Use of cyclic and acyclic carbonates as solvents for amino acids and quinine catalysed asymmetric reactions

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Eskertu nahiko nuke ikerketan eta doktoratua iraundu duen lau urteetan tesia idazten lagundu nauen jende guztiari.

Guztioi aurrez aurre eskertzen zaiatu naiz baina oraindik gelditzen zarete.

Eskerrik asko zuen laguntza, aholku eta iradokisunengatik. Eskerrak nire ikuskatzaileei, idazkaritza taldeari, HPLC and NMR taldeari, beiragilea taldeari, nire kide, senide eta lagunei. Oso pertsona zoriontsua izan naiz Bedson Eraikingeko jende zoragarria ezagutzeagatik, niretzat ez da erreza izan eta horregatik oso eskertua sentitzen nahiz laguntza asko jaso izanagatik.

Guztioi, eskerrik asko!

Abbreviations

Boc	Butyloxycarbonyl
DBAD	Dibenzylazodicarboxylate
DEAD	Diethylazodicarboxylate
DEC	Diethyl carbonate
DHQN	Dihydroquinine
DHQD	Dihydroquinidine
DMAC	Dimethylacetamide
DMC	Dimethyl carbonate
DCM	Dichloromethane
dr	Diastereomeric ratio
EC	Ethylene carbonate
ee	Enantiomeric excess
EO	Ethylene oxide
$[\alpha]_D$	Optical rotation
t_R	Retention time
DABCO	1,4-Diazabicyclo[2.2.2]octane
LDA	Lithium diisopropylamide
NMP	N-Methyl pyrrolidine
NOx	Nitrogen Oxides
PC	Propylene carbonate
PO	Propylene oxide
SDS	Sodium dodecylsulphonate
SOMO	Singly occupied molecular orbital
TBS	*tert*-Butyldimethylsilyl
t-Bu	tertiary-butyl
TFA	Trifluoroacetic acid
TfOH	Triflic Acid
VOC	Volatile organic compound solvents
VO(salen) $EtOSO_3$	Ethylsulfonate vanadium complex

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1. Introduction

1.1 Background of Asymmetric Catalysis

Since 1968, the concept of a catalyst is well defined as a substance which accelerates the rate of a chemical reaction without affecting its equilibrium position. Apart from accelerating the reaction, catalysts play an important role in the selectivity of chemical reactions; therefore totally different products can be obtained from a starting material when changing the catalytic system.

The scientific development of catalysis started only 200 years ago and its importance has been growing over time, especially in the pharmaceutical industry, and 90% of all fine and bulk chemicals are obtained with the assistance of a catalyst. Many organic intermediates necessary for the production of plastics, synthetic fibres, pharmaceutical products, dry cleaners, resins and pigments can only be manufactured efficiently by means of catalytic processes. In this context, the need for new asymmetric compounds in the pharmaceutical and agrochemical industries leads to a constant requirement for new processes and catalysts able to perform novel asymmetric reactions.

A recent literature survey showed that in the pharmaceutical industry there are about 1850 compounds of which about 1327 have synthetic origin and 523 have a natural origin isolated from biomass (plants, animals, fermentation or by modification of a natural product). These compounds can be classified as chiral or achiral. Many of the natural compounds display optical activity and exist in enantiomeric forms. Only eight exist as racemates, this is due to structural modifications. In contrast, for synthetic compounds, achiral chemicals make up a slight majority of the total (just over 50%). A large proportion of chiral compounds are used as racemic mixtures (467) and only a few as enantiomerically pure compounds (Figure 1).

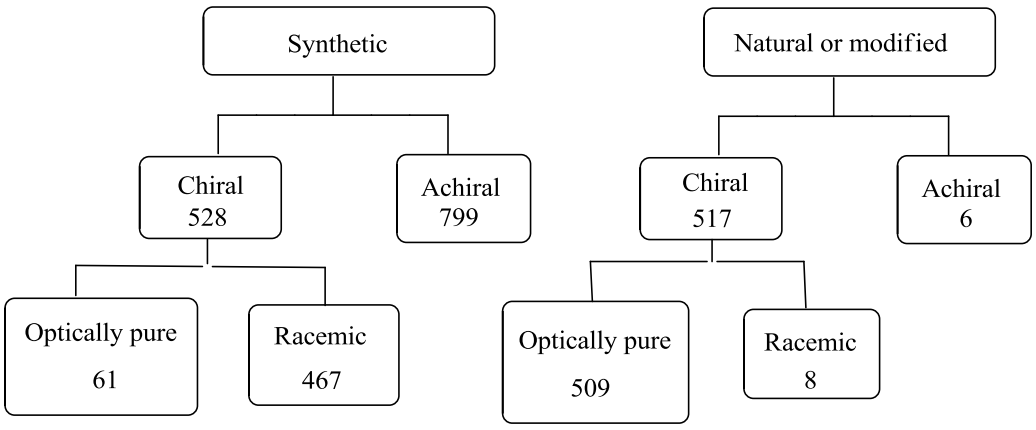


Figure 1.

Chirality is a fundamental symmetry property of 3D objects responsible for the non-superimposability of their mirror image. One atom can be connected with other atoms in the same order, but with different spatial arrangements. In such cases, there are two possible forms called enantiomers and the carbon which supports this difference is called an asymmetric or stereogenic centre. In some cases, a chiral compound can be different from its enantiomer through its biological properties (eg. taste or odor).[1] There are many cases that demonstrate this, for example the *S*-enantiomer of limonene possesses an aroma of lemon whereas *R*-limonene (the most common isomer) possesses an orange aroma (Figure 2). Another example is the case of the *L*-amino acids that do not possess taste or they are bitter whereas their enantiomers, the non-natural amino acids (*D*-amino acids) have a very sweet taste.[2]

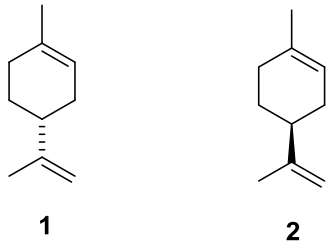


Figure 2. (*R*)-Limonene **1** and (*S*)-Limonene **2**.

Nature is stereoselective and often able to synthesise only one of the enantiomers of a chiral compound. One of the mysteries of life is why nature chooses the *L* (levorotatory) form for amino acids and *D* (dextrorotatory) form for sugars.

Differences in the properties and importance of enantiomers are best observed when they present physiological activities. Human beings and animals have the ability to metabolise *D*-glucose, but not *L*-glucose, which goes unnoticed in the digestive system. Leaves of the tobacco plant produce only *L*-nicotine whereas the sugar cane only produces *D*-sucrose. A countless number of chiral natural compounds are known.

A clear example of the importance of the concept of molecular asymmetry is the case of thalidomide[3] (Figure 3), a compound that was commercialized between 1958 and 1963 as a sedative and antinausea drug to be used during the first three months of pregnancy. This medicine caused millions of malformations in babies. A subsequent discovery revealed that the two enantiomers of thalidomide had different biological properties. The *R*-enantiomer was responsible for the sedative effect, but the *S*-enantiomer was found to be responsible for anomalies in fetus development. Moreover, subsequent scientific research confirmed that at physiological *pH*, the molecule racemises, hence the desired *R*-enantiomer was also prohibited for use in pregnant women. This discovery highlighted that the stereochemistry of drug molecules is an important factor to be taken into account, and thus asymmetric synthesis gained increased relevance.

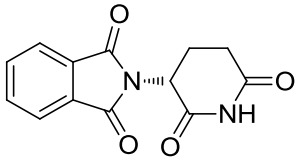
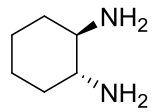


Figure 3. (*R*)-Thalidomide.

The main goal of asymmetric synthesis is the generation of single enantiomers of chiral compounds in a simple way. Different methods[4] can be used as shown in Figure 4; the resolution of racemates, the utilization of optically active natural molecules (chiral building blocks) and asymmetric synthesis through catalysis or auxiliaries.

The resolution of a racemate[5] has been widely used for obtaining single enantiomers. The process consists of a reaction of a racemate with an enantiomerically pure compound to afford two diastereomers that can be separated and converted back to the original enantiomers. However, resolution is undesirable as the maximum yield of product that can be obtained is 50% and the unwanted enantiomer must be disposed of.

The resolving agent can be recovered at the end of the process. A good example is (+)-tartaric acid used to resolve (*1R*, *2R*)-cyclohexane-1,2-diamine **3**.



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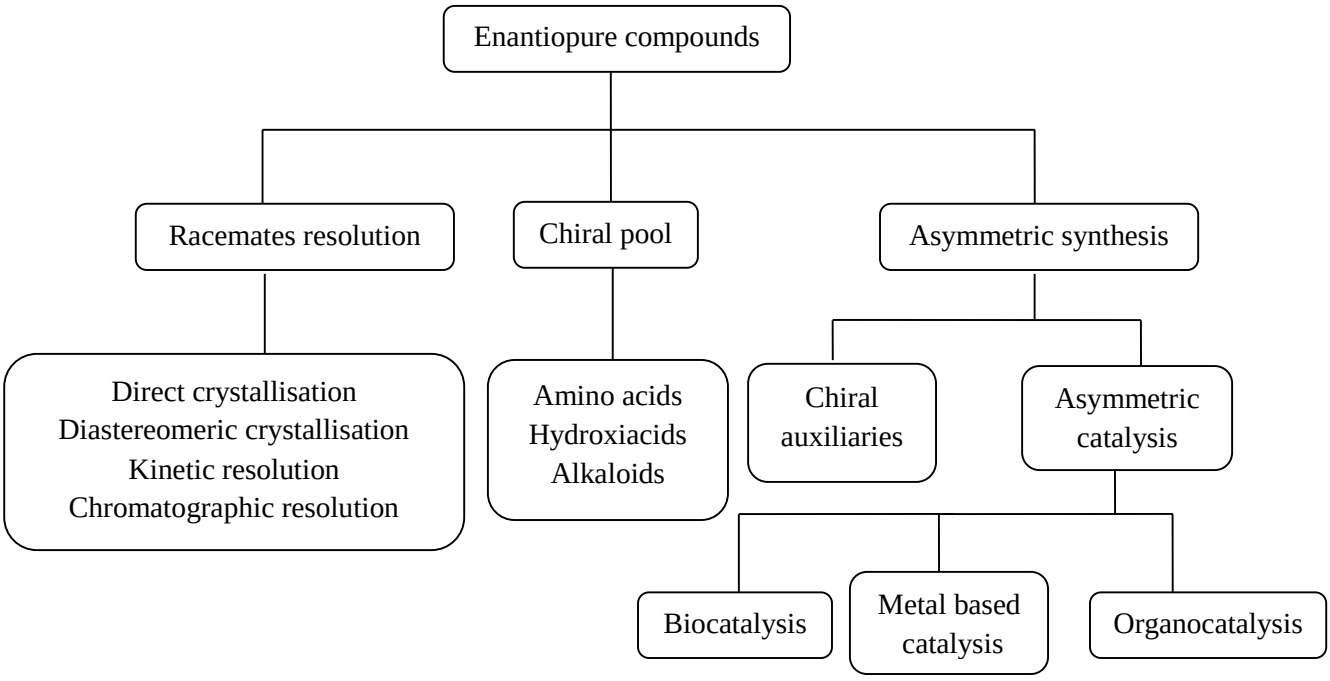


Figure 4. Methods for obtaining enantiomerically pure compounds.

The second option uses chiral starting materials that are already enantiomerically pure obtained from natural sources. Functional group transformations are then carried out until the desired compound is prepared. These transformations are carried out without loss of the configurational integrity in the initial stereogenic centers. In 1983 Hanessian introduced the concept of "Chiron" to describe these natural chiral molecules, such as amino acids, amino alcohols, hydroxy acids, alkaloids, terpenes, or sugars amongst others.

Asymmetric synthesis is the most attractive way for obtaining single enantiomers and it is widely used in industry due to its advantage in being able to transform a prochiral substrate into a chiral product.[6] The required chiral centres can be obtained by use of chiral auxiliaries, enzymes or non-enzymatic chiral catalysts, the latter requiring only a

relatively small amount of chiral catalyst which can sometimes be recovered at the end of the synthesis.

The employment of chiral auxiliaries[7] involves creating a covalent bond between the substrate and the optically pure auxiliary. The purpose of the auxiliary lies in the control of the stereoselectivity of subsequent reactions, giving rise to diastereomers, which are easily separable through conventional methods of chromatography.

The elimination of the auxiliary from the adduct completes the sequence, releasing the desired enantioenriched product. Compared to catalysis, this methodology requires two additional synthetic steps; one, the addition of the chiral auxiliary to the starting substrate and a second, to remove and recover the auxiliary to afford the final product. This strategy reached its peak in the 1980s and nowadays a wide range of auxiliaries for a large number of reactions are known. Some of the best known auxiliaries are shown in Figure 5.

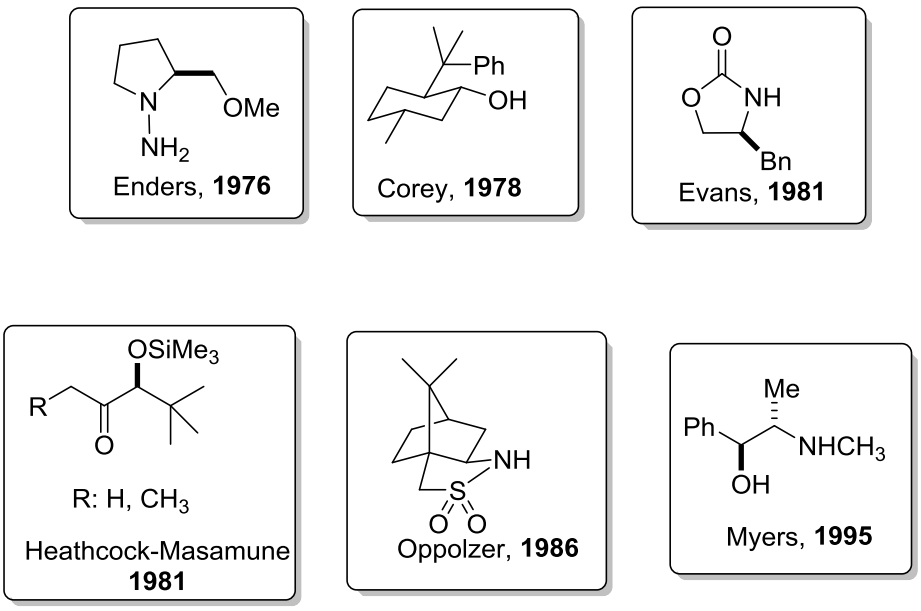


Figure 5. Example chiral auxiliaries.

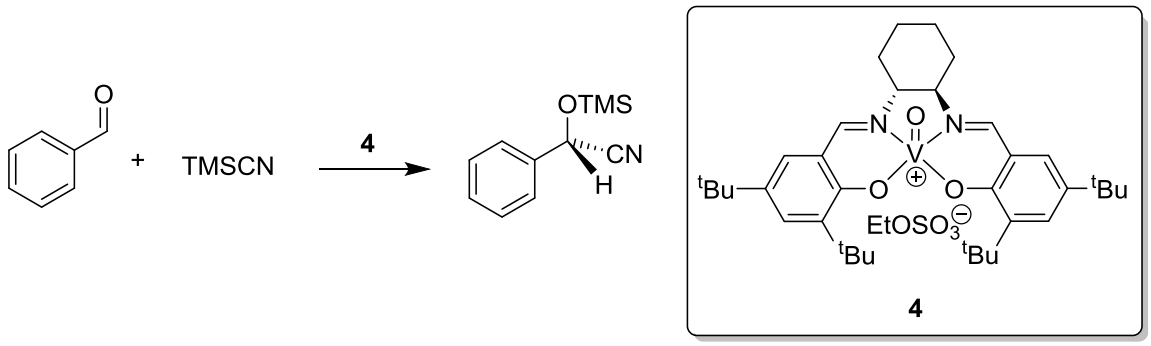
Asymmetric catalysis has become one of the most active areas of research in chemistry since the beginning of this century. In terms of the nature of the asymmetric catalyst, they can be classified into three groups: biocatalysts (enzymes), metal based catalysts and organocatalysts.

1.1.1 Enzymatic Catalysis

Enzymes[8] are highly effective biological catalysts used in nature to process or produce everything an organism requires to live. They consist of long amino acid chains that fold in a complex but highly specific manner in order to form the chiral environment necessary for an enantiopure molecule to be synthesized. Their catalytic power and specificity are their most important characteristics. These properties, and the efficiency with which they generate enantiomerically pure compounds, have made biocatalysis into one of the simplest alternatives for the stereoselective preparation of chiral compounds. The theoretical conversion of reactions catalysed by enzymes is 100%, constituting a very effective methodology for the synthesis of enantiomerically pure compounds. However, this high specificity results in a limitation in terms of generality and synthetic versatility, and several factors affect the activity of enzymes such as temperature, pH and concentrations of enzyme, substrate, and products which constitutes a major disadvantage in comparison to metal based catalysis or organocatalysis.

1.1.2 Metal Based Catalysis

Metal based catalysts have revolutionised organic synthesis. They are often used in catalytic asymmetric processes because of their high reactivity and high selectivity, being able to catalyse a reaction enantioselectively, with low catalyst loading and at room temperature. They are very popular in the bulk chemicals, fine chemicals and pharmaceutical industries, and applications also exist outside of these areas. One example is the synthesis of O-trimethylsilyl cyanohydrin ethers which has been carried out by North *et al.* [9] using a vanadium complex VO(salen) $EtOSO_3$ **4** as a catalyst (Scheme 1).



Scheme 1. The asymmetric trimethylsilylcyanation of benzaldehyde.

However, transition metal catalysis is not free from problems. One of the disadvantages of using metal catalysts is that they may leave toxic traces of metal in the product that can be difficult to remove completely from the reaction products. In pharmaceutical products this can prove problematic due to toxicity concerns.[10] The metals used are also often expensive. These disadvantages have led to organocatalysis becoming more prominent as an area of research.

1.1.3 Organocatalysis

The unfavorable features of metal based catalysts in organic synthesis can be overcome by using small organic molecules; organocatalysts. The term organocatalysis[11] was created by David MacMillan and describes the acceleration of chemical reactions by substoichiometric amounts of small organic molecules that do not contain a metal atom. Since the beginning of this century, asymmetric organocatalysis has become one of the most active areas of research in asymmetric synthesis, since they are usually robust, inexpensive, readily available and nontoxic because of the absence of a metal ion. Organocatalysts are generally stable and fairly easy to design and synthesize. In addition, they can be easily linked to a solid support, making them useful for industrial applications due to their versatility and low environmental impact.

A number of chiral organocatalysts have been used for asymmetric synthesis, including cinchona alkaloids such as quinine and various sugar, amino acid or peptide derived compounds, but the vast majority of catalytic systems are based on secondary amines which are usually more stable, less expensive, readily available, and can be applied under less demanding reaction conditions. Nowadays, research in organocatalysis is dominated by asymmetric reactions accelerated by "environmentally friendly" catalysts like the amino acid proline,[12] the most widely used catalyst for a wide range of asymmetric reactions with excellent results being obtained in many cases. Its high efficiency is clearly demonstrated in the asymmetric aldol reaction.

These organic molecules can catalyse chemical reactions through different mechanisms. The one focused on within this thesis is, the activation of reactions based on the nucleophilic/electrophilic properties of the catalyst, which is not consumed in the reaction and does not require parallel regeneration. This type of activation is reminiscent of conventional Lewis acid/base activation. For a better understanding of the described processes, a brief explanation of the fundamentals of the most representative activation modes regularly used in organocatalytic processes are described in the following section.

1.1.3.1 Modes of activation

From a mechanistic point of view, interactions between the catalyst and the substrate in asymmetric organocatalytic reactions are slightly different from the processes catalysed by metals. Organocatalysts provide a chiral environment for the activation of the nucleophile or the electrophile, or both at the same time through interactions that may be weak, as in the case of a hydrogen bond or ionic pair. They can be made stronger with the formation of a covalent bond, such as via enamine or iminium ion activation amongst others (Figure 6).

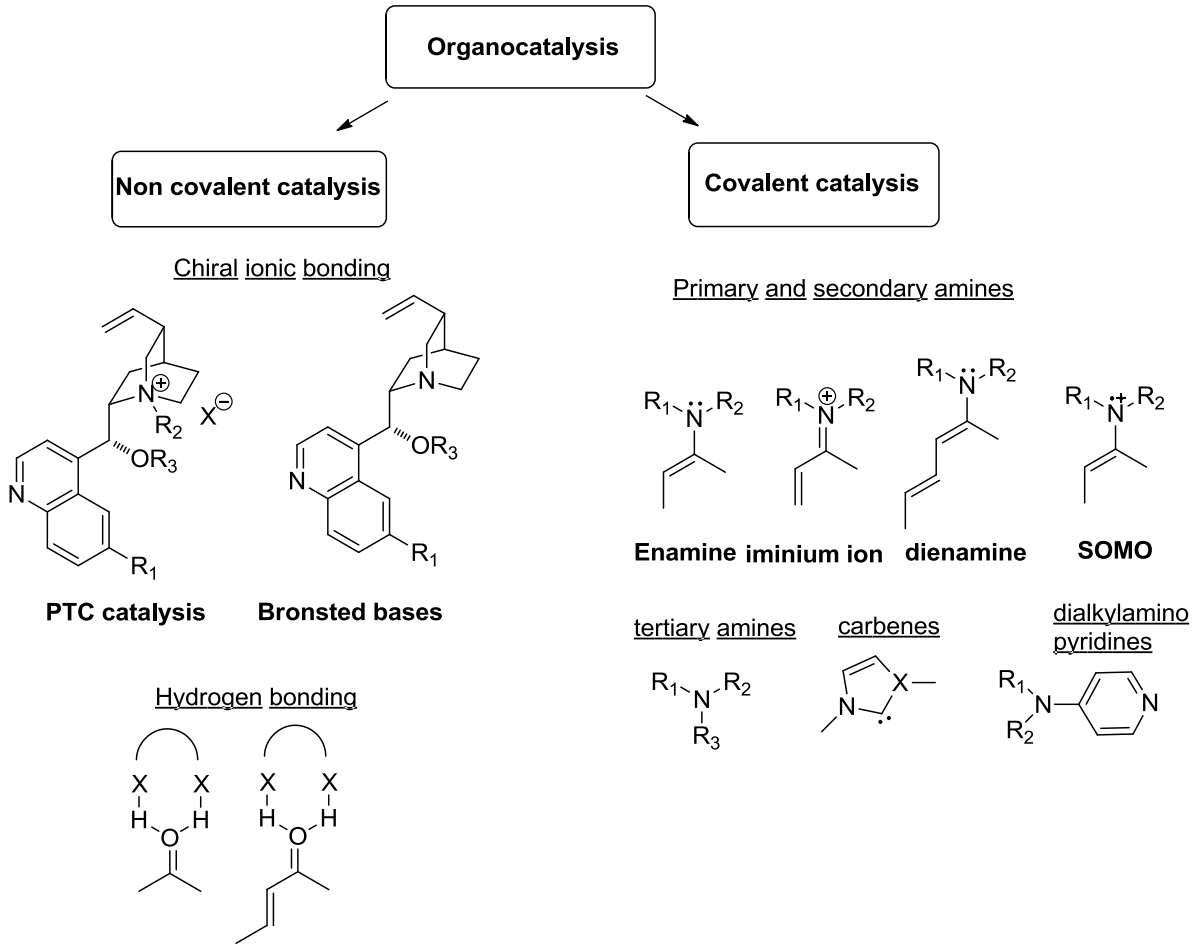


Figure 6. Representative organocatalytic strategies.

1.1.3.1.1 Non covalent catalysis

Enantioselective Phase Transfer Catalysis[13] (PTC) takes place through weak interactions via chiral ionic bond formation that contributes to enantiofacial discrimination. The reaction takes place in a two or three phase system, with vigorous agitation in a mixture of aqueous-non polar solvents. Catalysts that have led to the best results in this field are quaternary ammonium salts derived from cinchona alkaloids and binaphthylamines. Another type of catalyst with non-covalent bonds is that in which Bronsted bases[14] are used as catalysts. Bronsted bases abstract a proton from the pro-nucleophilic species to transform it into a more nucleophilic species, simultaneously creating a chiral environment through the formation of an ionic bond. Among the best known chiral Bronsted bases are tertiary amines, guanidines, amidines, imidazoles and cinchona alkaloids. The latter in organocatalytic reactions works in a similar way to enzymes in biological processes. They act by creating a chiral "pocket" around the substrate with the formation of ionic interactions with the anion, or through the existence of an additional coordinating group, such as a hydrogen bond acceptor that can contribute to the attachment of the electrophile, further improving its efficacy as shown in Figure 7.

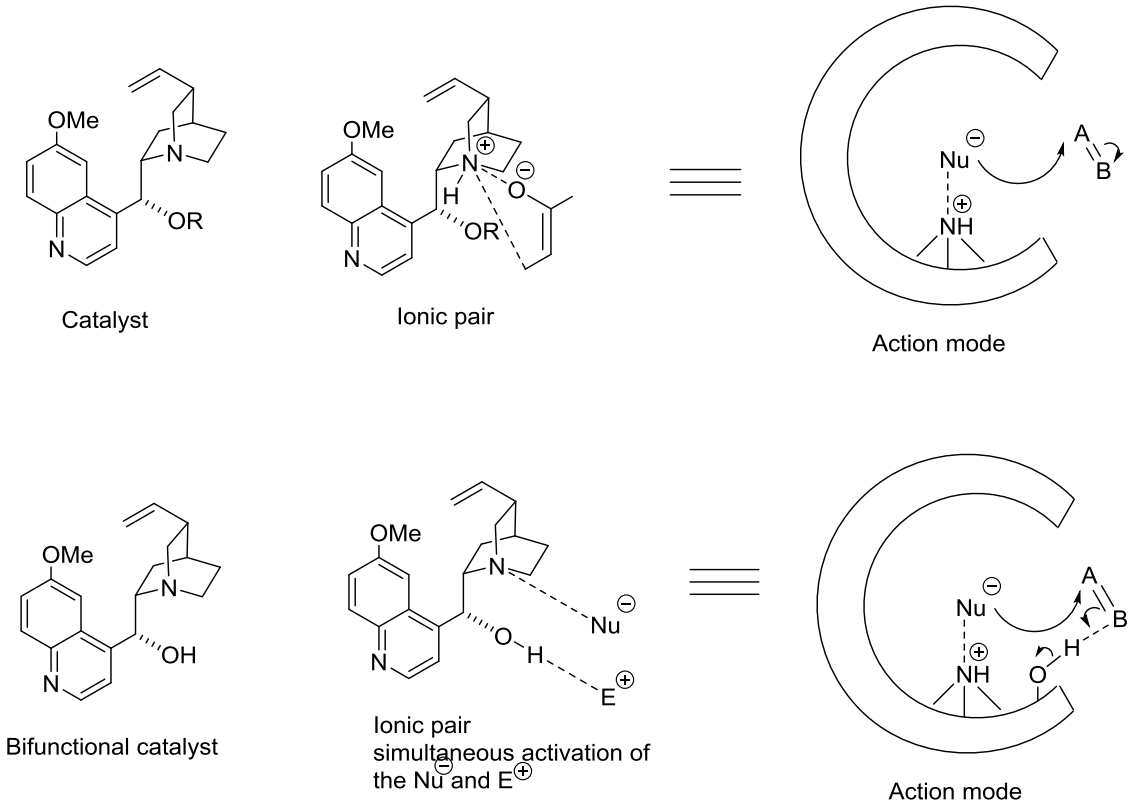
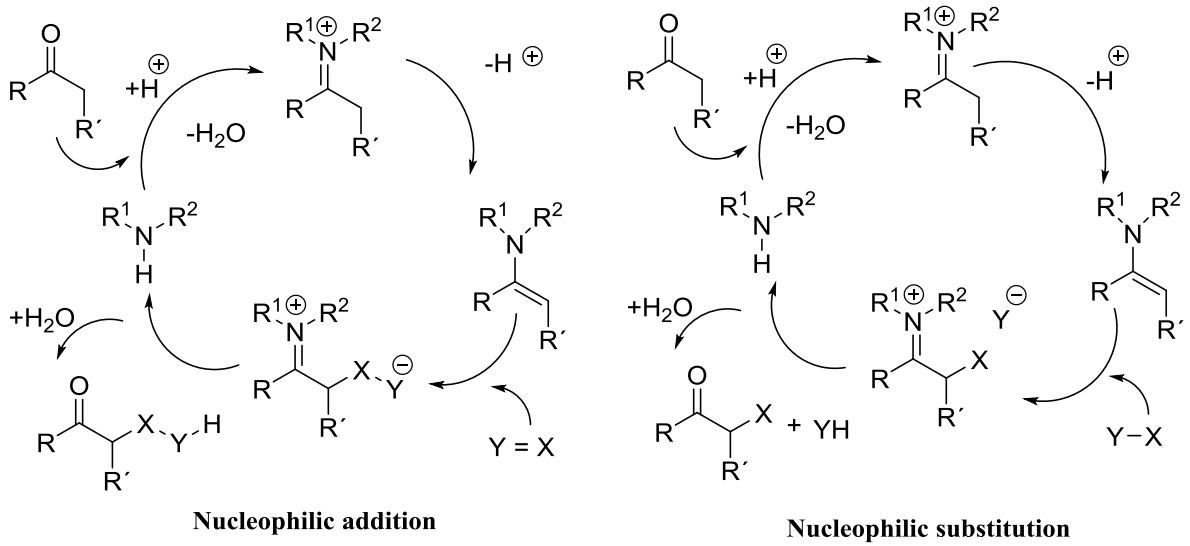


Figure 7. Activation mode of cinchona alkaloids acting as Brönsted bases.

The hydrogen bond itself can also be the only interaction responsible for the activation of the substrate. The hydrogen bond is one of the most important interactions in the structures that we are surrounded by in biology, a very important structural feature as seen in DNA bases. Recently, the activation of an electrophile by small chiral molecules with hydrogen bond donor groups has emerged as an important tool in enantioselective catalysis. This type of interaction lowers the electronic density of the electrophile, activating it for nucleophilic attack. This principle is frequently used by the catalysts present in nature, the enzymes, for acceleration of a wide range of chemical processes. Catalyst systems featuring activation through hydrogen bonding include ureas, thioureas, guanidines, diols, biphenols, carboxylic acids and chiral amides.

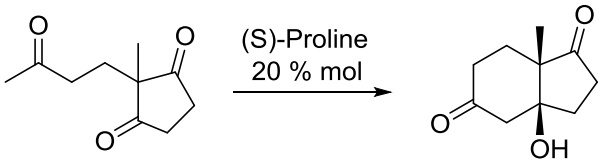
1.1.3.1.2 Covalent catalysis

Covalent catalysis has been developed in an extraordinary way for carbonyl substrates. The catalyst can activate not only the nucleophile through the formation of the corresponding chiral enamine but also the electrophile through formation of a chiral iminium ion. Alternatively other similar activation methods have been described such as via a dienamine intermediate and via a SOMO. Catalysis promoted by chiral tertiary amines, chiral carbenes and chiral dialkylaminopyridines has also been reported. The catalysis via enamine and iminium ion intermediates formed from primary and secondary amines are probably the most efficient and easiest way to activate the α-carbon and the carbon in the β position of ketones and aldehydes to form carbon-carbon and carbon-heteroatom bonds. In scheme 2 the catalytic cycles of enamine activation for both nucleophilic addition and substitution reactions are shown.



Scheme 2. Catalytic cycles of enamine activation for nucleophilic addition and substitution reactions.

Scheme 3 shows an example of the first asymmetric organocatalysed reaction via an enamine intermediate with high enantiocontrol, independently and simultaneouly discovered in the early 1970s by two groups; Hajos Parrish and Eder, Sauer and Wiechert.[15] The intramolecular reaction of a triketone was shown to be catalysed by *L*-proline to give a bicyclic aldol product in 99% yield and 93% enantiomeric excess.



Scheme 3. Hajos, Parrish, Eder, Sauer, Wiechert intramolecular aldol reaction.

This discovery had a strong economic impact in the pharmaceutical industry, as by performing this reaction it is possible to access the synthetic intermediate **5** which is of high value in the synthesis of steroids (cortisone, contraceptives), Figure 8.

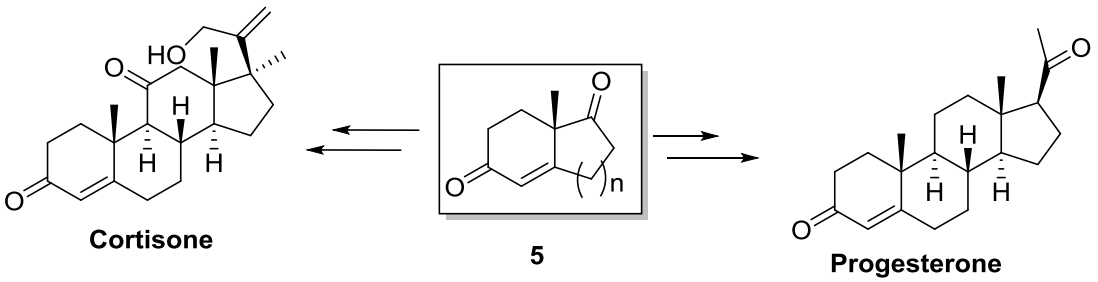


Figure 8

1.2 Organic Carbonate Solvents

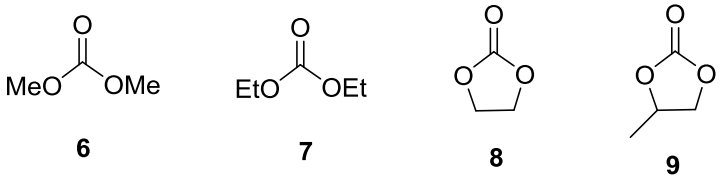
A solvent is often a key component in a chemical transformation as it controls the interactions and stability of transition states and intermediates, playing a pivotal role for achieving good conversion and selectivity. However, nowadays the solvent must not only be suitable for a reaction, but also be environmentally acceptable.[16] This acceptance is determined by the principles of so-called green chemistry[17] such as through the elimination of toxic auxiliaries, reagents or solvents, reduction of waste and use of more energy-efficient sustainable processes.

The term "green solvent"[18] is often used to describe their favorable environmental properties such as low toxicity, low vapor pressure and biodegradability. One aspect of this field is research into alternative replacement solvents. Ionic liquids (ILs), supercritical carbon dioxide[19,20], water[21,22,23], fluorinated solvents[24,25,26] or polyethers[27,28] are considered ideally suited to replace toxic and highly flammable volatile organic compound solvents (VOC) due to their high boiling and flash points. However they are only available in limited quantities and are expensive in comparison to VOCs, hence they are only used for smaller scale industrial applications such as for the manufacture of high-value products like pharmaceuticals or fine chemicals. Another disadvantage of ILs and fluorinated solvents is that they are not biodegradable[29] and the largely unknown toxicity is a major problem when considering them for use as green solvents. Polar nonprotic solvents like *N*,*N*-dimethylformamide (DMF) or *N*-methylpyrrolidin-2-one present not only high toxicity but also cause problems with waste during water-intensive workup and possible NOx formation when incinerated.

Progress in the search for alternative solvents has been made in recent years following the environmental, health and safety (EHS)[30] and life-cycle assessment (LCA)[31] surveys, finding in the 1950s, that organic carbonates are the "real" green

alternative for replacing conventional organic solvents such as dichloromethane, dimethylsulfoxide and dimethylformamide.

Organic carbonates can be divided into two major groups, cyclic and acyclic. The most industrially important organic acyclic carbonates are dimethyl carbonate **6** (DMC) and diethyl carbonate **7** (DEC). As for the cyclic carbonates, ethylene carbonate **8** (EC) and propylene carbonate **9** (PC) have been identified to be especially suitable as solvents (Figure 9).



6 **7** **8** **9**

Figure 9. **6** (DMC), **7** (DEC) **8** (EC), **9** (PC).

Organic carbonates offer various advantages as solvents. They are stable under ambient conditions and can be stored under an air atmosphere, and are not affected by moisture. Cyclic carbonates are notable for their physical properties including high dielectric constants, high boiling points and high dipole moments (Table 1).[32] EC is mostly used in mixtures with other liquids because of its high freezing point. Since it has good miscibility with water[33] as well as with a large variety of non-aqueous solvents,[34] solutions melting below room temperature having a wide range of dielectric constants may be created. PC is a versatile solvent, as it has an extensive liquid range and dissolves a large variety of organic and inorganic substances.[35] It is more commonly used than EC because it is a liquid at room temperature. Nevertheless, the polarity of EC is much higher than that of PC, which could lead to some interesting applications. DMC and DEC possess lower polarity and are only sparingly soluble in water in comparison to the cyclic carbonates. They are soluble in many organic solvents, particularly polar solvents, such as esters, ketones, ethers, alcohols and aromatic hydrocarbons. Unlike the cyclic carbonates they generally possess lower boiling points hence they are generally distilled at ambient pressure and can be removed by a standard rotary evaporator whereas cyclic carbonates have higher boiling points which make them more difficult to remove by distillation.

Nevertheless, aqueous extraction methods seem to be the most favoured work up procedure for cyclic carbonates during product isolation.

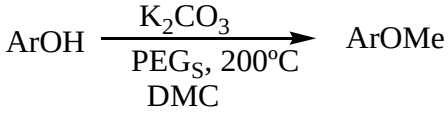
Table 1. Physical properties of organic carbonates.

Substance	EC	PC	DMC	DEC
Melting point [°C]	36	-49	4	-43
Boiling point [°C]	248	242	90	127
Density at 20°C [g/mL]	1.32	1.20	1.07	0.97
Dielectric constant	90 (40°C)	65 (25°C)	3.1 (20°C)	3.1 (20°C)
Dipole moments (D)	4.87	4.94	0.91	0.91

These properties mean that carbonates can be very useful as solvents for many chemical transformations, having the potential to replace traditional solvents.

Today, organic carbonate synthesis has already been commercialized and they are produced on a large-scale by various companies. Major products like dimethyl, propylene, or ethylene carbonates are available for about $2500/ton. In addition, organic carbonates are important raw materials for polyurethane synthesis, production of urea derivatives, and as phosgene or dimethyl sulfate substitutes for methylation reactions.[36]

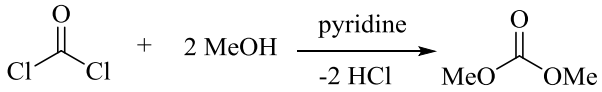
Cyclic carbonates can also be used as green solvents,[37] additives to gasoline,[38] thickeners for cosmetics[31e] and electrolytes for lithium batteries.[31] Diethyl carbonate is used as an intermediate for phenobarbital synthesis. Organic carbonates can also be used as alkylating agents under GL-PTC (Gas-Liquid Phase Transfer Catalysis) conditions (Scheme 4).[39]



Scheme 4. DMC as an alkylating agent under GL-PTC.

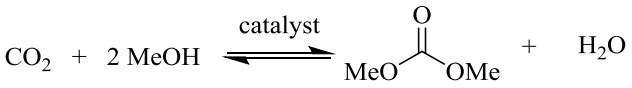
1.2.1 Alkyl Carbonate Synthesis

There are many different ways to synthesize alkyl carbonates. The industrial routes mainly use phosgene as a starting material (Scheme 5) however phosgene is classified as a highly toxic chemical as well as producing hydrochloric acid which has to be recycled or trapped as a salt (e.g. with pyridine). Therefore, other direct routes of synthesis have been investigated.



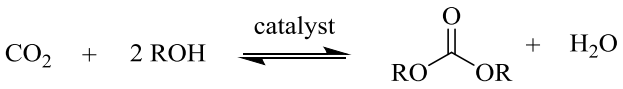
Scheme 5. Synthesis of dimethyl carbonate using phosgene.

The most straightforward process for their synthesis is by direct formation of DMC from methanol by condensation with CO_2. The reaction usually requires high temperatures and CO_2 pressure and an organostannane catalyst, though more recently new titanium and tin/acid catalysts have shown remarkable activity (Scheme 6).[40]

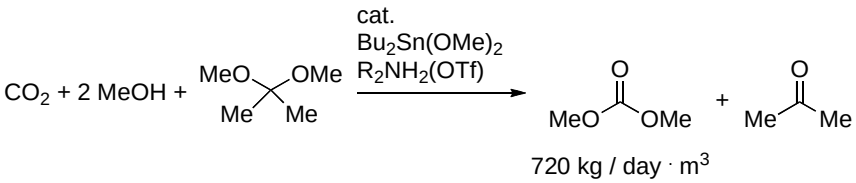


Scheme 6. Synthesis of DMC via dehydrative condensation.

Despite the attempts to improve this process, drawbacks are still related to catalyst decomposition and poor conversions due to product hydrolysis side-reactions. The use of more efficient dehydrating agents such as zeolites, orthoesters, or Mitsunobu's reagent[41] has been investigated, and showed significant improvement to the conversions, though the high cost of these dehydrating agents was not practical at any industrial level (Scheme 7). At the present time, condensation of methanol and CO_2 is the most efficient system for the synthesis of DMC;[42] the transformation is carried out at 180ºC and up to 300 atm, using acetals as dehydrating agents, with tin, titanium or zirconium alkoxide catalysts. This process leads to 720 kg/day (m^3) of production (Scheme 8).



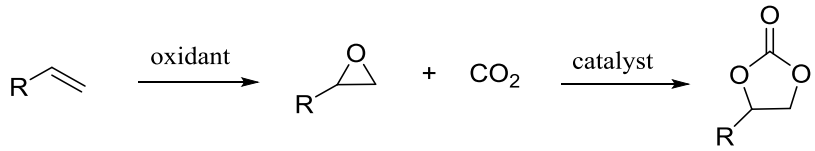
Scheme 7. Synthesis of non-cyclic carbonates.



Scheme 8. DMC synthesis via dehydrative condensation of methanol and CO_2 reported in the literature.

1.2.2 Cyclic carbonate synthesis

Cyclic carbonates[43] are often synthesised by the coupling of epoxides with carbon dioxide as shown in Scheme 9. This is the most common way of synthesis as the process is 100% atom efficient, and therefore does not produce any waste products.[44] The epoxide substrates can be obtained from alkenes by an oxidation reaction, which is well known in organic chemistry, due to the fact that the epoxide ring is an attractive target for nucleophilic attack with high regio- and stereocontrol. Carbon dioxide can come from commercial sources such as power stations, and the reactions can be performed under mild conditions such as atmospheric pressure and room temperature. The epoxidation step can be performed using "green oxidants"[45] (e.g. hydrogen peroxide).

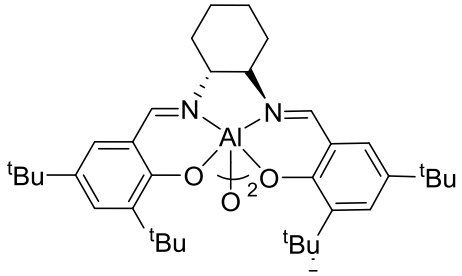


Scheme 9. Alkene epoxidation combined with CO_2 fixation.

Work by Braunstein[46] and Aresta *et al.*[47,48] showed how the synthesis of cyclic carbonates requires the activation of both carbon dioxide and epoxide and furthermore, that the synthesis of cyclic carbonates can be catalysed by organometallic catalysts such as metal (salen) complexes which activate the epoxide.

A review of the most important catalysts for the synthesis of cyclic carbonates has been reported.[49] Only a small group of catalysts showed satisfactory results under mild reaction conditions (room temperature and atmospheric pressure), since cyclic carbonate synthesis usually proceeded only at high temperature and/or high CO_2 pressure conditions. The most widely studied catalysts for the production of cyclic carbonates are metal(salen) complexes. These have been shown to be highly active in the presence of halide salts or amines as co-catalysts and they show satisfactory results under mild reaction conditions at room temperature and atmospheric pressure in batch processes or at temperatures of 100°C or below in a gas-phase flow reactor. This allows the production of cyclic carbonates with potential for utilising waste carbon dioxide from fixed site producers such as power stations,[50] oil refineries and chemical plants, especially as the catalysts have been shown to be compatible with the impurities present in power station flue gas.[51]

Many examples of these metal-salen complexes have been reported such as aluminium, chromium, zinc, cobalt and ruthenium complexes.[52] One good example is the reaction discovered by North's group, in 2007. They reported the development of a bimetallic aluminum(salen) complex **10** which, when used in conjunction with tetrabutylammonium bromide **11** constitutes the only catalyst system capable of catalysing the insertion of carbon dioxide into terminal epoxides at atmospheric pressure (1 atm = 760 mmHg) and room temperature.[53] This breakthrough offered for the first time a more environmentally friendly route to produce cyclic carbonates from carbon dioxide in good yields since aluminium is inexpensive, abundant and nontoxic.

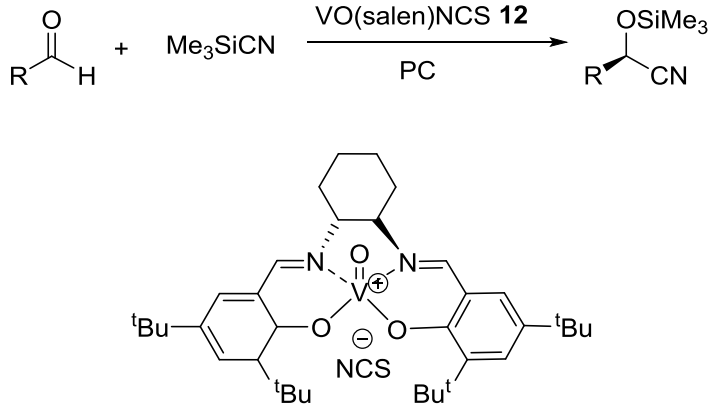


10 **11**

Bimetallic aluminum(salen) complex **10**, tetrabutylammonium bromide (TBAB) **11**.

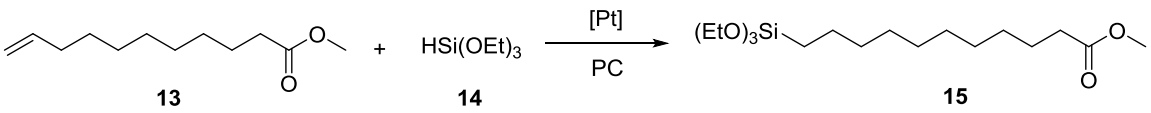
Moreover, North's group showed that PC could also be used as a solvent for the synthesis of other cyclic carbonates from carbon dioxide and epoxides and exploited this to carry out kinetic studies of the use of aluminium salen complex **10** for the synthesis of styrene carbonate.[54]

PC has also been used as a green solvent for asymmetric cyanohydrin synthesis[55] catalysed by isothiocyanate vanadium complex **12**. This asymmetric addition of trimethylsilyl cyanide to aldehydes (Scheme 10) is a 100% atom economical reaction, and is a synthetically useful process as it gives a highly versatile functionalised product containing a stereocentre. A range of 10 aromatic and aliphatic aldehydes gave high enantioselectivities (up to 93%) and conversions (up to 100%) in reactions carried out at or near room temperature with reaction times of 24 hours or less.



Scheme 10. Asymmetric cyanohydrin synthesis.

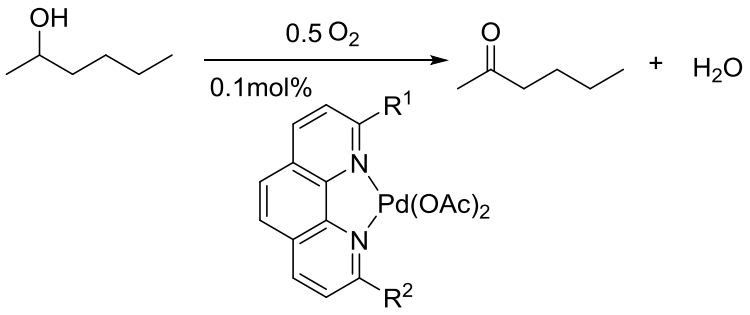
The separation of unsaturated fatty acid esters using PC as solvent is another interesting use which has been achieved by the platinum catalysed hydrosilylation reaction. The pure saturated ester **15** was separated from unreacted starting material via extraction with cyclohexane/PC, leading to an easy purification of the product (Scheme 11).[56]



Scheme 11. Reaction of methyl undec-10-enoate **13** with triethoxysilane **14** in a single phase to form 11- triethoxysilanylundecanoic acid methyl ester **15**.

The catalyst (neocuproine)$Pd(OAc)_2$ was found to show good catalytic activity for the oxidation of 2-hexanol when EC was used as cosolvent with water as a 1:1 ratio

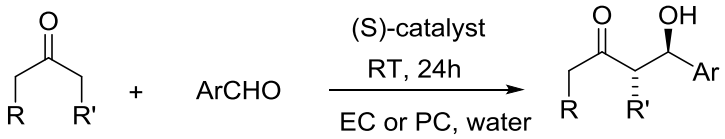
mixture (Scheme 12) compared to poorer results obtained when using mixtures of water and DMAC (dimethylacetamide) or DMF respectively.



Scheme 12. Oxidation of 2-hexanol.

These are just a selection of examples of an ever-increasing list of organic transformations that can be accomplished in cyclic carbonates as solvents.

