5,5-Tetramethoxypentan-3-yl)benzene

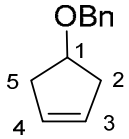


90

Synthesised from **87** using **General procedure 1** on a 5.10 mmol scale to give **90** (540 mg, 39 % yield) as a colourless oil.

IR ($CHCl_3$) v_{max}/cm^{-1} 1265 (C-O), 1124 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 2H, Ar), 7.22 (m, 3H, Ar), 4.09 (dd, *J* = 7.7, 4.2 Hz, 2H, H-1/5), 3.29 (s, 6H, 2xOMe), 3.22 (s, 6H, 2xOMe), 2.88 (m, 1H, H-3), 2.01 (ddd, *J* = 14.1, 7.7, 5.4 Hz, 2H, H-2/4), 1.84 (ddd, *J* = 14.1, 9.9, 4.2 Hz, 2H, H-2/4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (*i*-Ar), 128.3 (Ar), 127.6 (Ar), 126.0 (Ar), 102.6 (C-1/5), 52.6 (OMe), 52.5 (OMe), 39.4 (C-2/4), 37.6 (C-3); HRMS (ESI): *m/z* 291.1567 $[M + Na]^+$, $C_{15}H_{24}O_4Na$ requires 291.1572.

((Cyclopent-3-en-1-yloxy)methyl)benzene[283]

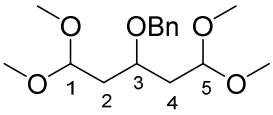


91

To a solution of cyclopent-3-en-1-ol (750 mg, 8.90 mmol, 1 equiv) in THF (50.0 ml) was added NaH (60% in mineral oil, 429 mg, 10.7 mmol, 1.2 equiv) at 0 °C and the reaction mixture was warmed to room temperature and stirred for a further 1 hour. Benzyl bromide (1.40 ml, 11.9 mmol, 1.5 equiv) was then added along with TBAI (329 mg, 0.890 mmol, 10 mol%) and the reaction mixture was warmed to reflux for 19 hours. When complete consumption of the alcohol was observed on TLC the reaction was quenched with water (50.0 ml) and extracted with ethyl acetate (3 x 30.0 ml). The organic layers were dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (2% ethyl acetate / petroleum ether) to give **91** (1.55 g, quantitative yield) as a colourless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.17 (m, 5H, Ar), 5.60 (m, 2H, H-3/4), 4.40 (s, 2H, Bn), 4.22 (m, 1H, H-1), 2.51 (m, 2H, H-2/5), 2.37 (m, 2H, H-2/5).

(((1,1,5,5-Tetramethoxypentan-3-yl)oxy)methyl)benzene

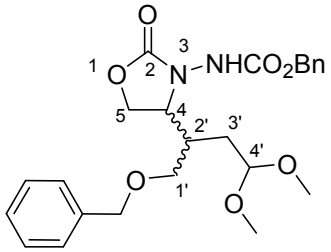


92

Synthesised from **91** using **General procedure 1** on a 5.74 mmol scale, to give **92** (800 mg, 47% yield) as a colourless oil.

IR ($CHCl_3$) ν_{max}/cm^{-1} 1276 (C-O), 1121 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.22 (m, 5H, Ar), 4.51 (dd, *J* = 6.6, 5.0, 2H, H-1/5), 4.49 (s, 2H, Bn) 3.65 (m, 1H, H-3), 3.28 (s, 6H, 2xOMe), 3.26 (s, 6H, 2xOMe), 1.87 (ddd, *J* = 14.4, 7.2, 5.0 Hz, 2H, H-2/4), 1.79 (ddd, *J* = 14.4, 6.6, 5.4 Hz, 2H, H-2/4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (*i*-Ar), 128.3 (Ar), 127.8 (Ar), 127.5 (Ar), 102.0 (C-1/5), 72.8 (Bn), 71.4 (C-3), 52.9 (OMe), 52.6 (OMe), 37.9 (C-2/4); HRMS (ESI): *m/z* 321.1677 $[M + Na]^+$, $C_{16}H_{26}O_5Na$ requires 321.1678.

Benzyl (4-(1-(benzyloxy)-4,4-dimethoxybutan-2-yl)-2-oxooxazolidin-3-yl)carbamate



94

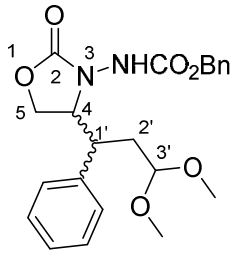
Dibenzyl azodicarboxylate (150 mg, 0.50 mmol, 1 equiv) was added to a mixture of bis-acetal **40** (700 mg, 2.24 mmol, 4.5 equiv), tetrazole catalyst (14 mg, 0.10 mmol, 20 mol%), MCA (246 mg, 2.60 mmol, 5.2 equiv), TFA (4.0 µl, 0.05 mmol, 0.1 equiv) and water (45 mg, 2.50 mmol, 5 equiv) in DCM (10.0 ml). The reaction mixture was kept at 4 °C until complete consumption of the DBAD was observed by TLC. On reaction completion, the reaction mixture was quenched with water (10.0 ml) and extracted with DCM (3 x 10.0 ml) and the organic extracts were washed with saturated $NaHCO_3$ (10.0 ml) and brine (10.0 ml). The organic layer was then dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. To the resultant residue was added MeOH (5.0 ml) and $NaBH_4$ (18.9 mg, 0.5 mmol, 1 equiv) at 0 °C and the mixture was allowed to warm up to room temperature over 15 minutes. NaOH (1.50 ml, 1M, 1.50 mmol, 3 equiv) was then added and the reaction was stirred for 2 hours at room temperature, when complete consumption of the hydrazine was observed on TLC. The reaction was quenched with saturated NH_4Cl solution (10.0 ml) and extracted with ethyl acetate (3 x 10.0 ml). The organic layers were dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (35% ethyl

acetate / petroleum ether) to give **94** (140 mg, 61% yield) as a colourless gummy oil and a mixture of diastereomers (dr = 74:26).

