Design, synthesis and evaluation of organocatalysts in 1,4-conjugate additions to nitroolefins and alkylidene malonates

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By

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Declaration

This is to certify that the material presented in this thesis has not been submitted previously for a Degree to this or any other university. All material presented, except where acknowledged and cited, is the original work of the author.

Declan Peter Patrick Gavin

Declan Gavin

National University of Ireland, Maynooth February 2012

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Dedication

To my parents, Andy and Kay, with love.

Thank you for everything

Abstract

A family of cinchona-based and thiourea pyrrolidine-based organocatalysts were synthesised and fully characterised. Their catalytic activity and selectivity in 1,4-conjugate additions involving the Michael acceptor, nitrostyrene, was evaluated. Thiourea catalysts based upon the cinchona alkaloid framework were found to exhibit excellent activity and enantioselectivity (up to 95% yield and 97% *ee*) at loadings of 10 mol% when 1,3-diketones were employed as the pronucleophile. This result demonstrated that a thiourea cinchona catalyst was much more efficient at catalysing this Michael addition than previously reported. The same thiourea organocatalysts were employed in the first successful Michael addition of the sterically challenging dipivaloylmethane to β-nitrostyrene. Thiourea catalysts based upon the pyrrolidine motif were also employed in the Michael addition of cyclohexanone to nitrostyrene, furnishing up to 97% yield and 48% *ee* .

The organocatalysed conjugate addition reactions involving less activated Michael acceptors, such as α,β-unsaturated diesters, ketones and acrylate esters was also investigated. Although these acceptors are challenging substrates and are considerably less reactive than nitrostyrene, we herein report the first organocatalytic Michael addition to an α,β-unsaturated diester using a H-bonding bifunctional catalyst. These thiourea catalysts were excellent promoters of the Michael addition of acetylacetone to dimethyl ethylidenemalonate and the yields were high (up to 99%) for all of the catalysts tested. Other Michael donors, such as nitromethane and malononitrile, were also successfully employed as nucleophiles in Michael additions to α,β-unsaturated diesters, with yields and enantioselectivities of up to 88% and 48% respectively.

Additionally, a family of β-substituted aminoacrylates were synthesised. Ethyl-3-(dimethylamino)acrylate proved to be a good Michael acceptor in the 1,4-conjugate addition of phenyllithium (64% yield). Variable temperature NMR spectroscopy was used to analyse the restricted rotation about the C-N bond in these aminoacrylates. The barrier to rotation about the C-N bond was calculated for a series of compounds. The effect of the steric bulk associated with the various N-substitutions had on the barrier to rotation was evaluated using Charton values.

List of abbreviations

Ac	Acetyl
Ar	Aryl
br	Broad
^{t}Bu	*tert*-Butyl
Boc	*tert*-Butyloxycarbonyl
$CDCl_3$	Deuterated chloroform
cm	Centimetre
cm^{-1}	Wavenumbers
d	Doublet
DCM	Dichloromethane
°C	Degrees Celsius
dd	Doublet of doublets
d.e.	Diastereomeric excess
δ	Chemical shift
dm	decimetre
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimenthy sulfoxide
d_6-DMSO	Deuterated dimethyl sulfoxide
dt	Doublet of triplets
ee	Enantiomeric excess
ESI	Electrospray ionisation
EtOAc	Ethyl acetate
EtOH	Ethanol
FTIR	Fourier Transform Infrared
g	gram
h	Hour
HCl	Hydrochloric acid
HOMO	Highest occupied molecular orbital
Hz	Hertz
IR	Infrared
J	Coupling constant
KBr	Potassium bromide
λ	Wavelength (nm)
LC	Liquid chromatography
LC/TOF-MS	Liquid chromatography time-of-flight mass spectrometry
L/min	Litres per minute
LUMO	Lowest unoccupied molecular orbital
M	Molar

m	Multiplet
Me	Methyl
MeOH	Methanol
Me_4Si	Tetramethylsilane
mg	milligram
MHz	Megahertz
min	Minute
mL	Millilitre
mmol	Millimole
m.p.	Melting point
µL	Microlitre
µM	Micromolar
N_2	Dinitrogen
NaCl	Sodium chloride
NaOH	Sodium hydroxide
NMR	Nuclear magnetic resonance
nm	Nanometre
OD	Optical density
OEt	Ethoxide anion
O_2	Molecular oxygen
pH	Logarithmic scale of concentration of hydronium ions ($-\log[H_3O^+]$)
PhMe	Toluene
pK_a	Minus log of association constant K_a of a given solution ($-\log K_a$)
ppm	Parts per million
PSIG	Pounds per square inch gauge
q	Quartet
s	Singlet
t	Triplet
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
UV/vis	Ultraviolet/visible
V	Volts

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1. Introduction

1.1 Introduction

The agrochemical and pharmaceutical industries are fields in which chirality and stereochemical control are of special relevance. Chirality is now a major theme in the design, discovery, development, launching and marketing of new drugs.[1] Stereoselective reactions are therefore of great significance, as the different enantiomers of a compound may have anomalous effects in biological systems. The thalidomide case in the 1960s is a notorious example of this behaviour. The drug was prescribed to pregnant women in Europe to alleviate sickness but, while one enantiomer was an antiemetic, the opposite enantiomer had teratogenic effects.

Two enantiomers of a chiral drug generally differ in pharmacodynamic and/or pharmacokinetic properties as a consequence of the stereoselective interaction with optically active biological macromolecules.[2] Metabolizing enzymes often display a preference for one enantiomer of a chiral drug over the other. The structural characteristics of these enzymes dictate the enantiomeric discrimination associated with the metabolism of chiral drugs.[3] When one stereoisomer is responsible for the biological effect of interest, its paired enantiomer could have a separate activity (desirable or undesirable), be an antagonist of the active compound or it may even be completely inactive. Thus the production of optically active drugs as single enantiomers can be economically desirable, since it could result in the reduction of the total administered dose.[1]

These factors have led to an increasing preference for single enantiomers in the pharmaceutical industry. In 1992 the U.S. Food and Drug Administration (FDA) issued a policy on stereoisomeric drugs encouraging the commercialisation of clinical drugs as single enantiomers. Amongst the strategies available to the synthetic organic chemist for controlling the stereochemical outcome of a reaction, catalysis has become the option of choice in the last 20 years.[1,4,5] Catalytic enantioselective methodologies represent a more direct and atom-economical approach than the use of chiral auxiliaries because the need for stoichiometric amounts of the chirality source and the additional attachment/removal synthetic steps are avoided. In this context, transition-metal complexes and enzymes were traditionally regarded as the two main classes of very efficient asymmetric catalysts.

Biocatalysts have for many years been considered quite limited in their scope due to the extremely high specificity shown by enzymes toward the substrate structure. This situation has improved recently with advances in biotechnology which allow the preparation of customised enzymes from genetically modified organisms.[6] Despite these progressions, enzymes are restricted to "natural" chemical processes and they cannot catalyse the broad spectrum of chemical transformations that transition-metal catalysts make possible, for example in the synthesis of complex natural products.[7]

Metal-catalysed reactions have, in the last 30 years, reached an exceptional level of sophistication.[5] The awarding of the Nobel Prize in 2001 to William S. Knowles, Ryoji Noyori and K. Barry Sharpless for the development of metal-catalysed oxidations and reductions is indicative of the importance of asymmetric catalysis in the chemical sciences. Because of their extraordinary reactivity and selectivity, transition metals are used extensively as catalysts in industry but they are not without their drawbacks. Generally speaking they are expensive and difficult to remove from the reaction products and can therefore often be retained in the isolated product.[8] Due to toxicity concerns, strict guidelines exist for pharmaceutically active ingredients which limit the levels of heavy metals in the drug substance, so their use in the synthesis of the active compound is not ideal.

Accordingly, organocatalysis has emerged as a favourable alternative for the asymmetric construction of bonds. Organocatalysts have several advantages. They are usually robust, inexpensive, non-toxic and readily available.[9] Because of their inertness toward moisture and oxygen, demanding reaction conditions are often not required and, crucially, the preclusion of heavy metals from the reaction mixture makes organocatalytic methods particularly attractive for the preparation of pharmaceutical products. Although the aim of this introduction is to give an overview of the scope of organocatalysis for the modern synthetic chemist and a vast range of chemical transformations have been subjected to stringent experimental scrutiny during the last decade, it is impossible to include reaction type in a review of this nature. The main focus of our own research was the organocatalytic conjuage addition to various Michael acceptors using cinchona-derived hydrogen bonding catalysts. The purpose of this introduction is to provide a backdrop for our research and thus this chapter focusses on the key concepts which encompass our own investigations in the area.

1.2 Historical background of asymmetric organocatalysis

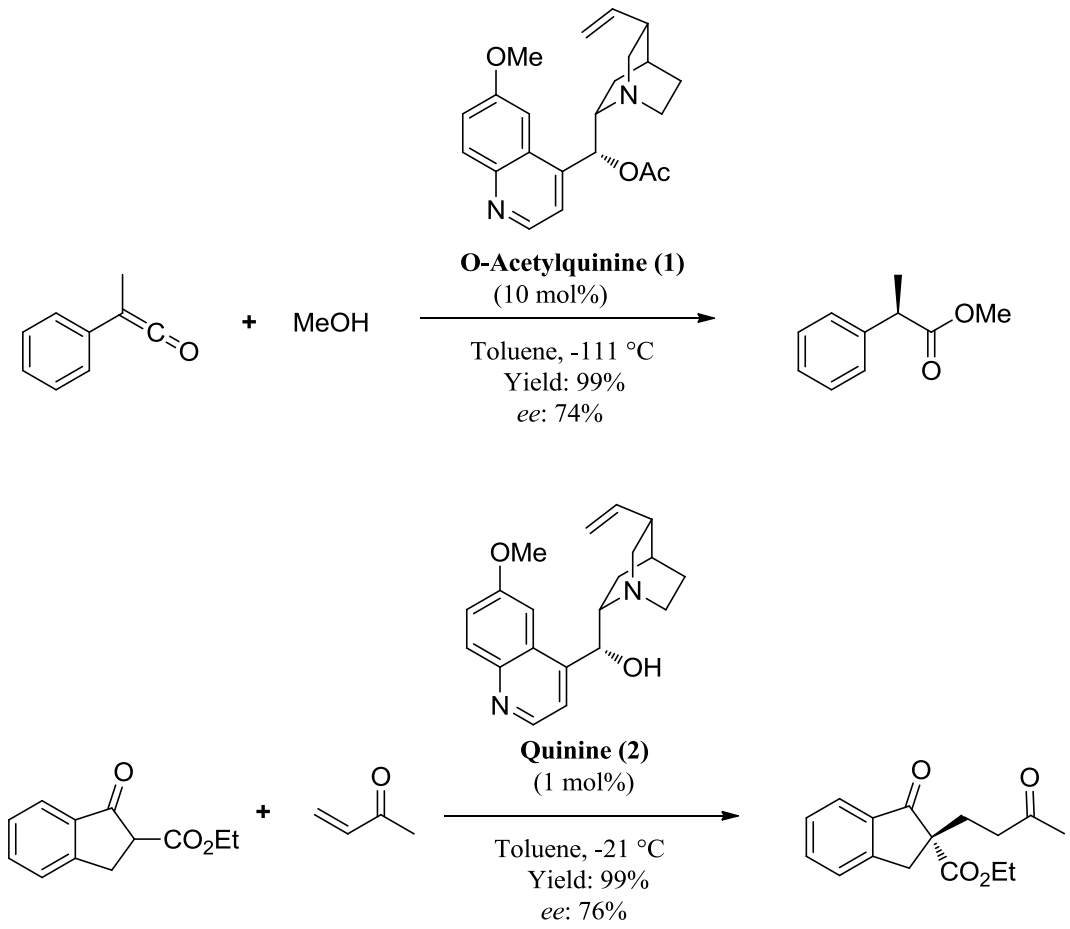
The etymology of the term "organocatalysis" can be traced back to a revolutionary publication by the group of MacMillan in 2000 reporting the amine-catalysed Diels-Alder reaction.[10] Conjoining the words "organic" and "catalysis" was a discerning move since the term is self explanatory – it describes the acceleration of a chemical reaction with a substoichiometric amount of an organic compound which does not contain a metal.[11]

1.2.1 Early development of organocatalytic reactions

Despite only recently being recognised as a valuable alternative to established metal-based methodologies in asymmetric synthesis, organocatalytic reactions look back on a venerable history and can even be considered as a key element in the origins of life. It is widely accepted that this type of catalysis played a determinant role in the formation of prebiotic building blocks, such as sugars, and thus allowed the spread of homochirality in living organisms.[1,11]

The early development of organocatalysis is excellently synopsised in a number of books and publications.[1,12,13] Naturally, the beginnings of organocatalysis occurred when attempting to understand the mechanism of enzymatic transformations with a small chiral molecule being intended to mimic enzyme behaviour (the same principle is applied today!). In 1908, George Bredig, who was interested in the origin of enzyme activity, found that the thermal decarboxylation of optically enriched camphorcarboxylic acid in the presence of (+)- or (−)-limonene proceeded with an enhancement of optical purity in the final product.[1] He also studied this reaction in the presence of natural alkaloids like nicotine and actually reported the first enantioselective C-C bond-forming reaction under metal-free conditions. In the process he observed that the addition of HCN to benzaldehyde in the presence of quinine or its pseudoenantiomer quinidine proceeded with some degree of enantioselection.[1] The German chemist Wolfgang Langebeck built upon these pioneering reports, researching the identification and explanation of enzymatic processes. He even published a book in 1949 entitled "Organic Catalysts and their Relations with Enzymes" in which he discussed the methods by which enzymes promote chemical reactions, with enamine-type reactions prominent.[1]

Probably the first organocatalytic, moderately enantioselective asymmetric reaction was reported by Pracejus in 1960, with the addition of methanol to methyl phenyl ketene in the presence of O-acetylquinine (Scheme 1.1).[1] It is significant that 50 years on from this discovery, cinchona alkaloids and their derivatives are still being used to successfully promote asymmetric transformations. Indeed, Wynberg and co-workers subsequently carried out extensive research on the use of these compounds to promote conjugate additions[14,15] and the first example reported by the group, a Michael addition, is also shown in Scheme 1.1. In an affirmation that would have a large bearing on organocatalytic techniques employed in the future, this group also observed that the natural cinchona alkaloids were more active than modified versions derived from functionalisation at the C9 hydroxyl group and they rationalised this by suggesting that the hydroxyl group was involved in activating the electrophile and facilitating its orientation towards attack from the nucleophile, thereby achieving stereocontrol. This is discussed further in detail in section 2.3.4.

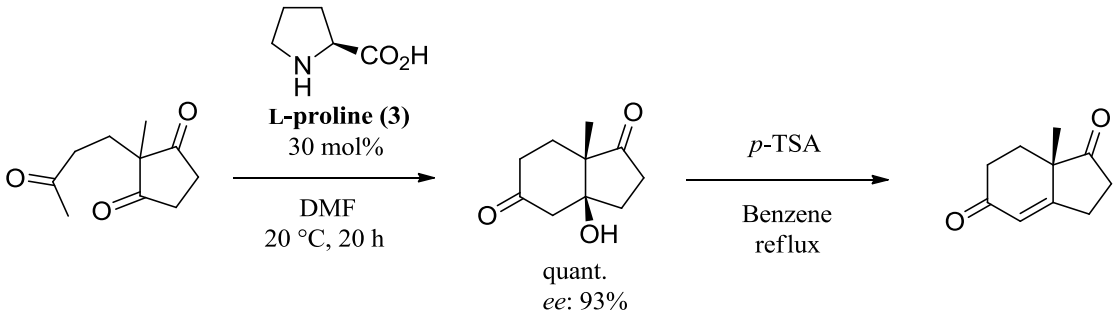


Scheme 1.1: The enantioselective ester synthesis from methyl phenylketene reported by Pracejus (top) and Wynberg's quinine catalysed Michael addition.[1,14,15]

In view of the clear precedent set by Wynberg it is surprising that this field did not witness immediate rapid growth and this is probably due to the fact that, for the following 20 years after this discovery, metal (ion) catalysis undoubtedly became the most vibrant area of research in synthetic chemistry.[16]

1.2.2 The Hajos-Parrish-Eder-Sauer-Wiechert reaction

Another highly significant event in the development of organocatalysis was the discovery of the proline-mediated intramolecular aldol reaction developed in the early 1970s,[17] shown in Scheme 1.2. The so-called Hajos-Parrish-Eder-Sauer-Wiechert reaction described for the first time the concept of a nucleophilic enamine in the catalytic cycle. It was independently developed by two industrial research groups at Hoffmann La Roche and Schering and is built on the foundations of enamine chemistry laid by Stork and Langeback.[18] The reaction is momentous because the simple amino acid, L-proline (Scheme 1.2 below) performs a direct intramolecular aldol addition between two carbonyl compounds (which, interestingly, is a reaction that is central to sugar metabolism),[19] with Hajos and Parrish realising that their "results may be considered an example of a simplified model of a biological system in which proline plays the role of an enzyme".[20]



Scheme 1.2: The Hajos-Parrish-Eder-Sauer-Wiechert reaction.[17]

This chemistry has been used extensively in steroid syntheses and several natural product syntheses and its reinvestigation by List and Barbas in the late 1990s paved the way for the exploration of various related reactions, including enantioselective intermolecular crossed-aldol and Mannich, Michael and Diels-Alder type transformations.[17]

1.2.3 More recent advances

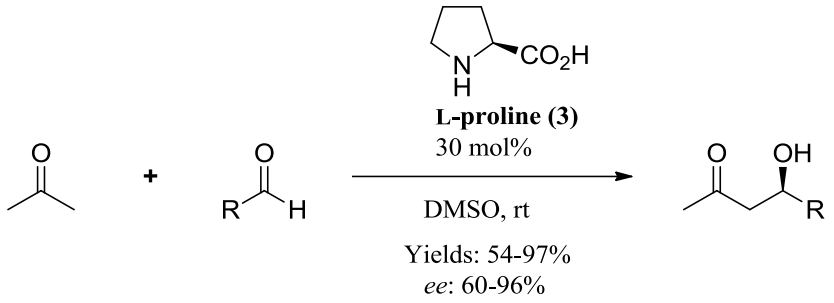
Owing to the aforementioned fervent interest in transition metal-mediated transformations during the intervening period, organocatalysis then suffered a lull in development. It is surprising, for example, that the catalytic potential of L-proline in asymmetric aldol reactions was not explored further at the time of the discovery of the Hajos-Parrish-Eder-Sauer-Wiechert reaction. L-Proline, perhaps the most well-known organocatalyst, is now recognised as a "privileged" compound in asymmetric synthesis (along with the cinchona alkaloids and TADDOL/binapthyl derivatives)[17] in terms of its dexterity and the breadth of reactions it is capable of catalysing, so much so that it has been called a "universal asymmetric catalyst".[20] In hindsight it is likely that organocatalytic transformations such as the Hajos-Parrish reaction were at the time regarded as unique chemical reactions rather than integral parts of a larger, interconnected field.[13]

Regardless of this, some very important events in the historic development of asymmetric organocatalysis did appear between 1980 and the late 1990s. Those worthy of mention include the chiral diketopiperazines developed by Inoue as chiral Brønsted acids for asymmetric hydrocyanation[17] reactions and studies some years later by Lipton[21] and Jacobsen[22] on the Strecker reaction using thiourea and peptide catalysts respectively. Efficient phase-transfer catalysts also appeared during this period when researchers at Merck reported high enantioselection when methylating 2-phenyl-1-indanone derivatives. The ubiquitous cinchona alkaloids were used to catalyse this transformation in the form of substituted *N*-benzylcinchoninium halides (50% NaOH/Toluene).[23,24]

1.2.4 Organocatalysis in its current form

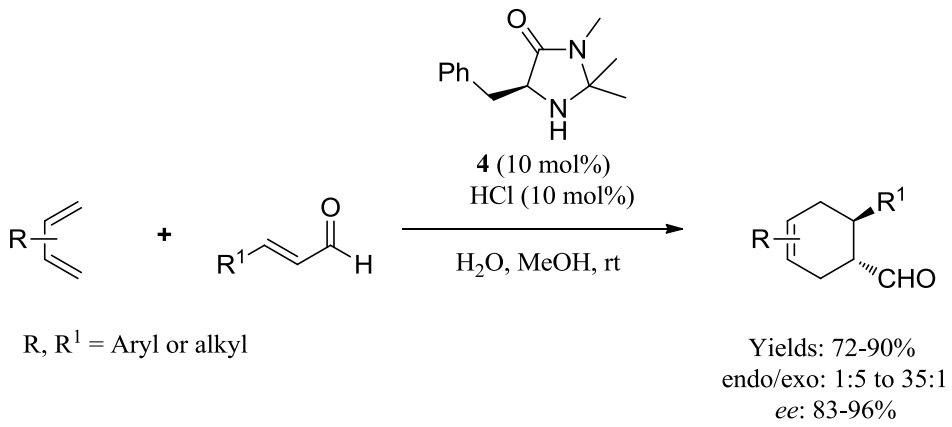
It wasn't until 2000 that Barbas and List reported their illustrious proline-catalysed enantioselective direct intermolecular aldol reaction (Scheme 1.3),[25] the first non-metallic small molecule catalysed example of this transformation. This work was borne out of earlier research using aldolase antibodies as catalysts for the aldol reaction[26] and, when viewed in the context of the breathtaking number of powerful asymmetric bond-forming reactions and stunning cascade reactions that are now accessible via organocatalytic protocols, it is difficult to fathom that this

groundbreaking research took place only little over a decade ago. The reaction itself involved the use of a large excess of the ketone donor (acetone), while the electrophilic aldehyde species tended to be aromatic, although one aliphatic acceptor was reported with high yields and enantioselectivities (isovaleraldehyde).



Scheme 1.3: Barbas and List's landmark reaction in the development of aminocatalysis.[25]

MacMillan's seminal report introducing the concept of iminium catalysis appeared in the same year.[10] This work described the stereoselective Diels-Alder reaction of α,β-unsaturated aldehydes with various dienes. Catalytic quantities of a series of chiral secondary amine.hydrochloride salts were used, of which the imidazolidinone catalyst **4** was the most successful, Scheme 1.4 below. It was in this paper that the term "organocatalysis" was coined by MacMillan as a substitute for the usually employed "metal-free catalysis", bestowing a new name upon a field which had existed for almost 100 years.



Scheme 1.4: MacMillan's seminal work on the iminium ion catalysed Diels-Alder reaction.[10]

These two highly influential publications paved the way for the development of organocatalysis as it is now known, and even the authors themselves could not have predicted the seismic effect that they would have on the art of asymmetric synthesis.

1.3 Types of catalysts

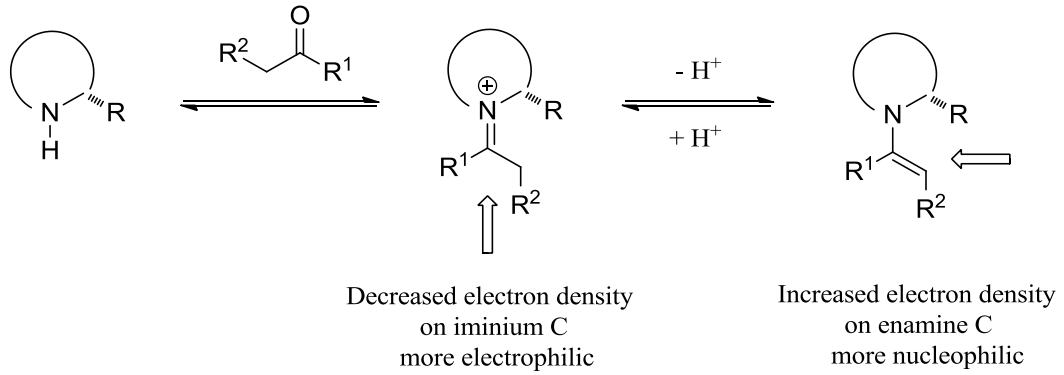
This introduction is ordered according to the different types of reaction being catalysed. Before considering them, it is pertinent to note that there are a limited number of "mechanistic categories" to which all of these reactions can be assigned. Broadly speaking, organocatalysts can be separated into two distinct classes. The first, referred to as "covalent catalysis", concerns processes that involve the formation of covalent adducts between catalyst and substrate(s) within the catalytic cycle. The other class is termed "non-covalent catalysis" and this describes processes which rely on non-covalent interactions such as hydrogen bonding or the formation of ion pairs.[12] It is important to realise that many organocatalysts act through both covalent and noncovalent interactions, using both to effect the reaction. They are known as "bifunctional catalysts" since they can display a dual acid/base character. The mechanistic properties of reactions promoted by covalent and noncovalent catalysts will now be discussed.

1.3.1 Covalent catalysis

Catalysts activating the substrate by forming a covalent bond are among the most widely used and studied types of organocatalysts.[11,27] This method of activation implies that reversible chemical reactions have to be available for (i) attaching of the catalyst to the substrate to allow activation and (ii) detaching the catalyst from the final product to permit catalyst turnover. Since there is a strong substrate-to-catalyst interaction, there is an effective and well-defined influence of the catalyst on the stereochemical outcome of the reaction. The disadvantage of this situation is that it may make catalyst turnover difficult and, to overcome this, high catalyst loadings and long reaction times are often required to achieve good conversion.[1] Chiral amines or aminocatalysts are undoubtedly the autocrats of this group. Four different methods of activation are known using aminocatalysts, all of which involve the reversible formation of an azomethine compound; enamine, iminium ion, iminium-radical cation

(also known as SOMO catalysis) and dienamine activation. Before examining these areas singularly it is necessary to contextualise them by considering the relationship between (secondary) amines and the carbonyl group.

Amine catalysts may give rise to either enamine or iminium ion intermediates (Scheme 1.5);[28] the former results in an increase in electron density at the reaction centre(s) and the latter corresponds to a decrease in electron density at the reaction centre(s). This chemistry is peculiar because of the facile equilibrium between the electron-rich and electron-poor states.



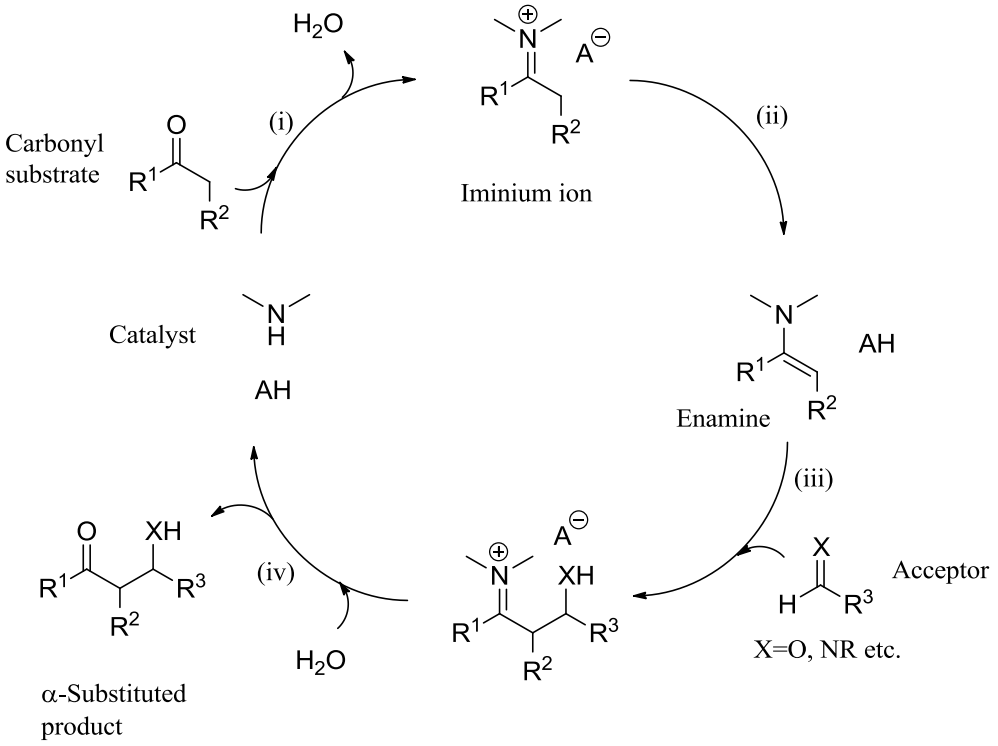
Scheme 1.5: The activation of a carbonyl compound by a secondary amine catalyst, showing iminium ion (centre) and enamine (right) species.[28]

Of course, this means that due to the equilibrium process, the same centre may act as a Lewis acid or a Lewis base, depending on the reaction conditions (since the species have opposite reactivities). Both intermediates are formed in the same mixture but the reaction conditions can dictate their relative concentrations. Through careful choice of reaction conditions, either intermediate may be favoured and this can allow chemical transformations which follow entirely different mechanistic pathways and usually result in different products.[17] The dual reactivity of the intermediates can even manifest itself in a single reaction, promoting transformations *via* enamine and iminium intermediates respectively, in a domino sequence.[29] Both intermediates have contributed handsomely to the development of organocatalysis over the last decade. From an organocatalytic point of view, these intermediates are vehicles to induce enantioselectivity in the chosen reaction and for this catalyst design is the essential component in the construction of a successful, stereoselective methodology. The recent work of Blackmond *et al*.[30] and Seebach and co-workers[31] has shed further light on the exact mechanism of enamine and iminium ion-based systems and this can only

allow organocatlaysis to extend its scope further into chemical transformations which have, heretofore, not been catalysed by purely organic molecules.

1.3.1.1 Enamine catalysis

The catalysis, by primary or secondary amines, of electrophilic substitution reactions at the α-position of carbonyl compounds is called enamine catalysis.[32] A generic example of activation by an enamine-based catalytic cycle is shown in Scheme 1.6. The cycle involves (i) the formation of an iminium ion between a donor carbonyl compound and the amine catalyst, (ii) the formation of an enamine intermediate from the iminium ion, (iii) (asymmetric) C-C bond formation between the enamine and the acceptor substrate and (iv) hydrolysis of the resulting iminium ion to release the product.



Scheme 1.6: The catalytic cycle of an enamine-based system.[32] Reaction arrows may be regarded as equilibria.

The foundation of this form of catalysis is the reversible generation of enamines from a catalytic amount of the chiral amine and a carbonyl compound. Iminium ion formation effectively lowers the LUMO energy of the system, making both nucleophilic additions and α-deprotonation more favourable.[33] Deprotonation leads to formation of

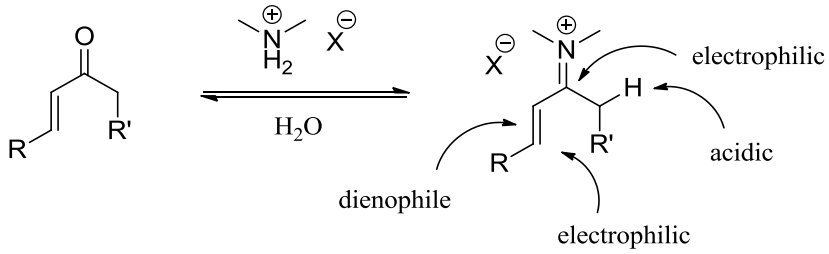
the enamine (increasing the energy of the HOMO), which is the actual nucleophilic carbanion equivalent and its reaction with the acceptor, followed by hydrolysis, provides the enantiomerically enriched product.

Since the beginning of this millennium the field of enamine catalysis has developed into a powerful strategy for asymmetric synthesis. It is one of the most exploited organocatalytic modes of action,[34] allowing the enantioselective α-functionalisation of enolisable aldehydes and ketones with a huge variety of electrophilies.

1.3.1.2 Iminium ion catalysis

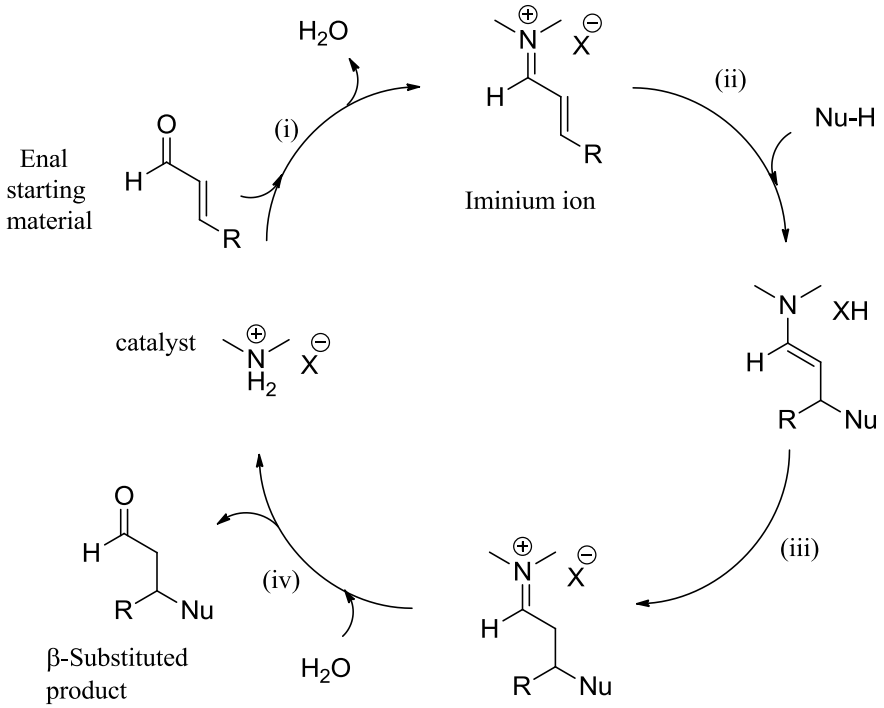
The condensation of aldehydes or ketones with primary amines results in an equilibrium where a considerable amount of imine is present.[35] This reaction was discovered in 1864 by Hugo Schiff. Primary amine derived imines are basic ($pK_a \approx 7$)[36] and they readily exist as iminium ions in solution. Aldehydes and ketones may also condense with secondary amines to form iminium cations, although these can only be isolated as salts of strong acids since deprotonation to form imines is not applicable. Both primary and secondary amines can be used in iminium ion catalysis. Primary amines always require the use of an external acid cocatalyst and this is also very common with secondary amines.[36]

The *in-situ* generation of an iminium ion from a carbonyl compound results in a lowering of the LUMO energy of the system. In this respect it is similar to Brønsted or Lewis acid activation of carbonyl compounds,[33] which is discussed further in section 1.3.2.1**.** These activated compounds exhibit interesting chemical reactivity and because the activation provided by iminium ion formation is very general, many different types of electrophile-nucleophile interactions are possible (Scheme 1.7). This includes nucleophilic additions, attacks by bases (resulting in enamine formation) and retroaldol type processes such as decarboxylation,[36] although iminium ion catalysis is most typically used for cycloadditions and conjugate additions to enals and enones.[33]



Scheme 1.7: The chemical reactivity associated with the iminium ion.

Scheme 1.8 depicts an example of this reactivity, showing the iminium catalytic cycle for the conjugate addition of a nucleophile to an enal. The cycle involves (i) the formation of the iminium ion from the amine catalyst and the enal starting material, (ii) attack of the nucleophile at the *β*-position of the "activated" electrophile, (iii) protonation at the α-position and (iv) hydrolysis of the resulting iminium ion to furnish the product.



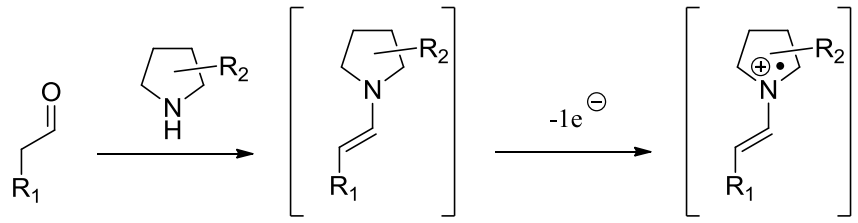
Scheme 1.8: The iminium catalytic cycle**.** Reaction arrows may be regarded as equilibria.

Unquestionably, iminium-ion catalysis has played a key role in the resurgence of metal-free catalysis since the turn of the century. MacMillan and co-workers were the trailblazers in this regard with their iminium-catalysed cycloadditions.[10] In addition, they were the first group to use the term "LUMO-lowering catalysis", the catalytic strategy pertaining to Lewis acids, to describe the iminium mechanistic process. The

generality of this concept and the simplicity of MacMillan's imidazolidinone catalyst family facilitated the discovery of a range of enantioselective iminium ion-catalysed processes, some of which are covered in subsequent sections.

1.3.1.3 SOMO catalysis

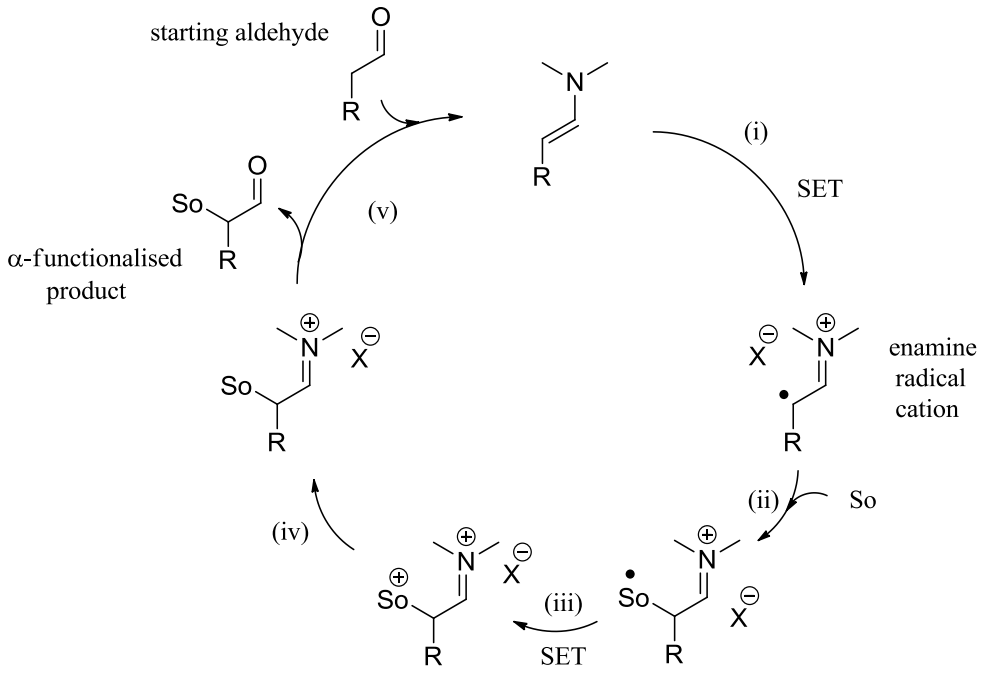
SOMO (Single Occupied Molecular Orbital) catalysis has recently been established in the field of organocatalysis. SOMO catalysis is unlike other amine-driven activation methods as it requires one-electron oxidation of an electron-rich enamine. This selectively generates a reactive cation with three π-electrons (Scheme 1.9 below), thereby providing access to a group of reagents that had not previously been applicable to aminocatalysis.[37]



Scheme 1.9: The concept of SOMO catalysis is based upon the reactivity of the enamine radical ion.[37]

Removal of the electron is normally performed using (up to 2 equivalents of) an oxidising agent such as CAN,[38] $[Ce(ONO_2)_6.(NH_4)_2]$, although it has been recently presented that radical generation can also be carried out using visible light and substoichiometric transition metal photoredox catalysts.[39]

In order for SOMO-catalysed reactions to proceed stereoselectively, the enamine must be more easily oxidised than the corresponding enol, and crucially, this oxidation changes the normal electronic properties of the enamine into those of an electrophile, allowing the direct α-functionalisation of aldehydes. The probable catalytic cycle for this process is shown in Scheme 1.10.[40]



Scheme 1.10 The probable catalytic cycle involving SOMO chemistry (So = somophile). Reaction arrows may be regarded as equilibria.

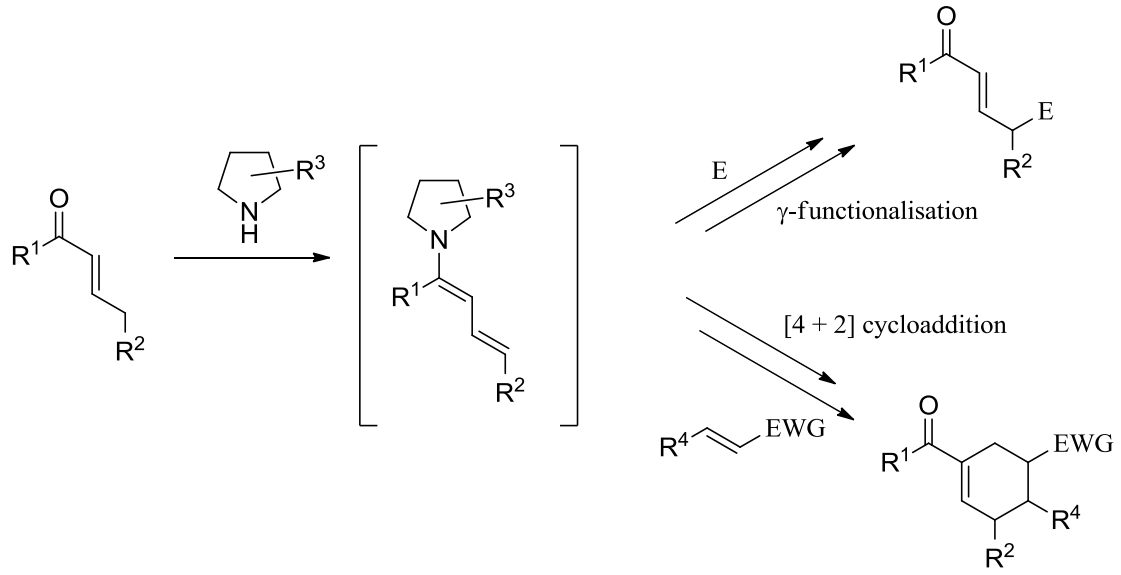
Step (i) involves the oxidation of the enamine to the enamine radical cation (for which there is experimental evidence) *via* a single electron transfer (SET).[41] Step (ii) sees this intermediate react with an electron donor (somophile), which is subsequently oxidised in step (iii). Transformation of the So-group (i.e. proton elimination or nucleophilic addition) occurs in step (iv) which affords the iminium ion and step (v) is simple hydrolysis, furnishing the α-functionalised product and the aminocatalyst.

SOMO activation constitutes an exciting new strategy for organocatalysis. Already, numerous radical-based C-X (X = C, O, N, S, halogen) asymmetric bond-forming reactions have been reported,[42] showing its potential as a vehicle for the stereocselective production of synthons.

1.3.1.4 Dienamine activation

Although dienamines have been utilised as reagents for decades,[43] they have only recently been employed as intermediates in organocatalyic reactions.[40] Introduced as a new organocatalytic technique in 2006 by Jørgensen and co-workers,[44] the dienamine intermediate facilitates nucleophilic character in α,β-unsaturated carbonyl compounds, rather than the customary electrophilic nature associated with these molecules.

Mechanistically it is again a HOMO-raising strategy, with the vinylogous nucleophilicity facilitated via the conjugated π-system (Scheme 1.11).



Scheme 1.11: The reactivity associated with the dienamine intermediate, showing vinylogous nucleophilic attack on an electrophile (E) and the inverse-electron-demand Diels-Alder reaction.

This methodology is finding increasing applications in asymmetric organocatalysis, most notably in asymmetric γ-alkylation,[45] inverse-electron-demand Diels-Alder reactions[46] (also shown in Scheme 1.11) and vinylogous Michael additions.[47] Although in its infancy, some important experimentation has already been conducted using this catalytic methodology and more impressive advances are expected to occur in the following years.

1.3.2 Noncovalent catalysis

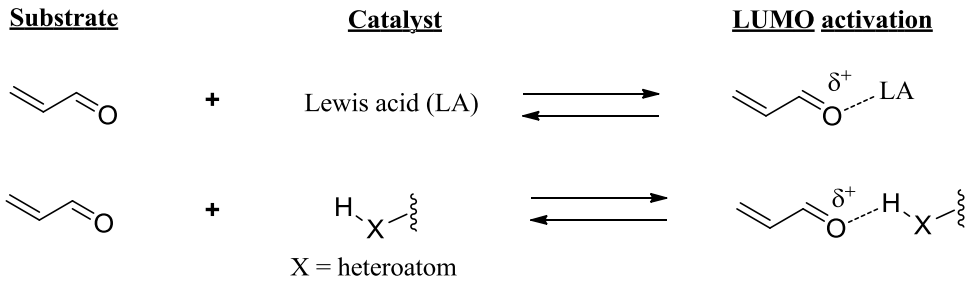
Non-covalent organocatalysts differ from their covalent cousins in that they accelerate chemical transformations through weak interactions. Neutral host-guest complexation and acid-base associations between catalyst and substrate are examples of noncovalent catalytic systems.[17] The former case is very similar to the manner in which many enzymes effect reactions, by bringing together the reactants at an active site and without the formation of covalent bonds. The latter mainly describes hydrogen bond catalysis, in which weak acid-base chiral complexation is responsible for promoting the reaction.

Other important reactions included in this group are those promoted through phase-transfer catalysis,[48,49] which involves the formation of chiral ion pairs and the use of chiral tertiary amines as bases in the activation of a nucleophile by deprotonation, to form a chiral ammonium salt.[50,51] In contrast to covalent catalysis, the weak interactions which define noncovalent catalysis allow for a high catalyst turnover and an advantageous consequence of this is that generally much lower catalyst loadings are needed to accelerate the chemical reaction.

1.3.2.1 Hydrogen bonding catalysis

Hydrogen bonding acts as nature's ubiquitous glue and is responsible for the three-dimensional structures of proteins, nucleic acids and many supramolecular assemblies. It is used in natural catalytic systems (enzymes, ribonucleases, antibodies etc.) to stabilise transition states and thus lower the kinetic barriers to reactions.[52] Recently this weak interaction has been used as a force for promoting chemical reactions. In this context the fast developing metal-free catalysis with small organic molecules has been described as utilising "artificial enzymes" or being "enzyme mimetics".[16] Surprisingly, this approach has long been underappreciated, particularly when one considers that nearly half of all enzymes do not carry a metal centre. A more detailed account of the historical development of H-bonding in asymmetric synthesis is given in section 2.3.4.

Metal based (or metal-ion based) Lewis acidic additives have long been used to activate an electrophilic component in a reaction and and these catalysts have proven to be extremely effective tools for the promotion of chemical transformations. However, only recently have chemists begun to utilise the simplest Lewis acid, the proton, in this respect. In general, the dramatic improvements in both rate and selectivity are ascribable to a lowering of the LUMO and in this respect H-bonding catalysis is comparable to metal-ion catalysis (Scheme 1.12). Both systems operate on the simple principle; once "bound" to an electrophile, they serve to decrease the electron-density of the species, thus activating it toward nucleophilic attack.



Scheme 1.12: Analogous activation of an electrophile via a Lewis acid and a hydrogen bond

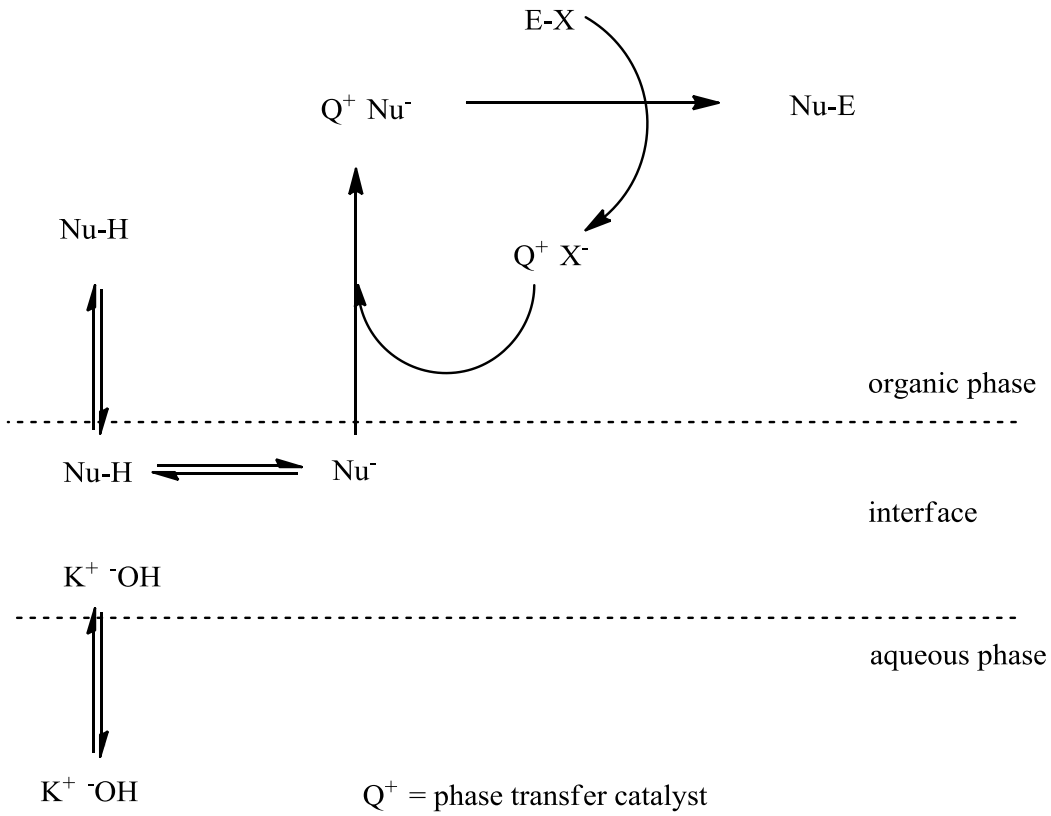
Chiral hydrogen bond donors have developed into an effective and versatile class of catalysts for enantioselective synthesis.[53] From a mechanistic viewpoint, the H-bonding between the chiral catalyst and the electrophile facilitates electrophile activation as well as transition state organisation.

1.3.2.2 Phase-transfer catalysis

Quaternary ammonium or phosphonium salts are known to accelerate the reaction between a nucleophile and an electrophile which are located in different immiscible phases. The key step in this process is the formation of an ion-paired intermediate. The nucleophile, which is placed in the aqueous phase, forms this ion-paired species with the catalyst and its solubility in the organic solvent is then increased. This facilitates the reaction of the nucleophile with the electrophile, which is also located in the organic phase. The term "phase-transfer catalysis" (PTC) was introduced by Starks in 1971[54] to explain the critical role of tetraalkylammonium or phosphonium salts in the reactions between two substances located in different immiscible phases, although the concept had coalesced in the late 1960s through the pioneering work by Starks himself and Makosa and Brändström.[1]

The general mechanism for phase-transfer catalysed reactions is shown in Scheme 1.13 below. The reaction typically incorporates an acidic pronucleophile, the electrophile, the catalyst and a Brønsted base (as a rule this is an inorganic salt such as a hydroxide or a carbonate). In the case shown below the base is potassium hydroxide. The mechanism starts with the activation of the pronucleophile (Nu-H) by deprotonation with the Brønsted base (KOH) at the interface between the organic and aqueous layers. Next, ion exchange with the catalyst (Q^+) gives a lipophilic chiral nucleophile, (Q^+Nu^-), which is able to penetrate into the organic phase where the nucleophilic

attack on the electrophile (E) takes place. The catalyst is responsible for the effective shielding of one of the stereotopic faces of the nucleophile, thereby inducing stereoselectivity in the overall reaction.