Cyclic carbonates are not only used for transition metal catalysed reactions. North's group have shown that they are very good solvents for asymmetric organocatalysed reactions on which this thesis will be based. They have proven that cyclic carbonates are an effective green alternative to more commonly used solvents such as dichloromethane or dimethyl sulfoxide in crossed-aldol reactions between ketones and aromatic aldehydes using the amino acid (*S*)-proline as catalyst (Scheme 13).



Scheme 13. Cross aldol reaction.

Therefore the aim of this project was to further develop the use of cyclic carbonates as solvents in asymmetric organocatalysed reactions since cyclic carbonates are non-toxic and easily synthesised by inserting CO_2 into an epoxide ring, therefore contributing as environmentally friendly solvents. The asymmetric reactions that have been chosen for the development of the use of cyclic carbonates are the aldol reaction, Mannich reactions and aminations. These reactions are discussed further in the next section.

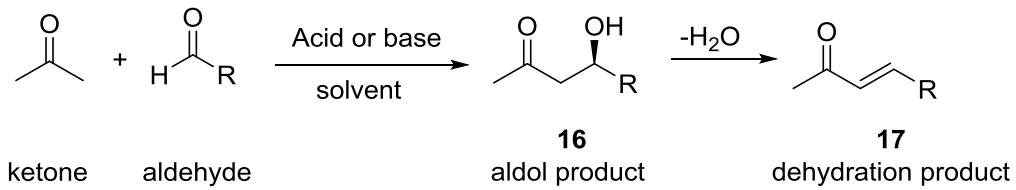
1.3 The importance of C-C and C-N bond forming reactions

The asymmetric catalytic formation of new carbon-carbon and carbon-nitrogen bonds in a regio-, stereo- and enantioselective manner, under organocatalytic conditions has been the focus of extensive studies for more than twenty years with the goal of developing functionalised optically active molecules with high structural diversity from simple and easily available starting materials. The targets include α-amino acids, α-amino aldehydes, and α-amino alcohols, all key chiral elements in many natural products as well as in medicinal chemistry.

The catalytic, enantioselective carbon-carbon bond forming reactions include the aldol reaction to generate β-hydroxycarbonyl compounds and Mannich reactions to generate β-amino carbonyls or β-carbonyl-α-amino acid derivatives from the addition to imines. The catalytic, enantioselective, direct carbon-nitrogen bond forming reactions using aldehydes and a nitrogen source constitute another of the simplest procedures for the construction of α-aminated products. In this thesis, aldol reactions, aminations and Mannich reactions will be given particular attention.

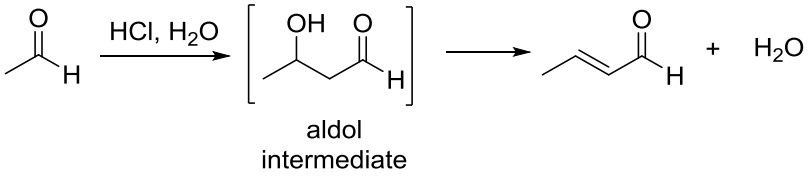
1.3.1 Aldol reactions

The aldol reaction is now amongst the best-known and most widely used methods for generating carbon-carbon bonds with stereocontrol. In the past two decades the aldol reaction (Scheme 14) has become one of the more versatile methods for the control of stereochemistry in the preparation of complex natural products. This useful transformation allows the formation of a carbon-carbon bond by the reaction of an enolizable carbonyl compound acting as a nucleophile with itself, or another carbonyl containing species acting as an electrophile to give β-hydroxy carbonyl compounds **16** known as aldols (aldehyde + alcohols) which are valuable intermediates in organic synthesis.



Scheme 14. Aldol Reaction.

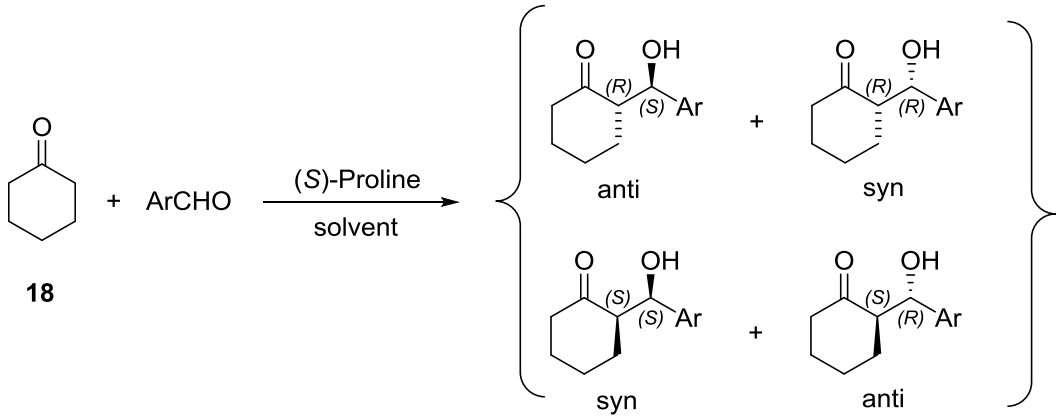
The aldol reaction requires an aldehyde or ketone that contains at least one α-hydrogen. The reaction can be catalysed under either basic or acidic conditions. The carbonyl carbon is electrophilic whereas the α-carbon becomes a nucleophile when it is deprotonated by a base. Under acidic or basic conditions the aldol may be dehydrated during the course of the reaction. When dehydration takes place, the reaction is called aldol condensation.[57] The aldol condensation was named by Wurtz who in 1872 reported the formation of (*E*)-2-butenal through the acid catalysed autocondensation of acetaldehyde. The aldol condensation is the reaction between a carbonyl compound, which behaves as a nucleophile in its enolate or enol form and another carbonyl which behaves as electrophile. The product of the reaction is α, β-unsaturated compound **17**.



Scheme 15. Aldol condensation.

In addition to the new carbon-carbon bond formed, one or more stereogenic centers can also be created. Anti- and syn-diastereomers are possible when the compound possesses two consecutive stereogenic carbons at the α and β positions. For this reason, this transformation has been widely used as a chemical test to prove the efficiency of new methodology, especially in asymmetric synthesis.[58] Modern methodology is not only capable of allowing aldol reactions to proceed in high yield, but also, with control of both the relative and absolute stereochemical configuration of these stereocenters.

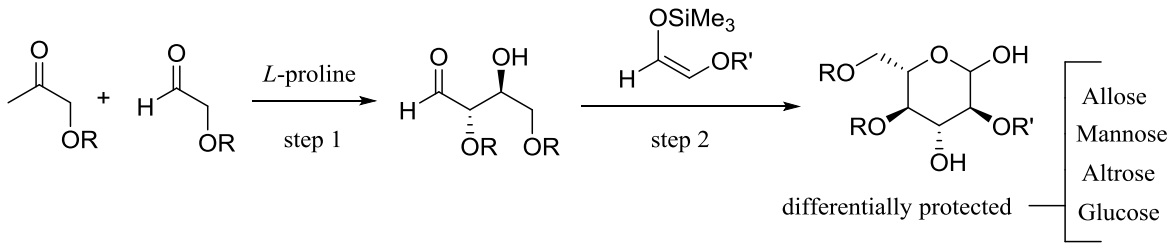
This ability to selectively synthesise a particular stereoisomer is significant because different stereoisomers can have very different chemical or biological properties. An example of these diastereomers is given in Scheme 16 showing the aldol reaction involving cyclohexanone **18** as the ketone catalysed by the amino acid (*S*)-proline. The two pairs of enantiomers, *RR*/*SS* and *RS*/*SR* are diastereomers of one another thus, the (*R*,*R*) and (*S*,*S*) enantiomers are diastereoisomers of the (*R*,*S*) and (*S*,*R*) enantiomers. In such cases, it is usual to consider the diastereoselectivity as well as the enantioselectivity of reactions.



Scheme 16. (*S*)-proline catalysed aldol reaction involving cyclohexanone.

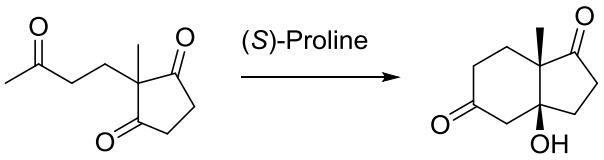
Catalysts that can promote this reaction include aldolase enzymes, Lewis bases, Lewis acids, and small organic molecules such as amino acids (see section 1.4.1). In general, asymmetric catalytic aldol reactions are mainly classified into the following categories: a) chiral auxiliary-based aldol reactions; b) Lewis acid-catalysed Mukaiyama-type and chiral Lewis base-catalyzed aldol reactions; and c) direct catalytic aldol reactions[59] which are atom- economical.[60]

Aldol additions of unmodified ketones or aldehydes promoted by small organic molecules arose from attempts to mimic the action of aldolase enzymes. This was discovered by Wurtz in 1872 although Kane previously described the known aldol condensation, it was the work of MacMillan that brought organocatalysts to the foreground, demonstrating the power of asymmetric organocatalytic aldol reactions with the synthesis of differentially protected carbohydrates (Scheme 17).



Scheme 17. MacMillan's synthesis of carbohydrates.

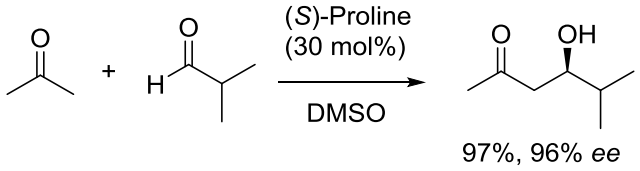
Scheme 18 shows an example of a type of asymmetric organocatalysis, discovered in the early 1970s by Hajos-Parrish-Eder-Sauer-Wiechert.[61] The intramolecular reaction of a triketone was shown to be catalysed by proline to give a bicyclic aldol product in 99% yield and with 93% enantiomeric excess. This reaction was soon adopted as the method of choice for the synthesis of steroidal ring systems. The intermolecular ketone-aldehyde variant was discovered by List, Barbas and Lerner in 2000,[62] and highly useful adaptations and applications of this procedure soon followed including enantioselective aldehyde–aldehyde coupling reactions,[63] very rapid carbohydrate[64] and polypropionate[65] syntheses, and very short total synthesis of natural products.[66]



Scheme 18. Hajos-Parrish-Eder-Sauer-Wiechert intramolecular aldol reaction.

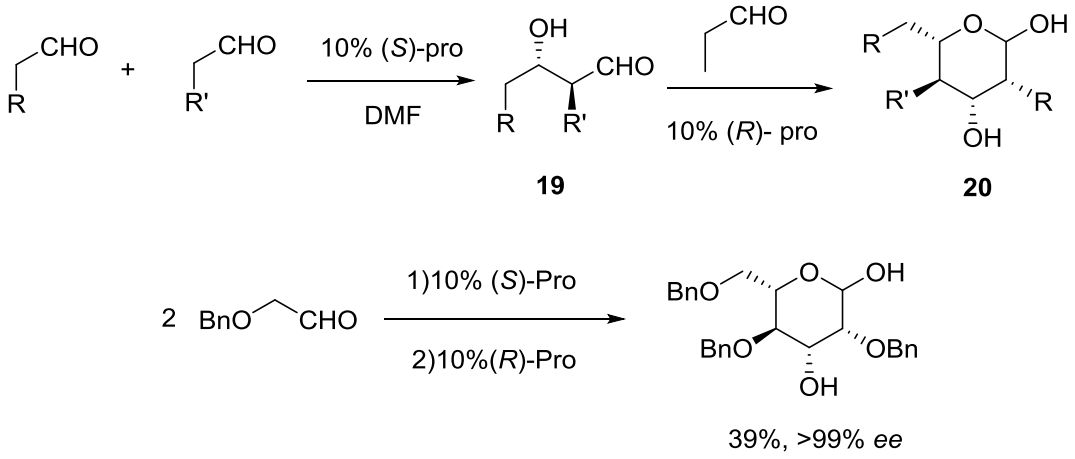
Lessons learnt from aldolase enzymes, the Hajos-Parrish-Eder-Sauer-Wiechert reaction, and the discovery of non-proteinogenic, metal complex-catalysed direct asymmetric aldol reactions,[67] led to the development of the first proline catalysed direct asymmetric intermolecular aldol reaction.[68] It was shown that there was a general limitation in the intermolecular reaction between a ketone and an aldehyde which is the requirement for a large excess of the ketone since aldehydes can also act as donors. The use of enolizable aldehydes has also long been problematic, but the proline-catalysed aldolisation has unexpectedly opened new routes towards this challenging goal.

For example, acetone (20 vol.%, ca. 27 equiv.) reacts with isobutyraldehyde in DMSO to give the corresponding aldol in excellent yield and ee (Scheme 19).



Scheme 19. Highly enantioselective proline-catalysed intermolecular aldol reaction.

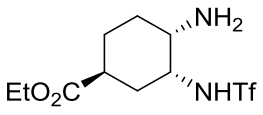
Enders and Grondal were also able to use the proline catalysed aldol addition for the synthesis of pentoses.[69] Very recently, Cordova and coworkers realised the two-step concept of MacMillan using proline as catalyst[70] showing that aldol product **19** obtained from an (*S*)-proline catalysed reaction can proceed in a second aldol reaction catalysed by (*R*)-proline, to give rise to carbohydrate **20** (Scheme 20).



Scheme 20. Proline catalysed carbohydrate synthesis according to Cordova & coworkers.

In addition to the highly efficient proline-derived organocatalyst, a wide number of chiral non-proline derivatives have been successfully applied as organocatalysts to promote asymmetric aldol reactions, giving in most cases stereoselectivities as high as those obtained with the proline-derived catalysts.

Examples of these organocatalysts are shown in Figure 10.



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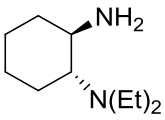

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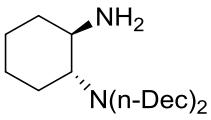

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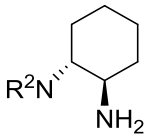

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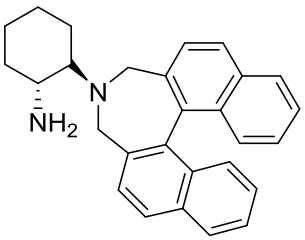

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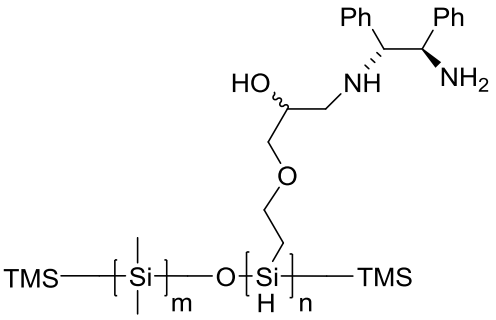

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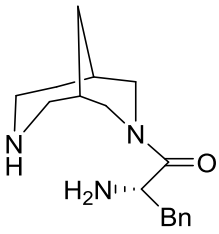

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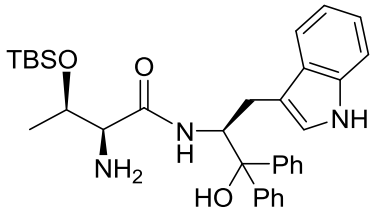

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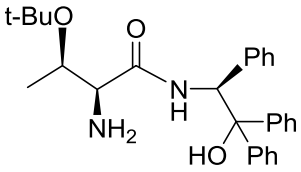

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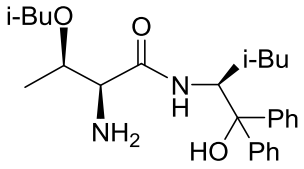

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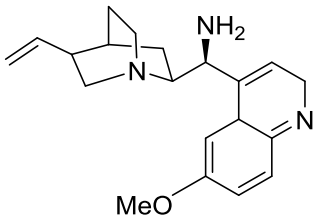

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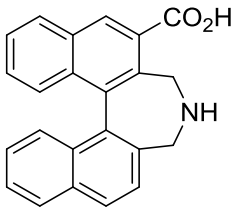

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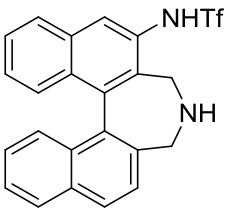

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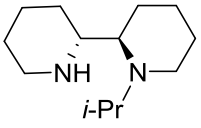
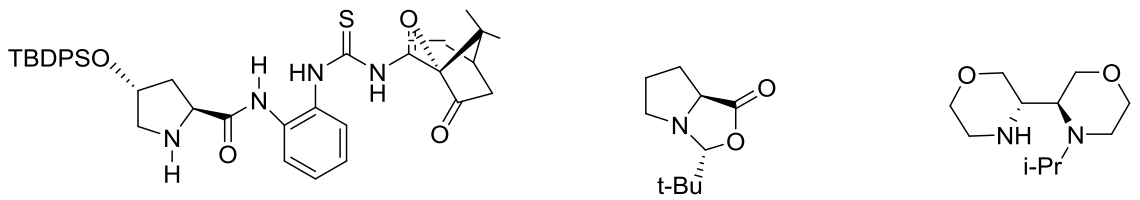


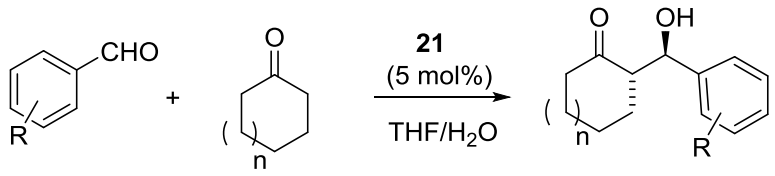
34 *i*-PrBP



35 **36** **37** *i*-PrBM

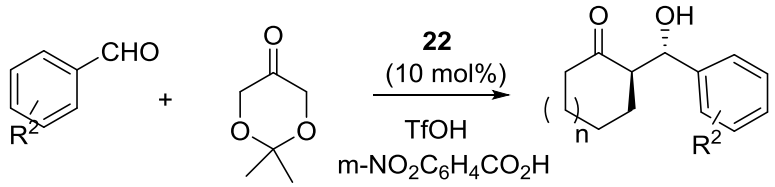
Figure 10.

Aldol reactions catalysed by these organocatalysts are shown in Schemes 21-35.

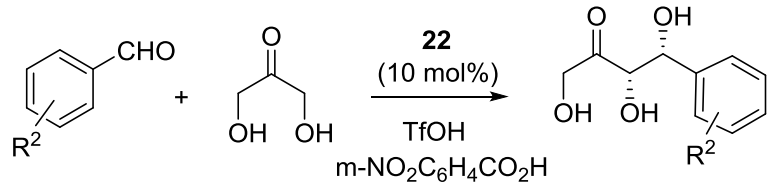


R = 4-NO_2, 3-NO_2, 4-CN, 4-CF_3, 4-Br, 4-CO_2Me, H, n = 1
R = 4-NO_2, n = 0

Scheme 21. Maruoka and Nakayama aldol reaction of cyclic ketones catalysed by cis-cyclohexyldiamine.[46]

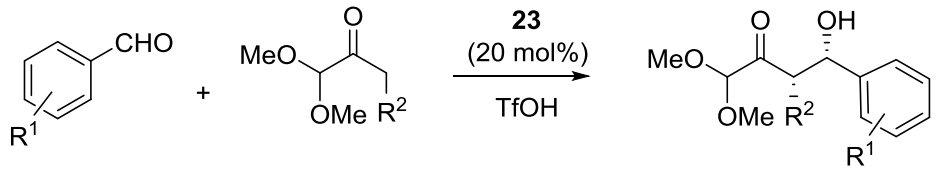


R^2 = 4-NO_2, 3-NO_2, 2-NO_2, 4-CN, 4-CF_3, 4-Ph
R^1 = Et



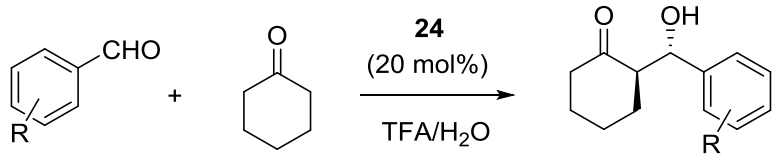
R^2 = 4-NO_2, 3-NO_2, 2-NO_2, 4-CN, 4-CF_3, 4-Cl, 3-Br, H
R^1 = n-Dec

Scheme 22. Aldol reaction of dihydroxyacetone catalysed by trans-cyclohexyldiamines.[47]



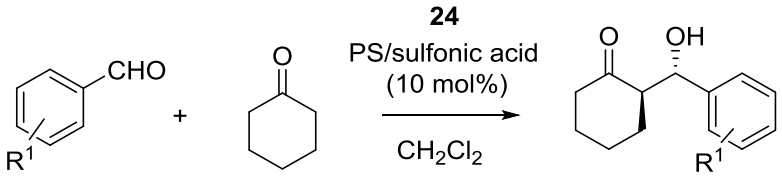
R^1 = 4-NO_2, 3-NO_2, 2-NO_2, 4-CN, 4-CF_3, with R^2 = H
R^1 = 4-NO_2, 3-NO_2, 2-NO_2, 4-CF_3, with R^2 = Me
R^1 = 4-NO_2 with R^2 = Et
R^1 = 4-NO_2 with R^2 = n-Pr

Scheme 23. Aldol reaction of pyruvic derivatives catalysed by trans- cyclohexyldiamine as demonstated by Cheng *et al*.[48]

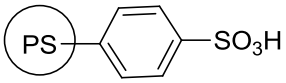


R = 4-NO_2, 3-NO_2, 2-NO_2, 4-CF_3,

Scheme 24. Aldol reactions of cyclohexanone catalysed by MNP-supported primary amine catalyst.[49]

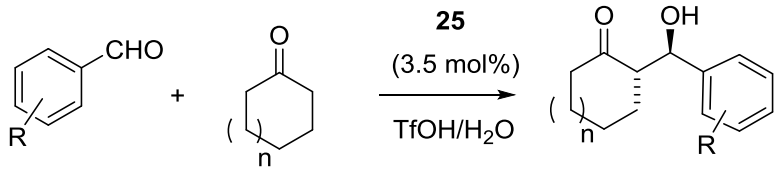


R^1 = 4-NO_2, 3-NO_2, 2-NO_2, with R^2= Et
R^1 = 4-CN, 4-CF_3, 4-Cl with R^2= n-Pr



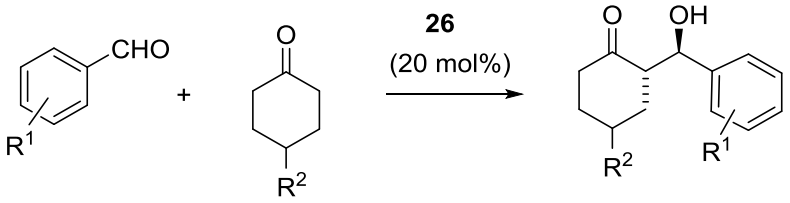
PS/sulfonic acid

Scheme 25. Aldol reaction of cyclohexanone catalysed by polymeric sulfonic acids.[50]



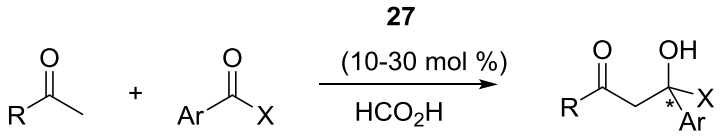
R = 4-NO_2, 3-NO_2, 2-NO_2, 4-CF_3, H with n = 1
R = 4-NO_2 with n = 0

Scheme 26. Aldol reaction of cyclic ketones catalysed by binaphthyl trans-cyclohexyldiamine.[51]



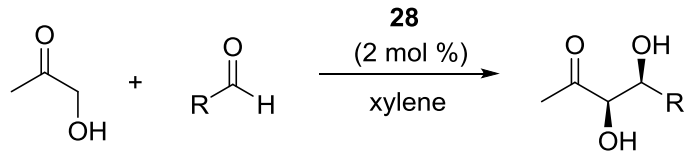
R^1 = 4-NO_2 , 2-NO_2 , R^2 = H
R^1 = 3-NO_2 , 4-CF_3 , R^2 = Me

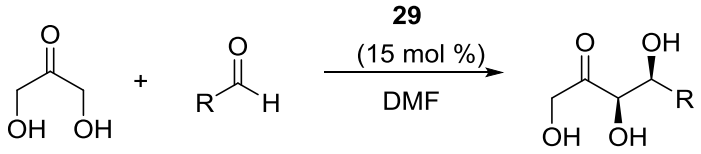
Scheme 27. Aldol reaction of cyclohexanones catalysed by polysiloxane-modified primary amine applied by Lai *et al*.[52]

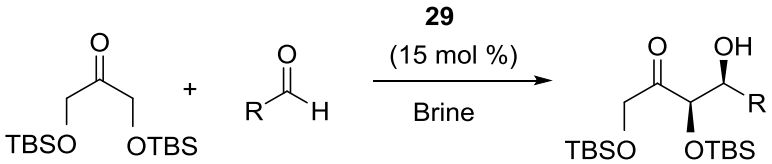


Ar = Ph, p-Tol, p-ClC_6H_4, m-Tol, R = Me, X = $PO(OEt)_2$
Ar = Ph, p-$MeOC_6H_4$, R = Me, X = $PO(OMe)_2$
Ar = Ph, R = Et, X = $PO(OEt)_2$
Ar = Ph, R = Et, X = CO_2Me
Ar = p-$NO_2C_6H_4$, R = Me, X = $(p\text{-}NO_2C_6H_4CH_2O)_2CH$
Ar = p-$NO_2C_6H_4$, R = Et, X = $(p\text{-}NO_2C_6H_4CH_2O)_2CH$
Ar = p-FC_6H_4, R = Me, X = CO_2Me
Ar = p-$NO_2C_6H_4$, R = Me, X = H

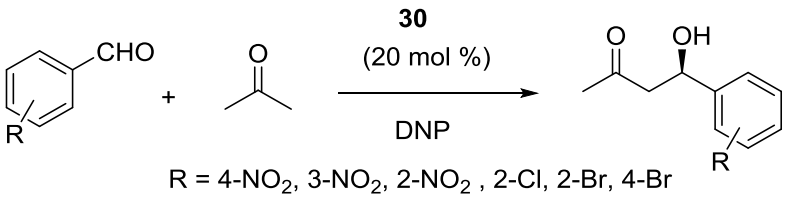
Scheme 28. Aldol reactions of functionalised ketones catalysed by bispidine-derived primary amine used by Hu *et al*.[53]



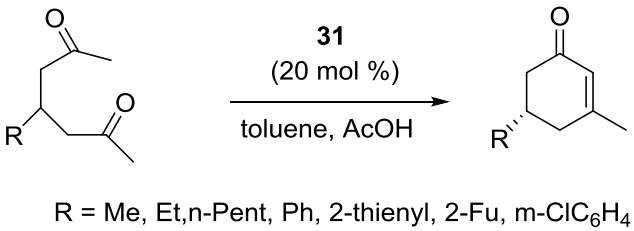




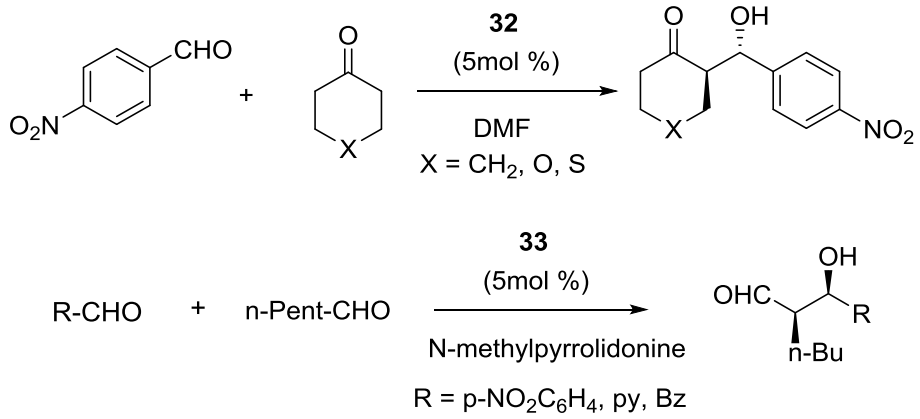
Scheme 29. Aldol reactions of ketones with aliphatic aldehydes catalysed by primary amino acid catalyst used by Barbas *et al*.[55]



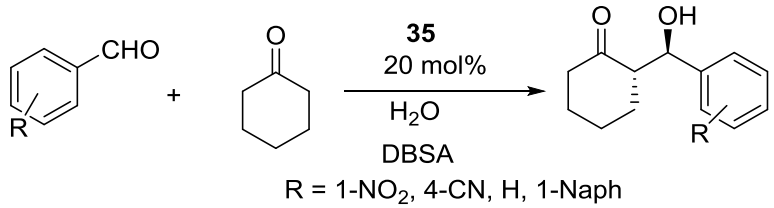
Scheme 30. Aldol reactions of acetone with aromatic aldehydes catalysed by primary amino acid catalyst and DNP as co-catalyst used by Da *et al*.[56]



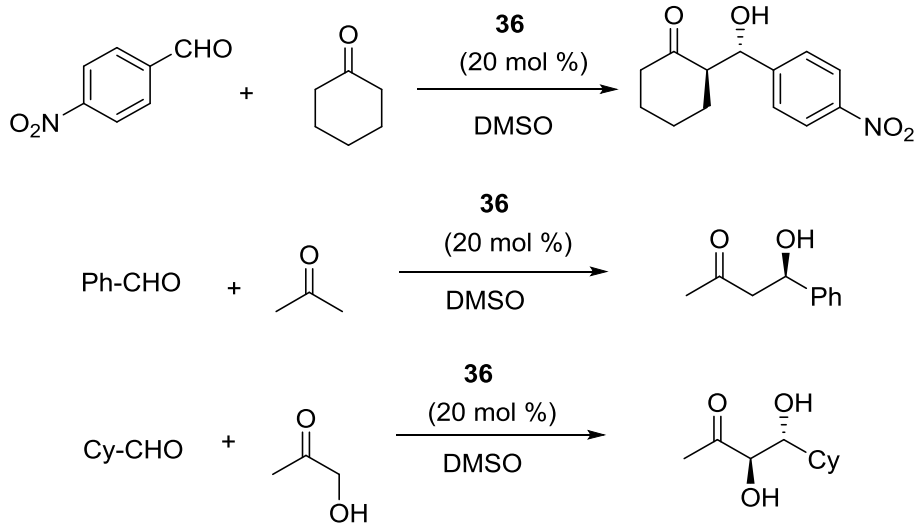
Scheme 31. Intramolecular aldol reactions of 4-substituted-2,6-heptanediones catalysed by quinine-derived primary amine used by List *et al*.[59]



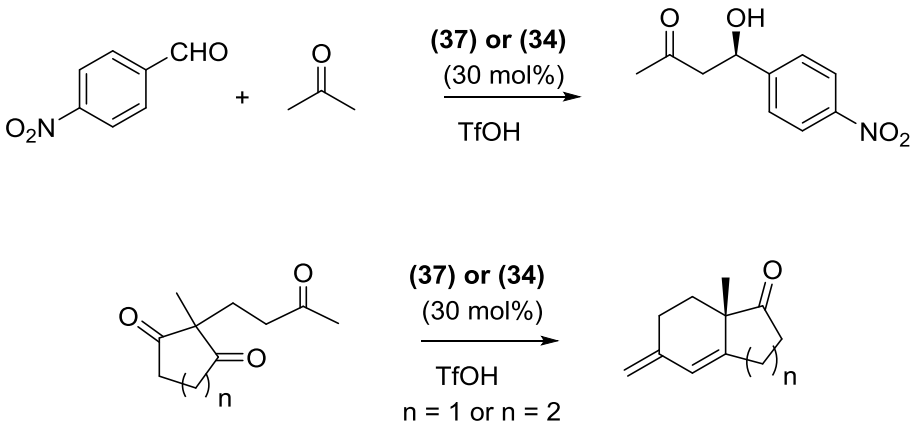
Scheme 32. Aldol reactions catalysed by binapthyl-based secondary amines used by Maruoka and Kano.[60]



Scheme 33. Aldol reactions of cyclohexanone with aromatic aldehydes catalysed by camphor-derived thiourea- secondary amine used by Chen et al.[61]



Scheme 34. Aldol reactions of ketones with aldehydes catalysed by Seebach's proline-derived oxazolidinone used by Vilarrasa *et al*.[62]



Scheme 35. Inter- and intramolecular aldol reactions of ketones catalysed by bimorpholine- and bipiperidine derivatives used by Kangar *et al*.[63]

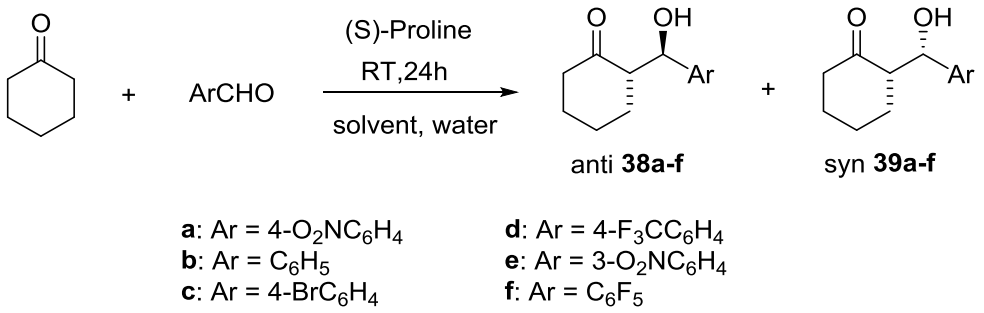
Moreover, trans-*N*,*N*-dipropyl diaminocyclohexane catalyst **24** (R^2 = propyl) was successfully introduced as the first magnetic nanoparticle-supported chiral primary amine catalyst and then applied to the asymmetric aldol reaction of cyclohexanone with various benzaldehydes, leading to the expected aldol products in excellent yields and enantioselectivities.

1.3.1.1 Proline-catalysed aldol reaction in cyclic carbonates

In addition to the choice of appropriate organocatalyst, the proper setup of the reaction conditions is essential to classify a catalytic reaction as sustainable. In particular, the selection of solvent is critical to maximize the environmental and economic benefits. The first commonly used solvents in aldol reactions like methanol, DMF, DMSO, acetonitrile, or chlorinated solvents[71,72,73] differ substantially in their use and limitations. The limitations for these solvents such as high prices, toxicity, or problems with purification have to be taken into consideration. Over the last few years, cyclic carbonates especially ethylene carbonate and propylene carbonates have been attracting increasing interest as green solvents due to their properties (as shown in section 1.2).

North's group has recently reported for the first time that proline is capable of catalysing aldol reactions in these sustainable solvents.[74,75,76] They showed that, under these conditions, catalysis of 100% atom economical cross-aldol reactions between an enolizable ketone and an aromatic aldehyde can be achieved with high diastereoselectivity and enantioselectivity. As a test reaction, the (*S*)-proline catalysed aldol reaction between cyclohexanone and 4-nitrobenzaldehyde was selected (Scheme

36). The reaction was first carried out in DMSO to provide comparison data. When anhydrous DMSO is used as a solvent, no product was obtained. Results are shown in Table 2. [77]



Scheme 36. (*S*)-proline catalysed aldol reaction involving cyclohexanone.

Table 2. (*S*)-proline catalysed synthesis of aldol products[a]

Solvent	(*S*)-proline (mol%)	Water (equiv)	Yield (%)	Syn:anti	ee^{syn}/ee^{anti} (%)
DMSO	10	0	0	-	-
DMSO	10	4	91	1:7.8	50/89
PC	10	0	45	1:1	40/74
PC	10	1	83	1:7.9	88/98
PC	10	2	63	1:4.3	41/96
PC	10	2	81[b]	1:13	90/99
PC	10	3	57	1:2.6	90/96
PC	10	4	49	1:12	84/99
PC	10	6	12	-	-
PC	10	8	8	-	-
PC	20	2	71	1:5.8	2/97
PC	30	4	72[c]	1:2.0	29/95
EC	10	1	92	1:9	91/98
EC	10	0	6	1:2	-

[a] All reactions were carried out for 24 h at room temperature with 2 equiv of cyclohexanone relative to 4-nitrobenzaldehyde.
[b] Reaction time 48 h.
[c] Reaction time 60 h.

However, the addition of 4 equivalents of water to the reaction mixture resulted in the formation of aldol products **38a**/**39a** with a high yield and favouring the enantiomerically enriched anti-isomer **38a**, (1:7.8) diastereoselectivity. Propylene carbonate as the solvent was more effective than DMSO, though the yield, diastereoselectivity and enantioselectivity were all still unsatisfactory with no water present. Addition of 1 equivalent of water (relative to the amount of 4-nitrobenzaldehyde) had a remarkably positive effect on all the reaction parameters. The influence of water on organocatalysed reactions has been studied extensively.[78,79] Since the reactions shown in table 4 are initially heterogeneous, it appears that the beneficial effect of adding a small amount of water is to enhance the solubility of proline in the reaction mixture, resulting in an increase in the rate of reaction due to an increase in the amount of catalyst present in solution, but if too much water is added then the prejudicial effect of water on the rate of reaction becomes increasingly apparent. This is consistent with the results shown in table 4 which show that the reaction is still in progress after 24 hours as the yield increases to 81% after 48 hours.

For these reactions, involving cyclohexanone, there was a significant difference in the chemical yield, diastereoselectivity, and enantioselectivity observed in the two solvents with ethylene carbonate being the more effective solvent.

Having selected 10 mol% of (*S*)-proline and one equivalent of water as the optimal reaction conditions, the extension of this chemistry to the aldol reaction between cyclohexanone and other aromatic aldehydes was investigated (Scheme 36). Results are tabulated in Table 3.[77]

Table 3. (*S*)-proline catalysed synthesis of aldol products[a]

Solvent	Aldehyde	Yield (%)	Syn:anti	ee^{syn}/ee^{anti} (%)
PC	PhCHO	12	1:4.4	77/56
PC	PhCHO	47[b]	1:4.5	67/80
EC	PhCHO	44	1:16	89/99
PC	4-BrC_6H_4CHO	18	1:4.7	89/96
PC	4-BrC_6H_4CHO	60[b]	1:4.8	80/96
EC	4-BrC_6H_4CHO	47	1:13	87/95
PC	4-$F_3CC_6H_4CHO$	49	1:4.7	68/93
EC	4-$F_3CC_6H_4CHO$	86	1:9	89/98
PC	3-$O_2NC_6H_4CHO$	22	1:7.4	92/92
EC	3-$O_2NC_6H_4CHO$	89	1:7.8	88/99
PC	C_6F_5CHO	98	0:100	-/98
EC	C_6F_5CHO	99	0:100	-/98

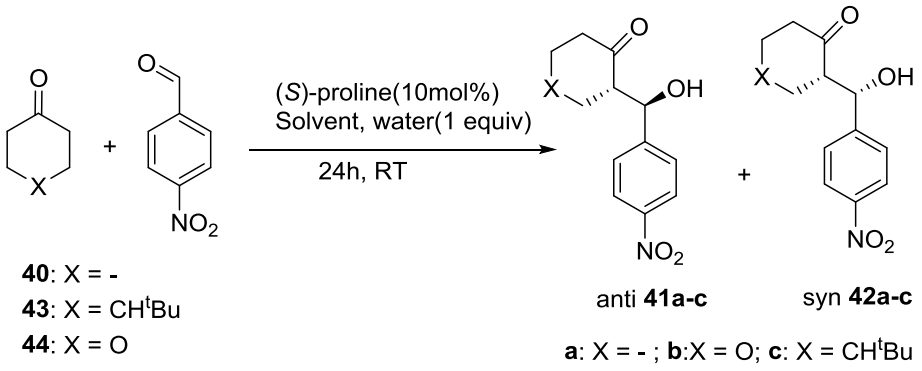
[a] All reactions were carried out for 24 hours at room temperature with 2 equiv of cyclohexanone relative to aldehyde using 10 mol % (*S*)-proline and with 1 equiv of water added to the reaction mixture.
[b] Reaction time 6 days.

Consistent with previous work on proline catalysed aldol reactions in other solvents, the best substrates were found to be electron-deficient aldehydes. Thus, in propylene carbonate, benzaldehyde gave a low yield of aldol products and poor enantioselectivity. However, the best results were again obtained using ethylene carbonate as solvent.

(*S*)-proline catalysed aldol reactions in cyclic carbonates have also been investigated between acetone and aromatic aldehydes under the same conditions, obtaining no consistent difference between the two solvents. However, the yields and enantioselectivities obtained compared favorably with those obtained in conventional solvents such as DMSO and DMF[80,81] or under solvent free conditions.[82]

It has been demonstrated that cyclic carbonates (ethylene and propylene carbonate) make excellent, sustainable solvents for (*S*)-proline catalysed cross-aldol reactions between ketones and aromatic aldehydes. With cyclohexanone used to form the enamine precursor, reactions in ethylene carbonate gave much better results compared to propylene carbonate, whereas with acetone as the enamine precursor, reactions in both solvents gave similar results.[77]

Cyclopentanone **40** was also an excellent substrate for proline-catalysed aldol reactions in cyclic carbonate solvents, giving adducts **41/42a-c** in 99% chemical yield in both solvents, (Scheme 37). The enantioselectivity and diastereoselectivity were both much higher in ethylene carbonate than in propylene carbonate (Table 4). However, the racemic product of the syn diastereomer was obtained. When t-butylcyclohexanone **43** and pyran-4-one **44** were used as substrate, good yields, diastereo- and enantioselectivities were obtained.



Scheme 37. Aldol reactions involving cyclohexanone derivatives and cyclopentanone.

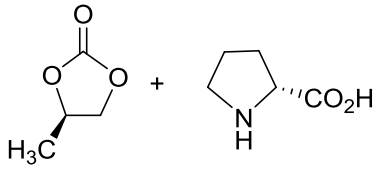
Table 4. Synthesis of keto-alcohols **41a-c** and **42 a-c**

Entry	Ketone	Solvent	Yield (%)	Syn:anti	ee^{syn}/ee^{anti} (%)
1	44	PC	99	1:7	68/94
2	44	EC	74	1:2.9	69/73
3	43	PC	58	1:1.7	61/90
4	43	EC	89	1:8.4	95/95
5	40	PC	99	1:1.2	2/39
6	40	EC	99	1:2.2	0/91

[a] All reactions were carried out for 24 h at room temperature with 2 equiv of cyclohexanone relative to 4-nitrobenzaldehyde.

Another interesting characteristic of propylene carbonate (in this case chiral PC, *R*-PC) is that it also displays a pronounced chiral solvent effect in these reactions and that, by use of the appropriate combination of solvent enantiomer and proline enantiomer, the enantio- and diastereoselectivity of organocatalysed aldol reactions can, in some cases, be significantly enhanced.

An example of this is shown in Table 5 selecting the aldol reaction between cyclohexanone and 4-trifluoromethylbenzaldehyde, carried out in both racemic and *R*-PC.[83] As the table shows better results were obtained when *R*-PC was used in combination with *R*-proline (matched pair) than when *R*-PC was used in combination with (*S*)-proline (mismatched pair). This effect has been observed with a wide variety of aldehydes.



matched pair

Table 5. Synthesis of aldol products **38a-f** and **39a-f** in chiral and achiral PC[a]

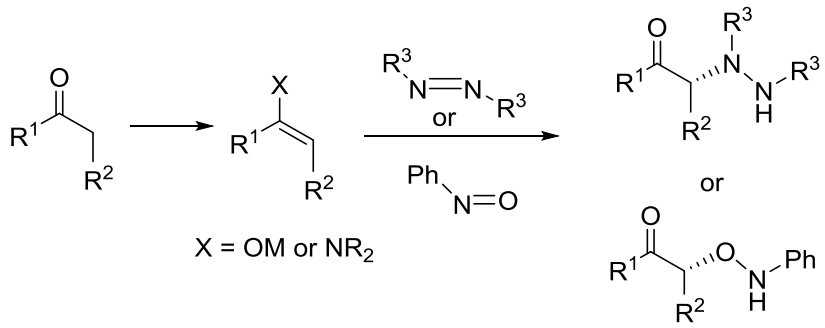
Entry	Aldehyde	Solvent	Proline	Yield (%)	Syn:anti	ee^{syn}/ee^{anti} (%)
1	4-$F_3CC_6H_4CHO$	(*RS*)-PC	(*S*)	49	1:4.7	68/93
2	4-$F_3CC_6H_4CHO$	(*R*)-PC	(*S*)	26	1:3.3	44/52
3	4-$F_3CC_6H_4CHO$	(*R*)-PC	(*R*)	63	1:6.3	66/96
4	4-$F_3CC_6H_4CHO$	(*R*)-PC	(*RS*)	43	1:6.1	0/1
5	PhCHO	(*RS*)-PC	(*S*)	47	1:4.5	77/93
6	PhCHO	(*R*)-PC	(*S*)	65	1:6	55/85
7	PhCHO	(*R*)-PC	(*R*)	75	1:7	75/96
8	4-BrC_6H_4CHO	(*RS*)-PC	(*S*)	21	1:4.8	73/95
9	4-BrC_6H_4CHO	(*R*)-PC	(*S*)	22	1:3	51/60
10	4-BrC_6H_4CHO	(*R*)-PC	(*R*)	36	1:4.5	82/97
11	4-$O_2NC_6H_4CHO$	(*RS*)-PC	(*S*)	83	1:7.9	86/91
12	4-BrC_6H_4CHO	(*R*)-PC	(*S*)	89	1:3.6	68/85
13	4-$O_2NC_6H_4CHO$	(*R*)-PC	(*R*)	94	1:5.9	79/91
14	3-$O_2NC_6H_4CHO$	(*RS*)-PC	(*S*)	22	1:7.4	91/92
15	3-$O_2NC_6H_4CHO$	(*R*)-PC	(*S*)	67	1:7.6	79/95
16	3-$O_2NC_6H_4CHO$	(*R*)-PC	(*R*)	72	1:9.2	86/96
17	C_6F_5CHO	(*RS*)-PC	(*S*)	98	0:100	-/98
18	C_6F_5CHO	(*R*)-PC	(*S*)	89	0:100	-/98
19	C_6F_5CHO	(*R*)-PC	(*R*)	98	0:100	-/98

[a] All reactions were carried out for 24 h at room temperature using 2 equiv of cyclohexanone, 10 mol % of proline, and 1 equiv of water (relative to the amount of aldehyde)

1.3.2 Amination reactions

The electrophilic α-amination of carbonyl compounds is an increasingly popular method for the synthesis of nitrogen containing molecules. The motivation to investigate enantioselective α-aminations of carbonyl compounds is provided by valuable synthetic targets such as α-amino aldehydes, α-amino acids, α-amino alcohols which are key chiral elements in many natural products and are also important in medicinal chemistry. The catalytic, enantioselective, direct C-N bond-forming reaction using aldehydes and a nitrogen source, such as azodicarboxylates, would constitute one of the simplest procedures for the construction of a stereogenic carbon center attached to a nitrogen atom. The most prominent heteroatom electrophilic amination reagent is the azodicarboxylate typically used in combination with chiral auxiliaries.[84]

The basic reaction consists of an enolate or enamine reacting with an electrophilic nitrogen (Scheme 38). The enolate may either be pre-formed (as a silyl enol ether, for example) or generated in-situ through "soft" enolization involving a Lewis acidic metal and a base. Enamines are also competent nucleophiles and form from the reversible condensation between an aldehyde or ketone and a secondary amine.



Scheme 38.

The reactions can be catalysed by either chiral Lewis acids or Lewis bases. For Lewis acid catalysis, there are two modes of activation and stereochemical induction (Figure 11). The chiral Lewis acid metal complex may generate a chiral metal enolate (**A**) by either "soft" enolization of the carbonyl or by transmetalation of a preformed enolate.

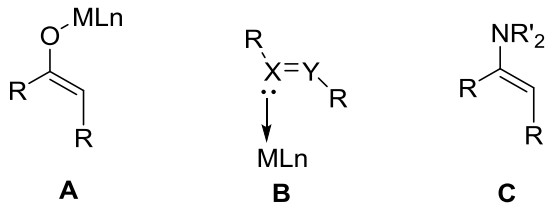
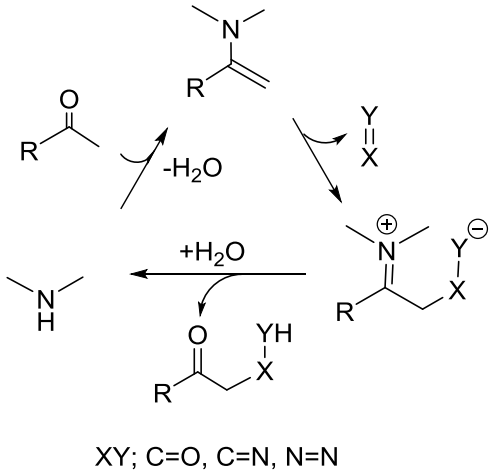


Figure 11. Modes for catalyst activation.