For the major diastereomer (separated using preparative TLC): $[\alpha]_D^{20}$ +3.17 (*c* = 0.6, DCM); IR ($CHCl_3$) ν_{max}/cm^{-1} 1775 (C=O), 1716 (C=O), 1245 (C-O), 1207 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 10H, Ar), 6.94 (br s, 1H, NH), 5.19 (s, 2H, Bn), 4.46 (m, 2H, Bn), 4.37 (m, 2H, H-4', H-5), 4.25 (m, 2H, H-4, H-5), 3.48 (m, 2H, H-1'), 3.30 (s, 3H, OMe), 3.30 (s, OMe), 2.26 (m, 1H, H-2'), 1.60 (m, 2H, H-3'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157 (C=O), 157 (C=O), 137.6 (*i*-Ar), 135.5 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 127.9 (Ar), 127.5 (Ar), 104.5 (C-4'), 73.4 (Bn), 71.4 (Bn), 68.4 (C-1'), 66.6 (C-5), 55.6 (C-4), 50.8 (OMe), 50.8 (OMe), 31.2 (C-2'), 30.4 (C-3'); HRMS (ESI): *m/z* 481.1946 $[M + Na]^+$, $C_{24}H_{30}N_2O_7Na$ requires 481.1942.

The ee (80%) was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.5 ml/min, λ = 258 nm); τ_{major} = 57.15 min, τ_{minor} = 69.77 min. The dr (74:26) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.4 ml/min, λ = 258 nm); τ_{major} = 47.37 min, τ_{minor} = 39.23 min.

Benzyl (4-(3,3-dimethoxy-1-phenylpropyl)-2-oxooxazolidin-3-yl)carbamate



95

Dibenzyl azodicarboxylate (894 mg, 0.30 mmol, 1 equiv) was added to a mixture of bis-acetal **90** (400 mg, 1.50 mmol, 5 equiv), tetrazole catalyst (8.0 mg, 0.06 mmol, 20 mol%), MCA (147 mg, 1.56 mmol, 5.2 equiv), TFA (2.3 µl, 0.025 mmol, 0.1 equiv) and water (27.0 mg, 1.50 mmol, 5 equiv) in DCM (0.60 ml). The reaction mixture was kept at 4 °C until complete consumption of the DBAD was observed by TLC. On reaction completion, the reaction mixture was quenched with water (10.0 ml) and extracted with DCM (3 x 10.0 ml) and the organic extracts were washed with saturated $NaHCO_3$ (10.0 ml) and brine (10.0 ml). The organic layer was then dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. To the resultant residue was added MeOH (3.0 ml) and $NaBH_4$ (11.0 mg, 0.30 mmol, 1 equiv) at 0 °C and the mixture was allowed to warm up over 15 minutes to room temperature. NaOH (0.9 ml, 1M, 0.90 mmol, 3 equiv) was then added and the reaction was stirred for 2 hours at room temperature, when complete consumption of the hydrazine was observed on TLC. The reaction was quenched with saturated NH_4Cl solution (10.0 ml) and extracted with ethyl

acetate (3 x 10.0 ml). The organic layers were dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was then purified by flash column chromatography (35% ethyl acetate / petroleum ether) to give **95** (87 mg, 70% yield) as a yellowish gummy oil and a mixture of diastereomers (dr = 68:22).

For the major diastereomer (separated using preparative TLC): $[\alpha]_D^{20}$ -18.0 (*c* = 0.25, DCM); IR ($CHCl_3$) ν_{max}/cm^{-1} 1778 (C=O), 1718 (C=O), 1240 (C-O), 1212 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 8H, Ar), 7.15 (m, 2H, Ar), 7.09 (m, 1H, N-H), 5.23 (s, 2H, Bn), 4.31 (m, 1H, H-5), 4.16 (m, 1H, H-4), 4.05 (dd, *J* = 6.3, 2.4 Hz, 1H, H-5), 3.95 (t, *J* = 6.6 Hz, 1H, H-3'), 3.27 (s, 3H, OMe), 3.22 (s, 3H, OMe), 3.10 (m, 1H, H-1'), 2.27 (m, 1H, H-2'), 1.93 (m, 1H, H-2'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 (C=O), 155.2 (C=O), 138.5 (*i*-Ar), 135.3 (*i*-Ar), 129.1 (Ar), 128.7 (Ar), 128.5 (Ar), 128.3 (Ar), 128.2 (Ar), 127.8 (Ar), 102.7 (C-3'), 68.3 (Bn), 65.9 (C-5), 60.1 (C-4), 53.7 (OMe), 53.0 (OMe), 44.8 (C-1'), 35.2 (C-2'); HRMS (ESI): *m/z* 437.1687 $[M + Na]^+$, $C_{22}H_{26}N_2O_6Na$ requires 437.1689.

The ee (76%) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.4 ml/min, λ = 258 nm); τ_{major} = 22.16 min, τ_{minor} = 31.99 min. The dr (68:32) was determined by chiral HPLC using a Chiralpak OD column (*n*-hexane:*i*-propanol = 90:10, flow rate = 0.4 ml/min, λ = 258 nm); τ_{major} = 22.16 min, τ_{minor} = 54.90 min.

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