Scheme 1.13: General mechanism for asymmetric phase-transfer catalysis.

Not all reactions proceeding under PTC conditions are carried out in an aqueous/organic biphasic mixture. Frequently, the inorganic base is included as a solid reagent in a solution of pronucleophile, electrophile and the catalyst in an organic solvent. In this case the translation of reagents between the two phases has to occur at the interface of the solid reagent.[1] These conditions are referred to as solid-liquid phase-transfer catalysis conditions.

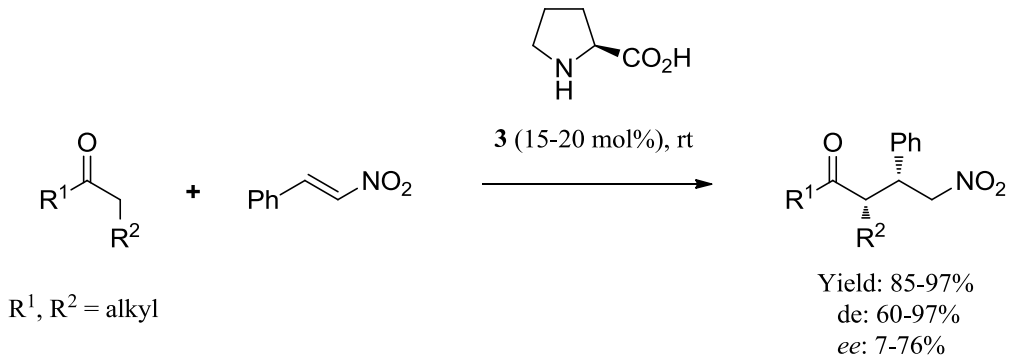
Reactions carried out under PTC conditions exhibit many practical advantages, not least mild reaction conditions, simple experimental protocols, easy scale up and the lack of a requirement for anhydrous solvents and an inert atmosphere.[55] Consequently, in the last two decades, PTC has become a topic of great scientific interest.

1.4 Nucleophilic additions to electron-deficient C=C bonds

The conjugate addition of nucleophiles to electron-poor alkenes is mild and atom-ecomonic method of forming C-C and C-heteroatom bonds. As a result of this it is one of the most widely investigated reactions in organic synthesis.[56] The asymmetric version of the Michael addition using chiral organocatalysts has been subject to a spectacular development in recent years,[1,27,57] so much so that it is arguably the most exploited sector in the discipline of organocatalysis.

1.4.1 Michael additions *via* enamine intermediates

One of the most studied transformations is the Michael addition of ketones and aldehydes with nitroalkenes[58] and, unsurprisingly, the first attempts in this field used proline to catalyse the reactions (Scheme 1.14)[9,59] *via* an enamine intermediate. Considering this was the first foray into the sphere of organocatalysed Michael additions, remarkably high diastereoselectivities and yields were obtained, even if the enantioselectivities were only moderate. Since these pioneering studies, many other modified chiral amines have been employed in this reaction with the aim of improving the enantioselectivity. The design rationale for proline catalysts implicates the H-bonding interaction of the electrophile with the acidic site on the catalyst in the stereochemical outcome of the reaction.



Scheme 1.14: Pioneering studies by Barbas, Enders and List into the Michael addition of ketones to nitrostyrene using L-proline as the organocatalyst.[9,59]

This *modus operandi* has been applied to differently modified chiral secondary amines, generally consisting of a 2-substituted pyrrolidine motif. Representative examples are shown below (Figure 1.1). Sulfonamide **5** was able to exert admirable stereocontrol

over the conjugate addition of cyclohexanone and derivatives of cyclohexanone to *β*-nitrostyrene (up to 98% ee and 99:1).[60] The thiourea-bearing compound **6** was used by Cao *et al*. to catalyse the Michael addition of cyclohexanone to dimethyl(4-nitrobenzylidene)malonate, furnishing the product in 88% ee and 80:20 dr. The same group exploited the abilities of other H-bonding functionalities in this reaction, including urea and triflate moieties.[61]

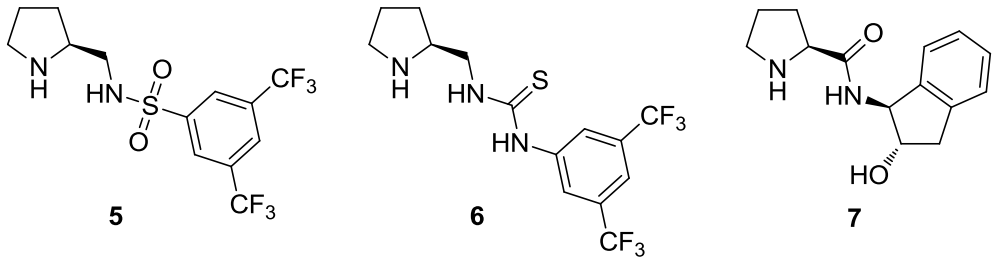
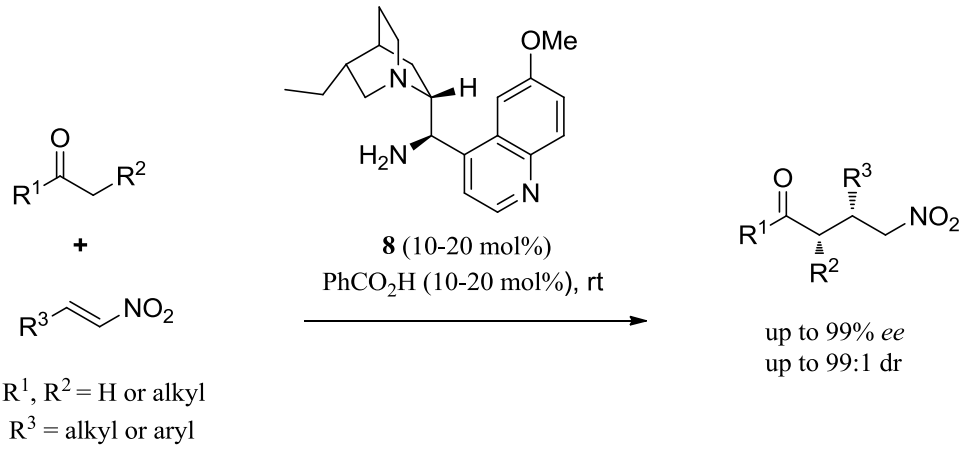


Figure 1.1: Representative examples of catalysts used in the conjugate addition of ketones to various Michael acceptors.[60-62]

Poor results were obtained from these catalysts when other cyclic ketones, acyclic ketones or aldehydes were employed as pronucleophiles. Nájera and co-workers later reported a selective synthesis using acyclic ketones in the presence of compound **4,** in particular the Michael reaction of 3-pentanone with *β*-nitrostyrene gave favourable results (up to 94% de and 80% *ee*).[62] This followed an exhaustive screen of different aminoalcohol-derived prolinamides catalysts. In this case the interaction between the electrophile and the nucleophile in a hydrogen-bonded network was also supported by computational studies.

Primary amines are also effective enamine catalysts. 9-Amino derivatives of the cinchona alkaloids have been used as catalysts for the addition of ketones and aldehydes to *β*-nitrostyrene, providing good results, particularly with acyclic ketones.[63] Amongst the cinchona derivatives tested the hydroquinidine compound, 9-amino-(9-deoxy)-epi-hydroquinidine, **8**, proved the most suitable catalyst for the reaction. A summary of this work by Connon and co-workers is shown in Scheme 1.15.[63] The best results were obtained in neat reactions, although 5 equivalents of pronucleophile were used.



Scheme 1.15: The enantioselective Michael addition of aldehydes and ketones to nitroalkenes reported by Connon and co-workers.[63]

The enantioselective Michael addition of aldehydes to nitroalkenes has become a very powerful transformation. This is illustrated by numerous important applications in the synthesis of valuable chiral compounds.[27] In general reactions involving enamine intermediates with aldehydes are more efficient than the corresponding ketone reactions, due to faster condensation with the catalyst and the fact that, sterically, there is greater scope for enamine geometry/conformation control.[1] Interestingly, catalysts which perform well in the addition of ketones to nitroolefins usually give poor results when aldehydes are used as the nucleophile.

Since the first study by Barbas *et al*,[64] where a series of chiral diamines were tested for their activity and selectivity using various aldehydes as the Michael donor, intensive research in this field has led to the discovery of several eloquent examples. The pyrrolidine derivative incorporating a morpholine ring, compound **7** below, was found to be the best catalyst tested, giving up to 78% *ee* and a 98:2 dr. The selectivity of this catalyst (and that of the 9-amino cinchona catalysts mentioned above) arises from the protonation of the tertiary amine moiety, leading to an ammonium salt which plays the role of the N-H acidic site in terms of interaction with the electrophile *via* hydrogen bonding. The group of Jacobsen utilised the known H-bonding proclivity of the thiourea group[16] accompanied by a primary amine to significantly improve the *ee* values when adding a selection of aldehydes to nitroalkenes. The most successful catalyst in this venture was compound **10**, shown below, which gave excellent selectivity (up to 99% *ee*). The Wang group found that compound **11**,[65] which is also an effective catalyst for α-aminoxylation and Mannich-type reactions,[66] furnished the

Michael product with superb selectivity (>90% *ee* and 90-95% de) when a selection of aldehydes were added to *β*-nitrostyrene.

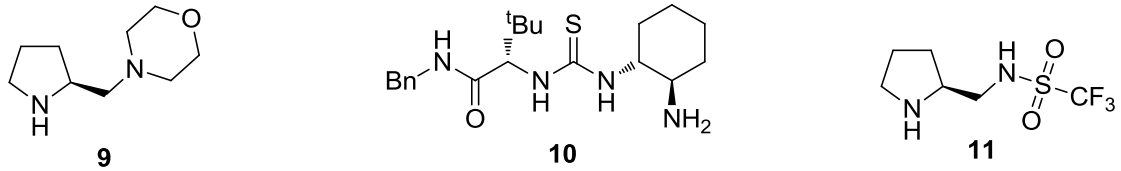
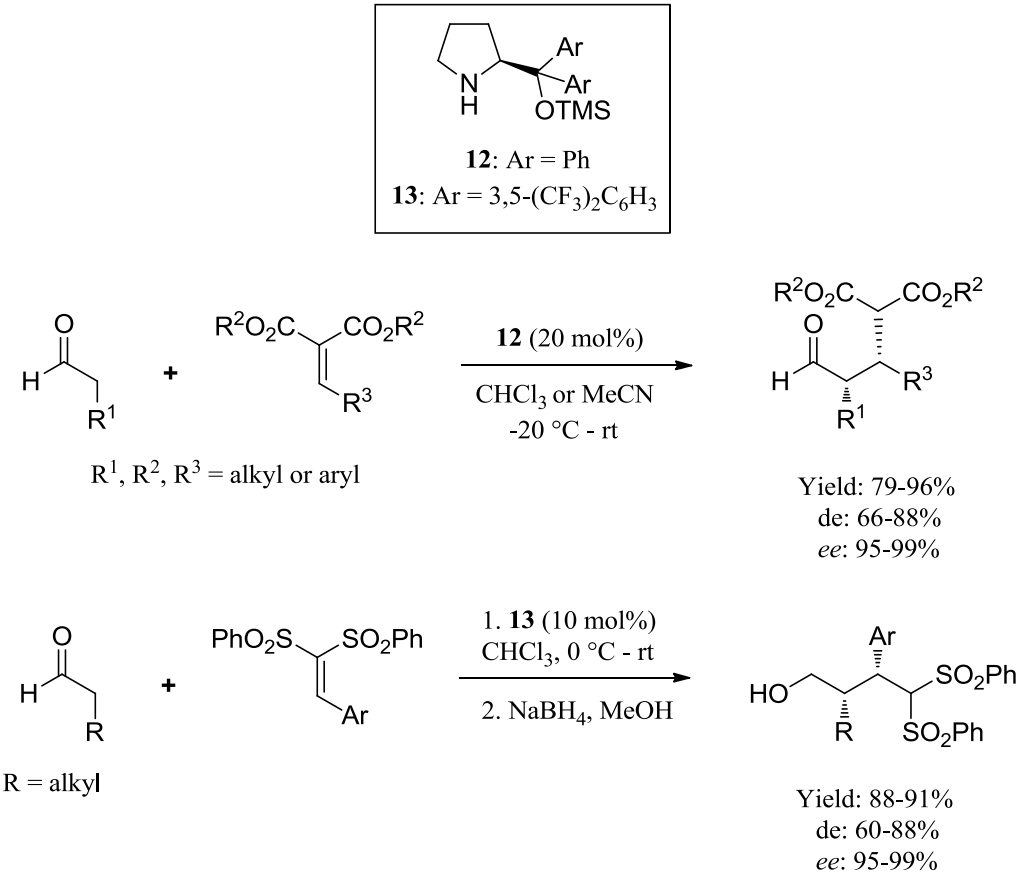


Figure 1.2: Catalysts used by the groups of Barbas, Jacobsen and Wang for the stereoselective addition of aldehydes to nitroalkenes.[64,65]

Apart from the use of H-bonding to stereoselectively direct attack on the electrophile, an alternative catalyst design consists of the introduction of bulky groups at the pyrrolidine ring, which would affect the stereochemical outcome of the reaction *via* steric shielding of one of the diastereotopic faces of the enamine intermediate. Probably the most efficacious catalyst in this context is O-TMS protected diarylprolinol **13** below, which was originally used by the group of Jørgensen in enamine-catalysed S_N2-type α-sulfenylation of aldehydes.[67] Hayashi and co-workers have found that this catalyst provided consistently excellent results in terms of yield and selectivities, and for a wide scope of aldehydes and nitroalkenes (typically 99% ee and up to 93:7 dr). One of the major drawbacks of many of the enamine-catalysed Michael additions reported has been the requirement for large excesses of the donor species. Other catalysts featuring steric bulk at the 2-position of the heteroatomic ring, such as the proline-derived spirolactams and α-methyl prolinamindes synthesised by Kelleher *et al*. have been successful in the asymmetric conjugate addition of aldehydes to *β*-nitrostyrene, without the need for such exorbitant quantities of pronucleophile.[30] Excellent stereoselectivities and enantioselectivities were achieved with low catalyst loadings and only 1.5 equivalents of Michael donor.

Michael additions to other *α,β*-unsaturated compounds have been studied by a number of research groups, with all of them reporting that the lower reactivity of the electrophiles compared to nitroalkenes led to much slower reactions and sometimes difficulties in reaching full conversion.[1] For example, additions to enones with aldehyde donors have received little attention, although catalyst **13** (Scheme 1.16 below) has been effective with alkylidenemalonates, a less reactive Michael acceptor. In 2008, Cordova and co-workers reported the first highly enantioselective conjugate

addition of aldehydes to both aliphatic and aromatic alkylidiene malonates[68] and in the same year, Lu *et al.* used vinyl sulfones as the acceptor with similarly impressive results,[69] both of which are shown in Scheme 1.16.



Scheme 1.16: Michael additions of aldehydes to alkylidene malonates and vinyl sulfones using Jørgensen's TMS-protected diaryl prolinol catalyst.[68,69]

Indeed, Jørgensen's catalysts **12** and **13** have shown remarkable versatility and have stereoselectively catalysed a vast array of conjugate addition reactions including additions to alkyl vinyl ketones,[70] Michael/aldol cascade reactions[29,71] and the intramolecular Rauhut-Currier-type reactions *via* dienamine activation.[72] Recently our own group has exploited the capabilities of catalyst **13** in the first organocatalytic 1,6-addition of aldehydes to dienic sulfones.[73]

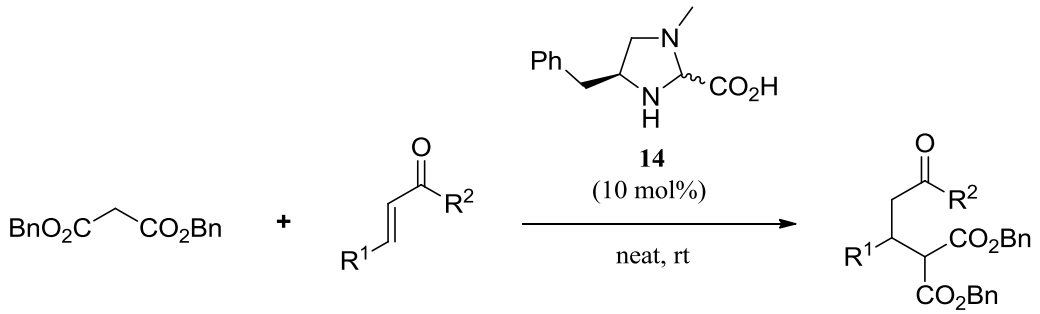
Overall, the enamine activation concept is a very positive development for the conjugate addition, since it allows for the convenient use of aldehydes and ketones as Michael donors. This methodology facilitates the preparation of many different chiral building blocks. The most significant limitation of this chemistry is the need for a

highly electrophilic acceptor and heretofore the use of other common α,β-unsaturated carbonyl substrates such as α,β-unsaturated esters or amides is still underdeveloped.

1.4.2 Michael additions *via* iminium ion catalysis

Iminium ion catalysis is the second possible mechanistic route for a primary or secondary amine to catalyse a conjugate addition. Although some very early examples of iminium-mediated reactions do exist, it was MacMillan's rationalisation of the concept in 2000 which allowed it to be applied to a host of other chemical transformations, as discussed in section 1.2.4. Indeed it wasn't long before other imidazolidinones, similar to the one used by MacMillan in the Diels-Alder cycloaddition, were applied to other reactions, including additions to electrophilic C=C bonds.

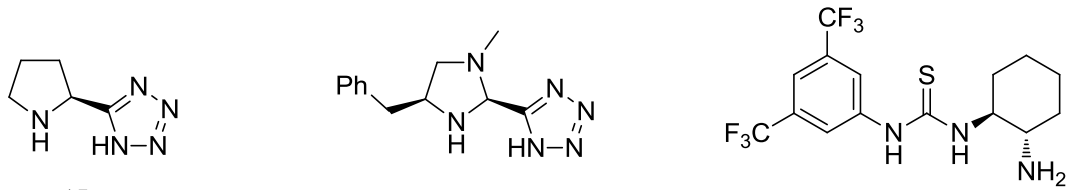
One of the first examples of a highly selective Michael addition using a variation of MacMillan's imidazolidinone (compound **14** below – featuring an imidazolidine backbone) as the catalyst was published by Jørgensen and co-workers in 2003, reporting the addition of malonate esters to enones.[74] Initial screening studies identified dibenzyl malonate as the optimum pronucleophile and it was added to a family of enones. A summary of their work is shown in Scheme 1.17.



Scheme 1.17: The Michael addition of dibenzyl malonate to enones using an imidazolidine compound to catalyse the reaction.[74]

In general, both the yields and enantioselectivities were high but the reaction times were long (typically 165 hours). Another substantial drawback associated with this protocol was the need for large excesses of pronucleophile. Ley and co-workers endeavoured to expand the utility of the reaction beyond dibenzyl malonate and in

doing so identified the tetrazole-bearing proline compound **15** as a suitable catalyst for the addition of dimethyl and diethyl malonate to enones, reporting *ee* values of up to 91% and yields as high as 94 % in the presence of only a slight excess of malonate ester.[75] However this methodology was quite restricted in terms of the breadth of enone acceptor applicable to it and it also required a stoichiometric equivalent of piperidine as an additive. It is possible that it assists the reaction by deprotonation of the malonate pronucleophile, although its role has not yet been fully established since changing the base affects not only the yields but also the enantioselectivities.



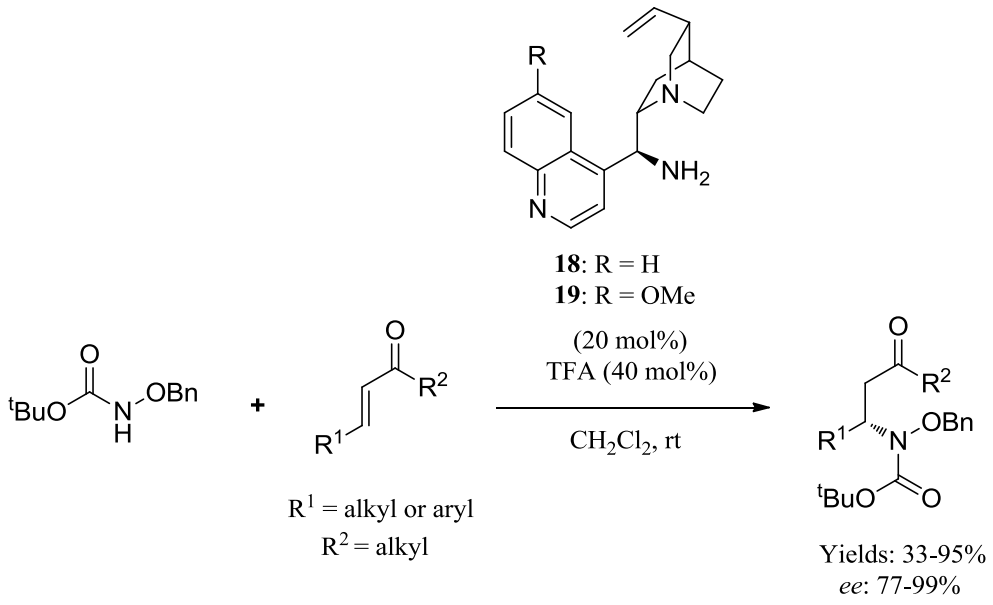
15 **16** **17**

Figure 1.3: Catalysts for the iminium-promoted addition of malonates and nitroalkanes to enones.[75-77]

The tetrazole functionality has also been tethered to an imidazolidine backbone, compound **16** above, and used to good effect in the conjugate addition of nitroalkanes to enones.[76] In general, good to excellent yields and enantioselectivities of up to 92% *ee* for α-substituted nitroalkane Michael donors were reported. Again, the principle drawback of this methodology was the excessive reaction times, which were as long as 300 hours in some cases. In the same reaction, Duan *et al.* have employed the use of the H-bonding thiourea moiety to allow preorganisation of the reactants to induce enantioselection with their simple cyclohexanediamine derived catalyst **17**,[77] Figure 1.3. Outstanding selectivity was achieved (92-99% *ee*) in the Michael addition of nitromethane to a broad range of acyclic enones in the presence of 15 mol% of this catalyst with ethyl acetate as the solvent but, disappointingly, the yields were predominantly only moderate to good over a reaction period of 5 days.

The iminium activation concept has successfully been applied to the conjugate addition of heteroatom-centred nucleophiles to α,β-unsaturated carbonyl compounds. Aza-Michael reactions in particular have been the focus of intensive research in the past few years. The β-amino carbonyl products arising from these reactions are attractive synthons as they are key constituents of many biologically active compounds and are also useful building blocks in total synthesis.[78] The most common obstacles

encountered when using sulpfur-, oxygen-, nitrogen- or phosphorous-based Michael donors are related to the reversibility of the conjugate addition step. This can often lead to low conversions or low configurational stability of the final products.[9] For this reason, the majority of the methods reported in this context incorporate an additional electrophile in the reaction design to quench the hetero-Michael product, thus overriding the reversibility of the reaction. On top of this, aza-Michael reactions involving the iminium activation concept have additional chemoselective issues to overcome because the nucleophile and the catalyst are both amine species. Therefore the role of both these reagents in the process must be clearly established, as the chiral amine catalyst must not undergo a conjugate addition reaction and likewise the amine reagent intended to be the nucleophille must not participate in iminium ion formation. Hence the key to success for the aza-Michael reaction under iminium activation relies mainly on the correct design of the nitrogen nucleophile to be employed. An accomplished demonstration of the use of this framework is shown in Scheme 1.18. *N*-Benzyloxycarbamates were very efficient Michael donors for the reaction with α,β-unstaurated ketones using 9-amino-quinine- and -cinchonidine-derivatives as catalysts for Deng *et al.*[79] The reaction proceeded with excellent yields and enantioselectivites in most cases and the structure of the catalyst could be altered slightly depending on the substitution pattern at the Michael acceptor.



Scheme 1.18: The enantioselective aza-Michael addition of N-benzyloxycarbamates to enones reported by Deng *et al*.[79]

The 9-amino-cinchona alkaloid derivatives are notable for their universality in asymmetric synthesis and conjugate iminium ion catalysis is no exception; apart from C-C and C-N bond forming reactions, these catalysts are prevalent in both sulfa- and oxa-Michael additions.[1]

Thus, the iminium ion concept has proved to be a very powerful approach for carrying out enantioselective conjugate additions of a broad range of nucleophiles to α,β-unsaturated aldehydes and ketones. Despite this, limitations still exist, principally with respect to the choice of Michael donor reagent and also the requirement for high catalyst loadings. Very often careful tuning of the donor's acidity and nucleophilicity is needed to achieve good conversions and selectivities. Moreover, many iminium-catalysed conjugate additions still require large loadings of catalyst (20-30 mol%), although these figures are expected to improve with increased understanding of the kinetic details of iminium reaction mechanisms.[36]

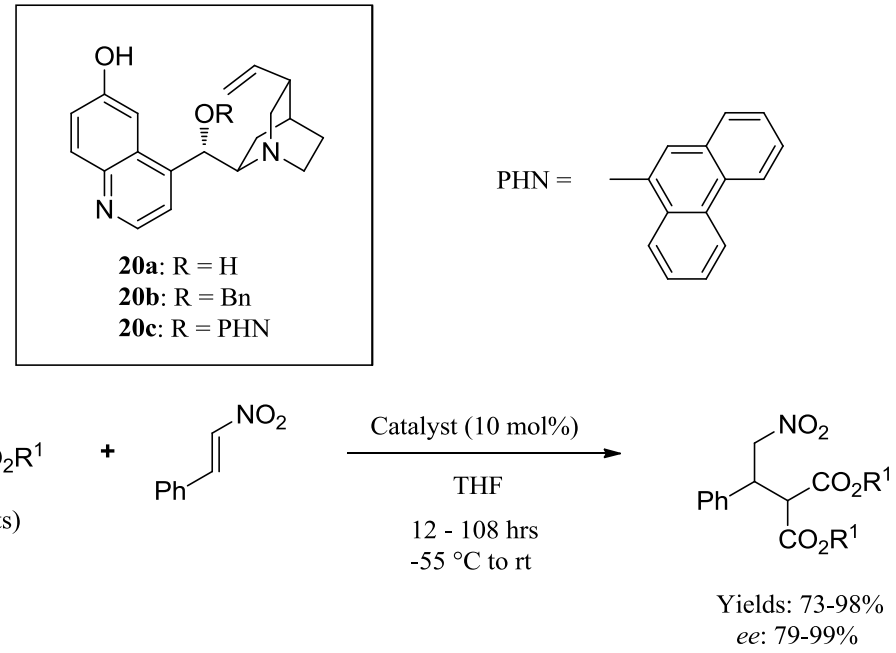
1.4.3 Michael additions *via* noncovalent catalysis

Michael additions *via* noncovalent catalysis require pronucleophiles with quite an acidic hydrogen. Pronucleophiles such as ketones or aldehydes are not compatible with H-bonding catalysis as a stronger base is required for nucleophile activation and this would deactivate the catalyst. Consequently, compounds containing resonance-contributing electron-withdrawing groups in a 1,3- relationship (for example malonate esters) to stabilise the forming negative charge upon deprotonation constitute the standard pronucleophilic species for these reactions.

H-bonding catalysts that operate *via* an enamine intermediate have been employed in the Michael addition of aldehydes and ketones to α,β-unsaturated compounds. Since the activation of the nucleophile *via* enamine formation is the key feature for the viability of these processes (as the activation of the electrophile is less relevant in most cases) this chemistry has already been covered in section 1.4.1.

Ever since Wynberg's research into the cinchona alkaloid-catalysed Michael addition, it seemed inevitable that this "privileged" class of compound would play a major role in the development of organocatalysis as a concept. Although cinchona alkaloid derivatives had been employed with great success in a range of reactions (including in

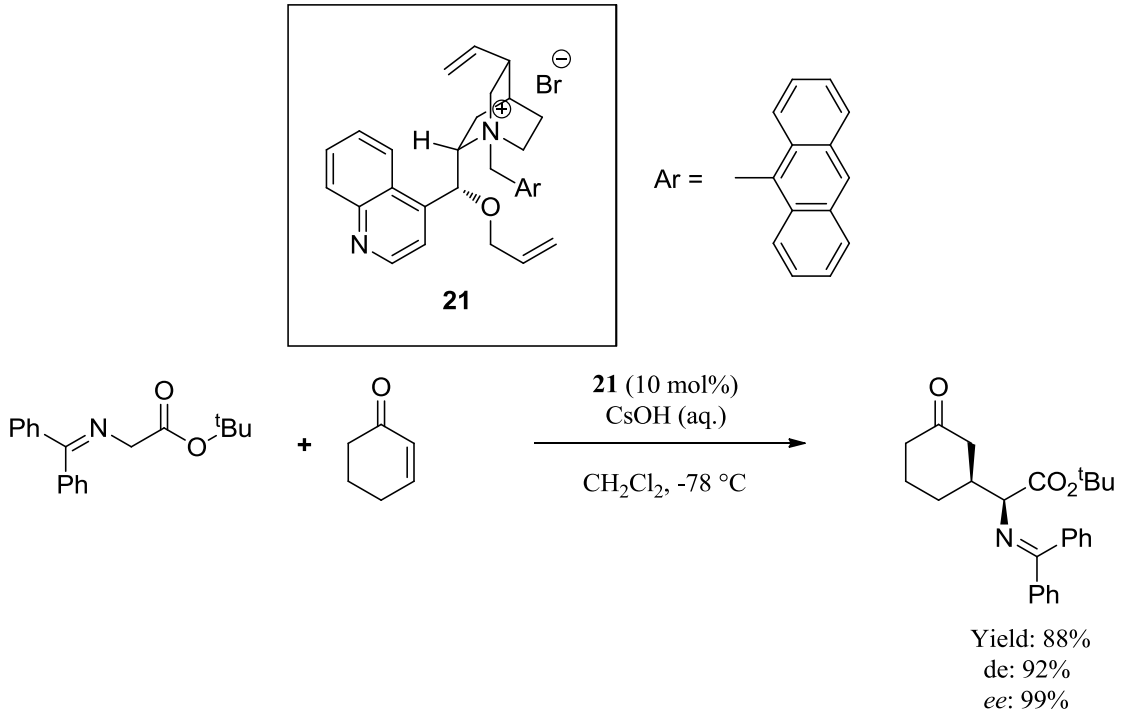
the sulfa-Michael addition) in the early part of the last decade,[80,81] the first highly enantioselective methodology developed using the cinchona family as catalysts for carbon-nucleophile addition to electron-deficient C=C bonds did not appear until 2004. Using nitroalkenes as the electrophile and di(m)ethyl malonate as the nucleophilic species, Deng and co-workers (like Wynberg) found that the selectivity of the natural alkaloid quinidine was modest.[82] Modifications introducing a hydroxyl functionality on the quinoline moiety to supply (in some cases additional) H-bonding character and/or increasing the steric bulk at the critical C9 stereocentre resulted in an admirable degree of stereocontrol, although temperatures as low as −55 °C (accompanied by reaction times of 108 hours) were required to achieve this. A summation of the highlights of Deng's work is shown in Scheme 1.19.



Scheme 1.19: Enantioselective addition of dimethyl and diethyl malonate to nitrostyrene catalysed by quinidine derivatives 20a, b and c.[82]

Indeed, quinidine and the other members of its family are also fundamentally associated with PTC and indubitably the most widely employed chiral PTC catalysts are quaternary ammonium salts derived from cinchona alkaloids.[49,55] Fittingly, the first reported enantioselective phase transfer reaction was catalysed by such a salt, derived from cinchonine.[23] This pioneering example exhibited the enantioselective application of enolates in an efficient alkylation reaction, but the extension of the concept to the conjugate addition took some time to appear. It did eventually become a very powerful tool in achieving stereocontrol in conjugate addition reactions, with the

cinchona family at the forefront of this progress. In this context, the general catalyst structure usually incorporates an aromatic substituent (such as a phenyl or anthracenyl ring) at the quaternary nitrogen atom to increase the lipophilicity of the catalyst and induce stereoselectivity in the reaction through steric shielding and/or interaction with the nucleophile or electrophile through π-stacking.[1] These catalysts often exhibit excellent stereocontrol. Some have found application in large-scale processes and have even found application as solid supported PTCs.[55] A paragon of this type of catalysis is shown in Scheme 1.20 below, where the Corey group found that in the conjugate addition of *tert*-butyl glycinate benzophenone imine to *α,β*-unsaturated ketones proceeded with excellent yields and enantioselectivities and, in the case of cyclohexenone, with almost complete diastereoselectivity.[83]

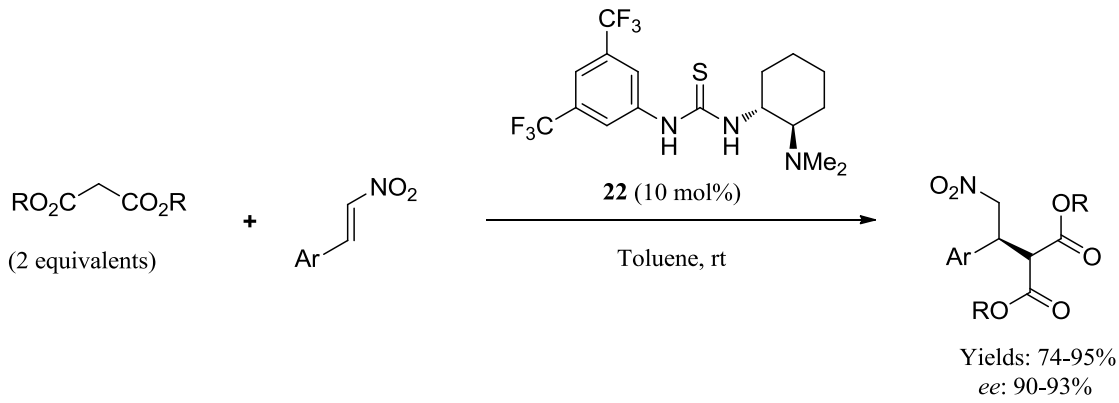


Scheme 1.20: The stereoselective conjugate addition of *tert*-butyl glycinate benzophenone imine to cyclohexenone catalysed by anthracenylmethylcinchonidinium bromide catalyst **21**.[83]

The (thio)urea functional group is of great importance in hydrogen-bonding catalysis. Along with a tertiary amine (to facilitate deprotonation of the pronucleophile) this functionality is present in many catalyst structures because of its strong H-bonding potential. The first example of a chiral thiourea H-bonding catalyst specifically designed for the Michael reaction of 1,3-dicarbonyl compounds to a nitroalkene was developed by Takemoto and published in 2003.[84] Takemoto's catalyst, **22** in Scheme 1.21, incorporated the *N*-aryl substituted thiourea moiety and a tertiary amino basic site

placed at a convenient position on the chiral backbone and catalysed the conjugate addition of malonate esters to β-aryl nitroalkenes with excellent yields and levels of stereocontrol.

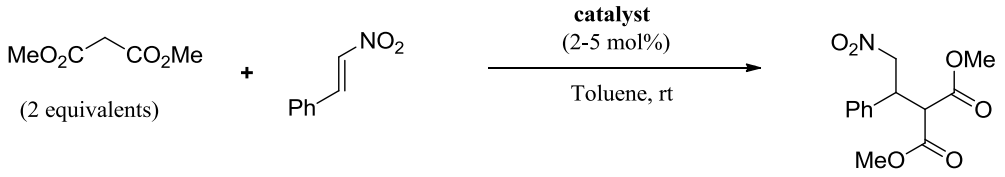
The Takemoto group later undertook a thorough investigation of the scope of the reaction,[85] incorporating 1,3-diketones and β-ketoesters as nucleophiles and varying the structure of the nitroalkene acceptor. The reaction tolerated the use of a broad spectrum of Michael donors, including β-keotesters, leading to the formation of adjacent stereocentres in good enantio- and diastereoselectivites. The Takemoto catalyst and its derivatives have proven to be excellent catalysts for promoting the stereoselective Michael addition to nitroalkenes of a myriad of pronucleophiles, including oxindoles,[86] dicyanoacrylates[87] and masked cyclic 1,3-diketones such as napthoquinols.[88]

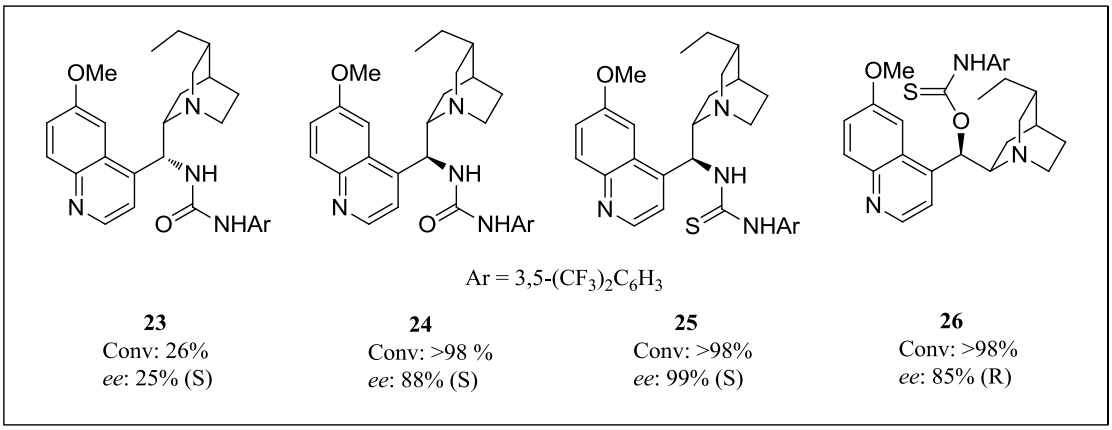


Scheme 1.21: Enantioselective Michael addition of malonates to β-nitrostyrene published by Takemoto and co-workers.[84]

Another family of catalyst which has displayed magnificent stereocontrol in Michael-type additions involving malonates is the cinchona alkaloid derived urea and thiourea organocatalysts. These catalysts have been employed on the conjugate addition of 1,3-diesters to β-nitrostyrene using remarkably low catalyst loadings, in some cases as little as 0.5 mol%. Connon and co-workers deduced that the absolute configuration at C9 of the cinchona substructure was crucial in order to reach high levels of selectivity,[89] Scheme 1.22. This is an indication of the cooperativity in the mode of action of the urea moiety and the basic quinuclidine ring as they need to be in the correct spacial arrangement for the synergetic activation of both the Michael donor and acceptor. Surprisingly, the natural C9 stereochemistry (ie. compound **23**) was relatively inactive; however its analogues with inverted C9 stereochemistry (**24**, **25** and

26) proved both active and highly selective bifunctional catalysts for the reaction. Concurrently, Soós *et al.* found a similar trend for the asymmetric addition of nitromethane to chalcones.[90]





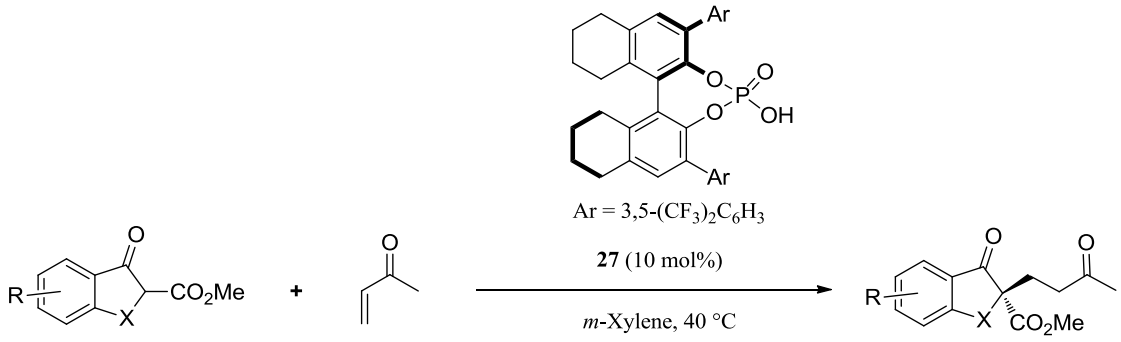
Scheme 1.22: Influence of the cinchona catalyst's structure on the yield and enantioselectivity of the Michael reaction of dimethyl malonate with *β*-nitrostyrene.[89]

Connon found that the use of pseudoenantiomeric hydroquinidine-based catalyst **26** led to a very efficient reaction but with an opposite sense of asymmetric induction to that observed for the hydroquinine-based compound **24**. Independently but simultaneously, Dixon *et al.* varied the structure of the catalyst in this reaction, using the parent alkaloid lacking the methoxy group on the quinoline moiety.[91] Like the Connon-Soós catalysts in Scheme 1.22 above, these epicinchonine derivatives furnished the Michael product (by and large) in excellent yields and enantioselectivites. They also proved compatible with *β*-alkyl substituted nitroalkenes as substrates, providing the expected final compounds with only a small decrease in enantioselectivity. The cinchona alkaloid-derived thiourea catalysts, which feature prominently in our own research, are superb facilitators of enantioselective additions to electrophilic C=C bonds,[1,9,53,92] the reasons for which are discussed in detail in section 2.4.

The use of carbonyl-containing Michael acceptors in conjugate addition reactions under H-bonding activation represents a more challenging proposition than the use of nitroalkenes. The lower Lewis-basicity of the carbonyl group compared to that of the

nitro group leads to a weaker interaction with the Brønsted acid catalyst and the ramifications of this can be two-fold; it may result in a low conversion or the competitive (and non-stereoselective) background reaction may prevail. Overall, this may lead to difficulties in controlling the spatial arrangement of the reagents during the conjugate addition step, something which is crucial if a stereoselective reaction is desired. Enals are even more troublesome than enones because of the added complication of possible direct addition instead of the desired 1,4-addition.

In spite of this, a number of reports have appeared showing that α,β-unsaturated carbonyl compounds can be employed as Michael acceptors in conjugate addition reactions. Bifunctional thiourea-tertiary amine catalysts feature prominently in this cluster, as their double H-bonding network leads to sufficient electrophile activation to promote nucleophilic attack. The first example in this context was the addition of nitromethane to chalcones, reported by the group of Soós,[90] in which the catalysts used by Connon *et al.* (Scheme 1.22) gave a high yielding (80-94%), enantioselective (89-98% *ee*) reaction. More recently there has been an example of chiral phosphoric acids such as **27** below employed in the addition of β-ketoesters to methyl vinyl ketone.[93]



Scheme 1.23: The Michael addition of β-ketoesters to vinyl ketones catalysed by chiral phosphoric acid **27**.[93]

Chiral phosphonium salts can also be employed successfully in PTC with α,β-unsaturated carbonyl Michael acceptors. In particular, binapthyl-containing phosphonium salts are outstanding catalysts in the conjugate addition of oxindoles to enones under PTC conditions.[94] Chiral ammonium salts are also a very effective catalyst for a range of asymmetric transformations, including conjugate additions.[49]

On reflection, the use of molecules able to activate the Michael acceptor by the formation of a catalyst-substrate complex is a very powerful methodology for the development of enantioselective conjugate additions. Generally speaking, a reasonably broad range of acceptor is tolerated, although the reaction proceeds in a more efficient way when substrates are able to engage in multiple H-bond interactions. Consequently, the use of certain families of α,β-unsaturated compounds as electrophiles is still rather underdeveloped.

1.5 Other Reactions involving cinchona alkaloid/thiourea catalysts

Apart from conjugate addition reactions, cinchona-derived and H-bonding organocatalysts have been used to effect a broad range of chemical transformations, with some catalysts incorporationg both features. The most prominent of these will now be discussed in brief.

1.5.1 Nucleophilic additions to C=O bonds

Nucleophilic attack on the carbonyl group constitutes another important category of reaction in the field of asymmetric organocatalysis. Of the chemical transformations fitting into this subgroup, by far the most prevalent is the use of an enolisable carbonyl compound as the nucleophile, also known as the aldol reaction. Other reactions of interest which are governed by the reactivity of the carbonyl group include the nitroaldol (or Henry) reaction, allylation reactions and the Benzoin condensation.

1.5.1.1 The Aldol reaction

The enantioselective organocatalytic aldol reaction has been profusely reviewed,[95,96] which is perhaps the best indication of its importance in modern catalytic synthesis. It is apodictically one of the most advanced synthetic reactions in the field of organocatalysis. In particular, proline and its derivatives have shown tremendous applicability in this field,

After Barbas and List reported their successful proline-catalysed enantioselective direct intermolecular aldol reaction in 2000 it was inevitable that this simple, abundant α-amino acid catalyst would be applied to chemical transformations involving other

reagents. This seminal report showed that, although proline typically reacts unproductively with aldehydes, the intermolecular reaction between a ketone and an aldehyde is possible if a large excess of the ketone donor is used,[25] see Scheme 1.3 in section 1.2.4. Indeed the difficulties encountered in the cross-aldol reaction are predictable; the reagents have a propensity to polymerise and both reactants can act as either the nucleophile or electrophile or both, leading to multiple products. The initial publications in the area minimised the bothersome side reactions by employing a large excess of pronucleophile – typically a ketone. For the use of simple and volatile ketones this is neither an economical nor a practical problem, but when more sophisticated ketones are used this large excess could be a severe drawback.

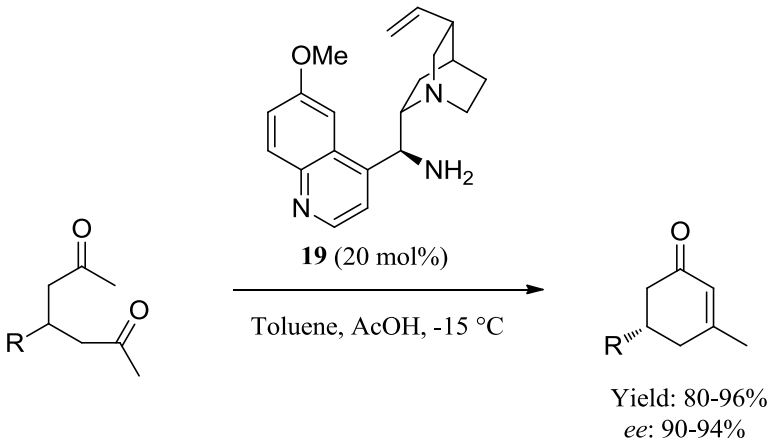
These studies also reported a number of other problems, most commonly dehydration of the aldol adduct and poor yields and selectivities, particularly for reactions involving unbranched aldehyde electrophiles.[97] However, in the ten years since its renaissance, organocatalysis has developed into a reliable method for inducing asymmetry in the aldol reaction through the perseverance of many research groups, with proline itself and proline derivatives to the forefront of this success.[96]

An excellent example of this rapid progress was published in 2005 by Enders and co-workers.[98] The proline-catalysed aldol reaction between 2,2-dimethyl-1,3-dioxan-5-one (a synthetic equivalent of dihydroxyacetone) and a selection of aldehydes was a biomimetic approach to the synthesis of various carbohydrate scaffolds in a fashion analogous to aldolase enzymes.[99] Another highly successful catalytic strategy for the stereoselective aldol reaction relies on the use of alternative H-bonding moieties at the 2-position of the proline ring. Extensive studies have been carried out using these catalysts in the aldolisation of cyclohexanone and its derivatives with halo-substituted and unsubstituted benzaldehyde,[100] with the H-bonding ability provided by a variety of functionalities, including prolinamide, thioamide and proline sulfonamide derivatives. Thiourea moieties have also proven to be effective H-bond donors in organocatalysed aldolisations of cyclohexanone with aromatic aldehydes in water.[101]

Along with the great success obtained with chiral catalysts based upon the pyrrolidine motif, other amine catalysts have been successfully used to catalyse asymmetric aldolisations, including many amino acids other than proline.[102] Several primary amine catalysts backboned by a chiral *trans*-1,2-diamine motif have also been

developed,[103] including catalysts tethered to magnetic nanoparticles.[104] Again, aldolisations using these catalysts are more efficient with cyclic ketones acting as the nucloephile.[42]

As ketones are less reactive than aldehydes they are considered unsuitable electrophiles in the Aldol reaction. However, additions involving ketones as the acceptor have been achieved and cinchona alkaloid-derived compounds have proven to be excellent promoters of this aldol reaction. Quinine-derived primary amine **19** was applied by List *et al*. to catalyse the intramolecular aldolisation of 4-substituted-2,6-heptanediones to chiral 5-substituted-3-methyl-2-cyclohexene-1-ones in 2008.[105] The products were afforded with excellent yields and enantioselectivities, as shown in Scheme 1.24. These compounds are high value synthetic targets and this stereoselective synthesis has been a long-term challenge in asymmetric catalysis.

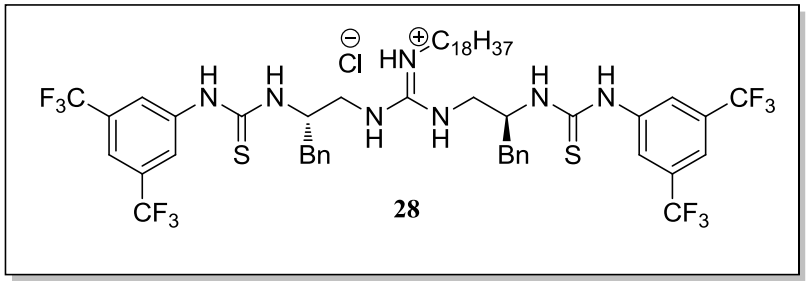


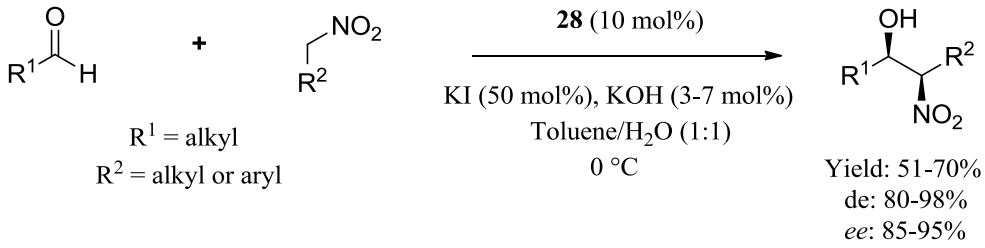
Scheme 1.24: Intramolecular aldolisations of 4-substituted 2,6-heptanediones catalysed by quinine-derived primary amine.