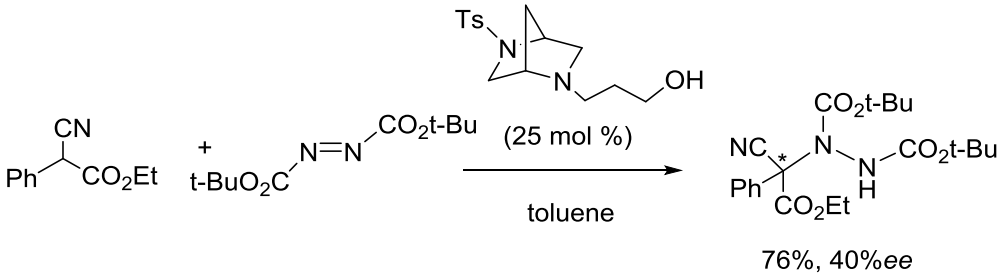
The chiral Lewis acid may also serve to activate the electrophile by coordination to either an oxygen or nitrogen lone pair (**B**). It is also possible that the Lewis acid complex plays both roles at once by forming a metal enolate, which may then bind to and activate the electrophile. Chiral Lewis bases catalyse these reactions by the reversible formation of a chiral enamine (**C**). The asymmetry is then transferred upon the reaction between this enamine and the electrophile, followed by imine hydrolysis of the product, which regenerates the catalyst to continue the cycle (Scheme 39).



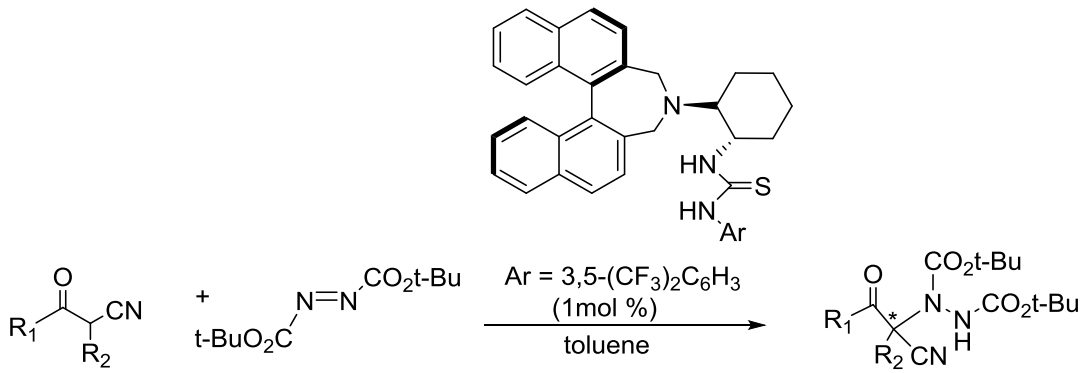
Scheme 39.

It has been shown that asymmetric electrophilic amination is possible in the presence of chiral promoters, leading to the expected aminated products with high stereoselectivities. The α-amination of carbonyls in the presence of a chiral catalyst was introduced by Evans *et al*. in 1997,[85] who employed a chiral magnesium-bis(sulfonamide) complex as the catalyst for the amination of *N*-acyloxazolidinones. Subsequently, much progress was made based on mixed copper (II)[86] and silver[87] catalysts with azodicarboxylate reagents.

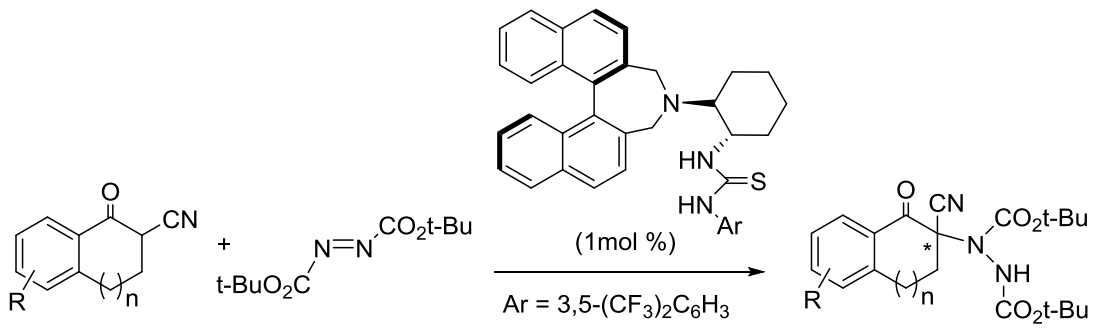
In 2008, Juaristi *et al*. evaluated a series of novel derivatives of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane as potential organocatalysts for the asymmetric amination of ethyl α-phenyl-α-cyano acetate with di-*tert*-butyl azodicarboxylate.[88] Among them, a bifunctional derivative provided the aminated product in an excellent yield and with moderate enantioselectivity (40%), as shown in Scheme 40. On the other hand, Kim *et al*. have obtained excellent enantioselectivities (97-99%) for the aminated products generated by the amination of α-cyanoketones with azodicarboxylates performed in the presence of a chiral thiourea-tertiary amine catalyst.[89] As shown in Scheme 41, good to excellent yields were achieved for all the substrates examined in this study at a low catalyst loading of 1 mol %.



Scheme 40. Amination of ethyl α-phenyl-α-cyano acetate.



R_1, R_2 = $(CH_2)_4$: 95% ee = 94%, R_1, R_2 = $(CH_2)_3$: 94% ee = 95%
R_1 = R_2 = Ph : 94% ee = 94%, R_1= Ph, R_2 = 2-Naph: 94% ee = 93%
R_1= Ph, R_2 = p-$MeOC_6H_4$: 93% ee = 99%

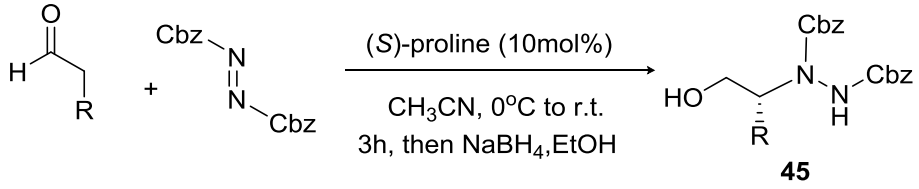


R = H, n = 0 : 95% ee = 97%, R = 5-Me, n = 0 : 92% ee = 97%
R = 5,6-$(Me)_2$, n = 0 : 85% ee = 98%
R = H, n = 1 : 94% ee = 99%, R = 6-Me, n = 1 : 94% ee = 99%

Scheme 41. Aminations of α-cyanoketones.

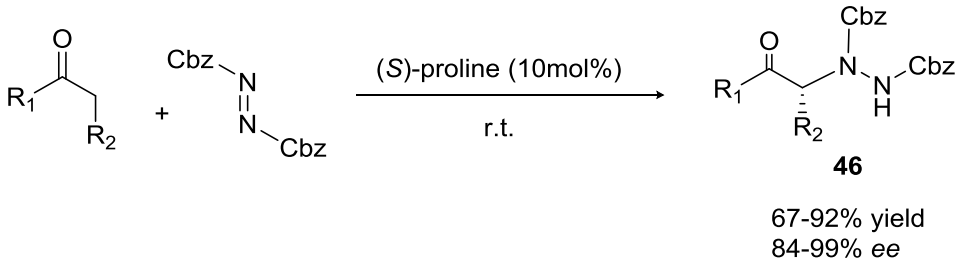
α-Aminations of carbonyl compounds catalysed by *L*-proline have been demonstrated to be efficient methods. Activation of the α-position of carbonyl compounds by forming enamines with proline allows them to attack the electrophilic N=N double bond to form C-N bonds. The first direct α-amination of aldehydes and ketones catalysed by *L*-proline was reported, respectively, by List[90] and Jørgensen[91] in 2002 (Scheme 42, Table 6). These reactions gave products **45** and **46,** respectively, in high yields and excellent enantioselectivities.

Table 6. Proline-catalysed direct asymmetric α-amination of five aldehydes.



45

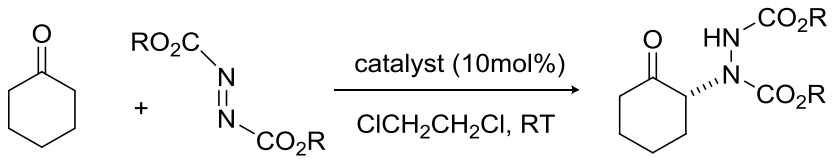
Product	R	Yield (%)	*ee* (%)
45a	*i*-Pr	99	96
45b	*n*-Pr	93	>95
45c	*n*-Bu	94	97
45d	Me	97	>95
45e	Bn	95	>95



Scheme 42. α-Aminations of aldehydes and ketones catalysed by *L*-proline.

This reaction was the first one which required a relatively low amount of an inexpensive and non-toxic catalyst available in both enantiomeric forms. Later, the reaction was extended to ketones, and produced the α-hydrazino adducts in good yields and enantioselectivities.

One straightforward method is the electrophilic α-amination of cyclohexanone with DEAD or DBAD catalysed by proline **47** or siloxyproline **48**[92] (Figure 12) as shown in Scheme 43, Table 7. This reaction produces valuable intermediates for the synthesis of 1,2-diazetidines[93] and peptides.[94]



Scheme 43. α-Amination reaction of cyclohexanone and DEAD or DBAD.

Table 7. Proline and siloxyproline catalysed amination reactions

Entry	Catalyst	R	t(h)	Yield (%)	ee (%)
1	**47**	Et	1.5	31	85
2	**48**	Et	1.5	89	85
3	**47**	Bn	3.0	50	75
4	**48**	Bn	3.0	86	94

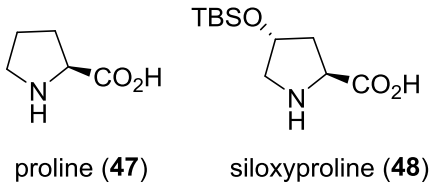
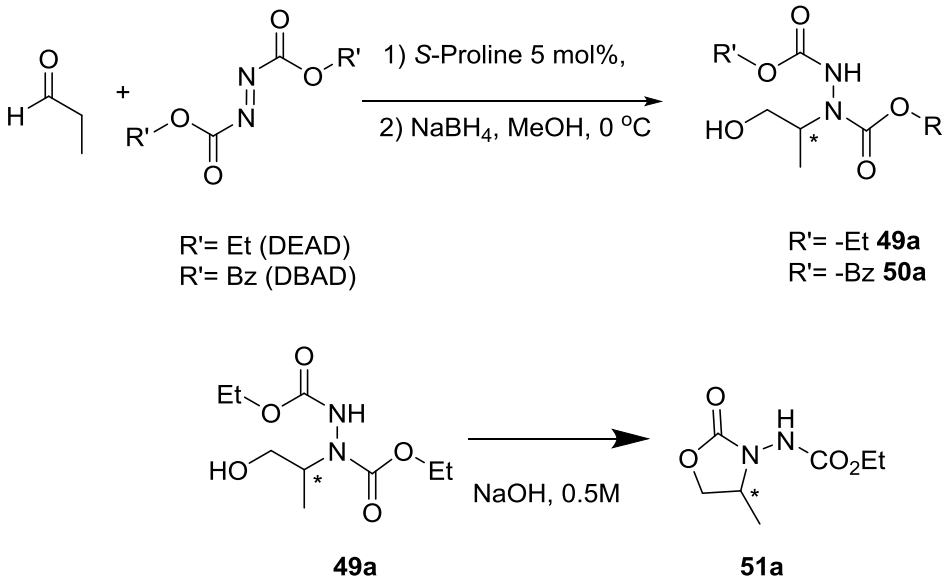


Figure 12. Organocatalysts examined in this study. TBS=tert-butyldimethylsilyl

1.3.2.1 Proline-catalysed amination reactions in cyclic carbonate solvents

With *L*-proline having been demonstrated to be an effective organocatalyst in the asymmetric amination of aldehydes[95] and ketones,[96] North's group extended the investigation by using cyclic carbonates as solvents. First the activity and enantioselectivity were compared in different cyclic carbonate solvents using propionaldehyde and dibenzyl azodicarboxylate (DBAD) with (*S*)-proline as catalyst (Scheme 44). As reported in Table 8, good yields were obtained after 2 hours in EC and PC, but enantioselectivities in both solvents were moderate and could be improved by decreasing the temperature. However, due to the relatively high freezing point of EC (35 ^{o}C), the temperature could not be lowered any further. Propylene carbonate (PC) was then chosen as the preferred solvent and the best results were achieved when the reaction was left for 24 hours at 0 ^{o}C (69% yield and 97% *ee*). When diethyl azodicarboxylate (DEAD) was used instead of DBAD, **49a** was obtained in lower yield and enantioselectivity (39 % yield, 66% *ee*).

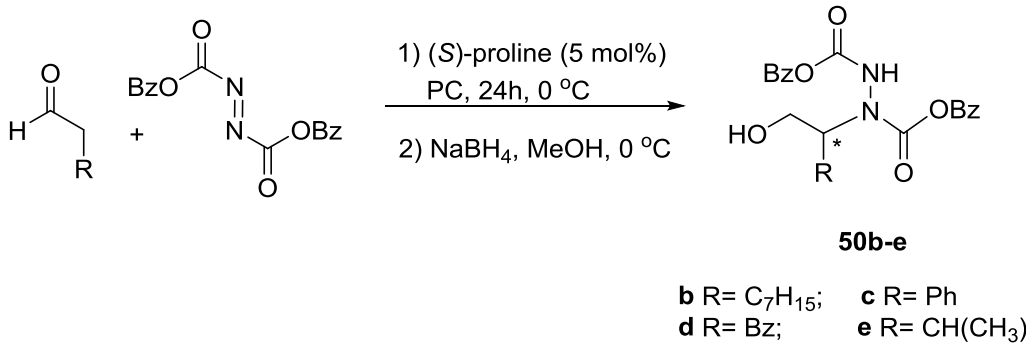


Scheme 44.

Table 8 Proline catalysed amination reactions with cyclic carbonate solvents

Entry	Solvent	Product	Time (h)	T(°C)	Yield(%)	*ee*(%)
1	CH_2Cl_2	**50a**	2	RT	86	98
2	EC	**50a**	2	RT	74	69
3	PC	**50a**	2	RT	81	80
4	PC	**50a**	2	0	18	99
5	PC	**50a**	24	0	69	97
6	PC	**51a**	24	0	39	66

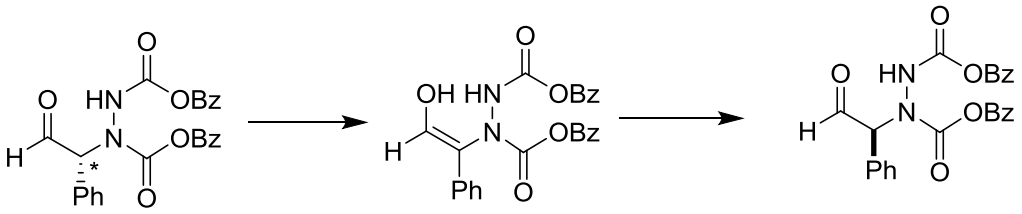
A wide range of aldehydes were tested (Scheme 45). As Table 9 shows, good results were obtained for almost all the substrates, comparable with those reported in the literature.[97,98] The exception was phenylacetaldehyde whose diamino derivative **50c** could only be obtained with 36% *ee* due to racemisation prior to reduction (Scheme 46).



Scheme 45.

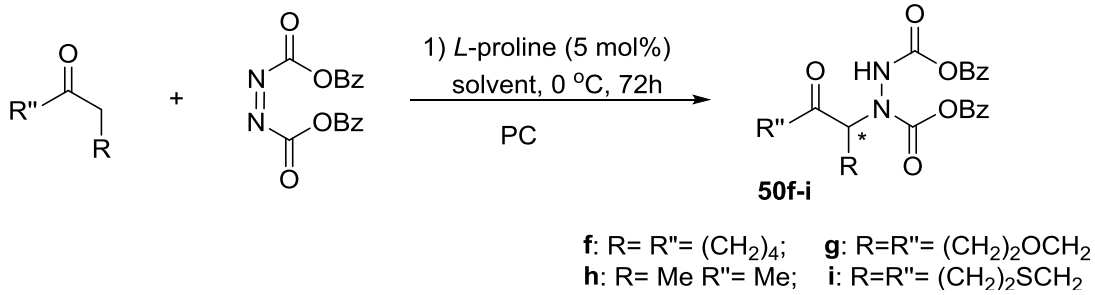
Table 9 Proline catalysed amination products from various aldehydes in propylene carbonate

Entry	Product	Yield (%)	*ee* (%)
1	**50a**	69	97
2	**50b**	41	90
3	**50c**	70	36
4	**50d**	76	99
5	**50e**	87	92



Scheme 46.

As cyclic carbonates were proven to be an efficient reaction media for the amination of aldehydes, a selection of ketones was used as substrates (Scheme 47) and results are shown in Table 10. Good results were obtained overall.



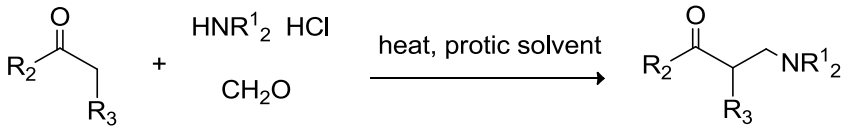
Scheme 47.

Table 10 Proline catalysed aminations of ketones in propylene carbonate

Entry	Product	Yield(%)	*ee* (%)
1	**50f**	71	77
2	**50g**	51	72
3	**50h**	31	52
4	**50i**	39	--

1.3.3 Mannich reactions

In 1912, Carl Mannich first reported the reaction that took his name. The reaction he reported was the condensation of formaldehyde with amines to form the corresponding iminium ion with a subsequent addition of a carbon nucleophile (enol). The product was a β-amino carbonyl compound and was named a Mannich base (Scheme 48).



Scheme 48. Mannich reaction.

All the reactions that are mentioned in this thesis use aldimines as the electrophilic partner, and for this reason a discussion of these compounds follows. Imines are aza-analogues of aldehydes, with a carbon-nitrogen double bond. A substituent on the nitrogen atom is required for their stability. Their main characteristic is the electrophilicity of the sp^2 carbon which can be adjusted using groups with different electronic properties on the nitrogen (Figure 13).

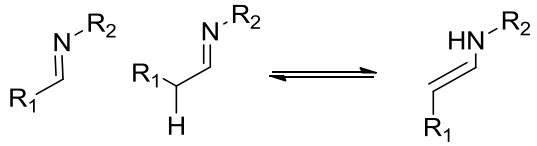
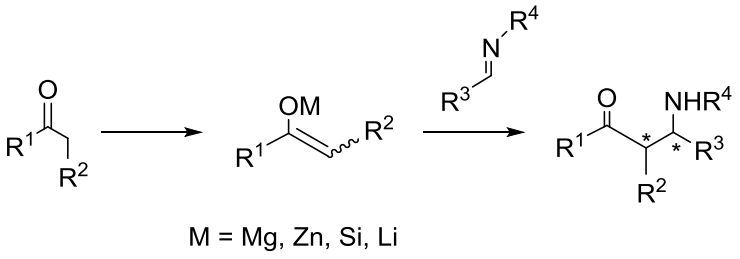


Figure 13. Imines.

Like aldol reactions, the Mannich reaction[99] (Scheme 49) is a classic method in asymmetric synthesis of great importance for generating chiral β-amino carbonyl compounds and their derivatives[100] through carbon carbon bond formation. The Mannich reaction involves an aldehyde, an amine and a ketone reacting in a three-component, one-pot synthesis.[101]As an alternative, the reaction can be performed as a nucleophilic addition of a carbon based nucleophile to the C=N bond of a preformed imine, which is prepared starting from the aldehyde and an amine. The Mannich reaction tolerates a wide range of acceptors, donors and amine components, and can be carried out in a variety of polar solvents.



Scheme 49. Mannich reaction.

Optically active β-amino carbonyl compounds are valuable amine-containing species since they are present in many products and commonly used as chiral building blocks for the synthesis of pharmaceuticals[102] or natural products[103] such as alkaloids,[104] nucleotides and peptides with unique structural properties.[105] In Figure 14 part of the synthesis of two alkaloids is shown in which a Mannich-type reaction is involved in an intramolecular cyclisation.

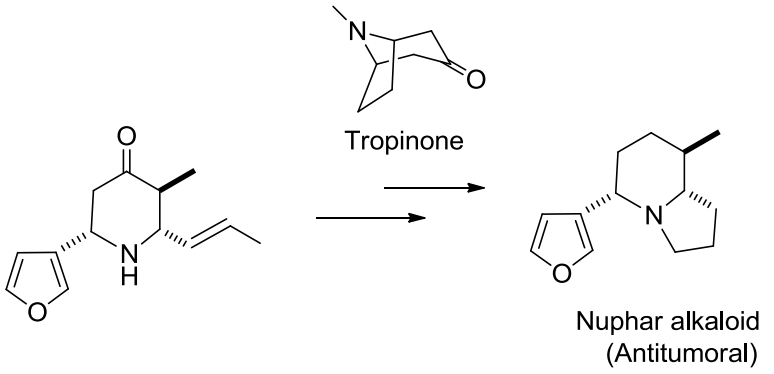


Figure 14.

The asymmetric version of this reaction allows the creation of two adjacent stereogenic centers in one reaction step depending on the nature of the donor component (carbonyl compound) and the acceptor (imine); hence the stereocontrol is of vital importance (Figure 15). Accordingly there is a demand for direct catalytic reactions that afford *syn* or *anti* Mannich products with high diastereo- and enantioselectivities.

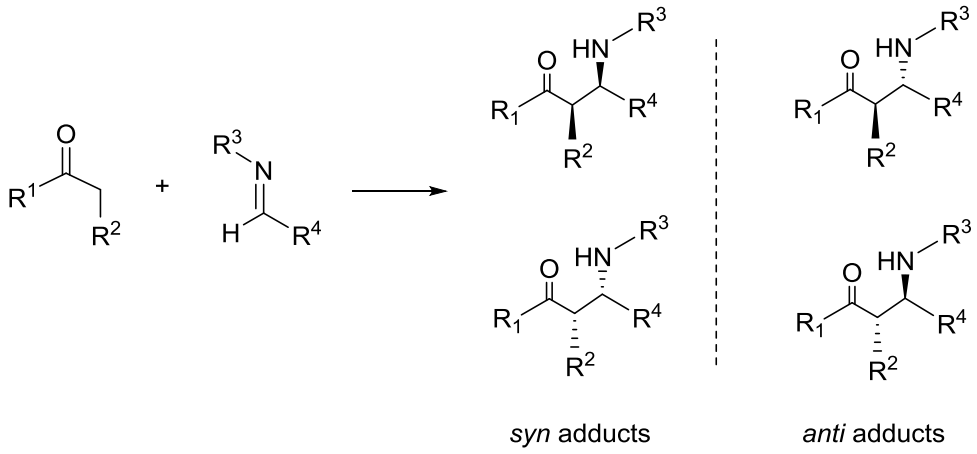
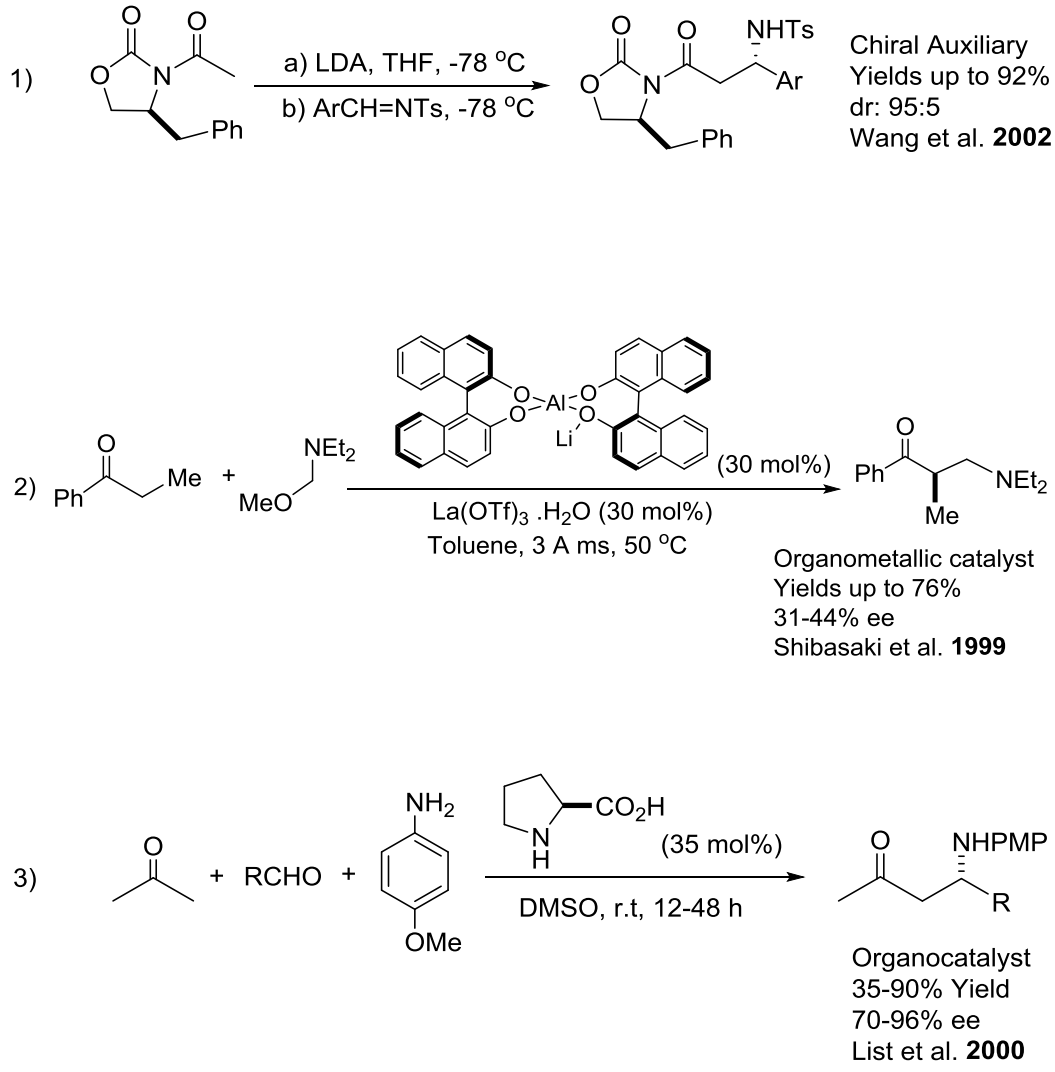
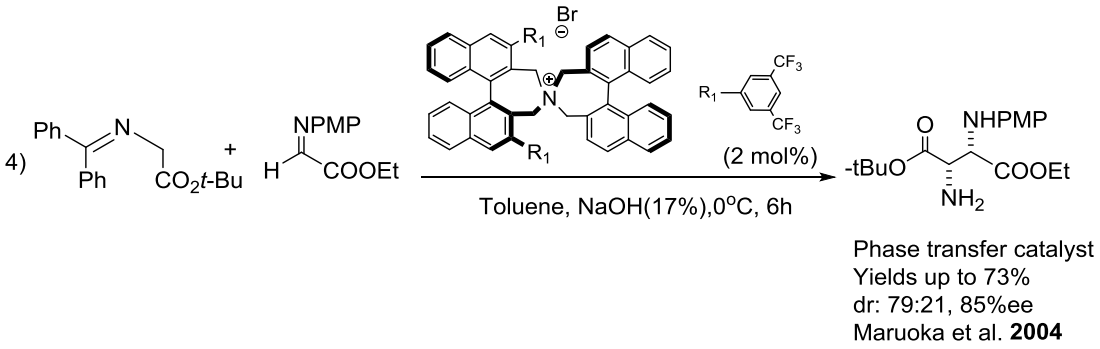


Figure 15. Possible stereoisomers from Mannich reaction.

The Mannich reaction has a mechanistic relationship with the aldol reaction as analagous donor substrates are involved in both chemical transformations. Despite these similarities, there has been less investigation of the Mannich reaction, in part, because the azomethine compounds involved in Mannich reactions are, in general, less electrophilic than their carbonyl analogues and also due to the problem of imine-enamine tautomerism that acts as a competitive process. Scheme 50 shows representative examples illustrating the development of the Mannich reaction.

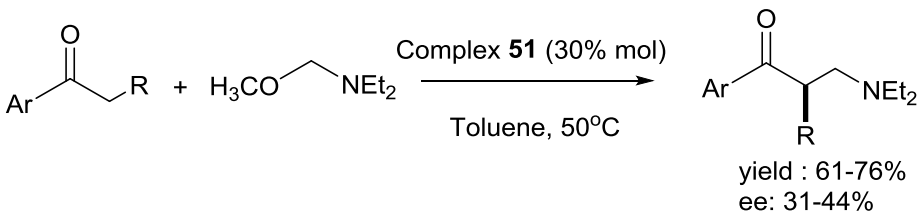


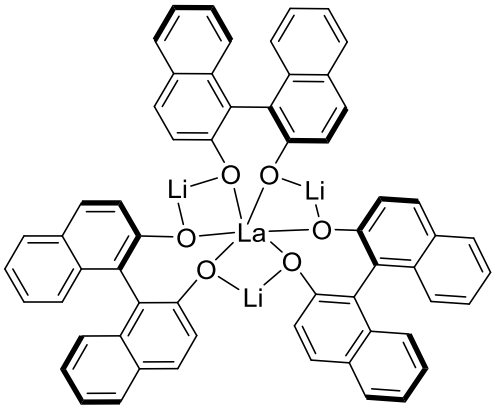


Scheme 50. Examples of the scope of Mannich reactions.

The first stereoselective methods for Mannich reactions were based on the use of chiral auxiliaries[106] that entailed the generation of the corresponding enolates and/or enamines in a predecing irreversible step, hence these methods are known as indirect methods (preformed enolates or enamine). In the late 90's the first catalytic asymmetric variants via enolates of silicon, which were generated in a prior step, and hence also indirect,[107] were documented.

In comparison to the indirect methods, direct methods are distinguished by having no need for prior generation of an enolate or equivalent in an independent or separate step. In this sense, the first catalytic asymmetric direct enantioselective Mannich reaction, although it was still far from giving satisfactory results, was carried out with an organometallic reagent. In 1999, Shibasaki and his group, based their work on investigations relating to enantioselective, direct aldol reaction with a $LaLi_3$tri(binaphthol) complex[108] **51** (LLB). They described the asymmetric direct Mannich reaction[109] shown in Scheme 51, obtaining the corresponding adduct with moderate enantioselectivity and yield.

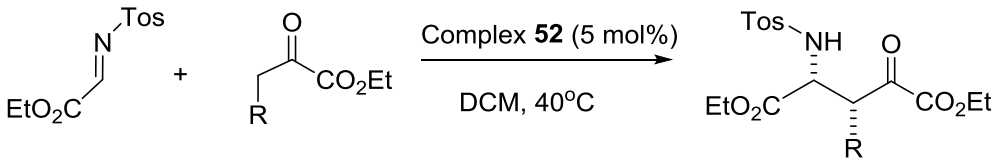




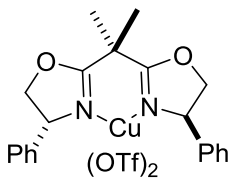
Complex **51**

Scheme 51. First direct catalytic asymmetric Mannich reaction.

Later the first effective catalytic asymmetric direct Mannich was reported by Jorgensen using an organometallic complex of $Cu(OTf)_2$ /bisoxazoline **52** that afforded the Mannich product in good yield with high stereoselectivity as shown in Scheme 52.[110]



Yield : 70-94%
(syn:anti)> 90:10
ee: 70-99%



Complex **52**

Scheme 52. First catalytic enantioselective efficient Mannich reaction.

Other organometallic complexes were subsequently developed as catalysts for the Mannich reaction,[111] Figure 16 shows some of the more high profile examples.[112]

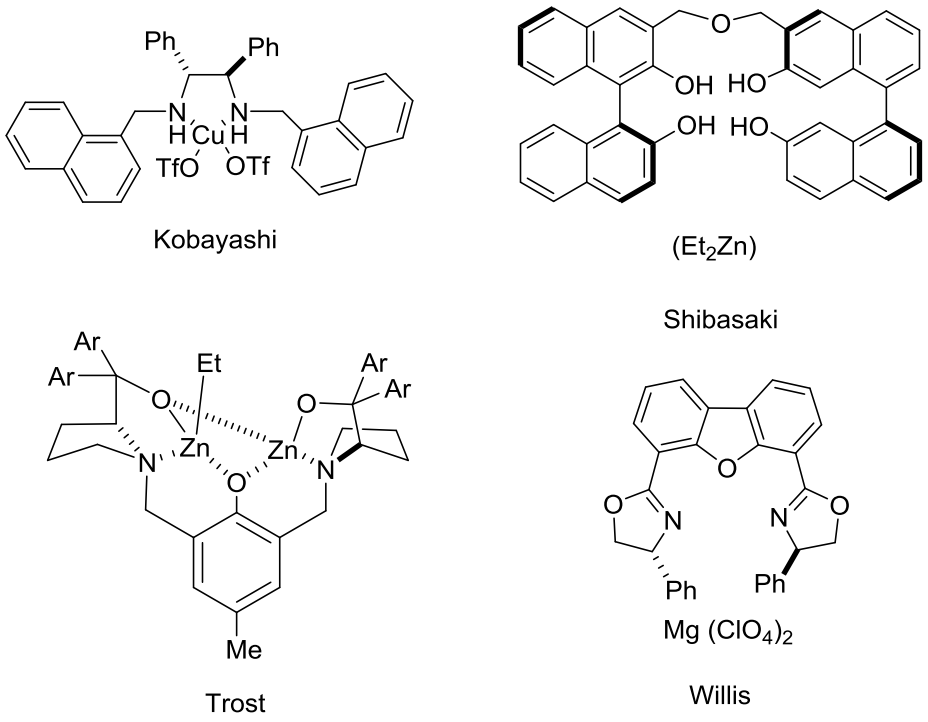
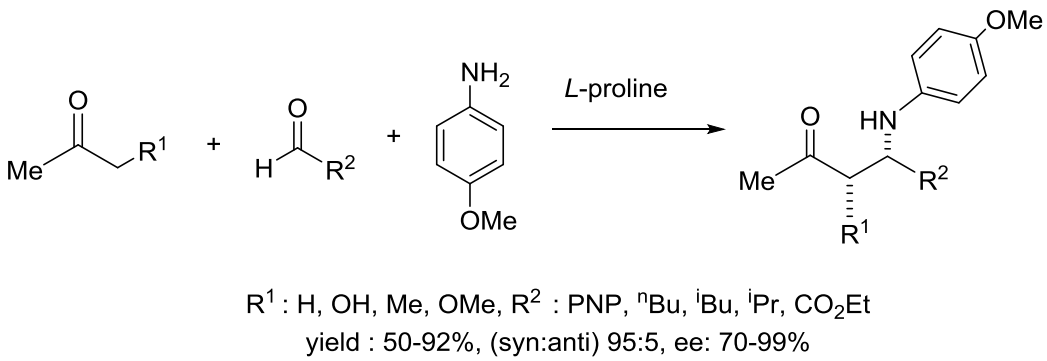


Figure 16. Other organometallic catalysts described for the Mannich reaction.

Diastereo- and enantioselective approaches were not only successfully investigated with organometallic species,[113] but also using organocatalysts.[114] In the last ten years, Mannich reactions via organocatalysis[115] have been widely studied, proving to be an efficient complement to the methods based around metal complexes. Amongst the studied organocatalysts, secondary amines have stood out due to their chemical and stereochemical efficiency. In this thesis we present Mannich products obtained by the enamine mechanism leading to products of syn- configuration. The organocatalytic *syn*-selective Mannich reaction has been comparatively more explored than the *anti*-selective reaction. A *Syn*-selective Mannich reaction using organocatalysis was described by List[116] and a little later by Barbas *et al*.[117] (Scheme 53).



Scheme 53. The first *syn*-selective Mannich reaction.

The same authors have proposed different transition states to explain the stereochemistry of the adducts obtained in the reaction.[18a,b,c,d,19a] These models postulate the reaction between the *Z*-imine and the enamine derived from the ketone and proline within a chair or boat conformation, and the carboxylic proton transfer from the proline to the nitrogen atoms (a and b in Figure 17). A transition state was subsequently proposed in which one internal hydrogen bond was not included (c in Figure 17).

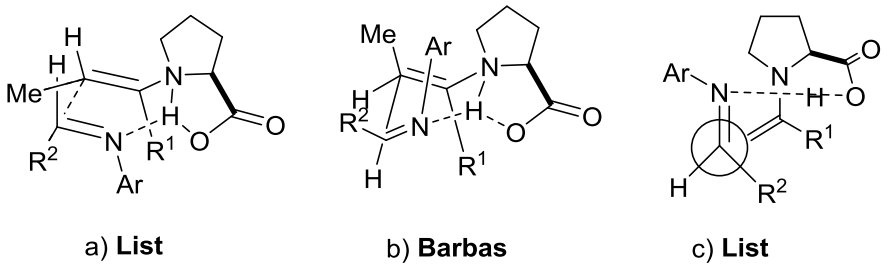


Figure 17.

Subsequently, Houk and collaborators added insight to the process through computational studies.[118] *E*-imines are much more stable than *Z*-imines,[119] the studied models of the transition states for the latter turned out to be less energetically favorable. Amongst all the possible transition states, the one with lowest activation energy turned out to be that represented in Figure 18a, which offers a satisfactory explanation for the experimentally observed stereochemistry. This same study applied to propionaldehyde (Figure 18b) predicts the preferential formation of the *syn*-diastereomer.

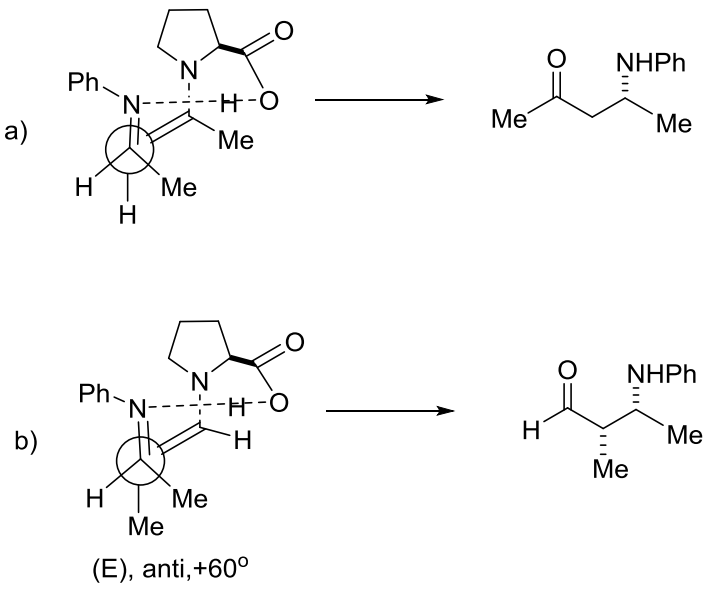


Figure 18. Explanation of the stereoselectivity obtained for the *L*-proline catalysed Mannich reaction.

This initial work by List and Barbas with proline and its derivatives,[120] was extended to *N*-BOC-imines as Mannich acceptors.[121] Different proline derived catalysts that also led to *syn*-adducts were then discovered. The main aim in terms of designing these catalysts was to overcome the limitations observed with proline, such as the high catalyst loading required (20-30 mol%) or that the Mannich reaction with *L*-proline has to be carried out in very polar solvents such as DMSO or DMF due to the low solubility of the amino acid in most of the common non-polar organic solvents. Some examples of these catalysts are shown in Figure 19 and a reaction showing how the use of polar solvents can be avoided is shown in Scheme 54.

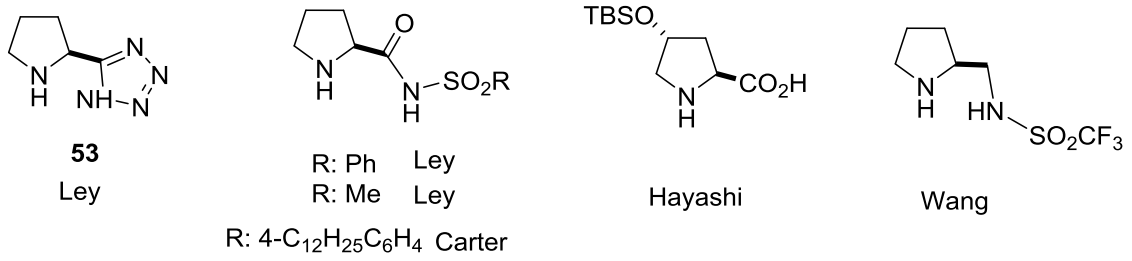
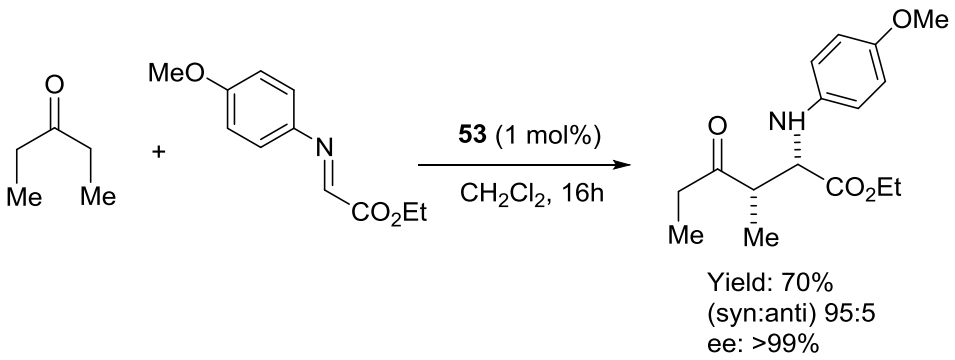


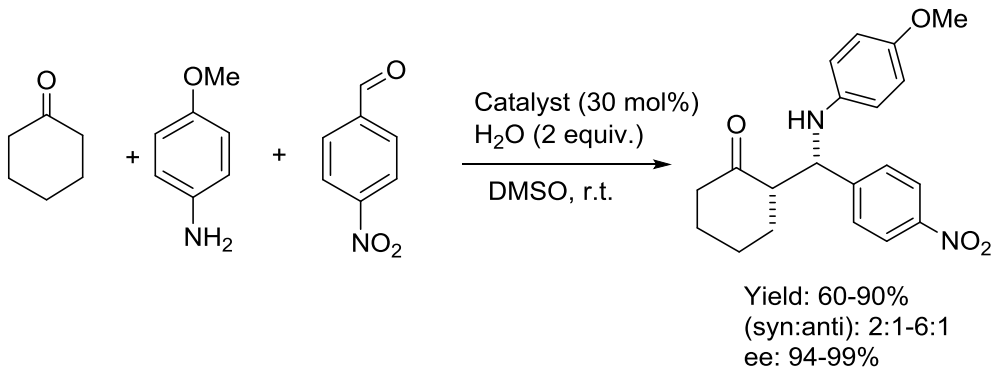
Figure 19.

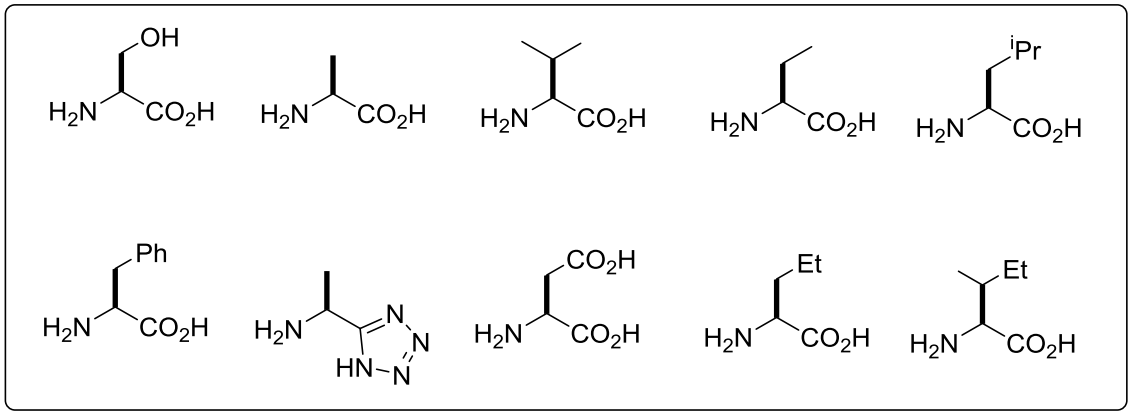
Example:



Scheme 54. *Syn*-selective Mannich reaction.

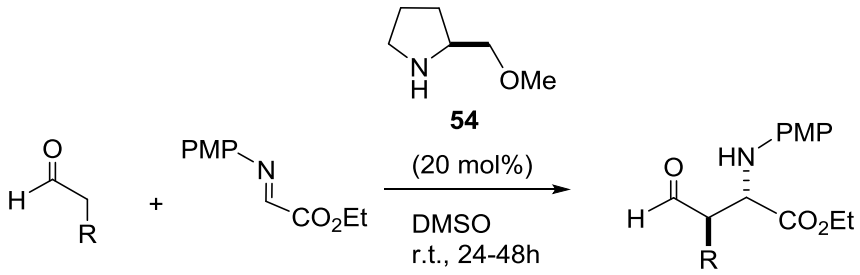
However in this thesis we are more focused on carrying out Mannich reactions using proline and other natural amino acids which can act in a similar role as proline in order to develop a simple and efficient catalytic system for the Mannich reaction. Acyclic amino acids (primary amines) are also able to promote the Mannich reaction. For example, Córdova *et al.*[122] discovered that, surprisingly, serine is able to catalyse the reaction between cyclohexanone, 4-nitrobenzaldehyde, and *p*-anisidine in DMSO (Scheme 55) with good control of diastereo- and enantioselectivity, obtaining the corresponding Mannich adducts of *syn*-configuration with good yields. In the reaction, only traces of product are observed from the competing aldol reaction, results that are an improvement over the ones obtained with proline under identical reaction conditions. After a wide study authors observed that almost all natural amino acids are capable of catalysing the reaction to some degree.





Scheme 55. Primary amines used for the *syn*-selective Mannich reaction.

Methods available for obtaining *anti*-Mannich adducts are limited. The first publication featuring the use of organocatalysis for the *anti*-selective Mannich reactions was reported in 2002. Barbas and Córdoba tried to modify the diastereoselectivity of the process by testing pyrrolidines which lacked the carboxylate group of the proline, thus avoiding the approach via hydrogen bonding and promoting, in turn, steric control. These authors discovered that secondary amines such as (*S*)-2-methoxymethyl pyrrolidine (SMP) (**54**) catalysed the reaction between aldehydes and *N*-PMP-imines derived from ethyl glyoxylate (Scheme 56).[123] The reaction produces mostly the corresponding anti-adducts although with moderate yields and moderate to good diastereo- and enantioselectivities (Table 11).



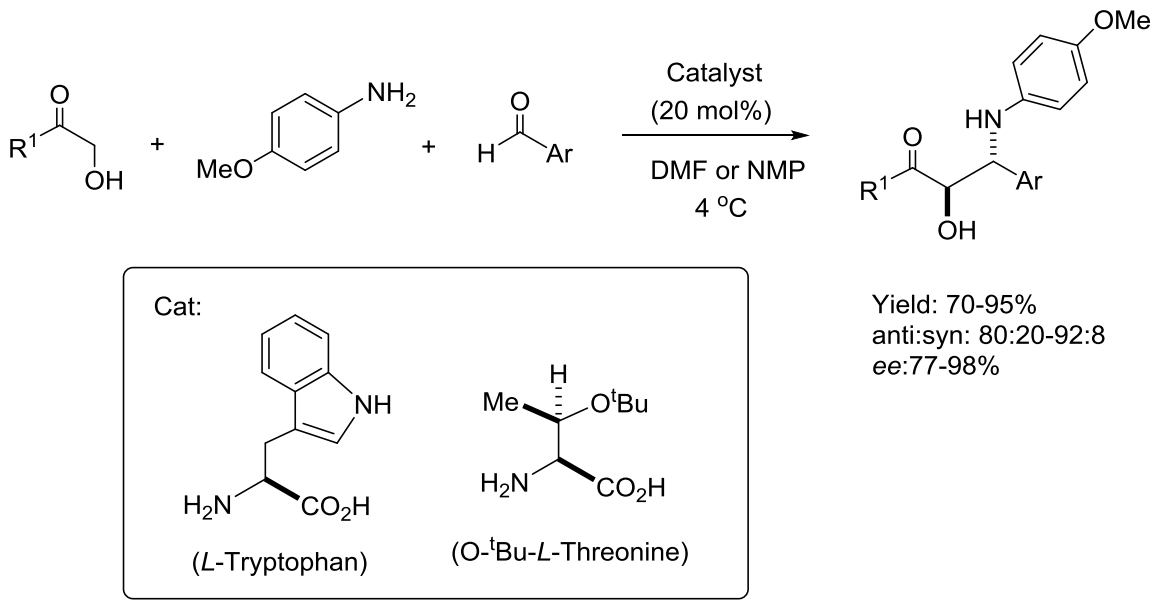
Scheme 56. First organocatalytic *anti*-selective Mannich reaction.