1.5.1.2 Other additions to C=O bonds

In addition to the classic aldol reaction, several modified versions have been reported. The asymmetric catalytic nitroaldol (Henry) reaction is an aldol-related synthesis of considerable interest, since β-nitro alcohols are valuable intermediates in the synthesis of a variety of chiral building blocks.[42] Although there are few examples of metal-free catalytic asymmetric Henry reactions, a look through the literature for the key catalysts used in this transformation reveals a familiar tale; cinchona alkaloids, phase transfer catalysts and thioureas all feature prominently, as do guanidine-based compounds.[106] In 2005, Nawasaga and co-workers developed the novel bifunctional catalyst **28**

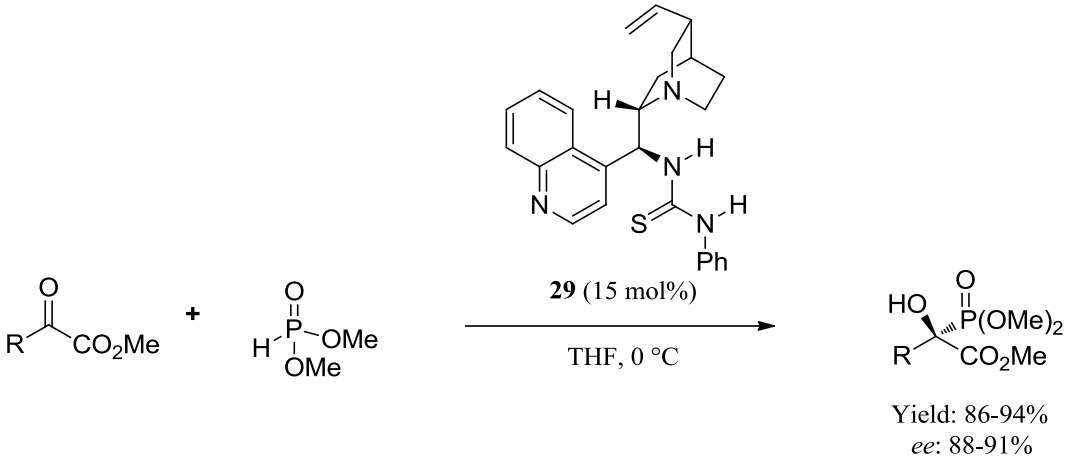
bearing guanidine and thiourea moieties in the same skeleton. It proved to be a highly effective catalyst for the addition of nitroalkanes to different aldehydes,[107] obtaining high *syn* diastereoselectivities and enantioselectivities, Scheme 1.25. The same group later investigated the nitroaldolisations of various aliphatic α-keto esters, again using catalyst **28**, and found that the corresponding tert-nitroaldols were provided in moderate to high yields (35-90%), low to high enantioselectivities (5-93% *ee*) and moderate to high diastereoselectivities (58-94% de) at sub-zero temperatures.[108]





Scheme 1.25: Enantio and *syn*-selective Henry reaction of aldehydes with nitroalkanes in presence of catalyst **28**.

Other cinchona alkaloid-derived compounds have been used in asymmetric additions to C=O bonds, including those possessing the thiourea moiety. A notable publication appeared in 2009 when Feng and co-workers reported the stereoselective hydrophosphonylation of α-ketoesters catalysed by cinchonidine-derived **29** in Scheme 1.26 below. A series of aromatic and heteroaromatic α-ketoesters reacted with dimethyl phosphite to afford the corresponding α-hydroxy phosphonates in high yields and enantioselectivities.[109] This is an excellent representation of the breadth of functional groups which thiourea organocatalysts are compatible with.



Scheme 1.26: Hydrophosphonylations of α-ketoesters catalysed by cinchona-derived **29**.[109]

Asymmetric organocatalysts have also been implicated in a number of other transformations involving stereoselective nucleophilic additions to C=O bonds, including the Petatis[110] and Bignelli[111] reactions, benzoin condensations[112] and the Morita-Baylis-Hillman (MBH) reaction.[113]

A vast amount of work has been done in the last decade to further develop and understand asymmetric control in nucleophilic additions to C=O bonds by organocatalytic methods. The asymmetric aldol reaction is therefore a remarkably advanced subgroup in the field of organocatalysis. A plethora of highly efficient and selective methodologies exist, using both proline-derived and non-proline-derived organocatalysts. Both the organocatalytic Henry and the MBH reactions are considerably less developed, although some efficient, stereoselective examples of both have been reported. Since organocatalysed processes represent a green approach to the synthesis of a compound, organocatalytic aldol or Henry reactions will surely be used profitably by industry in the future.

1.5.2 Nucleophilic additions to C=N bonds

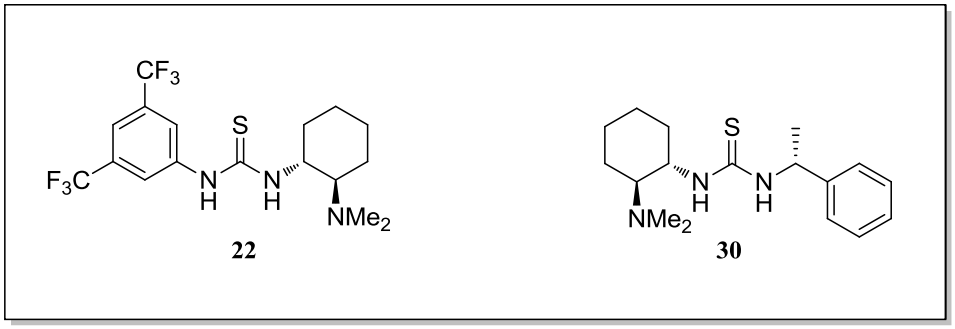
Nucleophilic additions to C=N bonds of imines and related compounds are of synthetic importance since α-branched amines are common substructures within biologically active materials. Hence this area has attracted much interest[114] and some of the more important reactions will now be discussed.

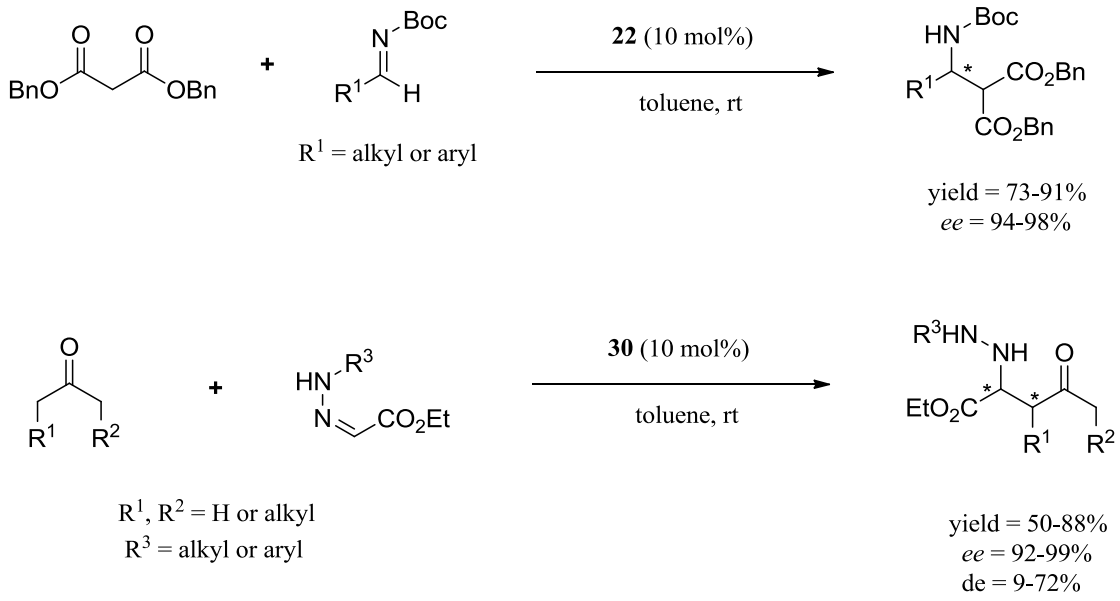
The Mannich reaction is perhaps the most widely studied nucleophilic addition to C=N bonds and involves an aldehyde, an amine and a ketone reacting in a three-component,

one-pot synthesis.[115] Alternatively, the reaction can be implemented as a nucleophilic addition of a C-nucleophile to a preformed imine (known as the indirect Mannich reaction). Organocatalytic Mannich reactions can be carried out in either fashion. A wide variety of chiral organocatalysts have been used to effect the asymmetric version of this reaction, but the most commonly used is L-proline.[116] Potential side reactions in Mannich-type reactions include self-condensations of the carbonyl starting materials or subsequent reactions of the thus-formed Mannich product with an additional imine equivalent. These problems affect the reaction yield but the latter can sometimes be avoided by using a large excess of the carbonyl compound.

In terms of catalyst structure, quite a large crossover exists between those which are used to promote the aldol and the Mannich reactions. Naturally, efficacious catalysts in the aldol reaction tend to be applicable in nucleophilic additions to C=N bonds also. In this vein many pyrrolidine-based catalysts have been tested in the Mannich reaction.[1] The strategy for stereoinduction in the reaction is analogous to that which has proven successful for the aldol reaction: the 2-postition of the ring is often substituted with either a H-bonding or a sterically inhibiting moiety.

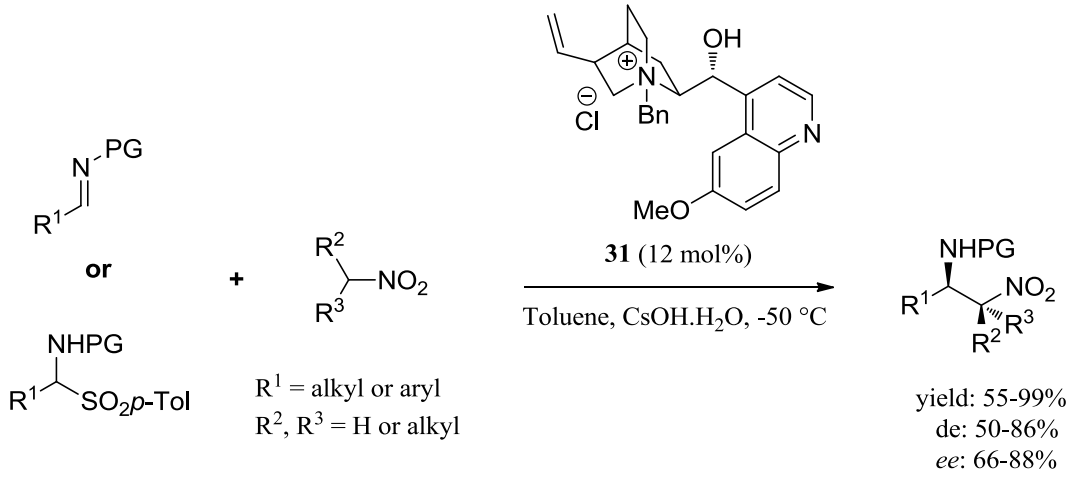
Moreover, catalysts which have proven suitable for the Michael reaction have been introduced as promoters of the Mannich reaction. A case in point is shown in Scheme 1.27. Takemoto's catalyst, **22**, delivered malonates to N-Boc protected imines with outstanding stereocontrol,[117] whilst its abilities as a promoter of the conjugate addition have been documented in section 1.4.3. Catalyst **30**, featuring a similar chiral structure as **22** but with a third stereocentre, was found by Tsogoeva *et al*. to be a stereoselective promoter of the Mannich-type reaction of unmodified ketones with stable α-hydrazonoesters.[118]





Scheme 1.27: Thiourea-catalysed Mannich reactions of malonates with N-Boc protected imines and ketones with α-hydrazonoesters.[117,118]

Unsurprisingly, phase-transfer catalysis has found applicability in nucleophilic additions to C=N bonds. Palomo *et al.* have developed an efficient protocol for the asymmetric aza-Henry reaction under PTC conditions, Scheme 1.28.[119]



Scheme 1.28: Aza-Henry reactions catalysed by cinchonidine-derived ammonium catalyst.[119]

This methodology is noteworthy because it also used the imine precursors, α-amido sulfones as the electrophilic component. It is valid for both non-enolisable and enolisable aldehyde-derived azomethines and it also tolerates a large selection of nitroalkanes.

Other nucleophilic additions to C=N bonds which have been investigated organocatalytically include the asymmetric Strecker and Aza-Morita-Baylis-Hillman reactions.[120] Overall, the area of organocatalytic additions to imines is considerably less developed than reactions involving their carbonyl cousins. However, considering the importance of chiral branched amines to the pharmaceutical industry, nucleophilic additions to C=N bonds is a sector of organocatalysis which is sure to attract more attention in the future.

1.5.3 Cycloaddition reactions

Cycloaddition reactions constitute another important and well-developed area in the field of asymmetric organocatalysis. Owing to the predominance of chiral mono- and poly-cyclic systems in natural products and pharmaceuticals,[121] the stereocontrolled construction of chiral carbo- and hetero-cycles is a topic of considerable relevance and consequently much energy has been expended in the pursuit of developing eloquent and dynamic catalytic systems.[122]

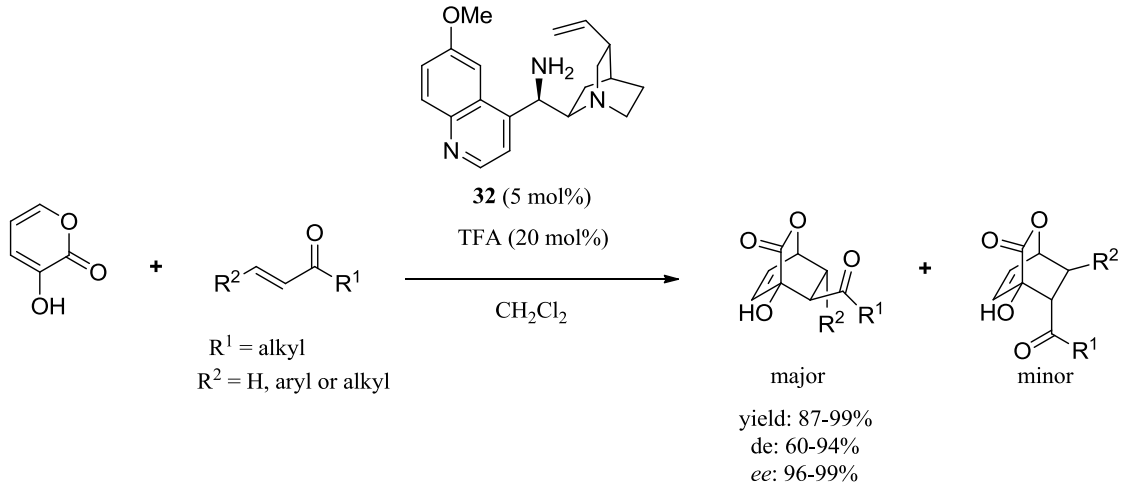
1.5.3.1 Diels-Alder cycloadditions

The Diels-Alder reaction is formally a [4 + 2] cycloaddition. It can give access to a broad range of six-membered rings in a regio- and stereo-controlled fashion.[123] The historical development of the Diels-Alder reaction can be viewed as a paradigm for the evolution of asymmetric synthesis over the last 30 years: the first practical enantioselective versions were achieved in the 1980s through the use of chiral auxiliaries; the 1990s witnessed the development of asymmetric metal-catalysed Diels-Alder reactions; and in the last 10 years asymmetric organocatalysed cycloadditions have attained excellent degrees of efficiency and stereoselectivity.

Of course, the reaction itself is intrinsically linked with the concept of organocatalysis since the term was coined in the MacMillan report of the cycloaddition of

cyclopentadiene with a range of aldehydes *via* an imidazolidinone hydrochloride salt catalyst.[10] Following this discovery that solely organic molecules can efficiently catalyse the reaction, the amine-catalysed Diels-Alder has been investigated in much detail[124] and it has been applied to both inter- and intramolecular reactions, including in the synthesis of natural products.[125]

Inevitably, the development of cinchona-catalysed asymmetric protocols for Diels-Alder and hetero-Diels-Alder has been the subject of several reports.[50,81] For example, the readily available 9-amino-quinidine, **32**, exhibited admirable stereocontrol on the asymmetric reaction of α,β-unsaturated ketones with 2-pyrones,[126] Scheme 1.29. In the presence of TFA as an additive the reaction afforded the *exo*-cycloadduct as the major product in superb enantiomeric excess of up to 99% in almost all cases. Moderate to excellent diastereoselectivities of 50-94% were obtained, but importantly the enantioselectivity of the reaction stayed constant when the aromatic moiety on the α,β-unsaturated ketone was changed to an aliphatic substituent.

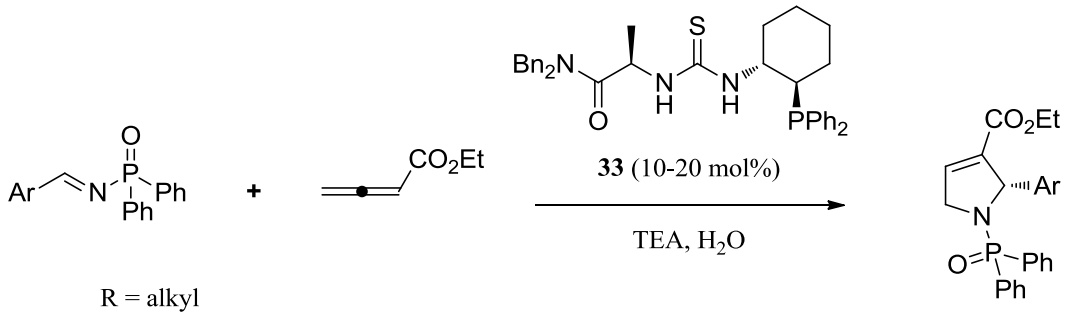


Scheme 1.29: Cinchona alkaloid-catalysed Diels-Alder reactions of 2-pyrones.[126]

1.5.3.2 Other cycloadditions

After the Diels-Alder reaction, the [3 + 2] cycloaddition is the second most common ring-forming reaction. Also known as the Huisgen cycloaddition, this transformation involves a reaction between 1,3-dipoles and a dipolarophile. Azomethine ylides have latterly become one of the most investigated classes of 1,3-dipoles and several methods for the synthesis of pyrrolidine derivatives have been developed based upon their cycloaddition chemistry.[42] [3 + 2] cycloadditions have also proven useful in the

enantioselective construction of dihydropyrroles. Notably the group of Jacobsen has employed this strategy in the highly enantioselective synthesis of a range of 2-aryl-2,5-dihydropyrrole derivatives,[127] Scheme 1.30. This phosphine-catalysed process involved the [3 + 2] cycloaddition between an *N*-phosphinoyl imine and an allene *via* catalyst **33** (which also incorporated a thiourea moiety) in the presence of TEA and water. The desired combination of high yields and superb enantioselectivities, up to 98% *ee,* was achieved in all cases.



Scheme 1.30: [3 + 2] Cycloadditions of allenes with *N*-phosphinoyl imines.[127]

[2 + 2] cycloadditions (and to a lesser extent [3 + 3] cycloadditions) have also been the subject of some investigation in the field of organocatalysis.[122] In fact, one of the earliest examples of organocatalysis was the asymmetric synthesis of β-lactones *via* a [2 + 2] cycloaddition catalysed by cinchona alkaloid derivatives.[128]

1.5.4 Miscellaneous Reactions

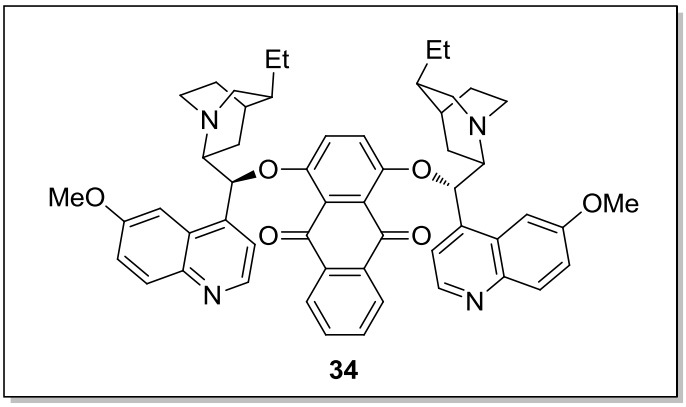
Catalysts bearing a thiourea moiety and/or based upon the cinchona framework have proven to be excellent promoters of a number of other chemical transformations which, from an organcatalytic point of view, have not been subjected to the intensive experimental scrutiny of many of the aforementioned reactions. Some of these reactions will now be discussed in brief.

1.5.4.1 Substitutions at aliphatic carbon

Halogenated compounds are important entities in organic synthesis, either as lynchpins for further transformations or for their applications in medicinal chemistry.[129] Accordingly, the enantioselective formation of these compounds is a deserved

objective in asymmetric synthesis.[130] Conveniently, organocatalysts have shown potential in this type of transformation, although all organocatalytic halogenations to date are α-halogenations of carbonyl compounds.[131] Several groups have shown that L-proline and its derivatives can catalyse the fluorination of carbonyl compounds. The fluorination of aldehydes has been more successful with the first direct enantioselective catalytic α-fluorination of aldehydes accomplished by MacMillan and co-workers in 2005,[132] although the groups of Jørgensen[133] and Barbas[134] independently reported similar studies almost simultaneously.

In 2008, Shibata *et al*. reported the first successful catalytic enantioselective fluorination based on the use of cinchona alkaloids.[135] They demonstrated that allyl silanes and silyl enol ethers underwent efficient enantioselective fluorodesilylation with *N*-fluorobenzenesulfonimide (NFSI) as the fluorine source and a catalytic amount of a bis-cinchona alkaloid as the catalyst. The corresponding fluorinated compounds were provided with enantioselectivities of up to 95% *ee*. The catalytic system was also applied to the fluorination of oxindoles with excellent yields and moderate to high enantioselectivities of up to 86% *ee*, Scheme 1.31. These reactions were carried out at low temperature (−80 °C) in a methylene chloride/acetonitrile mix.



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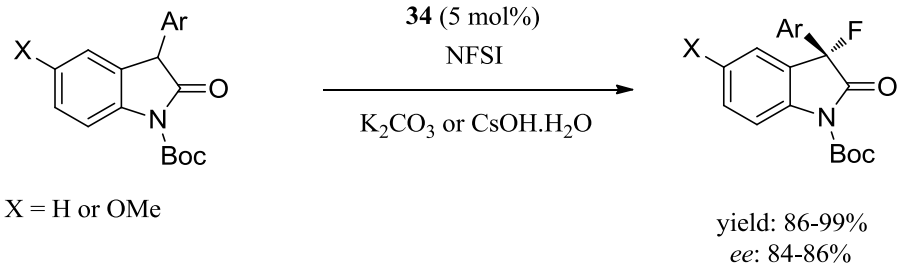


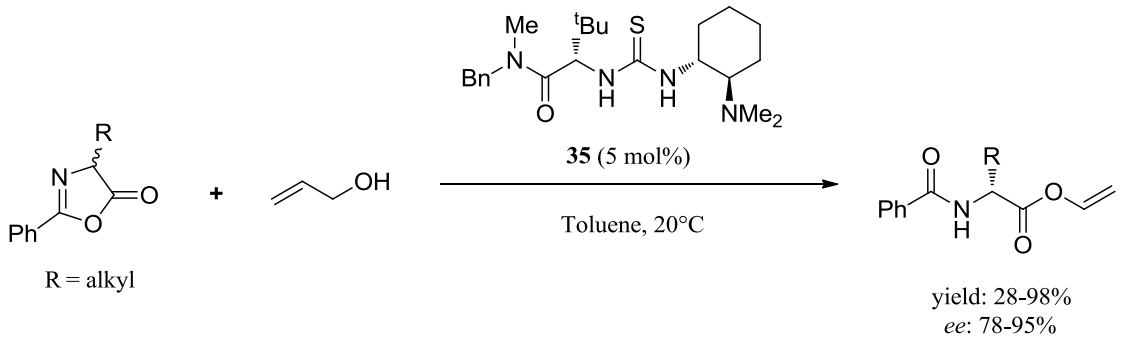
X = H or OMe

yield: 86-99%
ee: 84-86%

Scheme 1.31: Fluorination of oxindoles *via* bis-cinchona alkaloid catalyst.[135]

1.5.4.2 Kinetic resolutions and desymmetrisations

Most methods reported to date have employed enzymes, such as lipases or esterases, but the challenge of developing non-enzymatic asymmetric catalysts has been embraced by many research groups over the last decade.[136] In particular, the asymmetric acylation of alcohols using molecular catalysts has emerged as a viable alternative to the well-established enzymatic methods. In this context, a thiourea-based bifunctional organocatalyst (**35**) was used by Berkessel *et al.* in the highly enantioselective alcoholytic dynamic kinetic resolution of azalactones.[137]



Scheme 1.32: Thiourea-catalysed dynamic kinetic resolutions of azalactones.

A cinchona alkaloid-derived organocatalyst has been used by Connon and co-workers to promote the enantioselective dynamic kinetic resolution of azalactones with allylic alcohol, although in this case of substrates the urea derived catalysts proved to be superior to their thiourea analogues.[138] Interestingly, although unsurprisingly, it was also a cinchona-derived catalyst which was responsible for the first example of an organocatalysed kinetic resolution of racemic thiols.[139]

Although the challenge of developing easily accessible and effective non-enzymatic asymmetric acylation catalysts has been embraced by many research groups over the last decade, there is a surprising dearth of methodologies for organocatalytic kinetic resolution. Nevertheless, the concept is in its relative infancy and it is expected that new ways will be found to improve efficiency in non-enzymatic kinetic resolutions, making future methodologies more selective and versatile.[136]

1.6 General conclusions

The last ten years have witnessed a colossal growth in the field of organocatalysis and it has undoubtedly become the "third pillar" in the domain of enantioselective synthesis, along with enzymatic and transition metal catalysis. The phrase has now firmly and irreversibly established itself in the vernacular of the organic chemist.

Although reactions catalysed by purely organic molecules have been known for much longer, organocatalysis as a concept only coalesced in the year 2000 with publications by the groups of Barbas and MacMillan. A plethora of new methodologies have since been developed for carrying out asymmetric transformations which were previously only available under transition-metal catalysis. One of the most impressive aspects of this has been the concurrent development of several discrete components within this single concept. Organocatalysts operating by very different mechanistic profiles have demonstrated their excellence when applied to a diverse range of chemical reactions, often achieving outstanding levels of chemical efficiency and stereoselectivity.

Resulting from the operational, environmental and economic advantages associated with this methodology, organocatalysis continues to play an ever-increasing role in synthetic chemistry. Of course, the ultimate validation of any synthetic method is its successful application to the synthesis of structurally complex molecular targets, in particular those of biological or pharmaceutical relevance. Some have manifested themselves in the last few years,[140] and more and more transformations now meet the standards of established asymmetric reactions.

Despite the precocious development of the area over the last decade or so, several areas remain completely unexplored, and new concepts will surely arise within the more established ones. Since organocatalysis is in its relative infancy, newly emerging domains will doubtlessly pave the way for further development. Perhaps the most crucial area of research in the future will be the identification and development of important transformations and new reactivities which are not available using other branches of catalysis. Given the huge growth and impact of organocatalysis over the last decade, it will be very interesting to monitor the growth of the field over the next decade and beyond.

2. Nitroalkenes as Michael Acceptors

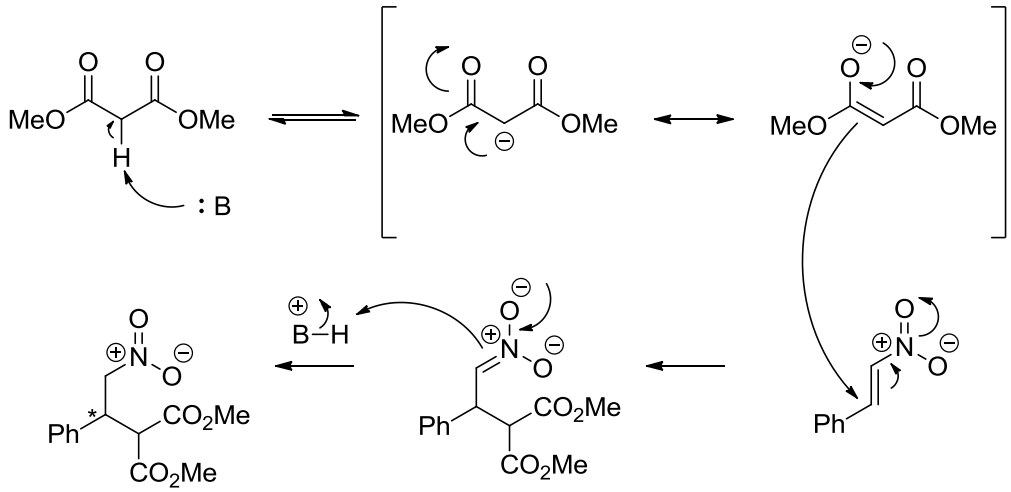
2.1 Introduction

The primary aim of this project was to perform carbon-carbon bond forming reactions using cinchona alkaloid based organocatalysts. We were particularly interested in the Michael addition, since it is one of the most widely used means for the stereoselective construction of carbon-carbon bonds in organic synthesis.[27,34,92,141] Owing to the increased demand for optically active compounds, much effort has been made to develop efficient, stereoselective methodologies. Indeed, remarkable advances have been made in the design of asymmetric catalysts containing metals.[142] Until the turn of the century, these transition-metal complexes and enzymes were the two main classes of proficient asymmetric catalysts. A change in perception has occurred in the last few years as chemists have realised that relatively simple organic molecules could be highly effective and remarkably enantioselective catalysts for a variety of important chemical transformations, not least the Michael addition.[11,12,143] This chapter will deal with the results arising from our investigations into the use of β-nitrostyrene as the electrophile in organocatalysed Michael addition reactions.

2.1.1 The Michael Addition

The Michael addition is an important atom-economical method for mild C-C bond formation. It is defined as a 1,4- or conjugate addition where the nucleophile is a carbanion.[144] The conjugate addition involving a carbon nucleophile is essentially an irreversible reaction,[145] a feature which is attractive to chemists from a kinetic viewpoint. The mechanism for the reaction is shown in Scheme 2.1 below, using dimethyl malonate as the pronucleophile and β-nitrostyrene as the electrophilic component. A base deprotonates the relatively acidic α-proton on the malonate ester to form the reactive negatively charged enolate ion (hence the term "pronucleophile"). This nucleophile then attacks at the β- position of the α,β-unsaturated compound. The electrons flow up along the π-system onto the electronegative oxygen, after which the double bond is reformed and the α-carbon acquires a proton to form the Michael product. In this case the new product has one chiral centre, since the nucleophilic species is symmetrical. Unsymmetrical nucleophiles yield a product with two new stereocentres. The Michael addition is one of the most versatile and widely used

methods of forming C-C bonds in organic synthesis[81,146] and this has been demonstrated by the number of examples in which it has been identified as a key strategic transformation in total synthesis.[9]

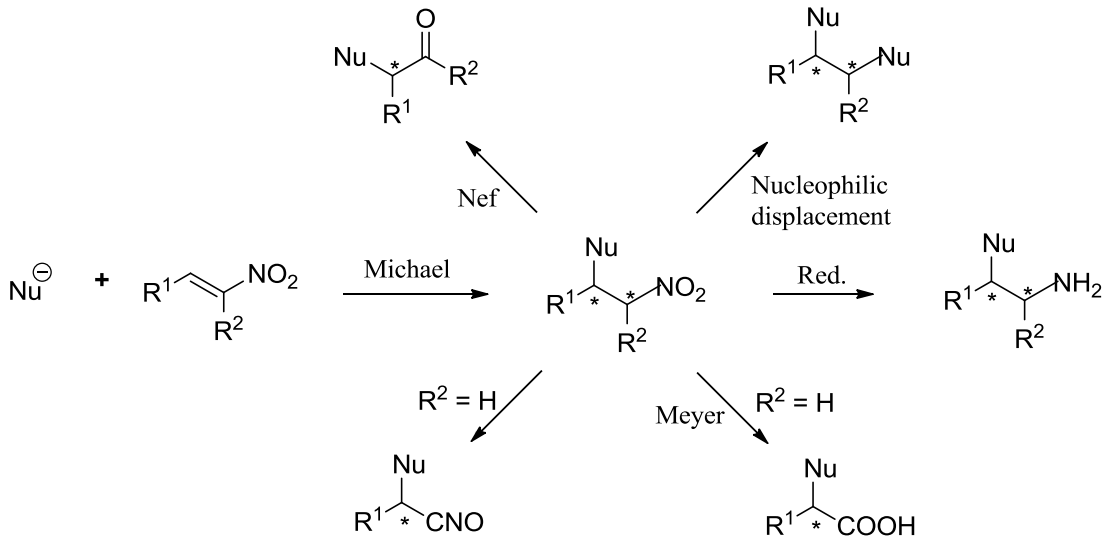


Scheme 2.1: The mechanism for the Michael addition.[145]

Indeed, the catalytic asymmetric version of this reaction employing chiral catalysts has developed significantly over the last few years.,[27,57] primarily due to the advent of organocatalysis. This is discussed in full in section 1.4.

2.1.2 The Nitroalkenes

Among the Michael acceptors the nitroalkenes stand out as being particularly attractive substrates for a number of reasons. Firstly, the nitro functionality itself is a very powerful electron-withdrawing group and this characteristic renders the nitroalkenes reactive substrates for 1,4-conjugate additions.[147] Secondly, because of the versatile reactivity of the nitro group it can be conveniently transformed into a host of other functional groups.[148] Some of the transformations that the nitro group can undergo, including the Nef reaction,[149] nucleophilic displacement,[150] reduction to an amine,[151] the Meyer reaction[152] and conversion into a nitrile oxide,[153] are shown in scheme 2.2.



Scheme 2.2: Reactions associated with the nitro group.[148]

Consequently, the nitroalkenes are extremely useful for the construction of highly functionalised synthetic building blocks. Lastly, unwanted side-reactions, such as direct addition at the heteroatom, are avoided, a problem which cannot be ignored when working with other functional groups such as ketones and particularly aldehydes.[145,154]

2.1.3 1,3-Diketones as pronucleophiles

The importance and usefulness of β-dicarbonyl compounds cannot be overemphasised. Currently, they are used in the construction of C-C bonds, in building carbo- and heterocycles, as versatile intermediates and synthons in multistep and complex organic synthesis, in modern stereo- and enantioselective synthesis and in medicinal, combinatorial and solid-phase chemistry.[155] Hence the preparation of compounds containing this subgroup has received much attention. In recent times impressive progress has been made using metal free organocatalysts in the asymmetric addition of aldehydes, ketones, ketoesters and malonate esters to nitroolefins. There has been fewer reports of successful additions of β-diketones to nitroolefins and this stimulated us to further investigate this reaction. To the best of our knowledge, Brunner *et al.* described the first enantioselective addition of a β-diketone to a nitroolefin in 1996 (*ee* < 30%),[156] with the first report of a highly enantioselective addition only appearing in 2005.[157] Subsequent publications by Wang[158] and Terada, [159] amongst others,[160] have

also described the selective addition of a β-diketone to β–nitrostyrene using bifunctional organocatalysts.

2.1.4 Cinchona alkaloids as organocatalysts

Cinchona alkaloids, such as quinine, Figure 2.1, and its stereoisomer quinidine, are known to serve as bifunctional organocatalysts and they currently play a very prominent role in the field of organocatalysis.[143,161] In 1981, Wynberg and Hiemstra[14] reported that these naturally occurring compounds were efficient (but moderately selective) catalysts for 1,4 addition of thiols to cyclohexenones. They proposed that the catalyst deprotonated the thiol through the basic quinuclidine nitrogen atom and postulated that the catalyst also stabilised the enolate formed in the 1,4-addition step (through hydrogen bonding with the hydroxyl moiety of the catalyst). This approach is inspired by the efficacy and selectivity of enzymatic catalysis.[162]

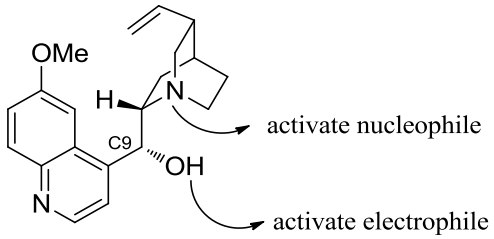
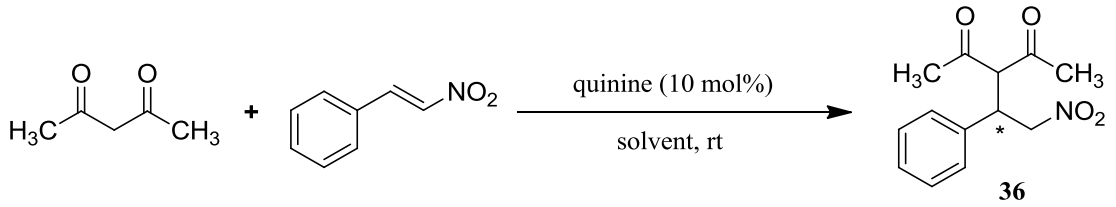


Figure 2.1: Quinine; a simple, naturally occurring organocatalyst exhibiting the basic quinuclidine ring and the H-bonding hydroxyl moiety.

A convenient feature of this privileged class of compounds is their availability in two pseudo-enantiomeric forms, therefore allowing access to both enantiomers of a product with similar selectivities (this is discussed in detail in section 2.3.1). Moreover, cinchona alkaloids have displayed considerable versatility as catalysts and are invaluable in almost every branch of chemistry concerned with chirality.[81] Apart from the conjugate addition, they have been used to catalyse a broad range of chemical transformations, including Baylis-Hillman, nitroaldol and electrophilic amination reactions.[161] From this perspective, the cinchona alkaloids seemed ideally placed to act as the cornerstone of our organocatalytic research.

2.2 Solvent screen

We anticipated that solvent choice would have a large effect on the catalytic activity of a bifunctional catalyst[82] and began our study by performing a solvent screen for the organocatalysed Michael addition of 2,4-pentandione to *β*-nitrostyrene, Scheme 2.2. Quinine was chosen as the model catalyst for the solvent screen as it is inexpensive and commercially available.



Scheme 2.2: The Michael addition of 2,4-pentanedione to *β*-nitrostyrene using quinine as the catalyst.

The results for the solvent screen are shown in Table 2.1. The stereochemistry of the major product was confirmed as (*R*) by comparing the specific rotation of the product with literature values.[159] For this initial study the reaction time was kept constant (24 hours) to allow an equitable comparison for the catalyst activity in the respective media.

Table 2.1: Solvent screen for the addition of 2,4-pentanedione (2 equiv) to *β*-nitrostyrene using quinine (10 mol%) as organocatalyst. All yields are isolated except entries 5 and 9, which were determined by ^{1}H NMR spectroscopy.

Entry	Solvent	Aprotic/ protic	Time (h)	Yield (%)[a]	*ee* (%)[b]	E_T30[163]	α[163]	β[163]
1	Toluene	Aprotic	24	89	16	33.9	0	0.11
2	MeCN	Aprotic	24	96	2	45.6	0.19	0.40
3	1,4-Dioxane	Aprotic	24	72	14	36	0	0.37
4	EtOAc	Aprotic	24	35	9	38.1	0	0.45
5	Acetone	Aprotic	24	82	3	42.2	0.08	0.43
6	THF	Aprotic	24	12	12	37.4	0	0.55
7	DMF	Aprotic	24	49	2	43.8	0	0.69
8	Ethylene Glycol	Protic	24	90	0	56.3	0.9	0.52
9	MeOH	Protic	24	80	2	55.4	0.98	0.66
10	1,4-butanediol	Protic	24	78	4	53.5	0.63	0.68
11	1-butanol	Protic	24	89	8	48.6	0.79	0.84

Results were examined for any correlation between yield or enantioselectivity with polarity (E_T30), H-bond donor ability (α values) and H-bond acceptor ability (β values).[163] A good correlation was observed when the enantiomeric ratio was plotted as a function of solvent polarity, E_T30 (Figure 2.2). The enantioselectivity directly depends on the solvent polarity with the less polar solvents giving superior enantioselectivity. A similar trend was observed in both aprotic solvents (Figure 2.2) and protic solvents (Figure 2.2, inset).

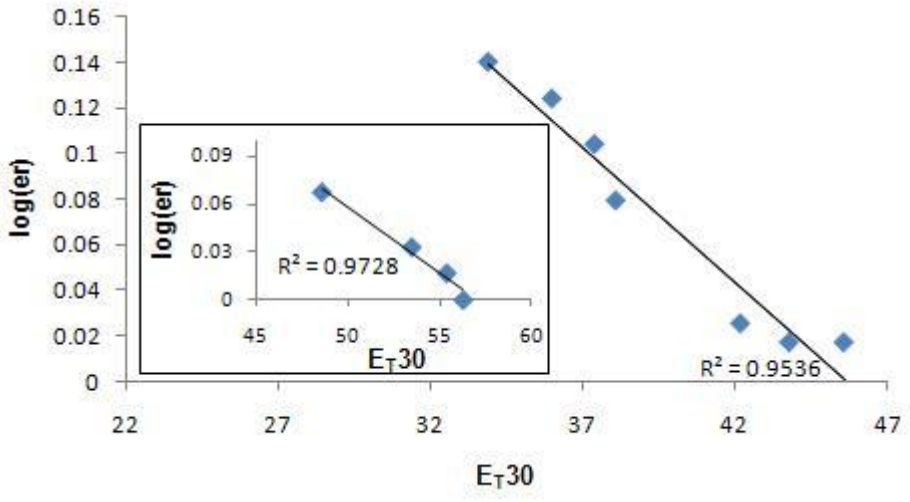


Figure 2.2: Plot of enantiomeric ratio (er) against polarity (E_T30) for aprotic solvents. Insert: Plot for protic solvents.

2.2.1 Effect of solvent on yield

No direct correlation was observed in terms of reaction yield, although there was a considerable variation from solvent to solvent. Whilst this was not unexpected, predictably the protic solvents gave high yields due to their ability to activate the Michael acceptor. Contrastingly, THF is conspicuous due its poor performance, giving a yield of just 12% after 24 hours. Toluene emerged as the highest yielding of the aprotic solvents.

2.2.2 Effect of solvent on enantioselectivity

No direct correlation was observed between enantioselectivity and H-bond donor (α) or H-bond acceptor (β) ability (Table 2.1), although the protic solvents did give poorer enantioselectivity when compared to the aprotic solvents. This was as expected as the

achiral protic solvents and chiral catalyst were anticipated to competitively activate the reaction,[82,84] thereby disrupting the catalyst's mode of action. Although acetonitrile generated a high yielding reaction it was not chosen for the subsequent catalyst screen due to its propensity to disrupt the hydrogen bonding action of bifunctional catalysts and hence lower the enantioselectivity (2% *ee* with quinine).

The less polar solvent, toluene, gave a good yield and an improved *ee* and was clearly more effective at promoting a selective reaction than the polar solvents. As such toluene was selected as the solvent of choice for the subsequent catalyst screen.

2.3 Catalyst screen

From an asymmetric synthesis viewpoint, arguably the most exciting property of the organocatalysts in the cinchona family is their adaptability. A quick scan of the literature reveals the striking diversity of modifications of the cinchona scaffold which are accessible, with various groups capable of conferring specific properties for promoting a broad spectrum of reactions.[17,81,161] This pliability supported our view that a cinchona derived catalyst would deliver a high-yielding, enantioselective Michael reaction for our chosen substrates. Accordingly, we undertook a series of experiments varying the catalyst structure whilst still retaining some of the core elements of the cinchona alkaloid; namely the quinuclidine ring and the quinoline moiety. The chiral scaffold, essential for the asymmetric construction of new bonds, would be provided by the cinchona backbone of the modified catalyst. We planned to adapt the catalyst structure in the hope of improving the enantioselectivity of the reaction without compromising on yield.

The role and choice of catalyst was explored in a catalyst screen involving several cinchona type organocatalysts. The Michael addition of 2,4-pentandione to *β*-nitrostyrene was employed as the model reaction, with toluene as the solvent of choice.

2.3.1 Other cinchona alkaloids

After testing quinine as a catalyst for the addition of 2,4-pentanedione to *β*-nitrostyrene it seemed logical to assess the catalytic ability of a selection of very similar, readily available compounds in the cinchona family. The structures of the eight major

compounds in the cinchona family are shown in Figure 2.3 and the experimental results from a selection of them are shown in Table 2.2.

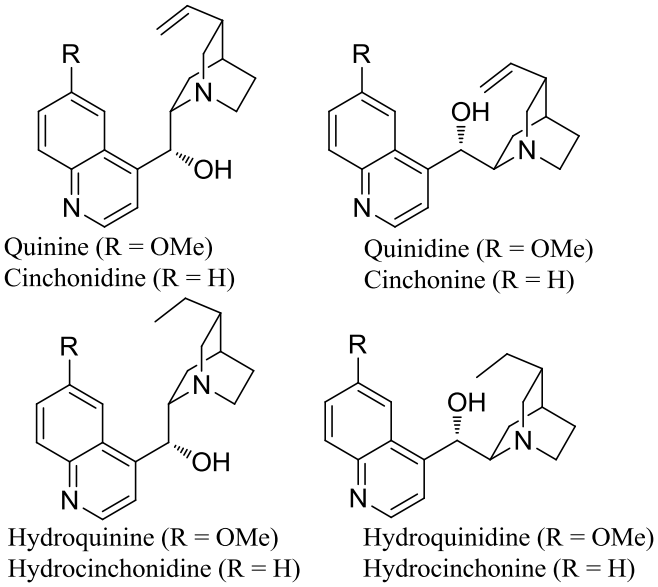


Figure 2.3: Structures of the eight major Cinchona alkaloids.

Predictably, minor changes in the catalyst structure resulted in trivial *ee* differences and overall the results show a similar pattern to those garnered for quinine; excellent conversion tainted by poor enantioselectivity.

Table 2.2: Yields and enantiomeric excess for the addition of 2,4-pentanedione (2 equiv) to nitrostyrene using unmodified members of the cinchona alkaloid family (10 mol%) as organocatalyst. All reactions were stirred in toluene for 24 hours.

Catalyst	Yield (%)	*ee* (%)
Quinine	89	16
Hydroquinine	92	16
Cinchonidine	82	4
Hydroquinidine	87	7
Cinchonine*	88	24

* Catalyst was 85% pure; the remainder was hydrocinchonine.

In the case of cinchonidine, the loss of the methoxy group on the quinoline motif marginally lowered both yield and enantioselectivity. Hydroquinine gave almost identical results to quinine, implying that the terminal olefin group on the quinuclidine ring has no effect on catalyst activity. Hydroquinidine and quinidine, and to a lesser extent cinchonine, exhibited poor enantiocontrol but their major products were the opposite configuration to the major products for the reactions catalysed by quinine,

hydroquinine and cinchonidine. This was to be expected given the pseudo-enantiomeric relationship between these stereoisomers. Figure 2.4 below shows quinidine, which, like all the cinchona alkaloids, has 5 stereogenic centres – N1, C3, C4, C8 and C9. At C8 and C9 it is stereogenically identical to cinchonine. Their related compounds, quinine and cinchonidine, have the opposite stereochemistry at C8 and C9.

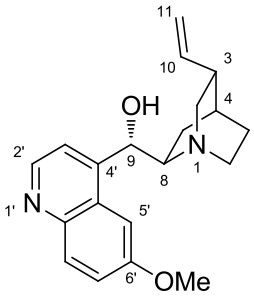


Figure 2.4: Quinidine, the pseudo-enantiomer of quinine.

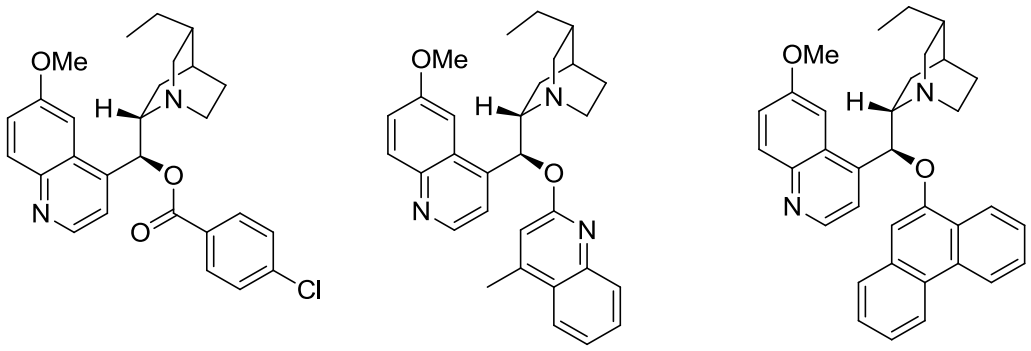
The absolute configurations at N1, C3 and C4 are homologous in every compound in the family. However, the other chiral carbons (C8 and C9) have opposite absolute configurations in quinine and quinidine (and in cinchonidine and cinchonine). These two chiral centres are considered responsible for the asymmetric induction in (organo)catalysis. Consequently, when a quinine derivative is employed as a chiral organocatalyst or ligand, the corresponding quinidine derivative usually gives the opposite enantiomer of the same product with comparable selectivity.[81,164] This proved to be the case in our research.

The poor enantioselectivity observed for these compounds was far from unexpected; the cinchona alkaloids have previously shown themselves to be only slightly selective catalysts in Michael type reactions using a range of substrates.[82,89] We therefore set about making small adjustments to the structure of the catalyst with the aim of gaining greater stereocontrol on the reaction.

2.3.2 Cinchona alkaloid ethers

The first subcategory of modified catalysts tested, compounds **37**, **38**, and **39**, are shown below (Figure 2.5). The three compounds are commercially available and were purchased from Aldrich. They are all similar in that the parent compound for each is

hydroquinidine, with its hydroxyl functionality having undergone a functional group interchange to an ether, or in the case of **37**, an ester. Although this deprived the catalysts of H-bonding ability we hoped that the increased steric bulk at the pivotal C9 position would improve the enantioselectivity of the catalyst by selectively blocking one face of the β-nitrostyrene acceptor at the conjugate addition step.



37 **38** **39**

Figure 2.5: Structures of modified cinchona catalysts **37**, **38** and **39**.

Deng and co-workers had previously reported excellent results for the addition of malonate esters to β-nitrostyrene using catalysts with increased steric bulk at the C9 position, albeit with a further modification of the parent compound whereby a potential H-bond donor was provided *via* a hydroxy group on the aromatic moiety.[82] These compounds have also been used extensively as catalysts in asymmetric dihydroxylations[165] and cyanation of ketones.[166] The results for our experiments are shown in Table 2.3.

Table 2.3: Yields and enantiomeric excess for the addition of 2,4-pentanedione (2 equiv) to β-nitrostyrene using modified hydroquinidine compounds (10 mol%) as organocatalyst. All reactions were stirred in toluene for 144 hours.

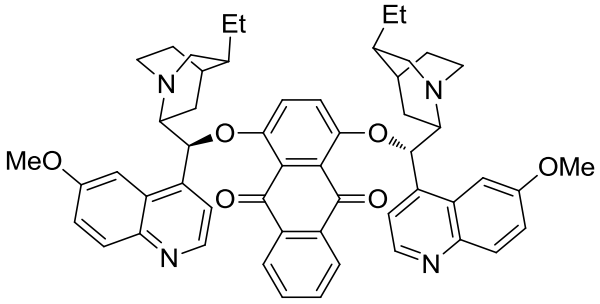
Catalyst	Yield (%)	*ee* (%)
37	42	21
38	32	11
39	53	35

Although there was a substantial jump in *ee* (35% for catalyst **27** compared to 16% for quinine), this was at the expense of yield. Quinine had borne an essentially quantitative amount of product in just 24 hours. By comparison, catalyst **39** could only furnish half of this in 144 hours, with the other catalysts even less effective. Again, it

is noteworthy that these catalysts afforded the opposite (*S*) enantiomer to quinine as the major stereoisomer, owing to the fact that the parent compound is quinidine.

2.3.3 Ether-bridged dimeric cinchona alkaloids

There have been several reports of asymmetric C-C bond forming reactions[81,167] employing the dimeric catalysts $(DHQD)_2PHAL$ **40**, $(DHQ)_2AQN$ **34** and $(DHQD)_2PYR$ **41**, all shown below (Figure 2.6). All three have been used to catalyse Michael additions with β-nitrostyrene (and α,β-unsaturated ketones) as the electrophile,[168] with the Sharpless ligand **41** in particular, in substoichiometric amounts, delivering superb enantio- and diastereoselectivities when using α,α-dicyanoalkylidenes as the nuclephilic species[169] and excellent enantioselectivities in the sulfa-Michael addition of aromatic thiols to cyclic enones.[170] Furthernore, this catalyst had proved compatible with 1,3-diketone pronucleophiles for Calter and co-workers in the Feist-Bénary reaction.[171] Catalyst **40** has also delivered excellent enantio- and diastereoselectivity in the Michael addition of 1,3-diketones to alkynones.[167] We investigated the catalytic ability of these two dimeric alkaloids, along with catalyst **34**, an excellent catalyst in the α-fluorination of oxindoles (as discussed in section 1.5.4.1)[135] and in dynamic kinetic resolutions,[172] for our chosen reaction. The results of these experiments are shown in Table 2.4.



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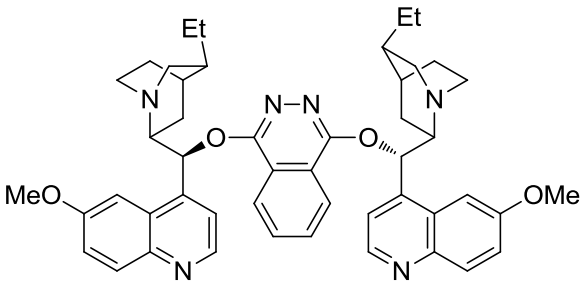

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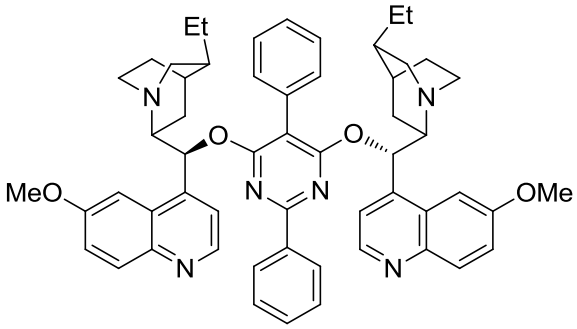


41

Figure 2.6: Structures of dimeric cinchona derived catalysts **34**, **40** and **41**

Catalysts **34** and **41** revisited the low yields which had characterised the cinchona alkaloid ether reactions, although the former did deliver, heretofore, the highest *ee*. On the contrary, **40** gave a superior yield and showed no selectivity.

Table 2.4: Yields and enantiomeric excess for the addition of 2,4-pentanedione (2 equiv) to *β*-nitrostyrene using dimeric cinchona alkaloids (10 mol%) as organocatalyst. All reactions were stirred in toluene for 144 hours.

Catalyst	Yield (%)	*ee* (%)
34	6	55
40	77	Racemic
41	7	5

Overall, the dimeric catalysts proved unsuitable for our chosen reaction. Catalyst **40** gave a yield approaching that of quinine but this was over a 144 hour period, compared to 24 hours for the unmodified alkaloids. This was a disappointing outcome given the catalysts' prowess as an enantioselective promoter of other reactions using similar substrates. Likewise, increasing the steric bulk at the pivotal C9 position had not brought about the improved *ee* values we had hoped for. Consequently we decided to alter our approach to the catalyst design.

2.3.4 Improving the H-bond donor ability

The results thus far have indicated that the presence of a hydrogen-bond donor is essential for the promotion of the reaction. All of the catalysts tested which did not have a hydroxyl group gave sluggish reactions. In contrast, those which did possess the –OH functionality consistently gave high yields (albeit with moderate to poor enantioselectivity).

Hiemstra and Wynberg, by whom the pioneering work in this field was done, established this by conducting systematic studies on catalyst structure for the 1,4-conjugate addition of thiophenol to cyclohexenone.[14] It has also been recognised by Cucinotta and co-workers, who corroborated the role of the alcohol functionality in the catalytic process by demonstrating that when the C9-OH was replaced with O-benzoyl the stereoselectivity of the reaction dropped drastically.[173] In their seminal publication,[14] Hiemstra and Wynberg actually predicted that derivitisation of cinchona alkaloids with the aim of improving H-bond donating ability would provide the catalyst with greater potential for performing chemical transformations, i.e. the catalyst would have an enhanced ability to activate the electrophilic partner in the reaction by providing a superior binding affinity.

2.4 Thiourea organocatalysts

Given that ureas, and in particular thioureas, are known to outperform traditional hydrogen-bond-donating additives such as methanol and water in 'mole per mole' comparisons,[174] it seemed a judicious move to replace the C9 hydroxy group on the cinchona structure with a *N′*-arylthiourea moiety. Connon *et al.* and Dixon and co-workers had independently found these compounds to be significantly more active and selective catalysts than the natural alkaloids themselves[89,91] in Michael additions using *β*-nitrostyrene as the electrophile and malonate esters as the pronucleophile. This chemistry had developed from the accomplishments of Sóos and co-workers,[90] who had found that the introduction of the more acidic thiourea moiety into the catalyst was necessary to obtain efficient catalytic activity for the conjugate addition of nitromethane to chalcones. The inspiration for this work could be credited to earlier publications by Curran,[175] Jacobsen[176] and Schreiner,[177,178] all of whom reported that thiourea additives significantly accelerated the rate of their chosen reactions.

2.4.1 *N′*-Arylthiourea moiety

Whilst Curran,[175] Jacobsen[176] and Schreiner[177,178] all contributed to the now conclusive evidence that thiourea compounds possess enormous ability as Lewis acids, Schreiner in particular (from a non-covalent organocatalysis viewpoint) disseminated a wealth of valuable information with his publications featuring simple *N*,*N′*-diaryl (thio)ureas as general acid organocatalysts in the early part of the decade. He reported that these compounds catalysed the Diels-Alder reaction between cyclopentadiene and α,β-unsaturated carbonyl compounds through a hydrogen-bonding mode of action. Thioureas were preferred over ureas because of their greater acidity (pK_a thiourea = 21.1, pK_a urea = 26.95)[179] and the fact that S is less electronegative than O, making self-association less favourable.[177] The tetra(trifluoromethyl)phenyl-substituted thiourea, Figure 2.7 below, was identified as the optimum catalyst for the reaction following some systematic structure variation. The powerful non-coordinating electron-withdrawing groups on the 3- and 5- position of the aromatic rings increased N-H acidity. It was also postulated that they rigidify the catalyst by polarising the adjacent H atoms, which facilitates a hydrogen-bonding interaction with the S atom (shown below). This stiffness is crucial to the efficacy of the catalyst; although thioureas and carbonyl compounds are known to complex, it is a modestly strong interaction of the order of 7 kcal mol^{-1} at room temperature in dichloromethane.[178,180] Therefore the attractive interactions are likely to be dominated by entropic effects. This implies that the strength of the interaction depends on the rigidity of the catalyst, i.e. the lack of flexibility is thought to minimise the entropic penalty upon complexation of the substrate.[177] The bidentate nature of the binding interaction is attractive also because it removes some conformational degrees of freedom.

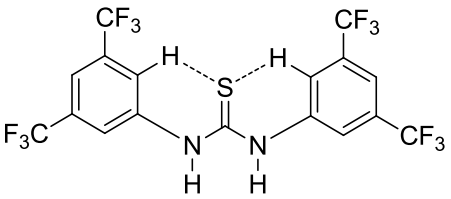


Figure 2.7: Schreiner's thiourea catalyst for the Diels-Alder reaction between cyclopentadiene and α,β-unsaturated carbonyl compounds. [178]

Catalyst rigidity and *N*-H acidity was also achieved by placing the trifluoromethyl groups on the 2- position of the aromatic ring but this hinders substrate/transition state

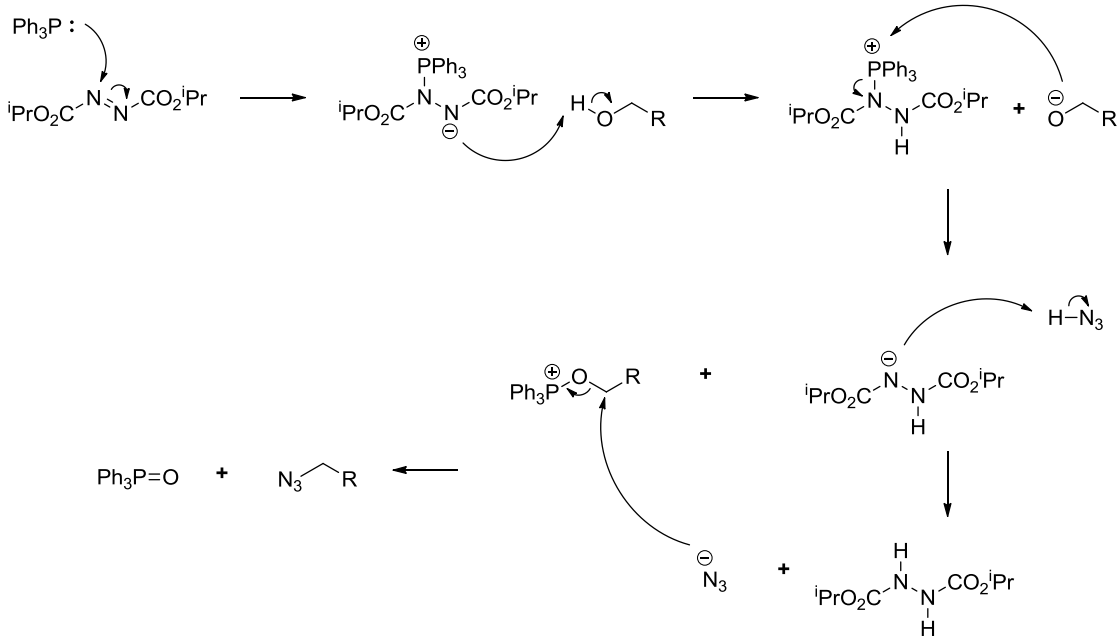
binding. Thus the 3,5-bis-trifluoromethyl substituted aromatic ring on the thiourea moiety was identified as the perfect accompaniment for the chiral environment and basic amine provided by the cinchona alkaloid.

2.4.2 Synthesis of thiourea catalysts

Thus, replacement of the C9 hydroxy group on the cinchona structure with a *N′*-arylthiourea moiety was desirable and a 2-step protocol for this transformation was identified in the literature.[89] It iinvolved a functional group interchange of the alcohol to a primary amine, followed by nucleophilic attack of this amine on the electron-poor carbon of the appropriate isothiocyanate compound to yield the thiourea product.

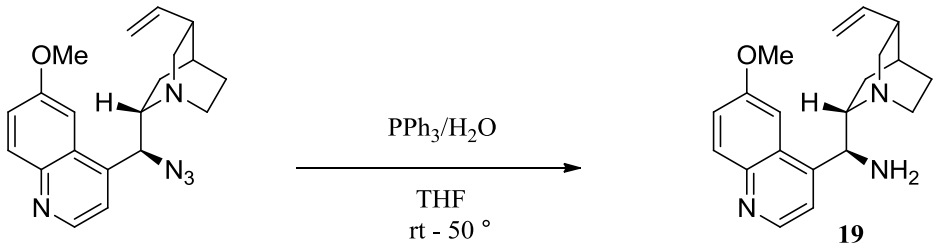
2.4.2.1 The Mitsunobu reaction

At the outset of our work in this area the accepted method for the preparation of the 9-amino-(9-deoxy)-cinchona alkaloids was to perform a Mitsunobu reaction on the alcohol, using an azide ion, garnered from the deprotonation of hydrazoic acid, as the nucleophile.[89,91] Clayden proposes the mechanism for this reaction as shown in Scheme 2.3 below.[145] Since it is S_N2 chemistry that is being performed the carbon adjacent to the –OH group (C9) always undergoes inversion of stereochemistry.



Scheme 2.3: Mechanism for the Mitsunobu reaction using an azide ion as the nucleophile.[145]

This method was certainly a means to an end as it involved preparing a solution of the highly explosive and toxic gas hydrazoic acid (in toluene), which had to be titrated against a standardised NaOH solution to calculate its concentration before it was used. The solution was prepared according to the protocol of Wolff.[181] More recently a new method has been developed which uses the safer and more convenient commercially available reagent diphenyl phosphorylazide.[182,183] Both approaches were followed by an *in-situ* Staudinger reduction (Scheme 2.4, where the product is 9-amino-(9-deoxy)-*epi*-quinine **19**), whereby the azide product was converted to a primary amine using triphenyl phosphine and water. This reaction is useful as it allows the use of $-N_3^-$ as an $-NH_2$ synthon.

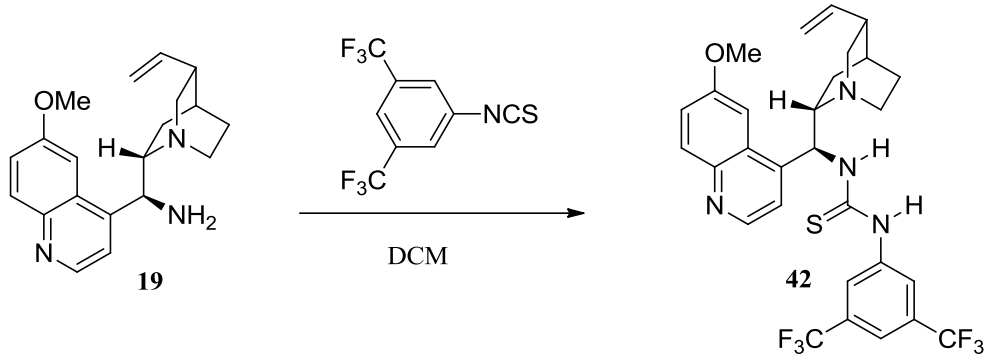


Scheme 2.4: Staudinger reduction of the cinchona-based azide to a primary amine.

Mitsunobu chemistry requires stringent air and moisture-free conditions but the amine product was typically > 90% pure by NMR spectroscopy and was always used in the next step without further purification. More recent publications have reported a synthesis which involves mesylating the –OH to convert it into a better leaving group and then attacking the C9 with an azide nucleophile, in the form of its sodium salt.[184]

2.4.2.2 Formation of the Thiourea

The thiourea product was prepared by reacting the 9-amino-(9-deoxy)-*epi*-cinchona alkaloid with the commercially available 3,5-(bis-trifluoromethyl)phenyl isothiocyanate, shown in Scheme 2.5. In this case the modified cinchona alkaloid is 9-amino-(9-deoxy)-*epi*-quinine.



Scheme 2.4: Preparation of the cinchona based thiourea organocatalysts.

As expected with amines, flash column chromatography was difficult with the thiourea catalysts and therefore purification was non-trivial. This step of the catalyst synthesis has been reported with poor yields[89,91] and this proved to be the case in our hands (32% – 52%), which is not ideal when one considers the high molecular weight of the compound (and hence the relatively large mass required in catalytic reactions).

2.4.3 Literature Reports of thiourea organocatalysts

Cinchona alkaloid derived thiourea organocatalysts had been previously reported as powerful (and importantly highly enantioselective) catalysts in Michael additions to β-nitrostyrene using malonate esters as the nucleophile.[89,91] Generally speaking, β-diketones are less reactive than their malonate ester cousins and this may be rationalised by the assumption that they are (to varying degrees) enolised and their enols are stabilised by strong intramolecular H-bonding.[185]

Possibly because of their diminished reactivity, literature reports of organocatalytic β-diketone additions to β-nitrostyrene are less prevalent than malonate additions. Prior to our own investigations, there had been one previous report of a Michael addition of 2,4-pentanedione to β-nitrostyrene using a cinchona derived thiourea organocatalyst - by Wang and co-workers.[158] They had reported a mediocre 47% yield in 48 hours with THF as the solvent, albeit with excellent enantioselectivity. Nonetheless, this seemed to be a peculiar result given that we had previously found that the natural alkaloids, with their inferior H-bonding ability compared to the thiourea compounds, had given quantitative product yields in some solvents in half the time reported by Wang. This, coupled with the fact that these catalysts had previously shown themselves to be

excellent enantioselective promoters of Michael additions to *β*-nitrostyrene using similar pronucleophiles,[89,91] indicated that the reaction conditions used in this publication were not optimised. In light of this we conducted a series of experiments to ascertain if the cinchona derived thiourea catalysts would provide the high yielding, enantioselective reaction we expected.

2.4.4 Varying the structure of the thiourea organocatalyst

We had previously found that varying the parent alkaloid core had brought about detectable variations in *ee*, Table 2.2 (and where the stereochemistry at C8 and C9 was inverted the opposite stereoselectivity was observed in the product – section 2.3.1). We therefore synthesised a family of thiourea cinchona catalysts and their structures are shown in Figure 2.8. Catalyst **42** was synthesised from 9-amino-(9-deoxy)-*epi*-quinine (**19**) whilst the parent compounds for catalysts **43** and **44** were 9-amino-(9-deoxy)-*epi*-quinidine (**32**) and 9-amino-(9-deoxy)-*epi*-cinchonidine (**18**) respectively.

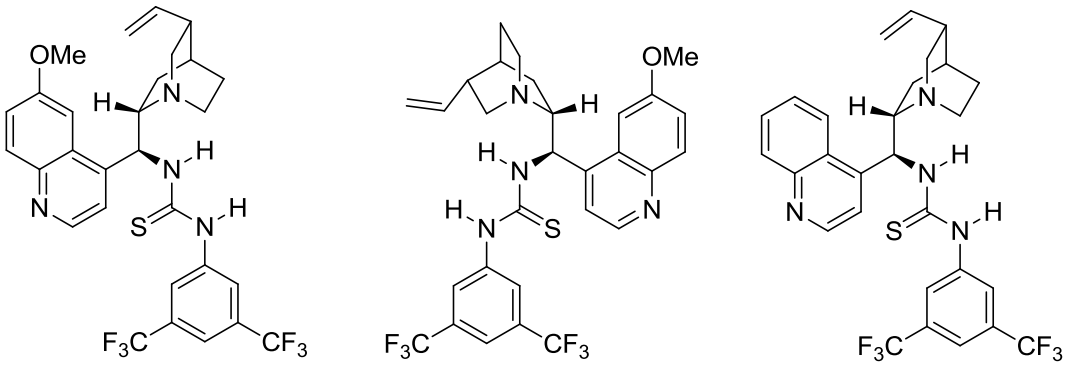


Figure 2.8: The structures of the thiourea catalysts used for the addition of 2,4-pentanedione to *β*-nitrostyrene.

The catalysts were tested for their activity in the addition of 2,4-pentanedione to *β*-nitrostyrene, with toluene as the solvent of choice. The results of these experiments are shown in Table 2.5.

Table 2.5: Results for the addition of 2,4-pentanedione (2 equiv) to nitrostyrene using thiourea compounds (10 mol%) derived from the cinchona alkaloid family as organocatalyst. All reactions were carried out in toluene at room temperature.

Catalyst	Parent alkaloid	Time (h)	Yield (%)	*ee* (%)	Product configuration
42	Quinine	1	95	97	(*S*)
43	Quinidine	1	92	94	(*R*)
44	Cinchonidine	1	96	92	(*S*)

Gratifyingly, increasing the H-bonding proclivity of the catalyst *via* the thiourea moiety resulted in indubitably superior activity and enantioselectivity. All three catalysts furnished the product in excellent yields in just 1 hour. In the case of **44**, loss of the methoxy group on the quinoline ring resulted in a slight drop in *ee*. The stereochemistry of the major product generated by catalyst **42** was (*S*) configured whilst the corresponding major product associated with quinine, its parent alkaloid, was (*R*) configured. This was to be expected since they have opposite configurations at C9 due to the Mitsunobu chemistry performed on quinine during the process of synthesising catalyst **42**. The (*R*) product enantiomer was provided by catalyst **43**, whose parent alkaloid was quinidine. The HPLC chromatograms in Figure 2.9 below confirm the accessibility of both product stereoisomers for this reaction. Connon and co-workers have also observed parallel reversal of selectivity in the addition of malonate esters to β-nitrostyrene.[89]

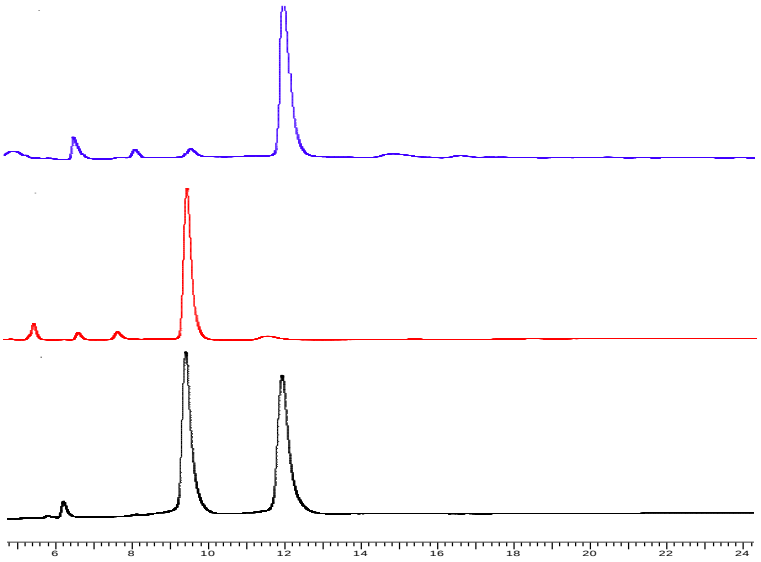


Figure 2.9 HPLC chromatograms of the product arising from the addition of 2,4-pentanedione to *β*-nitrostyrene. ─ product of reaction promoted by catalyst **42**. ─ product of reaction promoted by catalyst **43**. ─ racemic product, KO^{t}Bu used as base.

Interestingly, the above results demonstrate how crucial choice of solvent is. In fact, the efficacy and elegance of this particular family of catalysts in this specific reaction appears to have been previously misrepresented. The excellent result given by catalyst **42** above is a marked improvement from the results outlined by Wang *et al.* in 2005,[158] who reported a 47% yield in 48 hours for the same catalyst in THF.

2.4.5 Mode of action

A number of reports exist investigating the mechanistic aspects of bifunctional catalysis by natural cinchona alkaloids[173] and their thiourea analogues[186] but the mechanism specifically relating to the Michael addition has received only limited consideration. In a general sense it is clear that these compounds are capable of organising the reaction centres to their optimal arrangement to achieve enantioselectivity. This is obvious from the high *ee* values obtained from these catalysts.

One widely accepted rationalization has been presented by Takemoto *et al.*,[85] who undertook some kinetic studies, using his own chiral bifunctional thiourea catalyst shown in Figure 2.10. Using this catalyst, Takemoto's group had reported the addition of 2,4-pentanedione to *β*-nitrostyrene in excellent yields and enantioselectivity. Since nitro groups are known to form hydrogen bonds with (thio)ureas,[187] the electrophile is

assumed to be activated *via* H-bond assisted coordination of this functionality to the thiourea (below, Figure 2.10). The protonated tertiary amine (resulting from the deprotonation of the pronucleophile) then directs the enolate to attack the less hindered face. This implies that the C-C bond formation step takes place *via* the formation of a ternary H-bonded complex and the enantioselectivity in the reaction resulting from the binding mode of the nitroolefin to the thiourea.

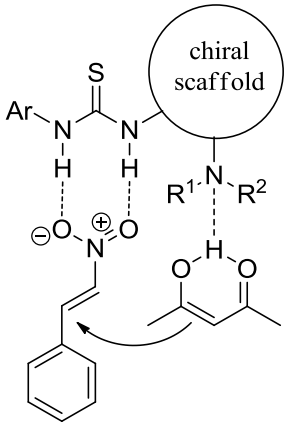


Figure 2.10: Dual activation concept proposed by Takemoto *et al*, showing activation of the electrophile by the thiourea moiety and formation of the enolate by the tertiary amine.[85]

However, in an exclusively theoretical study later published by Pápai and Sóos,[188] it was shown that while calculations do support Takemoto's hypothesis, and explain the preferred stereochemistry of the product, an opposite coordination scheme is actually energetically slightly more stable. By examining the various conformations of the catalyst itself and investigating substrate binding through density functional theory calculations they were able to predict the optimal structural orientation of all three components in the reaction in relation to one another. After an exhaustive computational study, their work culminated in the prediction that the activation of the electrophilic component is achieved through an interaction with the protonated amine rather than with the H-bond donors of the thiourea. Figure 2.11 below shows the schematic view of that transition state as deduced by Pápai and Sóos. The key intermediate in this model is the catalyst-nucleophile ion pair which is characterized by multiple H-bonds involving the *N*-H groups of the thiourea as well.

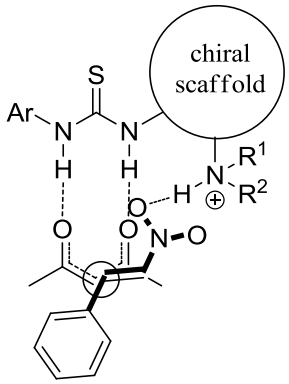


Figure 2.11: More recent coordination scheme proposed by Sóos *et al*, depicting the most energetically favourable arrangement of nucleophile, electrophile and thiourea organocatalyst.[188]

This transition state represents a more energetically desirable pathway for the C-C coupling process as compared to Takemoto's (albeit logical) proposition and accounts for (and agrees with) the enantioselectivity observed in the reaction, as it predicts the preferential relative orientation of the approaching substrates in a well-defined chiral environment.

Figure 2.12 shows the structure of Takemoto's catalyst, **22** and the quinine derived thiourea organocatalyst **42** used in our experiments. The compounds comprise the same active sites and when examined closely, they are very similar. The thiourea moiety and the basic tertiary amine are the same number of bonds away from each other in both structures. Furthermore the chiral carbons are in the same positions relative to both of the critical functional groups and this appears to be the most favourable relative arrangement of the Lewis acid and amine moieties to deliver a stereoselective conjugate addition. Given the notable structural similarities of both catalysts, it is reasonable to assume that the reaction pathway evaluated for 2,4-penatandione and β-nitrostyrene using Takemoto's catalyst is also applicable to the reaction mechanism pertaining to our own catalysts.

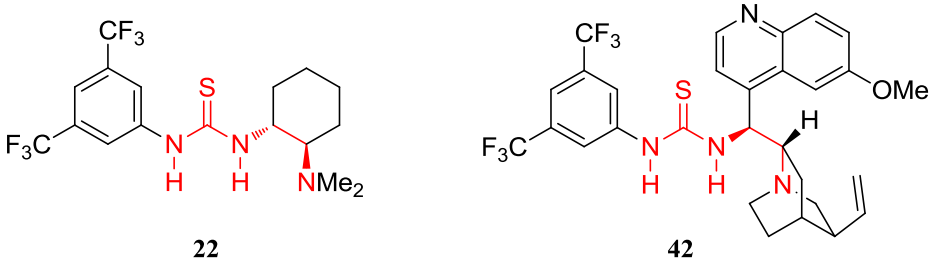


Figure 2.12: The structures of Takemoto's catalyst (**22**) and quinine-derived thiourea catalyst **42**.

2.4.6 Varying the pronucleophile

The quinine derived thiourea catalyst's excellent performance with 2,4-pentanedione prompted us to investigate the scope of this reaction in terms of the structure of the pronucleophile. The structures of the compounds chosen for this screen are shown in Figure 2.13, pronucleophiles 1-8.

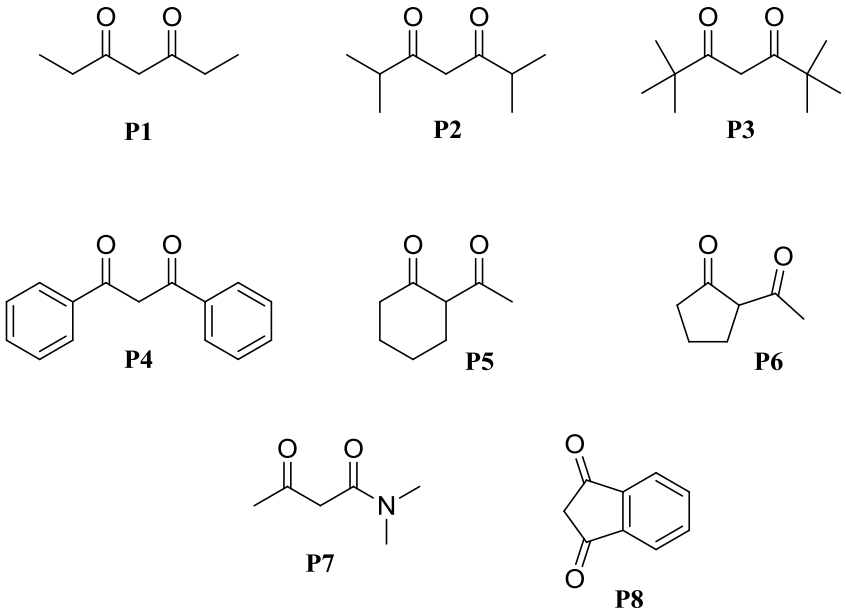


Figure 2.13: 1,3-Dicarbonyl compounds screened in the pronucleophile study.

A number of these compounds have been added to *β*-nitrostyrene using metal based systems[189,190], while Toma and co-workers have conducted a thorough examination of the reactivity of a broad range of Michael donors[185] using pyrrolidine based catalysts in ionic liquids. Although some have been investigated using thiourea based compounds to promote the reaction.[191] none of the pronucleophiles shown in Figure 2.13 had been reported with cinchona-derived thiourea catalysts. As catalyst **42** had furnished the

highest *ee* with 2,4-pentanedione it was the catalyst of choice for this set of experiments, the results of which are shown in Table 2.6.

Table 2.6: Results for the addition of pronucleophile (2 equiv) to *β*-nitrostyrene using catalyst **42** (10 mol%) to promote the reaction. All reactions were carried out in toluene at room temperature.

Pronucleophile	Yield (%)	Time (h)	*ee* (%)	Product
P1	92	1	96	**45**
P2	84	6	93	**46**
P3	30	96	99	**47**
P4	93	4	94	**48**
P5	0	96	-	-
P6	89	12	70*	**49**
P7	0	96	-	-
P8	0	1	-	-

* Diastereomeric ratio = 1:1.2 (determined by ^{1}H NMR), *ee* of major isomer = 70%.

The results gleaned from this study were compelling. Augmenting the aliphatic chain by a single carbon (3,5-heptanedione, pronucleophile **P1**) did not have any discernable effect on the reaction. On the other hand, altering the substitution to an isopropyl group (pronucleophile **P2**) did result in a longer reaction time. Interestingly, while the extra steric bulk associated with this group did affect the time it took for the reaction to go to completion, it did not improve the *ee* as one might have expected.[190] The symmetrical aromatic pronucleophile, dibenzoylmethane (**P4**), gave a reaction time of 4 hours, which is considerably longer than the corresponding reactions involving 2,4-pentanedione or 3,5-heptanedione. It is probable that the slight raise in steric mass[192] is accountable for this since dibenzoylmethane and 2,4-pentanedione have almost identical pK_a values (13.35 and 13.3 in DMSO respectively).[179]

N,*N*-dimethylacetoacetamide (**P7**) proved totally unreactive and this can be attributed to the fact that it has a significantly higher pK_a value (18.2 in DMSO)[193] than that of the other 1,3-dicarbonyl compounds tested. The amide functionality is less electron-withdrawing than the keto group and hence the *α*-hydrogen becomes less acidic. It is likely in this case that deprotonation does not happen, since the unreacted starting materials were returned. The cyclic diketone, 1,3-indandiole (**P8**), furnished no conjugate addition product whatsoever, most likely due to its inclination to react with itself in both basic and acidic conditions. This pronucleophile is a notoriously reactive

entity and is known to self condense easily,[194] although it has been compatible with *β*-nitrostyrene previously with a less potent catalyst promoting the reaction.[185] Its heightened reactivity is due to the fact that its enol form cannot be stabilised by hydrogen bonding like that of the acyclic ketones.

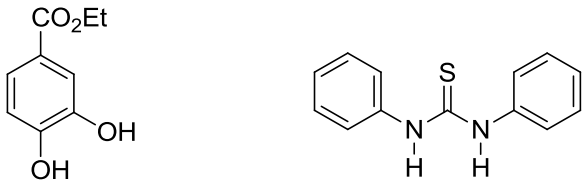
The cyclohexyl derivative **P5** was another unreactive substrate. Toma and co-workers reported the same result for this compound in their ionic liquid proline catalysed addition to *β*-nitrostyrene. They suggested that the reduced reactivity was due to the geometry of **P5** which allows the formation of a hydrogen bond-stabilised enol. Despite this result catalyst **42** was capable of constructing contiguous stereocentres when the ring size was decreased to the cyclopentyl derivative **P6** and this resulted in a change in geometry and a high yielding Michael reaction. This reaction was notable for a drop in *ee* in comparison to the values obtained for the other Michael donors and the dr was also disappointing, indicating that the catalyst is perhaps more congruous with single stereocentre construction for this reaction. There is a precedent for this poor diastereoselectivity (coupled with excellent enantioselectivity) with alternative Michael acceptors such as enones.[195]

2.4.6.1 Dipivaloylmethane as the pronucleophile

The ^{t}Bu substituted *β*-diketone, dipivaloylmethane, compound **P3** in Figure 2.13, was expected to be too sterically hindered to undergo a Michael addition. To our delight catalyst **42** successfully generated a Michael addition of dipivaloylmethane to β-nitrostyrene. To the best of our knowledge, the chiral or achiral Michael addition of dipivaloylmethane to an activated olefin has never been reported.

After a successful organocatalytic reaction our attentions turned to synthesising the racemic product in order to calculate the *ee* for the reaction. Heretofore our racemic products had been conveniently generated using KO^{t}Bu (5 mol%) as the base. This, along with DABCO and triethylamine in various substoichiometric and stoichiometric quantities, returned unreacted starting material when used with this sterically demanding substrate. The fact that the Michael addition would occur in the presence of the catalyst indicated that a Lewis acid moiety was required along with the basic amine to synergistically promote the reaction. Accordingly, H-bonding additives which had been successfully employed in several other chemical transformations

involving stubborn substrates[196] were used in conjunction with the aforementioned bases in various ratios. The structures of the additives are shown in Figure 2.14.



50 **51**

Figure 2.14: Structures of the H-bonding additives used in conjunction with a base with the aim of promoting the conjugate addition of dipivaloylmethane to *β*-nitrostyrene

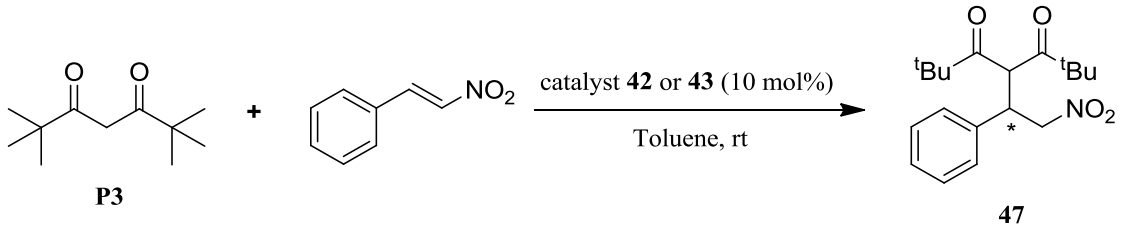
Much to our disappointment, all of the experiments conducted using this strategy returned unreacted starting material. Another approach that proved unsuccessful was using less sterically imposing bases to create the enolate, with the presumption that they would be more capable of acquiring the proton in such a congested region. However, sodium methoxide and even sodium hydride did not generate a Michael addition product. The reaction conditions for these experiments are shown in Table 2.7.

Table 2.7: Reaction conditions employed in the quest for a racemic product in the Michael addition of dipivaloylmethane to nitrostyrene.

Base (mol%)	Additive (mol%)	Solvent	Time (h)	Temperature
KO^{t}Bu (5)	-	Toluene	96	rt
KO^{t}Bu (20)	-	Toluene	96	rt
KO^{t}Bu (100)	-	Toluene	96	rt
DABCO (20)	-	Toluene	96	rt
DABCO (100)	-	Toluene	96	rt
NaOMe (20)	-	MeOH	24	rt
NaOMe (30)	-	MeOH	24	rt
DABCO (20)	**50** (20)	Toluene	96	rt
DABCO (100)	**50** (50)	Toluene	96	rt
KO^{t}Bu (20)	**50** (20)	Toluene	96	rt
Et_3N (20)	**50** (20)	Toluene	96	rt
DABCO (20)	**51** (20)	Toluene	96	rt
DABCO (100)	**51** (50)	Toluene	96	rt
KO^{t}Bu (20)	**51** (20)	Toluene	96	rt

Et_3N (20)	**51** (20)	Toluene	96	rt
Et_3N (100)	**51** (20)	Toluene	96	65 °C
NaH (110)	-	THF	12	rt

At this stage it appeared that we had exhausted all possibilities and the fact that these attempts to generate a racemic addition of dipivaloylmethane to nitrostyrene were so fruitless indicates how challenging this transformation is. Despite this setback we already had a catalyst at our disposal which could provide the opposite enantiomer to catalyst **42**. Since catalyst **43** had generated the (*R*) product enantiomer and catalyst **42** the (*S*) adduct with acetylacetone, a parallel outcome was expected when the pronucleophile was changed to dipivaloylmethane.



Scheme 2.5: The organocatalytic addition of dipivaloylmethane to nitrostyrene.

The results for both experiments are shown below in Table 2.8. As anticipated, **42** and **43** provided access to both product stereoisomers (Scheme 2.5) and the catalysts' opposite selectivity allowed accurate determination of *ee*. The HPLC chromatograms were consistent with opposite selectivity and again, this was corroborated by $[\alpha]_D$ value determination.

Table 2.8: Results of the organocatalytic addition of dipivaloylmethane to nitrostyrene. Reactions were carried out in toluene at room temperature.

Catalyst	Yield (%)	Time (h)	*ee* (%)
42	30	96	99
43	45	96	92

Both catalysts furnished products of high enantiomeric purity. The reactions were sluggish and the yields were moderate due to the large *tert*-butyl substituents. Overall, this was a very pleasing result as, to the best of our knowledge, a synthesis of this compound, asymmetric or otherwise, has not been reported before. As the reaction was unsuccessful when a range of unhindered bases were used, the difficulty in getting

this reaction to proceed is almost certainly due to the unreactive nature of the enolate of dipivaloylmethane (brought about by the proximity of the sterically demanding *tert*-butyl groups).

The difficulties encountered whilst attempting to obtain a racemic product illustrate how powerfully effective the cinchona derived thiourea catalysts are for performing this type of chemical transformation. The synergistic cooperation of a number of functional groups is one of the key features of enzyme activity and, of course, organocatalysis itself has evolved from this extraordinary concept. Far stronger bases than quinuclidine were used to deprotonate the nucleophile in the attempted synthesis of the racemic compound, along with additives to activate the electrophilic component, but ultimately they were unsuccessful. Contrastingly, the coherent alliance of the Lewis acidic thiourea moiety and basic amine in the one molecule could generate, in the case of catalyst **42** at least, an almost enantiopure conjugate addition product. It is possible that this is due to entropic factors, since two catalysts would be required for the Michael addition to occur using an achiral base and a H-bonding additive, therefore requiring greater order in the catalytic system.

2.5 Covalent catalysts

As discussed in section 1.4, covalent catalysts have also been used to effect the Michael addition of ketones and aldehydes to electron-deficient double bonds, including *β*-nitrostyrene. Indeed, tremendous endeavour in this area recently has resulted in the development of several efficient protocols for this important transformation and in this context chiral pyrrolidine is considered a "privileged" framework for asymmetric organocatalysis. Accordingly, pyrrolidine-based organocatalysts bearing bulky groups,[197] H-bonding functionalities[53] or salt moieties[198] at the 2-position of the pyrrolidine ring have been identified as efficient catalysts. Many of these catalysts exclusively utilise a single catalytic *modus operandi*, i.e. stereocontrol in the reaction is achieved through either a H-bonding moiety or the use of a sterically demanding group at the 2-position. Representative examples are shown in Figure 2.15 below. The thiourea-bearing compound **6** was a highly stereoselective catalyst for Ni and co-workers in the conjugate addition of cyclohexanone to nitrostyrene[60] while Jørgensen's catalyst **12**, featuring the bulky *α,α*-diphenyl

trimethylsilyl ether group, was used by Cao *et al.* for the addition of aldehydes to alkylidene malonates.[61] Both of these catalysts are discussed in Section 1.4.1.

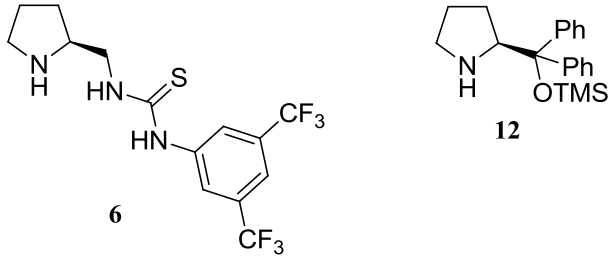


Figure 2.15: Representative examples of pyrrolidine catalysts with H-bonding (**6**) and sterically demanding (**12**) moieties at the 2-position to induce stereocontrol.[60,61]

2.5.1 Catalyst rationale

Although bulky catalysts[197,199] are proven as stereoselective promoters of the Michael addition, generally speaking catalyst efficiency is low as up to 20 mol% loading is often required.[200] Since H-bonding catalysts facilitate electrophile activation by acting as a Lewis acid the notion of combining the two modes of action in a single molecule appealed to us. It was expected that the selectivity of the reaction could be controlled by steric interactions and also through a H-bonding association with the electrophilic component in the reaction, which would simultaneously enhance the catalytic efficiency by activating the electron-poor species toward nucleophilic attack. In order to maximise the steric effect on the stereochemical outcome of the reaction by blocking one enamine face, the bulky group needed to be close to the secondary amine, i.e. at the 2-position, and we proposed that the hydrogen bond donor could activate the acceptor and direct its approach from the less hindered enamine face from the 4-postion of the pyrrolidine ring. Figure 2.16 shows a graphic representation of this hypothesis, with the sterically bulky group at the 2-position of the ring blocking nucleophilic attack from above the enamine intermediate and the H-bonding motif providing a platform to deliver the electrophile from below.

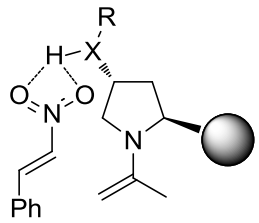


Figure 2.16: The rationale for our pyrrolidine-based enamine organocatalysts, incorporating a sterically bulky group and a H-bonding motif.

This blueprint had already proved successful for Paloma and co-workers,[201] who had achieved excellent diastereo- and enantioselectivities in the addition of aldehydes to β-nitrostyrene using *trans*-4-hydroxyprolylamides such as **52** and **53** below (Figure 2.17) as the catalyst. As the thiourea group had proven to be a vastly superior asset to the hydroxyl group in our catalytic reactions to date we believed that the more powerful hydrogen bonding group would provide a more dynamic, versatile catalyst for asymmetric conjugate addition reactions.

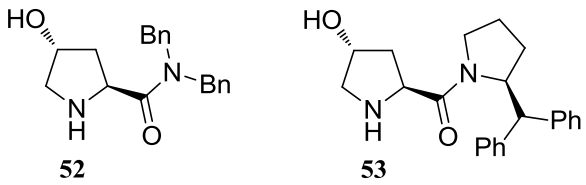


Figure 2.17: Catalysts used by Paloma *et al.* in the catalytic asymmetric conjugate addition of aldehydes to nitrostyrene.

We were also interested in exploring the effect of changing the stereochemistry at the crucial 4-postition of the ring. This curiosity arose from an interesting result published during our investigations when the group of Peng reported excellent yields and stereoselectivities for the conjugate addition of cyclohexanone to nitrostyrene using compound **65** in Figure 2.18 below as the catalyst.[202] **65** had syn-stereochemistry and we would have expected this stereochemical arrangement to be problematic as it would deliver the electrophile to the face that is sterically blocked. Peng's result was surprising and peculiarly this group did not report a direct comparative result for the same catalyst with the opposite stereochemistry at the 4-position of the ring. Owing to this we proposed two catalytic structures, shown in Figure 2.18, fully expecting catalyst **63**, featuring (theoretically at least) the more convenient spatial orientation for the stereoselective promotion of a 1,4-conjugate addition reaction, to exhibit superior stereoselectivity. Esters had not previously been used as a potential steric blocking

moiety at the 2-position and would allow the catalyst structure to be easily adjusted, perhaps with the use of a bulkier group such as an isopropoxy ester. Peng himself had reported an excellent result (98: 2 dr and 97% *ee)* in the Michael addition of cyclohexanone to *β*-nitrostyrene using a catalyst with the same stereochemistry at the 2- and 4-positions of the pyrrolidine ring as **63**. In this case the bulky group at the 2-position was provided by a *tert*-butyldiphenylsilyl ether moiety.[202]

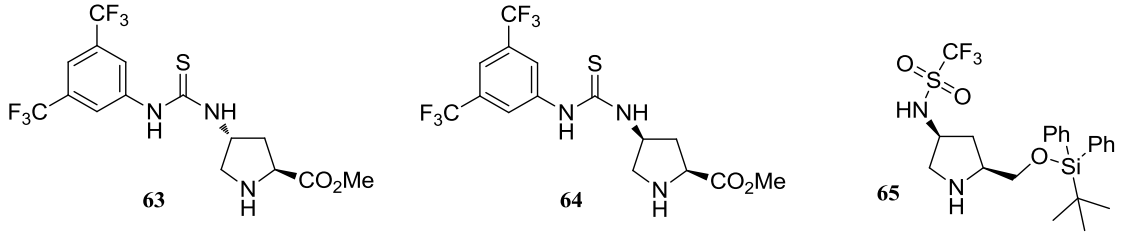


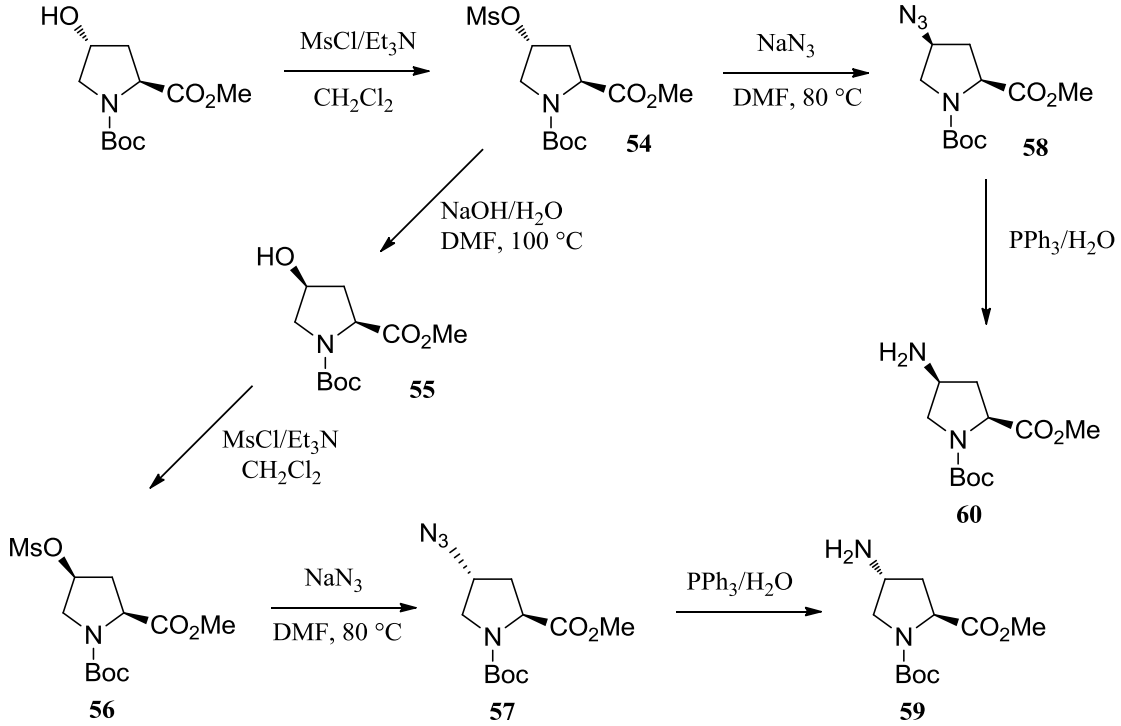
Figure 2.18: The structures of catalysts **63** and **64** with Peng's catalyst with syn-stereochemistry (**65**).

We were particularly intrigued by the possibilities of this two-pronged methodology for more challenging and unexplored Michael acceptors such as *α,β*-unsaturated ketones and esters, but initially we endeavoured to test or hypothesis using *β*-nitrostyrene as the electrophilic component.