Table 11 Reaction between aldehdyes and *N*-PMP imines catalysed by **54**

Entry	R	Yield (%)	anti:syn	*ee*(%)
1	^{i}Pr	52	95:5	82
2	^{t}Bu	57	95:5	92
3	Et	44	80:20	75
4	^{n}Bu	54	90:10	74
5	^{n}Pent	78	95:5	76
6	^{n}Hex	68	95:5	76
7	$^{n}CH_2CH=CH(CH_2)_4CH_3$ *trans*	67	95:5	78

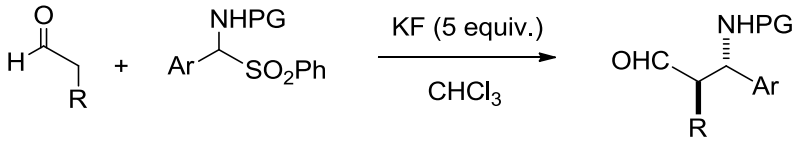
It was not until 2005 that Jørgensen[124] continued work on the *anti*-selective Mannich reaction by using α,α-diarylprolinol as catalyst to produce Mannich products effectively in terms of yield and enantioselectivity. From a mechanistic point of view, it has been shown that *L*-proline and derived catalysts that act through hydrogen bonding lead to *syn*-adducts, whereas prolinol amine derivatives that act through steric hindrance lead to mainly *anti*-adducts.

Apart from examples with secondary amines, Barbas III *et al*. have described *anti*-selective Mannich reactions using primary amines, such as natural amino acids or derivatives as catalysts (Scheme 57).[125] In addition, the imines employed in this case are aromatic, and this is one of the few examples of Mannich reactions which uses relatively unreactive imines.



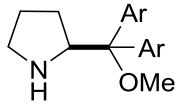
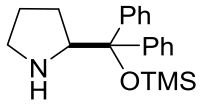
Scheme 57. Primary amines that catalyse the *anti*-Mannich reaction.

This thesis focuses on the one pot synthesis of β-amino aldehydes from *N*-Boc-protected α-amido sulfones[126,127] and aldehydes. The use of carbamates as precursors of azomethines had already been described by Melchiorre in 2008 who described the anti-selective Mannich reaction with aromatic *N*-Boc and *N*-Cbz imines. Imines are generated *in situ* from the corresponding α-amidosulfones in the presence of a catalyst (**55** or **56**) and five equivalents of potassium fluoride as a base, with notable results[128] (Scheme 58).



Scheme 58. *Anti*-selective Mannich reaction between *N*-Boc and *N*-Cbz imines and aldehydes catalysed by **55** and **56**.

Table 11: 55 and **56** catalysed Mannich reaction of protected imines catalysed

Catalyst	R	Prot. Gp	Yield (%)	dr(anti:syn)	*ee* (%)
 **55** (10 mol%)[30]	Me	Boc	87	92:8	98
	Me	Cbz	94	86:14	94
 **56** (10-20 mol%)[31]	Me	Boc	76-94	83:17	76-96
	Bu				
	Bn				
	^{i}Pr	Boc, Cbz	60-95	86:14-92:8	84-99

List found that reacting preformed *N*-Boc-imines with aldehydes in acetonitrile with 20% (*S*)-proline produced chiral Boc-protected β-amino aldehydes. For instance isovaleraldehyde and 2-napthaldehyde derived *N*-Boc-imines in the presence of proline for 12 hours at 0°C afforded the corresponding β-amino aldehyde with a yield of 82%, dr of >99:1 and *ee* of 98%.[129] Boc protecting groups are stable to bases, and can be deprotected by acids.

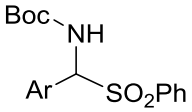


Figure 20. General structure of α-amido sulfone.

It is possible to generate *N*-Boc imines in situ by the use of reagents with a good leaving group α to the nitrogen atom. α-Amido sulfones are ideal precursors for this chemistry as they are 'bench' stable and have a good leaving group, SO_2Ph α to the amine (Figure 20). They are also easily obtained by reacting tert-butyl carbamate with sodium benzenesulfinate and the desired aldehyde.[130] Zhao and Córdova *et al*. devised a one-pot synthesis of β-amino aldehydes from aldehydes and α-amidosulfones[131]which provides the basis for work reported later in this thesis. They found that the (*S*)-proline catalysed reaction between 2-napthaldehyde derived amido sulfone and propanal afforded the corresponding *syn*- and *anti*- β-amino aldehydes via an imine intermediate, with high enantioselectivity (*ee syn*, 96% *ee anti* 94%, dr 50:50). Different inorganic bases were screened in an attempt to improve the diastereomeric ratio and they found that 5 equivalents of KF with chloroform as solvent gave the greatest yield, with a dr of 91:1 and *ee syn* >99%.

Figure 21 shows the mechanism of α-amido sulfone synthesis; the lone pair on the nitrogen attacks the δ^+ carbonyl carbon. Hydrogen transfer occurs and an α-carbinolamine is formed. The OH is protonated by the formic acid to provide a better leaving group. The reaction occurs by an S_N1 mechanism as the lone pair on the nitrogen is used to create a C=N bond, eliminating water and forming an iminium ion. The benzene sulfinic acid attacks the carbon of the iminium ion, resulting α-amido sulfone which is non-polar and hence precipitates out of solution.

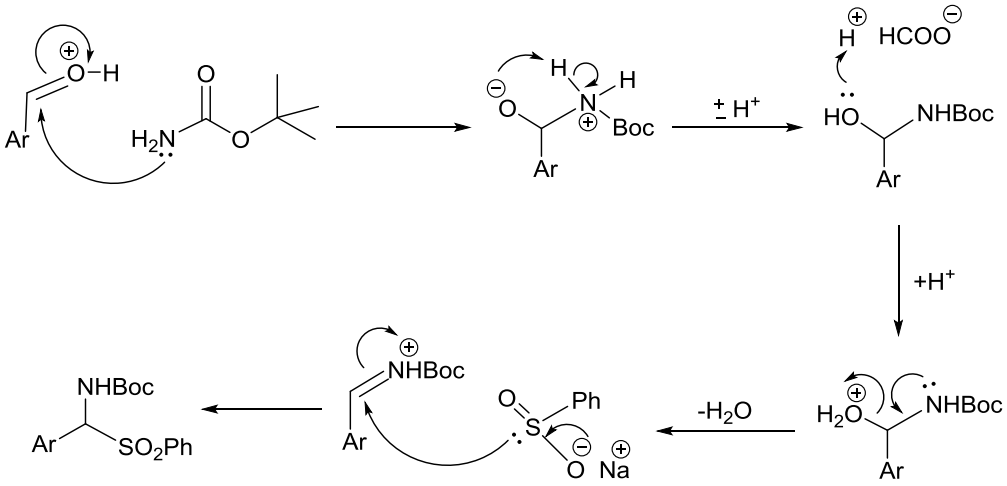


Figure 21.Mechanism for the synthesis of α-amido sulfones.

Figure 22 shows how the α-amido sulfone forms an imine *in situ*; SO_2Ph is a good leaving group as it is a fairly stable anion. The lone pair on the nitrogen forms a double bond and eliminates SO_2Ph. As the base KF dissociates, K^+ forms a salt with the anion and F^- deprotonates the nitrogen to form an imine.

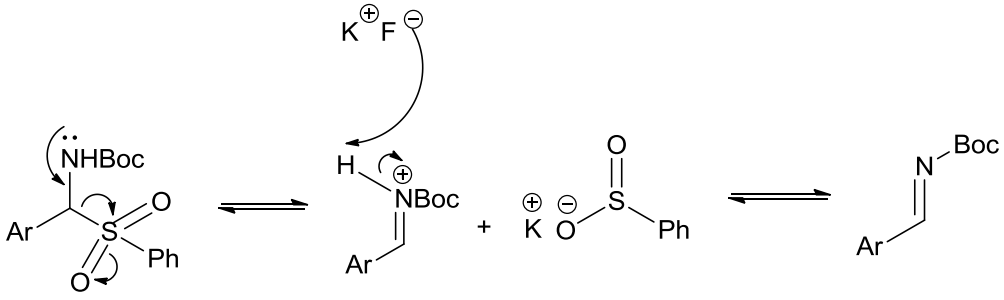


Figure 22. Mechanism of imine formation in situ.

For the mechanism of β-amino aldehyde synthesis, proline catalyses the reaction by firstly protonating the carbonyl on the aldehyde making it more reactive. The lone-pair on proline nitrogen then attacks the carbonyl carbon. The positively charged nitrogen loses H^+ to the base present and the OH is protonated by the weak conjugate acid HF to make it a better leaving group. The lone pair on nitrogen forms a C=N double bond and eliminates water to form an iminium ion. The water generated in the last step can reprotonate the carbanion, regenerating the carboxylic acid group, meanwhile the iminium ion tautomerises to form an enamine. The enamine is a soft nucleophile and attacks the imine formed by the α-amido sulfone. A six-membered chair transition state is formed due to the proton on the carboxylic acid group being stabilised by hydrogen bonding on the nitrogen. As the carboxylic group on proline is coming out of the plane, the reaction occurs on the *re*-face of the enamine. The lone pair on nitrogen belonging to proline forms a double bond, pushing the enamine to form a C-C with the imine, and an N-H bond is formed between the nitrogen of the imine and the H of the carboxylic acid. ^-OH attacks the C=N to neutralise the positive charge on N, forming a C-O bond. Nitrogen is protonated by HF and the carbanion deprotonates the OH, regenerating the carboxylic acid group and forming a C=O double bond, eliminating and regenerating proline. The major diastereomer of the amino aldehyde formed has syn geometry; bulky groups prefer to sit in an equatorial position in the six-membered chair like transition state. However, if the Boc group on the imine sits equatorial it eclipses the H which hinders bond formation. As well as this, the *R* group of the enamine is eclipsed by the Ar group on the imine which results in steric hinderence. The imine is oriented in a way that both the Ar group and Boc group sit axially in the transition state, which affords *syn* geometry in the product.

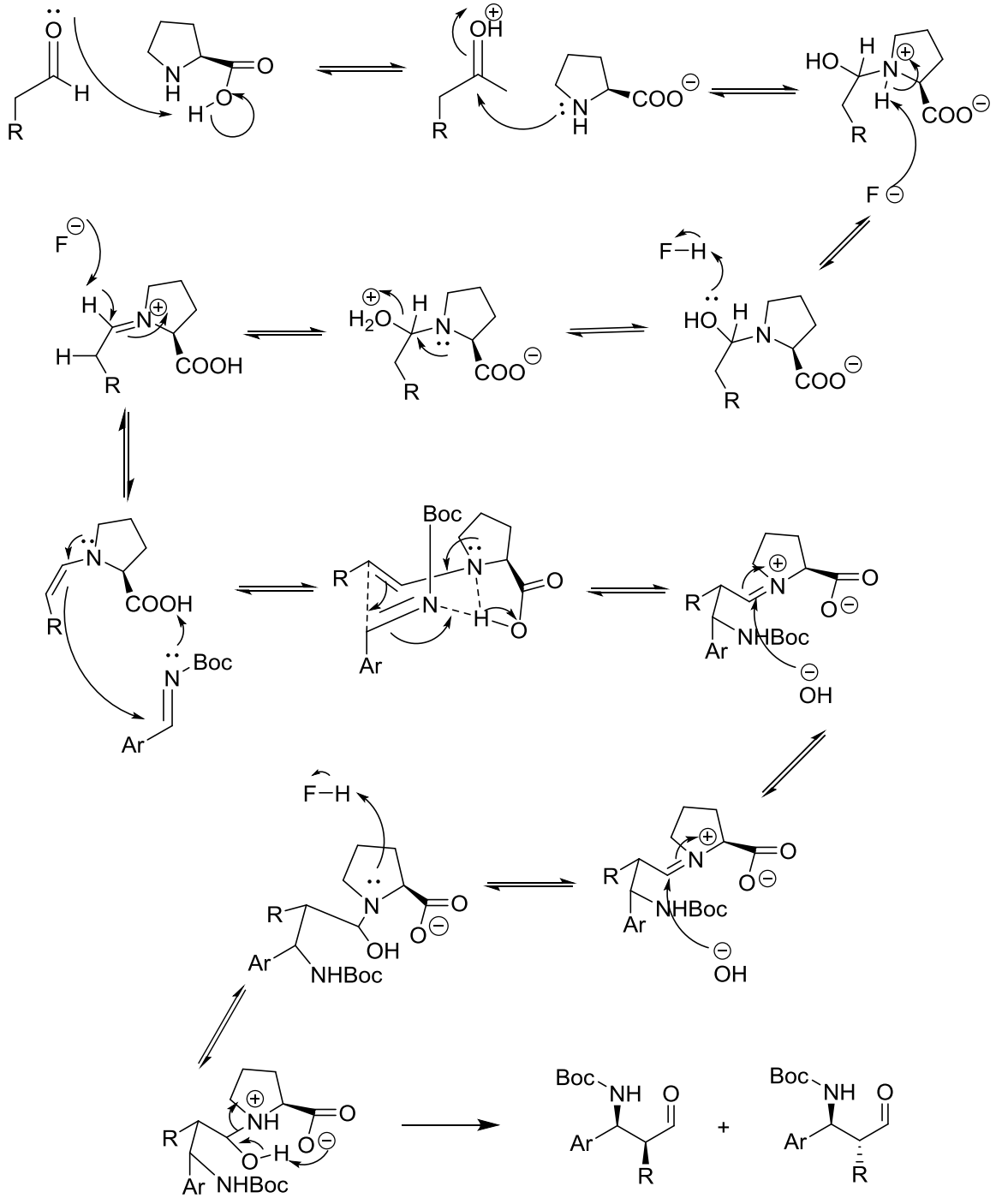
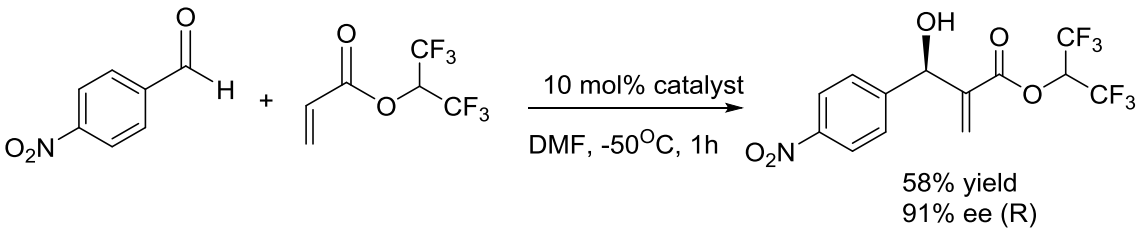


Figure 23. Mechanism for proline-catalysed mannich-type β-amino aldehyde synthesis

1.4 Cinchona Alkaloids in Asymmetric Organocatalysis

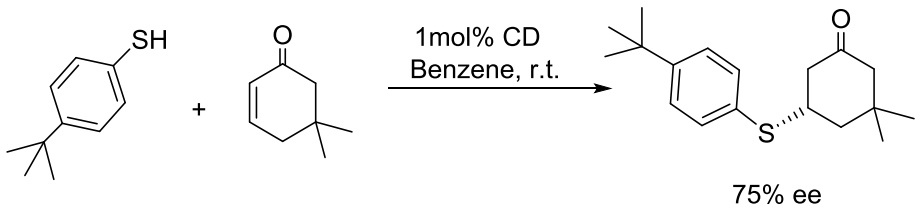
Cinchona alkaloids represent a large class of natural products that possess several important features rendering them useful as asymmetric organocatalysts. They are readily available, being easily extracted from the bark of the cinchona trees that are cultivated above 1400 m in equatorial climatic zones, between the Bolivian and Venezuelan Andes, and Indonesia (isle of Java). From the extract of the bark more than 30 alkaloids have been isolated (5-15% w/w). Four of these represent 50% of all the alkaloids: quinine (**QN**), quinidine (**QD**), cinchonidine (**CD**), and cinchonine (**CN**). Not surprisingly, these four alkaloids are used in chemistry as chiral bases, as they are inexpensive and available as both diastereomers, allowing access to either enantiomeric product from catalysis.

Their use as nucleophilic catalysts was first described over twenty years ago in an elegant synthesis of β-lactones by Wynberg and Staring[132] involving a cycloaddition between activated aldehydes and ketenes. The asymmetric synthesis of bicyclic lactones[133] via an intramolecular aldolactonization process catalyzed by O-acetyl quinidine as well as the dimerization of methyl ketene to form optically active polypropionate synthons are two examples[134,135] of the high level of stereoselectivity that these alkaloids can achieve. Notably, Leckta utilised benzoyl quinine as a catalyst for the highly enantioselective preparation of asymmetric β-lactams via an imine-lactamization process. Modest yields (45-65%), but high diastereoselectivity (99:1) and excellent enantioselectivity (96-99%), resulted for a variety of aryl, alkyl and alkoxy-substituted β-lactams.[136] A particularly interesting example of cinchona alkaloid catalysis has been employed in the first catalytic, highly enantioselective Baylis-Hillman reaction (Scheme 59).[137]



Scheme 59. Asymmetric Baylis-Hillman reaction.

A considerable improvement in Cinchona chiral catalysis in was achieved in the 1970s. Wynberg, Hiemstra and co-workers studied several reactions catalysed by quinine and its derivatives, obtaining excellent results and mechanistic data for the addition of thiophenol to 5,5-dimethylcyclohexen-2-one (Scheme 60).[138,139]



Scheme 60. The enantioselective Michael addition of thiophenols to enones.

A pioneering example was carried out by Wynberg and Hiemstra in 1981; they used cinchonidine **CD** in the addition of some thiophenol derivatives to cyclic α,β unsaturated ketones.[140] Dramatic enhancements were made in the 1980s and 1990s. Indeed, Cinchona alkaloid derivatives were used in the phase transfer alkylation of glycine derivatives,[141] and in the Sharpless asymmetric dihydroxylation.[142] After all these successful and significant results, Cinchona alkaloids are now recognised as a privileged class of chiral catalyst.[143]

The structures of the four alkaloids are quite interesting. It is possible to identify three different parts: the quinoline ring, the *vic*-amino function and the bicyclic moiety (Figure 24). In all these bases five stereogenic centers are present, and the chiral quinuclidinic nitrogen is the most important as it is responsible of the direct transfer of chirality in catalysis.

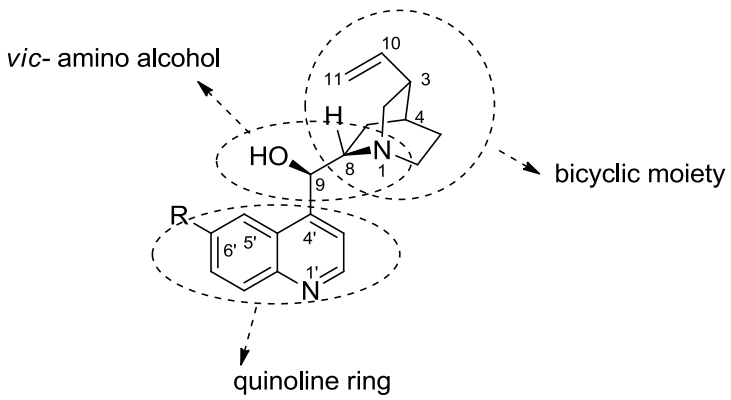
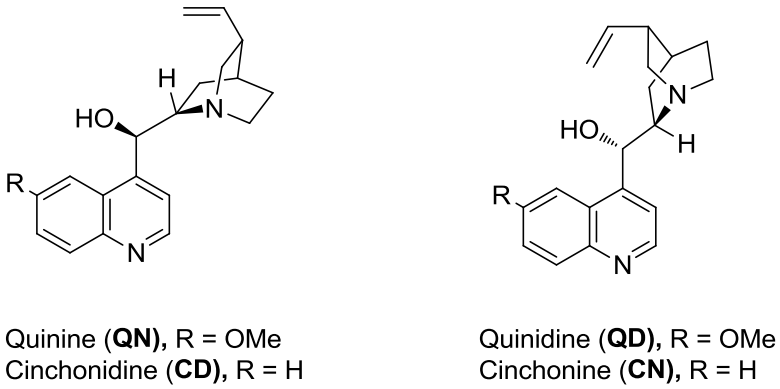


Figure 24. Cinchona alkaloids structure.

The four bases are diastereoisomers, but are considered to be pseudo-enantiomers. Indeed, the N-C(8)-C(9)-O is usually the centre of the catalytic activity. Quinine vs. quinidine and cinchonidine vs. cinchonine have opposite absolute configurations at these stereogenic centres and this means that very often these pairs of diastereoisomers act as enantiomers (Figure 25).



Quinine (**QN),** R = OMe
Cinchonidine (**CD),** R = H

Quinidine (**QD),** R = OMe
Cinchonine (**CN),** R = H

Figure 25. A pseudoenantiomeric relationship.

Furthermore, as mentioned above, in the molecules both Brønsted acid (C(9)OH) and base coexist, so it is possible to activate both the nucleophile and the electrophile. This behaviour makes several Cinchona alkaloid derivatives operate as bifunctional organocatalysts. The mentioned alkaloids are very versatile structures which possess many functional groups suitable for derivatization. They can therefore be used to synthesise a large number of catalysts.

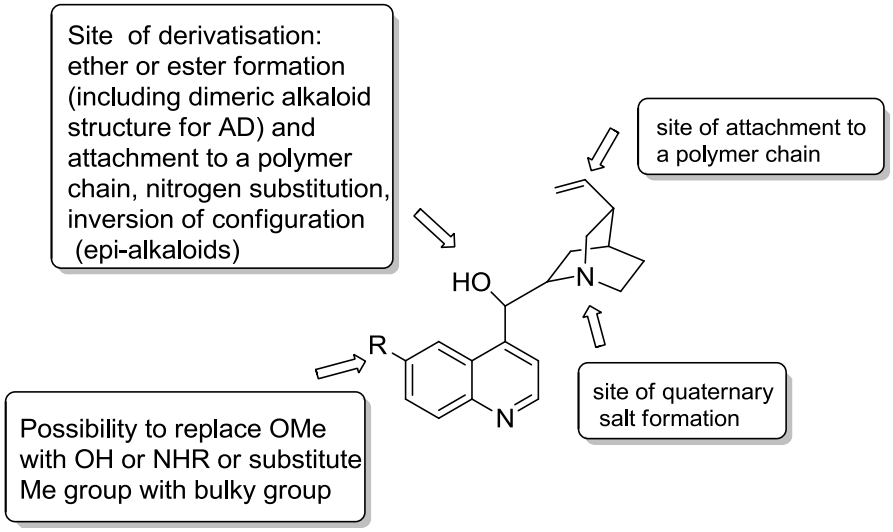


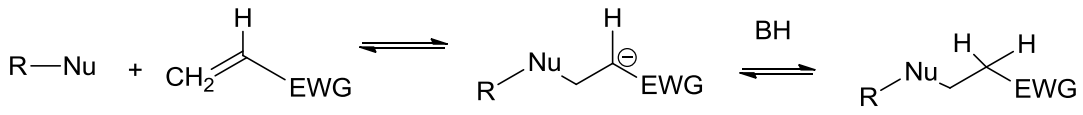
Figure 26. Preferred sites of derivatization.

In general, the C(9)-OH, quinolinic OMe and quinuclidinic nitrogen are the preferred functional groups for the derivatizations. The C(9)-OH can be alkylated, the quinolinic OMe can be replaced in favour of a free hydroxyl group or an amino group, re-alkylated with bulky substituents; finally, but probably more important, the tertiary nitrogen can be alkylated to obtain a quaternary ammonium salt, used very often for phase-transfer catalysis (PTC). Moreover, there is another important modification in Cinchona alkaloid chemistry, as the catalysts could be anchored in a solid support by different processes: polymerisation of the double bond, anchoring the catalyst by alkylating the C(9)- OH, or the quinuclidinic nitrogen for the phase transfer catalysts (Figure 26).

Considering the background of results achieved by the cinchona alkaloids, it was decided to explore Michael addition reactions using an organocatalytic protocol mediated by Cinchona alkaloids.

1.4.1 Michael Additions

The Michael addition reaction was discovered by Arthur Michael[144] and consists of the nucleophilic addition of a carbanion to an α, β-unsaturated carbonyl compound. It belongs to the larger class of conjugate additions. The enantioselective Michael reaction represents one of the most useful methods for the mild formation of C-C bonds in organic chemistry.[145] The reaction typically refers to the base catalysed addition of a nucleophile such as an enolate anion, also called a "Michael donor", to an activated electrophilic α,β-unsaturated carbonyl-containing compound, the "Michael acceptor", resulting in a "Michael adduct", as shown in Scheme 61[146,147]



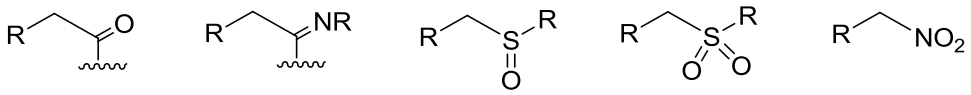
Scheme 61. Schematic depiction of the Michael addition reaction of a compound with an electron-withdrawing group (EWG) to an activated C-C multiple bond.

Nitroalkanes,[148] malonate esters,[149] ketoesters,[150] 1,3-diketones,[151] nitroesters,[152] 1,3-dinitriles,[153] cyanoacetic acid esters[7c] and phenylacetic acid esters,[7d] are examples of valuable nucleophiles for the conjugate addition to σ,β-unsaturated systems. In many cases, only one or two types of nucleophile can react with a specific electrophile. For example, more reactive nitroalkanes have served as nucleophiles for the conjugate addition reaction of α,β-unsaturated carbonyls.[154]

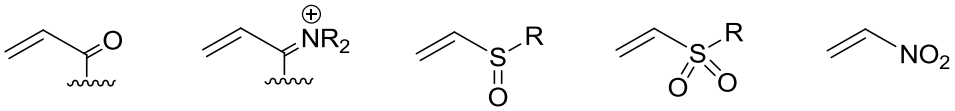
It is worth noting that although, the Michael addition is generally considered to be the addition of enolate nucleophiles to activated olefins, a wide range of non-enolate nucleophiles possess sufficient nucleophilicity to perform as Michael donors. Some examples include amines, thiols, and phosphines. When non-enolates are used, the Michael reaction is typically referred to as 'Michael-type additions' which will not be covered in this thesis. Due to the many types of Michael additions in the literature, the focus here will be on investigating the carbon-carbon bond forming Michael addition.

The Michael acceptor possesses an electron withdrawing and resonance stabilizing activating group, which stabilizes the anionic intermediate. Michael addition acceptors are far more numerous and varied than donors, due to the abundance of electron withdrawing activating groups that enable the Michael addition to olefins and alkynes. Acrylate esters, acrylonitrile, acrylamides, maleimides, alkyl methacrylates, cyanoacrylates and vinyl sulfones serve as Michael acceptors and are commercially available. Less common, vinyl ketones, nitro ethylenes, α,β-unsaturated aldehydes, vinyl phosphonates, acrylonitrile, vinyl pyridines, azo compounds and even β-keto acetylenes and acetylene esters also serve as Michael acceptors.[155]

Examples of Michael donors:

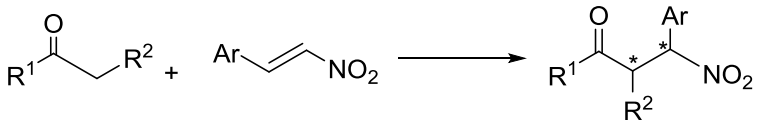


Examples of Michael acceptors:



The acceptors used have been restricted to α,β-unsaturated ketones,[156,157,158, 159] aldehydes,[160a] and esters.[13b] The use of nitroolefins as Michael acceptors for the asymmetric reaction has proven to be a challenging task despite the fact that nitroolefins are more active than α,β-unsaturated carbonyls[161] and the versatile nitro groups can be readily transformed into a variety of functionalities.[162] Only the work involving catalytic enantioselective addition of stabilized soft nucleophiles will be reported here.

The Michael adducts are essential parts of biologically important natural products. The addition of nucleophiles to Michael acceptors is an important reaction for the synthesis of highly functionalised synthetic building blocks in organic synthesis as a result of the products possessing various functional groups, such as nitro, ester and ketone. Nitro-alkenes stand out amongst Michael acceptors due to the synthetic versatility of the nitro group. The range of nucleophiles employed in Michael additions to nitro-alkenes is extensive, and includes carbon, oxygen, nitrogen, phosphorus and sulphur based examples.[163] Nowadays, the Michael addition of ketones with nitroolefins has become undoubtedly, a convenient way to access to γ-nitroketones **57** and optically active nitroalkanes, which are important building blocks for agricultural and pharmaceutical compounds[164] (Scheme 62).



57

Scheme 62.

The reaction is also catalysed with acids, particularly Lewis acids such as boron trifluoride, aluminum trichloride, and zinc chloride[165] as shown in Figure 27; the Lewis acid coordinates to the carbonyl of the acrylate to activate the olefin. The coordinated complex will then react with the nucleophile to obtain the same adduct as in the base catalysed Michael addition.

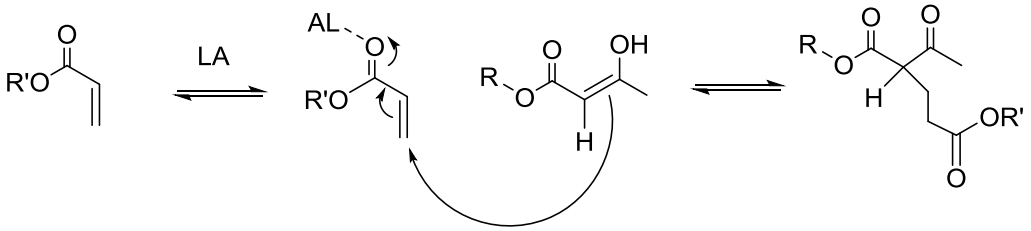


Figure 27. Lewis- acid catalysed Michael addition reaction.

However this thesis will be focused on investigating base catalysis which is most prominently used in the carbon-carbon bond forming Michael additions. The mechanism is explained according to a base catalysed addition such as the addition of ethyl acetoacetate to methyl acrylate[166]. The mechanism of the reaction is fairly straightforward, with every step being in equilibrium and thermodynamically dependent on the relative strengths of the base and the type of acetoacetate. The acetoacetate is first deprotonated by the base, providing an enolate anion (Michael donor) (Figure 28). The enolate anion then reacts in a 1,4-conjugate addition to the olefin of the acrylate (Michael acceptor). The carbonyl of the acrylate stabilizes the resulting anion until proton transfer occurs, regenerating the base. The overall driving force for the conjugate addition is the enthalpic change that accompanies replacement of a π-bond with a σ-bond. Thus, there is the preference for 1,4-addition over 1,2-addition. In some cases however, kinetically controlled reaction conditions can afford attack at the carbonyl carbon rather than at the β-carbon of the olefin.[167]

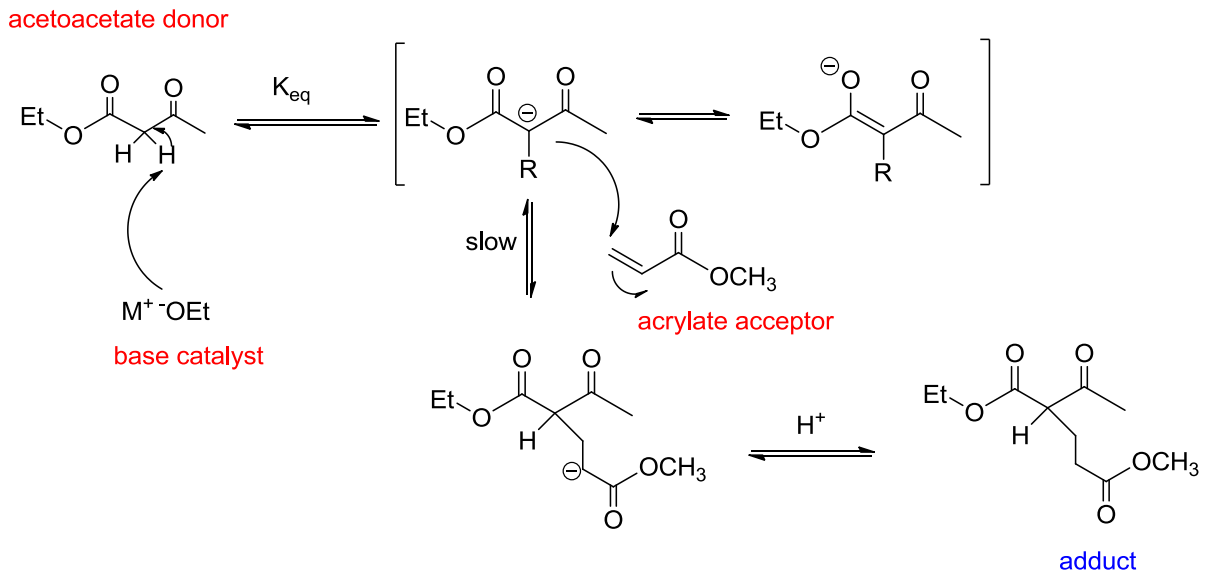


Figure 28. General carbon-Michael reaction mechanistic scheme.

Since the first reported example of catalytic enantioselective Michael addition reaction by Wynberg[168] in 1975, there has been many publications in this area which has become one of the most important methods for enantioselective C-C bond formation.

1.4.2 Use of Cinchona Alkaloids as catalysts in Michael Additions

Although there have been many reports of enantioselective Michael additions with chiral catalysts, including metal-based catalysts and multimetallic catalysts as well as organic catalysts,[169] as mentioned before bifunctional chiral cinchona alkaloids have been demonstrated as effective promoters for the activation of nucleophilic enol species and α,β-unsaturated carbonyls via acid-base interactions. One reported example is the conjugate addition of dimethyl malonate ester **58** to chalcone **59** under neat conditions at room temperature (Scheme 63). The reaction was evaluated using different cinchona alkaloids as shown in Figure 29 and the results are shown in Table 13.

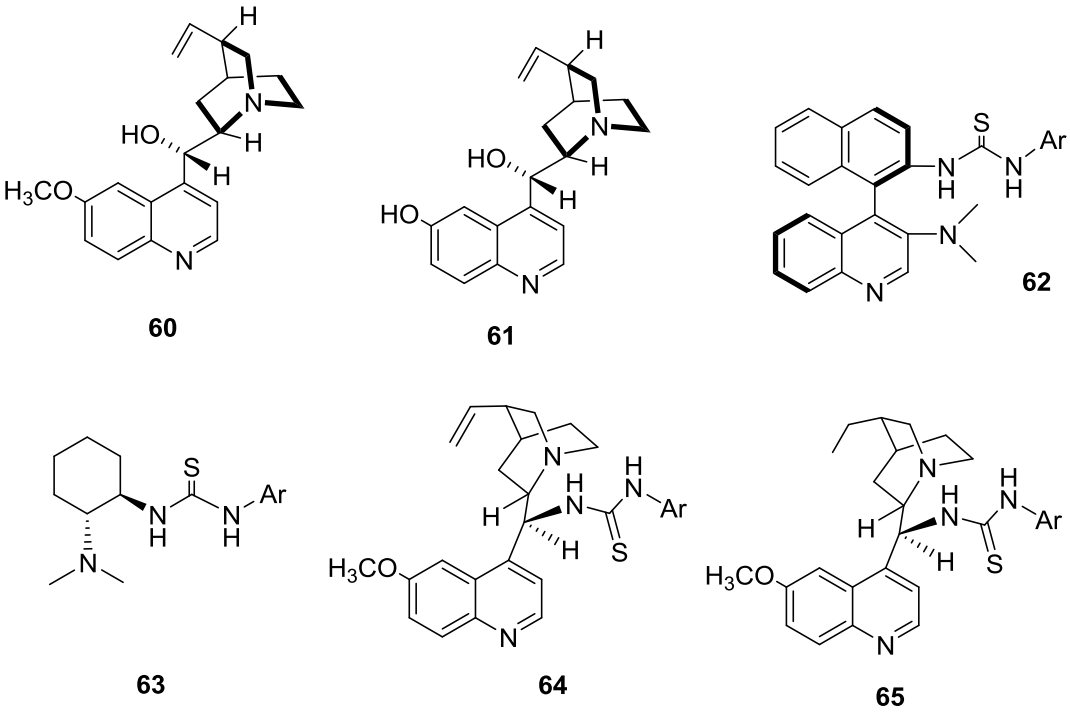
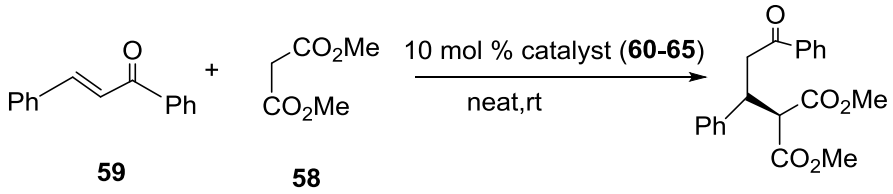


Figure 29.

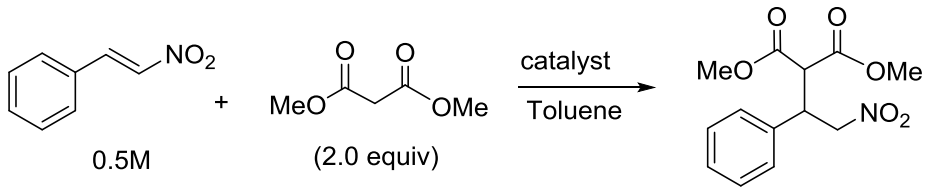


Scheme 63.

Table 13. Results of exploratory studies of the catalytic asymmetric conjugate addition reaction of dimethyl malonate **58** and trans-chalcone **59**.

Entry	Catalyst	t(h)	Yield (%)	*ee* (%)
1	**60**	96	73	rac
2	**61**	48	85	rac
3	**62**	96	78	20
4	**63**	96	88	79
5	**64**	72	82	81
6	**65**	72	86	84

The results showed that the reaction took place efficiently in good yields although for catalysts **60**-**62**, poor enantioselectivities were observed. In contrast, amine thioureas **63**-**65** afforded a higher enantiomeric excess.



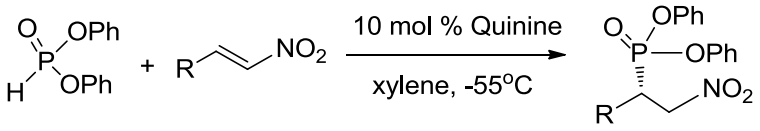
Scheme 64

Table 14 Catalysed addition of dimethyl malonate to nitrostyrene

Entry	Catalyst	Mol (%)	t (h)	Conv (%)	*ee* (%)[b]
1	DHQ	5	24	>98	12
2	9-epi-DHQ	5	144	46	18
3	DHQD	5	24	>98	1
4	DHQU	5	24	26	25
5	DHQDU	5	144	25	17
6	9-epi-DHQU	5	5	>98	74
7	9-epi-DHQU	2	24	>98	88
8	9-epi-DHQDU	2	30	>98	79
9	9-epi-DHQT	2	24	>98	90
10	9-epi-DHQDT	2	30	>98	85
11	9-epi-DHQT	2	30	>98	99

Nitroolefins are attractive Michael acceptors since their strongly electron withdrawing nitro group can be readily transformed into a variety of functionalities.[170] A number of reports of enantioselective Michael additions have been published involving nitroalkenes as Michael acceptors in which Michael reactions are promoted by different types of cinchona alkaloid and their derivatives. Deng *et al*. reported the use of cinchona alkaloid derivatives to catalyse the addition of dimethyl malonate to nitroalkenes in excellent yield and ee (Scheme 64, Table 14).

The Michael addition of phosphorus containing compounds to nitroolefins is a convenient method for the synthesis of β-nitrophosphonates which are then transformed to chiral α-substituted β-aminophosphonic acids[171,19] which have increasing applications in peptide and medicinal chemistry.[172,173] One of the naturally occurring cinchona alkaloids that can promote these reactions is Quinine. An example of this is shown in Scheme 65, Table 15. The reaction carried out in xylene gave the highest enantioselectivity.



Scheme 65

Table 15. The scope of quinine catalysed asymmetric Michael addition of diphenyl phosphite to trans-β- nitrostyrene.

Entry	R	t (days)	Yield (%)	*ee* (%)
1	Ph	6	82	70
2	4-F-C_6H_4	6	85	77
3	4-Cl-C_6H_4	6	82	72
4	4-Me-C_6H_4	6.5	83	80
5	4-MeO-C_6H_4	7	78	75
6[a]	3-BnO-4-MeO-C_6H_3	5	82	82
7[a]	3,4-(OCH_2O)C_6H_3	5	78	81

[a] Reaction performed at -20 °C.

2. Results and Discussion

2.1 Introduction: Application of Amino acids in Asymmetric Reactions

The α-amino acids are an important group of natural products. In addition to the twenty amino acids commonly found in proteins, over 700 non-proteinogenic α-amino acids are known. There has been much interest in the synthesis of both proteinogenic and unnatural amino acids because of their importance in biosynthesis, their use as enzyme inhibitors, their application for the investigation of enzyme mechanisms, and their medicinal properties. Some proteinogenic amino acids have been stereospecifically transformed into non-proteinogenic amino acids, however the synthesis is complicated both by the diverse range of side groups found in natural amino acids, and by the presence of at least one chiral centre. Therefore this thesis will focus on the proteinogenic α-amino acids which can be obtained from natural sources and are commercially available at low cost.

Ten of these twenty amino acids are named as essential amino acids as they cannot be synthesised by humans and therefore must be supplied in the diet. Among them are valine, histidine, arginine, leucine, methionine, threonine, isoleucine, lysine, tryptophan, and phenylalanine. The other ten are named as non-essential amino acids that can be synthesised by the human body and are alanine, proline, glycine, serine, cysteine, asparagine, glutamine, glutamic acid, aspartic acid and tyrosine. Since natural amino acids were shown to be able to catalyse some organic reactions, they have been extensively investigated as chiral catalysts in organic synthesis. Asymmetric reactions that are catalysed by amino acids have received increased attention in recent years. We focus this thesis on carrying out carbon-carbon bond forming reactions using chiral amino acids in order to provide the chiral basis to obtain enantiomerically pure building blocks.

(*S*)-proline could be regarded as the simplest enzyme, and is a cornerstone in the field of organocatalysis due to the fact that it has been used as a catalyst for a wide range of asymmetric reactions with excellent results in many cases. Its high efficiency has been clearly demonstrated in the organocatalytic enantioselective direct aldol reaction of aldehydes and ketones carried out in organic or aqueous media, due to the conformational restrictions imposed by its cyclic structure, and the presence of a secondary amino group. In addition, proline is inexpensive and readily available in both enantiomeric forms. Its two functional groups can act both as an acid and a base and can also facilitate chemical

transformations in concert, similar to enzymatic catalysis. Moreover, proline as a chiral bidentate ligand can form catalytically active metal complexes (Figure 30). This makes proline play a fundamental role for the synthesis of chiral building blocks.

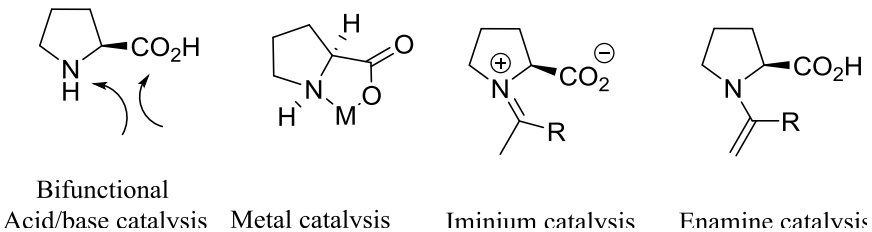
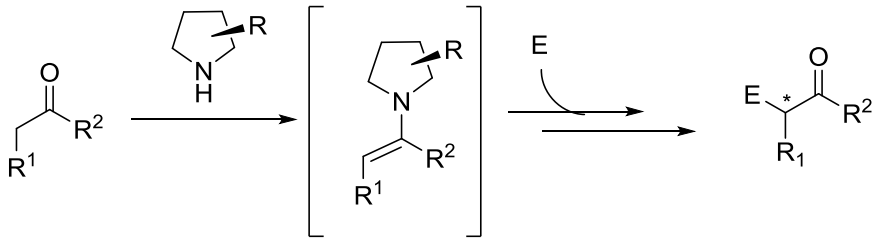


Figure 30. Modes of action in proline catalysis

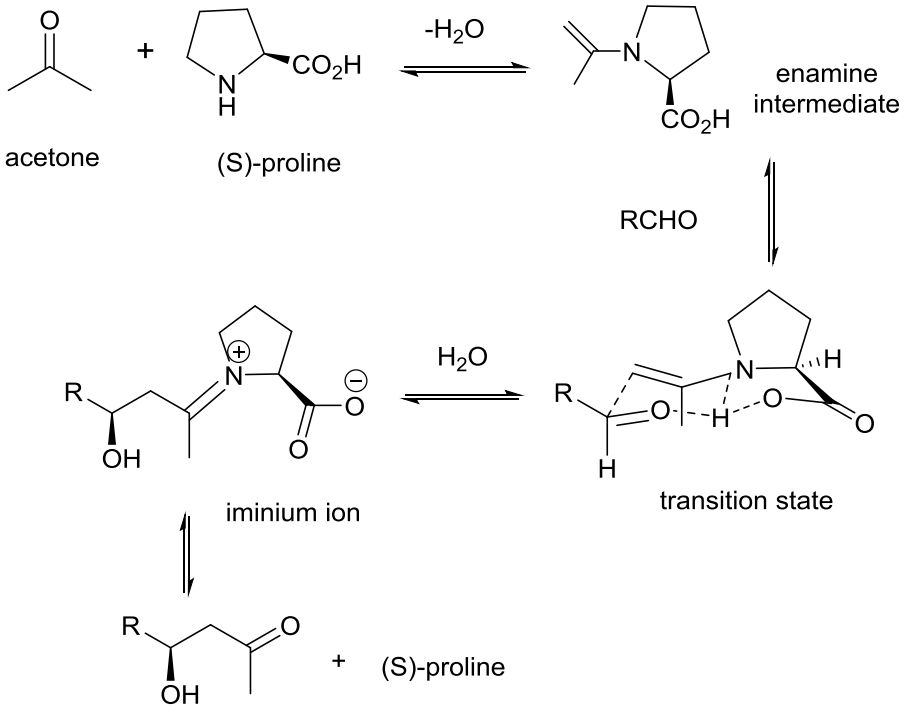
The catalytic cycle of the proline catalysed aldol reaction proceeds via an enamine intermediate,[174] with an initial condensation of the secondary amine with a carbonyl functionality that leads to a nucleophilic enamine intermediate, which reacts with an electrophilic reagent (Scheme 66).



Scheme 66. Enamine activation. E = electrophile

The hydrogen bond between the carboxylic acid atom of the proline moiety and a carbonyl group is a prerequisite for the asymmetric induction. The length of the hydrogen bond is one of the criteria that allow selection between the diastereotopic carbonyl groups.

The chiral catalyst (*S*)-proline determines which diastereoisomer has the higher population. It has been shown that the major diastereomer is that in which *S*-proline is coordinated to the *re*-face of the aldehyde, giving (*R*,*S*) and (*R*,*R*) adducts. The products derived from the minor diastereomer are those in which *S*-proline is coordinated to the *si*-face of the aldehyde (Scheme 67). The rate of the enamine formation is affected by two factors, the basicity and steric environment of the secondary amino group and the nature and environment of the carbonyl group.



Scheme 67. Mechanism of asymmetric induction with acetone of the proline catalysed intermolecular aldol reaction

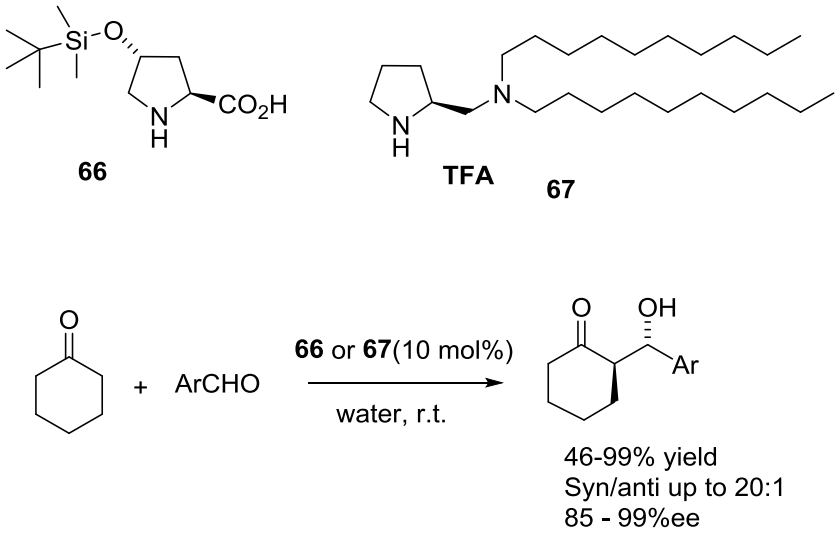
The development of methods for stereoselective aldol reactions has been intensively investigated for more than 20 years, and this reaction is now among the most powerful in the synthetic chemist's arsenal for stereocontrolled carbon-carbon bond formation. Therefore, with the aim of developing a catalyst/green solvent system where both enantiomers of the catalyst were available at low cost, the use of other amino acids has also been investigated as catalysts for asymmetric aldol reactions. The results are reported in section 2.2.3

2.2 Aldol reactions

2.2.1 Influence of water in Aldol reactions

Organic reactions in water have attracted considerable attention in recent years since water is the most environmentally safe solvent.[175] The varied interactions between water and substrates (hydrogen bonding, polarity, acidity, hydrophobicity) make water an interesting candidate as a solvent from an industrial and laboratory perspective. With respect to proline, water[176] as an additive has successfully been shown to influence the outcome of the reactions and is already understood in part.[177]

The research groups of Barbas[178] and Hayashi[179] independently reported efficient and highly hydrophobic proline-derivatives; chiral catalysts for direct aldol reactions which act with high enantiocontrol in the presence of a large excess of water without the assistance of organic solvents (Scheme 68).