2.5.2 Catalyst synthesis

The commercially available *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester provided a convenient starting point for the catalyst synthesis. The single diastereomer incorporated adaptable functional groups at the desired 2- and 4-positions on the pyrrolidine ring. In order to tether a thiourea group to the ring a primary amine group was required at the 4-position. A three-step synthetic sequence was applied for the purpose of replacing the hydroxyl group (Scheme 2.6). This chemistry had previously been implemented by Peng and co-workers on similar pyrrolidine-based compounds.[202] Treatment with mesyl chloride and triethylamine afforded the isolable **54** in quantitative yield. In the presence of the azide ion at 80°C, the *O*-mesylated product underwent an S_N2 reaction to give compound **58,** and inversion of the stereochemistry at the 4-position. Since it was desirable to have both diastereoisomers (2*S*, 4*S* and 2*S*, 4*R*) of the final catalyst available for testing, hydrolysis of the *O*-mesyl moiety in **54** was necessary to allow access to the *N*-Boc-*cis*-4-hydroxy-L-proline methyl ester **55**. Careful reaction conditions were required to avoid the unwanted

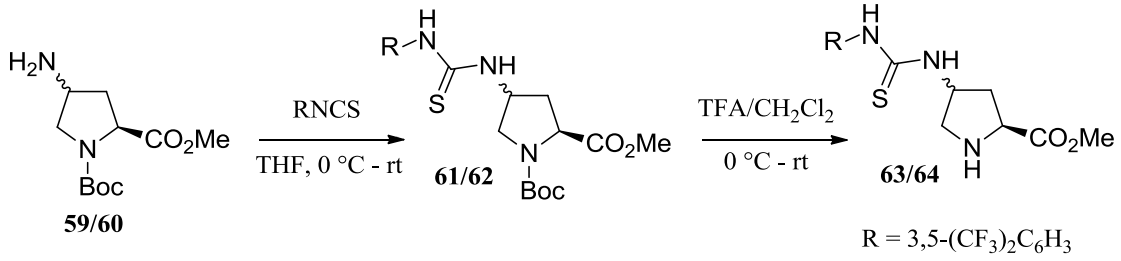
hydrolysis of the methyl ester. Heating compound **54** at 100 °C in a 10% w/v aqueous NaOH solution in DMF for 16 hours followed by flash column chromatography provided the desired product, albeit in a moderate yield of 51%.



Scheme 2.6: The synthesis of amine stereoisomers **59** and **60** from the commercially available starting material N-Boc-*trans*-4-hydroxy-L-proline methyl ester.

The *cis*-hydroxyl product **55** was then subjected to *O*-mesylation followed by nucleophilic attack by the azide anion to give product **57**, which had the opposite stereochemistry at the 4-position to compound **58.** The corresponding amines, **59** and **60**, were synthesised *via* a Staudinger reduction followed by flash column chromatography to remove the unwanted triphenylphosphine oxide by-product.

The H-bonding functionality on the catalyst was provided by a thiourea group, acquired from the nucleophilic attack of the amine on an aromatic isothiocyanate, Scheme 2.7.



Scheme 2.7: Synthesis of pyrrolidine-based thiourea catalysts using 3,5-bis(trifluoromethyl)phenyl isothiocyanate. Compounds **59**, **61** and **63** feature a *trans*-relationship between the substituents at the 2- and 4-positions of the pyrrolidine ring, while compounds **60**, **62** and **64** feature a *cis*-relationship between the two.

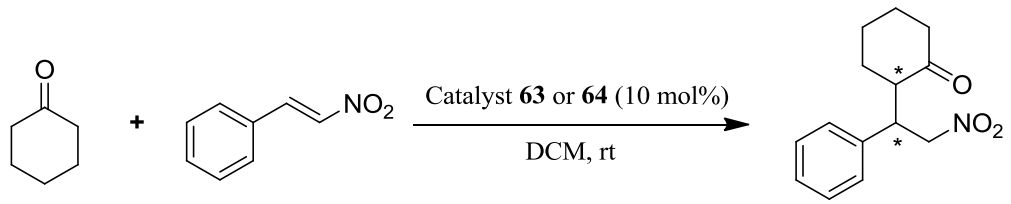
Finally, the *tert*-butyloxycarbonyl protecting group on the pyrrolidine ring was removed following literature protocol,[202] although the yields for this particular step were poor (19-34%). It is probable that the used of a strong acid in the deprotection step caused the degradation of the thiourea functionality and this is responsible for the poor isolated yields of the product.

2.5.3 Catalyst testing

In general, better results are obtained when aldehydes and not ketones are employed as Michael donors in enamine catalysis. This is because aldehydes react much faster with the secondary amine catalyst and also because the geometry and conformation control of the condensed intermediate is more trivial due to the significant difference in size between the substituents on the enamine moiety.[1] We performed our initial test reactions using two common aldehydic Michael donors, n-valeraldehyde and isovaleraldehyde, as the nucleophile in the presence of 10 mol% of catalysts **63** and **64** in DCM. The catalyst loading was lower than the conventional quantities employed in enamine catalysis (20-30 mol%) as we expected the thiourea moiety to accelerate the reaction through activation of the electrophile, thereby increasing the catalyst efficiency. Much to our surprise, only starting material was recovered after 4 days. Even the addition of a Brønsted acid co-catalyst, benzoic acid, in the presence of 5 equivalents of aldehyde, did not result in formation of the expected product.

As it is not unusual for a catalyst to exhibit specificity towards one Michael donor over another we turned our attention to ketones, although literature examples indicate that primary amines are more active catalysts for the Michael addition of ketones to β-nitrostyrene.[9] In comparison to aldehydes, the use of these substrates is potentially

problematic; ketones are less reactive toward nucleophilic attack from secondary amines and since more sterically congested enamine intermediates are formed, lower catalytic activity is inevitable. Furthermore, geometry control of the enamine at the conjugate addition step can be difficult to achieve due to the availability of α-protons on either side of the carbonyl functionality, although this can be avoided when symmetrically substituted ketones (e.g. cyclohexanone) are employed because of the chemical equivalence of the two possible regioisomers. Hence, cyclohexanone has been frequently used as a Michael donor in conjugate additions, often with a high degree of stereoselectivity,[203] and it was chosen as the ketone Michael donor for our test reactions, Scheme 2.8. Again, the loading of the catalyst was kept at 10 mol% and DCM was chosen as the solvent due to the catalysts poor solubility in toluene. The expected product was formed and the results for the reactions are shown in Table 2.9. Both reactions were stirred for 96 hours and only 2 equivalents of the ketone were required. This is substantially more economical than standard literature methodologies,[204] some of which necessitated up to 10 equivalents of the ketone with similar reaction times to our own.[200,202]



66

Scheme 2.8: The Michael addition of cyclohexanone (2 equivalents) to *β*-nitrostyrene using pyrrolidine-based organocatalysts.

In both cases, the syn diastereomer was found to be the major product and the diastereomeric bias was similar for both catalysts. The *cis*-catalyst **64** incited practically no enantioselectivity (6% *ee*) in the reaction. As predicted, the reversal of the stereochemistry at the 4-postition prompted a dramatic improvement in enantioselectivity, from 6% up to 48% *ee*. This result, an almost 3:1 enantiomeric ratio, was unsurprising given the spatial arrangement of the thiourea and ester moieties respectively. The higher stereoselectivity may be explained by the acyclic synclinal transition state model originally proposed by Seebach.[205] As predicted in section 2.5.1, the ester group can shield one face of the enamine intermediate, allowing the

nitrostyrene acceptor to approach from the nonshielded side to give the observed major enantiomer.

Table 2.9: Results for the organocatalytic addition of cyclohexanone to nitrostyrene using pyrrolidine-based catalysts **63** and **64**. Reactions were carried out in DCM at room temperature.

Catalyst	Yield (%)	d.r.[a]	*ee*[b] (%)	e.r.
63	87	80: 20	48	74: 26
64	97	86: 14	6	53: 47

[a] Determined by ^{1}H NMR spectroscopy. [b] *ee* of major diastereomer.

The marked difference in enantioselectivity between catalysts **63** and **64** had proven that, from a stereoselectivity point of view, the *trans* relationship between the substitutions at the 2- and 4-positions of the heteroatomic ring is a far more effective catalytic arrangement than the corresponding *cis* stereoisomer. Notwithstanding this, it is clear that the catalyst design needed to be optimised in order to achieve a highly selective synthesis; perhaps the methyl ester was too small and a more sterically demanding group at the 2-position, such as the α,α-diphenyl trimethylsilyl ether functionality used so effectively in Jørgensen's catalyst or a more sterically encumbering ester, would improve enantiodiscrimination. The fact that the change in stereochemistry at the carbon bound to the thiourea moiety did result in a much improved *ee* implies that the H-bonding motif plays a big role in the stereochemical outcome of the reaction, but it is likely that augmenting the steric bulk closer to the heteroatom on the ring would result in elevated levels of stereoselectivity.

Future work in the group will further explore the undoubted potential of this chemistry, not only in this reaction but also with other Michael acceptors. Recently the concept of tethering a thiourea moiety to the 4-position of a pyrrolidine-based silyl ether catalyst has been applied to the conjugate addition of aldehydes and ketones to nitroolefins only and syn-selective adducts were formed in excellent enantioselectivities and diastereoselectivities,[202] but thus far it has not been extended to other, less prominent acceptors such as alkylidene malonates or α,β-unsaturated ketones.

2.6 Conclusion

In conclusion, we have demonstrated that thiourea bifunctional compounds derived from the cinchona alkaloids are very powerful organocatalysts for the Michael addition of 1,3-diketones to *β*-nitrostyrene. This reaction exhibits considerable versatility as a range of pronucleophiles can be added enantioselectively to the activated olefin.

The catalysts which lacked a H-bonding motif almost exclusively furnished no product, indicating that the presence of a Lewis acidic moiety is essential for electrophile activation and hence product formation. While the natural or parent alkaloids are proficient at promoting the conjugate addition they lack the H-bonding proclivity to catalyse the reaction enantioselectively – this is provided by the thiourea moiety and the catalysts which contain this functionality are capable of bestowing the conjugate addition product with up to 97% enantiomeric excess in 1 hour.

It is also clear that solvent polarity has a significant effect on enantioselectivity in the quinine catalysed Michael addition of acetylacetone to *β*-nitrostyrene, with less polar solvents giving a superior enantiomeric ratio. Solvent choice in this reaction is critical, since catalyst **42** is much more effective at catalysing this reaction, under the improved conditions, than previously thought. A dramatic improvement in yield and reaction time than previously reported is observed when the solvent is changed from THF to toluene (47% → 95%, 48h → 1h).

The thiourea bifunctional organocatalysts **42** and **43** were able to promote the challenging Michael addition of dipivaloylmethane to *β*-nitrostyrene for the first time, demonstrating both the power and efficacy of these caltalysts. Attempts to synthesise a racemic version of the product proved ineffective even when strenuous reaction conditions were employed, displaying the difficulties associated with stimulating reactivity in this sterically hindered substrate.

Finally, we have shown that pyrrolidine-based organocatalysts **63** and **64** were able to promote the Michael addition of cyclohexanone to *β*-nitrostyrene. These catalysts were not compatible with aldehyde Michael donors, although it is not unusual for organocatalysts to exhibit this sort of preference for one functional group over another. Catalyst **63**, featuring a *trans* relationship between the substitutions at the 2- and 4-

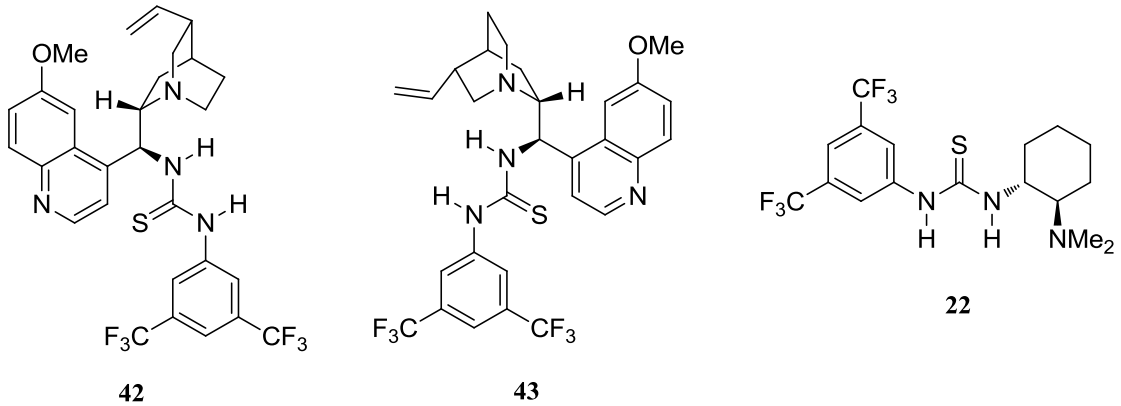
positions of the heteroatomic ring, displayed far superior enantioselectivity in this reaction than its diastereoisomer **64**.

3. *α,β*-Unsaturated Esters as Michael Acceptors

3.1 Introduction

The organocatalytic conjugate addition of carbon nucleophiles to a variety of acceptors has been extensively investigated in recent years,[1,27,57] with nitroalkenes featuring as by far the most common Michael acceptor.[53,148] A smaller number of well-designed catalytic enantioselective conjugate additions of aldehydes and ketones to vinyl sulfones,[206] maleimides,[207] benzoquinones,[208] enones[209] and vinyl phosphonates[210] have also been recently reported. Of these the vast majority employ enamine catalysis. Based upon our experimentation with the H-bonding thiourea organocatalysts and the excellent selectivities attained with β-nitrostyrene we were optimistic that a similarly effective methodology could be developed for other, less "activated" α,β-unsaturated compounds.

Of the potential catalysts which could effect such reactions, the quinine derived thiourea catalyst **42** was an automatic choice due to its excellent performance in previous organocatalytic experiments. As we were interested in gaining access to both enantiomers of a given product its C9 stereoisomer **43**, derived from quinidine, was also used. This catalyst had exhibited inferior selectivity and activity to **42** in previous reactions involving β-nitrostyrene, both in our own experiments and in those conducted by other research groups.[89] For this reason Takemoto's catalyst **22** was also employed because it has the same stereochemistry at the asymmetric carbons beside the H-bonding and basic moieties respectively as **43.** It was therefore expected to preferentially form the same enantiomer of the Michael product, possibly in a more stereoselective manner.



42 **43** **22**

Figure 3.1: The catalysts used for studies involving less common Michael acceptors.

3.2 α,β-Unsaturated esters

Of the potential electron-withdrawing groups applicable to α,β-unsaturated electrophiles we were particularly interested in the reactivity of ester-bearing acceptors because of the diverse chemistry associated with this functional group[145] and the resulting inherent synthetic value of the chiral product synthons. As can be seen from Figure 3.2, esters can be conveniently transformed into amides, carboxylic acids, tertiary and primary alcohols and other ester moieties.

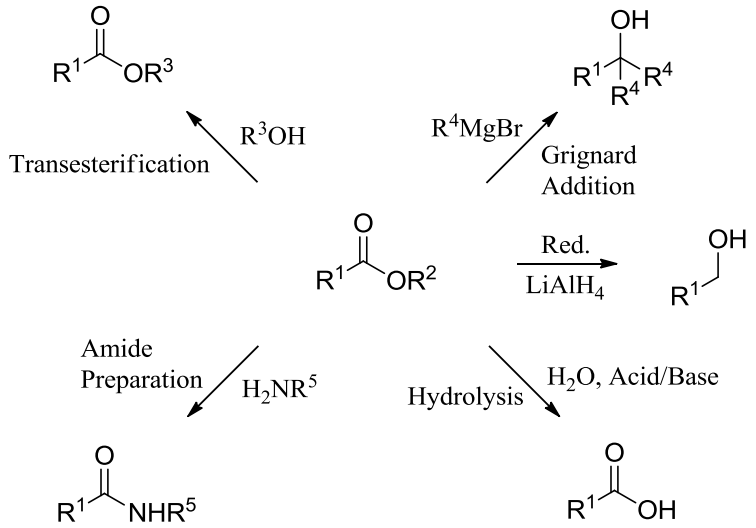
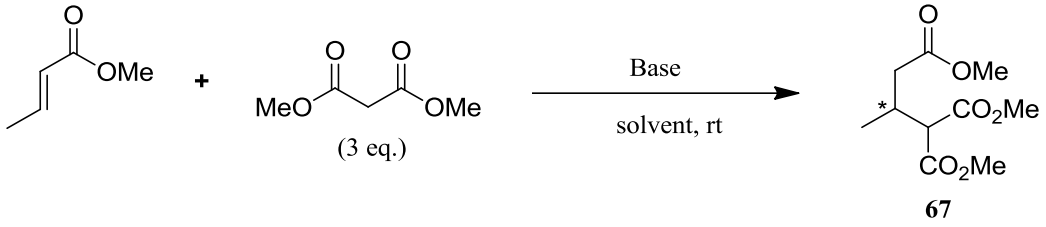


Figure 3.2: The reactivity associated with the ester functionality.[145]

Methyl crotonate, Scheme 3.1 below, was chosen as the Michael acceptor for our first experiments as it is a simple α,β-unsaturated ester and it does not have a sterically bulky group on the β-carbon which could impede reactivity. The nucleophile for this set of reactions was dimethyl malonate, chosen because of its ubiquity as a Michael donor in H-bonding organocatalytic conjugate addition reactions.[92] Following an extensive solvent screen, diethyl ether proved to be the best solvent for this transformation (Table 3.1, 5 mol% KOtBu used as base).



67

Scheme 3.1: The conjugate addition of dimethyl malonate to methyl crotonate.

In the presence of just 5 mol% of KO^{t}Bu, the racemic product could be isolated in 94% yield after 4 days. Despite this encouraging result, we were conscious that these reactants could only be compatible from an organocatalytic perspective if amines with similar basicities to those present in our organocatalysts were capable of promoting the reaction. To this end we undertook a series of experiments varying the catalyst and using diethyl ether as the solvent, Table 3.1. Ionic bases, including K_2CO_3 and NaOMe, were able to furnish the product in good to excellent yields at stoichiometric and substoichiometric loadings. It is also notable that KO^{t}Bu performed better in the presence of a solvent than under neat reaction conditions.

Table 3.1: Results of the solvent screen for the addition of dimethyl malonate to methyl crotonate to yield product **67**. All reactions were stirred at room temperature for 96 hours in the presence of 5 mol% base.

Solvent	Yield (%)
Acetone	78
DCM	49
MeOH	0
MeCN	89
DMF	81
Toluene	48
THF	67
Diethyl ether	94
EtOAc	13
EtOH	0

Regrettably, amine bases proved totally ineffective, even when applied in stoichiometric amounts. Common bases such as triethylamine and DABCO returned unreacted starting material. The more basic heteroatomic bicycle, quinuclidine, also the basic moiety in our thiourea organocatalysts, gave an identical result and even the presence of the H-bonding group in quinine did not encourage the formation of the product.

Table 3.2: Results for the addition of dimethyl malonate to methyl crotonate using a selection of bases. The solvent for these reactions was diethyl ether.

Base	Loading (mol%)	Time (h)	Yield (%)
KO^tBu	5	96	94
KO^tBu*	5	120	72
K_2CO_3	100	96	88
K_2CO_3	10	96	35
NaOMe	100	96	65
NaOMe	10	96	22
Et_3N	100	96	0
DABCO	100	96	0
Quinuclidine	100	96	0
Quinine	100	96	0

* Neat reaction conditions.

The greater reactivity of the pronucleophile in reactions involving ionic bases may be ascribable to the mechanism by which the reaction proceeds. Bases such as NaOMe and KO^tBu will fully deprotonate the malonate ester to form a "naked" carbanion, which is reactive enough to attack the β-carbon of the crotonate acceptor. This reaction therefore proceeds *via* a specific base mechanism (Figure 3.3). Contrastingly, the amine catalysts are more likely to operate *via* a general base catalysis mechanism. This requires a synergistic cooperation from the three reactants where deprotonation and nucleophilic attack occur in a concerted process, Figure 3.3.[145] Here, the amine catalyst does not remove the α-proton from the malonate starting material but does remove it in the transition state.

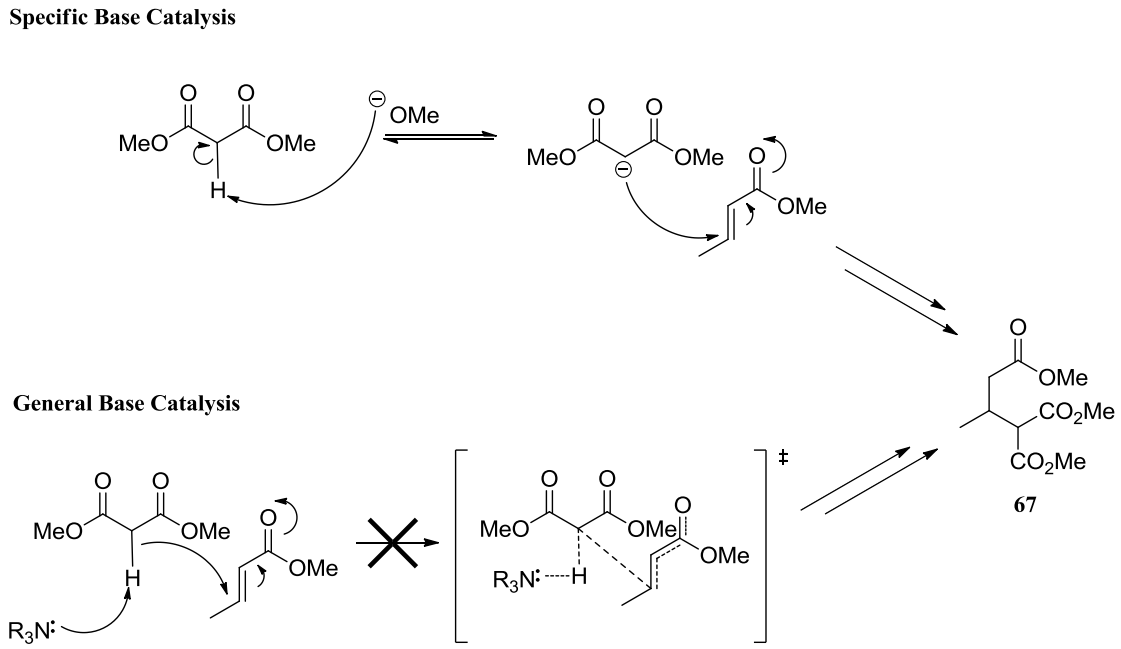


Figure 3.3: Specific versus General Base Catalysis for the addition of dimethyl malonate to methyl crotonate, favoured by ionic and nitrogen bases respectively.[145]

H-bonding amine catalysts are very effective in the addition of dimethyl malonate to nitroolefins.[85,89,91] As the amine catalysed addition of the same Michael donor to methyl crotonate failed one can conclude that the α,β-unsaturated ester is not sufficiently electrophilic to facilitate the addition. Only specific base catalysis will allow the reaction to prevail. Therefore, organocatalytic, stereoselective promotion of conjugate addition reactions by amine-based cinchona alkaloids and their analogues involving these substrates as Michael acceptors *via* H-bonding catalysis is not feasible.

3.3 Dimethyl ethylidenemalonate

As an organocatalytic Michael addition to a crotonate ester was not possible, our prerogative was then to modify the structure of the Michael acceptor to render it more reactive. We surmised that placing another ester functionality at the α-carbon would increase the electrophilicity of the β-carbon sufficiently to permit attack from the 1,3-dicarbonyl pronucleophiles. Hence, with two activating groups present, alkylidene malonate Michael acceptors (Scheme 3.2) would exhibit higher reactivity in conjugate additions. In addition, it was anticipated that due to the ability of alkylidene malonates to engage in two-point binding with Lewis acids[211] (Figure 3.4), our thiourea-based

organocatalysts would provide a favourable environment to further promote the desired reaction.

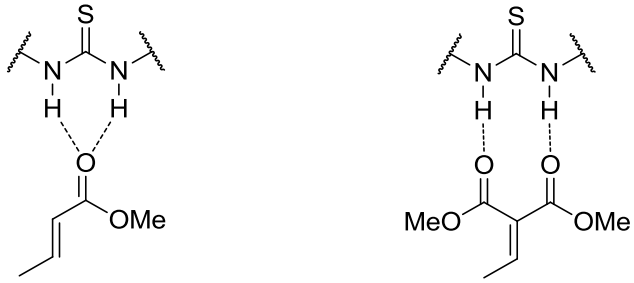
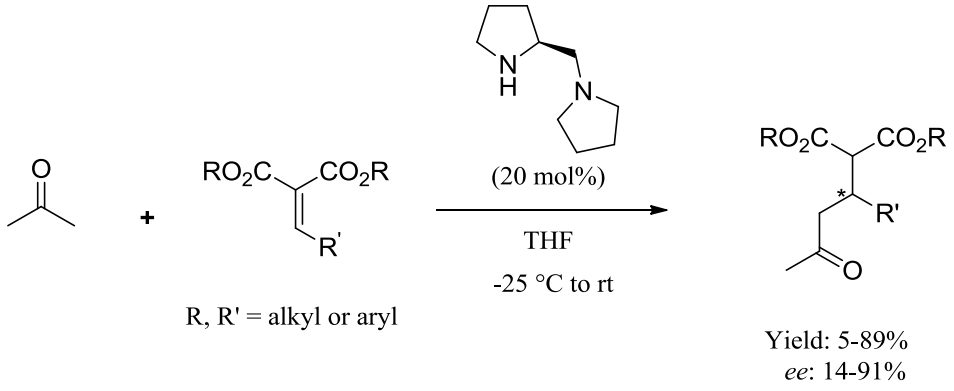


Figure 3.4: Activation of the crotonate ester and the alkylidene malonate *via* the thiourea moiety. [211]

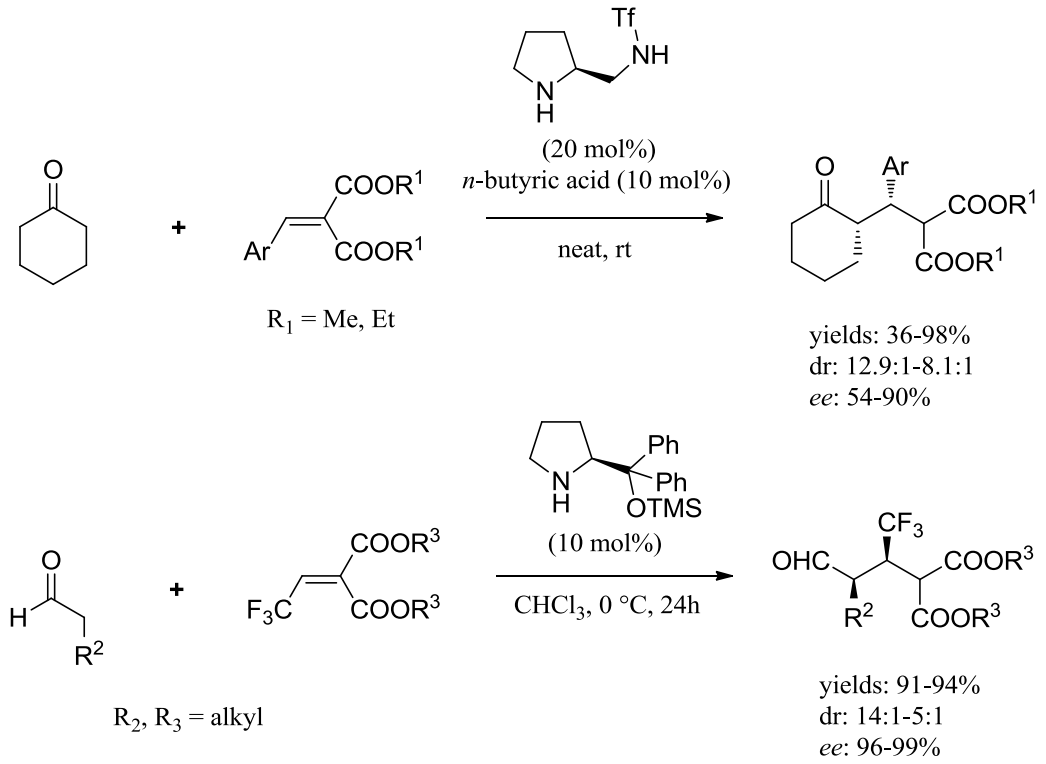
The chiral products arising from these reactions are synthetically useful, since the catalytic asymmetric conjugate addition of carbon-centred nucleophiles to alkylidene malonates provides a practical route to pharmaceutically and biologically important molecules.[212] Although the vast majority of these catalytic strategies utilise organometallic complexes to promote the reaction, a limited number of organocatalytic Michael additions of ketones and aldehydes[68,213] to alkylidene malonates have been reported. The initial work involving these substrates emanated from the group of Barbas,[214] Scheme 3.2. Although some very good enantioselectivities were reported, these were almost exclusively obtained at low temperature and therefore at the expense of yield.



Scheme 3.2: The Michael addition of acetone to various alkylidene malonates as reported by by Barbas *et al.*[214]

A handful of more recent studies have also outlined stereoselective additions to both aromatic and aliphatic alkylidene malonates. However, mechanistically they all employ enamine catalysis and the reactions themselves are quite limited both in terms

of substrate scope and catalyst activity. In particular, the yields showed a high dependence upon the nature of the substituents on both the Michael donor and alkylidene malonate acceptor.[61,215] Examples of the heavy dependence on substrate selection for the success of these additions is shown in Scheme 3.3. Tang *et al*. have reported the Michael addition of ketones to aromatic alkylidene malonates *via* a *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide catalyst. Although a number of different ketone pronucleophiles were employed in this study, cyclohexanone was the only species which gave both a high-yielding and stereoselective reaction. Indeed, ketone additions are much more successful in this context, although Lu and co-workers have reported a conjugate addition to alkylidene malonate acceptors using an aldehydic Michael donor and Jørgensen's catalyst.[61,213] However, in order to incite sufficient electrophile reactivity in this system they had to use an electron-withdrawing $-CF_3$ moiety on the *β*-carbon of the acceptor.



Scheme 3.3: Additions to alkylidene malonates reported by the groups of Tang (top) and Lu (bottom).[61,213]

In light of the restrictions associated with the organocatalytic Michael addition of carbanions to alkylidene malonates, we endeavoured to construct a stereoselective, organocatalytic methodology utilising our own H-bonding catalysts.

Despite the encouraging, if sparse, aforementioned organocatalytic Michael additions to alkylidene malonates, it is worth noting at this point that these substrates exhibit diminished reactivity in Michael additions when compared to, say, nitroalkenes. The group of Mayr have published a considerable body of work on the electophilicities and nucleophilicities of a broad spectrum of structurally diverse compounds and have created a "reactivity database" by calculating the rate constants for reactions of electron-rich and electron-poor species. They have thereby established a general reactivity scale for nucleophiles and electrophiles through parameterization of defined reference compounds[147,216-218] and, although their database does not take steric factors into account, it is a relevant indication of the reactivity of the compounds it describes. In this context, *E* is the general electrophilicity parameter and as such, it is an indication of a compound's inclination to react with an electron-rich moiety. On the Mayr scale *β*-nitrostyrene[147] is given an E value of −13.85, while the phenyl-substituted *α,β*-unsaturated diester, diethyl benzylidenemalonate,[217] has an E value of −20.55. This is a perceptible indication of the reduced reactivity of alkylidene malonate Michael acceptors compared to nitroalkenes, which accounts for the dearth of orgaoncatalytic additions to the former in the literature. We were therefore under no illusions regarding the difficulty of our task.

Another slight concern existed regarding the acidity of the protons on the γ-carbon of the diester (Figure 3.5) and indeed the potential of analogous activated alkylidene compounds acting as a nucleophile has already been exploited in vinylogous Michael additions.[168,219]

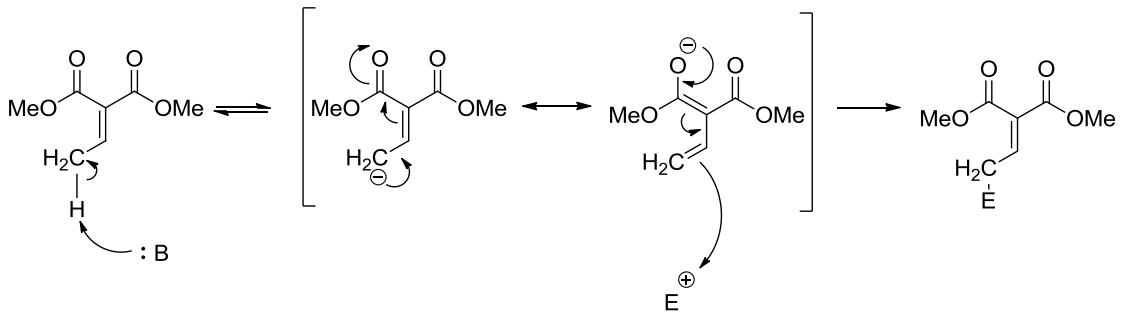


Figure 3.5: The acidity of the γ-protons in alkylidene malonates and the potential nucleophilicity of the resulting carbanion.

In an attempt to minimise the risk of unwanted side reactions involving this latent carbanion we proposed to change the pronucleophile from a 1,3-diester to the more acidic 1,3-diketone. A contributory resonance structure arising from electron-pair

donation from the alkoxy group of the ester is accountable for the slight increase in pK_a when compared to its diketone cousin, Figure 3.6.[179]

pK_a = 16.4 pK_a = 13.3

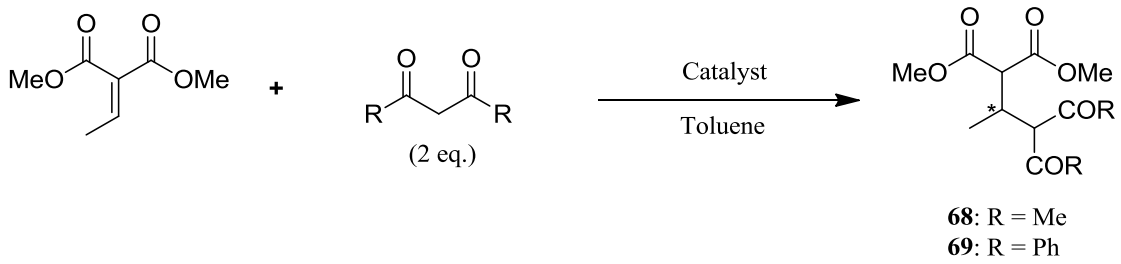
Figure 3.6: pK_a values for dimethyl malonate and acetylacetone.[179] Both values were measured in DMSO.

Hence, in a reaction mixture, the catalyst should preferentially deprotonate the acetylacetone molecule and not the alkylidenemalonate. This would nullify the potential acidity issue of the acceptor while simultaneously allowing us to broaden the functional diversity of the product.

3.3.1 Diketones as the pronucleophile

Acetylacetone, the simplest 1,3-diketone, was chosen as the inintial carbanion source for this set of reactions. The diphenyl-substituted pronucleophile, dibenzoylmethane, was also tested, as there was a concern that the product (**68**) arising from the acetylacetone addition would not be separable by chiral HPLC. The rationale for availing of the phenyl-substituted diketone was that the presence of the aromatic moieties on the product molecule would allow more trivial separation of the enantiomers. Whilst this concern was a valid one, it did not come to pass as ultimately the enantiomers of product **68** were separable when an extremely non-polar solvent mix (98: 2 hexane: isopropanol) was employed.

The results of the experiments involving these 1,3-diketones are shown in Table 3.3. Intriguingly, the reaction times were relatively short and the yields were uniformly high. To the best of our knowledge, this is the first organocatalytic Michael addition to an α,β-unsaturated diester which was promoted by a H-bonding bifuctional catalyst. Formation of the racemic products were equally trivial; 5 mol% of KO^{t}Bu was sufficient to achieve quantitative yield for both pronucleophilles.



68: R = Me
69: R = Ph

Scheme 3.3: The organocatalytic Michael addition of 1,3-diketone pronucleophiles to dimethyl ethylidenemalonate.

Unfortunately, whilst the yields were excellent, none of the catalysts exhibited worthwhile enantiodiscrimination and the *ee* values were poor across the board. As predicted, catalysts **43** and **22** favoured the same product enantiomer, while catalyst **42** showed a slight preference for the opposite stereoisomer. The highest *ee* for this set of reactions arose from the use of dibenzoylmethane as the pronucleophile and thiourea **42** as the catalyst.

The lower enantioselectivities are probably ascribable to the inferior Lewis basicity of the carbonyl functionality compared to that of the nitro group.[1] This results in a weaker interaction between the electrophile and thiourea group of the catalyst, which in turn allows the competitive and non-stereoselective background reaction to prevail. Indeed, it is possible that the reaction may be occurring to some extent in an autocatalytic fashion, whereby deprotonation of the acetylacetone molecule is performed by the Michael addition product.

Table 3.3: Results of the Michael addition of acetylacetone and dibenzoylmethane to dimethyl ethylidenemalonate to yield compounds **68** and **69**.

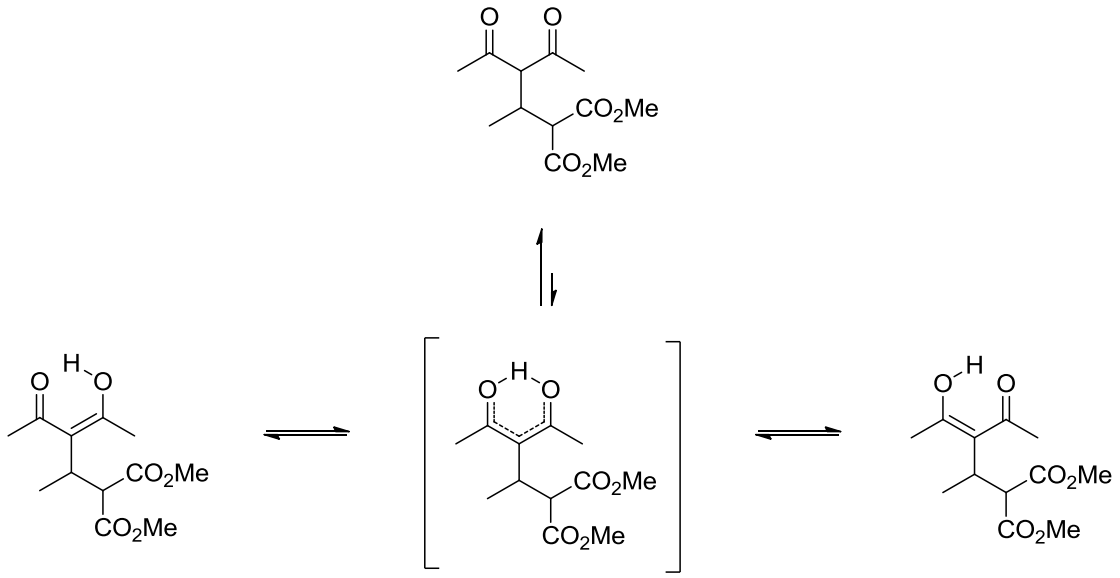
R	Catalyst	Loading (mol%)	Time (h)	Yield (%)	er	ee (%)	$[\alpha]_D^{25}$ *
Me	KO^{t}Bu	5	5	97	-	-	-
Me	**42**	10	12	99	60: 40	20	−30
Me	**43**	10	24	87	43: 57	14	50
Me	**22**	10	24	99	42: 58	16	30
Ph	KO^{t}Bu	5	5	88	-	-	-
Ph	**42**	10	24	96	64: 36	28	

* (c = 0.002, CH_2Cl_2)

Although the enantioselectivities were disappointing, we were encouraged by the fact that the Michael acceptor exhibited adequate reactivity as to the best of our knowledge, a catalytic Michael addition to an alkylidenemalonate acceptor promoted by a non-covalent organocatalyst has not been previously reported. We were excited by this positive result and confident that a more selective reaction could be achieved through the alteration of the Michael acceptor structure.

3.3.1.1 Keto-enol tautomerism in product 68

Despite the fact that it is a simple molecule, the NMR spectra for compound **68** are rather more complicated than one might expect and some interesting signals are present. The presence of keto-enol tautomerism in acetylacetone and other 1,3-dicarbonyl compounds containing enolisable α-hydrogens is well-known (and equally well-documented).[145,220] The phenomenon of keto-enol tautomerism is not present in the Michael products from the addition of 1,3-diketones to β-nitrostyrene and, to the best of our knowledge, has not been reported in other organocatalysed conjugate addition products. The initial ^{1}H NMR spectrum was run in $CDCl_3$ and it revealed several unexpected signals. The most conspicuous of these was the apparent duplication of the methyl group doublet at approximately 1.2 ppm and the presence of extra singlets close to peaks for the methyl groups of the ketone and the methoxy peaks of the ester, Figure 3.7. Further investigation, involving variance of the NMR solvent, confirmed the presence of two tautomeric structures, Scheme 3.4. The enol form is known to predominate in acetylacetone,[220] but the opposite is the case in adduct **68**.



Scheme 3.4: The keto-enol tautomerism of compound **68**.

Figure 3.7 shows the ^{1}H NMR spectrum of compound **68**, with $CDCl_3$ as the solvent. Owing to the fact that there is a great excess of the keto-form, only the enol signals which integrate to 3 are immediately obvious, as mentioned above. These peaks are labelled on the spectrum, along with the peaks arising from the keto-form. The presence of the enol tautomer was confirmed in the ^{13}C NMR spectrum in $CDCl_3$ also, Figure 3.8, where all of the carbons in the molecule are accounted for. Figure 3.9 confirms the presence of the ester and ketone carbonyl peaks in the enol form of the molecule.

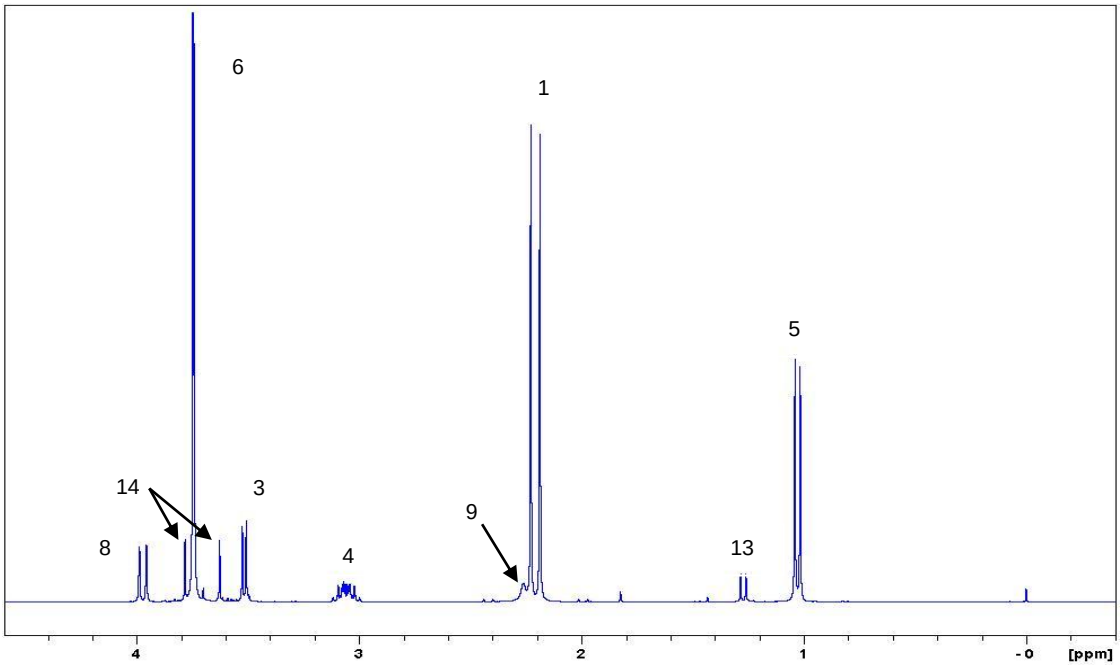
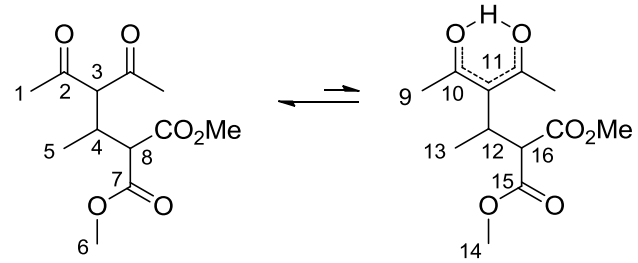


Figure 3.7: ^{1}H NMR spectrum of compound **68** in $CDCl_3$.



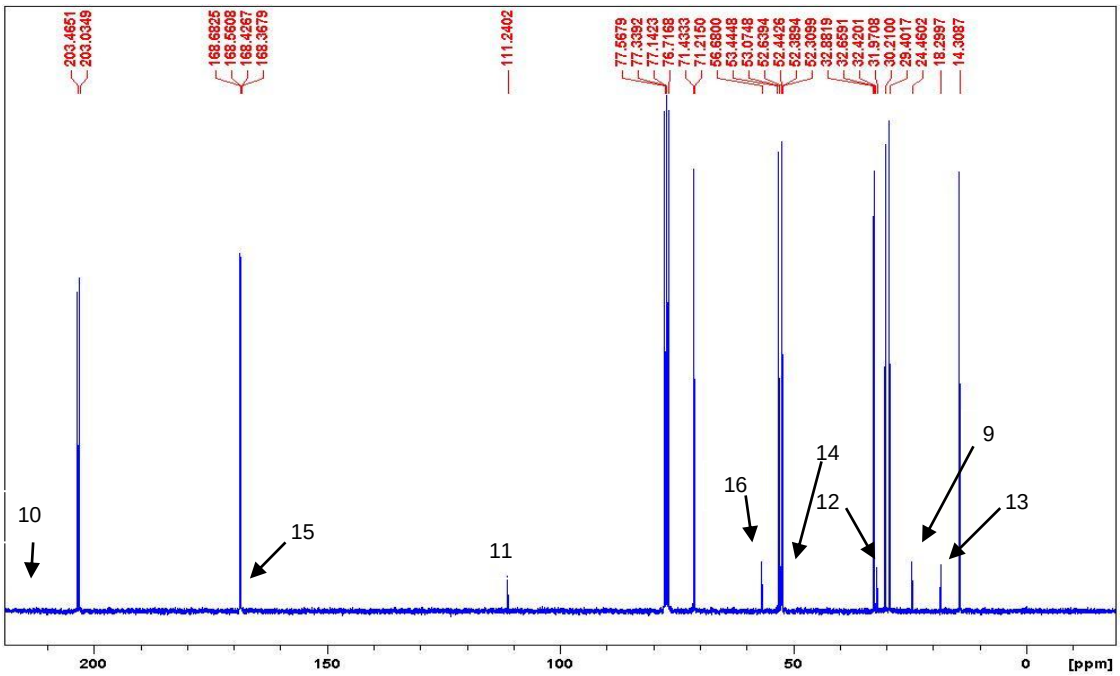


Figure 3.8: ^{13}C NMR spectrum of compound **68** in $CDCl_3$.

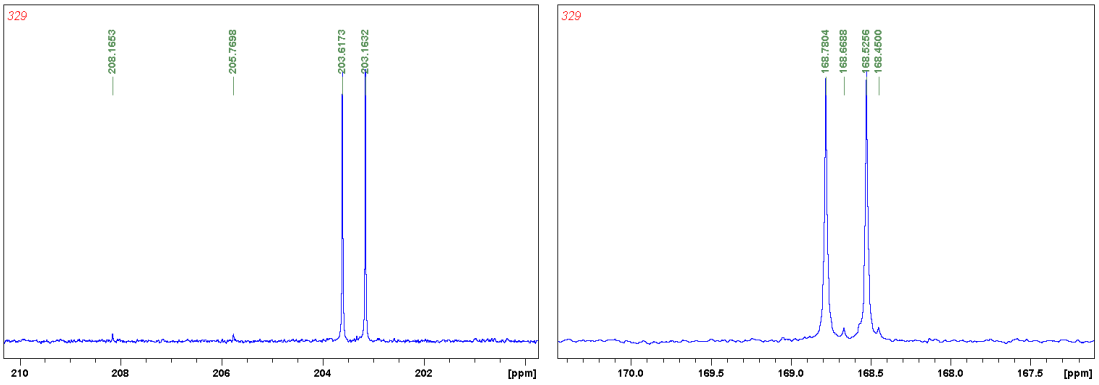


Figure 3.9: Part of the ^{13}C NMR spectrum of compound **68** confirming the presence of the ketone carbonyl peaks (left) and the ester carbonyl peaks (right) of its enol-form.

The peak for the alkene carbon (11) is clearly present at 111.2 ppm and there is a corresponding peak at 100.3 ppm in the ^{13}C NMR spectrum of acetylacetone, which verifies the presence of the enol tautomer.

The percentage of enol tautomer present in a selection of deuterated solvents is shown in

Table 3.4 and Figure 3.10 shows the spectra run in the 3 different solvents. The enol peaks are clearly present in $CDCl_3$ but they are notably diminished in CD_3OD and have all but disappeared in d_6-DMSO. This is expected since a corresponding descending trend occurs in the respective solvents with acetylacetone,[220] albeit with a much higher proportion of enol tautomer present. Generally speaking, more polar, protic solvents (especially those with a tendency towards hydrogen bonding) such as MeOH and DMSO are associated with a decline in enol content, since, in the absence of competing intermolecular hydrogen bonding, intramolecular hydrogen bonding will be more pronounced.[221] As dilution can affect the keto-enol equilibrium a constant concentration (0.3 mg/mL) was used with each solvent.

Table 3.4: Percentage tautomer composition of compound **68** in various deuterated solvents.

Solvent	$CDCl_3$	CD_3OD	d_6-DMSO
% Enol	7.4	6.1	3.4

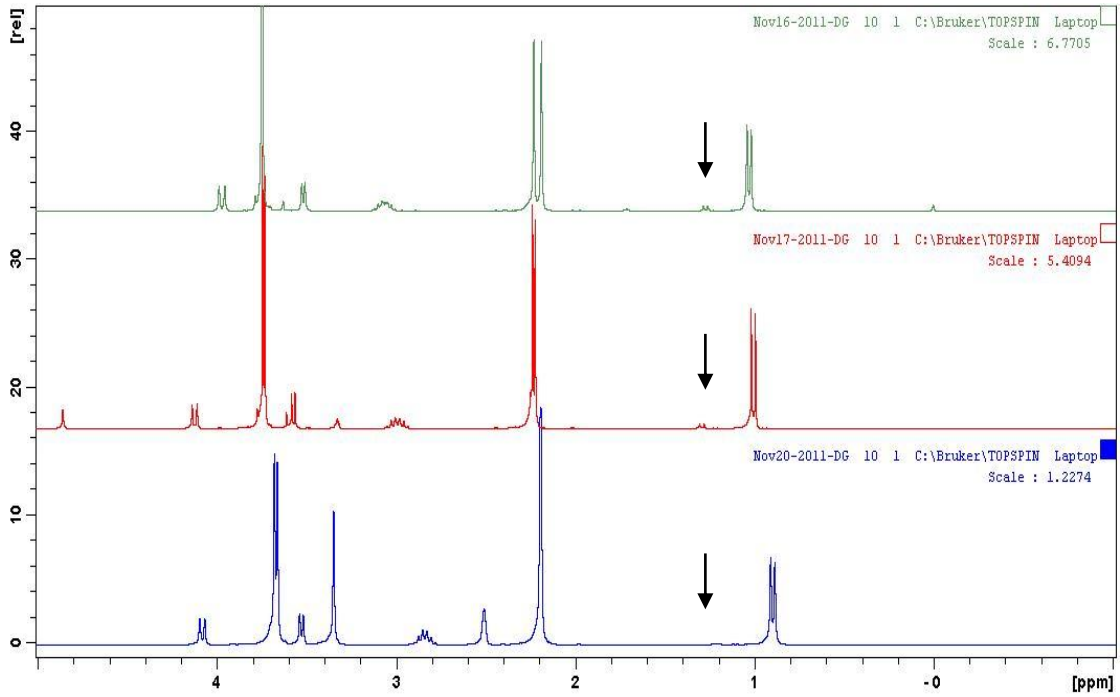


Figure 3.10: ^{1}H NMR spectra of compound **68**. Spectra were run in; — $CDCl_3$. — CD_3OD. — d_6-DMSO.