Scheme 68. Aldol reactions promoted by TBDM siloxyproline **66** or didecyl aminoproline **67**

Another example[180] of organocatalyst that was found to be efficient for direct aldol reactions in water with high enantioselectivity[181] is the artificially designed organocatalyst, shown in Figure 31.

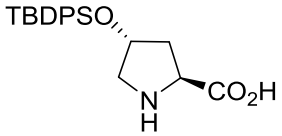
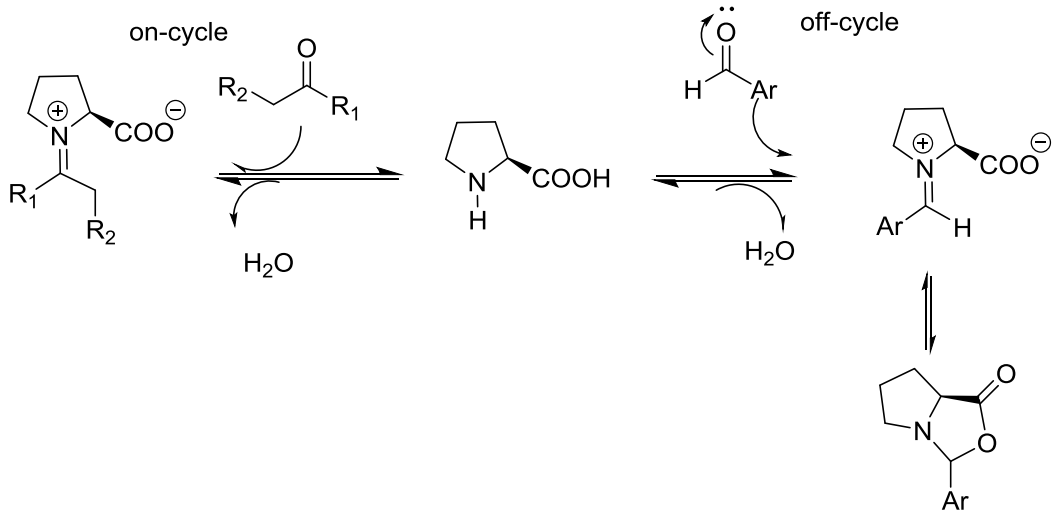


Figure 31

These organocatalysts are based on proline with appropriate hydrophobic groups. Natural amino acids can be divided into three different groups: hydrophobic, hydrophilic, and neutral. Six of them possess hydrocarbon-like side chains.[182] This results in a tendency for nonpolar groups to contact each other, with an accompanying decrease in their interactions with water, and engage in hydrophobic interactions. Thus, it was reasoned that such hydrophobic amino acid catalysts would balance the influence of hydrophobic interaction and hydrogen bonding in the transition state in water.[183] The effectiveness of the aromatic amino acids as catalysts compared to proline and other acyclic amino acids can be attributed to the solubility of the catalysts. While proline dissolves in water, aromatic and aliphatic amino acids are mainly hydrophobic and are only partially soluble in water, which results in heterogeneous mixtures.

In some cases, proline catalysed reactions can be carried out under solvent-free conditions;[184]although water[185] and ionic liquids[186] have also been used as alternative solvents for proline organocatalysed reactions, but the green credentials of these solvents have been questioned[187] and water is known to inhibit proline catalysed aldol reactions.[188] From a chemical point of view, water often inhibits the activity of the catalyst or is often found to distort transition states of the reaction due to its ability to form hydrogen bonds, resulting in lowered enantioselectivity therefore demanding a higher catalyst loading. A coherent mechanistic rationalization of the role of water in aldol reactions employing aromatic aldehydes shows that the intrinsic kinetic effect of water within the catalytic cycle is a suppression of reaction rate (Scheme 69).



Scheme 69.

The presence of water suppresses formation of key intermediates within the cycle as well as reversibly and irreversibly formed spectator species such as oxazolidinones and oxapyrrolizidines, respectively. The net effect on the observed productivity of the reaction will depend on the balance between these two effects. This work highlights the complex role that water plays both on and off the catalytic cycle and the need to separate these effects to achieve mechanistic understanding.

2.2.2 Literature results

2.2.2.1 Experiments with proline

Cyclic carbonates, especially ethylene carbonate **1** and propylene carbonate **2** started to attract interest as green solvents for metal-catalyzed reactions. North's group have reported for the first time, the use of cyclic carbonates as sustainable solvents in conjunction with the use of the natural product (*S*)-proline as an asymmetric organocatalyst. Also studied by North's group, was the effect of the chiral propylene carbonate as solvent for proline-catalyzed aldol reactions between enolizable ketones and aromatic aldehydes (Scheme 70, Table 14).[189] When enantiomerically pure propylene carbonate is used, the combination of (*R*)-proline and (*R*)-propylene carbonate constitutes a matched pair, while (*S*)-proline and (*R*)-propylene carbonate constitutes a mismatched pair (Figure 32).

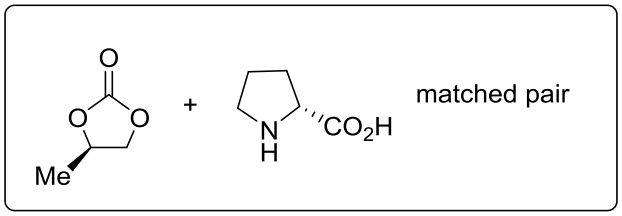
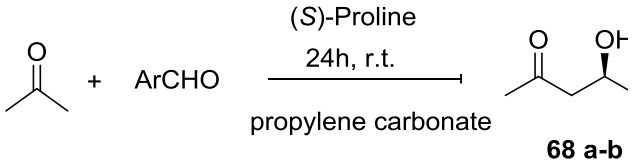


Figure 32



a: Ar = 3-$O_2NC_6H_4$; **b**: Ar = C_6F_5

Scheme 70. Synthesis of Aldol Products **68a-b** from acetone

Table 16. Proline catalysed synthesis of aldol products[a]

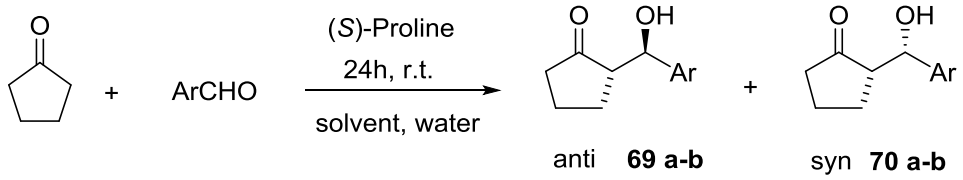
Entry	Catalyst	Aldehyde	Solvent	Yield (%)	*ee* (%)[a]
1	(*S*)-proline	3-$O_2NC_6H_4CHO$	PC	99	51(*R*)
2	(*S*)-proline	3-$O_2NC_6H_4CHO$	(*R*)-PC	98	47(*R*)
3	(*R*)-proline	3-$O_2NC_6H_4CHO$	(*R*)-PC	99	57(*S*)
4	(*S*)-proline	C_6F_5CHO	PC	85	83(*R*)
5	(*S*)-proline	C_6F_5CHO	(*R*)-PC	99	76(*R*)
6	(*R*)-proline	C_6F_5CHO	(*R*)-PC	99	83(*S*)

[a] Determined by chiral HPLC analysis on a Chiralpak AD-H column and comparison of retention times with literature data[190] and racemic standards.[191]
[b]After chromatographic purification.

As shown in Table 16, reactions involving 3-nitrobenzaldehyde and pentafluorobenzaldehyde as substrate showed little difference in the chemical yield when carried out in racemic or chiral propylene carbonate. Only for reaction carried out with pentafluorobenzaldehyde as substrate (Entry 4) gave lower yield in nonracemic propylene carbonate. For pentafluorobenzaldehyde (Entries 4-6), the mismatched solvent/catalyst system gave a product with lower enantiomeric excess than either the matched system or the use of racemic solvent.

Following on from these results obtained in North's group[192], the reaction of cyclopentanone with 3-nitrobenzaldehyde and pentafluorobenzaldehyde was studied

(Scheme 71). The results obtained (Table 17) show high activity for these substrates in terms of yield. However, low ratios of *syn* to *anti*-diastereomers were obtained and the *syn*-diastereomer was obtained almost in its racemic form for 3-nitrobenzaldehyde.



a: Ar = 3-$O_2NC_6H_4$; **b**: Ar = C_6F_5

Scheme 71. (*S*)-proline catalysed aldol reaction involving cyclopentanone

Table 17. Proline catalysed synthesis of aldol products[a]

Entry	Catalyst	Aldehyde	Solvent	Yield	Syn: anti	ee^{syn} / ee^{anti}
1	*DL*-proline	3-$O_2NC_6H_4CHO$	EC	93	1:6.1	0/1
2	*L*-proline	3-$O_2NC_6H_4CHO$	EC	77	1:1.8	0/92
3	*L*-proline	3-$O_2NC_6H_4CHO$	PC	76	1:1.8	10/88
4	*DL*-proline	3-$O_2NC_6H_4CHO$	(*R*)-PC	85	1:2.7	3/1
5	*D*-proline	3-$O_2NC_6H_4CHO$	(*R*)-PC	82	1:1.75	3/95
6	*L*-proline	3-$O_2NC_6H_4CHO$	(*R*)-PC	61	1:1.8	2/92
7	*DL*-proline	C_6F_5CHO	EC	68	1:4	0/0
8	*L*-proline	C_6F_5CHO	EC	65	1:6.3	47/95
9	*L*-proline	C_6F_5CHO	PC	48	1:4	68/99
10	*D*-proline	C_6F_5CHO	(*R*)-PC	58	1:3.4	95/99

[a] All reactions were carried out using 1.0 mmol aldehyde and 2.0 mmol ketone in the presence of 0.1 mmol catalyst and 1 mL solvent with 18 µL water for 24 hours at room temperature.

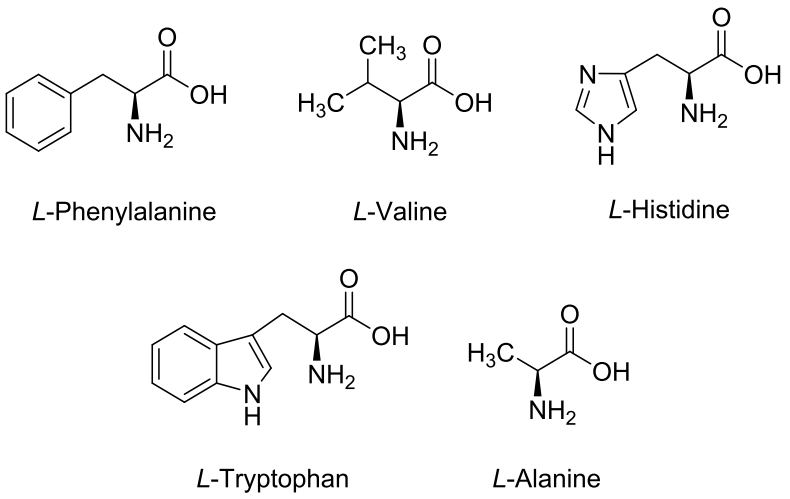
Using the matched pair of *D*-proline and (*R*)-PC (Table 17, entry 5) in the reaction with 3-nitrobenzaldehyde, high enantioselectivities are obtained. This is also reflected in the reaction with pentafluorobenzaldehyde, giving the highest enantioselectivities for both the *anti* and the *syn* diastereomer (Table 17, entry 10). The ratio of *syn* to *anti* diastereomer for the reactions employing pentafluorobenzaldehyde is higher than the ones obtained with 3-nitrobenzaldehyde although the reaction is slower with pentafluorobenzaldehyde as judged by the low yield (Table 17, entry 8-10). When *L*-proline is used as the catalyst in the aldol reaction between cyclopentanone and

pentafluorobenzaldehyde, the chemical yield was much lower in PC than in EC (Table 17, entry 8, 9).

The reaction studied in the remainder of this chapter was the phenylalanine (**72**) and tryptophan (**78**) catalysed aldol reactions between cyclohexanone and different aldehydes in cyclic carbonates (See sections 2.4.2, 2.4.3).

2.2.2.2 Experiments with other amino acids

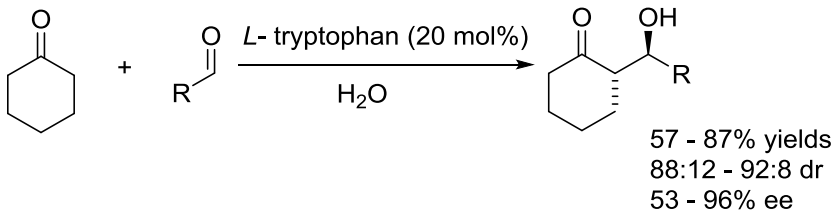
Although proline has received the most attention, other amino acids such as phenylalanine, valine, histidine, tryptophan and alanine (shown below) have also been found to be efficient as organocatalysts being capable of stereoselective catalysis in the crossed aldol reaction.



L-Phenylalanine *L*-Valine *L*-Histidine

L-Tryptophan *L*-Alanine

For example, *L*-alanine, the simplest chiral amino acid, induced excellent levels of diastereoselectivity and enantioselectivity in aldol reactions between ketone donors and aromatic aldehyde acceptors.[193] Cyclic ketones consistently afforded good selectivities, while the single acyclic substrate gave only modest results. Amedjkouh[194] found that in water, *L*-tryptophan gave the best conversion and selectivity in the model reaction of cyclohexanone with aromatic aldehydes. The process proved to be fairly general using only a twofold excess of cyclohexanone (Scheme 72). Fair to excellent levels of diastereoselectivity were obtained, while enantioselectivity ranged from poor to excellent.



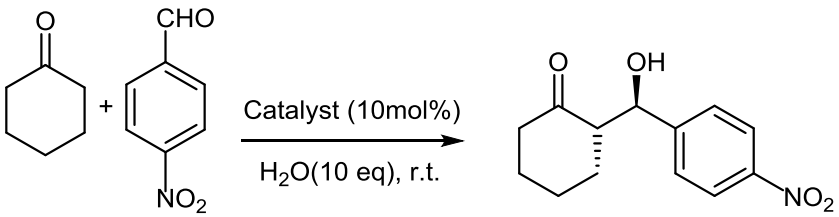
Scheme 72. Tryptophan catalysed aldol reactions

Deng and Cai surveyed conditions for optimising the same model reaction using *L*-alanine as the catalyst.[195] They found that 20 mol % of a surfactant (SDS) was required for efficient catalysis. Amedjkouh, Deng and Cai also evaluated *L*-phenylalanine as the catalyst, but observed very different results when the reactions were conducted in the presence of a surfactant. From the results shown in Table 18, it appears that the proportion of surfactant used is very important to the activity of the organocatalyst. This data highlights the importance of stoichiometry in these aqueous organocatalytic processes.

Table 18. Importance of stoichiometry of SDS in phenylalanine catalysed aldol reactions under aqueous conditions

Catalyst (mol %)	Additive (mol %)	Yield (%)	Syn:anti	ee^{anti}(%)
L-phe (20)	None	52	1:19	76
L-phe (20)	SDS (100)	0	-	-
L-phe (30)	SDS (20)	78	38:62	-

Since *L*-tryptophan proved to be a good catalyst, further work has been carried out to test the catalytic effects of a few more amino acids (Table 19) in direct aldol reactions using the model reaction as shown in Scheme 73.



Scheme 73. (*S*)-catalyst catalysed aldol reaction involving cyclohexanone

Table 19. Direct Asymmetric Aldol Reactions Catalysed by Primary Amino acids

Catalyst	Time/h	Yield (%)	Syn:anti	*ee* (%)
L-Alanine	109	32	1:12	0
L-Tyrosine	28	<5	-	-
L-Serine	96	<10	-	-
L-Histidine	57	59	1:1.5	8
L-Arginine	18	83	1:1.4	14
L-Valine	144	84	1:4	65
L-Phenylalanine	48	75	1:4	70
L-Isoleucine	96	67	1:5	83
L-Leucine	96	81	1:3	79
L-Threonine	82	30	1:2	76
L-Cysteine	96	23	1:3	73
L-Tryptophan	23	85	1:4	86

Overall, as has been stated, tryptophan was the best catalyst, yielding the desired product in a relatively short reaction time, in high chemical yield, with good diastereoselectivity and excellent enantioselectivity.

2.2.3 Results

2.2.3.1 Initial Catalyst Screening

In continuation of our studies concerning environmentally benign catalytic reactions, we carried out a systematic investigation of twelve primary, proteinogenic amino acids **71-83** and trans-4-hydroxy (*S*)-proline (**83**) (Figure 33) were selected as potential catalysts for asymmetric aldol reactions. Primary amino acids **71-83** were selected to include all amino acids, which had previously been reported to give good results in conventional solvents[196,197] as well as to include a variety of functional groups within the amino acid sidechain. Secondary amino acid **83** was also included based on literature precedent[198] and due to the successful results previously obtained with (*S*)-proline as catalyst in cyclic carbonate solvents.[199] All thirteen of these amino acids were tested as catalysts for the aldol reactions between cyclohexanone and 4-nitrobenzaldehyde in both propylene and ethylene carbonate as solvent under the

conditions we have previouly optimised for proline catalysed reactions (Scheme 73). Only four of the amino acids were found to display any catalytic activity at all under these conditions, and of these, reactions catalysed by (*S*)-alanine (**71**) and (*S*)-valine (**79**) gave conversions estimated at less than 5%. In contrast, (*S*)-phenylalanine (**72**) and (*S*)-tryptophan (**78**) were found to be effective catalysts in both solvents and the results with these amino acids are summarized in Table 20.

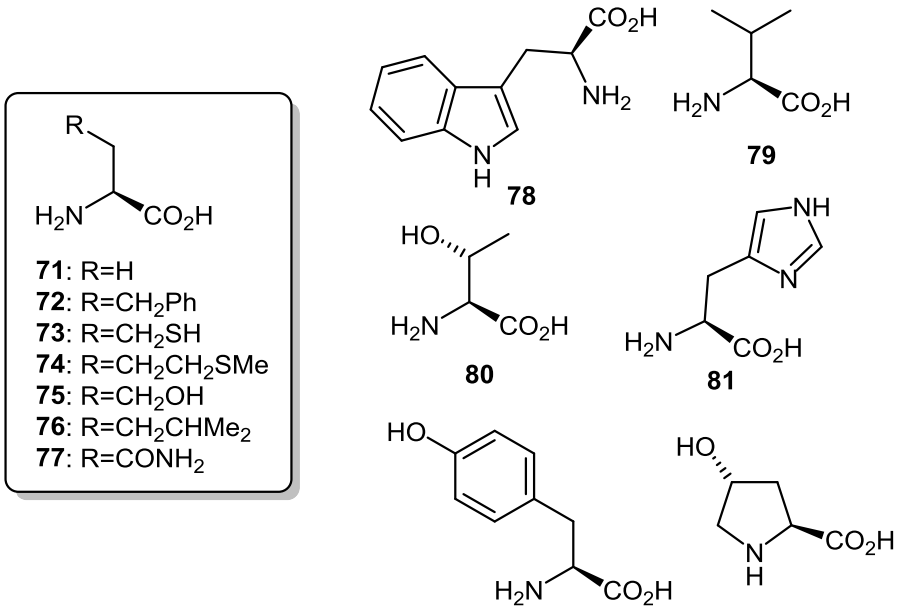
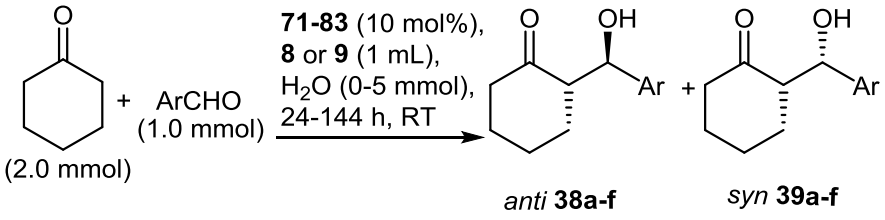


Figure 33. Organocatalysts **71**-**83**



a: Ar= 4-$O_2NC_6H_4$; **b**: Ar= C_6H_5; **c**: Ar= 4-BrC_6H_4;
d: Ar= 4-$F_3CC_6H_4$; **e**: Ar= 3-$O_2NC_6H_4$; **f**: Ar= C_6F_5

Scheme 74. Organocatalysed aldol reaction of aromatic aldehydes and cyclohexanone

Table 20. Aldol reactions catalysed by phenylalanine (**72**) and tryptophan (**78**)

Entry	Catalyst	Solvent[a]	Yield (%)	**39a/38a**[b]	*ee* (**39a/38a**)[c]
1	**72**	PC	29	1:6.6	3/85
2	**72**	EC	52	1:8.3	4/84
3	**78**	PC	55	1:7.0	8/86
4	**78**	EC	90	1:9.5	9/89

[a] H_2O (1.0 mmol) was added to the cyclic carbonate solvent.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by chiral HPLC. The major enantiomers of **38a** and **39a** are those shown in Scheme 74.

It is apparent from the results presented in Table 20 that both amino acids preferentially catalysed the formation of the *anti*-diastereomer **38a** of the aldol product and that tryptophan **78** was a more effective asymmetric catalyst than phenylalanine **72** in terms of yield, diastereoselectivity and enantioselectivity.

It is also clear that for both catalysts, EC is a better solvent than PC. EC was also the more effective solvent for proline catalysed aldol reactions,[17] and this presumably reflects the greater polarity of this solvent.[200] Phenylalanine and tryptophan are amongst the most hydrophobic amino acids, and hence will have the highest solubility in non-protic solvents such as cyclic carbonates PC and EC. This may account for their enhanced catalytic activity relative to the other amino acids studied. The enantioselectivity obtained using phenylalanine is significantly higher than that previously reported (for reactions conducted in water), and the results obtained with tryptophan as catalyst are comparable with those previously reported in a range of conventional solvents.[201] In view of this, and in view of the negligible difference in enantioselectivity between the four catalyst/solvent combinations, it was decided to optimise reactions involving both catalysts **72** and **78** in both solvents PC and EC.

2.2.3.2 Phenylalanine-Catalysed Reactions

Our previous work has shown that the amount of water present in the cyclic carbonate solvent can have a dramatic effect on the yield, diastereoselectivity and enantioselectivity of proline catalysed aldol reaction.[202] Addition of small amounts of water is beneficial as it increases the solubility of the amino acid. However, water is also

known to be an inhibitor of amino acid catalysed aldol reactions,[203] so there is an optimal concentration of water in the reactions. Therefore, the number of equivalents of water (relative to 4-nitrobenzaldehyde) added to aldol reactions in both cyclic carbonate solvents was varied and the results are presented in Table 21.

Table 21. Influence of Water on Aldol Reactions Catalysed by Phenylalanine[a]

Entry	Solvent	H_2O(equiv)	Yield (%)	**39a**/**38a**[b]	*ee*(**39a**/**38a**)[c]
1	PC	1	29	1:6.6	3/85
2	PC	2	42	1:7.4	1/81
3	PC	3	62	1:8.6	19/79
4	PC	4	51	1:12.5	12/82
5	PC	5	60	1:7.8	17/83
6	EC	1	52	1:8.3	8/80
7	EC	2	60	1:8.9	15/80
8	EC	3	67	1:10.3	23/80
9	EC	4	61	1:8.0	21/87
10	EC	5	61	1: 8.3	12/81
11	(*R*)-PC	5	57	1:7.4	20/82
12[d]	(*R*)-PC	5	38	1:7.1	17/76

[a] Unless otherwise stated, reactions were catalysed by (*S*)-**72**.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC. The major enantiomers of **38a** and **39a** are those shown in Scheme 74 except for entry 12 where the opposite enantiomer of **38a** and **39a** was formed in excess.
[d] Using (*R*)-**72**

For both solvent systems, the chemical yield was found to increase as the amount of water present increased from one to three equivalents and then fell back slightly when the amount of water was increased further. A similar trend was apparent in the diastereoselectivities of the aldol reaction, though for reactions carried out in propylene carbonate, the optimal results were obtained when four equivalents of water were added (Table 21, entry 4), whilst with ethylene carbonate as solvent, addition of three equivalents of water was optimal (Table 21, entry 8). Interestingly, for both solvents the enantioselectivity of the major, *anti*-diastereomer **38a** remained essentially constant at 83±4% as the amount of water added was increased, whilst the enantiomeric excess of the minor, *syn*-diastereomer **39a** increased markedly, though only to a maximum value of 19-23%, in the presence of three equivalents of water.

Overall, the addition of five equivalents of water was felt to give the optimal balance between yield and stereoselectivity for reactions in propylene carbonate (Table 21, entry 5), whilst addition of four equivalents of water was similarly optimal for reactions carried out in ethylene carbonate (Table 21, entry 9). Propylene carbonate (**9**) is a chiral molecule and all results reported above were obtained using racemic solvent. We have previously shown that proline catalysed aldol reactions exhibit a chiral solvent effect when carried out in propylene carbonate, with the combination of (*R*)-proline and (*R*)-**9** forming a matched pair resulting in higher yields and stereoselectivities.[204] Therefore, phenylalanine catalysed reactions were carried out in enantiomerically pure (*R*)-**9** in the presence of five equivalents of water (Table 21, entries 11 and 12). Interestingly, in this case the combination of *R*-solvent and *R*-catalyst (Table 21, entry 12), appeared to be the mismatched pair, giving the lower yield and enantiomeric excess for **38a**/**39a**. There was however, no significant difference in the diastereoselectivity of these two reactions and no advantage to using (*R*)-**9** with (*S*)-phenylalanine compared to use of the racemic solvent (Table 21, entries 5 and 11).

Table 22. Phenylalanine Catalysed Aldol Reactions of Cyclohexanone[a]

Entry	Solvent	Aldehyde	Yield (%)	**39**/**38**[b]	*ee*(**39**/**38**)[c]
1[d]	PC	PhCHO	34	1:2.3	58/58
2	EC	PhCHO	79	1:6.6	68/93
3[d]	PC	4-BrC_6H_4CHO	69	1:2.6	93/78
4	EC	4-BrC_6H_4CHO	76	1:7.1	66/80
5	PC	4-$F_3CC_6H_4CHO$	14	1:9.3	50/90
6	EC	4-$F_3CC_6H_4CHO$	55	1:8.0	38/67
7	PC	3-$O_2NC_6H_4CHO$	20	1:9.4	18/87
8	EC	3-$O_2NC_6H_4CHO$	17	1:11.0	16/88
9	PC	C_6F_5CHO	83	1:8.7	n.d.[e]/90
10	EC	C_6F_5CHO	79	1:3.0	n.d.[e]/86

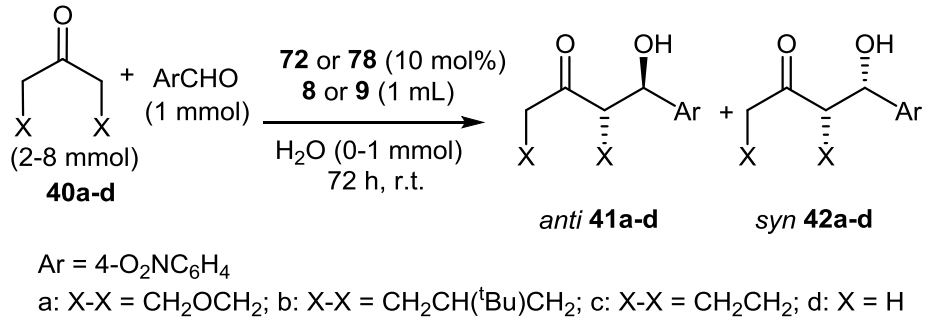
[a] H_2O (5.0 or 4.0 mmol) was added to solvents PC and EC respectively. All reactions were carried out at least in duplicate and gave consistent results.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by chiral HPLC.
[d] Reaction time: 6 days.
[e] No separation of the peaks for the *syn*-diastereomer could be obtained on AD-H or AS-H HPLC columns; n.d. = not determined.

The conditions of Table 21, entries 5 and 9 were therefore adopted as standard and the reaction of cyclohexanone with five other aromatic aldehydes was investigated under these conditions (Scheme 74). As shown in Table 22, benzaldehyde and 4-bromobenzaldehyde were both slow reacting substrates in propylene carbonate (Table 22, entries 1 and 3), with reaction times of six days required to obtain low to moderate yields of aldol products **38b,c/39b,c**.

These reactions also exhibited relatively poor diastereoselectivity. In contrast, reactions carried out in ethylene carbonate were faster, significantly more diastereoselective and, in the case of benzaldehyde, far more enantioselective (Table 22, entries 2 and 4). Ethylene carbonate has previously been found to be the better solvent in the corresponding proline catalysed reactions[17] and this was attributed to the greater polarity of ethylene carbonate stabilising the aldol transition state.[205] 4-Trifluoromethylbenzaldehyde also exhibited a marked increase in reaction rate in ethylene carbonate compared to propylene carbonate (Table 22, entries 5 and 6), though in this case the diastereoselectivity of the reaction was similar in the two solvents and the enantioselectivity of the reaction was significantly higher in propylene carbonate than in ethylene carbonate.

3-Nitrobenzaldehyde was a very slow reacting substrate in both solvents (Table 22, entries 7 and 8). This was unexpected since previous work using proline as the catalyst had shown that whilst the isolated yield of **38e/39e** from a reaction in propylene carbonate was only 22%, use of ethylene carbonate as solvent gave **38e/39e** in a yield of 89%.[17] However, in both solvents, 3-nitrobenzaldehyde gave products **38e**/**39e** with high enantioselectivity. Previous work has shown pentafluorobenzaldehyde to be an extremely reactive and stereoselective substrate in proline-catalysed aldol reactions.[7] For phenylalanine catalysed reactions (Table 22, entries 9 and 10), both solvents gave good yields of aldol products **38f/39f**, though the diastereoselectivity was higher in propylene carbonate than in ethylene carbonate and the enantioselectivities were about 10% lower than those obtained in proline catalysed reactions. Overall, the yields and enantioselectivities obtained in the phenylalanine catalysed reactions tend to be lower than those obtained in the corresponding proline catalysed reactions, though the diastereoselectivities are in some cases higher for phenylalanine catalysed reactions.

Since 4-nitrobenzaldehyde appeared to be the best substrate for phenylalanine catalysed aldol reactions, the use of this aldehyde with four other ketones **40a-d** was investigated as shown in Scheme 75 and the results are presented in Table 23. Preliminary experiments showed that some of these reactions were very slow, so they were all left for 72 hours and in the case of substrates **40a,d** the amount of ketone used was increased (to 5 and 8 equivalents respectively), in an attempt to obtain reasonable yields of aldol products **41a-d**/**42a-d**. In all cases however, the isolated yields of aldol products **41a-d**/**42a-d** were low to moderate even after a reaction time of 72 hours with only cyclopentanone (**40c**) giving respectable yields of aldol products **41c**/**42c**.



Ar = 4-$O_2NC_6H_4$

a: X-X = CH_2OCH_2; b: X-X = $CH_2CH(^tBu)CH_2$; c: X-X = CH_2CH_2; d: X = H

Scheme 75. Organocatalysed synthesis of aldol products from ketones and 4-nitrobenzaldehyde

For the synthesis of aldol product **41a**/**42a**, the diastereo- and stereoselectivity obtained in propylene and ethylene carbonate (Table 23, entry 1 and 2) were inferior to those previously reported for reactions using proline as catalyst.[17b] Similarly, for substrate **40b** the enantiomeric excess of aldol product **41b** obtained using phenylalanine as catalyst was much lower in both solvents (Table 23, entries 3 and 4) than that obtained from the same reaction with proline as catalyst.[17b] Cyclopentanone (**40c**) which gave the highest yields with phenylalanine as catalyst also gave some of the best stereoselectivities. Thus, the diastereoselectivity in both solvents (Table 23, entries 5 and 6) was better than those obtained using proline as catalyst, and the enantioselectivity obtained in propylene carbonate was also much higher when using phenylalanine rather than proline as catalyst.[7b] When acetone (**40d**) was used as substrate, the chemical yield of aldol product **41d** was extremely low, but the enantioselectivity was higher than that obtained using proline as catalyst in the same solvent.[17b]

Table 23. Phenylalanine-Catalysed Aldol Reactions of 4-Nitrobenzaldehyde[a]

Entry	Solvent	Ketone (equiv)	Yield (%)	**42/41**[b]	*ee*(**42/41**)[c]
1	PC[d]	**40a** (5)	36	1:4.1	15/50
2	EC[d]	**40a** (5)	42	1:3.0	41/65
3	PC[d]	**40b** (2)	26	1:2.7	n.d.[e]/35
4	EC[d]	**40b** (2)	40	1:4.4	n.d.[e]/31
5	PC[d]	**40c** (2)	64	1:4.7	57/76
6	EC[d]	**40c** (2)	70	1:7.5	66/83
7	PC	**40d** (8)	12		76
8	EC	**40d** (8)	8		29

[a] All reactions were carried out in duplicate and gave consistent results.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC.
[d] H_2O (1.0 mmol) was added to the solvent.
[e] No separation of the peaks for the *syn*-diastereomer could be obtained on AD-H or AS-H HPLC columns; n.d. = not determined.

2.2.3.3 Tryptophan-Catalysed Reactions

Aldol reactions catalysed by tryptophan in cyclic carbonate solvents **8** and **9** were optimised in the same way as those catalysed by phenylalanine. Table 24 shows the results obtained when the tryptophan catalysed asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde was carried out in the presence of 0-5 equivalents of water (relative to 4-nitrobenzaldehyde). It is clear from the data in entries 1-3 and entries 4-6, that for tryptophan catalysed aldol reactions in either solvent, the chemical yield decreases as the amount of water added to the reactions increases, but both the diastereoselectivity and enantioselectivity increase as the amount of water present increases. This is a very different trend to that observed for phenylalanine catalysed reactions (Table 21), and for tryptophan catalysed aldol reactions, the addition of one equivalent of water in either solvent gave the best compromise between yield and stereoselectivity.

Table 24. Influence of Water on Aldol Reactions Catalysed by (*S*)-tryptophan (**78**)[a]

Entry	Solvent	H_2O(equiv)	Yield (%)	**39a**/**38a**[b]	*ee*(**39a**/**38a**)[c]
1	PC	0	81	1:2.6	-20/62
2	PC	1	55	1:7.0	14/85
3	PC	5	45	1:8.7	7/87
4	EC	0	98	1:3.9	-27/94
5	EC	1	90	1:9.5	7/95
6	EC	5	50	1:12.1	26/87
7	(*R*)-PC	0	66	1:5.0	-27/86
8[d]	(*R*)-PC	0	97	1:3.6	10/-87

[a] Unless otherwise stated, reactions were catalysed by (*S*)-**78**. All reactions were carried out in duplicate and gave consistent results.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC. A minus sign indicates that the major enantiomer had the opposite absolute configuration to that shown in Scheme 74.
[d] Using (*R*)-**78**

The use of enantiomerically pure (*R*)-propylene carbonate as solvent was also investigated with tryptophan as solvent (Table 24, entries 1, 7, 8). A pronounced chiral solvent effect was observed on the chemical yield of the reaction with the combination of (*R*)-**9** and (*R*)-**78** being the matched pair whilst (*R*)-**9** and (*S*)-**78** were the mismatched pair. The effect on the stereoselectivity of the reactions was less apparent as both reactions in (*R*)-**9** gave higher diastereo- and enantioselectivities than the reaction carried out in racemic **9** and both chiral solvent/catalyst pairs gave essentially identical enantioselectivities for the major, *anti*-diastereomer **38a**. Again, these results contrast with those obtained with phenylalanine as the catalyst where the combination of (*R*)-**9** and (*S*)-**72** appeared to be the matched pair, but are consistent with the results previously obtained using proline as catalyst.

An unexpected feature of tryptophan catalysed aldol reactions was that the absolute configuration of the *syn*-aldol product **39a** was influenced by the presence or absence of water in the reactions. Thus, for reactions carried out in either ethylene or propylene carbonate in the presence of water (Table 24, entries 2, 3, 5, 6), the product had *R*,*R*-configuration (as shown in Scheme 74). However, in the absence of water the *syn*-product had *S*,*S*-configuration (Table 24, entries 1, 4, 7) or, in the case of Table 21, entry 8, had *R*,*R*-configuration when *S*,*S* would have been expected {due to the use of (*R*)-tryptophan as catalyst}. This variation in absolute configuration was not observed for the

anti-diastereomer **38a**, nor was it seen for either diastereomer in phenylalanine-catalysed reactions (Table 21).

A possible explanation of these results is that, in the absence of water, the indole nitrogen of tryptophan can act as a base and induce the epimerisation of aldol products **38a**/**39a** since they still possess an acidic proton adjacent to the carbonyl group. Epimerisation of the major enantiomer of the *anti*-diastereomer **38a** would generate the enantiomer of *syn*-diastereomer **39a**. Since the *anti*-diastereomer is the major product, if sufficient epimerisation occurs, this will lower and eventually invert the configuration of the *syn*-diastereomer. In contrast, considerable epimerisation of the minor, *syn*-diastereomer would be required to have any noticeable effect on the enantiomeric excess of the *anti*-diastereomer, and there is insufficient *syn*-diastereomer present to ever invert the absolute configuration of the *anti*-diastereomer. It appears that water hydrogen bonds to the indole nitrogen, reducing its basicity and inhibiting this epimerisation.

Table 25. Tryptophan-Catalysed Aldol Reactions of Cyclohexanone[a]

Entry	Solvent	Aldehyde	Yield (%)	**39**/**38**[b]	*ee*(**39**/**38**)[c]
1[d]	PC	PhCHO	46	1:10.7	2/87
2[d]	EC	PhCHO	48	1:8.9	6/87
3[d]	PC	4-BrC_6H_4CHO	56	1:12.7	5/89
4[d]	EC	4-BrC_6H_4CHO	83	1:7.1	47/89
5	PC	4-$F_3CC_6H_4CHO$	74	1:2.7	3/93
6	EC	4-$F_3CC_6H_4CHO$	16	1:1.9	17/76
7	PC	3-$O_2NC_6H_4CHO$	24	1:11.6	22/95
8	EC	3-$O_2NC_6H_4CHO$	45	1:12.4	20/91
9	PC	C_6F_5CHO	86	0:1	-/86
10	EC	C_6F_5CHO	98	0:1	-/63

[a] H_2O (1.0 mmol) was added to solvent. All reactions were carried out in duplicate and gave consistent results.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by chiral HPLC.
[d] Reaction time: 6 days.

The conditions of Table 24, entries 2 and 5 were used to study the tryptophan catalysed reaction between cyclohexanone and five other aromatic aldehydes, giving the results shown in Table 25. Benzaldehyde was again found to be a slow reacting substrate, with reactions requiring six days to give even moderate yields of aldol products **38b**/**39b**

(Table 25, entries 1 and 2). However, in both solvents, the major product **38b** was obtained with excellent enantioselectivity and good diastereoselectivity, the latter being especially apparent in the reaction carried out in propylene carbonate (Table 25, entry 1).

4-Bromobenzaldehyde was also a slow reacting substrate (Table 25, entries 3 and 4) and in this case the highest yield was obtained when using ethylene carbonate **8** as solvent (Table 25, entry 4) whilst the best diastereoselectivity was obtained in propylene carbonate **9** (Table 25, entry 3).

Unusually, 4-trifluoromethylbenzaldehyde gave a much higher chemical yield from a reaction carried out in propylene carbonate than from that one conducted in ethylene carbonate (Table 25, entries 5 and 6). The enantioselectivity of the major product **38d** and the diastereoselectivity were also higher in propylene carbonate. In contrast, 3-nitrobenzaldehyde gave the highest yield in ethylene carbonate, though the diastereoselectivity and enantioselectivities of **38e**/**39e** were very similar in both solvents (Table 25, entries 7 and 8).

Table 26. Tryptophan-Catalysed Aldol Reactions of 4-Nitrobenzaldehyde[a]

Entry	Solvent	Ketone (equiv)	Yield (%)	**23/24**[b]	*ee*(**23/24**)[c]
1	**9**[d]	**40a** (5)	75	1:2.0	80/35
2	**8**[d]	**40a** (5)	55	1:3.3	78/47
3	**9**[d]	**40b** (2)	38	1:1.3	n.d.[e]/78
4	**8**[d]	**40b** (2)	64	1:1.7	n.d.[e]/28
5	**9**[d]	**40c** (2)	56	1:5.4	44/75
6	**8**[d]	**40c** (2)	81	1:6.5	43/81
7	**9**	**40d** (8)	5		40
8	**8**	**40d** (8)	17		37

[a] All reactions were carried out in duplicate and gave consistent results.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC.
[d] H_2O (1.0 mmol) was added to the solvent.
[e] No separation of the peaks for the *syn*-diastereomer could be obtained on AD-H or AS-H HPLC columns; n.d. = not determined.

Pentafluorobenzaldehyde was found to be a good substrate for tryptophan catalysed aldol reactions since in both solvents, only the *anti*-diastereomer **38f** of the aldol product was formed and this was obtained in high yield (Table 25, entries 9 and 10). The enantioselectivity was, however, far higher in propylene carbonate than in ethylene

carbonate, with the result in propylene carbonate being comparable to that obtained in the corresponding phenylalanine catalysed reaction (Table 22, entry 9).

The use of tryptophan to catalyse the aldol reaction between 4-nitrobenzaldehyde and ketones **40a-d** was also investigated (Scheme 75) and the results are presented in Table 26.

For substrate **40a**, the chemical yields obtained using tryptophan as catalyst (Table 26, entries 1 and 2) were much higher than those obtained in the phenylalanine catalysed reactions (Table 23, entries 1 and 2). The diastereoselectivity of the reaction in ethylene carbonate was also comparable to that obtained using phenylalanine as catalyst, though the enantiomeric excess of the major, *anti*-product **41a** was lower in both solvents when using tryptophan as catalyst. A similar trend was observed with substrate **40b** (Table 26, entries 3 and 4) where the chemical yield of the tryptophan catalysed reaction was higher in both solvents than that obtained using phenylalanine as catalyst (Table 23, entries 3 and 4). However, the diastereoselectivities were lower in the tryptophan catalysed reactions than in the phenylalanine catalysed reactions. The enantiomeric excess of product **41b** was much higher when prepared using tryptophan in propylene carbonate than from the corresponding reaction in ethylene carbonate, or from either phenylalanine catalysed reaction.

When cyclopentanone (**40c**) was used as the substrate, the tryptophan catalysed reaction in ethylene carbonate proceeded in higher yield and gave *anti*-aldol product **41c** with similar enantioselectivity to the corresponding phenylalanine catalysed reaction, but the diastereoselectivity was higher for the phenylalanine catalysed reaction (Table 23 and 7, entry 6). In contrast, use of propylene carbonate as solvent gave exactly the opposite result, the chemical yield was higher in the phenylalanine catalysed reaction but the diastereoselectivity was higher in the tryptophan catalysed reaction and the enantiomeric excess of the major product **41c** was similar (75-80%) in both solvents (Table 23 and 7, entry 5). Finally, acetone (**40d**) was again found to be a very poor substrate, giving very low yields of aldol product **41d** with enantioselectivities of 37-40 % (Table 26, entries 7 and 8).

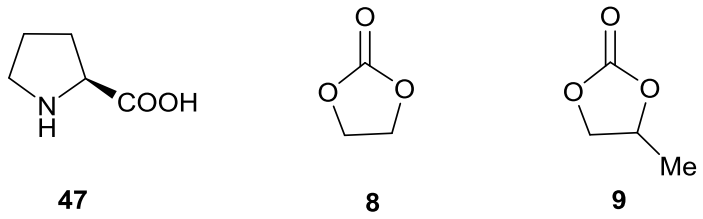
2.2.4 Conclusions

In conclusion, we have shown that phenylalanine (**72**) and tryptophan (**78**) can be used as alternatives to proline as organocatalysts for aldol reactions between enolisable ketones and non-enolisable aldehydes in ethylene and propylene carbonate as solvent. The optimal catalyst and solvent combination needs to be determined on a substrate to substrate basis and in some cases the use of enantiomerically pure propylene carbonate as solvent is advantageous. Although the stereoselectivities obtained in the primary amino acid catalysed reactions are usually slightly lower than those obtained in the corresponding proline catalysed reactions, the use of the primary amino acids is potentially advantageous when the *anti*-aldol product obtained using the *R*-amino acid catalyst is required in view of the relatively high cost of (*R*)-proline. Thus, we have demonstrated that both enantiomers of *anti*-aldol products can be obtained using catalysts which are directly available from biological sources in green solvents.

2.3 Amination reactions

2.3.1 Introduction

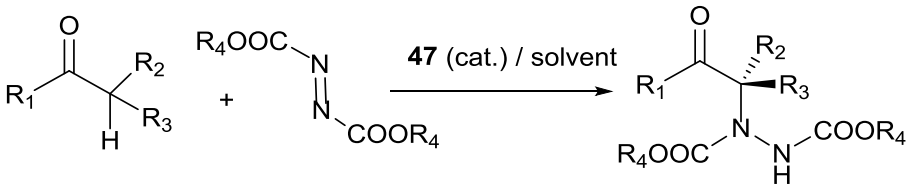
α-Aminations of carbonyl compounds catalysed by proline (47) have been demonstrated to be an efficient method to generate valuable synthetic targets such as *α*-amino aldehydes in medicinal chemistry.[206,207] Most of these reactions are performed in polar aprotic solvents such as DMF, DMSO or chlorinated solvents[208,209] and although the reaction usually gives best results when performed in chlorinated solvents (such as dichloromethane and 1,2-dichloroethane), in our investigation we have further studied such reactions in cyclic carbonate solvents (Figure 34) since they have been shown to be environmentally friendly alternative solvents



47 **8** **9**

Figure 34. (*S*)-Proline (47), ethylene carbonate (**8**), propylene carbonate (**9**).

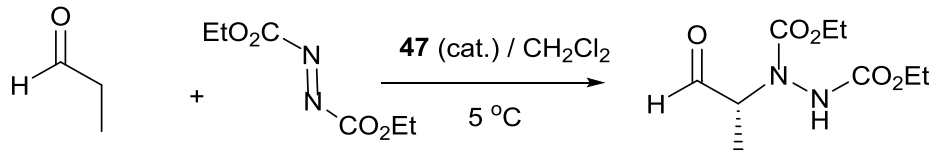
Propylene carbonate (**9**) was found to be a sustainable replacement for dichloromethane and acetonitrile in proline catalysed α-hydrazinations of aldehydes and ketones (Scheme 76). This was developed initially by North *et al.*[210] (See section 2.3.2).



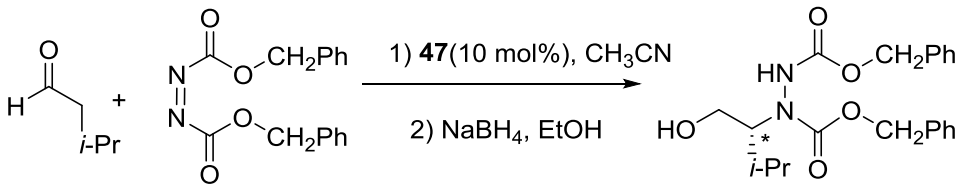
Scheme 76. Proline catalysed α- hydrazination of carbonyl compounds

2.3.2 Literature results

Proline catalysed α-hydrazination of aldehydes and ketones by diazodicarboxylates was first studied employing dichloromethane[211] (Scheme 77), acetonitrile[212] (Scheme 78) or an ionic liquid [213] as the solvent.



Scheme 77. Proline catalysed α- amination of propionaldehyde

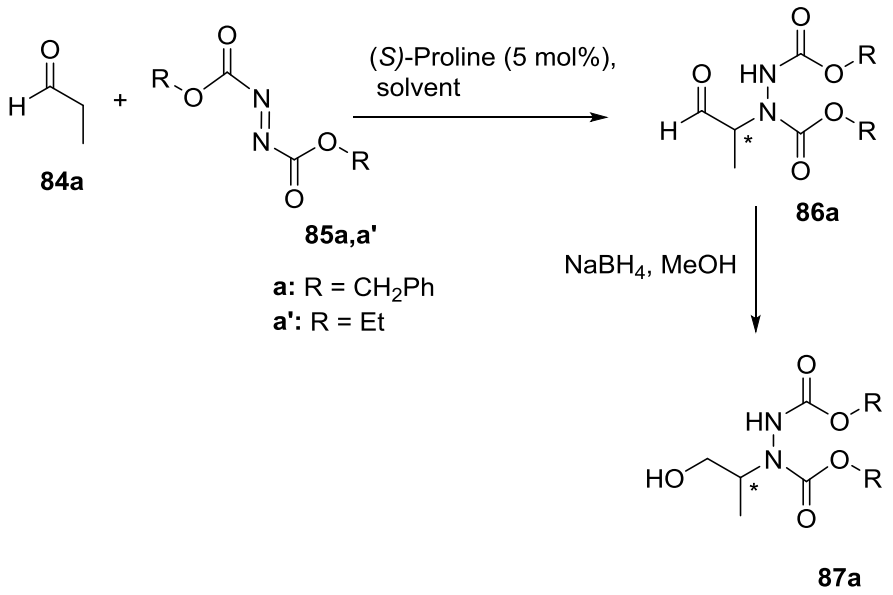


Scheme 78. Proline catalysed α- amination of isobutyraldehyde

In 2002 List found the proline-catalyzed reaction of aldehydes with azodicarboxylates to be a highly efficient and enantioselective process. For example, isobutyraldehyde (1.5 equiv) reacts with dibenzyl azodicarboxylate (1 equiv) at 20°C to give the expected product in 99% yield and 86% ee (after in situ $NaBH_4$ reduction to the primary alcohol).

2.3.3 Previous results obtained by our group

For initial studies, the reaction between propanal (**84a**) and dibenzyl azodicarboxylate (**85a**) catalysed by (*S*)-proline (**47**, 5 mol%) was selected (Scheme 79) since there is literature precedent for this reaction[7] and the benzyl groups provided a convenient chromophore for our chiral HPLC system. The initially produced aldehyde **86a** was immediately reduced to the more stable alcohol **87a** by treatment with sodium borohydride and all yields and enantioselectivities refer to the formation of isolated compound **87a**. The results are presented in Table 27.



Scheme 79. Proline catalysed *α*-hydrazination of propanaldehyde in cyclic carbonates

Table 27. Effect of solvent and temperature on proline catalysed *α*-hydrazinations of propanal.

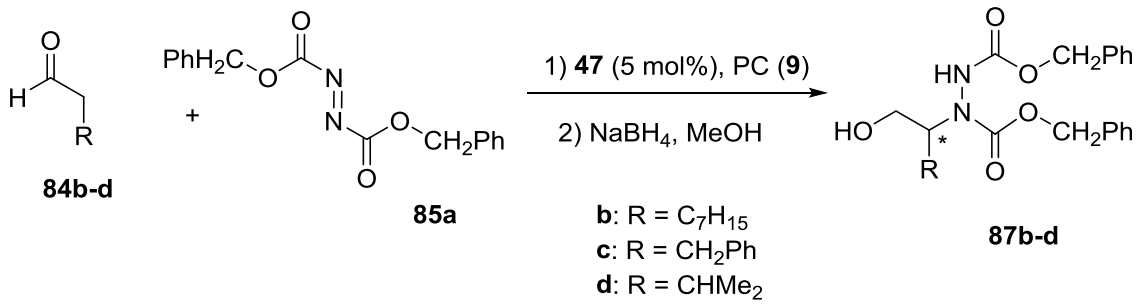
Entry	Solvent	Time (h)	T (°C)	Yield(%)	ee(%)[a]
1	DCM	2	RT	86	98
2	EC	2	RT	74	69
3	PC	2	RT	81	80
4	PC	2	0	18	99
5	PC	24	0	69	97

[a] ee and absolute configuration obtained by chiral HPLC of alcohol **87a**.[9]

Entry 1 of Table 27 shows the result of a control experiment carried out in dichloromethane which confirmed that alcohol **87a** was obtained in excellent yield (86%) and enantioselectivity (98%) under these conditions. The absolute configuration of alcohol **87a** was determined to be *R*- on the basis of comparison of the chiral HPLC retention times with literature.[214]

Entries 2 and 3 of Table 27 show the results of experiments carried out in cyclic carbonates **8** and **9** under conditions which are otherwise identical to entry 1. In both cases, alcohol **87a** was obtained in good yield, but with lower enantiomeric excess than that obtained in dichloromethane. To improve the enantioselectivity of the reaction, the effect of lowering the reaction temperature was investigated. This was only possible with propylene carbonate (**9**) as solvent, and at 0 °C the reaction in propylene carbonate gave alcohol **87a** with excellent enantioselectivity (99%), but in low yield (18%) after a standard reaction time of two hours (Table 27, entry 4). To increase the chemical yield, the reaction time was extended to 24 hours (Table 27, entry 5) and under these conditions alcohol **87a** was obtained in good yield (69%) and with excellent enantioselectivity (97%). An attempt to use diethyl azodicarboxylate (**85a'**) in place of the dibenzyl derivative was not successful as alcohol **87a'** could not be detected on our HPLC system.

Taking the conditions of Table 27, entry 5 as optimal, the applicability of the chemistry to three other aldehydes was investigated as shown in Scheme 80.



Scheme 80. Proline catalysed α-hydrazination of aldehydes in propylene carbonate

Nonanal (**84b**) gave alcohol **87b** with good enantioselectivity but only moderate yield (Table 28, entry 1). Aldehydes **84c** and **84d** gave the corresponding alcohols **87c** and **87d** in both good yield and with excellent enantiomeric excesses. The enantiomeric excesses of alcohols **87a,c,d** compare favourably with those reported in the literature for the corresponding product prepared using 10 mol% of (*S*)-proline in dichloromethane[215] or acetonitrile[7] and in each case the (*R*)-enantiomer of the alcohol was formed predominantly.[9]

Table 28. Proline catalysed α-hydrazinations of aldehydes in propylene carbonate.

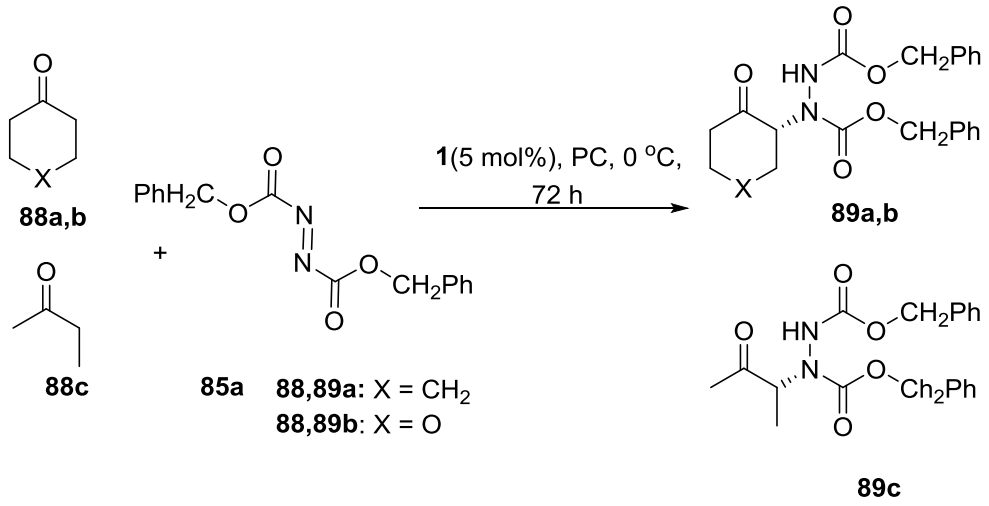
Entry	Product	Time (h)	T (^{o}C)	Yield[c](%)	ee(%)
1	**87b**	24	0	41	90[b]
2	**87c**	24	0	76	99[a]
3	**87d**	24	0	87	92[a]

[a] ee and absolute configuration obtained by chiral HPLC of alcohol **87**.[9]

[b]ee obtained by chiral HPLC of alcohol **87**, absolute configuration assigned by analogy with other products.

[c] Isolated yield of alcohol **87** after purification by flash chromatography.

Having demonstrated that propylene carbonate was a suitable solvent for the asymmetric α-hydrazination of aldehydes, the use of ketones as substrates was investigated. There are only two previous reports of proline-catalysed ketone hydrazination,[216, 8] indicating that this is a more difficult undertaking than the use of aldehydes as substrates. Cyclohexanone (**88a**) was chosen as the first test substrate and initial experiments showed that whilst reaction with dibenzyl azodicarboxylate (**85a**) did indeed occur under the standard conditions developed for aldehyde substrates, the reaction was much slower and required a reaction time of 72 hours to produce a reasonable yield of α-hydrazinoketone **89a** (Scheme 81).



Scheme 81. Proline catalysed α-hydrazination of ketones in propylene carbonate

Table 29. Proline catalysed reaction of ketones with dibenzyl azodicarboxylate

Entry	Ketone	Product	Yield(%)	ee (%)
1	**88a**	**89a**	71	77[a]
2	**88b**	**89b**	51	72[b]
3	**88c**	**89c**	31	52[a]

[a] ee and absolute configuration obtained by chiral HPLC[217,218]
[b]ee obtained by chiral HPLC, absolute configuration assigned by analogy with product **89a**.

Compound **89a** was found to be more stable than the corresponding aldehyde adducts **86a-d** and could be isolated and characterized without the need to reduce the ketone to the corresponding alcohol. Two other ketones **88b,c** were converted into *α*-hydrazinoketones **89b,c** under the same conditions and the results are shown in Table 29.

The cyclic ketones **88a,b** were found to be reasonable substrates for proline catalysed *α*-hydrazination in propylene carbonate, giving products **89a,b** in good yield and with respectable enantiomeric excesses (Table 29, entries 1 and 2). Butanone (**88c**) was not a good substrate, giving only a moderate yield of product **89c** and with lower enantioselectivity than that observed for the cyclohexanone derivatives (Table 29, entry 3). Notably however, this substrate did react regioselectively, as no evidence for formation of the product derived from reaction at the methyl group of ketone **88c** was observed.

2.3.4 Results

In an attempt to obtain better results by using other amino acids as catalysts following on from previous results obtained in North's group,[5] the reaction of propanal **84a** with dibenzyl azodicarboxylate (**85a**, DBAD) was selected as a test reaction (Scheme 82), using 5 mol% of catalyst, one equivalent of dibenzyl azodicarboxylate and 1.5 equivalents of propionaldehyde as the previously optimized conditions. Then the reaction was tested with thirteen different amino acids as catalysts (Figure 35) using ethylene and propylene carbonate as solvents in continuation of our studies concerning environmentally benign catalytic reactions as previously investigated for asymmetric aldol reactions (Section 2.2.3, Figure 33).

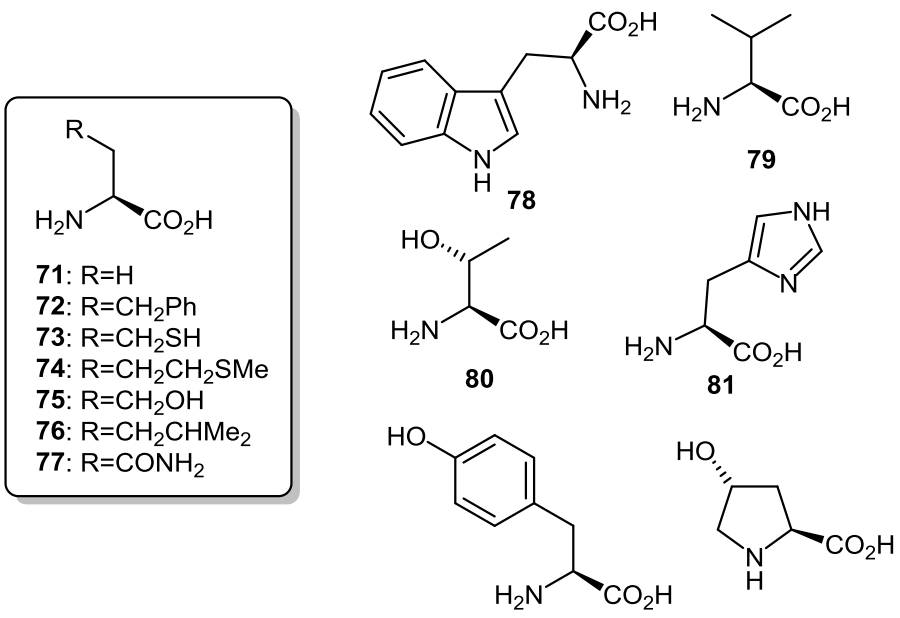
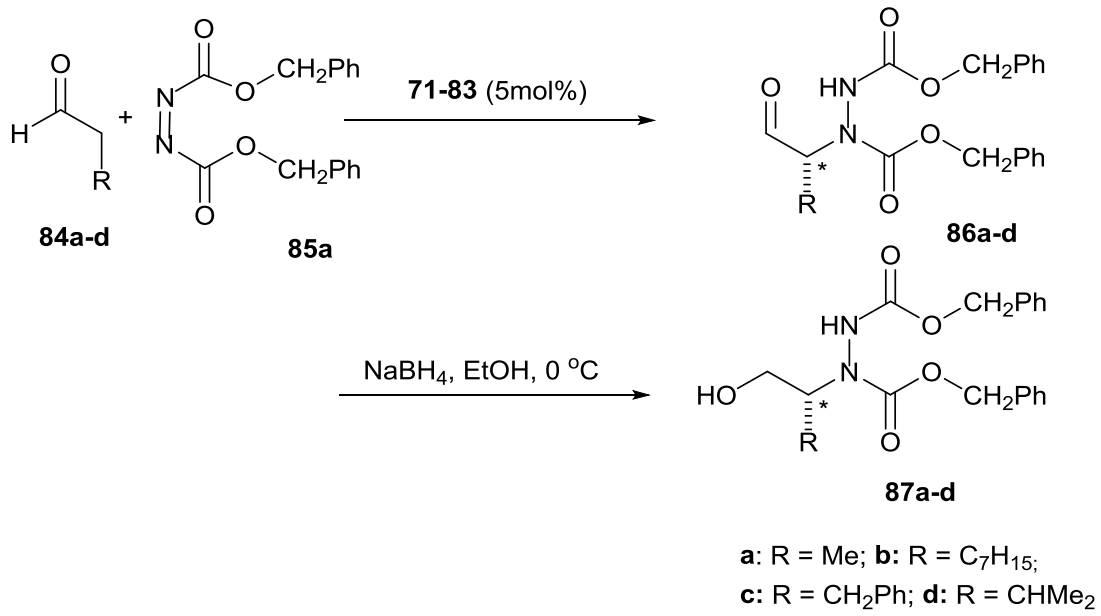
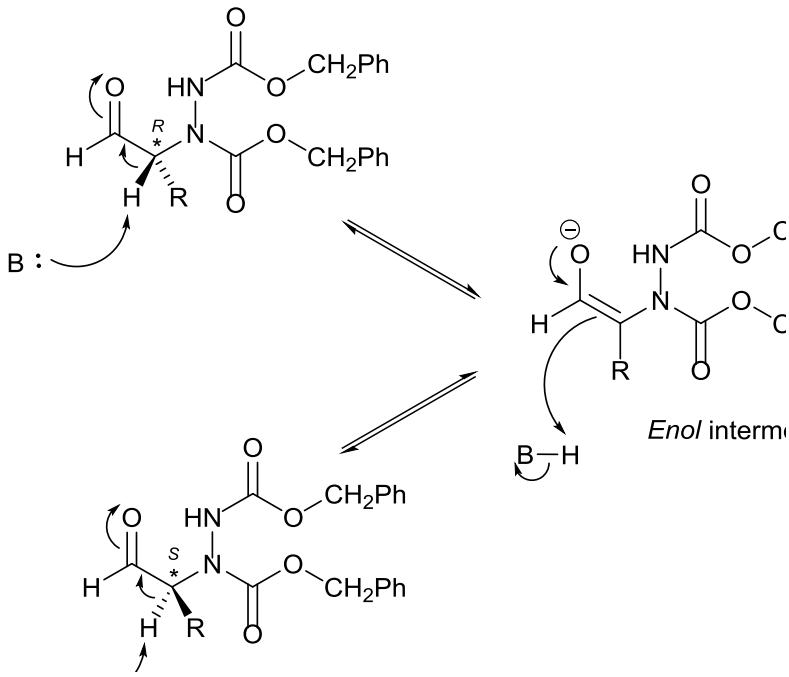


Figure 33. Organocatalysts **71-83** used in this study for the amination reactions.



Scheme 82. Amino acid-catalysed α-amination of carbonyl compounds

As before, the resulting aldehyde **86** was reduced using $NaBH_4$ in EtOH at 0^oC to afford the corresponding alcohol **87**. The enantiomeric excess of the products formed by the direct α-amination of aldehydes may decrease slowly over time due to racemisation caused by the acidity of the proton in the α-position next to the carbonyl group as shown in Scheme 83. By reducing the aldehyde group present in the intermediate, this prevents the racemisation process from occurring.



Scheme 83. Mechanism of racemisation via an enol intermediate

Unsatisfactory results were achieved when the reaction was performed with organocatalysts **71**-**83**. Only a few of the amino acids were found to display any catalytic activity, however, conversions were poor at less than 5% under these conditions in reactions carried out in propylene carbonate. In contrast, the results obtained when the reaction was performed in ethylene carbonate were much higher. Propylene carbonate has previously been found to be the better solvent in the corresponding proline catalysed reactions, however when the reaction is carried out with primary amino acids as catalysts, ethylene carbonate turned out to be the best solvent. This can be attributed to the greater polarity of ethylene carbonate controlling the interactions and stability of the transition states and intermediates (Figure 36).

The results of the amino acids that displayed catalytic activity are summarized in Table 30.

Table 30. Amination reactions catalysed by primary amino acids in ethylene carbonate

Entry	*L*-Catalyst	Yield(%)[a]	ee (%)[b]
1	Methione (**74**)	5	80
2	Serine (**75**)	5	91
3	Threonine (**80**)	5	84
4	Asparagine (**77**)	5	47
5	Alanine (**71**)	5	88
6	Histidine (**81**)	5	72

To a stirred solution of dibenzyl azodicarboxylate (1.00 mmol) and aldehyde (1.5 mmol) in ethylene carbonate (3ml), *L*-amino acid (5mol %) was added. The reaction was stirred at room temperature for 24 hours before reduction.

[a] Isolated yield of **87a** after purification by flash chromatography.

[b] ee of compounds **87a** determined by chiral HPLC on a Chiralpak AS-H column; major product has the (*R*)-configuration.

Regarding the enantioselectivity, organocatalyst *L*-serine **75** was found to be the best catalyst giving 91% *ee* for compound **87a** (Table 30, entry 2) however with a yield less than 15%. The difference in the enantiomeric excesses between them can be explained with the transition state for the reaction. As a secondary amine, the proline amine functionality is known to have a higher *pKa* when compared with other primary amino acids, it would therefore be expected that the iminium intermediate would be more stable, the higher equilibrium promoting the catalytic cycle to a greater extent towards the enamine (Figure 36, Scheme 84). In addition, these catalysts are not particularly hydrophobic; catalysts with more bulky substituents can effectively protect reactive sites from water molecules and also shield one of the sites from nucleophilic attack resulting in a higher enantioselectivity.

This study revealed a structure/activity relationship involving a cyclic secondary amine moiety and an acidic proton in appropriate spatial proximity for efficient catalysis to occur with the five-membered pyrrolidine ring as the best secondary cyclic amine moiety.

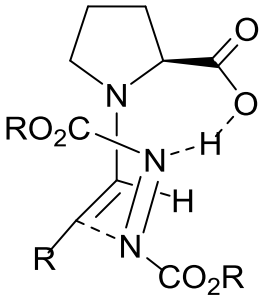
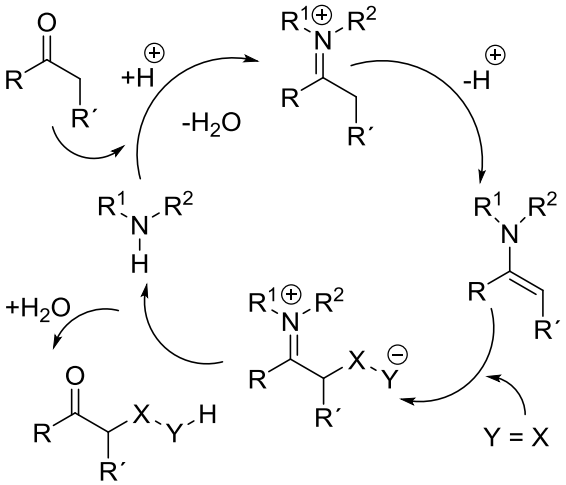


Figure 36. Proline enamine-involving transition state[219]

The approach of the azodicarboxylate is directed by interaction of the incoming nitrogen atom with the proton of the carboxylic acid of the amino acid-enamine intermediate.



Scheme 84. Enamine reaction cycle

Next, with the conditions given previously (Scheme 82) serine was the chosen catalyst for further α-amination reaction studies with the three different aldehydes that have been previously utilised for proline-catalysed aminations (**84b-d)** to assess the general utility of this reaction. The results are shown in Table 31.

Table 31. Serine-catalysed reactions of aldehydes with DBAD in ethylene carbonate

Entry	Aldehyde **R**	Product	Yield(%)[a]	ee (%)[b]
1	Me	**87a**	5	91
2	C_7H_{15}	**87b**	3	68
3	$CHMe_2$	**87c**	3	96
4	CH_2Ph	**87d**	3	69

To a stirred solution of dibenzyl azodicarboxylate (1.0 mmol) and aldehyde (1.5 mmol) in ethylene carbonate (3 mL), *L*-serine (5mol %) was added. The reaction was stirred at room temperature for 24 hours before reduction.

[a] Isolated yield of **87** after purification by flash chromatography.

[b] ee of compounds **87a-d** determined by chiral HPLC on a Chiralpak AS-H column; major product has the (*R*)-configuration.

The yields obtained were unexpectedly low when compared with proline catalysed aminations. A possible explanation of these results is that, when serine (5 mol%) is stirred with the aldehyde (1.5equiv) in ethylene carbonate at room temperature most of the serine remains undissolved, and conversion into enamine is not sufficient.[220] However all the aldehydes afforded product **87a-d** with good to high enantiomeric excess despite the low yield. The chiral induction was not as good as those obtained previously using proline which gave higher results for each of the aldehydes shown in Table 2 (between 90-97%). In addition, the yields obtained in the proline catalysed system were far greater from 41-87% (Table 28).

2.3.5 Conclusions

Attempts to carry out amination reactions with amino acids **71-83** as catalysts in propylene and ethylene carbonate showed cyclic carbonates not to be efficient reaction media for the amination of aldehydes under these conditions due to low yields. As serine gave the highest enantiomeric excess further studies were undertaken.

Direct α-amination of various unmodified aldehydes with azodicarboxylates catalysed by serine was not a practical method to obtain α-aminated alcohols. The desired α-aminated alcohols were not obtained with good yields and so unfortunately this data cannot be compared favourably to the results previously reported.

The extension of serine catalysed *α*-amination reactions of benzyl diazocarboxylate with ketones was not carried out as the results obtained for aldehydes were very low and it is expected that ketones would be even less reactive.

In conclusion, direct *α*-aminations catalysed by amino acids **71-83** unfortunately does not represent an alternative for (*S*)-proline catalysed *α*-amination reactions.

2.4 Mannich reactions

2.4.1 Introduction

The direct catalytic Mannich reaction has opened the path to new routes for the synthesis of *α*- and β-amino acid derivatives, γ-amino alcohols, *syn*- and *anti*-1,2-amino alcohols, and β-lactams which are valuable amine-containing compounds utilised as building blocks for pharmaceutical compounds and natural products.[221] This chapter focuses on the direct organocatalytic asymmetric Mannich reactions between α-amido sulfones (Figure 1) and unmodified aldehydes (Scheme 85). Amino acids have been employed as catalysts for the addition of aldehydes to *N*-*p*-methoxy-phenyl (PMP) imines[222] and *N*-carbamoyl imines such as *N*-Boc-imines,[223] *N*-Cbz-imines[224] and *N*-(phenylmethylene)benzamides.[225] However, because of their inherent high reactivity, *N*-carbamoyl imines are rather sensitive towards moisture and air, their preparation is rather troublesome and their storage requires precautions. A possibly more economical route to avoid these drawbacks is the *in situ* generation of the imine through the use of precursors with a good leaving group at the carbon α to the nitrogen atom. *α*-Amido sulfones are ideal precursors for this chemistry as they are bench-stable solids and have a good leaving group, SO_2Ph at the carbon *α* to the amine (Figure 37). They are also easily obtained by condensation of a carbamate and a sodium aryl sulfinate with the desired aldehyde[226] (See next section).

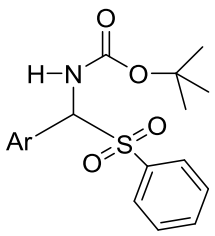
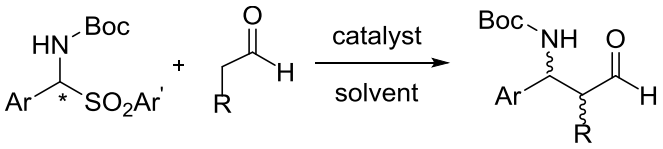


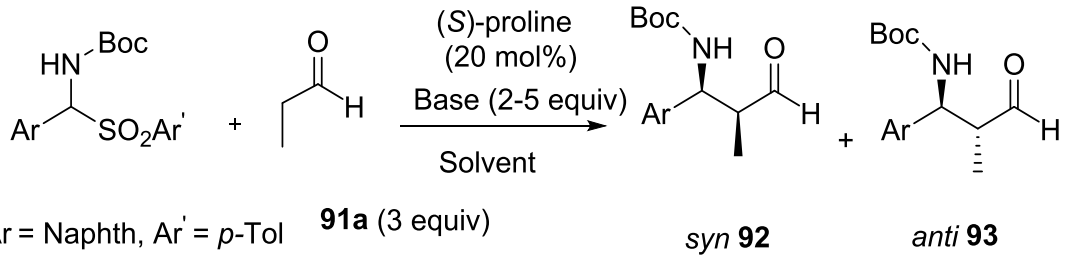
Figure 37. General structure of α-amido sulfones



Scheme 85. Direct organocatalytic asymmetric Mannich reactions between α-amido sulfones and aldehydes

2.4.2 Literature results

In 2010 Zhao & Córdova *et al*. devised a one-pot synthesis of β-amino aldehydes from aldehydes and α-amido sulfones[227] (Scheme 86). It was found that 20 mol% of *S*-proline catalysed the reaction between 2-napthaldehyde derived amido sulfone **90** and propanal **91a** yielding the corresponding *syn* and *anti* *β*-amino aldehydes, with high enantioselectivity (Table 32, Entry 1). First, different inorganic bases were screened (Table 30) to improve the diastereomeric ratio of **92** with proline as catalyst, finding that 5 equivalents of potassium fluoride with chloroform as a solvent gave the highest yield, with a *dr* of 91:1 and *ee* >99% (Table 32, Entry 4). The use of DMF or DCM as solvent resulted in higher yields but lower diastereoselectivities (Table 32, entries 6 and 7).



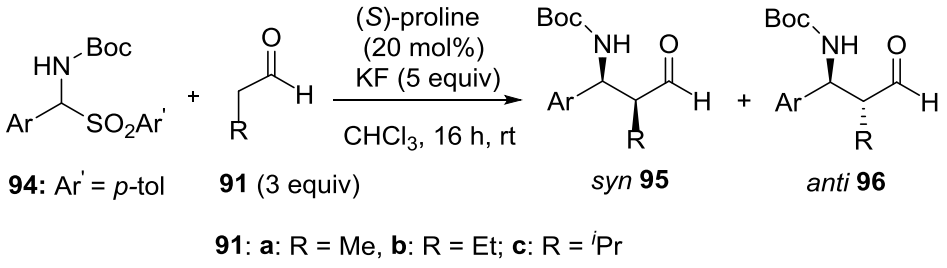
Scheme 86. Direct organocatalytic asymmetric Mannich reactions between α-amido sulfone **90** and propanal **91a**

Table 32. Screening of inorganic bases for the enantioselective reaction of **90** and **91**[a]

Entry	Base	Solvent	Yield(%)[b]	dr[c]	ee^{syn} / ee^{anti} (%)[d]
1	K_2CO_3[e]	$CHCl_3$	71	50:50	96/94
2	K_3PO_4[e]	$CHCl_3$	76	50:50	87/85
3	NaF[e]	$CHCl_3$	14	67:33	99/99
4	KF[e]	$CHCl_3$	84	91:9	98/n.d.[g]
5	KF[f]	$CHCl_3$	45	93:7	97/n.d.[g]
6	KF[e]	DMF	72	50:50	36/36
7	KF[e]	DCM	67	83:17	99/99

[a] Experimental conditions: a mixture of **90** (0.25 mmol), propanal **91a** (0.75 mmol), base and catalyst (20 mol%) in solvent (1.25 mL) was stirred at r.t. for 16 h.
[b] Isolated combined yield of pure compounds **92** and **93**
[c] *Syn* / *anti* ratio determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] ee determined by chiral-phase HPLC analysis of pure aldehyde **92**.
[e] 5 equiv of base was used.
[f] 2.5 equiv of base was used.
[g] n.d. = not determined

Encouraged by these results, an investigation of the catalytic asymmetric one-pot reaction between various α-amido sulfones and different aldehydes with KF as base and (*S*)-proline as organocatalyst was carried out (Scheme 87, Table 33).



91: **a**: R = Me, **b**: R = Et; **c**: R = ^{i}Pr

Scheme 87. Direct organocatalytic asymmetric Mannich reactions between α-amido sulfones **94** and aldehydes **91**[a]

Table 33. Asymmetric Mannich reactions between α-amido sulfones **94** and aldehydes **91**[a]

Entry	Ar	R	Yield(%)[b]	Syn: anti[c]	*ee*(%)[d]
1	Ph	Me	67	91:9	90
2	4-ClC_6H_4	Me	92	90:10	98
3	4-$MeOC_6H_4$	Me	90	89:11	99
4	4-MeC_6H_4	Me	72	95:5	99
5	Ph	Et	76	91:9	99
6	Ph	^{i}Pr	47	95:5	99

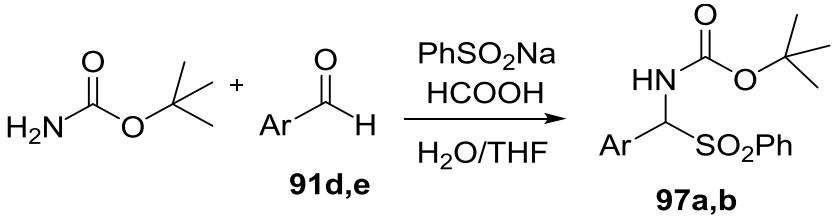
[a] Experimental conditions: a mixture of **94** (0.25 mmol), aldehydes **91** (0.75 mmol), potassium fluoride (1.25 mmol) and (*S*)-proline (20 mol%) in $CHCl_3$ (1.25 mL) was stirred at r.t. for 16 h.
[b] Isolated combined yield of pure compound **95** and **96**
[c] Syn / anti ratio determined by ^{1}H NMR analysis.
[d] ee determined by chiral-phase HPLC analysis of pure aldehyde **95**.

As shown in Table 33 the one-pot organocatalytic reactions between α-amido sulfones **94** and unmodified aldehydes **91** proceeded with high chemo- and enantioselectivity to furnish *β*-amino aldehydes in high yields with 90-99% *ee*. Therefore, this method has been used in our laboratory for further investigation to observe the effects on stereochemistry and enantioselectivity when using cyclic carbonates as solvents in order to assess their potential particularly that of ethylene and propylene carbonate, as green replacements to traditional solvents.

2.4.3 Results

2.4.3.1 Synthesis of α-amido sulfones

Firstly, the synthesis of the α-amido sulfone **97a,b** was carried out using aromatic aldehydes **91d,e**, *tert*-butyl carbamate and benzenesulfinic acid sodium salt[228] (Scheme 88).



91d,e **97a,b**

d: Ar = $NO_2C_6H_4$; **e**: Ar = Ph

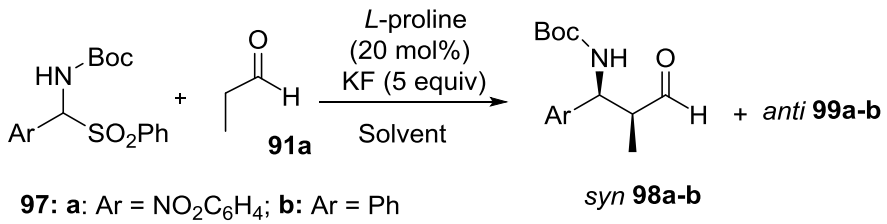
Scheme 88. Synthesis of α-amido sulfones **97a,b**

Aldehydes with different chemical properties were chosen in order to observe any trends in reactivity that may occur and relate them to the properties of the solvent or reagents, thus achieving a more comprehensive idea as to whether cyclic carbonates can replace traditional solvents used for proline catalysed asymmetric Mannich reactions. *p*-nitrobenzaldehyde **91d** and benzaldehyde **91e** were chosen as substrates to carry out the synthesis of the α-amido sulfones. *p*-nitrobenzaldehyde **91d** has a strongly electron withdrawing group in the para-position to the aldehyde and is a good chromophore which makes it appropriate for HPLC analysis. Benzaldehyde **91e** also has a good chromophore however it lacks the electron withdrawing nitro group making the proton on the chiral carbon of the α-amido sulfones **97b** less acidic. The different properties of each aldehyde will create a variation in the electrophilicity at the α-amido sulfone's chiral carbon causing it to react at different rates in a particular solvent.

p-Nitrobenzaldehyde **91d** is the most reactive aldehyde due to the strongly electron withdrawing nitro group in the para-position to the aldehyde; it can be electron withdrawing by resonance due to its lone pairs and electron withdrawing by induction due to a resonant positive charge on the nitrogen. This pulls electron density from the carbonyl carbon making it more strongly charged δ^+ and thus more prone to nucleophilic attack from the carbamate.

2.4.3.2 Synthesis of β-amino aldehydes in cyclic carbonates

The asymmetric Mannich reaction between *α*-amido sulfones **97a,b** and propanal **91a** was selected to test the reaction with cyclic carbonates (Scheme 89) under the same reaction conditions previously used in the literature, when using chloroform as solvent (Scheme 87, Table 33, Entry 1).



Scheme 89. Screening of solvents for *L*-proline catalysed Mannich reactions between α-amido sulfones **97a,b** and propanal **91a**[a]

Table 34. Direct organocatalytic asymmetric Mannich reactions between α-amido sulfone **97a,b** and aldehydes **91a** catalysed by *L*-proline[a]

Entry	Amido sulfone	Solvent	Yield(%)[b]	dr[c]	ee^{syn} / ee^{anti}(%)[d]
1	**97a**	$CHCl_3$	<5	50:50	59/66
2	**97a**	EC	<5	50:50	43/48
3	**97a**	PC	<5	50:50	44/48
4	**97b**	$CHCl_3$	49	50:50	93/88
5	**97b**	EC	60	50:50	67/84
6	**97b**	PC	11	50:50	82/78

[a] Experimental conditions: a mixture of **97a,b** (0.25 mmol), propanal **91a** (0.75 mmol), KF (1.25 mmol) and *L*-proline (20 mol%) in solvent (1.25 mL) was stirred for 16 h, at r.t. for reactions carried out with PC and at 30ºC for reactions carried out with EC.
[b] Isolated combined yield of pure compound **98** and **99**
[c] Syn / anti ratio determined by ^{1}H NMR analysis.
[d] ee determined by chiral-phase HPLC analysis of pure aldehyde **98**.

Results in Table 34 show clear differences for proline catalysed Mannich reactions in terms of yields when using α-amido sulfones **97a** or **97b**. In addition, the enantiomeric excesses of Mannich products turned out to be higher when using **97b** compared to those obtained when using **97a**. Ethylene carbonate is the best solvent to use because although it gives similar enantioselectivity than propylene carbonate, the yield is much higher (Entries 5 and 6). Therefore α-amido sulfone **97b** and ethylene carbonate were the chosen substrate and solvent respectively to screen the asymmetric Mannich reaction between *α*-amido sulfone **97b** and unmodified aldehydes under the optimised reaction conditions previously presented in the Section 2.2 using different amino acids as catalyst. These were the same amino acids previously tested for aldol and amination reactions (Figure 38).

Only three of the amino acids provided the desired product under these conditions: *L*-proline (Table 32, Entry 5) *L*-tyrosine (**82**) and trans-hydroxy-*L*-proline (THP, **83**). The results with these amino acids are summarized in Table 35.

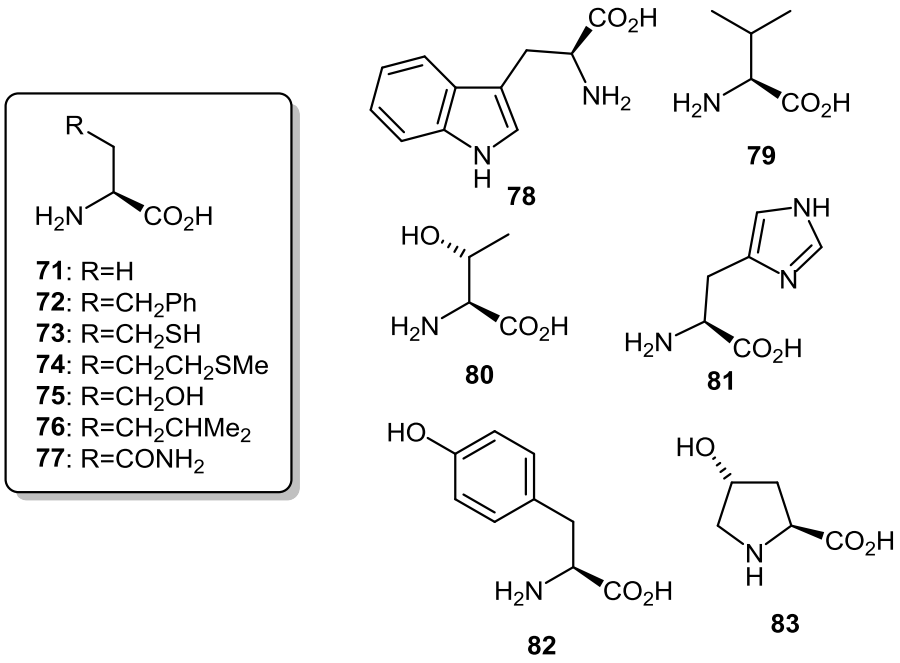


Figure 33. Amino acid based organocatalysts **71-83**.

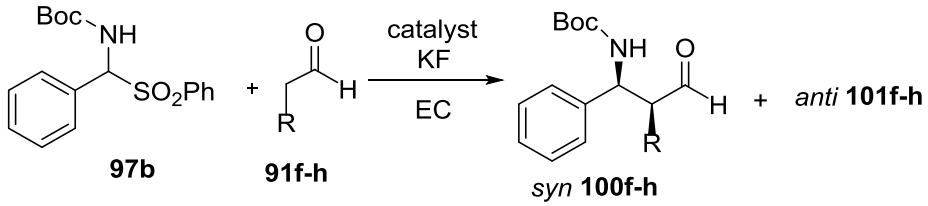
Table 35. Mannich reactions catalysed by amino acids in ethylene carbonate[a]

Entry	Catalyst	Yield(%)[b]	dr[c]	ee^{syn} / ee^{anti}(%)[d]
1	*L*-proline	60	50:50	67/84
2	THP(**83**)	42	50:50	85/85
3	*L*-tyrosine	15	50:50	22/45

[a] Experimental conditions: a mixture of **97b** (0.25 mmol), propanal **91a** (0.75 mmol), KF (1.25 mmol) and *L*-amino acid **71-83** (20 mol%) in EC (1.25 mL) was stirred for 16 h at 30°C.
[b] Isolated combined yield of pure compound **98** and **99**
[c] Syn / anti ratio determined by ^{1}H NMR analysis.
[d] ee determined by chiral-phase HPLC analysis of pure aldehyde **98**.

The reaction catalysed by (*S*)-tyrosine (**82**) gave a yield of 15% and trans-hydroxy-*L*-proline (**83**) gave a product yield of 42%. In contrast, (*S*)-proline was found to be the most effective catalyst in ethylene carbonate affording 60% combined yield of product **98** and **99**.

To widen the scope of the reaction three other aldehydes **91f-h** were used under the previous reaction conditions with proline and trans-hydroxy-*L*-proline as catalysts (Scheme 90) and ethylene carbonate as solvent.



f: R = C_7H_{15}; **g:** R = CH_2Ph; **h:** R = $CHMe_2$

Scheme 90. Synthesis of *β*-amino aldehydes in different aldehydes

Table 36. Direct organocatalytic asymmetric Mannich reactions between α-amido sulfone **97b** and aldehydes **91f-h**[a] in ethylene carbonate.

Entry	Catalyst	Aldehyde	Product	Yield(%)[b]	Syn: anti[c]	ee^{syn} / ee^{anti}(%)[d]
1	*L*-pro	**91f**	**100f/101f**	40	58:42	27/78
2	THP	**91f**	**100f/101f**	82	50:50	64/83
3	*L*-pro	**91g**	**100g/101g**	30	69:31	62/98
4	THP	**91g**	**100g/101g**	36	64:36	27/83
5	*L*-pro	**91h**	**100h/101h**	39	61:39	46/26
6	THP	**91h**	**100h/101h**	65	50:50	28/21

[a] Experimental conditions: a mixture of **97b** (0.25 mmol), aldehyde **91f-h** (0.75 mmol), KF (1.25 mmol) and *L*-proline (20 mol%) in EC (1.25 mL) was stirred at 30°C for 16 h.
[b] Isolated combined yield of pure compound **100f-h** and **101f-h**
[c] Syn / anti ratio determined by ^{1}H NMR analysis.
[d] ee determined by chiral-phase HPLC analysis of pure aldehyde **100f-h**.

These reactions exhibited relatively poor diastereoselectivity with the best ratio of 69:31 for proline catalysed Mannich reactions when using aldehyde **91g**. Trans-hydroxy-*L*-proline afforded β-amino aldehydes with higher yield compared to *L*-proline. The reaction of nonanal (**91f)** with **97b** in the presence of trans-hydroxy-*L*-proline gave product in the highest yield (82%) and 83 % *anti*-enantioselectivity (Table 36, Entry 2). However the same reaction catalysed by proline provided the Mannich product in moderate yield but maintained high enantioselectivity of the anti diastereomer. The same trend can be seen for hydrocinnamaldehyde (**91g)** which gave the highest *anti*-enantioselectivity for *L*-proline catalysed Mannich reactions, although the yield obtained was only 30%. In contrast, for isovaleraldehyde (**91h)** the enantiomeric excess of Mannich *syn*-product **100f** obtained using trans-hydroxy-*L*-proline as catalyst was much lower than that obtained from the same reaction with proline as catalyst although the enantiomeric excess of **101f** was low in both reactions.

To summarize, trans-hydroxy-*L*-proline gives higher yields but diastereoselectivity is better with proline, however in practice both are still very low. Enantioselectivity for the *anti*-diastereomer does not differ much by varying the catalyst and in two cases they are rather high. *Syn*-enantioselectivity is low to moderate. Significant differences are apparent between the catalysts with the same aldehyde substrate, but the results are better with trans-hydroxy-*L*-proline in two examples and better with proline in one other case.

2.4.4 Conclusions

In conclusion, we have shown that trans-hydroxy-*L*-proline may be used in some cases as alternative to proline as an organocatalyst for Mannich reactions between α-amido sulfones and non-enolisable aldehydes in ethylene carbonate as solvent although proline continues its role of being the best catalyst for Mannich reactions. Without any clear trend, it appears that the optimal catalyst and solvent combination needs to be determined on a substrate to substrate basis.

Similar to amination and aldol reactions ethylene carbonate turns out to be the best solvent when the Mannich reaction is carried out with amino acids **71-83** as catalysts.

This study unfortunately has not proven the compatibility of ethylene carbonate as a replacement to traditional solvents for organocatalytic Mannich reactions. Chloroform seems to give better results in terms of enantioselectivities and diastereoselectivities although the reaction in some cases seems to proceed faster with ethylene carbonate. As has already been mentioned in this thesis, it was expected that ethylene carbonate would afford higher yields as its dielectric constant is higher than that of propylene carbonate. The higher the dielectric constant the higher the polarity, hence the more stable the intermediate will be, therefore yields are expected to be higher.

Diastereomeric ratios appear to be around 1:1 when propanal is used in the reaction. As shown in Table 34, when using different aldehydes, in general the diastereomeric ratios observed seem to be due to steric interactions within the transition state of the mechanism which suggests that the choice of reagents is more important than the solvent system used when influencing diastereoselectivity. For example, the

diastereomeric ratio of the product observed was higher when *α*-amido sulfone with large aryl substituents **97a** was used with aldehyde **91h** which has a branched alkyl group; whereas using α-amido sulfone containing smaller aryl substituent (**97b)** the diastereomeric ratio observed when reacted with **91h** was lower. Therefore the high ratios may be due to steric interactions between the different substituents on the aryl group of the sulfone and those of the aldehyde.

It is known that higher temperature affects the enantioselectivity. Some of the enantioselectivities achieved were encouraging, giving over 90% under ambient reaction conditions which makes these results potentially important to industry as scaling a reaction that does not require high temperatures or high pressures is very advantageous. Despite the low cost of amino acids, the reactions use 20 mol% catalyst which is a relatively high loading, and therefore one area in which this methodology could be improved would be by reducing the amount of proline or trans-hydroxy-*L*-proline used without impacting the enantioselectivity or yield.

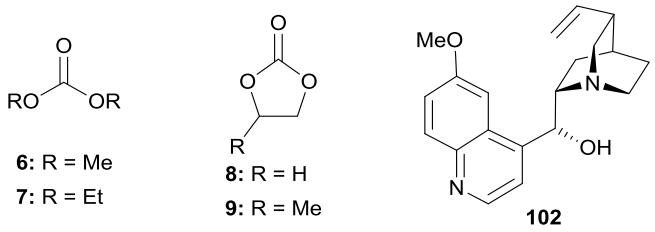
2.5 Michael Additions

2.5.1 Introduction

Non-natural catalysts often offer improved solubility and enhanced reactivity compared to the direct use of natural products as catalysts, but sacrificing the green characteristics associated with using unmodified natural products[229] due to the need to carry out multi-step transformations to prepare the catalyst.

Another aspect of organocatalysis that has been rather neglected is the reaction solvent, even though this usually constitutes the bulk of the reaction mass. Amino acid catalysed reactions are often carried out in solvents such as DMF or DMSO to facilitate the solubility of the zwitterionic compound. Other organocatalysed reactions have been carried out in solvents such toluene, acetonitrile, dichloromethane or chloroform.[2] However, these solvents are petrochemically derived and have hazards associated with their toxicity with the potential to generate contaminated aqueous waste and NOx / SOx on incineration.[230]

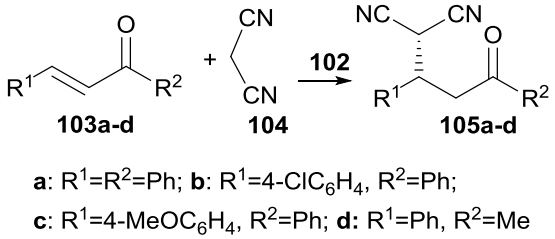
To overcome the solvent limitations associated with the use of unmodified natural products as organocatalysts, we have recently reported the use of ethylene **8** or propylene **9** carbonate as green polar aprotic solvents for amino acid catalysed reactions.[231] As has been mentioned in section 1.2, cyclic carbonates **8** and **9** have high dielectric constants (90 and 65 respectively). In contrast, acyclic carbonates such as dimethyl **6** and diethyl **7** carbonate have a much lower dielectric constant (3.1) and so can be considered as apolar solvents. Carbonates have also been used as solvents for uncatalysed and metal catalysed reactions [232] and are used as electrolytes for lithium ion batteries. The green credentials[233] of cyclic carbonates are supported by their low toxicity, facile hydrolysis to innocuous by-products[234] and the potential benefit of utilising waste carbon dioxide in their synthesis. Compounds **6**,**8** and **9** were included in a recent listing of industrially recommended green solvents.[235] In this section we show that acyclic diethyl carbonate **7** can be used as a green solvent for quinine (**102**) catalysed Michael additions.



As mentioned in Section 1.4.2, bifunctional chiral cinchona alkaloids have been demonstrated to be effective promoters for the activation of nucleophilic enol species and α,β-unsaturated carbonyls via acid-base interactions. One of the cinchona alkaloids that can promote Michael additions is quinine (**102**).

2.5.2 Michael Addition of Malononitrile to Enones. Previous results

In 2009,[236] Lattanzi and coworkers reported an efficient highly asymmetric addition of malononitrile **104** to aryl vinyl ketones **103** using unmodified quinine **102** as the organocatalyst to give Michael adducts **105** with 74-95% enantiomeric excess under optimised conditions (-18 ^{o}C and 10 mol% catalyst) as shown in Scheme 91.[237]



Scheme 91. Quinine catalysed asymmetric Michael additions

The Michael addition of malononitrile **104** to trans-chalcone **103a** was firstly performed in the presence of different cinchona alkaloids under different conditions as shown in Table 37. The chosen solvent among the apolar solvents tested (entries 7-9) was toluene since most of the reactions mediated by cinchona alkaloids proceeded best in this medium.