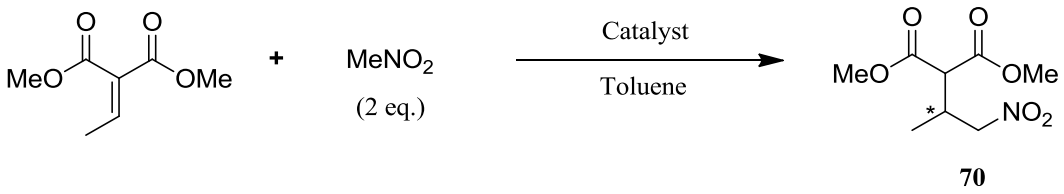
Additional verification of the negligible amount of enol-form present in DMSO came in the form of the ^{13}C NMR spectrum of compound **68** run in this solvent, in which the enol peaks were absent. Interestingly, and somewhat surprisingly given the similarities in structure of a number of compounds synthesised, this phenomenon did not occur in any other Michael addition products we generated arising from nucleophilic additions with acetylacetone.

3.3.2 Alternative pronucleophiles

Following the poor enantioselection of the diketone donors, we undertook a series of experiments to test the applicability of other pronucleophiles in conjugate additions to alkylidene malonates. Nitroalkanes are excellent candidates for use as Michael donors. The nitronate carbanion can be generated *in situ* under mild conditions due to the nitro group's ability to stabilise the adjacent negative charge. In this way they are comparable to 1,3-dicarbonyl compounds and as such, nitroalkanes are capable pronucleophiles in organocatalytic reactions and have proven suitable for conjugate additions.[42] Moreover, their compatibility with bifunctional cinchona-based thiourea

organocatalysts has been established by Soós and co-workers, who reported the highly enantioselective addition of nitromethane to chalcones in 2005.[90]

Resultantly, nitromethane was chosen as the first non-carbonyl containing pronucleophile, Scheme 3.5. A large excess (sometimes up to 10 equivalents or more)[76,222] of pronucleophile accompanied by an iminium ion-promoting organocatalyst has been a particularly fruitful combination for Michael reactions incorporating simple organic nitro compounds.[36] In our case, the number of equivalents of nitromethane was deliberately kept as low as possible because of the nitro group's well-known ability to bind to the thiourea moiety (*via* two hydrogen bonds between the NH groups and the highly electron-rich oxygen atoms of the nitro functionality).[1] We were therefore concerned that a large excess would disrupt our catalyst's ability to effect the reaction by replacing the electrophile as the Lewis base and sought to minimise the risk of this occurring by employing only two equivalents of nitromethane. The results for this set of experiments are shown in Table 3.5.



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Scheme 3.5: The Michael addition of nitromethane to dimethyl ethylidenemalonate.

Again, the reactions were stirred at room temperature for 96 hours. As had been observed in previous experiments, the quinine-derived catalyst **42** exhibited superior activity than its pseudoenantiomer, while in this case Takemoto's catalyst produced the highest yield of the three catalysts.

Table 3.5: Results for the Michael addition of nitromethane to dimethyl ethylidenemalonate to yield compound **70**. All reactions stirred for 96h.

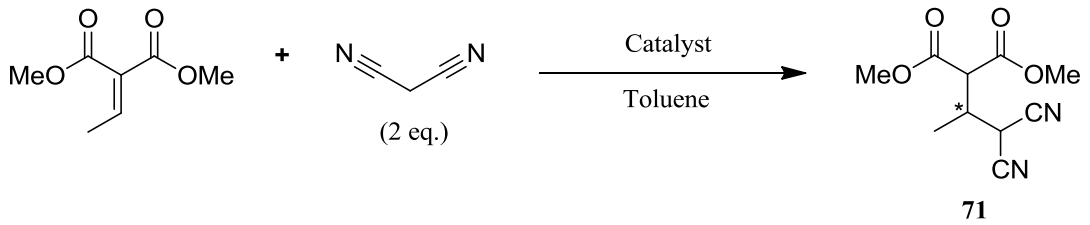
Catalyst	Loading (mol%)	Yield (%)	er	*ee*	$[\alpha]_D^{25}$ *
KO^tBu	5	75	-	-	-
42	10	73	74: 26	48	−10
43	10	38	33: 67	34	10
22	10	84	28: 72	44	20

* (c = 0.002, CH_2Cl_2)

From a selectivity point of view, nitromethane was a more successful nucleophilic source than either of the 1,3-dicarbonyl compounds tested. Catalyst **42** exhibited a good degree of stereochemical bias, providing the expected product in a 3:1 enantiomeric ratio. Catalyst **43** showed slightly poorer selectivity than its stereoisomer, while catalyst **22** showed similar enantioselectivity to **42**.

Malononitrile is a reagent whose *α*-hydrogens have a comparable acidity to those in acetylacetone (11.1 and 8.6 in DMSO respectively)[179] and thus it has analogous potential as a carbaonion source. Curiously, given the diverse and synthetically valuable chemistry associated with the nitrile group,[145] this pronucleophile has been scarcely utilised in organocatalytic Michael additions. This is possibly due to its tendency to polymerise in basic conditions. Notwithstanding this, publications exist recording the organocatalytic conjugate addition of malononitrile to *β*-nitrostyrene[185] and chalcones.[195] Bifunctional thiourea organocatalysts have very recently been used in conjunction with the dicyano pronucleophile, albeit with moderate enantioselectivities,[223] and it therefore appeared to be a suitable candidate for our studies relating to the reactivity of dimethyl ethylidenemalonate.

The malononitrile carbanion proved to be a very active nucleophile, with reaction times considerably shorter than the corresponding acetylacetone reactions, Table 3.6. Purification of the final product by flash column chromatography was problematic due to malononitrile's propensity to co-elute with the product on the silica column. This resulted in lower isolated yields than one might expect from reactions which, from inspection of the crude NMR spectra, had proceeded with 100% conversion.



71

Scheme 3.6: The Michael addition of malononitrile to dimethyl ethylidenemalonate.

A further (and more frustrating) complication with product **71** was that, despite an exhaustive search involving the use of several different chiral columns and a myriad of solvent systems, we were unable find conditions to separate the enantiomers on the HPLC instrument and so the *ee* values were undeterminable. Again, from the $[\alpha]_D$ values, both catalysts **22** and **43** showed a preference for the opposite enantiomer to that favoured by catalyst **42**.

Table 3.6: Results for the Michael addition of malononitrile to dimethyl ethylidenemalonate to yield compound **71**.

Catalyst	Loading (mol%)	Time (h)	Yield (%)	*ee*	$[\alpha]_D^{25}$ *
KO^tBu	5	12	75	-	-
42	10	4	82	-	10
43	10	6	79	-	−70
22	10	2	88	-	−10

* (c = 0.002, CH_2Cl_2)

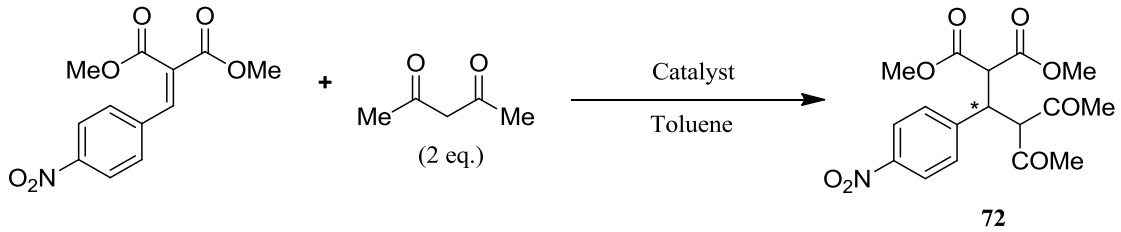
Having explored various pronucleophiles, we then decided to vary the Michael acceptor in an effort to improve reactivity.

3.4 Aromatic alkylidene malonates

The simplest aromatic β-substituted α,β-unsaturated diester, dimethyl benzylidenemalonate, was tested using the same reaction conditions as those employed for dimethyl ethylidenemalonate with acetylacetone as the pronucleophile. After stirring for several days in the presence of the thiourea organocatalysts, only starting material was returned.

3.4.1 Para-nitro activating group

The poor reactivity of the aromatic alkylidene malonate is not unexpected; these substrates are notoriously reluctant to react with nucleophiles.[218] Evidently the electron-donating effect of the π-electrons from the phenyl ring onto the β-carbon is sufficient to reduce the reactivity of the substrate. The addition of a nitro substituent on the aromatic ring has provided a convenient way of reversing this effect for a number of groups.[61,68,215,224] The aforementioned work of Mayr, in which the electrophilicity parameter, *E*, for both dimethyl benzylidene malonate and dimethyl (4-nitrobenzylidene)malonate were calculated, confirmed the increase (from −20.55 to −17.67 respectively) in electrophlicity of the β-carbon when a *para*-nitro group was placed on the aromatic ring.[217] As a result, we employed dimethyl (4-nitrobenzylidene)malonate as the acceptor in the Michael addition of acetylacetone, Scheme 3.8. The results for these experiments are shown in Table 3.7 below.



72

Scheme 3.7: The Michael addition of acetylacetone to dimethyl (4-nitrobenzylidene)malonate.

Although a considerable leap in enantioselectivity was apparent with this substrate compared to the corresponding experiments involving dimethyl ethylidenemalonate, the reactions were very sluggish, with poor yields even after 4 days. This clearly shows the reduced reactivity of the acceptor as catalyst **42** was able to furnish the Michael product from the alkyl-substituted diester in quantitative yield after only 12 hours. In contrast to the additions of nitromethane and malononitrile to dimethyl ethylidenemalonate, whereby the quinine-derived thiourea catalyst **42** exhibited superior activity to its pseudoenantiomer **43**, the yields for both catalysts were similar over the 96 hour period.

In contrast to the disappointing yields, all of the catalysts exhibited a pleasing degree of stereocontrol in this reaction. The best indication of this can be seen in the reaction catalysed by compound **42**, which gave the highest *ee* of the three catalysts; 73%. This figure represents a dramatic improvement on the selectivity (20% *ee*) observed in the

corresponding conjugate addition involving dimethyl ethylidenemalonate as the acceptor. Catalyst **22** favoured the opposite enantiomer and attained a similar selectivity to **42**, while the quinidine-derived thiourea catalyst **43** also furnished the product with an improved enantioselectivity when compared to the addition of acetylacetone to other alkylidene malonate electrophiles.

Table 3.7: Results for the Michael addition of acetylacetone to dimethyl (4-nitrobenzylidene)malonate to yield compound **78**. All reactions stirred for 96h.

Catalyst	Loading (mol%)	Yield (%)	er	*ee*
KO^tBu	5	56	-	-
42	10	28	86.5: 13.5	73
43	10	17	78: 22	56
22	10	10	16.5: 83.5	67

* (c = 0.002, CH_2Cl_2)

We postulate that the improved selectivity is a consequence of the lower reactivity of dimethyl (4-nitrobenzylidene)malonate compared to dimethyl ethylidenemalonate. As discussed in section 3.3.1, the carbonyl group weakly interacts with the Lewis acidic moiety in the catalyst. In the case of the β-alkyl-substituted acceptor, dimethyl ethylidenemalonate, the β-carbon is sufficiently electrophilic to allow the competitive non-stereoselective background reaction to occur. The phenyl-substituted dimethyl benzylidenemalonate was too unreactive for even a H-bonding catalysed conjugate addition to occur. The inclusion of the *para*-nitro group on the phenyl ring of the α,β-unsaturated compound increases its electrophilicity slightly. It is possible that this nitro-acceptor is too unreactive to allow the background non-stereoselective addition and that it requires some interaction with the thiourea moiety to sufficiently activate it toward nucleophilic attack, Figure 3.11. Thus, the catalyst is able to impose its chiral environment on the reagents and a more stereoselective reaction occurs. The autocatalytic Michael addition, which would furnish the racemic product, is unable to proceed due to the lack of reactivity of the uncoordinated, and thus unactivated, electrophile.

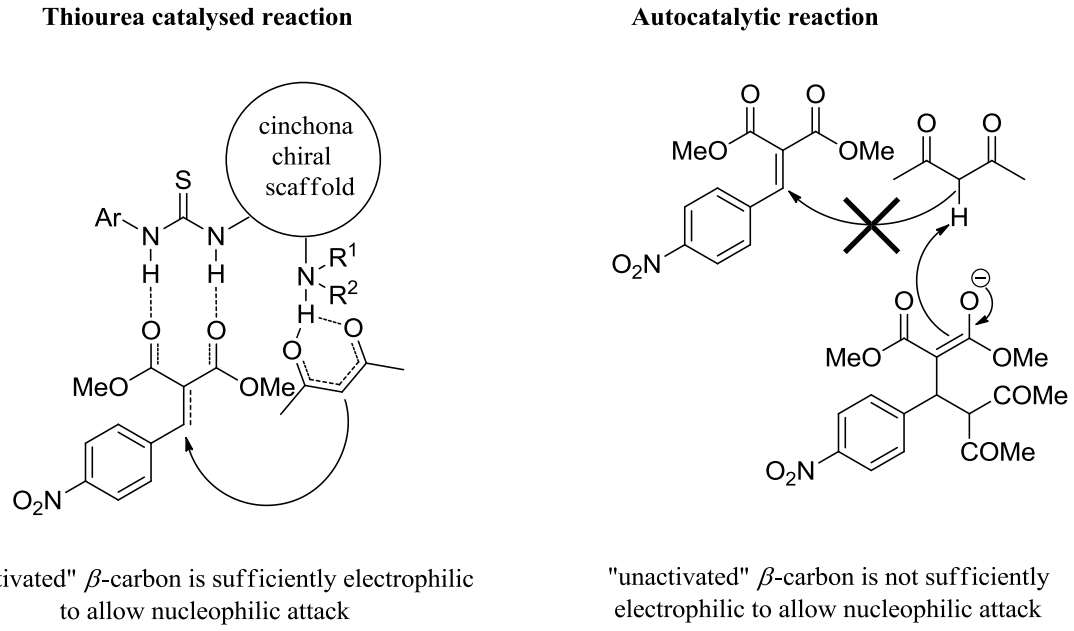


Figure 3.11: Hypothesis for the improved enantioselectivity in the Michael addition of acetylacetone to dimethyl(4-nitrobenzylidene)malonate.

Despite the encouraging enantioselectivities, the poor yields for these reactions rendered this methodology impracticable and reluctantly the decision was taken to modulate our approach to the Michael addition involving β-aromatic alkylidenemalonate acceptors.

3.4.2 The RAMP-/SAMP-hydrazone methodology

Since the pioneering work of the mid-1970s, (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and its enantiomer RAMP (Figure 3.12) have been amongst the most powerful and widely used chiral auxiliaries in asymmetric synthesis.[225]

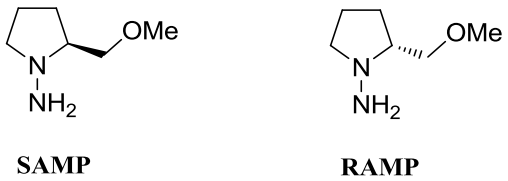
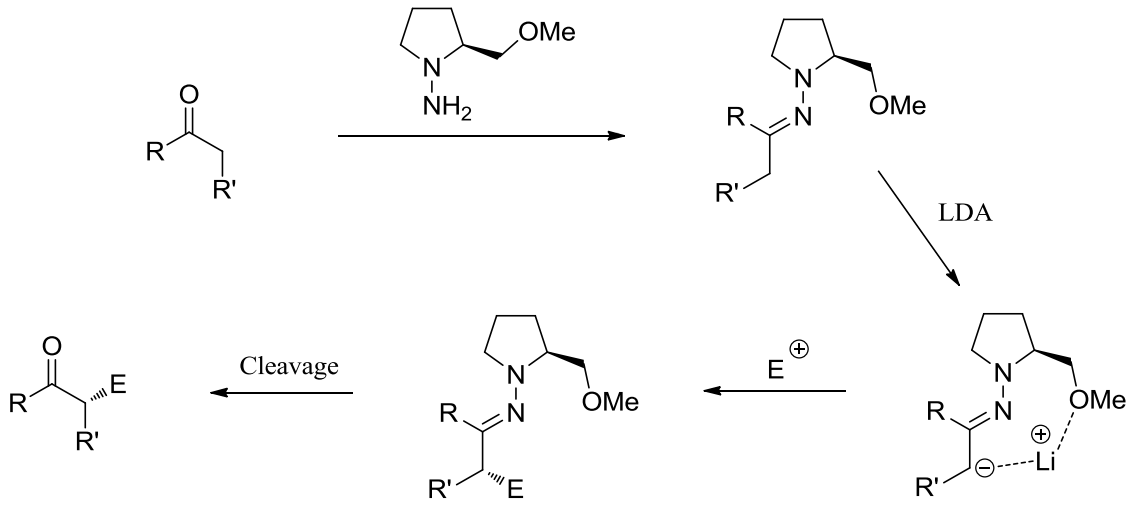


Figure 3.12: SAMP and RAMP; synthetically useful chiral auxiliaries.[225]

Indeed, the RAMP-/SAMP-hydrazone methodology, as it is known, has been implicated in a host of enantioselective chemical transformations, including alkylations, aldol and Michael reactions, cycloadditions and nucleophilic additions to C=N bonds.[226] The procedure, shown in Scheme 3.8, involves transformation of

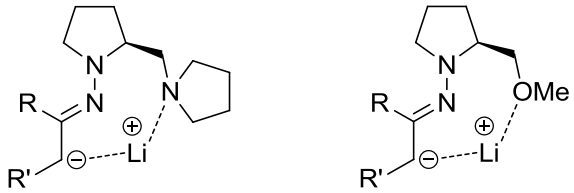
carbonyl compounds to the corresponding RAMP or SAMP hydrazone, followed by deprotonation by means of lithium diisopropylamide, or other lithium bases, and trapping of the intermediate azaenolates with various electrophiles. Finally, hydrazone cleavage can be performed to provide the desired product.[227] It has been shown to have a very broad range of applications[226,228] and generally generates products with high selectivity, due to the rigidity of the five-membered ring and the ability to coordinate metal ions. The selectivity in reactions involving the RAMP/SAMP-methodology arises from the systematic blocking of the top face of the carbanion by the chiral auxiliary, thereby only allowing nucleophilic attack to occur from below the hydrazone nucleophile.



Scheme 3.8: The procedure for the RAMP-/SAMP-hydrazone methodology.[226]

The rich synthetic utility of RAMP-/SAMP-hydrazone methodology is evident from the frequency of its use in natural product synthesis.[229] Our interest in the procedure was derived from the fact that the hydrazone carbanion would be a sufficiently reactive nucleophile to attack the dimethyl benzylidenemalonate Michael acceptor, which was unreactive in our Michael additions using thiourea organocatalysts. The concept of applying this chemistry to an α,β-unsaturated diester was not without precedent; Enders and co-workers had reported the asymmetric Michael addition of lithiated methyl ketone SAMP-hydrazones to 2-benzylidenemalonates over 20 years ago.[230] However, our curiosities lay in the exploration of alternative hydrazones and their selectivity in this reaction. Specifically, the potential for replacement of the methoxy

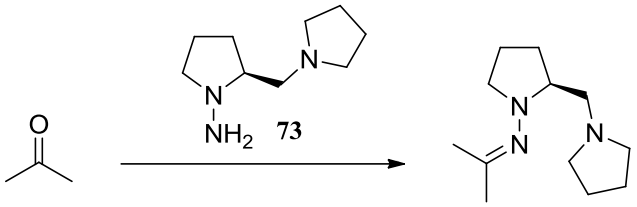
functionality in RAMP or SAMP with a tertiary amine, compound **74** in Figure 3.13. It was expected that the nitrogen lone pair of electrons would bind to the lithium cation to fashion the chiral environment, thereby inducing enantioselectivity in the conjugate addition. Furthermore, we postulated that the use of a heterocycle would provide greater conformational rigidity in the metalation step, thereby increasing the level of stereocontrol.



74

Figure 3.13: The analogous lithiation of SAMP (right) and (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-hydrazone **74**.

Accordingly, we chose to test the efficacy of the hydrazone resulting from the condensation of a carbonyl compound and the pyrrolidine-substituted (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-amine **73**, Scheme 3.9. This compound was synthesised by our collaborator, Dr. Gerard McGlacken at University College, Cork. The asymmetric hydrazone **74** was easily obtained by mixing the chiral auxiliary **73** with acetone and stirring overnight, followed by short-path distillation.

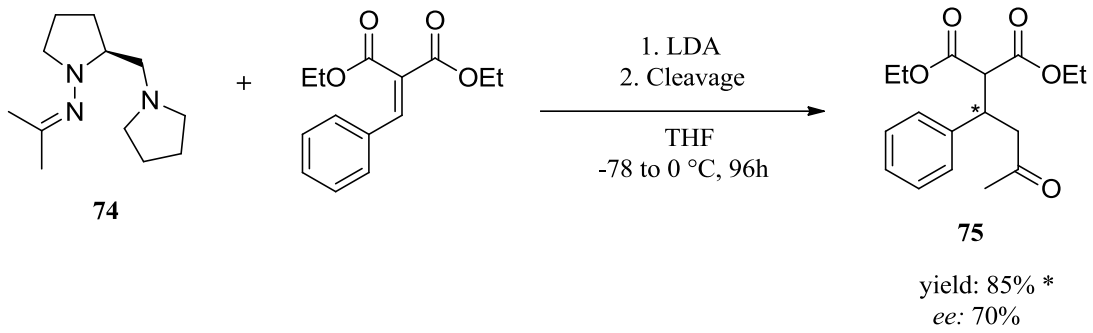


74

Scheme 3.9: The condensation of acetone with (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-amine to yield imine **74**.

Hydrazone **74** was then used in a Michael addition to diethyl benzylidenemalonate (Scheme 3.10), following a similar procedure to that reported by Enders *et al.*[230] for the SAMP-controlled Michael addition of acetone to the same substrate. This methodology involved deprotonation by lithium diisopropylamide at 0 °C, after which it was cooled to −78 °C. Upon addition of the Michael acceptor, the solution was stirred at −78 °C for 2 hours after which it was allowed to warm back up to 0 °C.

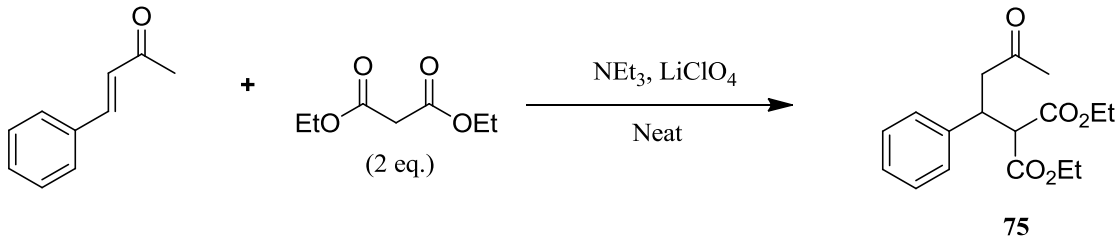
Although the reaction was monitored by TLC, it was worked up after 96 hours with some starting material still remaining.



Scheme 3.10: The addition of chiral hydrazone **74** to diethyl benzylidenemalonate and subsequent cleavage to yield product **75**. * based on recovered starting material.

The chiral hydrazone **74** was able to furnish the functional group-heavy product **75** in 70% *ee* (Scheme 3.11). The reaction provided the product in an 85% yield, showing that this procedure for perfoming conjugate additions to alkylidene malonates is both high-yielding and stereoselective.

In ordet to ascertain the enantioselectivity of the reaction in Scheme 3.11, racemic **75** was also required. Although it would be possible to repeat the above synthesis using an achiral *N*-amino pyrrolidine auxiliary, a more facile synthesis has been reported by Saidi and co-workers, in which the relative roles of the functional group-containing moieties are reversed. Here, the 1,3-diester becomes the nucleophile and the ketone, 4-phenyl-3-buten-2-one, is the electrophilic species (Scheme 3.11).[231] In this system the presence of the perchlorate salt is critical for the promotion of the reaction, presumably due to its ability to act as a Lewis acid.[232]



Scheme 3.11: Alternative synthesis of compound **75** *via* the Michael addition of dimethyl malonate to 4-phenyl-3-buten-2-one.[231]

This reaction proceeded with a good yield in only 30 minutes. This was an exciting development as, ostensibly at least, the reaction could work with our thiourea

organocatalysts, as, in effect, the catalysts marry the acidic properties of the perchlorate and the basicity of the triethylamine in one molecule. Regrettably, the reaction showed no sign of product formation after several days in the presence of catalysts **42**, **43** and **22**, both under neat reaction conditions and in toluene. When 10 mol% of the organocatalyst was applied in the presence of 5 mol% of $LiClO_4$, the reaction was completed in under 1 hour, however only the racemic product was formed.

3.5 Conclusion

From the outset, we were aware that α,β-unsaturated esters and diesters would be challenging acceptors in organocatalytic Michael additions involving hydrogen bonding catalysts. The lack of literature concerning conjugate additions to these substrates is testament to this fact. Despite this, we have reported the first organocatalytic Michael addition to an α,β-unsaturated diester using a H-bonding bifunctional catalyst. These thiourea catalysts were excellent promoters of the Michael addition of acetylacetone to dimethyl ethylidenemalonate and the yields were high for all of the catalysts tested. Unfortunately, the enantioselectivities did not match the impressive conversions. The lower selectivity associated with this substrate may be due to the lower Lewis basicity of the carbonyl group compared to, say, the nitro group.[1,233] This, of course, leads to a weaker interaction with the Lewis acid catalyst, which can result in a situation whereby the competing non-stereoselective background reaction prevails. It is possible that covalent catalysis would be more successful in these conditions since there is a strong substrate-to-catalyst interaction and therefore a more pronounced and well-defined influence of the catalyst on the stereochemical outcome of the reaction.

Nitromethane and malononitrile have also proved able pronucleophiles in Michael additions to diethyl ethylidenemalonate. Unfortunately the product arising from the malononitrile addition was inseparable by chiral HPLC so deduction of the enantioselectivity in these reactions was not possible. Nitromethane was a successful pronucleophile from a selectivity point of view, with quinine-derived thiourea catalyst **42** furnishing the Michael product in an almost 3: 1 enantiomeric ratio.

An aromatic ring on the β-position of the α,β-unsaturated diester renders the acceptor unreactive in Michael additions involving thiourea organocatalysts. The use of a para-nitro group on the ring can somewhat circumvent this inherent lack of reactivity, and this reaction proceeds with admirable stereocontrol, albeit at the expense of yield. It is thought that the reduced reactivity of the acceptor results in only the catalysed selective reaction prevailing. The autocatalytic Michael addition, which would furnish the racemic product, is unable to proceed due to the lack of reactivity of the uncoordinated, and thus unactivated, electrophile. This accounts for the improved stereoselectivity in this reaction when compared to the experiments performed using the more reactive diethyl ethylidenemalonate.

The use of a chiral auxiliary is one way of overcoming the reluctance of the benzylidenemalonate acceptor to react and the presence of a concrete, covalent chiral environment ensures that the reaction proceeds in a stereoselective manner. In this context, the chiral (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-amine, featuring a tertiary amine Lewis base to coordinate to the lithium ion, offers an excellent alternative to the established chiral auxiliaries such as RAMP or SAMP. 70% *ee* was achieved in the conjugate addition of acetone to diethyl benzylidenemalonate using this chiral auxiliary.

4. Variable Temperature Studies on *β*-Aminoacrylates

4.1 Aminoacrylate substrates

We turned our attention to aminoacrylates as a final extension to our exploration of challenging Michael acceptors. The Michael type addition to aminoacrylates represents a novel route to chiral amines and β-amino acids. Chiral amines are of primary biological importance. Their significance to the chemical industry is a result of the fact that they are some of the most common and useful subunits found in chiral drugs.[234] Optically active α- and β-amino acids highly desirable synthetic targets since they are necessary chiral amine building blocks for the preparation of a host pharmaceutical and agrochemical targets including peptides, proteins and other biologically active molecules.[235] As such, we were excited about the possibilities of creating a new route to these novel optically active chiral amines.

The aminoacrylates are, according to our knowledge, rather unexplored as Michael acceptors in stereoselective Micheal-type reactions. Fleming and co-workers have reported a high-yielding 1,4-conjugate addition of phenyllithium to an aminoacrylate but this is the only example of such in the literature.[236] Fleming's reaction clearly demonstrates the aminoacrylate's role as a Michael acceptor but, in the absence of a chiral ligand, the reaction furnished only a racemic mixture of the chiral product. Aminoacrylates are even less reactive than simple crotonate esters, owing to the resonance contributor arising from the donation of the lone pair of electrons from the nitrogen into the conjugated π-system. Therefore, from an organocatalytic perspective, reactions involving these substrates as Michael acceptors are not feasible. Another source of concern is the potential for amino-elimination from the Michael product to yield the α,β-unsaturated ester, Figure 4.1.

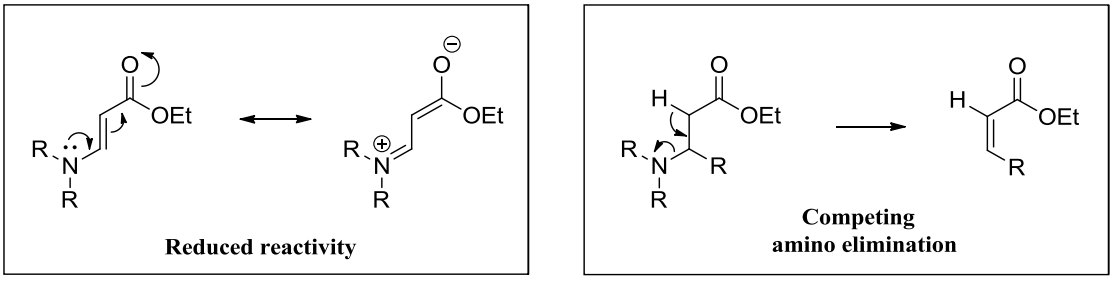
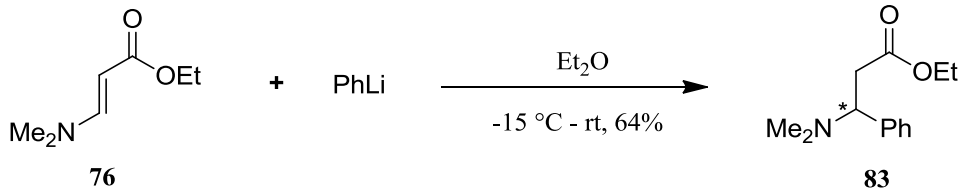


Figure 4.1: The resonance contributor in β-aminoacrylates (left) which accounts for their lack of reactivity in 1,4-conjugate additions and the potential competing amino elimination (right).

Organometallic reagents are strong enough nucleophiles to react with β-aminoacrylates. Herein we also report the addition of an organolithium nucleophile to ethyl-3-(dimethylamino)acrylate, Scheme 4.1.[236] Despite our concerns about the potential for amino-elimination in the product, the synthesis was straightforward. The phenyllithium solution was added to a solution of the aminoacrylate (**76**) in diethyl ether at −15 °C, whereupon it was stirred for 30 minutes at this temperature and a further 3 hours at room temperature. Short-path distillation yielded the purified product **83**.



Scheme 4.1: The conjugate addition of phenyllithium to ethyl-3-(dimethylamino)acrylate.[236]

This preliminary result indicates that β-aminoacrylates can act as Michael acceptors. Although outside the scope of this thesis, future work will include the development of an asymmetric copper catalysed reaction and explore the use of several organometallic reagents (Grignard, organozinc and organoaluminiun reagents).

The synthesis of the Michael acceptor, ethyl-3-(dimethylamino)acrylate **76**, is discussed in section 4.2.2. During the aminoacrylates's characterisation we noticed that it exhibited restricted rotation about the C-N bond. This prompted us to conduct a short investigation into the conformational isomerisation processes of aminoacrylates.

4.2 Rotation about the C-N bond in β-aminoacrylates

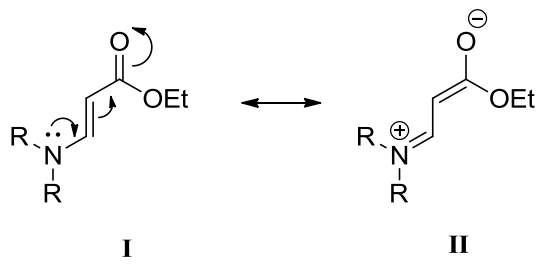
Conformational isomerisation processes, such as rotation about the C-N bonds of amides, have long held great interest for organic chemists.[237,238] The first report of slow rotation about a C-N bond as detected by NMR spectroscopy and the first measurement of the rotational barrier involved the simple amide *N*,*N*-dimethylformamide (DMF).[237] There is currently much interest in this phenomenon in a broader sense due to its role in the behaviour of more complex molecules. Some of this interest derives from the clues about electronic structure provided by the corresponding energy barriers,[239] although arguably a more significant reason comes in

the form of biochemical applications, such as the role that peptide bond isomerisation can play in limiting the rate of protein folding[240] and the observation of rotamase enzymes that catalyse this isomerisation.[241]

4.2.1 Dynamic NMR

Molecules are in constant motion, and the different conformations which are interconverted *via* bond rotations and other molecular gymnastics often have different NMR spectra. Generally speaking, the rotation that occurs about the C-C bond is so rapid that it is impossible for the NMR spectrometer to detect the resonances of each of the conformers. In the majority of organic molecules, this situation leaves all equivalent hydrogens to have the same average electronic environment and therefore identical chemical shifts (see section 4.3).

Restricted rotation about a C-N bond is a well-known phenomenon which has traditionally been associated with amides,[242] although this effect can also be seen in extended π-systems which fall into the category of "push-pull" olefins, such as enaminonitriles[243] or β-amino-α,β-unsaturated ketones.[244] β-Aminoacrylates, interesting compounds due to their potential to undergo conjugate additions to form biologically and pharmaceutically important chiral amine synthons, also exhibit this restricted rotation. Figure 4.2 shows the partial double-bond character of the C-N bond in these compounds arising from the contribution of canonical form **II**. This feature is responsible for the unusually high, for a formal single bond, barrier to rotation about the C-N bond. Another consequence of this partial double-bond character is the non-equivalence, geometrically and magnetically, of the nitrogen substituents.



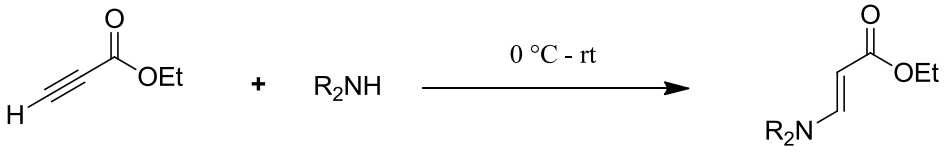
I **II**

Figure 4.2: The resonance contributors in β-aminoacrylates which gives rise to the restricted rotation about the C-N bond.

These *β*-aminoacrylates therefore exist in rotationally related forms and NMR spectroscopy can be used to study the kinetics of these exchanges. The use of NMR to measure rate parameters is generally called *dynamic NMR*, or simply DNMR. As such, we were interested in the determining whether the steric bulk associated with the *N*-substitutions in these molecules had any effect on the barrier to rotation about the C-N bond.

4.2.2 Synthesis of *N*-substituted aminoacrylates

The aminoacrylate family was synthesised from a propiolate ester and the appropriate amine, Scheme 4.2. The products were purified *via* short-path distillation.



Scheme 4.2: Synthesis of the N-substituted aminoacrylate family.

It was possible to synthesise a whole family of these compounds by varying the substitution on the secondary amine starting material.

4.2.3 The Heisenberg Uncertainty Principle

The Heisenberg uncertainty principle tells us that in order to resolve NMR signals (i.e. to record them separately), a "sufficient" time is necessary. This time, Δt, is the life-time of any state we wish to detect. The Uncertainty Principle is expressed either in terms of the uncertainty in energy (ΔE) or in frequency by substituting the Planck equation, $E = h\upsilon$, appropriately.[245]

$$\Delta E \,.\, \Delta t \approx h/2\pi$$

or

$$\Delta \upsilon \,.\, \Delta t \approx 1/2\pi$$

Processes such as the "slow" rotation about the C-N bond in amides occur at rates (measured in s^{-1}) which can be deduced from the life-times of each of the separate states (Δt, measured in s). Therefore, slow rates (long life-times) lead to separate

NMR signals, while fast rates (short life-times) lead to overlapped or coalesced signals.

4.3 Ethyl-3-(dimethylamino)acrylate

The dimethyl-substituted enamine, ethyl-3-(dimethylamino)acrylate (**76**), was the first molecule in the family to be synthesised and have its variable temperature NMR spectra assessed. Due to the simplicity of the signal arising from the *N*-substitution at room temperature (a singlet integrating to 6, appearing at approximately 2.8 ppm), this compound is the ideal representative example with which to discuss the theory behind the spectra shown in Figure 4.3. Over the temperature range the olefinic protons are present in the NMR spectra as doublets at 7.4 and 4.5 ppm respectively while the ethoxy ester group is easily identified as a quartet at 4.1 ppm and a triplet at 1.2 ppm.

In mutual rotations such as that exhibited by ethyl-3-(dimethylamino)acrylate the principle conformers are equienergetic, Figure 4.3. This type of exchange, where the equilibrium produces indistinguishable molecules, is termed *mutual site exchange*. The energy of activation, E_A, for this mutual rotation to occur, is comparable to the energy barrier to rotation, and it is possible to calculate E_A from the measured temperature dependence of the appearance of the spectrum.[245] This is discussed in more detail in section 4.3.3.

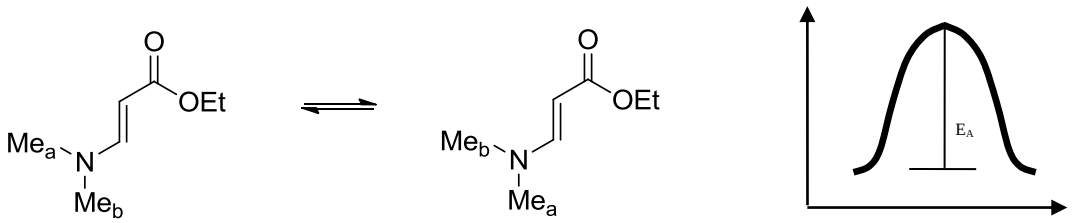


Figure 4.3: The mutual rotation in ethyl-3-(dimethylamino)acrylate.

At lower temperatures, restricted rotation around the C-N bond produces different shielding zones for the methyl groups, so two methyl resonances arise in the spectrum. As the sample temperature is raised, rotation about the bond becomes more rapid; consequently the life-time of each methyl group in each separate shielding zone is reduced. The signals broaden and, eventually the life-times become so short (rotation so rapid) that only one resonance is detected, which is mid-way between the separate signals.

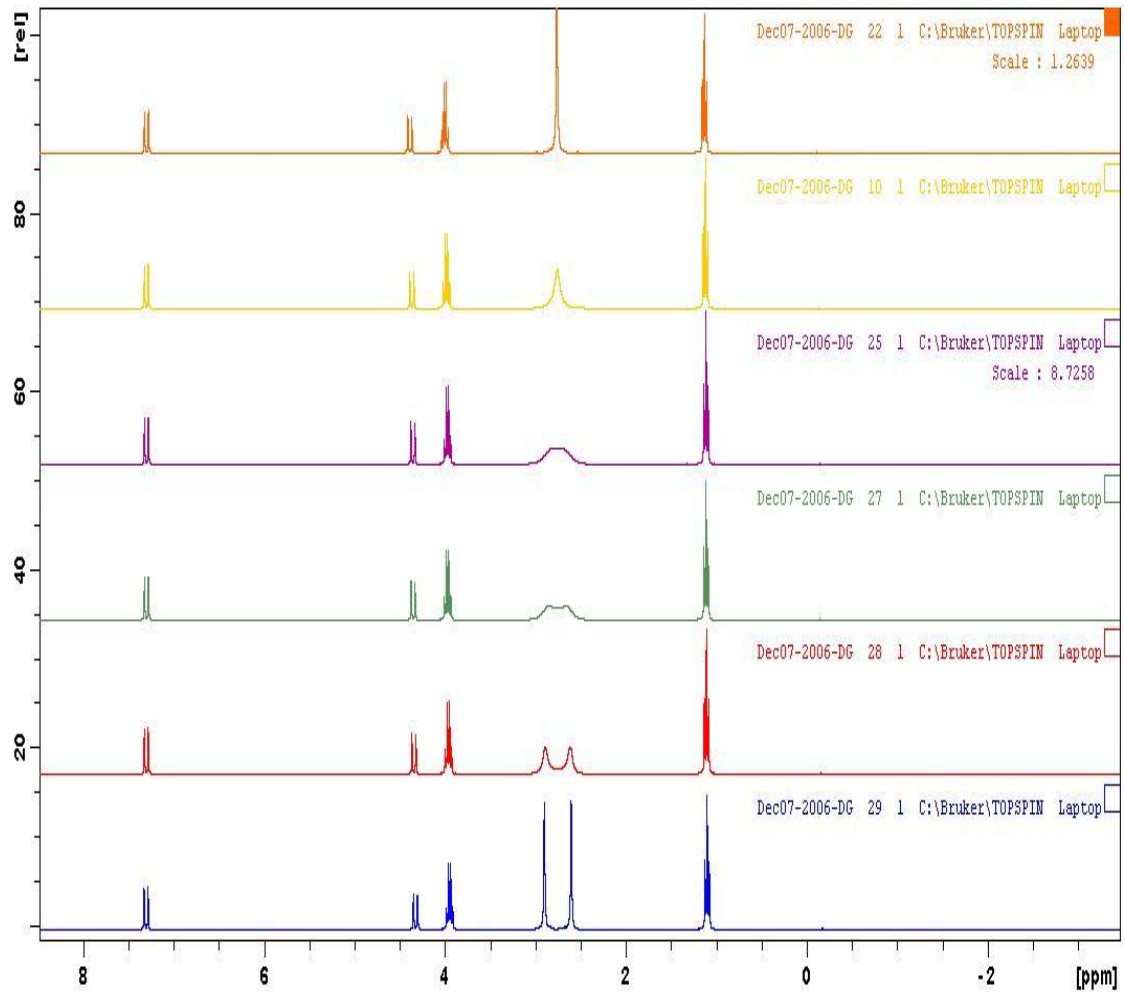


Figure 4.4 The VT ^{1}H NMR spectra (in $CDCl_3$) for ethyl-3-(dimethylamino)acrylate. Spectra recorded at; — 45 °C, — 25 °C, — 7 °C (coalescence temperature), — 5 °C, — −5 °C, — −25 °C.

When a sample of ethyl-3-(dimethylamino)acrylate was warmed to 45 °C, the rotation about the C-N bond was sufficiently fast for the averaged-out methyl signal to become quite sharp. As the temperature dropped (along with the rate of rotation about the C-N bond) this sharp peak broadened until a single, flat-topped peak was observed. The temperature at which this happens is called the coalescence temperature. In the case of ethyl-3-(dimethylamino)acrylate the coalescence temperature is 7 °C (Figure 4.4). Below the coalescence temperature the signal gradually splits into two separate peaks.

At −25 °C the sample is cold enough to slow the C-N rotation (and elongate the lifetime of each state), thereby allowing the spectrometer to "see" the individual methyl resonances. Consequently, two separate signals of perfectly equal intensity are observed.

4.3.1 The temperature of coalescence and its significance

The coalescence temperature is defined as the temperature at which the appearance of the spectrum changes from that of two separate peaks to a single, flat-topped peak. The importance of the coalescence temperature is highlighted by considering the spectra in Figure 4.4. In simple dynamic processes like this where the exchanging nuclei are not coupled to each other, H. S. Gutowsky showed that at the coalescence temperature (T_c) the rate constant, k_c, is given by:

$$k_c = 2.22\ \Delta\upsilon$$

where $\Delta\upsilon$ is the separation in Hz between the two signals in the absence of rotation.[246] Thus, it is possible to quantify the speed of the exchange at this temperature.

4.3.2 Energy of activation

In order to demonstrate the energy fluctuations in the mutual site exchange displayed by ethyl-3-(dimethylamino)acrylate, we previously implied that the energy barrier to rotation about the C-N bond is analogous to E_A, the activation energy (Figure 4.3). This is not entirely accurate since it wrongfully assumes E_A to be independent of temperature. Strictly, the free energy of activation ($\Delta G^{\ddagger}$), the enthalpy of activation ($\Delta H^{\ddagger}$) and the entropy of activation ($\Delta S^{\ddagger}$) are interconnected by $\Delta G = \Delta H - T\Delta S$, and different experimental procedures are required to measure each separate parameter.[245]

The energy of activation, E_A, for a simple reaction such as the rotation of β-aminoacrylates, can be deduced form the Arrhenius equation, which also includes the rate constant, k:

$$k = A \exp(-E_A/RT)$$

where R is the gas constant, T is the absolute temperature and A roughly corresponds to the fraction of species that reach the transition state and pass over to the "product" side of the reaction. A is assumed to be a constant even though it does vary slightly with temperature. Here the value of E_A would be found by plotting $\ln k$ against $1/T$, but this is only applicable for those reactions which give a straight line graph. A more broadly applicable approach comes in the form of the Eyring equation.

4.3.3 The free energy of activation $\Delta G^{\ddagger}$

The Eyring equation, which can be expressed in a number of different ways, can be written

$$k = K \frac{k_B T}{h} \exp\left(-\Delta G‡/RT\right)$$

here, k is the rate constant, k_B is the Boltzmann constant, h is Planck's constant and $\Delta G^{\ddagger}$ is the free energy of activation. Since this equation incorporates $\Delta G^{\ddagger}$ and $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, both the enthalpy and entropy of the system are accounted for.[245] The 'constant' K is analogous to the 'constant' A in the Arrhenius equation but, provided the transition state can easily transfer energy to the surroundings (and this is commonly true) then K is near unity.

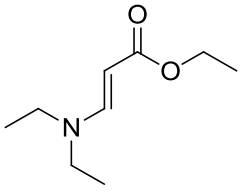
If the value of k_c is substituted into the Eyring equation, the natural log is converted to $\log_{10}$ and the values for the constants k_B, h and R are also substituted in, then the Eyring equation usefully evolves to

$$\Delta G^{\ddagger} = 19.12\ T_c\ (10.32 + \log T_c - \log k_c)$$

The Gutowsky equation is used to find the rate of rotation, k_c, at the temperature of coalescence, T_c. Thus, the free energy of activation for this (and many other) exchange processes can be evaluated approximately from T_c using the Eyring equation in this form.[245,246]

4.4 Ethyl-3-(diethylamino)acrylate

Ethyl-3-(diethylamino)acrylate (**77**), Figure 4.5, was synthesised from ethyl propiolate and a 20% aqueous solution of diethylamine.



77

Figure 4.5: The chemical structure of ethyl-3-(diethylamino)acrylate (**77**).

The VT ^{1}H NMR spectra for this compound are shown in Figure 4.6. The gradual slowing of the rotation about the C-N bond, 35 °C to −35 °C, can be observed by monitoring the CH_2 signal of the NEt_2 group, which appears just above 3 ppm.

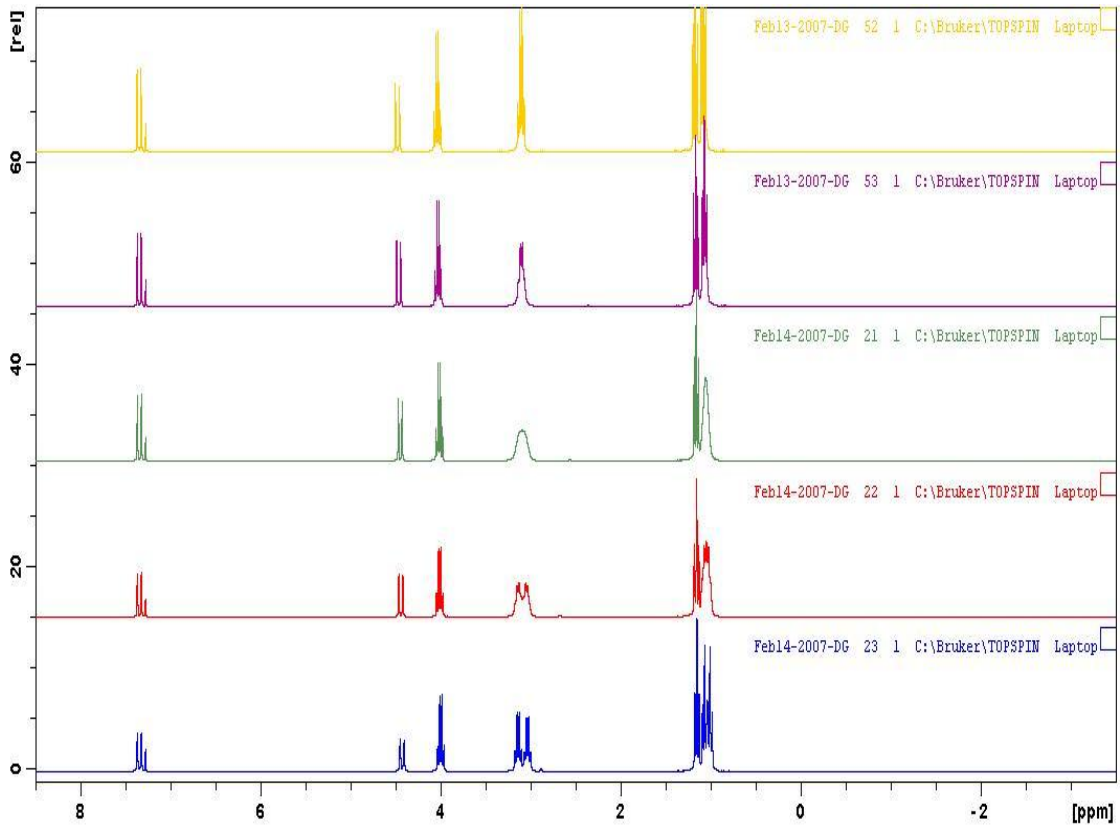
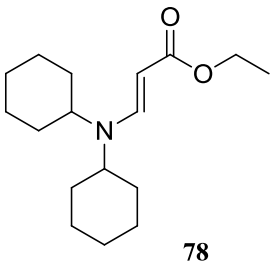


Figure 4.6: The VT ^{1}H NMR spectra (in $CDCl_3$) for ethyl-3-(diethylamino)acrylate. Spectra recorded at; — 35 °C, — 15 °C, — −4 °C (coalescence temperature), — −15 °C, — −35 °C.