Table 37. Michael addition of malononitrile **104** to trans-chalcone **103a** promoted by Cinchona alkaloids under different conditions.[a]

Entry	Catalyst (mol%)	Solvent	t (h)	Yield (%)[b]	ee (%)[c]
1	cinchonidine(20)	toluene	16	80	44(*S*)
2	cinchonine(20)	toluene	20	40	43(*R*)
3	quinidine(20)	toluene	16	97	63(*R*)
4	quinine(20)	toluene	16	98	82(*S*)
5	DHQD(20)	toluene	20	80	60(*R*)
6	DHQN(20)	toluene	18	80	79(*S*)
7	quinine(20)	*p*-xylene	18	98	81(*S*)
8	quinine(20)	*m*-xylene	19	98	81(*S*)
9	quinine(20)	CH_2Cl_2	18	94	62(*S*)
10	quinine(20)	CH_3CN	21	90	15(*S*)
11	quinine(20)	CH_3OH	19	98	*rac*
12[d]	quinine(10)	toluene	20	98	86
13[e]	quinine(10)	toluene	18	74	92

[a] Reaction conditions: **103a**(0.2 mmol), **104** (0.24 mmol), catalyst (0.04mmol) in 0.4 mL of solvent.
[b] Isolated yield of **105a** after purification by flash chromatography.
[c] *ee* of compound **105a** determined by chiral HPLC. Absolute configuration determined by comparison with optical rotation in the literature.
[d] Reaction performed at c = 0.2M with respect to **103a**.
[e] Reaction performed at -18°C and at c = 0.1M with respect to **103a**.

Quinine proved to be the most efficient compound, affording product **105a** in 98% yield and 82% *ee* (entry 4). The reaction catalysed by quinine was then carried out with different enones to widen the scope in the asymmetric Michael addition, in order to have access to diversely functionalised and synthetically useful chiral adducts (Table 38). The adducts were isolated in excellent yields and with high asymmetric induction (up to 95% *ee*).[263]

Table 38. Asymmetric Michael addition of malononitrile **104** to enones **103** promoted by quinine in toluene at -18 °C.[a]

Entry	R^1	R^2	t (h)	Yield (%)[b]	ee (%)[c]
1	Ph	Ph	60	99	92
2	4-ClC_6H_4	Ph	86	98	92
3	4-$MeOC_6H_4$	Ph	136	95	91
4[d,e]	Ph	Me	120	28	rac

[a] Reaction conditions: **103** (0.2 mmol), **104** (0.24 mmol), quinine (0.02 mmol) in 2 mL of solvent.
[b] Isolated yields after purification by flash chromatography.
[c] *ee* of compound **105** determined by chiral HPLC.
[d] Using 20 mol % of quinine.
[e] Reaction performed at c = 0.5M with respect to **103a**.

2.5.3 Results

Whilst this 100% atom economical reaction is synthetically attractive as it produces richly functionalised products, it does have two drawbacks: the reaction times were 60-186 hours and high yields and enantioselectivities were only obtained in petrochemically derived aromatic hydrocarbon solvents (toluene or xylene) which are less than ideal solvents, especially from an environmental perspective.[238] Therefore, we felt that this reaction would allow us to extend our previous work on carbonate solvents for organocatalysed reactions to a different class of catalysts and reactions.

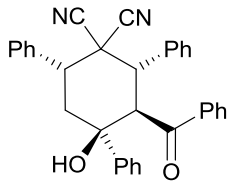
Initial studies were carried out using chalcone **103a** as the Michael acceptor with 1.2 equivalents of malononitrile **104** and with 20 mol% of quinine to increase the reaction rate. The results of this study are shown in Table 39.

Table 39. Michael addition of malononitrile **104** to chalcone **103a**

Entry	Solvent	t (h)	T (°C)	**103a:104**	Yield (%)[a]	**108a:106**	*ee* (%)[b]
1	toluene	20	18	1:1.2	98	1:0	87
2	CH_3OH	20	18	1:1.2	90	1:0	0
3	EC	20	18	1:1.2	82	4.4:1	11
4	*RS*-PC	20	18	1:1.2	80	11.6:1	12
5	*R*-PC	20	18	1:1.2	80	13.5:1	12
6	DMC	20	18	1:1.2	98	8.8:1	48
7	DMC	72	0	1:1.2	98	4.3:1	31
8	DEC	20	18	1:1.2	95	21:1	56
9	DEC	72	0	1:1.2	98	1:1	52
10	DEC	72	-20	1:1.2	98	1:1.7	47
11	DEC	20	18	1:5	98	1:0	64
12	DEC	20	0	1:5	98	1:0	56
13	DEC	72	-20	1:5	90	1:0	42
14	DEC	72	-40	1:5	80	1:0	44

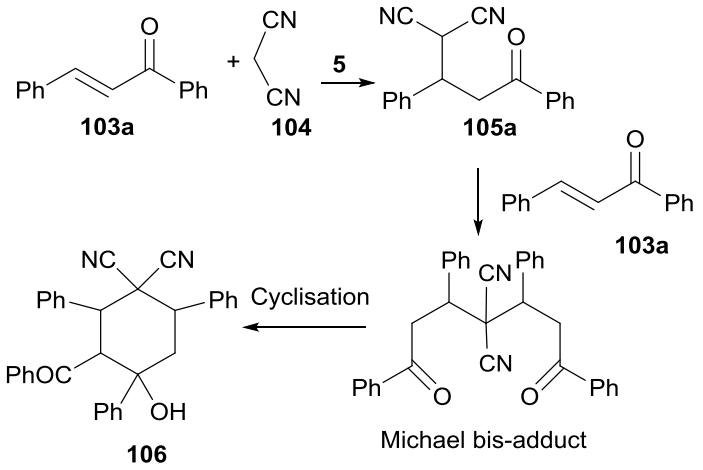
[a] Isolated yield of **105a+106** after purification by flash chromatography. Compounds **105** and **106a** were not readily separable.
[b] *ee* of compound **105a** determined by chiral HPLC on a Chiralpak AD-H column.

Entries 1 and 2 confirm the results of Lattanzi and coworkers showing that high chemical yields are obtained in both toluene and methanol, but high levels of asymmetric induction are only obtained in the very non-polar solvent. Entries 3-5 then show that the use of polar cyclic carbonates as solvents give product **105a** in high yield, but with greatly reduced enantiomeric excess compared to reactions carried out in toluene. The use of enantiomerically pure propylene carbonate was also not advantageous in this case (compare entries 4 and 5). In addition, a minor side product was observed in these reactions.



106

This was isolated and determined to be cyclohexanol derivative **106** resulting from a tandem double Michael addition of malononitrile to two molecules of chalcone **103a** followed by an intramolecular aldol reaction (Scheme 92).



Scheme 92. An unexpected cyclisation of Michael addition reaction.

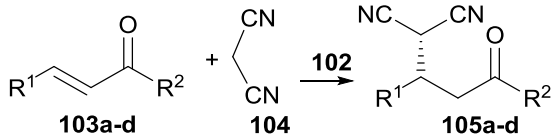
The structure and formation of racemic **106** in related racemic Michael additions has been reported before, as has the relative stereochemistry of its four stereocentres.[239] In this case, unfortunately, we were not able to separate the enantiomers by HPLC.

The mode of action of quinine in this reaction likely involves it acting as a Brønsted base to remove one of the acidic protons from malononitrile. Thus, to get efficient asymmetric induction during the Michael addition of the resulting malononitrile anion, it is necessary for the chiral cation and achiral anion to form a tight ion pair. It is also likely that π-π interactions between the aromatic rings of quinine and enone **103** are important to organise the reaction components and maximise the asymmetric induction, since only aryl enones form effective substrates for this reaction.[263]

A polar solvent (such as cyclic carbonates **8** and **9**) would disrupt both the tight ion pair and any π-π interactions, thus resulting in the significantly reduced asymmetric induction. To overcome this problem, the use of much less polar, acyclic carbonate solvents **6** and **7** was therefore investigated. The use of dimethyl carbonate as solvent at either 18 or 0 ^{o}C (entries 6 and 7) gave the same chemical yield as a reaction in toluene, but whilst the enantioselectivity increased relative to the use of cyclic carbonates as solvent, it was still only around half that observed in toluene. The use of diethyl carbonate as solvent gave even better results (entry 8), with a high yield and a high ratio of **105a:106**, though the enantiomeric excess of product **105a** was still only moderate. Attempts to increase the enantioselectivity of the reaction by lowering the reaction temperature (entries 9 and 10) were unsuccessful as not only did the enantiomeric excess of compound **105a** decrease as the temperature was lowered, but the amount of by-product **106** formed increased significantly and at -20 ^{o}C it became the major product (entry 10).

The use of other cinchona alkaloids as catalysts was briefly investigated under the conditions of Table 39, entry 9. Under these conditions quinidine, cinchonine and cinchonidine gave compound **106** as the only product in 84, 55 and 59% chemical yield respectively.

To avoid the formation of by-product **106**, the ratio of malononitrile **104** to chalcone **103a** was increased to 5:1. As shown in Table 39, entry 11, this resulted in the exclusive formation of product **105a** in excellent chemical yield and with further improved enantiomeric excess. However, attempts to further improve the enantioselectivity of the reaction by lowering the reaction temperature (entries 12-14) were again unsuccessful as both the rate of reaction and its enantioselectivity decreased as the temperature was lowered. The quinine catalysed Michael addition of malononitrile to three other α,β-unsaturated ketones **103b-d** was also investigated in diethyl carbonate and the results are shown in Table 40.



103a-d **104** **105a-d**

a: R^1=R^2=Ph; **b**: R^1=4-ClC_6H_4, R^2=Ph;

c: R^1=4-MeOC_6H_4, R^2=Ph; **d:** R^1=Ph, R^2=Me

Scheme 93. Quinine catalysed asymmetric Michael additions

Table 40. Michael addition of malononitrile **104** to enones **103b-d**

Entry	Enone	t (h)	T (°C)	**103b-d:104**	Yield (%)[a]	**105b-d:106**	*ee* (%)[b]
1	**103b**	24	18	1:1.2	72	8.5:1	45
2	**103b**	72	-20	1:1.2	81	5.2:1	44
3	**103b**	24	18	1:5	73	1:0	49
4	**103b**	72	-20	1:5	90	1:0	63
5	**103c**	24	18	1:1.2	90	10.8:1	54
6	**103c**	72	-20	1:1.2	41	7.2:1	54
7	**103c**	24	18	1:5	79	1:0	55
8	**103c**	72	-20	1:5	74	1:0	45
9	**103d**	24	18	1:1.2	16	1:1	9
10	**103d**	72	18	1:1.2	21	1:1.7	6
11	**103d**	72	0	1:1.2	33	1:0	9
12	**103d**	72	-20	1:1.2	46	1:0	10

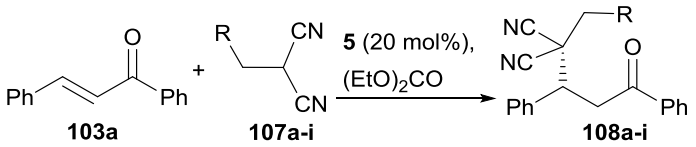
[a] Isolated yield of **105b-d+106** after purification by flash chromatography.
[b] *ee* of compounds **105b-c** determined by chiral HPLC on a Chiralpak AD-H column, *ee* of compound **105d** determined by chiral HPLC on a Chiralpak AS-H column.

For these substrates, formation of cyclohexanol derivatives analogous to structure **106** was observed when using 1.2 equivalents of malononitrile. However, by increasing the ratio of malononitrile **104** to enone **103b-d** to 5:1 by-product **106** was not obtained. For substrate **103b** (entries 1-4), the highest chemical yield and enantioselectivity was observed from a reaction carried out at -20 °C using five equivalents of malononitrile (entry 4). These are directly comparable to the optimal results obtained with substrate **103a** in diethyl carbonate (Table 39, entry 11). Electron rich substrate **103c** gave lower enantioselectivities (Table 40, entries 5-8) and in this case the best combinations of chemical yields and enantioselectivity were obtained at 18 °C (entries 5 and 7). Benzylidene acetone **103d** was a very poor substrate (entries 8-12), giving at best a moderate chemical yield and very low enantioselectivity (entry 12). These results suggest the importance of π-π interactions involving an aromatic ring at the R^2 position of substrate **103** in obtaining good levels of asymmetric induction.

The enantiomeric excesses reported in Tables 39 and 40 are all lower than the 91-92% enantiomeric excess reported for the synthesis of compounds **105a-c** in toluene. However, we reasoned that if the size of the malononitrile enolate was increased, this

would increase the facial discrimination between the enantiotopic faces of the enone and result in higher levels of asymmetric induction.

Therefore, we investigated the Michael addition of α-monosubstituted malonitrile derivatives **107a-i** to chalcone **103a** to give ketones **108a-i** as shown in Scheme 94. The results of this study are given in Table 41. The results using dinitrile **107a** was not encouraging, giving compound **108a** with low enantiomeric excess at room temperature, though in high chemical yield (entry 1). Lowering the reaction temperature to -20 ^{o}C dramatically reduced the chemical yield (even after a reaction time of 72 h), without improving the enantioselectivity of the reaction (entry 2).



103a **107a-i** **108a-i**

a: R=Ph; **b:** R=4-BrC_6H_4; **c:** R=4-ClC_6H_4; **d:** R=3-ClC_6H_4; **e:** R=2-ClC_6H_4; **f:** R=4-O_2NC_6H_4; **g:** R=4-MeOC_6H_4; **h:** R=4-F_3CC_6H_4; **i:** R=4-C_6F_5

Scheme 94. Quinine catalysed asymmetric Michael additions of α-monosubstituted malononitriles

In contrast, the introduction of a remote bromine atom in compound **107b** dramatically improved the enantioselectivity of the reaction. Thus, whilst at room temperature (entry 3) only minimal asymmetric induction occurred, lowering the reaction temperature to -20 ^{o}C gave compound **108b** with high chemical yield and high enantiomeric excess (entry 4). However, further lowering the reaction temperature to -30 ^{o}C lowered both the chemical yield and the enantiomeric purity of compound **108b** (entry 5).

Table 41. Quinine catalysed Michael addition of α-substituted malononitriles **107a-i** to enone **103a**

Entry	**107**	t (h)	T (°C)	Yield (%)[a]	ee (%)[b]
1	**a**	24	18	80–96[c]	22–30[c]
2	**a**	72	-20	20[c]	24–31[c]
3	**b**	24	18	74	9
4	**b**	72	-20	96–98[c]	86–91[c]
5	**b**	72	-30	86–97[d]	66–74[d]
6	**c**	24	18	40	4
7	**c**	72	-20	33	24
8	**d**	24	18	91	6
9	**d**	72	-20	90	27
10	**e**	24	18	8	5
11	**e**	72	-20	59	22
12	**f**	24	18	97	45
13	**f**	72	-20	15-39[c]	52–67[c]
14	**g**	24	18	75	12
15	**g**	72	-20	95–98[c]	67–86[c]
16	**h**	24	18	6	1
17	**i**	24	18	51	11
18	**i**	24	-20	76	12
19	**i**	72	-20	80	25

[a] Isolated yield of **108a-i** after purification by recrystallization.
[b] *ee* determined by chiral HPLC on a Chiralpak AD-H column.
[c] Range of values obtained from reactions carried out in triplicate.
[d] Range of values obtained from reactions carried out in duplicate.

The introduction of a chlorine atom onto the aromatic rings of substrates **107c-e** gave results that appeared to be independent of the location of the substituent and which resembled the unsubstituted substrate **107a** rather than brominated substrate **107b**. Thus, for each of substrates **107c-e**, less than 10% enantioselectivity was observed at room temperature (entries 6, 8 and 10) and this increased to 22-27% at -20 °C (entries 7, 9, 11). The trend in chemical yield is less clear, though this is likely to be affected by the purification of products **108c-e** by recrystallisation.

Substrate **107f** with a nitro group on its aromatic ring gave Michael adduct **108f** in high yield and with moderate enantiomeric excess from a reaction carried out at room temperature (entry 12). However, lowering the reaction temperature to -20 ^{o}C substantially lowered the chemical yield whilst only marginally increasing the enantioselectivity of the reaction (entry 13). The structure of product **108f** was confirmed by X-ray analysis (Figure 39).

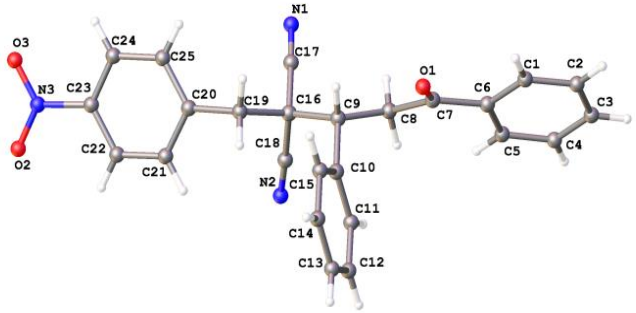


Figure 39. ORTEP diagram of compound **11f**

Substrate **107g** with a methoxy group on the 4-position of its aromatic ring resembled 4-bromobenzyl malononitrile **107b** in its reactivity. Thus, at room temperature, adduct **108g** was obtained in good yield but with only 12% enantiomeric excess (entry 14). However, by lowering the reaction temperature to -20 ^{o}C and extending the reaction time to 72 hours, both the chemical yield and enantiomeric excess of compound **108g** could be substantially increased; with the enantiomeric excess increasing up to 86% (entry 15). Fluorinated substrates **107h-i** were poor substrates for the reaction. Thus, trifluoromethyl derivative **107h** gave a very low yield of essentially racemic **108h** even at room temperature (entry 16) and whilst the chemical yield obtained using pentafluorophenyl substrate **107i** was higher, product **108i** was obtained with an enantiomeric excess of, at best, 25% (entries 17-19).

2.5.4 Conclusions

We have shown that diethyl carbonate can replace toluene as a solvent for quinine catalysed Michael additions. Whilst reactions using malononitrile as the nucleophile precursor gave products with lower enantiomeric excesses than those obtained in toluene, some α-substituted malononitriles were excellent nucleophile precursors, giving Michael

adducts with up to 91% enantiomeric excess from reactions carried out in diethyl carbonate. However, the chemical yields and enantioselectivities were highly variable which may be due to the complex nature of the intermolecular interactions in this system as the degree of asymmetric induction is likely to be influenced by both the tightness of the ion pair and the nature of the π-π interactions between the enone, malononitrile and quinine.

3. General Conclusions

The presence of green chemistry[240] as a major topic in the literature has increased dramatically since the start of the new millenium. The high number of communications within this area indicates that this is now a hot topic. One of the key aims of my research is to investigate alternative or so-called 'green solvents'. A solvent that must be both environmentally friendly and also to possess the properties required for the reaction in question. Organic solvents (**6-9**, Figure 9) are the ones chosen in this thesis since they have been assesed to be a greener, sustainable alternative; this means that it has an advantage over more traditional solvents with regard to toxicity, the energy required for its synthesis and disposal, as well as the amount of waste produced in the process.

Ethylene and propylene carbonates (**8**,**9**, figure 9), which can be prepared from epoxides and carbon dioxide, were shown to be effective solvents for the proline-catalysed, 100% atom economical, asymmetric aldol reaction between enolisable and non-enolisable carbonyl compounds. The optimal cyclic carbonate to use for a particular aldol reaction, along with the need for water as a co solvent, appeared to be determined by the polarities of the various components present in the reaction mixture. Cyclic carbonates have also been applied in amination and Mannich reactions with less success as summarised below.

The use of acyclic carbonates (**6**,**7,** figure 9) have also been investigated for quinine catalysed Michael additions. Michael addition adducts are usually performed in apolar solvents such toluene, thus it is expected that dimethyl carbonate **6** and diethyl carbonate **7** would give better results than ethylene or propylene carbonate which are more polar than diethyl or dimethyl carbonate. These acyclic carbonates can be

considered as apolar solvents due to their low dielectric constant (3.1). It has been shown that diethyl carbonate can, in some cases, replace toluene as a solvent for quinine catalysed Michael additions, affording Michael adducts with up to 91% enantiomeric excess.

The other aim of this report was focused on the asymmetric reactions promoted by organocatalysts such as unmodified natural products including amino acids (**71-83)** and quinine. The use of organocatalysts often involves mild reaction conditions with the ability to obtain both enantiomers of the catalytic product. It offers the possibility of carrying out key chemical transformations without the need for expensive, toxic, and scarce transition or lanthanide metal based catalysts. Organocatalysed reactions might be more convenient than those using metal complexes if the absence of metal contaminants is strictly required. They offer a favourable alternative to metals as they possess lower toxicity, are cheaper and can often be used under a non-inert atmosphere with wet solvents. Small organic molecules also offer the possibility of being recovered and reused, unlike many transition metal catalysts. Amino acids and the cinchona alkaloid quinine readily meet this requirement. For these reasons the importance of the use of organocatalysts in organic synthesis has increased considerably in recent years, especially in pharmaceutical industries. Of the multitude of organocatalysts reported, only proline seems to have a wide ranging activity for a number of carbon-carbon bond forming reactions. It has been proven that it is the most effective promoter of asymmetric aldol reactions. Proline also catalyses Mannich and amination reactions under very mild conditions, offering good to high yields and enantioselectivity.

L-proline is more commonly used than *D*-proline and easily available at lower cost (£0.38/g vs. £14.00/g in March 2014). Other amino acids have potential uses as organocatalysts and typically their respective *D*-isomers are comparatively cheaper than *D*-proline. This would allow access to both stereoisomers of catalysed reaction products. Therefore our aim was to look for different amino acids directly available from biological sources in 'green' reaction media that could act as replacement to proline organocatalysed reactions in more traditional solvent systems. Natural amino acids **71-83** (Figure 33) were chosen. Although proline has received the most attention, we have also shown that phenylalanine and tryptophan have also been found to be efficient as organocatalysts, capable of stereoselective catalysis in the cross aldol reaction between enolisable ketones and non-enolisable aldehydes in ethylene and propylene carbonate as solvent. This leads

to a more economical way to perform aldol reactions than using the more expensive proline rather than tryptophan and phenylalanine as mentioned earlier.

(*S*)-Serine gave the highest enantiomeric excess for the α-aminations in ethylene carbonate as solvent, however the desired α-aminated alcohols were not obtained in good yield. Proline therefore continues in its role of being the best organocatalyst for amination reactions. Trans-hydroxy-*L*-proline may be used in some cases as an alternative organocatalyst to proline for Mannich reactions between α-amido sulfones and non-enolisable aldehydes in ethylene carbonate as solvent. In some other cases results obtained in the corresponding proline-catalysed reactions were higher.

Similar to aldol and amination reactions, ethylene carbonate (**8**) turned out to be the best solvent when the Mannich reaction is carried out with amino acids **71-83** as catalysts. This is expected due to its high dielectric constant. Chloroform seems to give better results in terms of enantioselectivity and diastereoselectivity, although the reaction in some cases proceed faster with ethylene carbonate.

Overall, it has been shown in this thesis that organic carbonates act as alternative solvents to conventional toxic ones such as DMF, DMSO and halogenated solvents as well as aromatic solvents such toluene for aldol, Mannich, amination and Michael addition reactions catalysed by proline, other amino acids (**71-83**) and the cinchona alkaloid quinine. In some cases, yields obtained were not as good as for proline catalysed reactions, however, I believe that would be possible to enhance such results by experimenting with different substrates and / or reaction conditions such temperature, catalyst loading or time.

4. Experimental Section

4.1 Chemicals and Instrumentation

Propylene carbonate, used as solvent, was distilled from CaH_2 under reduced pressure and acetone was distilled from $CaCO_3$. Both solvents were then stored over molecular sieves. Liquid aldehydes were freshly distilled prior to use. Other commercially available chemicals (Alfa Aesar, Aldrich, Fluka, Acros) were used as received. Distillations were carried out on a Büchi Kugelrohr GKR-50 apparatus. Chromatographic separations were performed using silica gel 60 (230– 400 mesh, Davisil).

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or Jeol Oxford 400 spectrometer at resonance frequencies of 300/400 and 75/100 MHz respectively. ^{19}F NMR spectra were recorded on the Oxford 400 spectrometer at a resonance frequency of 367 MHz. Chemical shifts are expressed in parts per million (ppm) and multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of these. All spectra were recorded at r.t. in $CDCl_3$. DEPT 90 and DEPT 135 experiments were used to determine the number of hydrogen atoms attached to each carbon atom.

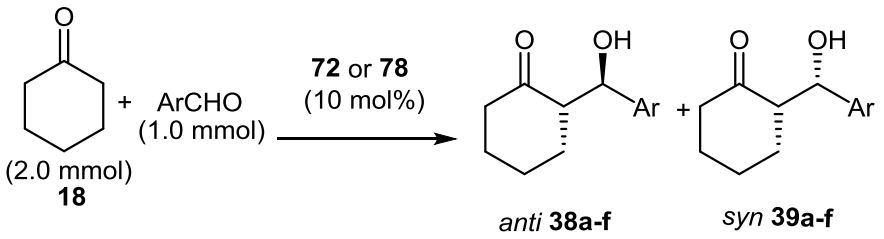
High- and low- resolution electrospray ionisation (ESI) mass spectra were recorded on a Waters LCT Premier LCMS spectrometer using direct injection of the sample in MeOH. Infrared spectra were recorded at room temperature on a *Varian* 800 FT-IR Scimitar series spectrometer, measuring specific absorbance intensities as: broad (br), strong (s), medium (m), or weak (w). Optical rotations were measured on a Polaar 2001 Optical Activity polarimeter. The sample concentration is reported in g/100mL of the specified solvent. The solutions were prepared in a volumetric flask, and measured in a one decimetre long curvette. Melting points were obtained using a Stuart melting point SMP3 system.

Analytical chiral HPLC was performed using a Varian Prostar system comprising binary pumping modules, a diode array detector and autosampler and equipped with a Daicel Chiralcel OD-H, AD-H or AS-H column (25 cm by 4.6 mm), using a mixture of i-PrOH and hexane as eluent. The column, solvent and flow rate are given for each compound.

X-ray data were collected on an Oxford Diffraction Gemini A Ultra diffractometer at 150 K with CuKα radiation (λ =1.54184 Å) or at Diamond Light Source beamline I19 with synchroton radiation (λ =0.6889 Å).

4.2 Experimental for Aldol reactions

4.2.1 Aldol reactions between cyclohexanone and aromatic aldehydes catalysed by phenylalanine (72) and tryptophan (78).



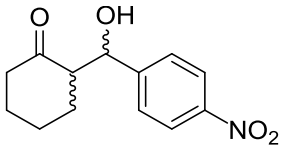
a: Ar= 4-$O_2NC_6H_4$; **b**: Ar= C_6H_5; **c**: Ar= 4-BrC_6H_4;
d: Ar= 4-$F_3CC_6H_4$; **e**: Ar= 3-$O_2NC_6H_4$; **f**: Ar= C_6F_5

To a mixture of (*S)*-amino acid **72** or **78** (10 mol% relative to the aldehyde) and aldehyde (1mmol) was added propylene or ethylene carbonate **9** or **8** (1 mL), cyclohexanone **18** (196 mg, 2 mmol), and H_2O (0-5 mmol) under an inert atmosphere. The resulting mixture was stirred at room temperature for 24-144 hours. The reaction mixture was then poured into H_2O (10 mL) and extracted with Et_2O (10 mL). The organic phase was washed with H_2O (7 × 10 mL), dried (Na_2SO_4), and the solvent removed *in vacuo*. The residue at this stage was analysed by ^1H NMR spectroscopy and chiral HPLC to obtain the diastereoselectivity and enantioselectivities. The residue was then purified by column chromatography (gradient from hexane-EtOAc, 9:1 to 4:1) to give the aldol products. All of the aldol products are known compounds and the absolute configuration of the major enantiomer of the aldol products was determined by comparison of the chiral HPLC retention times with literature data.[241]

General procedure for the preparation of racemic samples of compounds 20a-f/21a-f:
To a mixture of *DL*-amino acid **72** or **78** (10 mol%) and aldehyde (1mmol) was added propylene carbonate (1 mL), cyclohexanone **18** (196 mg, 2 mmol), and H_2O (1 mmol) under an inert atmosphere. The resulting mixture was stirred at r.t. for 24 h. The reaction mixture was then poured into H_2O (10 mL) and extracted with Et_2O (10 mL). The organic phase was washed with H_2O (7 × 10 mL), dried (Na_2SO_4), and the solvent removed *in vacuo*.

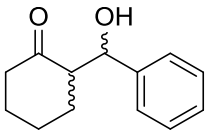
Characterization Data for compounds 20a-f/21a-f:

(2*S*,1'*R*)-and(2*S*,1'*S*)-2-[1'-Hydroxy-1'-(4-nitrophenyl)-methyl]cyclohexanone 38a/39a



Obtained as yellow crystals in 61% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ(syn) = 8.20 (2H, d, *J* = 8.8 Hz, ArH), 7.50 (2H, d, *J* = 8.4 Hz, ArH), 5.48 (1H, br, CHOH), 3.17 (1H, d, *J* = 3.3 Hz, OH), 2.7-2.6 (1H, br, CH), 2.5-2.3 (2H, br, CH_2), 2.2-2.1 (1H, br, CH), 1.9-1.8 (1H, br, CH), 1.7-1.4 (4H, br, CH); δ(anti) = 8.20 (2H, d, *J* = 8.7 Hz, ArH), 7.50 (2H, d, *J* = 8.6 Hz, ArH), 4.90 (1H, dd, *J* = 3.1, 8.4 Hz, CHOH), 4.07 (1H, d, *J* = 3.2 Hz, OH), 2.6-2.5 (2H, br, CH), 2.4-2.3 (1H, br, CH), 2.2-2.1 (1H, br, CH), 1.9-1.8 (1H, br, CH), 1.7-1.3 (4H, br, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(syn) = 213.4 (CO), 149.2 (ArC), 147.4 (ArC), 126.7 (ArCH), 123.4 (ArCH), 70.3 (CH), 56.9 (CH), 42.6 (CH_2), 27.7 (CH_2), 26.1 (CH_2), 24.9 (CH_2); δ(anti) = 214.1 (CO), 148.6 (ArC), 147.8 (ArC), 127.9 (ArCH), 123.4 (ArCH), 74.0 (CH), 57.3 (CH), 42.6 (CH_2), 30.8 (CH_2), 27.6 (CH_2), 24.7 (CH_2); HPLC: AD-H column, hexane/^{i}PrOH (95:5) as solvent system, flow rate 0.5 mL/min, detection at 254 nm, retention times syn = 54.8 (minor) and 69.0 min (major), retention times anti = 77.5 (minor) and 108.9 min (major); *ee* syn: 21% anti: 87%.

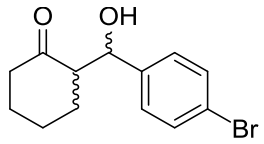
(2S,1'R)-and (2S,1'S)-2-[1'-Hydroxy-1'-phenylmethyl]cyclohexanone 38b/39b



Obtained as a white solid in 79% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ(syn) = 7.4-7.2 (5H, m, ArH), 5.39 (1H, d, *J* = 2.2 Hz, *syn*-CHOH), 4.78 (1H, d, *J* = 8.8 Hz, *anti*-CHOH), 4.1-4.0 (1H, br, OH), 2.7-2.6 (1H, m, CH), 2.5-2.3 (2H, m, CH), 2.1-2.0 (1H, m, CH), 1.8-1.5 (5H, m, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 214.7 (CO), 141.5 (ArC), 128.1 (ArCH), 126.9 (ArCH), 125.7 (ArCH), 70.6 (CH), 57.2 (CH), 42.6 (CH2), 27.9 (CH_2), 26.0 (CH_2), 24.9 (CH_2); *m*/*z*(ES^+) 227 ($M+Na^+$, 45), 226 (100), 201 (85); Found (ES^+) 431.2185 and 227.1032, $C_{26}H_{32}O_4Na$ $(2M+Na)^+$ requires 431.2185, $C_{13}H_{16}O_2Na$

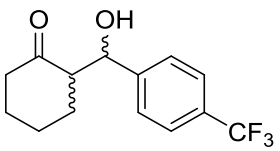
$(M+Na)^+$ requires 227.1048; HPLC: AD-H column, hexane/^{i}PrOH (90:10) as solvent system, flow rate 0.5 mL/min, detection at 220 nm, retention times syn = 15.5 (major) and 18.0 min (minor), retention times anti = 24.6 (major) and 22.7 min (minor); *ee* syn: 68% anti: 93%.

(2S,1'R)-and(2S,1'S)-2-[1'-Hydroxy-1'-(4-bromophenyl)methyl]-cyclohexanone 38c/39c



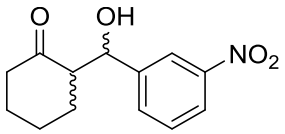
Obtained as a white solid in 76% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ(syn) = 7.46 (2H, d, *J* = 8.4 Hz, ArH), 7.19 (2H, d, *J* = 8.3 Hz, ArH), 5.33 (1H, d, *J* = 2.0 Hz, *syn*-CHOH), 4.74 (1H, d, *J* = 8.7 Hz, *anti*-CHOH), 4.0-3.5 (1H, br, OH), 2.6-2.4 (2H, m, CH), 2.4-2.3 (1H, m, CH), 2.1-2.0 (1H, m, CH), 1.9-1.4 (5H, m, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(syn) = 214.3 (CO), 140.7 (ArC), 131.2 (ArCH), 127.5 (ArCH),120.5 (ArCBr), 69.1 (CH), 56.8 (CH), 42.6 (CH_2), 30.7 (CH_2), 27.9 (CH_2), 24.9 (CH_2); δ(anti) = 215.2 (CO), 140.0 (ArC), 131.4 (ArCH), 128.7 (ArCH), 121.7 (ArCBr), 74.1 (CH), 57.3 (CH), 42.6 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 24.7 (CH_2); *m*/*z*(ES^+) 591 (2(^{81}Br)M+Na^+,50), 589 (2(^{81}Br+^{79}Br)M+Na^+ , 100), 587 (2(^{79}Br)M+Na^+ , 50), 454 (95), 347 (60), 185 (90); Found (ES^+) 589.0390, $C_{26}H_{30}O_4$ ^{79}Br^{81}BrNa $(2M+Na)^+$ requires 589.0390; HPLC: AD-H column, hexane/^{i}PrOH (90:10) as solvent system, flow rate 0.5 mL/min, detection at 220 nm, retention times syn = 27.6 (minor) and 32.3 min (major), retention times anti = 45.9 (minor) and 54.6 min (major); *ee* syn: 66% anti: 80%.

(2S,1'R)-and(2S,1'S)-2-[1'-Hydroxy-1'-(4-trifluorophenyl)methyl]-cyclohexanone 38d/39d



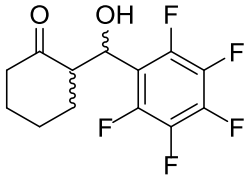
Obtained as a white solid in 55% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ(syn) = 7.59 (2H, d, *J* = 8.5 Hz, ArH), 7.42 (2H, d, *J* = 7.9 Hz, ArH), 5.44 (1H, br, CHOH), 3.09 (1H, br, OH), 2.6-2.5 (1H, m, CH), 3.1-2.3 (2H, m, CH), 2.2-2.0 (1H, m, CH), 1.9-1.5 (5H, m, CH); δ(anti) = 7.61 (2H, d, *J* = 8.3 Hz, ArH), 7.44 (2H, d, *J* = 7.6 Hz, ArH), 4.84 (1H, d, *J* = 8.6 Hz, CHOH), 4.02 (1H, br, OH), 2.6-2.5 (1H, m, CH), 3.1-2.3 (2H, m, CH), 2.1-2.0 (1H, m, CH), 1.9-1.5 (5H, m, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(syn) = 214.5 (CO), 145.7 (ArC), 129.1 (q, *J* = 40.5 Hz, CF_3), 126.2 (ArCH), 125.3 (ArCH), 120.0 (q, *J* = 4.2 Hz, $ArCCF_3$), 70.3 (CH), 57.0 (CH), 42.7 (CH_2), 27.9, (CH_2), 26.0 (CH_2), 24.9 (CH_2); δ(anti) = 215.2 (CO), 145.1 (ArC), 130.2 (q J 40.4 Hz, CF_3), 127.5 (ArCH), 125.4 (ArCH) 122.5 (q, *J* = 4.5 Hz, $ArCCF_3$), 74.3 (CH), 57.3 (CH), 42.7 (CH_2), 30.8 (CH_2), 27.8 (CH_2), 24.8 (CH_2); ^{19}F NMR (400 MHz, $CDCl_3$): δ(syn) -77.8(s); δ(anti) - 78.0(s); *m*/*z*(ES^+) 273 (MH^+, 100); Found (ES^+) 273.1112, $C_{14}H_{16}O_2F_3$ MH^+ requires 273.1102; HPLC: AD-H column, hexane/^{i}PrOH (90:10) as solvent system, flow rate 0.5 mL/min, detection at 254 nm, retention times syn = 14.4 (minor) and15.8 min (major), anti = 21.0 (minor) and 25.7 min (major); *ee* syn: 38% anti: 67%.

(2S,1'R)-and(2S,1'S)-2-[1'-Hydroxy-1'-(3-nitrophenyl)methyl]-cyclohexanone 38e/39e



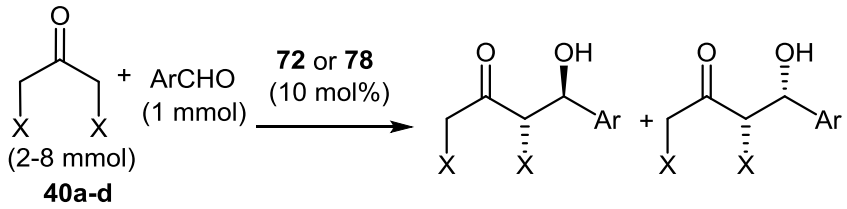
Obtained as a yellow oil in 20% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ(syn) = 8.2-8.1 (2H, m, ArH), 7.67 (1H, d, *J* = 7.7 Hz, ArH), 7.52 (1H, t, *J* = 7.9 Hz, ArH), 5.47 (1H, d, *J* = 2.0 Hz, CHOH), 3.16 (1H, br, OH), 2.7-2.6 (1H, m, CH), 2.5-2.3 (2H, m, CH), 2.2-2.0 (1H, m, CH), 1.9-1.5 (5H, m, CH); δ(anti) = 8.2-8.1 (2H, m, ArH), 7.67 (1H, d, *J* = 7.7 Hz, ArH), 7.52 (1H, t, *J* = 7.9 Hz, ArH), 4.89 (1H, d, *J* = 8.5 Hz, CHOH), 4.10 (1H, br, OH), 2.7-2.6 (1H, m, CH), 2.5-2.3 (2H, m, CH), 2.2-2.1 (1H, m, CH), 1.9-1.5 (5H, m, CH); *m*/*z*(ES^+) 521 ($2M+Na^+$, 100), 454 (30), 347 (25), 226 (60); Found (ES^+) 521.1887, $C_{26}H_{30}N_2O_4Na$ $(2M+Na)^+$ requires 521.1900; HPLC: AD-H column, hexane/^{i}PrOH (95:5) as solvent system, flow rate 0.5 mL/min, detection at 254 nm, retention times syn = 53.1 (minor) and 58.4 min (major), retention times anti = 67.1 (major) and 86.2 min (minor); *ee* syn: 18% anti: 87%.

(2S,1'R)-2-[1'-Hydroxy-1'-pentafluorophenyl)methyl]-cyclohexanone 39f



Obtained as a white solid in 83% yield. Mp 99-101 ºC; $[\alpha]_D^{20}$ = -19.0 (c = 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.26 (1H, d, *J* = 9.6 Hz, CHOH), 4.00 (1H, br, OH), 3.0-2.9 (1H, m, CH), 2.6-2.5 (1H, m, CH), 2.1-2.0 (1H, m, CH), 1.9-1.7 (2H, m, CH), 1.7-1.5 (3H, m, CH), 1.3-1.2 (1H, m, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 214.0 (CO),145.2 (ddd, *J* = 311.6, 10.5, 4.9 Hz, *ortho*-ArCF), 140.8 (dtt, J = 317.9,16.8, 6.5 Hz, *para*-ArCF), 137.5 (dtt, *J* = 316.1, 15.8, 4.8 Hz, *meta*-ArCF), 113.7 (td, *J* = 19.4, 3.8 Hz, ArC), 65.8 (CH), 54.2 (CH), 42.3(CH_2), 30.1 (CH_2), 27.5 (CH_2), 24.4 (CH_2); ^{19}F NMR (400 MHz, $CDCl_3$): δ = –176.5 (2F, d, *J* = 21.1 Hz *ortho*-CF), –192.6 (1F, t, *J* = 23.6 Hz, *para*-CF), –201.9 (2F, br, *meta*-CF); *m*/*z*(ES^+) 317 ($M+Na^+$, 12), 270 (20), 258 (30), 226 (70), 185 (100); Found (ES^+) 317.0573, $C_{13}H_{11}F_5O_2Na$ $(M+Na)^+$ requires 317.0577; HPLC: AD-H column, hexane/^{i}PrOH (88:12) as solvent system, flow rate 0.5 mL/min, detection at 210 nm, retention times anti = 12.9 (major) and 15.9 min (minor); *ee* anti: 90%.

4.2.2 Aldol reactions between ketones and 4-nitrobenzaldehyde catalysed by phenylalanine (72) and tryptophan (78).



Ar = 4-$O_2NC_6H_4$

a: X-X = CH_2OCH_2; b: X-X = $CH_2CH(^tBu)CH_2$; c: X-X = CH_2CH_2; d: X = H

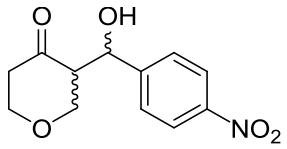
To a mixture of (*S*)-amino acid **72** or **78** (10 mol%) and ketone **40** (2 mmol for acetone and cyclopentanone, 5 mmol for pyranone, and 8 mmol for acetone) was added propylene or ethylene carbonate (1 mL), 4-nitrobenzaldehyde (151 mg, 1 mmol), and H_2O (1 mmol except for reactions involving acetone as substrate when no H_2O was added) under an inert atmosphere. The resulting mixture was stirred at r.t. for 72 hours. The reaction mixture was then poured into H_2O (10 mL) and extracted with Et_2O (10 mL). The organic phase was

washed with H_2O (7 × 10 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The residue at this stage was analysed by ^1H NMR spectroscopy and chiral HPLC to obtain the diasteroselectivity and enantioselectivities. The residue was then purified by column chromatography (gradient from hexane-EtOAc, 9:1 to 1:1) to give the aldol products. All of the aldol products are known compounds and the absolute configuration of the major enantiomer of the aldol products was determined by comparison of the chiral HPLC retention times with literature data.

General procedure for the preparation of racemic samples of compounds 41/42a-d[242]:
To a mixture of *DL*-amino acid **72** or **78** and ketone **40** (2 mmol for acetone and cyclopentanone, 5 mmol for pyranone, and 8 mmol for acetone) was added propylene or ethylene carbonate (1 mL), 4-nitrobenzaldehyde (151 mg, 1 mmol), and H_2O (1 mmol except for reactions involving acetone as substrate when no H_2O was added) under an inert atmosphere. The resulting mixture was stirred at room temperature for 72 hours. The reaction mixture was then poured into H_2O (10 mL) and extracted with Et_2O (10 mL). The organic phase was washed with H_2O (7 × 10 mL), dried (Na_2SO_4), and the solvent removed *in vacuo*.

Characterization Data for compounds 41/42a-d:

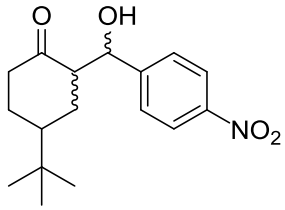
(2S,1'R)-and(2S,1'S)-2-[1'-Hydroxy-1'-(4-nitrophenyl)methyl]4-oxocyclohexanone 41a/42a[243,244]



Obtained as a white solid in 42% yield; $[\alpha]_D^{23}$ = +1.3 (c = 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ(syn) = 8.14 (2H, d, *J* = 8.6 Hz, ArH), 7.50 (2H, d, *J* = 8.6 Hz, ArH), 5.45 (1H, br, CHOH), 4.0-3.7 (2H, m, 2 x CHO), 3.21 (1H, br, OH), 2.7-2.3 (5H, m, CH); δ(anti) = 8.14 (2H, d, *J* = 8.6 Hz, ArH), 7.50 (2H, d, *J* = 8.6 Hz, ArH), 4.93 (1H, d, *J* = 8.1 Hz, CHOH), 4.3-3.7 (4H, m, CH_2OCH_2), 3.43 (1H, t, *J* = 9.8 Hz, CHCO), 3.1-2.3 (3H, m, CH_2CO + OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 147.8, 147.6, 127.5, 123.8, 71.3, 69.8, 68.4, 57.7, 42.8; *m*/*z*(ES^+) 525 ($2M+Na^+$, 15), 454 (60), 413 (60), 347 (100), 306 (90), 263 (100); Found (ES^+) 525.1473, $C_{24}H_{26}N_2O_{10}Na$ ($2M+Na^+$) requires 525.1485; HPLC: AD-H column, hexane/^{i}PrOH (80:20) as solvent system, flow rate 1.0 mL/min, detection at 254 nm, retention

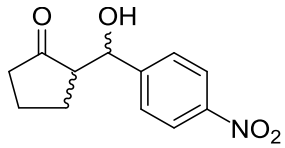
times syn = 31.8 (major) and 38.7 min (minor), retention times anti = 50.3 (minor) and 58.3 min (major); *ee* syn: 41% anti: 65%.

(2S,1'R)-and(2S,1'S)-2-[1'-Hydroxy-1'-(4-nitrophenyl)methyl]4-tert-butylcyclohexanone 41b/42b[245,246,247]



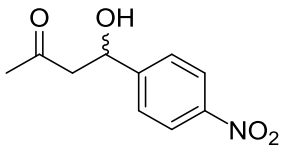
Obtained as a white solid in 40% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ(syn) = 8.15 (2H, d, *J* = 8.4 Hz, ArH), 7.43 (2H, d, *J* = 8.5 Hz, ArH), 5.36 (1H, br, CHOH), 3.08 (1H, br, OH), 2.8-2.6 (1H, m, CH), 2.5-2.0 (3H, m, CH), 2.0-1.4 (4H, m, CH), 0.72 (9H, s, $(CH_3)_3$); δ(anti) = 8.16 (2H, d, *J* = 8.6 Hz, ArH), 7.48 (2H, d, *J* = 8.6 Hz, ArH), 4.92 (1H, d, *J* = 9.0 Hz, CHOH), 3.65 (1H, br, OH), 2.6-2.5 (1H, m, CH), 2.5-2.0 (3H, m, CH), 2.0-1.4 (4H, m, CH), 0.72 (9H, s, $(CH_3)_3$); *m*/*z*(ES^+) 305 (M^+, 10), 257 (40), 185 (100); Found (ES^+) 305.1627, $C_{17}H_{23}NO_4$ (M^+) requires 305.1627; HPLC: AD-H column, hexane/^{i}PrOH (85:15) as solvent system, flow rate 1.0 mL/min, detection at 254 nm, retention times anti = 9.0 min (major) and 17.8 (minor); *ee* anti: 31%.

(2S,1'R)-and(2S,1'S)-2-[1'-Hydroxy-1'-(4-nitrophenyl)methyl]cyclopentanone 41c/42c[248,249,250,251,252]



Obtained as an orange solid in 70% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ(syn) = 8.21 (2H, d, *J* = 8.9 Hz, ArH), 7.51 (2H, d, *J* = 8.4 Hz, ArH), 5.42 (1H, br, CHOH), 2.70 (1H, br, OH), 2.5-2.0 (4H, m, CH), 2.0-1.4 (3H, m, CH); δ(anti) = 8.21 (2H, d, *J* = 8.9 Hz, ArH), 7.53 (2H, d, *J* = 8.9 Hz, ArH), 4.84 (1H, d, *J* = 9.1 Hz, CHOH), 4.78 (1H, br, OH), 2.5-2.0 (3H, m, CH), 2.0-1.4 (4H, m, CH). HPLC: AS-H column, hexane/^{i}PrOH (85:15) as solvent system, flow rate 0.8 mL/min, detection at 254 nm, retention times syn = 29.6 (major) and 63.7 min (minor), retention times anti = 32.7 (minor) and 43.5 min (major); *ee* syn: 66% anti: 83%.

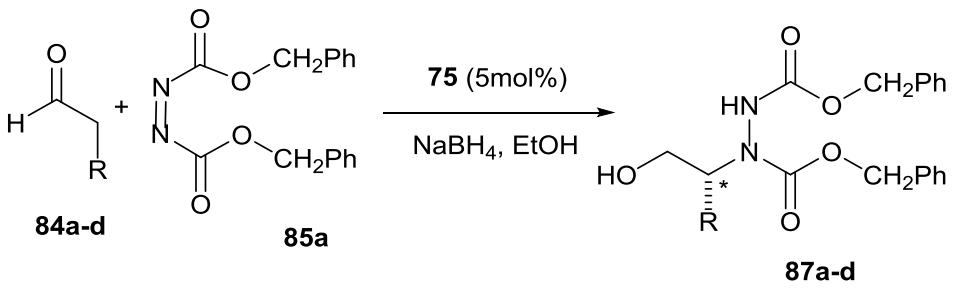
(*R*)-4-Hydroxy-4-(4-nitrophenyl)-2-butanone 41d[253,254,255]



Obtained as yellow crystals in 12% yield. Mp 59-61°C; $[\alpha]^{20}_D$ = +45.7 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.21 (2H, d, *J* = 8.8 Hz, ArH), 7.54 (2H, d, *J* = 8.4 Hz, ArH), 5.27 (1H, m, CHOH), 3.58 (1H, d, *J* = 3.2 Hz, OH), 2.8-2.9 (2H, m, CH_2CHOH), 2.22 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.5, 149.9, 147.4, 126.4, 123.8, 68.9, 51.5, 30.7; HPLC: AS-H column, hexane/^{i}PrOH (70:30) as solvent system, flow rate 0.5 mL/min, detection at 254 nm, retention times = 22.3 (major) and 27.4 min (minor). *ee*: 76%.

4.3 Experimental for Aminations

4.3.1 General procedure for the synthesis of alcohols 25



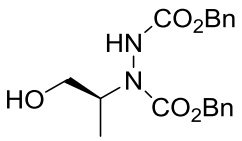
a: R = Me; **b:** R = $C_7H_{15;}$ **c:** R = CH_2Ph; **d:** R = $CHMe_2$

To a stirred solution of dibenzyl azodicarboxylate (**85a**, 298.0 mg, 1.0 mmol) and an aldehyde **84a-d** (1.5 mmol) in ethylene carbonate (3 mL) was added (*S*)-serine, (5.3 mg, 0.05 mmol). The reaction was stirred at room temperature for 24 hours, then quenched by the addition of H_2O (5 ml), extracted with Et_2O (20 ml), washed with further H_2O (4 × 10 mL), and dried with anhydrous Na_2SO_4. The solvent and excess of aldehyde were removed by evaporation *in vacuo*. The residue was then treated with ethanol (10 mL) and $NaBH_4$ (40.0 mg, 1.05 mmol) and stirred for 10 minutes at room temperature. The reaction was then worked up with aqueous ammonium chloride solution (10 mL) and

ethyl acetate (20 mL). The organic layer was separated, dried with Na_2SO_4 and the solvent evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with hexane: ethyl acetate (85: 15) to give alcohols **87a-d**. The HPLC retention times of the enantiomeric products were determined using racemic samples of compounds **87a-d** which were prepared from reactions catalysed by (*R*,*S*)-proline in dichloromethane or propylene carbonate at room temperature.

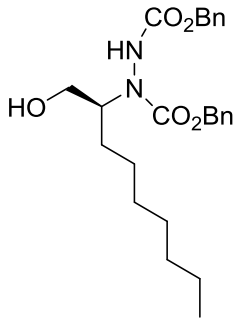
Characterization Data for compounds 87a-d:

Dibenzyl (*R*)-1-(1-methyl-2-hydroxyethyl)hydrazine-1,2-dicarboxylate 87a[256]



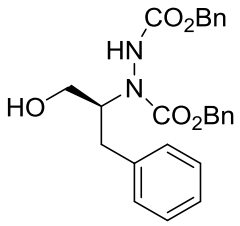
Obtained as a yellow oil in 10% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.85 (d, *J* = 6.9 Hz, 3H, CH_3), 3.4-3.5 (m, 2H, CH_2OH), 4.0-4.5 (m, 2H, CH + OH), 4.9-5.2 (m, 4H, 2 x CH_2Ph), 7.0-7.4 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.5, 56.4, 63.6, 68.0, 128.5, 128.6, 128.9, 129.0, 135.8, 136.3, 157.0, 159.0. ν_{max} (neat) 3271 br, 2955 s, 1715 cm^{-1} s; $[\alpha]_D^{20}$ = -32.0 (c = 0.4, $CHCl_3$); HPLC: Chiralpak AS-H using hexane: ^{i}PrOH (95:5) as solvent at a flow rate of 0.5 mL/min, retention times 22.2 (major) 24.7 (minor) minutes.

Dibenzyl (*R*)-1-(1-heptyl-2-hydroxyethyl)hydrazine-1,2-dicarboxylate 87b[257]



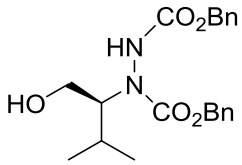
Obtained as a colorless oil in 10% yield. ν_{max} (neat) 3267 br, 2963 s, 1716 cm^{-1} s; $[\alpha]_D^{20}$ = -26.0 (c = 0.4, $CHCl_3$); m/z(ES^+) 465 ($M+Na^+$, 10), Found (ES^+) 465.2348, $C_{25}H_{34}N_2O_5Na$, ($M+Na^+$) requires 465.2365; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.7-0.9 (m, 3H, CH_3), 1.0-1.4 (m, 12H, $Me(CH_2)_6$), 3.2-3.5 (m, 2H, CH_2OH), 4.0-4.4 (m, 2H, OH + CH), 5.0-5.2 (m, 4H, 2xCH_2Ph), 6.9 (s, 1H, NH) 7.0-7.4 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.9, 22.5, 26.0, 27.9, 29.0, 29.3, 31.6, 60.8, 62.1, 68.2, 127.7, 128.0, 128.1, 128.2, 128.4, 128.5, 135.3, 135.9, 157.4, 159.1; HPLC: Chiralpak AS-H using hexane: ^{i}PrOH (95:5) as solvent at a flow rate of 0.5 mL/min, retention times 39.4 (major) and 69.1 (minor) minutes.

Dibenzyl (*R*)-1-(1-benzyl-2-hydroxyethyl)hydrazine-1,2-dicarboxylate 87c



Obtained as a white solid in 10% yield. Mp 105-106 °C; νmax (neat) 3272 br, 2963 s, 1716 cm^{-1} s; $[\alpha]_D^{20}$ = +11.1 (c = 0.9, $CHCl_3$); m/z(ES^+) 443 ($M+Na^+$, 50), 863 ($2M+Na^+$), 1283 ($3M+Na^+$); Found (ES^+) 443.1550, $C_{24}H_{24}N_2O_5Na$, ($M+Na^+$) requires 443.1583; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.4-2.7 (m, 2H, CH_2Ph), 3.3-3.6 (m, 2H, CH_2OH), 4.4-4.6 (m, 2H, OH+CH),4.9-5.2(m, 4H, 2 x OCH_2Ph), 6.8-7.4 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 68.0, 68.3, 128.2, 128.5, 128.7, 128.8, 128.9, 129.0, 129.1, 129.2, 129.4, 135.1, 135.7, 137.3, 156.7, 158.8; HPLC: Chiralpak AS-H using hexane: iPrOH (90:10) as solvent at a flow rate of 0.5 mL/min, retention times 18.2 (minor) and 39.4 (major) minutes. ee: 69%.

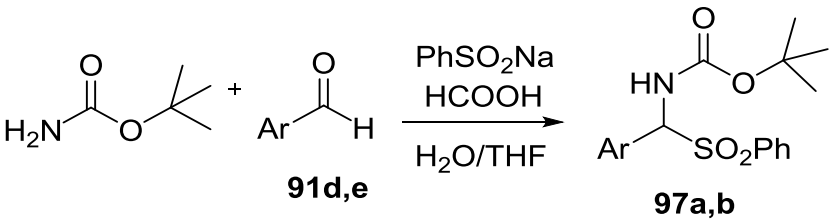
Dibenzyl(*R*)-1-(1-(1-methyl)ethyl-2-hydroxyethyl)hydrazine-1,2-dicarboxylate 87d



Obtained as a yellow oil in 10% yield. ν_{max} (neat) 3272 br, 2963 s, 1716 cm^{-1} s; $[\alpha]_D^{20}$ = -21.0 (c = 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.6-1.0 (m, 6H, 2 x CH_3), 1.4-1.7 (m, 1H, $CHMe_2$), 3.3-4.4 (m, 4H, $NCHCH_2OH$), 4.9-5.2 (m, 4H, 2 x CH_2Ph), 6.8 (s, 1H, NH), 7.1-7.4 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.3, 20.0, 27.5, 60.4, 67.2, 68.4, 127.7, 128.0, 128.1, 128.2, 128.4, 128.6, 135.2, 135.9 , 156.4, 157.4; HPLC: Chiralpak OD-H using hexane ^{i}PrOH (90:10) as solvent at a flow rate of 1.0 mL/min; retention times 14.4 (major) and 17.7 (minor) minutes; *ee*: 96%.

4.4 Experimental for Mannich reactions

4.4.1 General procedure for the preparation of α-amido sulfones[258]



91d,e **97a,b**

d: Ar = $NO_2C_6H_4$; **e**: Ar = Ph

a) Preparation of α-amido sulfone 97a:

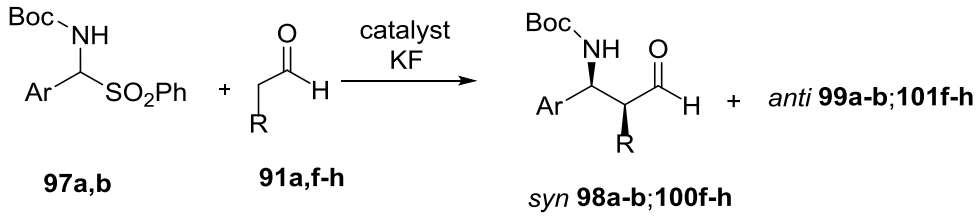
In a 50 mL round bottomed flask tert-butyl carbamate (0.586 g, 5 mmol) was dissolved in a mixture of water and THF (5 mL : 2 mL) and then sodium benzenesulfinate (0.821 g, 5 mmol) was added. To the stirred solution, formic acid (1.2 mL) and *p*-nitrobenzaldehyde (0.756 g, 5.4 mmol) were sequentially added and the reaction mixture was stirred for 18 hours at room temperature. The resulting white precipitate was filtered under vacuum and purified by recrystallisation from hexane/ethyl acetate (4:1). The

product was obtained as a white solid in 92% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.27 (s, 9H, CH_3), 5.77 (d, 1H, J = 9Hz, CH), 6.04 (d, 1H, J = 6Hz, NH), 7.56-7.73 (m, 5H, ArH), 7.95 (d, 2H, J = 8.4 Hz, ArH), 8.28 (d, 2H, J = 8.8 Hz, ArH).

b) Preparation of α-amido sulfone 97b[259]:

In a 50 mL round bottomed flask, tert-butyl carbamate (0.586 g, 5 mmol) was dissolved in a mixture of water and THF (5 mL: 2mL) and then sodium benzenesulfinate (0.821 g, 5 mmol) was added. To the stirred solution, formic acid (1.2 mL) and benzaldehyde (0.55 mL, 5.4 mmol) were sequentially added and the reaction mixture was stirred for 18 hours at room temperature. The resulting white precipitate was filtered under vacuum and purified by recrystallisation from hexane/ethyl acetate (4:1) and recovered by vacuum filtration. The product was obtained as a white solid in 65% yield. Mp 153-154 °C; IR (KBr) ν 3362, 2975, 2495, 1713, 1311, 1146 cm^{-1}; Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.29; H, 6.05; N, 4.07. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.08 (s, 9H, CH_3). 5.56 (d, 1H, *J* = 10.5 Hz, CH), 5.75 (d, 1H, *J* = 12 Hz, NH), 7.20-7.30 (m, 5H, ArH), 7.34-7.50 (m, 3H, ArH), 7.74 (d, 2H, *J* = 7.2 Hz, ArH).

4.4.2 General procedure for the synthesis of β-amino aldehydes.



97: a: Ar = 4-$NO_2C_6H_4$; **b**: Ar = Ph
91: a: Me; **f:** R = C_7H_{15}; **g:** R = CH_2Ph; **h:** R = $CHMe_2$

a) Synthesis of β-amino aldehyde 98a (R=Me)

In a 50 mL round bottomed flask (*S)*-proline (0.023 g, 20 mol%) was dissolved in ethylene carbonate (1.25 mL). To the stirring mixture, α-amido sulfone **97a** (0.098 g, 0.25 mmol) and potassium fluoride (0.073 g, 1.25 mmol) were added. Propionaldehyde **91a** (0.055 mL, 0.75 mmol) was added and the reaction mixture was stirred for 16 hours at 30 ^{o}C. The reaction mixture was quenched with brine (5 mL) and washed with diethyl ether (3 x 25 mL). Next, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography using hexane: ethyl acetate (10:1) as eluent to afford the corresponding aldehyde as a white solid in <5% yield. Mp 127-128 °C; IR (KBr) ν 3379, 2977, 1721, 1683, 1524, 1174 cm^{-1}; Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.30; H, 7.99; N, 5.40. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.09 (d, *J* = 3.2 Hz, 3H, CH_3), 1.46 (s, 9H, CH_3), 2.89 (br s, 1H, NH), 5.1-5.2 (m, 2H, CH), 7.3-7.4 (m, 5H, ArH), 9.74 (s, 1H, C(O)H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.3, 28.3, 51.6, 54.7, 80.1, 125.8, 126.7, 127.7, 128.8, 155.1, 203.0. Enantiomeric excess was determined by chiral HPLC performed with a Chiralpak AS-H column using hexane: ^{i}PrOH (90:10) as solvent at a flow rate of 0.5 mL/min; ee syn: 43%, anti: 48%.

a) Synthesis of β-amino aldehyde 98b (R=Me):[260]

In a 50 mL round bottomed flask (*S)*-proline (0.023 g, 20 mol%) was dissolved in ethylene carbonate (1.25 mL). To the stirring mixture, α-amido sulfone **97b** (0.087 g, 0.25 mmol) and potassium fluoride (0.073 g, 1.25 mmol) were added. Propionaldehyde **91a** (0.055 mL, 0.75 mmol) was added and the reaction mixture was stirred for 16 hours at 30 ^{o}C. The reaction mixture was quenched with brine (5 mL) and washed with diethyl ether (3 x 25 mL). Next, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography using hexane: ethyl acetate (10:1) as eluent to afford the corresponding aldehyde as a white solid in 60% yield. Mp 127-128 °C; IR (KBr) ν 3379, 2977, 1721, 1683, 1524, 1174 cm^{-1}; Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.30; H, 7.99; N, 5.40. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.09 (d, *J* = 3.2 Hz, 3H, CH_3), 1.46 (s, 9H, CH_3), 2.89 (br s, 1H, NH), 5.1-5.2 (m, 2H, CH), 7.3-7.4 (m, 5H, ArH), 9.74 (s, 1H, C(O)H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.3, 28.3, 51.6, 54.7, 80.1, 125.8, 126.7, 127.7, 128.8, 155.1, 203.0. Enantiomeric excess was determined by chiral HPLC performed with a Chiralpak AS-H column using hexane: ^{i}PrOH (95:5) as solvent at a flow rate of 0.5 mL/min; *ee* syn: 67%, anti: 84%.

The reaction was repeated exactly as above using trans-hydroxy-*L*-proline as the catalyst and ethylene carbonate **2** as solvent at 30^{o}C (42% yield); *ee* syn: 85% anti: 85%.

The reaction was repeated exactly as above using *L*-tyrosine as the catalyst and ethylene carbonate **2** as solvent at 30°C (15% yield); *ee* syn: 22% anti: 45%.

b) Synthesis of β-amino aldehyde 100f (R = C_7H_{15}):[261]

In a 50 mL round bottomed flask, (*S*)-proline (0.115 g, 20 mol%) was added to ethylene carbonate (3 mL). To the stirring mixture, α-amido sulfone **97b** (0.434 g, 1.25 mmol) and potassium fluoride (0.363 g, 6.25 mmol) were added. Nonanal **91f** (0.645 mL, 3.75 mmol) was added last and the reaction mixture was stirred for 16hours at 30°C. The reaction mixture was quenched with brine (5 mL) and washed with diethyl ether (3 x 25 ml). Next, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography using hexane: ethyl acetate (10:1) as eluent to afford the corresponding aldehyde as white solid in 40%. HRMS (ESI) calcd for $C_{22}H_{33}NO_3Na$ $(M^+Na)^+$: 382.2358, Found: 382.2382; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59-1.11 (m, 18H, CH_2-CH_3), 1.76- 1.60 (m, 1H, CH), 2.08-1.94 (m, 2H, CH), 2.75-2.63 (m, 1H, CH), 5.02-4.87 (m, 2H, CH), 5.33-5.24 (m, 1H, NH), 5.29 (d, 1H, J = 7.7 Hz, CH), 5.84-5.70 (m, 1H, CH), 7.36-7.19 (m, 5H, Ar-H), 9.57 (d, J = 1.6 Hz, 1H, OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.3, 25.4, 27.2, 28.2, 28.6, 29.2, 33.5, 54.4, 56.7, 76.7, 77.0, 77.3, 79.7, 114.1, 126.7, 127.5, 128.6, 138.8, 139.5, 154.9, 203.5, Enantiomeric excess was determined by chiral HPLC performed with a Chiralpak AS-H column using hexane: ^{i}PrOH (95:5) as solvent at a flow rate of 0.5 mL/min; *ee* syn: 27% anti: 78%.

The reaction was repeated exactly as above using trans-hydroxy-*L*-proline as the catalyst and ethylene carbonate **8** as solvent at 30°C (82% yield). *ee* syn: 64% anti: 83%.

c) Synthesis of β-amino aldehyde 100g (R=CH_2Ph):[4]

In a 50 mL round bottomed flask, (*S*)-proline (0.115 g, 20 mol%) was added to ethylene carbonate (3 mL). To the stirring mixture, α-amido sulfone **97b** (0.434 g, 1.25 mmol) and potassium fluoride (0.363 g, 6.25 mmol) were added. 3-Phenylpropionaldehyde **91g** (0.494 mL, 3.75 mmol) was added last and the reaction mixture was stirred for 16 hours at 30°C. The reaction mixture was quenched with brine (5 mL) and washed with diethyl ether (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*.

The crude product was purified by column chromatography using hexane: ethyl acetate (10:1) as eluent to afford the corresponding aldehyde as white solid in 30% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.4 (s, 9H, $3CH_3$), 2.8 (dd, 1H, *J* = 4.0, 14.1 Hz, CH), 3.0-3.1 (m, 1H, CH), 3.1-3.3 (m, 1H, NH), 5.0-5.3 (m, 1H, CH), 7.09 (d, 2H, *J* = 7.2 Hz, ArH), 7.1-7.2 (m, 1H, ArH), 7.2-7.3 (m, 6H, ArH), 7.3-7.4 (m, 2H, ArH), 9.63 (d, 1H, *J* = 1.5 Hz, OCH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 34.2, 56.7, 59.4, 80.0, 125.9, 126.9, 127.6, 128.3, 128.9, 129.1, 140.5, 141.5, 156.5, 202.8; Enantiomeric excess was determined by chiral HPLC performed with a Chiralpak AS-H column using hexane: ^{i}PrOH (95:5) as solvent at a flow rate of 0.5 mL/min; *ee* syn: 62% anti: 98%.

The reaction was repeated exactly as above using trans-hydroxy-*L*-proline as the catalyst and ethylene carbonate **8** as solvent at 30^{o}C (36% yield). *ee* syn: 27% anti: 83%.

d) Synthesis of β-amino aldehyde 100h (R= $CHMe_2$):[262]

In a 50 mL round bottomed flask, (*S*)-proline (0.115 g, 20 mol%) was added to ethylene carbonate (3 mL). To the stirring solution; α-amido sulfone **97b** (0.434 g, 1.25 mmol) and potassium fluoride (0.363 g, 6.25 mmol) were added. 3-Methylbutyraldehyde **91h** (0.406 mL, 3.75 mmol) was added last and the reaction mixture was stirred for 16 hours at 30^{o}C. The reaction mixture was quenched with brine (5 mL) and washed with diethyl ether (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography using hexane: ethyl acetate (10:1) as eluent to afford the corresponding aldehyde as bright yellow oil in 39% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.96 (d, *J* = 7.1 Hz, 3H, CH_3), 0.98 (d, *J* = 9.6, 3H, CH_3), 1.34 (d, *J* = 5.5 Hz, 9H, CH_3), 2.76 (m, 1H, CH), 4.80 (s, 1H, NH), 5.11 (s, 1H, CH), 7.1-7.2 (m, 2H, ArH), 7.2-7.3 (m, 1H, ArH), 7.27 (d, *J* = 5.7 Hz, 1H, ArH), 7.31 (dd, *J* = 3.6, 2.1 Hz, 1H, ArH), 9.59 (d, *J* = 3.0 Hz, 1H, OCH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.5, 141.5, 140.5, 129.1, 128.9, 128.3, 127.6, 126.9, 125.9, 80.0, 59.4, 56.7, 48.6, 34.2, 28.3. Enantiomeric excess was determined by chiral HPLC performed with a Chiralpak AS-H column using hexane: ^{i}PrOH (95:5) as solvent at a flow rate of 0.5 mL/min; *ee* syn: 46% anti: 26%.

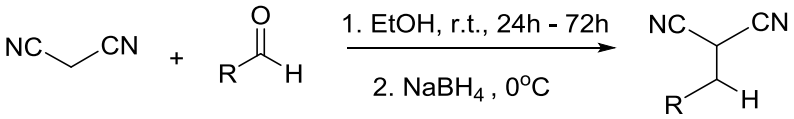
The reaction was repeated exactly as above using trans-hydroxy-*L*-proline as the catalyst and ethylene carbonate **8** as solvent at 30^{o}C (65% yield). *ee* syn: 28% anti: 21%.

Racemic adducts were prepared by Mannich reaction of the corresponding aldehyde **91** (3.75 mmol) and α-amido sulfone **97** promoted by catalyst *DL*-proline (0.115 g, 20 mol%) using $CHCl_3$ (3 mL) as solvent at room temperature for 16 hours, following the same procedure as above for the synthesis of β-amino aldehydes **98-101**.

4.5 Experimental for Michael additions

4.5.1 Synthesis of monosubstituted malononitriles

One-Pot Reductive Alkylation of Malononitrile with Aromatic Aldehydes; General Procedure[263]



a: R=Ph; **b:** R=4-$MeOC_6H_4$; **c:** R=4-BrC_6H_4;
d: R=4-ClC_6H_4; **e:** R=3-ClC_6H_4; **f:** R=2-ClC_6H_4;
g: R=4-$NO_2C_6H_4$; **h:**4-$F_3CC_6H_4$; **i:**F_5C_6

Malononitrile (661 mg, 10 mmol) was dissolved in 95% EtOH (10 mL) and to this solution was added the appropriate aromatic aldehyde (10 mmol). The solution was stirred at room temperature until precipitation was complete or overnight.[264] Additional EtOH (20 mL) was added and the mixture cooled to 0 °C in an ice bath. $NaBH_4$ (169 mg, 5 mmol) was introduced to the vigorously stirred mixture and the reduction was complete in about 20 min.

Extraction method workup: To the reaction mixture was added H_2O (50 mL) and CH_2Cl_2 (25 mL), followed by aq 1.0 M HCl until all hydride was quenched. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated via rotaryevaporation and then under high vacuum, and purified via recrystallization.

Characterization Data for monosubstituted malononitrile is reported in the literature with compounds showing the identical published spectroscopy data.

Benzylmalononitrile [265]

The general procedure was followed using malononitrile (0.667g, 10.09 mmol), benzaldehyde (1.071 g, 10.09 mmol), and $NaBH_4$ (0.196 g, 5.18 mmol) to afford a white solid; yield: 1.538 g (98%); Mp 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4-7.3 (m, 5 H, Ph), 3.90 (t, *J* = 7.0 Hz, 1 H, CH), 3.29 (d, *J* = 7.0 Hz, 2 H, CH_2).

(4-Methoxybenzyl)malononitrile [6]

The general procedure was followed using malononitrile (0.682 g, 10.3 mmol), 4-methoxybenzaldehyde (1.388 g, 10.2 mmol), and $NaBH_4$ (0.193 g, 5.10 mmol) to afford a white solid; yield: 1.799 g (94%); Mp 88-89.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 3.86 (t, *J* = 7.0 Hz, 1 H), 3.82 (s, 3 H), 3.24 (d, *J* = 7.0 Hz, 2 H).

(4-Bromobenzyl)malononitrile [266]

The general procedure was followed using malononitrile (1.321 g, 20 mmol), 4-bromobenzaldehyde (3.700 g, 20 mmol), and $NaBH_4$ (0.3785 g, 10 mmol) to afford a white solid; yield: 4.432 g (94%); Mp 96-97.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 3.94 (t, *J* = 6.6 Hz, 1 H), 3.23 (d, *J* = 6.6 Hz, 2 H).

(4-Chlorobenzyl)malononitrile [7]

The general procedure was followed using malononitrile (0.660 g, 10 mmol), 4-chlorobenzaldehyde (1.411 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol) to afford a white solid; yield: 1.831 g (96%); Mp 62-63.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.1 Hz, 2 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 3.92 (t, *J* = 6.7 Hz, 1 H), 3.27 (d, *J* = 6.7 Hz, 2 H).

3-Chlorobenzylmalononitrile [267]

The general procedure was followed using malononitrile (1.321 g, 20 mmol), 3-chlorobenzaldehyde (2.814 g, 20 mmol), and $NaBH_4$ (0.377 g, 10 mmol) to afford an oil; yield: 3.322 g (87%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.18 (m, 4 H), 3.95 (t, *J* = 7.6 Hz, 1 H), 3.23 (d, *J* = 7.6 Hz, 2 H).

2-Chlorobenzylmalononitrile [268]

The general procedure was followed using malononitrile (0.660 g, 10 mmol), 2-chlorobenzaldehyde (1.405 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol) to afford an oil; yield: 1.792 g (94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.32 (m, 4 H), 4.11 (t, *J* = 8.0 Hz, 1 H), 3.46 (d, *J* = 8.0 Hz, 2 H).

(4-Nitrobenzyl)malononitrile [7]

The general procedure was followed using malononitrile (0.660 g, 10 mmol), 4-nitrobenzaldehyde (1.51 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol) to afford a white solid; yield: 1.94 g (96%); Mp 156-155.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 4.05 (t, *J* = 6.8 Hz, 1 H), 3.43 (d, *J* = 6.8 Hz, 2 H).

(4-(Trifluoromethyl)benzyl)malononitrile[268]

The general procedure was followed using malononitrile (0.660 g, 10 mmol), 4-trifluorobenzaldehyde (1.74 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol) to afford a white solid; yield: 2.30 g (51%); Mp 78-79.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, 2 H, *J* = 8.1 Hz, Ph), 7.48 (d, 2H, *J* = 8.1 Hz, Ph), 3.96 (t, 1H, *J* = 13.5 Hz, CH), 3.36 (d, 2H, *J* = 6.6 Hz, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 139.7, 130.4, 124.4, 111.5, 36.0, 24.4. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -62.7.

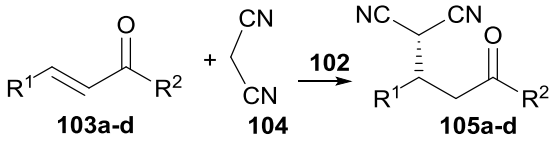
(2,3,4,5,6-Pentafluorobenzyl)malononitrile[269,13]

The general procedure was followed using malononitrile (0.660 g, 10 mmol), 2,3,4,5,6-pentafluorobenzaldehyde (1.51 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol) to afford a white solid; yield: 0.73 g (60%); Mp 95-96.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03 (t, 1H, *J* = 15.6 Hz, CH), 3.49 (d, 2H, *J* = 7.8 Hz, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 140.5, 137.0, 114.6, 113.0, 22.8, 20.9. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -140.8, -150.3, -159.2.

General procedure for the preparation of racemic samples of compounds 105a-d and 108a-i

Enone **103a-d** (0.2 mmol) and DABCO (5.0 mg, 0.04 mmol) were dissolved in MeOH (2 mL). Malononitrile **104** or **107a-i** (0.24 mmol) was added and the reaction mixture was stirred at 20 °C for 20 h. The solvent was then removed *in vacuo* and the residue recrystallized from Et_2O to give racemic samples of compounds **105a,b,d** and **108a-i**. Compound **105c** is an oil and was used without purification.

4.5.2 General procedure for the Michael addition of malononitrile to enones 103a-c



103a-d **104** **105a-d**

a: R^1=R^2=Ph; **b**: R^1=4-ClC_6H_4, R^2=Ph;
c: R^1=4-$MeOC_6H_4$, R^2=Ph; **d:** R^1=Ph, R^2=Me

Enone **103a-c** (0.2 mmol) and quinine (12.9 mg, 0.04 mmol) were dissolved in diethyl carbonate (3 mL). Malononitrile **104** (66.7 mg, 1.0 mmol) was added and the reaction mixture stirred at 18 or -20°C for 20-72 hours. The solvent was then removed in vacuo and the residue directly purified by flash chromatography (petroleum ether/Et_2O, 90/10) to give compound **105a-c**. The enantiomeric excess of compounds **105a-c** was determined by chiral HPLC using a Chiralpak AD-H column (hexane/^{i}PrOH 80:20 as solvent system, 1.0 mL/min, detection at λ=254 nm).

Enone **103d** (0.2 mmol) and quinine (12.9 mg, 0.04 mmol) were dissolved in diethyl carbonate (3 mL). Malononitrile **104** (16 mg, 0.24 mmol) was added and the reaction mixture stirred at -20°C for 72 h. The solvent was then removed in vacuo and the residue recrystallized from Et_2O to give compound **105d** (19.5 mg, 46%) as a white solid. The enantiomeric excess of compound **105d** was determined to be 10% by chiral HPLC using a Chiralpak AS-H column (hexane/^{i}PrOH 70:30 as solvent system, 1.0 mL/min, λ=254 nm).

Characterization Data for compounds 105a-d.

(*S*)-2-Cyano-3,5-diphenyl-5-oxo-pentanonitrile (105a)[270]

Obtained as a white solid (53.7 mg, 98%) with 64% enantiomeric excess (t_R = 8.8 (minor) and 11.0 (major) minutes); Mp 109-113 ^oC (lit 109-111 ^oC); $[\alpha]_D^{20}$ = -3.0 (c = 0.30, $CHCl_3$); ν_{max} 3048, 2984, 2911, 2400 and 1627 cm^{-1}; m/z (ESI) Found 297.1004, $C_{18}H_{14}N_2ONa$ $(M+Na)^+$ requires 297.0998; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.99 (2H, d, *J* = 8.6 Hz, ArH), 7.64 (1H, t, *J* = 7.4 Hz, ArH), 7.6-7.4 (7H, m, ArH), 4.67 (1H, d, *J* = 5.0 Hz, CHCN), 3.97 (1H, dt, *J* = 8.4, 5.3 Hz, PhCH), 3.74 (1H, dd, *J* = 18.4, 8.3 Hz, CH_2); 3.66 (1H, dd, *J* = 18.6, 5.6 Hz, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 196.8, 136.6, 135.8, 134.3, 129.4, 129.3, 129.0, 128.2, 128.1, 111.9, 111.8, 41.3, 40.2, 28.9.

(*S*)- 3-(4-Chlorophenyl)-2-cyano-5-phenyl-5-oxo-pentanonitrile (105b)[271]

Obtained as a white solid (55.5 mg, 90%) with 63% enantiomeric excess (t_R = 13.0 (minor) and 17.2 (major) minutes); Mp 124-127 ^oC (lit 124-125 ^oC); $[\alpha]_D^{20}$ = -2.2 (c = 0.30, $CHCl_3$) for sample with 92% *ee*); ν_{max} 2884, 1681 and 1597 cm^{-1}; m/z (ESI) Found 331.0605, $C_{18}H_{13}N_2O^{35}Cl$ Na $(M+Na)^+$ requires 331.0605; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (2H, d, *J* = 7.2 Hz, ArH), 7.65 (1H, t, *J* = 7.4 Hz, ArH), 7.52 (2H, t, *J* = 7.8 Hz, ArH), 7.5-7.4 (4H, m, ArH), 4.64 (1H, d *J* 5.0 Hz, CHCN), 3.96 (1H, dt, *J* = 8.2, 5.4 Hz, PhCH), 3.71 (1H, dd, *J* = 18.5, 8.3 Hz, CH_2); 3.62 (1H, dd, *J* = 18.4, 5.5 Hz, CH_2).

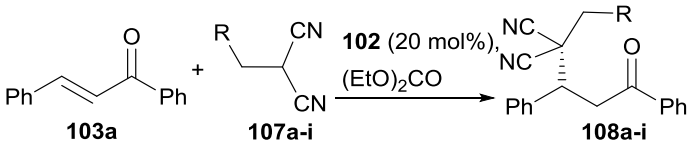
(*S*)- 3-(4-Methoxyphenyl)-2-cyano-5-phenyl-5-oxo-pentanonitrile (105c)[272]

Obtained as a colourless oil (54.7 mg, 90%) with 54% enantiomeric excess (t_R = 9.6 (minor) and 14.2 (major) minutes); $[\alpha]_D^{20}$ = -2.17 (c = 0.30, $CHCl_3$); ν_{max} 3377, 2224, 1731, 1681 and 1581 cm^{-1}; m/z (ESI) Found 327.1102, $C_{19}H_{16}N_2O_2Na$ $(M+Na)^+$ requires 327.1104; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (2H, dd *J* 8.5, 1.4 Hz, ArH), 7.64 (1H, tt, *J* =7.4, 1.4 Hz, ArH), 7.51 (2H, t, *J* = 7.3 Hz, ArH), 7.38 (2H, d, *J* = 8.7 Hz, ArH), 6.96 (2H, d, *J* = 8.8 Hz, ArH), 4.63 (1H, d, *J* = 5.0 Hz, CHCN), 3.93 (1H, dt, *J* = 8.3, 5.3 Hz, ArCH), 3.83 (3H, s, OCH_3), 3.72 (1H, dd, *J* = 18.4, 8.4 Hz, CH_2); 3.62 (1H, dd, *J* = 18.5, 5.5 Hz, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 196.9, 160.2, 135.9, 134.3, 129.3, 129.0, 128.5, 128.2, 114.7, 112.1, 111.8, 55.4, 40.7, 40.3, 29.2.

(*S*)-2-Cyano-3-phenyl-5-methyl-5-oxo-pentanonitrile (105d)

Obtained as a white solid (19.5 mg, 46%) with 10% enantiomeric excess (t_R = 8.8 (minor) and 11.0 (major) minutes); Mp 109-113 ^oC; $[\alpha]_D^{20}$ -3.0 (c = 0.30, $CHCl_3$) (lit28 $[\alpha]_D^{25}$ -12.5 (c = 0.20, $CHCl_3$)); ν_{max} 3048, 2984, 2911, 2400 and 1627 cm^{-1}; m/z (ESI) Found 297.1004, $C_{18}H_{14}N_2ONa$ $(M+Na)^+$ requires 297.0998; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.99 (2H, d J 8.6 Hz, ArH), 7.64 (1H, t J 7.4 Hz, ArH), 7.6-7.4 (7H, m, ArH), 4.67 (1H, d J 5.0 Hz, CHCN), 3.97 (1H, dt J 8.4, 5.3 Hz, PhCH), 3.74 (1H, dd J 18.4, 8.3 Hz, CH_2); 3.66 (1H, dd J 18.6, 5.6 Hz, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 206.2, 135.8, 134.3, 129.4, 128.1, 111.9, 111.8, 41.3, 40.2, 28.9.

4.5.3 General procedure for the Michael addition of α-substituted malononitriles 107a-i to chalcone 103a

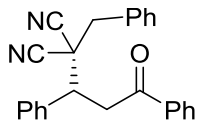


a: R=Ph; **b:** R=4-BrC_6H_4; **c:** R=4-ClC_6H_4; **d:** R=3-ClC_6H_4; **e:** R=2-ClC_6H_4; **f:** R=4-$O_2NC_6H_4$; **g:** R=4-$MeOC_6H_4$; **h:** R=4-$F_3CC_6H_4$; **i:** R=4-C_6F_5

Trans-chalcone **103a** (41.6 mg, 0.2 mmol) and quinine (12.9 mg, 0.04 mmol) were dissolved in diethyl carbonate (3 mL). α-Substituted malononitrile **107a-i** (0.24 mmol) was added and the reaction mixture was stirred at 18 to -30 °C for 24-72 h. The solvent was then removed in vacuo and the residue recrystallized from Et_2O to give compounds **108a-i.** The enantiomeric excess of compounds **108a-i** was determined by chiral HPLC using a Chiralpak AD-H column (hexane/^{i}PrOH 80:20 as solvent at a flow rate of 1 mL/min, detection at 254 nm).

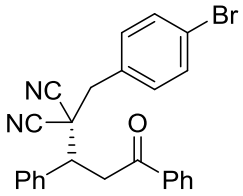
Characterization Data for compounds 108a-i:

(*S*)-4,4-Dicyano-1,3,5-triphenylpentan-1-one (108a)[273]



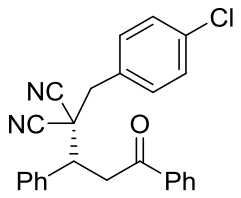
Obtained as pale yellow solid (69.9 mg, 96%) with 30% enantiomeric excess from a reaction at 18 ºC for 24 h (t_R = 9.6 (minor) and 24.4 (major) minutes). Mp 119-124ºC; $[\alpha]^{23}_D$ = - 10.2 (c = 1, $CHCl_3$); ν_{max} 3030, 2981, 2390, 1690 cm^{-1}; m/z (ESI) Found 387.1469, $C_{25}H_{20}N_2ONa$ $(M+Na)^+$ requires 387.1468; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (2H, dd, *J* = 8.5, 1.4 Hz, ArH), 7.7-7.3 (13H, m, ArH), 4.2-4.0 (2H, m, CH_2CO + CHPh), 3.8-3.6 (1H, m, CH_2CO), 3.06 (1H, d, *J* = 13.7, $PhCH_2$), 2.85 (1H, d, *J* = 13.6, $PhCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 195.1, 136.0. 135.7, 133.8, 132.2, 130.1, 129,2, 129.1, 128.94, 128.87, 128.8, 128.7, 128.1, 115.3, 114.4, 47.3, 45.2, 42.4, 41.4.

(*S*)-5-(4-Bromophenyl)-4,4-dicyano-1,3-diphenylpentan-1-one (108b)



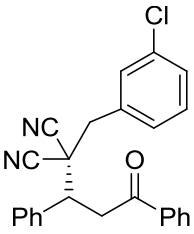
Obtained as yellow solid (86.8 mg, 98%) with 91% enantiomeric excess from a reaction at -20 ºC for 72 h (t_R = 13.7 (minor) and 27.5 (major) minutes). Mp 172-177 ºC; $[\alpha]^{23}_D$ = -2.4 (c = 1, $CHCl_3$); ν_{max} 3030, 2981, 2400 and 1700 cm^{-1}; m/z (ESI) Found 467.0599, $C_{25}H_{19}N_2O^{81}BrNa$ $(M+Na)^+$ requires 467.0553; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (2H, d, *J* = 8.5 Hz, ArH), 7.6-7.2 (10H, m, ArH), 7.20 (2H, d, *J* = 8.4 Hz, ArH), 4.2-4.0 (2H, m, CH_2CO + CHPh), 3.73 (1H, dd, *J* = 23.0, 8.9 Hz, CH_2CO), 3.03 (1H, d, *J* = 13.7, $ArCH_2$), 2.80 (1H, d, *J* = 13.7, $ArCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 195.0, 136.5, 135.9, 133.7, 132.2, 131.8, 131.4, 129.3, 129.2, 129.1, 128.8, 128.1, 123.3, 115.2, 114.3, 47.7, 45.1, 42.1, 41.7.

(*S*)-5-(4-Chlorophenyl)-4,4–dicyano-1,3-diphenylpentan-1-one (108c)



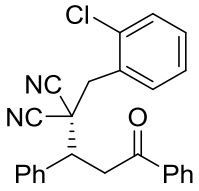
Obtained as white solid (26.3 mg, 33%) with 24% enantiomeric excess from a reaction at -20 ^{o}C for 72 h (t_R = 8.8 (minor) and 16.7 (major) minutes). Mp 129-132 ^{o}C; $[\alpha]^{23}_{D}$ = -8.8 (c = 1, $CHCl_3$); ν_{max} 3030, 2981, 2390 and 1688 cm^{-1}; m/z (ESI) Found 420.9902, $C_{25}H_{19}N_2O^{35}ClNa$ $(M+Na)^+$ requires 421.1078; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (2H, dd, *J* = 8.5, 1.5 Hz, ArH), 7.6-7.3 (12H, m, ArH), 4.2-4.0 (2H, m, CH_2CO + CHPh), 3.77 (1H, dd, *J* = 15.7, 1.1 Hz, CH_2CO), 3.36 (1H, d, *J* = 14.0, $ArCH_2$), 3.08 (1H, d, *J* = 14.0, $ArCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 195.1, 136.6, 136.0, 135.4, 133.6, 131.6, 130.3, 130.1, 129.2, 129.1, 128.8, 128.1, 127.3, 115.2, 114.4, 48.0, 44.1, 41.6, 38.7.

(*S*)-5-(3-Chlorophenyl)-4,4–dicyano-1,3-diphenylpentan-1-one (108d)



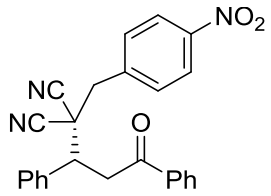
Obtained as yellow solid (71.7 mg, 90%) with 27% enantiomeric excess from a reaction at -20 ^{o}C for 72 hours (t_R = 9.8 (minor) and 19.6 (major) minutes). Mp 130-132 ^{o}C; $[\alpha]^{23}_{D}$ = -8.4 (c = 0.5, $CHCl_3$); ν_{max} 3030, 2981, 2390 and 1690 cm^{-1}; m/z (ESI) Found 421.1106, $C_{25}H_{19}N_2O^{35}ClNa$ $(M+Na)^+$ requires 421.1078; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (2H, d, *J* = 7.6 Hz, ArH), 7.7-7.2 (12H, m, ArH), 4.2-4.0 (2H, m, CH_2CO + CHPh), 3.8-3.6 (1H, m, CH_2CO), 3.03 (1H, d, *J* = 13.7, $ArCH_2$), 2.81 (1H, d, *J* = 13.8, $ArCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 194.9, 136.0, 135.4, 134.7, 134.1, 133.8, 130.2, 130.1, 129.3, 129.2, 129.1, 128.9, 128.8, 128.3, 128.1, 115.1, 114.1, 47.4, 44.9, 41.9, 41.5.

(*S*)-5-(2-Chlorophenyl)-4,4–dicyano-1,3-diphenylpentan-1-one (108e)



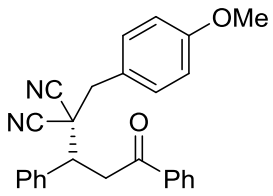
Obtained as white solid (47.0 mg, 90%) with 22% enantiomeric excess from a reaction at -20 ºC for 72 hours (t_R = 10.3 (minor) and 24.6 (major) minutes). Mp 161-165 ºC; $[\alpha]^{23}_D$ = +1.6 (c = 1, $CHCl_3$); ν_{max} 3030, 2981, 2390 and 1665 cm^{-1}; m/z (ESI) Found 420.9701, $C_{25}H_{19}N2O^{35}ClNa$ $(M+Na)^+$ requires 421.1078; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (2H, d, *J* = 7.3 Hz, ArH), 7.7-7.2 (12H, m, ArH), 4.2-4.0 (2H, m, CH_2CO + CHPh), 3.73 (1H, dd, *J* = 22.5, 8.2 Hz, CH_2CO), 3.03 (1H, d, *J* = 13.7, $ArCH_2$), 2.81 (1H, d, *J* = 13.8, $ArCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 194.9, 136.0, 135.5, 135.0, 133.8, 131.5, 130.6, 129.3, 129.2, 129.1, 128.9, 128.8, 128.1, 115.1, 114.2, 47.3, 45.1, 41.7, 41.5.

(*S*)-4,4-Dicyano-5-(4-nitrophenyl)-1,3-diphenylpentan-1-one (108f)



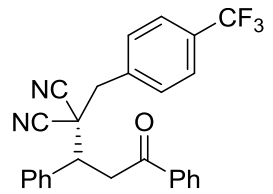
Obtained as orange solid (79.3mg, 97%) with 45% enantiomeric excess from a reaction at 18 ºC for 24 hours (t_R = 24.6 (minor) and 36.6 (major) minutes). Mp 140-146 ºC; $[\alpha]^{23}_D$ = -6.0 (c = 1, $CHCl_3$); ν_{max} 3030, 2981, 2340 and 1687 cm^{-1}; m/z (ESI) Found 432.1355, $C_{25}H_{19}N_3O_3Na$ $(M+Na)^+$ requires 432.1319; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (2H, d, *J* = 8.8 Hz, ArH), 7.96 (2H, d, *J* = 8.5 Hz, ArH), 7.7-7.3 (10H, m), 4.2-4.0 (2H, m, CH_2CO + CHPh), 3.75 (1H, dd, *J* = 16.3, 1.9 Hz, CH_2CO), 3.17 (1H, d, *J* = 13.6, $ArCH_2$), 2.93 (1H, d, *J* = 13.6, $ArCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 194.8, 148.2, 139.3, 135.9, 135.2, 133.9, 131.2, 129.4, 129.3, 128.9, 128.8, 128.1, 124.1, 114.8, 113.8, 47.5, 44.7, 41.9, 41.5.

(*S*)-4,4-Dicyano-5-(4-methoxyphenyl)-1,3–diphenylpentan-1-one (108g)



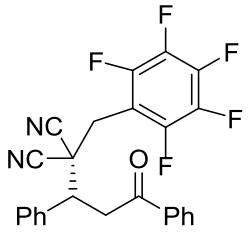
Obtained as yellow solid (74.8 mg, 95%) with 86% enantiomeric excess from a reaction at -20 ºC for 72 hours (t_R = 12.1 (minor) and 32.7 (major) minutes). Mp 167-169 ºC; $[\alpha]^{23}_D$ = +2.6 (c = 1, $CHCl_3$); ν_{max} 3030, 2981, 2350 and 1690 cm^{-1}; m/z (ESI) Found 418.1643, $C_{26}H_{22}N_2O_2Na$ $(M+Na)^+$ requires 417.1573; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (2H, d, *J* = 8.5 Hz, ArH), 7.7-7.3 (8H, m, ArH), 7.27 (2H, d, *J* = 8.6 Hz, ArCH), 6.92 (2H, d, *J* = 8.7 Hz, ArH), 4.2-4.0 (2H, m, CH_2CO + CHPh), 3.82 (3H, s, OCH_3), 3.8-3.7 (1H, m, CH_2CO), 3.06 (1H, d, *J* = 13.8, $ArCH_2$), 2.84 (1H, d, *J* = 13.8, $ArCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 195.1, 159.9, 136.0, 135.7, 133.7, 131.3, 129.2, 129.0, 128.9, 128.8, 128.1, 124.1, 115.5, 114.5, 114.2, 55.2, 47.1, 45.6, 41.7, 41.4.

(*S*)-4,4-Dicyano-1,3-diphenyl-5-(4-trifluoromethylphenyl) pentan-1-one (108h)



Obtained as white solid (5.2 mg, 6%) with 1% enantiomeric excess from a reaction at 18 ºC for 24 hours (t_R = 12.2 (minor) and 16.7 (major) minutes). Mp 146-148 ºC; $[\alpha]^{23}_D$ = -5.2 (c = 1, $CHCl_3$); ν_{max} 3030, 2981, 2390 and 1690 cm^{-1}; m/z (ESI) Found 455.1375, $C_{26}H_{19}N_2OF_3Na$ $(M+Na)^+$ requires 455.1342; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (2H, d, *J* = 7.3 Hz, ArH), 7.7-7.3 (12H, m, ArH), 4.2-4.0 (2H, m, CH_2CO + CHPh), 3.73 (1H, dd, *J* = 25.0, 10.3 Hz, CH_2CO), 3.12 (1H, d, *J* = 13.6, $ArCH_2$), 2.89 (1H, d, *J* = 13.6, $ArCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 195.0, 136.5, 136.3, 135.8, 133.7, 131.4 (q, *J* = 33.0 Hz), 130.7, 129.4, 129.3, 129.1, 128.9, 128.1, 125.9 (q, *J* = 3.5 Hz), 47.8, 45.0, 42.3, 41.7; ^{19}F NMR (400 MHz, $CDCl_3$): δ = -62.7.

(*S*)-4,4-Dicyano-5-(pentafluorophenyl)-1,3-diphenylpentan-1-one (108i)



Obtained as white solid (72.6 mg, 80%) with 25% enantiomeric excess from a reaction at -20 ºC for 72 hours (t_R = 12.1 (minor) and 18.9 (major) minutes). Mp 139-143 ºC; $[\alpha]^{23}_D$ = -9.2 (c = 1, $CHCl_3$); ν_{max} 3030, 2981, 2390 and 1690 cm^{-1};); m/z (ESI) Found 477.0988, $C_{25}H_{15}N_2OF_5Na$ $(M+Na)^+$ requires 477.0997; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (2H, d, *J* = 7.3 Hz, ArH), 7.7-7.3 (8H, m, ArH), 4.3-4.0 (2H, m, CH_2CO + CHPh), 3.75 (1H, dd, *J* = 16.8, 2.0 Hz, CH_2CO), 3.28 (1H, d, *J* = 14.4, $ArCH_2$), 3.03 (1H, d, *J* = 14.4, $ArCH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 194.7, 144.9, 135.8, 135.0, 133.9, 129.5, 129.0, 128.8, 128.6, 128.5, 128.1, 122.1, 114.4, 113.5, 113.0, 47.7, 43.0, 41.5, 30.1; ^{19}F NMR (400 MHz, $CDCl_3$): δ = -159.7 (2F, tt, *J* = 17.8, 12.0 Hz), -150.8 (1F, t, *J* = 22.0 Hz), -137.9 (2F, dd, *J* = 25.5, 11.6 Hz).

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