The coalescence temperature is −4 °C for this compound, which is considerably lower than the corresponding value for its methyl-substituted relation. However, one cannot draw any conclusions from the coalescence temperature as it is only one of two parameters to be inserted into the modified Eyring equation ($\Delta\upsilon$ being the other). At −35 °C it is possible to clearly see separate quartets, representing the CH_2 of both N-ethyl substitutions.

4.5 Ethyl-3-(dicyclohexylamino)acrylate

Ethyl-3-(dicyclohexylamino)acrylate (**78**), Figure 4.7, was synthesised from ethyl propiolate and dicyclohexylamine.



78

Figure 4.7: The chemical structure of ethyl-3-(dicyclohexylamino)acrylate (**78**).

The VT ^{1}H NMR spectra for this compound are shown in Figure 4.8. The proton attached to the substituted carbon on the cyclohexyl ring is apparent at 3.2 ppm.

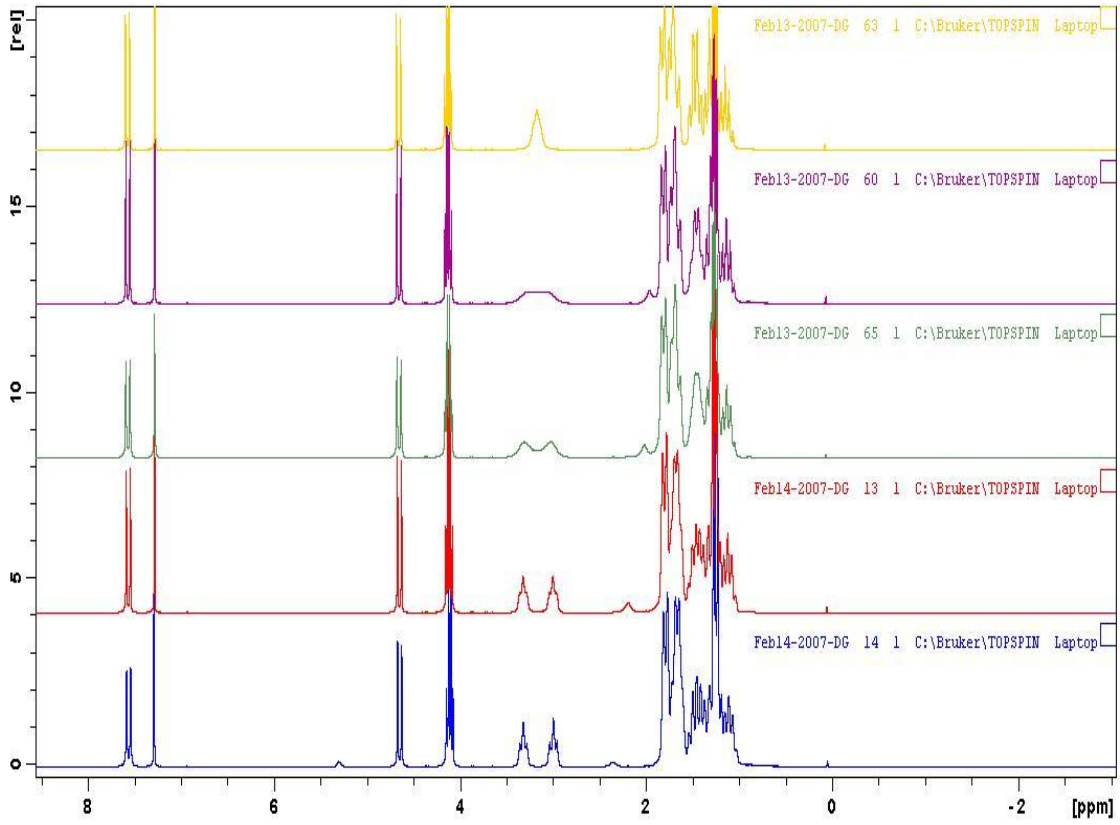
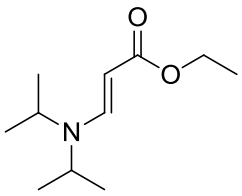


Figure 4.8: The VT ^{1}H NMR spectra for (in $CDCl_3$) ethyl-3-(dicyclohexylamino)acrylate. Spectra recorded at; — 45 °C, — 22 °C (coalescence temperature), — 15 °C, — −5 °C, — −45 °C.

The coalescence temperature is 22 °C for ethyl-3-(dicyclohexylamino)acrylate.

4.6 Ethyl-3-(diisopropylamino)acrylate

Ethyl-3-(diisopropylamino)acrylate (**79**), Figure 4.9, was synthesised from ethyl propiolate and diisopropylamine.



79

Figure 4.9: The chemical structure of ethyl-3-(diisopropylamino)acrylate (**79**).

The VT ^{1}H NMR spectra for this compound are shown in Figure 4.10. The septet representing the proton attached to the secondary carbon on the isopropyl group is evident at 3.6 ppm.

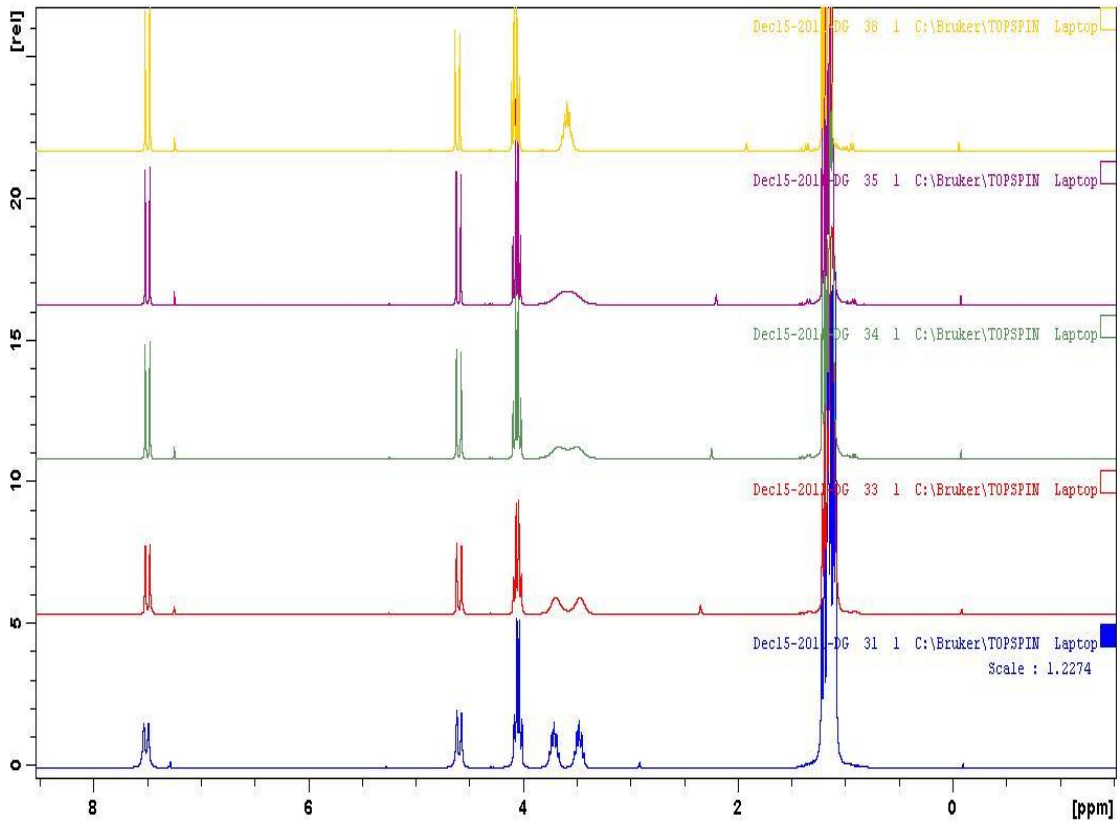
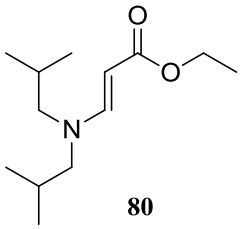


Figure 4.10: The VT ^{1}H NMR spectra for (in $CDCl_3$) ethyl-3-(diisopropylamino)acrylate. Spectra recorded at; — 40 °C, — 10 °C (coalescence temperature), — 5 °C, — −5 °C, — −45 °C.

The coalescence temperature is 10 °C for this compound.

4.7 Ethyl-3-(diisobutylamino)acrylate

Ethyl-3-(diisobutylamino)acrylate (**80**), Figure 4.11, was synthesised from ethyl propiolate and diisobutylamine.



80

Figure 4.11: The chemical structure of ethyl-3-(diisobutylamino)acrylate (**80**).

The VT ^{1}H NMR spectra for this compound are shown in Figure 4.12. In this set of spectra, two signals are seen to split into discrete peaks at lower temperatures, namely the signals for the protons on the methylene bridge which is directly bound to the nitrogen atom (2.9 ppm) and the proton on the secondary carbon atom onto which the two methyl groups are bound (1.9 ppm). The former signal is used to identify the coalescence temperature (5 °C) since it is representative of the protons closest to the olefinic bond.

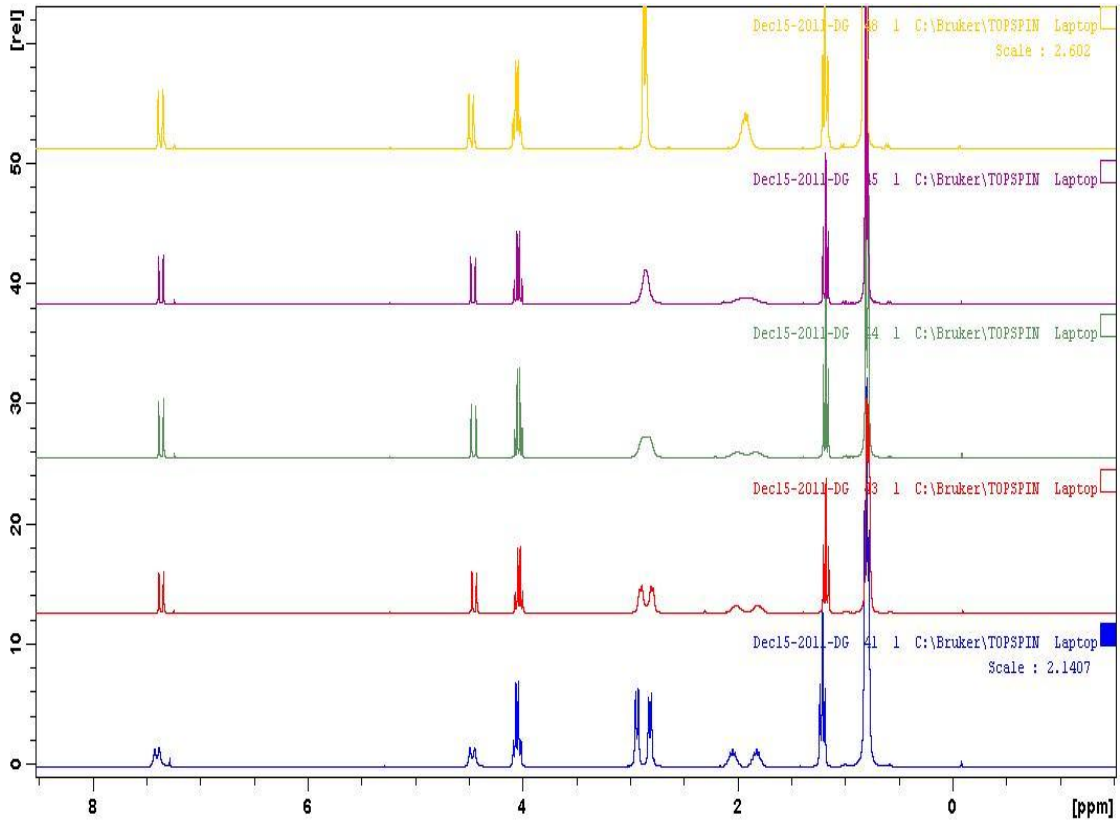
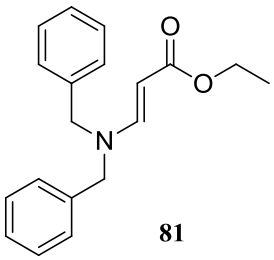


Figure 4.12: The VT NMR spectra for (in $CDCl_3$) ethyl-3-(diisobutylamino)acrylate. Spectra recorded at; — 40 °C, — 13 °C, — 5 °C (coalescence temperature), — −5 °C, — −45 °C.

4.8 Ethyl-3-(dibenzylamino)acrylate

Ethyl-3-(dibenzylamino)acrylate (**81**), Figure 4.13, was synthesised from ethyl propiolate and dibenzylamine.



81

Figure 4.13: The chemical structure of ethyl-3-(dibenzylamino)acrylate (**81**).

The VT ^{1}H NMR spectra for this compound are shown in Figure 4.14.

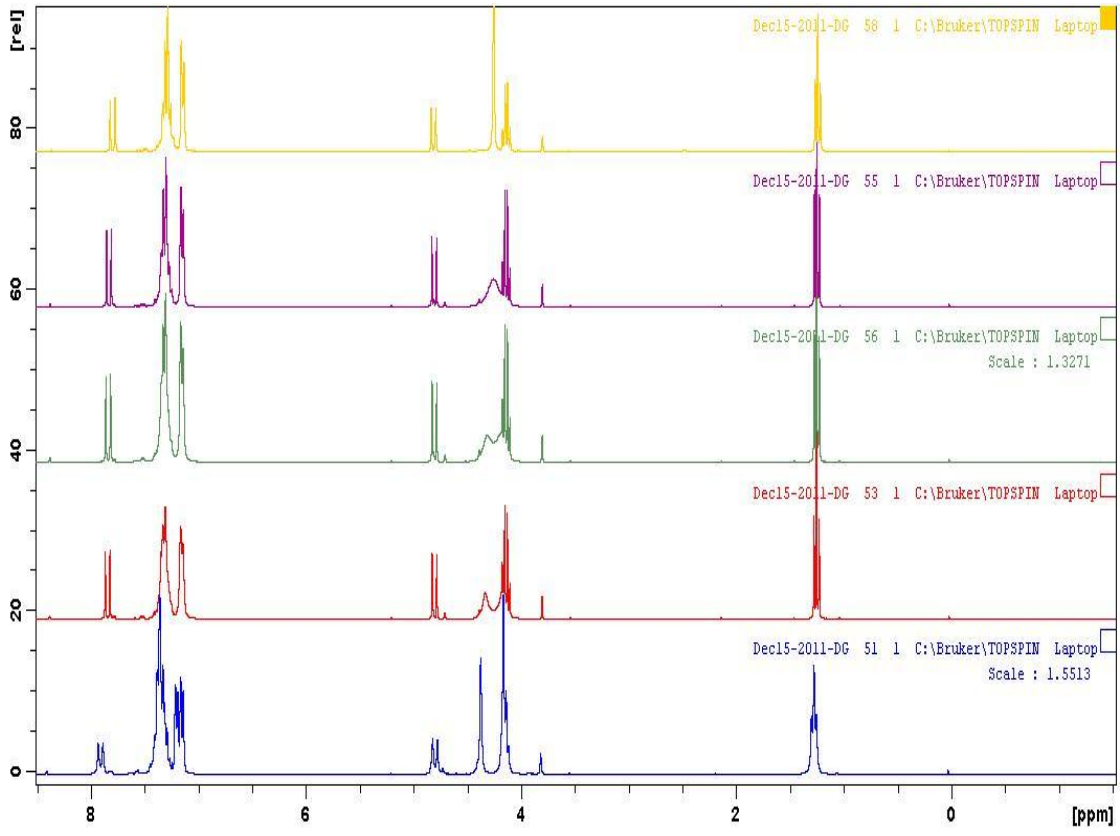


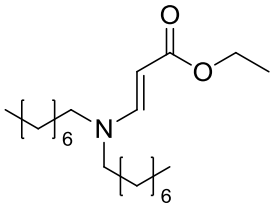
Figure 4.14: The VT ^{1}H NMR spectra for (in $CDCl_3$) ethyl-3-(dibenzylamino)acrylate. Spectra recorded at; — 40 °C, — 6 °C (coalescence temperature), — 0 °C, — −5 °C, — −45 °C.

The singlet for the methylene bridge appears at 4.18 ppm, and is a broad singlet at temperatures close to room temperature. At 40 °C the C-N bond rotation is sufficiently rapid to sharpen the signal. At ambient temperature, the signal for

methylene bridge on the benzyl group occurs at a similar ppm to the CH_2 signal for the ethyl group. The signals separate into two discrete peaks at lower temperatures; one of these benzyl CH_2 signals overlaps with the CH_2 signal from the ethoxy group (Figure 4.14). The coalescence temperature is 6 °C for ethyl-3-(dibenzylamino)acrylate.

4.9 Ethyl-3-(dioctylamino)acrylate

Ethyl-3-(dioctylamino)acrylate (**82**), Figure 4.15, was synthesised from ethyl propiolate and dioctylamine.



82

Figure 4.15: The chemical structure of ethyl-3-(dioctylamino)acrylate (**82**).

As can be seen from the spectra shown in Figure 4.16, the signal for the CH_2 adjacent to the N atom on the octyl substitution appears at approximately 3 ppm. At ambient temperature and above this signal appears as a triplet, as expected. In the vicinity of the temperature of coalescence (9 °C) the signal is a broad singlet, but when the temperature is dropped sufficiently both signals are present and resolved as distinct triplets.

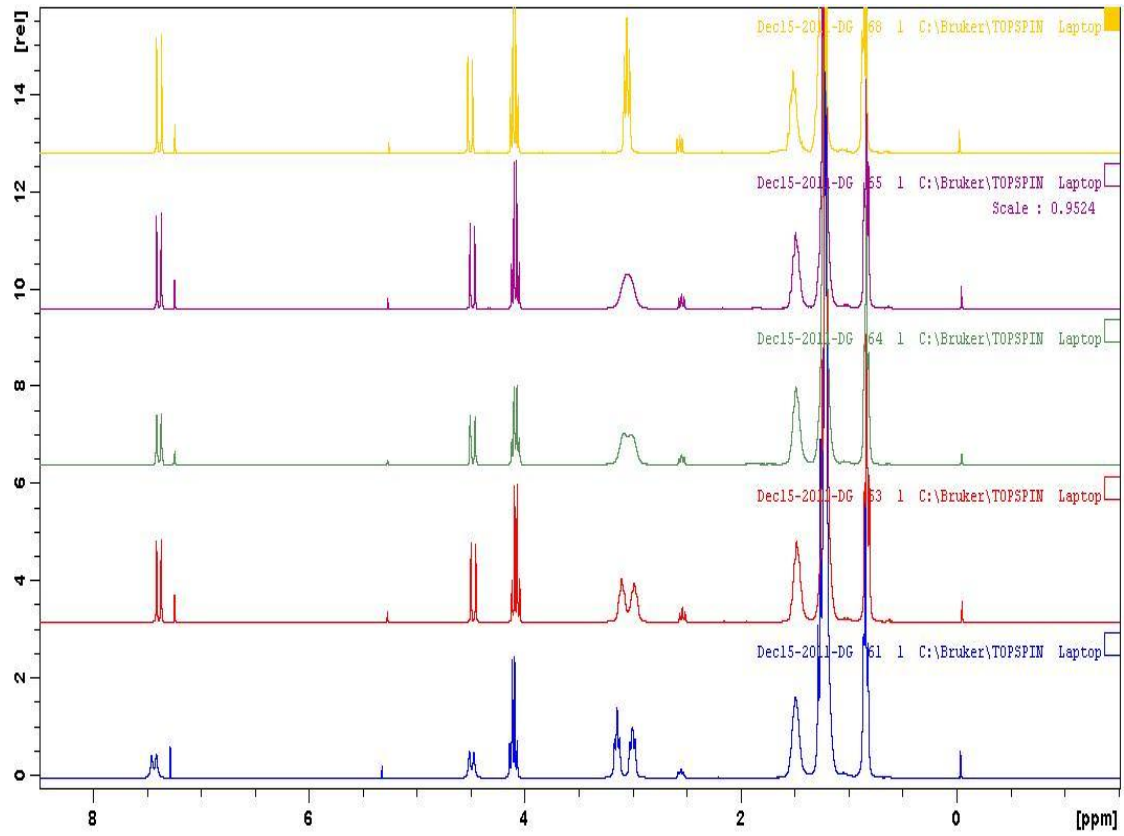


Figure 4.16: The VT ^{1}H NMR spectra for (in $CDCl_3$) ethyl-3-(dicyoctylamino)acrylate. Spectra recorded at; — 40 °C, — 9 °C (coalescence temperature), — 5 °C, — −5 °C, — −45 °C.

The coalescence temperature for ethyl-3-(dioctylamino)acrylate is 9 °C.

4.10 Barrier to rotation about the C-N bond

As discussed in section 4.3.3, the barrier to rotation about the C-N bond in *N*-substituted *β*-aminoacrylates can be calculated using the modified Eyring equation;

$$\Delta G^{\ddagger} = 19.12\ T_c\ (10.32 + \log T_c - \log k_c)$$

Where T_c is the temperature of coalecscence (in Kelvin) and k_c, the rate of rotation, can be determined from the Gutowsky equation;

$$k_c = 2.22\ \Delta\upsilon$$

where $\Delta\upsilon$ is the difference (in Hertz) between the signals when they have split into discrete peaks at low temperature. In the case of ethyl-3-(dimethylamino)acrylate this value is 89.1 Hz, making k_c = 197.8 Hz. The temperature of coalescence for this

compound is 280.15 K, thus the free energy of activation (the barrier to rotation) about the C-N bond is 56.1 kJ mol^{-1}. Corresponding calculations were performed on all 7 compounds and the results have been tabulated below (Table 4.1).

Table 4.1: The barrier to rotation about the C-N bond of the family of disubstituted β-aminoacrylates.

Compound	R	T_c	$\Delta\upsilon$ (Hz)	k_c (Hz)	$\Delta G^{\ddagger}$ (kJ mol^{-1})
76	Me	280.15	89.1	197.8	56.1
77	Et	269.15	31.1	69.0	56.2
78	Cyclohex	295.15	96.7	214.7	59.0
79	^{i}Pr	283.15	70.7	157.0	57.3
80	^{i}Bu	278.15	66.8	148.3	56.2
81	Bn	279.15	67.1	150.0	56.5
82	Oct	282.15	42.8	95.0	58.4

Despite the obvious variation in structure and molecular weight of the substituent R, there is not a large difference in the calculated barrier to rotation about the C-N bond. For example, the methyl substituted compound **76** has a very similar $\Delta G^{\ddagger}$ value to its isobutyl-substituted relation **80**. This is surprising, given the large difference in molecular weight of the two groups.

4.10.1 Significance of the steric bulk of the substituent

The steric bulk of a substituent can be conveniently quantified using Charton values.[247] Steric effects were first treated quantitatively by Taft, who defined parameters characteristic of a substitution by monitoring various substitution reaction rates and comparing them to a reference reaction. The aforementioned work of Charton and co-workers built upon Taft's work, by using a modified version of Taft's equation to define steric-effect substituent constants based on Van der Waals radii. They did this by investigating the rates of acid-catalysed esterifications as a function of steric effects.[192] Resulting from Charton's endeavour, the parameter υ was defined which describes the steric potential of a substituent. The same group have also established

the utility of the υ parameters,[247,248] including one study investigating barriers to internal rotation.[249] The υ values for the *N*-substitution were procured from the work of Charton[192,250] (Table 4.2) as we were interested in whether there was a correlation between the steric hindrance associated with the substitution and the barrier to rotation about the C-N bond.

Table 4.2: The barriers to rotation about the C-N bond in the compounds in our family of β-aminoacrylates and their respective Charton values.

Compound	R	$\Delta G^{\ddagger}$ (kJ mol^{-1})	υ
76	Me	56.1	0.52
77	Et	56.2	0.56
80	^{i}Bu	56.2	0.98
81	Bn	56.5	0.70
79	^{i}Pr	57.3	0.76
82	Oct	58.4	0.68*
78	Cyclohex	59.0	0.87

* No Charton value available, but 0.68 is the value assigned to several similar *n*-alkyl substituents, such as *n*-C_9H_{19}, *n*-$C_{11}H_{23}$ and *n*-$C_{13}H_{27}$.

In order to observe any potential correlations it was necessary to put the results into graphic form (Figure 4.17). Resultantly, the barrier to rotation about the C-N bond (*x*-axis) and the steric potential of the substituent (*y*-axis) was plotted. Generally, it appears that the larger substituents do have a discernable influence on the C-N bond's rate of rotation. It is apparent that the larger groups such as the cyclohexyl and octyl-substituted aminoacrylates do have a larger barrier to rotation (59 kJ mol^{-1} and 58.4 kJ mol^{-1} respectively) than compounds with smaller substituents such as methyl-substituted **76** (56.1 kJ mol^{-1}). Despite this, there is a lack of concrete interdependence and the graph does not follow a congruent pattern. The minor increase in $\Delta G^{\ddagger}$ for larger substitutions could be simply put down to the "heavier" moieties slightly retarding the rate of rotation because of their greater bulk. Interestingly, the barrier to rotation for the two compounds featuring a secondary carbon atom directly bonded to the nitrogen (the cyclohexyl-substituted **78** and the iso-propyl-substituted **79**) is perceptibly higher (59.0 and 57.3 kJ mol^{-1} respectively) than

that of the compounds featuring a primary carbon adjacent to the nitrogen, such as methyl-substituted **76** (56.1 kJ mol^{-1}), ethyl-substituted **77** (56.2 kJ mol^{-1}) and isobutyl-substituted **79** (56.2 kJ mol^{-1}).

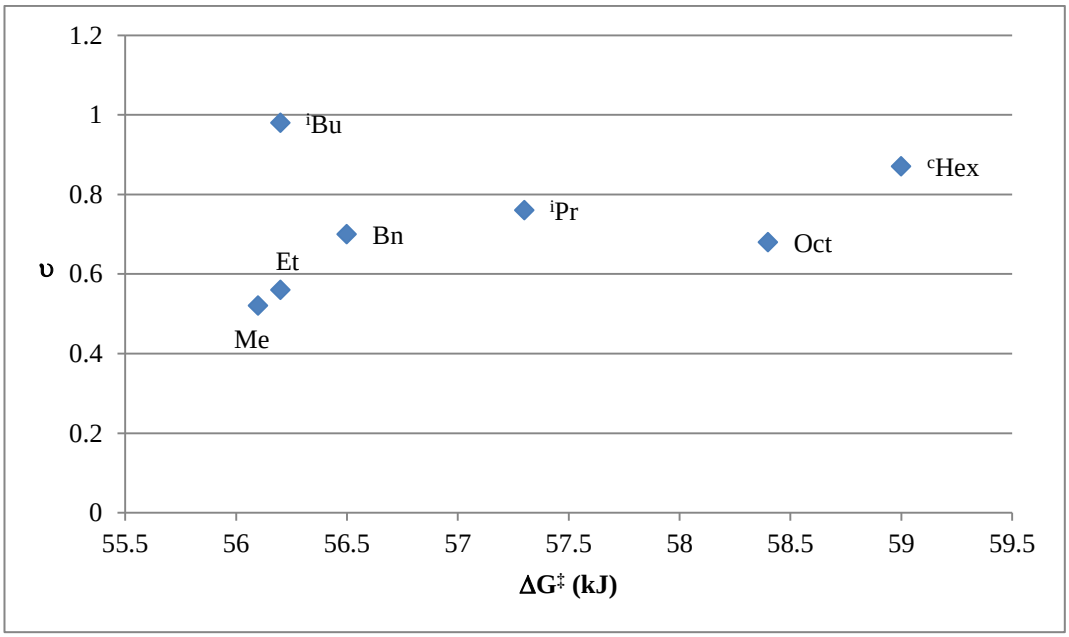
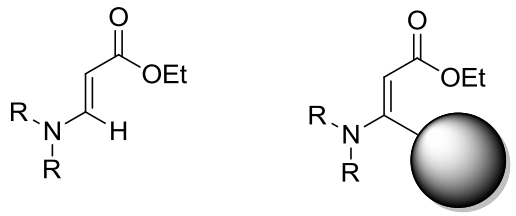


Figure 4.17: Graph of barrier to rotation (*x*-axis) against Charton value (*y*-axis). The compounds are labelled according to their *N*-substituents for ease of identification.

As the olefinic functionality is only monosubstituted, it is not implausible that there would not be a great variation in the barriers to rotation about the C-N bond in these compounds. The nitrogen substituents are spatially relatively isolated and are unlikely to encounter a situation whereby a steric interaction would hinder their progress. It is probable that the introduction of a second sterically-demanding substituent on the *β*-carbon would result in a more incremental increase in the barrier to rotation (Figure 4.18), since larger groups on the nitrogen could interfere with such a moiety and result in a prohibitive interaction which would hinder rotation.



Steric clash unlikely in the presence of H

Introduction of a large group at β-carbon increases chance of steric clash

Figure 4.18: *α,β*-unsaturated aminoacrylate which is monosubstituted at the *β*-carbon (left) and (right) the introduction of a sterically challenging moiety at the *β*-carbon.

The dependence of a second substituent at the *β*-carbon on the C-N barrier to rotation of these aminoacrylates will be investigated by our group in the future and we expect that it would have a significant influence on the rate of rotation.

Furthermore, the sheer range of substituent and the relatively small differences in the barrier to rotation in our family of *β*-aminoacrylates further serve to indicate that, from a steric point of view, the *N*-substituent has a modest influence upon the rate of rotation about the C-N bond. Perhaps a stronger influence would be electronic in nature, Figure 4.19. This may be particularly true in the absence of another spacially demanding substituent at the *β*-carbon of the molecule.

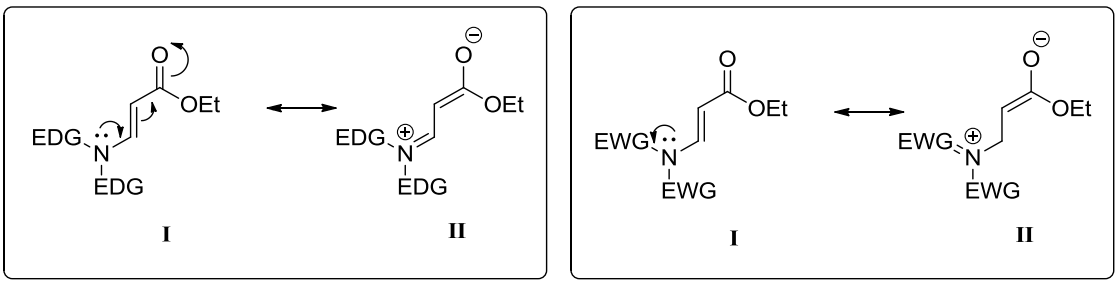


Figure 4.19: Electron-donating (left) and electron-withdrawing (right) *N*-substitutions on *α,β*-unsaturated aminoacrylates.

An electron-donating substituent on the nitrogen atom (left) would increase the contribution of canonical contributor II, thereby resulting in a larger barrier to rotation about the C-N bond owing to the increased C=N double-bond character. An electron-withdrawing moiety on the amine would have precisely the opposite effect and would likely lower the rotational barrier. Future work in our group will also focus on experimentally investigating this theory.

4.11 Conclusion

The rotation about the C-N bond in a family of β-aminoacrylates was investigated. The *N*-substitution was systematically varied in this family. A series of VT ^{1}H NMR experiments were undertaken to study the effect of steric bulk on the C-N barrier to rotation in these molecules. The barrier to rotation about the C-N bond in these molecules was calculated using the modified Eyring equation and the steric potential of each *N*-substitution was parameterised using Charton values.

The barrier to rotation in these molecules was then plotted against the Charton value of the respective *N*-substitution in order to establish a possible connection between the size of the substitution and the rate of rotation about the C-N bond in the molecule. A linear relationship between the steric effect of the *N*-substitution and the barrier to rotation about the C-N bond was not observed, although an increase was observed for compounds featuring a secondary carbon atom adjacent to the nitrogen on the *N*-substitution compared to those with a primary carbon in this position.

5. Antimicrobial Studies

5.1 Introduction

The Stephens group also conduct research into the design, synthesis and evaluation of new antimicrobial agents. Therefore we took the opportunity to test our compounds which fell under the description of cinchona alkaloid or thiourea. Both cinchona and thiourea-based compounds have been reported as antimicrobial agents.[251,252]

The cinchona family has a long history in medicinal chemistry. Quinine is famous for its antimalarial properties[251] and its medicinal history dates back as far as the 17th century. Cinchona derived compounds inhibit the growth of infections such as *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[253] For example, quinine sulphate has been shown to inhibit the internalisation/invasion efficacy of *E. Coli*.[254] The aromatic subunit present in the cinchona alkaloids, the quinoline ring, is present in the antimalarial compound chloroquine and this moiety is structurally similar to the well-known antibiotics, the quinolones. Quinolones were first discovered as a by-product of chloroquine production in the early 20th century.[255] The first quinolone antibiotic, nalidixic acid (Figure 5.1), was brought into clinical use in 1962 and the quinolone family are now prominent broad spectrum antibiotics used to treat a range of infections.[251]

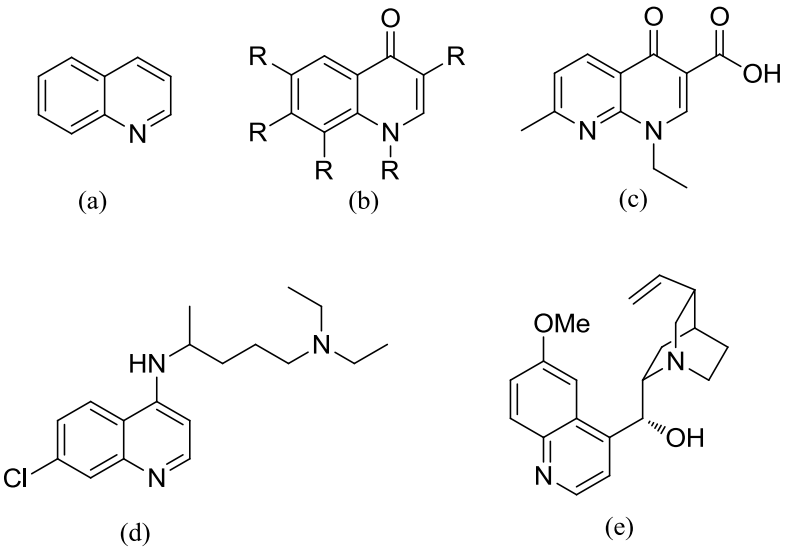
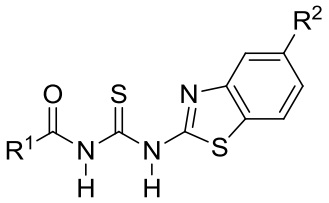


Figure 5.1: Structures of (a) quinoline, (b) generic quinolone antibiotic, (c) nalidixic acid, (d) chloroquine, (e) quinine.

Thioureas have enormous potential as biological agents, since they possess antibacterial and antifungal properties[256] and they can act as herbicides and

rodenticides.[257] They possess low acute toxicity for mammals and are very effective in curing a number of crop diseases.[258] Recently thiourea derivatives bearing a benzathiazole moiety (Figure 5.2) have been tested for antibacterial activity against Gram-negative and Gram-positive bacteria and have shown broad-spectrum activity against these microorganisms.[252] In another recent, separate study, the thioureido amide of fluoroquinolone has shown significant biological activity against a number of bacteria, including *E. coli*, *S. aureus* and *P. aeruginosa*.[259]



R^1 = aryl, alkyl
R^2 = H, NO_2, NH_2, Br

Figure 5.2: The structure of the thiourea derivatives which have exhibited antimicrobial activity. [252]

There is currently a dire need for new antimicrobial compounds. In April 2010, Ireland was reported to have the EU's highest rate of *Escherichia coli* infection,[260] while estimates of the cost of MRSA infection in Irish hospitals is €23 million per year.[261] Over the past decade, resistance to antibiotics has emerged as a major global crisis. Microbes which are resistant to clinically approved antibiotics are increasingly common and this situation is compounded by the alarming lack of new drugs coming to market.[262] We are reaching a disturbing point where we are no longer confidently able to treat a growing number of bacterial infections.

5.2 Results

The testing was carried out as a paid service by Institute of Technology, Tallaght. The structures of the compounds tested are shown in Figure 5.3.

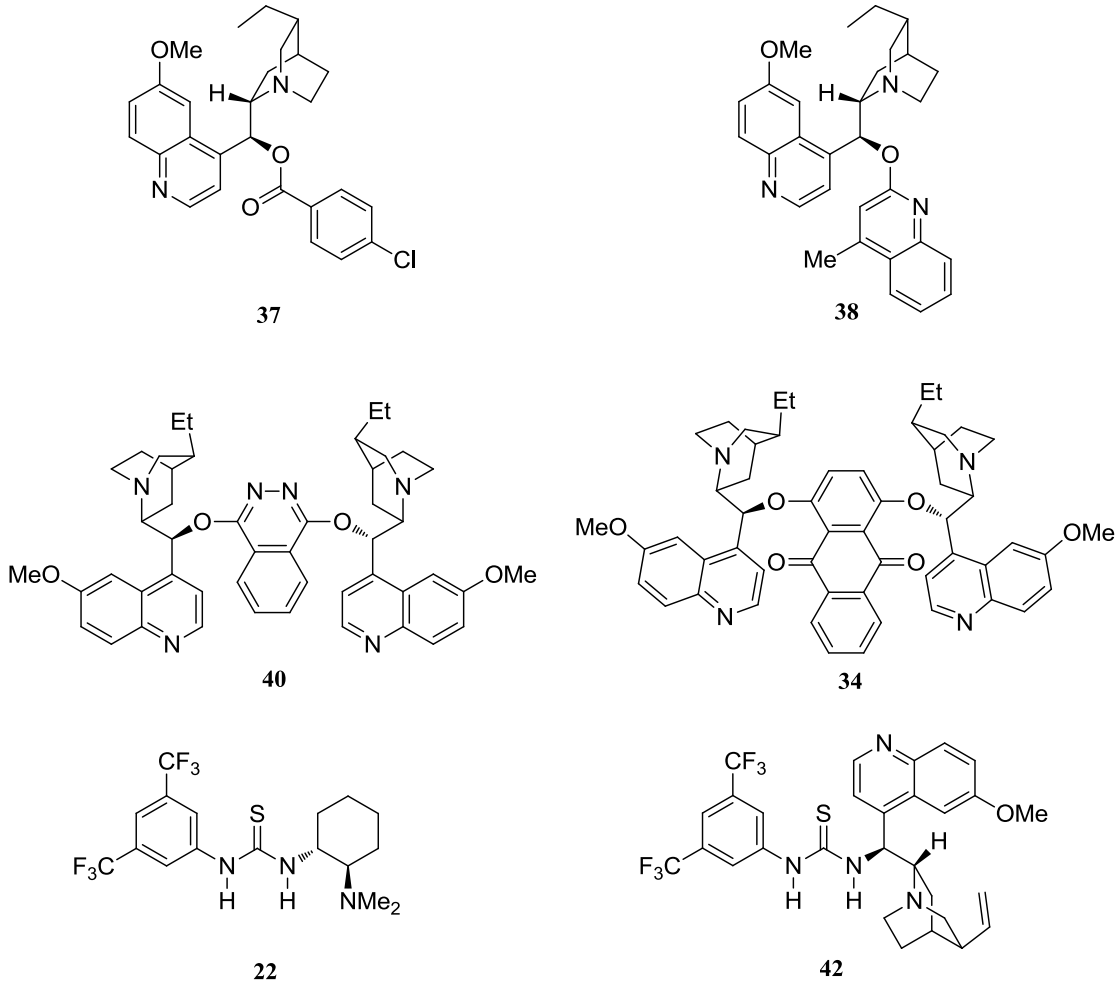
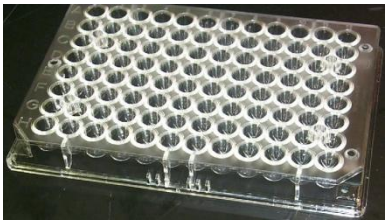


Figure 5.3: The structures of the compounds tested for activity against *S. aureus* and *E. coli*.

The testing itself was carried out on 96-well, flat bottom tissue culture plates (Figure 5.4). The susceptibility of each bacteria was assessed following the method described by Kelly *et al*.[263] The OD_{600nm} of the overnight cultures was determined using a spectrophotometer (Biophotometer, Eppendorf) and diluted in nutrient broth to produce cultures with an OD_{600nm} of 0.1. 100 mL of the cell suspension was added to each well of a 96-well plate containing varying concentrations of the compound being assessed (100-0.78 mg/ml) in 100 ml of nutrient broth. The plate was incubated for 24 hours at 37 ^{o}C. The optical density was read at 540 nm using a microplate reader. Growth was quantified as a percentage of control.



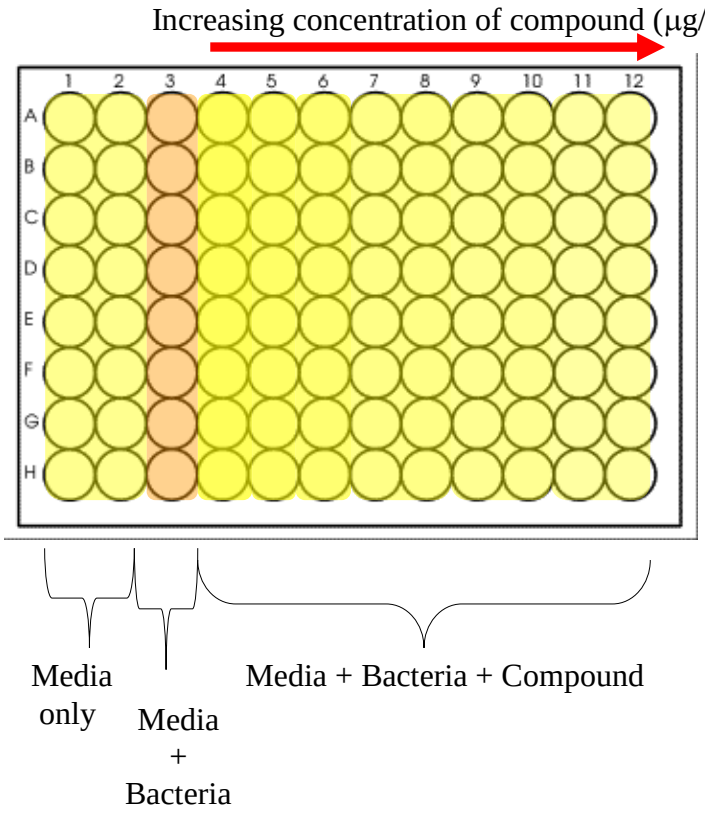


Figure 5.4: Schematic of the culture plates in which the testing was done.

The six compounds were screened against *S. aureus* NCIMB 12702 and *E. coli* NCIMB 9485 (both of which were clinical isolates from a urinary tract infection patient, St. James Hospital, Dublin). The results for the testing against *E. coli* are shown in Figure 6.5. Only one of the compounds tested (**22**) showed any perceptible antimicrobial activity against this bacteria in the tested range, while compounds **42** and **37** showed slight activity at high concentrations.

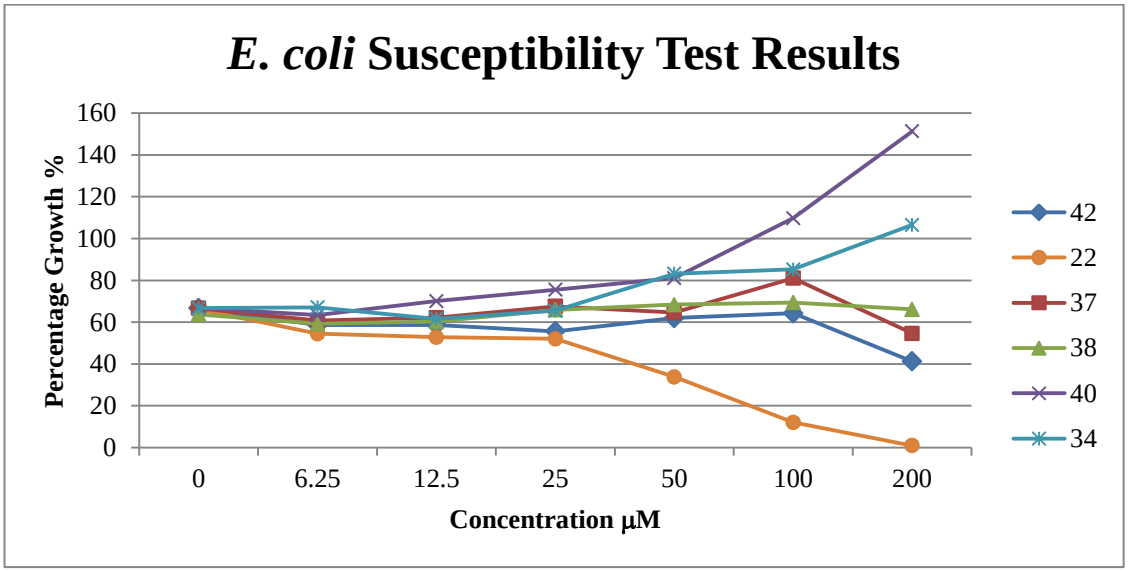


Figure 5.5: Susceptibility test results for activity against *E. coli*.

The results for the testing against *S. aureus* are shown in Figure 5.6. Gratifyingly, compounds **42** and also **22** showed excellent antibacterial activity. These compounds exhibited MIC_{90} values of 6.25 µM and 23.8 µM respectively. These results compare favourably with well-known antibiotics ciprofloxacin and sparfloxacin, which have MIC_{90} values of 1.51 µM and 1.81 µM respectively for *S. aureus*.[264]

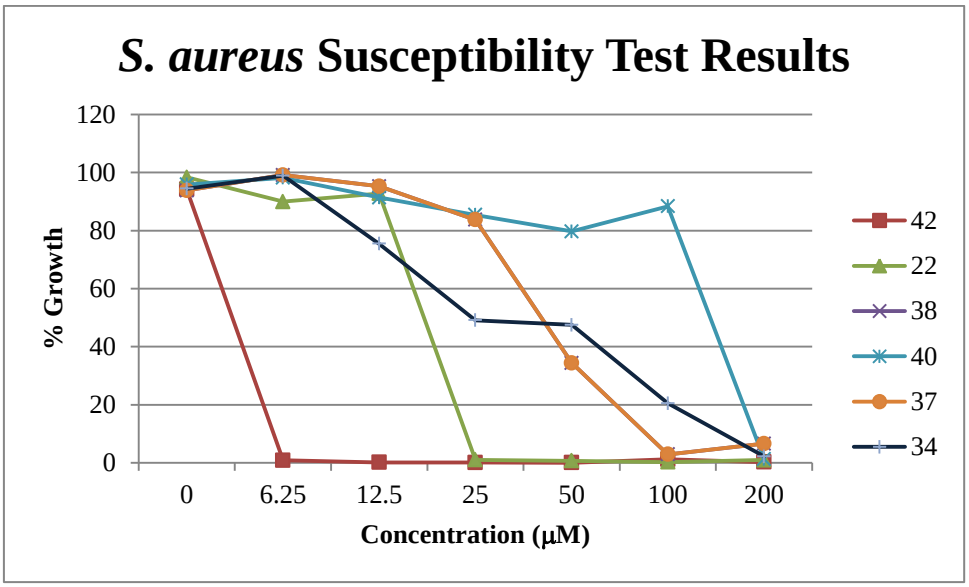


Figure 5.6: Susceptibility test results for activity against *S. aureus*.

The two compounds which were most active against *S. aureus* were also tested for antimicrobial activity against the gram negative *P. aeruginosa* PA01, Figure 5.7. Neither showed significant antimicrobial activity in the tested range.

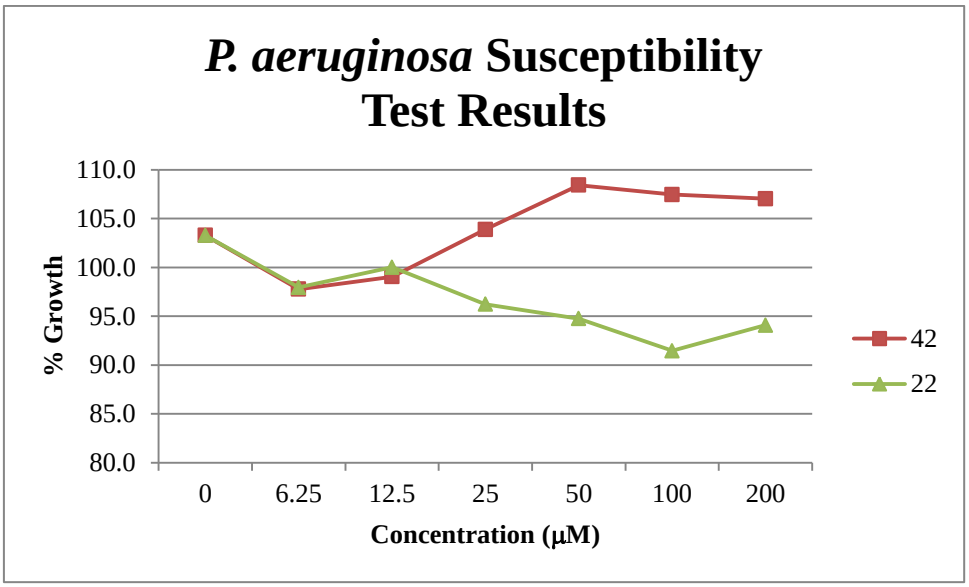


Figure 5.7: Susceptibility test results for activity against *P. aeruginosa*.

The compounds tested displayed greater bacteriostatic activity against the gram positive *S. aureus* than *E. coli* or *P. aeruginosa* (both gram negative). One possible reason for this greater activity against the gram positive *S. aureus* may relate to the ability of the compound to enter the cell. Gram positive bacteria have a cell wall which contains one plasma membrane whereas gram negative bacteria have a cell wall which contains two membranes, a plasma membrane and an outer membrane. Figure 5.8 shows a simplified depiction of the cell walls of gram-positive and gram-negative bacteria. [251]

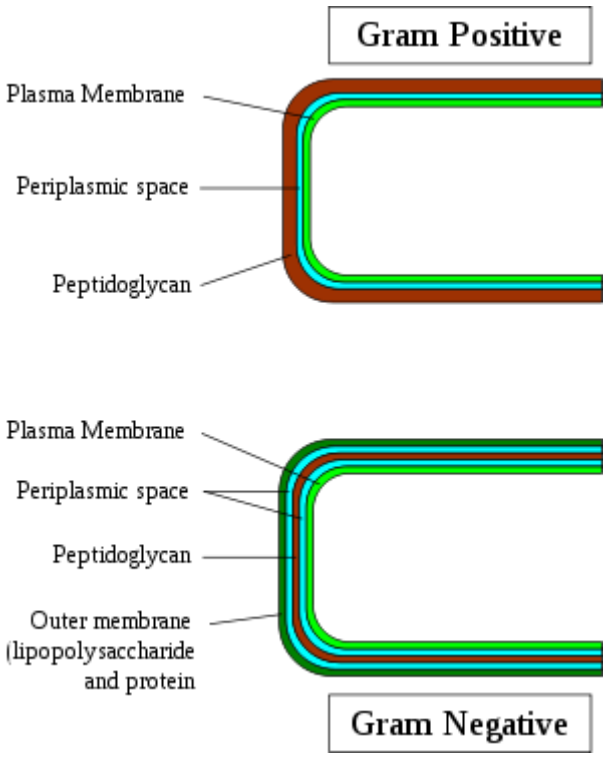


Figure 5.8: Gram-positive and gram-negative cell walls.

One could suggest that this second membrane may play a role in inhibiting the entrance of the compound into the cell. However, this is only one possible reason, there are numerous possibilities with regards to how the compound may be acting on the cell. Investigation into the compounds mechanism of action will need to be carried out.

5.3 Significance of results and future work

These preliminary results indicate that compounds bearing a thiourea moiety and basic nitrogen may be effective antimicrobial agents against *S. aureus*. The two compounds which exhibited bactericidal character have comparable structures, Figure 5.9.

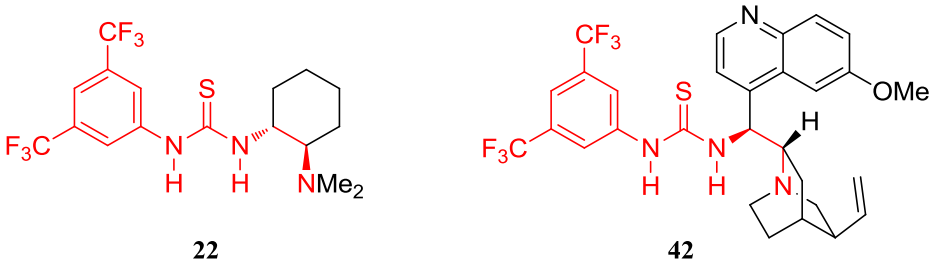


Figure 5.9: The structural similarities in compounds **42** and **22**.

Current work in our group is focussing on systematically altering the structure of the compound in order to decipher which functional groups are essential for the antibacterial action. This SAR type study is aimed at determining which chemical groups are responsible for evoking the biological effect in *S. aureus* and uses Lipinski's rule of five to optimise the structure of the compound. Lipinski's rule of five is a rule of thumb for evaluating whether a chemical compound would make a likely orally active drug in humans. The rule was formulated in 1997 by Christopher Lipinski, based on the observation that most medication drugs are relatively small, lipophilic molecules.[265] Lipinski's rule states that, in general, an orally active drug has no more than one violation of the following criteria:

- A molecular weight less than 500
- No more than five hydrogen bond donors
- No more than 10 hydrogen bond acceptors
- A calculated log P (cLogP) value less than 5 (log P is a measure of a drug's hydrophobicity).[251]

As can be seen from Table 5.1, compound **42** has a molecular weight greater than 500 and a cLogP greater than 5. Therefore alteration of the structure may be required. For example, removal of the CF_3 groups would simultaneously lower the cLogP value (to 4.3833) and the molecular weight (to 458.62 amu), bringing both into the specified ranges. Compound **22** also has a cLogP value which is greater than 5, although it does meet the other requirements.

Table 5.1: Lipinski's rule of five applied to compounds **42** and **22**.

Compound	m.w. (amu)	# H-bond donors	# H-bond acceptors	cLogP
42	594.61	2	2	6.1493
22	413.42	2	2	5.0984

In conclusion, this work represents exciting lead results. Both compounds **42** and **22** attained MIC_{90} values which are close to that of popular antibiotics such as ciprofloxacin and sparfloxacin. We anticipate that alteration of the structure of these

lead compounds will generate molecules with improved efficacy and drug-like properties.

6. Experimental

6.1 Instrumentation

Reagents and reactants were purchased from Aldrich or Alfa Aesar and used as received unless otherwise stated. Solvents were distilled before use and dried (if required) according to standard procedures.[262]

All NMR spectra were recorded on a Bruker Avance spectrometer at a probe temperature of 25 °C, unless otherwise stated, operating at 300 MHz for the ^{1}H nucleus and 75 MHz for the ^{13}C nucleus. Low temperature NMR spectroscopy experiments were carried out by cooling the probe with liquid nitrogen blow off. Spectra were recorded in $CDCl_3$ unless otherwise stated, with Me_4Si used as internal standard. Chemical shifts are given in ppm downfield form the internal standard and coupling constants are given in Hz. ^{13}C NMR spectra were recorded with complete proton decoupling.

Melting point analyses were carried out using a Stewart Scientific SMP11 melting point apparatus and are uncorrected.

Mass spectrometry was carried out on an Agilent LC/TOF-MS model 6210 Time-Of-Flight LC/MS with an electrospray source positive and negative (ESI+/−), capillary 3500 V, nebuliser spray 30 psig, drying gas 5 L/min and source temperature 325 °C. The fragmentor was used at 175 V. The LC was run on a 1200 series model and injection volumes were typically 10 μL. Column used was an Agilent Eclipse XBD-C18. A diameter of 5-micron was employed. The mobile phase constituted A (acetonitrile with 0.1 % formic acid) and B (0.1 % aqueous formic acid) with a gradient of 5 % A to 100 % at a flow rate of 0.5 mL/min over 15 minutes.

Flash column chromatography was performed using silica gel 60 (Merck, 0.040-0.063 mm). Analytical thin layer chromatography was carried out on aluminium sheets pre-coated with Merck TLC Silica gel 60 F_{254}. Developed sheets were visualised using a portable UVltec CV-006 lamp (λ= 254, 365 nm) or the appropriate stain.

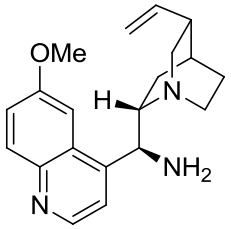
Chiral High Performance Liquid Chromatography (HPLC) was performed on a Perkin-Elmer Totalchrom using a CHIRALCEL IA, IB or IC column (250 x 4.6 mm).

Optical rotations were measured on a Bellingham + Stanley ADP410 polarimeter in a 0.5 dm polarimeter tube.

Low temperature reactions were carried out in an ethanol bath and the temperature was controlled by a Julabo FT920 controller.

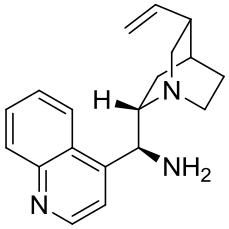
6.2 Synthesis of cinchona based-organocatalysts and related compounds

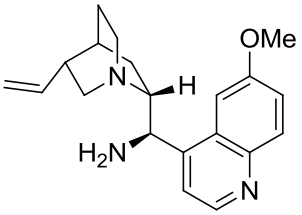
6.2.1 Synthesis of 9-Amino-(9-deoxy)-*epi*-quinine (19)[89]



A solution of hydrazoic acid in toluene (5.18 mL, 0.449 M, 2.33 mmol) was added to a stirred solution of quinine (0.496 g, 1.53 mmol) and triphenylphosphine (0.483 g, 1.84 mmol) in dry THF (15 mL) *via* syringe under argon. The solution was cooled to 0 °C and after 5 minutes at this temperature diisopropyl azodicarboxylate (0.36 mL, 1.84 mmol) in THF (2 mL) was added dropwise *via* syringe. The solution was allowed to warm to room temperature and was stirred for 4 hours, after which triphenylphosphine (0.401g, 1.53 mmol) in THF (2 mL) was added in one portion. The mixture was stirred until gas evolution ceased (approx. 4 hours). Water (1 mL) was then added and the solution was stirred for a further 4 hours. The reaction was then concentrated *in vacuo* and the residue partitioned between DCM and 2.0 M HCl (1:1, 20 mL). After the mixture was vigorously shaken the aqueous layer was separated and washed with DCM (2 x 10 mL portions). The aqueous layer was then concentrated under reduced pressure and the residue partitioned between 0.5 M NaOH and DCM (1:1, 100 mL). The organic layer was separated and the aqueous layer was re-extracted with DCM (2 x 10 mL portions). The combined organic extracts were dried over Na_2SO_4 and concentrated to yield a brown oil (0.418 g, 84%) which was used without further purification.

6.2.2 Synthesis of 9-amino-(9-deoxy)-*epi*-cinchonidine (18) and 9-amino-(9-deoxy)-*epi*-quinidine (32)[182]



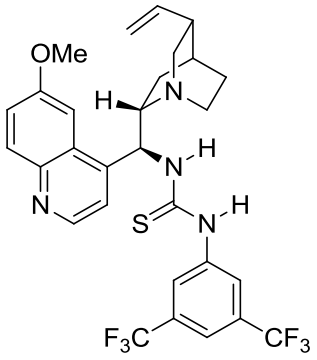


Diisopropyl azodicarboxylate (DIAD, 0.73 mL, 3.7 mmol) was added to a solution of quinidine or cinchonidine (3.1 mmol) and triphenylphosphine (0.97 g, 3.7 mmol) in dry THF (10 mL) at 0 °C. After 5 minutes, a solution of diphenylphosphoryl azide (DPPA, 0.8 mL, 3.7 mmol) in dry THF (5 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature. After being stirred overnight, the solution was heated at 50 °C for 2 hours. Triphenylphosphine (1 g) was then added and the heating was maintained until gas evolution ceased (approx. 3 hours). The solution was cooled to room temperature and water (1 mL) was added. After stirring for 4 hours, the solvents were removed and the residue was partitioned between DCM and 2.0 M HCl (1:1, 20 mL). The aqueous phase was extracted with DCM (3 x 10 mL), made alkaline with a saturated solution of Na_2CO_3 and extracted with DCM. Concentration of the dried extracts afforded a yellow residue (typically 90% yield) which was used without further purification.

6.2.3 General procedure for the preparation of the cinchona-derived thiourea organocatalysts[90]

A solution of the 9-amino-(9-deoxy)-*epi*-cinchona alkaloid (2.8 mmol) in dry DCM was cooled to 0 °C. After 10 minutes at this temperature 3,5-(bis-trifluoromethyl)phenyl isothiocyanate (0.52 mL, 2.85 mmol) was added *via* syringe with stirring. The resulting solution was allowed to warm to room temperature. It was stirred for 12 hours and then concentrated under reduced pressure. The residue was purified by flash column chromatography to yield the desired product.

6.2.3.1 Organocatalyst 42



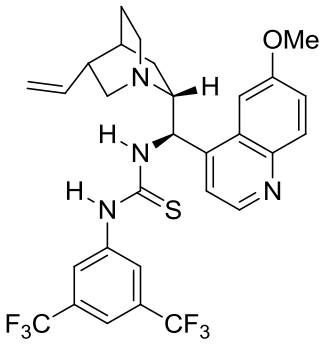
Prepared from 9-amino-(9-deoxy)-*epi*-quinine (**19**). Flash column chromatography (elution gradient: 100% DCM to 93:6:1 DCM: MeOH: Et_3N) afforded organocatalyst **42** (0.34 g, 32%) as a white amorphous solid.

^{1}H NMR ($CDCl_3$): δ 8.32 (app s, 1H, ArH), 7.82 (app s, 3H, ArH), 7.67 (app s, 2H, ArH), 7.31 (dd, *J* = 6.5, 2.3 Hz, 1H, ArH), 6.95 (s, 1H, ArH), 5.88 (br s, 1H, C*H*NHC=S), 5.76-5.64 (m, 1H, C*H*=CH_2), 5.03-4.97 (m, 2H, CH=CH_2), 3.97 (s, 3H, OCH_3), 3.47 (app s, 1H*) 3.25 (app s, 1H*), 3.14-3.06 (m, 1H*), 2.86-2.70 (m, 2H*), 2.32 (app s, 1H*), 1.73-1.61 (m, 3H*), 1.44-1.36 (m, 1H*), 0.93-0.86 (m, 1H*). *Quinuclidine ring.

^{13}C NMR ($CDCl_3$): δ 180.6 (C=S), 158.1, 147.2, 144.5 (3 x ArC), 140.8 (*C*H=CH_2), 132.1, 131.9 (2 x ArC), 132.5 (q, *J* = 33.5 Hz, *C*-CF_3), 131.3, 128.8, 128.0 (3xArC), 122.9 (q, *J* = 273.2 Hz, CF_3), 122.1, 121.0 (2 x ArC), 118.7 (q, *J* = 3.6 Hz, CF_3-C=*C*), 115.0 (CH=*C*H_2), 102.2 (ArC), 60.8 (C*), 55.8 (OCH_3), 54.7 (*C*HNHC=S), 54.7, 41.5, 39.1, 27.6, 27.1, 25.9 (6 x C*). *Quinuclidine ring.

HRMS: m/z 595.1947 [$C_{19}H_{29}NO_4$ $(M + H)^+$ requires 595.1961]

6.2.3.2 Organocatalyst 43



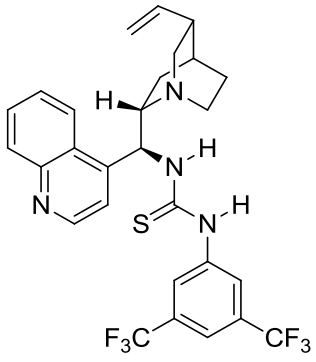
Prepared from 9-amino-(9-deoxy)-*epi*-quinidine (**32**). Flash column chromatography (elution gradient: 100% DCM to 93:6:1 DCM: MeOH: Et_3N) afforded organocatalyst **43** (0.43 g, 52%) as a white amorphous solid.

^{1}H NMR ($CDCl_3$): δ 8.63 (d, *J* = 4.5 Hz, 1H, ArH), 7.99 (d, *J* = 9.1 Hz, 1H, ArH), 7.93 (app s, 2H, ArH), 7.65 (app s, 2H, ArH), 7.39 (dd, *J* = 9.1, 2.4 Hz, 1H, ArH), 7.29 (d, *J* = 4.5 Hz, 1H, ArH), 6.0 (br s, 1H, C*H*NHC=S), 5.92-5.81 (m, 1H, C*H*=CH_2), 5.21 (dd, *J* = 11.2 Hz, 2H, CH=CH_2), 3.97 (s, 3H, OCH_3), 3.41-3.23 (m, 2H*), 3.12-2.82 (m, 3H*), 2.44-2.36 (m, 1H*), 1.73 (app. s, 1H*), 1.68-1.50 (m, 2H*), 1.35-1.26 (m, 1H*), 1.10-1.00 (m, 1H*). *Quinuclidine ring.

^{13}C NMR ($CDCl_3$): δ 181.0 (C=S), 158.3, 147.4, 144.8 (3 x ArC), 140.2 (*C*H=CH_2), 132.1, 131.9 (2 x ArC), 132.4 (q, *J* = 33.5 Hz, *C*-CF_3), 131.3, 127.9, 123.3 (3 x ArC), 123.0 (q, *J* = 273.2 Hz, CF_3), 122.0, 119.0 (2 x ArC), 118.5 (q, *J* = 3.6 Hz, CF_3-C=*C*), 115.8 (CH=*C*H_2), 101.8 (ArC), 61.4 (C*), 57.5 (OCH_3), 54.7 (*C*HNHC=S), 48.7, 46.9, 38.2, 26.9, 25.5, 24.8 (6 x C*). *Quinuclidine ring.

HRMS: m/z 595.1940 [$C_{19}H_{29}NO_4$ $(M + H)^+$ requires 595.1961]

6.2.3.3 Organocatalyst 44



Prepared from 9-amino-(9-deoxy)-*epi*-cinchonidine (**18**). Flash column chromatography (elution gradient: 100% DCM to 93:6:1 DCM: MeOH: Et_3N) afforded organocatalyst **44** (0.35 g, 42%) as a white amorphous solid.

^{1}H NMR ($CDCl_3$): δ 8.63 (app s, 1H, ArH), 8.42 (br s, 1H, ArH), 8.06 (d, *J* = 8.4 Hz, 1H, ArH), 7.81 – 7.58 (m, 5H, ArH), 7.15 (br s, 1H, ArH), 5.91 (br s, 1H, C*H*NHC=S), 5.70 – 5.58 (m, 1H, C*H*=CH_2), 4.98 – 4.93 (m, 2H, CH=CH_2), 3.36 – 3.04 (m, 3H*), 2.76 – 2.67 (m, 2H*), 2.30 (br s, 1H*), 1.75 – 1.58 (m, 3H*), 1.35 – 1.27 (m, 1H*), 0.97 – 0.85 (m, 1H*). *Quinuclidine ring.

^{13}C NMR ($CDCl_3$): δ 180.6 (C=S), 149.9, 148.4, 146.5 (3 x ArC), 140.7 (*C*H=CH_2), 139.9 (ArC), 132.6 (q, *J* = 33.5 Hz, *C*-CF_3), 130.2, 129.5, 127.0, 126.7, 124.0, 123.8 (6 x ArC), 122.9 (q, *J* = 273.2 Hz, CF_3), 118.9 (q, *J* = 3.4 Hz, CF_3-C=*C*), 115.0 (CH=*C*H_2), 102.2 (ArC), 61.3 (C^*), 54.9 (*C*HNHC=S), 54.9, 41.2, 39.1, 27.5, 27.1, 25.6 (6 x C^*). *Quinuclidine ring.

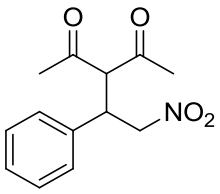
HRMS: m/z 565.1867 [$C_{28}H_{27}N_4SF_6$ $(M + H)^+$ requires 565.1855]

6.3 Synthesis of Michael addition adducts

6.3.1 Procedure for conjugate addition reactions using nitrostyrene as the Michael acceptor

To a stirred solution of *trans*-β-nitrostyrene (75 mg, 0.5 mmol) and 1, 3-dicarbonyl compound (2 equiv., 1 mmol) in toluene (2 mL) was added the chiral organocatalyst (0.05 mmol, 10 mol%). Upon consumption of the nitrostyrene (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford the conjugate addition product.

6.3.1.1 3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (36)[85]



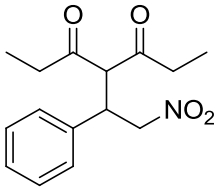
Flash column chromatography (2: 3 hexane: diethyl ether) afforded **36** as a white solid.

^{1}H NMR ($CDCl_3$): δ 7.35-7.27 (m, 3H, ArH), 7.20-7.17 (m, 2H, ArH), 4.68-4.60 (m, 2H, NO_2CH_2), 4.38 (d, *J* = 10.5 Hz, 1H, C*H*$(COCH_3)_2$), 4.28-4.2 (m, 1H, NO_2CH_2C*H*), 2.30 (s, 3H, CH_3), 1.95 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ 201.8, 201.0 (2 x C=O), 136.0 (Q ArC), 129.3, 128.5, 128.3, 128.0 (4 x ArC), 78.2 (NO_2CH_2), 70.6 (*C*H$(COCH_3)_2$), 42.8 (NO_2CH_2*C*H), 30.47, 29.7 (2 x CH_3).

HPLC (Chiralpak IA, 15% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t_1 = 8.43 min, t_2 = 10.45 min.

6.3.1.2 4-(2-Nitro-1-phenylethyl)heptane-3,5-dione (45)[185]



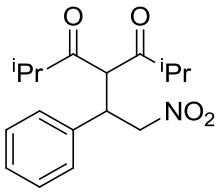
Flash column chromatography (2: 3 hexane: diethyl ether) afforded **45** as a white solid.

^{1}H NMR ($CDCl_3$): δ 7.42-7.24 (m, 3H, ArH), 7.22-7.12 (m, 2H, ArH), 4.69-4.62 (m, 2H, NO_2CH_2), 4.38-4.23 (m, 2H, NO_2-CH_2CH and $CH(COCH_2CH_3)_2$), 2.64-2.42 (m, 2H, $COCH_2CH_3$), 2.40-2.23 (m, 1H, $COCH_2CH_3$), 2.21-2.03 (m, 1H, $COCH_2CH_3$), 1.06 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 0.77 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$).

^{13}C NMR ($CDCl_3$): δ 204.5, 203.3 (2 x C=O), 136.3 (Q ArC), 129.2, 128.4, 127.9 (3 x ArC), 78.0 (NO_2CH_2), 69.2 ($CH(COCH_2CH_3)_2$), 43.0 (NO_2-CH_2CH), 36.83 ($COCH_2CH_3$), 36.38 ($COCH_2CH_3$), 7.49, 7.31 (2 x $COCH_2CH_3$).

HPLC (Chiralpak IA, 15% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t_1 = 8.43 min, t_2 = 10.45 min.

6.3.1.3 2,6-Dimethyl-4-(2-nitro-1-phenylethyl)heptane-3,5-dione (46)[190]



Flash column chromatography (2: 1 hexane: diethyl ether) afforded **46** as a white solid.

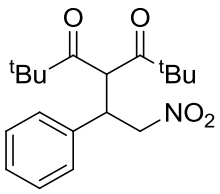
^{1}H NMR ($CDCl_3$): δ 7.5-7.07 (m, 5H, ArH), 4.74 (dd, J = 12.8, 9.2 Hz. 1H, NO_2CH_2), 4.62 (dd, J = 12.8, 4.2 Hz, 1H, NO_2CH_2), 4.53 (d, J = 9.8 Hz, 1H, $CH(COCH(CH_3)_2)_2$), 4.3 (ddd, J = 14.0, 9.2, 4.2 Hz, 1H, NO_2-CH_2CH), 2.72 (sept, J = 6.8 Hz, 1H, $CO(CH(CH_3)_2)_2$), 2.48 (m, 1H, $CO(CH(CH_3)_2)_2$), 1.07 (d, J = 6.8 Hz, 6H, $CO(CH(CH_3)_2)_2$), 0.84 (d, J = 6.8 Hz, 3H, $CO(CH(CH_3)_2)_2$), 0.72 (d, J = 6.8 Hz, 3H, $CO(CH(CH_3)_2)_2$).

^{13}C NMR ($CDCl_3$): δ 207.8, 207.4 (2 x C=O), 136.5 (Q ArH), 129.1, 128.4, 128.2 (3 x ArH), 75.6 (NO_2CH_2), 67.3 ($CH(COCH(CH_3)_2)_2$), 43.3 (NO_2-CH_2CH), 41.1, 41.0 (2 x $CO(CH(CH_3)_2)_2$), 18.7, 18.2, 18.0, 17.8 (4 x $CO(CH(CH_3)_2)_2$).

m.p.: 127-128 °C.

HPLC (Chiralpak IA, 15% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t_1 = 5.2 min, t_2 = 6 min.

6.3.1.4 2,2,6,6-Tetramethyl-4-(2-nitro-1-phenylethyl)heptane-3,5-dione (47)



Flash column chromatography (6: 1 hexane: diethyl ether) afforded **47** as a white solid.

^{1}H NMR ($CDCl_3$): δ 7.33-7.22 (m, 5H, ArH), 5.58 (dd, *J* = 10.8, 4.2 Hz. 1H, NO_2CH_2), 4.96 (d, *J* = 4.2 Hz, 1H, *H*C(CO $C(CH_3)_3)_2$), 4.69 (dd, *J* = 14.0, 2.8 Hz, 1H, NO_2CH_2), 4.2-4.14 (m, 1H, NO_2-CH_2C*H*), 1.34 (s, 9H, $C(CH_3)_3$), 0.82 (s, 9H, $C(CH_3)_3$).

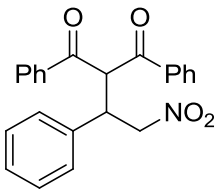
^{13}C NMR ($CDCl_3$): δ 209.5, 208.9 (2 x C=O), 134.5 (Q ArH), 129.1, 128.3, 127.8 (3 x ArH), 75.6 (NO_2CH_2), 59.4 (H*C*(CO $C(CH_3)_3)_2$), 45.4 (NO_2-CH_2*C*H), 44.7, 44.0 (2 x *C*$(CH_3)_3$), 28.2, 25.8 (2 x $(CH_3)_3$).

m.p.: 156-158 °C.

HRMS: m/z 356.1831 [$C_{19}H_{28}NO_4$ $(M + H)^+$ requires 356.1832]

HPLC (Chiralpak IA, 3% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t_1 = 8.4 min, t_2 = 9.3 min.

6.3.1.5 2-(2-Nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione (48)[185]



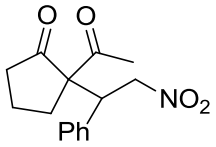
Flash column chromatography (3: 1 hexane: diethyl ether) afforded **48** as a white solid.

^{1}H NMR ($CDCl_3$): δ 7.87-7.76 (m, 4H, ArH), 7.56-7.48 (m, 2H, ArH), 7.41-7.31 (m, 4H, ArH), 7.26-7.14 (m, 5H, ArH), 5.86 (d, *J* =8.1 Hz, 1H, C*H*$(COPh)_2$), 4.99 (dd, *J* = 6.8 Hz, 2H, NO_2CH_2), 4.62 (m, 1H, NO_2-CH_2C*H*).

^{13}C NMR ($CDCl_3$): δ 194.2, 193.6 (2 x C=O), 136.8, 136.2, 135.8 (3 x Q ArH), 134.1, 133.8, 129.0, 128.9, 128.8, 128.6, 128.3, 128.2 (8 x ArH), 77.3 (NO_2CH_2), 59.9 ($CH(COPh)_2$), 44.9 (NO_2-CH_2CH).

HPLC (Chiralpak IA, 30% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t_1 = 8.2 min, t_2 = 15 min.

6.3.1.6 2-Acetyl-2-(2-nitro-1-phenylethyl)cyclopentanone (49)[185]



Flash column chromatography (1:3 diethyl ether: hexane) afforded **49** as a white solid.

Major Diastereomer:

^{1}H NMR ($CDCl_3$): δ 7.35-7.29 (m, 3H, ArH), 7.22-7.16 (m, 2H, ArH), 5.02 (dd, *J* = 13.1, 11 Hz, 1H, NO_2CH_2), 4.60 (dd, *J* =13.1, 3.8 Hz, 1H, NO_2CH_2), 4.28 (dd, *J* = 11.1, 3.8 Hz, NO_2-CH_2CH), 2.19 (s, 3H, $COCH_3$), 2.17-2.04 (m, 1H, CH_2), 2.02-1.93 (m, 1H, CH_2), 1.79-1.64 (m, 3H, CH_2), 1.47-1.33 (m, 1H, CH_2).

^{13}C NMR ($CDCl_3$): δ 217.0, 203.2 (2 x C=O), 135.2 (Q ArC), 129.1, 128.8, 128.6 (3 x ArC), 76.9 ($CCOCH_3$), 70.2 (NO_2CH_2), 47.2 (NO_2-CH_2CH), 39.4 (CH_2), 31.1 (CH_2), 26.7 ($COCH_3$), 19.4 (CH_2).

HPLC (Chiralpak IB, 20% isopropyl alcohol in hexane, 1 mL/min, 238 m): t_1 = 11.4 min, t_2 = 16.7 min.

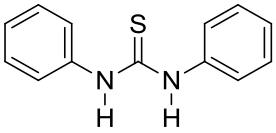
Minor Diastereomer:

^{1}H NMR ($CDCl_3$): δ 7.35-7.24 (m, 5H, ArH), 4.87 (dd, *J* = 13.6, 11.6 Hz, 1H, NO_2CH_2), 4.50 (dd, *J* = 13.6, 3.9 Hz, NO_2CH_2), 4.39 (dd, *J* = 11.6, 3.9 Hz, 1H, NO_2-CH_2CH), 2.61-2.54 (m, 1H, CH_2), 2.34 (s, 3H, $COCH_3$), 2.28-2.12 (m, 1H, CH_2), 2.02-1.92 (m, 1H, CH_2), 1.80-1.67 (m, 3H, CH_2).

^{13}C NMR ($CDCl_3$): δ 213.1, 202.8 (2 x C=O), 134.2 (Q ArC), 129.5, 128.9, 129.5 (3 x ArC), 76.6 ($CCOCH_3$), 71.2 (NO_2CH_2), 46.3 (NO_2-CH_2CH), 38.7 (CH_2), 27.2 (CH_2), 26.6 ($COCH_3$), 19.5 (CH_2).

HPLC (Chirlapak IB, 20% isopropyl alcohol in hexane, 1 mL/min, 238 m): t_1 = 10.1 min, t_2 = 28.7 min.

6.3.2 Synthesis of 1,3-Diphenylthiourea (51)[266]



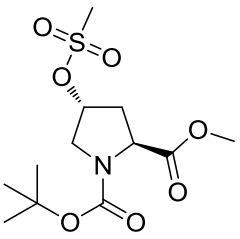
Phenyl isothiocyanate (1.2 mL, 10 mmol) was stirred in DCM at 0 °C for 10 mins. Aniline (0.9 mL, 10 mmol) was then added dropwise. The reaction mixture was stirred for a further 30 mins at 0 °C and then allowed to warm to room temperature. After 1 hour at room temperature the mixture was again cooled to 0 °C, by which time the product had precipitated out of solution. The crude product was filtered and recrystallised by dissolving it in hot $CHCl_3$ and cooling it at -20 °C overnight. It was then filtered to yield **51** as a white crystalline solid (1.69 g, 74%).

^{1}H NMR ($CDCl_3$): δ 7.99 (br s, 2H, NH), 7.44 – 7.35 (m, 8H, ArH), 7.30 – 7.25 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$): δ 179.9 (C=S), 137.1 (Q ArC), 129.6, 127.1, 125.3 (3 x ArC).

6.4 Synthesis of pyrrolidine-based organocatalysts and related compounds

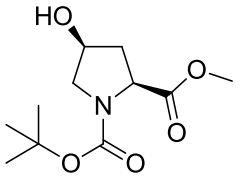
6.4.1 *N*-Boc-*trans*-4-(methylsulfonyl)oxy-L-proline methyl ester (54)



A solution of *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester (1.053 g, 4.3 mmol) in dry DCM under an argon atmosphere was cooled to 0 °C. Mesyl chloride (0.40 mL, 5.17 mmol, 1.2 eq) and triethylamine (0.78 mL, 5.6 mmol, 1.3 eq) were added consecutively *via* syringe. The solution was allowed to warm to room temperature and then stirred for 12 hours. It was then diluted with DCM (80 mL) and washed with brine (40 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to yield *N*-Boc-4-*trans*-(methylsulfonyl)oxy-L-proline methyl ester (**54**) as a whitish solid which was used without further purification. Yield: 1.4 g (quantitative).

^{1}H NMR ($CDCl_3$): δ 5.32-5.25 (m, 1H, CH), 4.48–4.38 (m, 1H, CH), 3.87–3.72 (m, 1H, CH_2), 3.75 (s, 3H, OCH_3) 3.17-3.10 (m, 1H, CH_2), 3.07 (s, 3H, OSO_2CH_3), 2.60–2.46 (m, 1H, CH_2), 2.23–2.14 (m, 1H, CH_2), 1.38 + 1.33 (2 x s, 9H, $OC(CH_3)_3$).
^{13}C NMR ($CDCl_3$): δ 173.1, 172.9 ($COOCH_3$), 153.1, 152.8 (COO^tBu), 79.9 ($C(CH_3)_3$), 78.1, 77.9 ($COSO_2CH_3$), 57.1, 57.0 ($CCOOCH_3$), 52.9, 52.4 (OCH_3), 45.8 (CH_2), 38.6 (SO_2CH_3), 37.3 (CH_2), 28.4, 28.3 ($C(CH_3)_3$).

6.4.2 Synthesis of *N*-Boc-*cis*-4-hydroxy-L-proline methyl ester (55)[202]

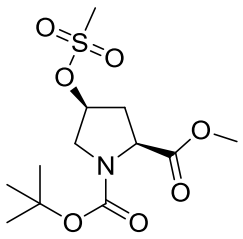


To a solution of **54** (1.38 g, 4.27 mmol) in DMF (15 mLs) was added 10% w/v aqueous NaOH solution (10 mLs). The solution was stirred at 80 °C for 24 hours. It

was then allowed to cool, diluted with DCM (100 mLs) and washed with brine (3 x 30 mLs). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to yield a yellow oil. This oil was purified by flash column chromatography (2:1 hexane: diethyl ether) to give of *N*-Boc-*cis*-4-hydroxy-L-proline methyl ester (**55**) as a white solid. Yield: 0.541 g (51%).

^{1}H NMR ($CDCl_3$): δ 4.30–4.19 (m, 2H, C*H*OH + OH), 3.69 (s, 3H, OCH_3), 3.76-3.65 (s, 1H, CH(COOMe)), 3.50-3.46 (m, 1H, CH_2), 2.33-2.24 (m, 1H, CH_2), 2.09-1.99 (m, 1H, CH_2), 1.45 + 1.40 (2 x s, 9H, $OC(CH_3)_3$).
^{13}C NMR ($CDCl_3$): δ 174.9, 174.8 (*C*$OOCH_3$), 154.5, 153.8 (COO^tBu), 80.6, 80.3 (*C*$(CH_3)_3$), 57.9, 57.6 (*C*$COOCH_3$), 52.9, 52.8 (OCH_3), 53.6 (CHOH), 38.6 (CH_2), 37.8 (CH_2), 28.4, 28.3 (C(*C*$H_3)_3$).

6.4.3 Synthesis of *N*-Boc-*cis*-4-(methylsulfonyl)oxy-L-proline methyl ester (56)[202]



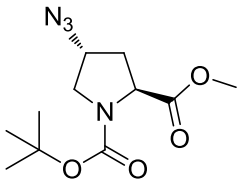
A solution of **55** (1.053 g, 4.3 mmol) in dry DCM under an argon atmosphere was cooled to 0 °C. Mesyl chloride (0.40 mL, 5.17 mmol, 1.2 eq) and triethylamine (0.78 mL, 5.6 mmol, 1.3 eq) were added consecutively *via* syringe. The solution was allowed to warm to room temperature and then stirred for 12 hours. It was then diluted with DCM (80 mL) and washed with brine (40 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to yield *N*-Boc-4-*cis*-(methylsulfonyl)oxy-L-proline methyl ester (**56**) as a whitish solid which was used without further purification. Yield: 1.38 g (quantitative).

^{1}H NMR ($CDCl_3$): δ 5.20-5.15 (m, 1H, CH), 4.39–4.29 (m, 1H, CH), 3.78–3.63 (m, 2H, CH_2), 3.66 (s, 3H, OCH_3), 2.99 (s, 3H, OSO_2CH_3), 2.60–2.46 (m, 1H, CH_2), 2.23–2.14 (m, 1H, CH_2), 1.38 + 1.33 (2 x s, 9H, $OC(CH_3)_3$).
^{13}C NMR ($CDCl_3$): δ 172.6, 172.4 (*C*$OOCH_3$), 153.8, 153.2 (COO^tBu), 80.8 (*C*$(CH_3)_3$), 78.2, 78.0 (*C*OSO_2CH_3), 57.4, 57.1 (*C*$COOCH_3$), 52.4, 52.2 (OCH_3), 45.8 (CH_2), 38.6 (SO_2CH_3), 37.3 (CH_2), 28.2, 28.1 (C(*C*$H_3)_3$).

6.4.4 Synthesis of *N*-Boc-4-azido-L-proline methyl esters

To a solution of **54** or **56** (1.47 g, 4.5 mmol) in dry DMF (20 mLs) was added NaN_3 (0.72 g, 2.45 eq) under an argon atmosphere. The reaction was stirred at 70 °C for 16 hours. After being allowed to cool, it was diluted with DCM (120 mL) and washed with brine (60 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to yield a yellow oil which was used without further purification.

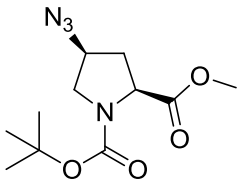
6.4.4.1 *N*-Boc-*trans*-4-azido-L-proline methyl ester (57)



N-Boc-*trans*-4-azido-L-proline methyl ester (**57**) was prepared from **56**. Yield: 1.097 g (87%).

^{1}H NMR ($CDCl_3$): δ 4.45–4.30 (m, 1H, CH), 4.19–4.09 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 3.78–3.66 (m, 1H, CH), 3.52–3.43 (m, 1H, CH_2), 2.55–2.40 (m, 1H, CH_2), 2.21–2.13 (m, 1H, CH_2), 1.47 + 1.42 (2 x s, 9H, $OC(CH_3)_3$).
^{13}C NMR ($CDCl_3$): δ 172.3, 172.0 ($COOCH_3$), 153.6, 153.4 (COO^tBu), 80.5 ($C(CH_3)_3$), 59.3, 58.3 (CN_3), 57.7, 57.4 ($CCOOCH_3$), 52.4, 52.3 (OCH_3), 51.3, 50.8 (CH_2), 36.0, 35.1 (CH_2), 28.4, 28.3 ($C(CH_3)_3$).
HRMS: m/z 271.1407, [$C_{11}H_{19}N_4O_4$ $(M + H)^+$ requires 271.1401]
$[\alpha]_D^{25} = -4.0$ (c 0.002, CH_2Cl_2)

6.4.4.2 *N*-Boc-*cis*-4-azido-L-proline methyl ester (58)



N-Boc-*cis*-4-azido-L-proline methyl ester (**58**) was prepared from **54**. Yield: 0.972 g (77%).

^{1}H NMR ($CDCl_3$): δ 4.45–4.301 (m, 1H, CH), 4.20–4.12 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 3.74–3.67 (m, 1H, CH), 3.52–3.43 (m, 1H, CH_2), 2.54–2.43 (m, 1H, CH_2), 2.22–2.14 (m, 1H, CH_2), 1.47 + 1.42 (2 x s, 9H, $OC(CH_3)_3$).

^{13}C NMR ($CDCl_3$): δ 173.2, 172.8 (*C*$OOCH_3$), 152.9, 152.1 (COO^tBu), 80.1 (*C*$(CH_3)_3$), 59.7, 58.7 (CN_3), 57.1, 56.7 (*C*$COOCH_3$), 52.9, 52.6 (OCH_3), 51.3, 50.2 (CH_2), 36.4, 35.4 (CH_2), 28.4, 28.3 ($C(CH_3)_3$).

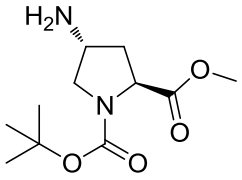
HRMS: m/z 271.1375 [$C_{11}H_{19}N_4O_4$ $(M + H)^+$ requires 271.1401]

$[\alpha]_D^{25} = -5.0$ (c 0.002, CH_2Cl_2)

6.4.5 Synthesis of *N*-Boc-4-amino-L-proline methyl esters

To a solution of **57** or **58** (0.92 g, 3.4 mmol) in dry THF was added PPh_3 (1.34 g, 5.1 mmol, 1.5 eq) under an argon atmosphere. The solution was stirred for 4 hours at room temperature, after which H_2O (0.1 mL) was added. The reaction was then stirred at 80 °C for 12 hours and the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography (elution gradient: 100% EtOAc to 85:10:5 EtOAc: MeOH: Et_3N) to yield a colourless oil.

6.4.5.1 *N*-Boc-*trans*-4-amino-L-proline methyl ester (59)



N-Boc-*trans*-4-amino-L-proline methyl ester (**59**) was prepared from **57**. Yield: 0.331 g (38%).

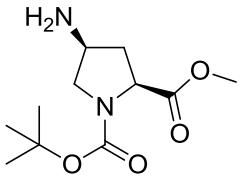
^{1}H NMR ($CDCl_3$): δ 4.34–4.20 (m, 1H, *H*$CCOOCH_3$), 3.74 (s, 3H, OCH_3), 3.69–3.62 (*H*CNH_2), 3.57–3.48 (m, 1H, CH_2), 3.28-3.23 (m, 1H, CH_2), 2.51–2.42 (m, 1H, CH_2), 1.85–1.77 (m, 1H, CH_2), 1.46 + 1.41 (2 x s, 9H, $OC(CH_3)_3$).

^{13}C NMR ($CDCl_3$): δ 173.9, 173.1 (*C*$OOCH_3$), 155.1, 154.1 (COO^tBu), 80.4, 80.3 (*C*$(CH_3)_3$), 70.2, 70.1 (CNH_2), 57.6, 57.1 (*C*$COOCH_3$), 54.6 (CH_2), 52.3, 52.1 (OCH_3), 39.0, 38.5 (CH_2), 28.0, 27.6 ($C(CH_3)_3$).

HRMS: m/z 245.1496, [$C_{11}H_{21}N_2O_4$ $(M + H)^+$ requires 245.1506]

$[\alpha]_D^{25}$: −6.0 (c 0.002, CH_2Cl_2)

6.4.5.2 *N*-Boc-*cis*-4-amino-L-proline methyl ester (60)



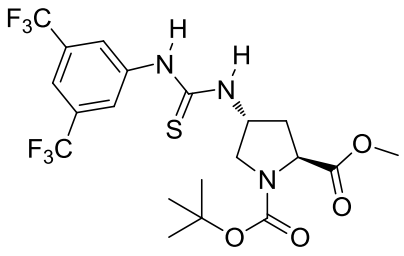
N-Boc-*cis*-4-amino-L-proline methyl ester (**60**) was prepared from **58**. Yield: 0.296 g (34%).

^{1}H NMR ($CDCl_3$): δ 4.48 (br s, 1H, NH), 4.44–4.37 (m, 1H, *H*CCOOCH$_3$), 3.79–3.67 (*H*CNH$_2$), 3.73 (s, 3H, OCH$_3$), 3.61–3.43 (m, 2H, CH$_2$), 2.63 (s, 1H, NH), 2.35–2.23 (m, 1H, CH$_2$), 2.10–2.01 (m, 1H, CH$_2$), 1.46 + 1.40 (2 x s, 9H, OC(CH$_3$)$_3$).
^{13}C NMR ($CDCl_3$): δ 173.7, 173.5 (*C*OOCH$_3$), 154.6, 154.0 (COO^{t}Bu), 80.4, 80.3 (*C*(CH$_3$)$_3$), 70.1, 69.4 (CNH$_2$), 58.0, 57.5 (*C*COOCH$_3$), 54.7 (CH$_2$), 52.3, 52.1 (OCH$_3$), 39.1, 38.5 (CH$_2$), 28.4, 28.3 (C(*C*H$_3$)$_3$).
HRMS: m/z 245.1508 [$C_{11}H_{21}N_2O_4$ $(M + H)^+$ requires 245.1506]
$[\alpha]_D^{25}$: −5.0 (c 0.002, CH_2Cl_2)

6.4.6 Synthesis of *N*-Boc-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl esters

To a solution of **59** or **60** (0.27 g, 1.1 mmol) in dry THF was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.3 mLs, 1.5 eq) *via* syringe under an argon atmosphere. The resulting solution was stirred for 12 hours, after which the solvent was removed under reduced pressure. The crude product was subjected to flash column chromatography (2:1 diethyl ether: hexane) to yield a white solid.

6.4.6.1 *N*-Boc-*trans*-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester (61)



N-Boc-*trans*-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester (**61**) was prepared from **59**. Yield: 0.406 g (71%).

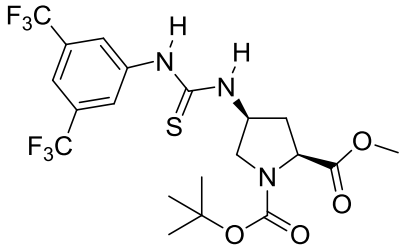
^{1}H NMR ($CDCl_3$): δ 8.70 (br s, 1H, NH), 8.15 (s, 1H, ArH), 8.09 (s, 1H, ArH), 7.62 (s, 1H, ArH), 5.14–4.98 (m, 1H, NH), 4.36–4.19 (m, 1H, *H*CCOOCH$_3$), 3.77 (s, 3H, OCH$_3$), 3.65 (s, 1H, CH), 3.57–3.53 (m, 1H, CH), 2.29–2.20 (m, 1H, CH), 1.63 (s, 2H, CH$_2$), 1.46 (s, 9H, C(CH$_3$)$_3$).

^{13}C NMR ($CDCl_3$): δ 181.2, 180.9 (*C*OOCH$_3$), 172.4, 172.2 (C=S), 155.6, 155.1 (COO^{t}Bu), 140.5, 140.3 (ArC), 132.0 (q, *J* = 33.5 Hz, *C*-CF$_3$), 122.1 (q, *J* = 273.1 Hz, CF$_3$), 122.9, 121.3 (ArC), 118.2, 117.7 (ArC), 82.4 (*C*(CH$_3$)$_3$), 80.0 (CNH), 58.0, 57.5 (*C*COOCH$_3$), 53.6, 53.1 (CH$_2$), 52.7, 52.5 (OCH$_3$), 37.3, 36.4 (CH$_2$), 28.4, 28.3 (C(*C*H$_3$)$_3$).

HRMS: m/z 516.1395 [$C_{20}H_{24}F_6N_3O_4S$ $(M + H)^+$ requires 516.1386]

$[\alpha]_D^{25}$: −15.0 (c 0.002, CH_2Cl_2)

6.4.6.2 *N*-Boc-*cis*-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester (62)



N-Boc-*cis*-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester (**62**) was prepared from **60**. Yield: 0.360 g (53%).

^{1}H NMR ($CDCl_3$): δ 8.36 (br s, 1H, NH), 7.85 (s, 1H, ArH), 7.81 (s, 1H, ArH), 7.72 (s, 1H, ArH), 5.26–5.19 (m, 1H, NH), 4.35–4.24 (m, 1H, *H*CCOOCH$_3$), 3.77–3.65 (m, 2H, CH$_2$) 3.64 (s, 3H, OCH$_3$), 2.60–2.45 (m, 1H, CH), 2.10-1.98 (m, 1H, CH$_2$), 1.43 + 1.38 (2 x s, 9H, C(CH$_3$)$_3$).

^{13}C NMR ($CDCl_3$): δ 181.2, 180.9 (*C*OOCH$_3$), 172.4, 172.2 (C=S), 155.6, 155.1 (COO^{t}Bu), 140.5, 140.3 (ArC), 132.0 (q, *J* = 33.7 Hz, *C*-CF$_3$), 123.1 (q, *J* = 272.6 Hz, CF$_3$), 122.9, 122.5 (ArC), 118.2, 117.7 (ArC), 82.3 (*C*(CH$_3$)$_3$), 77.2 (CNH), 57.9, 57.4 (*C*COOCH$_3$), 53.5, 53.1 (CH$_2$), 52.5, 52.2 (OCH$_3$), 37.2, 36.4 (CH$_2$), 28.4, 28.3 (C(*C*H$_3$)$_3$).

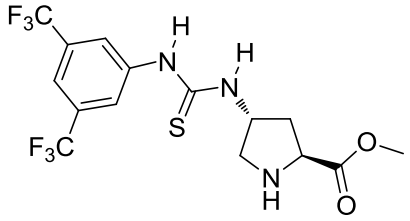
HRMS: m/z 538.1201 [$C_{20}H_{23}F_6N_3O_4SNa$ $(M + Na)^+$ requires 538.1206]

$[\alpha]_D^{25}$: −15.0 (c 0.002, CH_2Cl_2)

6.4.7 Synthesis of 4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester organocatalysts

A solution of **61** or **62** (1.86 g, 3.6 mmol) in DCM (12 mL) was cooled to 0 °C. TFA (3.2 mL) was then added slowly. The mixture was allowed to warm to room temperature and it was stirred for a further 3.5 hours. The solvents were removed under reduced pressure (including the excess TFA) and the resulting oil was basified to pH 8 using saturated aqueous $NaHCO_3$ solution. Following an extraction with DCM (100 mL), the organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (97: 3 diethyl ether: MeOH) to yield the organocatalyst as a white solid.

6.4.7.1 *Trans*-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester (63)



Trans-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester (**63**) was prepared from **61**. Yield: 0.28 g (19%).

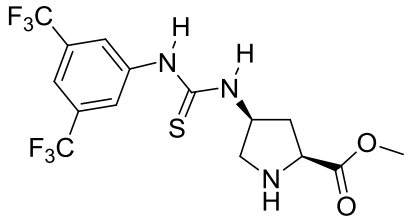
^{1}H NMR ($CDCl_3$): δ 7.89 (s, 2H, ArH), 7.68 (s, 1H, ArH), 7.60 (br s, 1H, HNCS), 7.22 (br s, 1H, HNCS) 4.98 (br s, 1H, NH), 3.93-3.89 (m, 1H, CH), 3.65 (s, 3H, OCH_3), 3.38–3.22 (m, 2H, CH_2), 2.52–2.41 (m, 2H, CH_2), 2.05-1.99 (m, 1H, CH).

^{13}C NMR ($CDCl_3$): δ 179.9 (*C*$OOCH_3$), 173.8 (C=S), 139.3 (Q ArC), 132.5 (q, *J* = 33.7 Hz, *C*-CF_3), 131.8 (ArC), 126.6 (q, *J* = 273.3 Hz, CF_3), 124.0 (ArC) 65.9 (CNH), 58.3 (*C*$COOCH_3$), 55.3 (CH_2), 52.6 (OCH_3), 35.8 (CH_2).

HRMS: m/z 416.0861 [$C_{20}H_{24}F_6N_3O_4S$ $(M + H)^+$ requires 416.0862]

$[\alpha]_D^{25}$: −10.0 (c 0.002, CH_2Cl_2)

6.4.7.2 *Cis*-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester (64)



Cis-4-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)-L-proline methyl ester (**64**) was prepared from **62**. Yield: 0.51 g (34%).

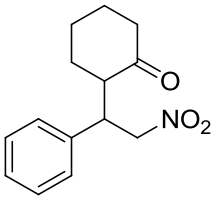
^{1}H NMR ($CDCl_3$): δ 8.94 br s, 1H, HNCS), 7.89 (s, 2H, ArH), 7.67 (s, 1H, ArH), 7.66 (br s, 1H, HNCS), 4.96 (br s, 1H, NH), 3.89 (dd, J = 4.9 Hz, CH), 3.65 (s, 3H, OCH_3), 3.27–3.19 (m, 2H, CH), 2.50–2.40 (m, 1H, CH), 2.31 (br s, 1H, CH), 2.04 (d, *J* = 7.2 Hz, CH).

^{13}C NMR ($CDCl_3$): δ 179.9 (*C*OOCH_3), 175.9 (C=S), 139.3 (Q ArC), 132.5 (q, *J* = 33.8 Hz, *C*-CF_3), 131.8 (ArC), 126.5 (q, *J* = 273.5 Hz, CF_3), 124.0 (ArC) 65.9 (CNH), 58.3 (*C*$COOCH_3$), 55.3 (CH_2), 52.6 (OCH_3), 35.8 (CH_2).

HRMS: m/z 416.0868 [$C_{20}H_{24}F_6N_3O_4S$ $(M + H)^+$ requires 416.0862]

$[\alpha]_D^{25}$: −15.0 (c 0.002, CH_2Cl_2)

6.4.7.3 2-(2-nitro-1-phenylethyl)cyclohexanone (66)



To a stirred solution of *trans*-β-nitrostyrene (75 mg, 0.5 mmol) and cyclohexanone in DCM (2 mL) was added the chiral organocatalyst (0.05 mmol, 10 mol%). The reaction mixture was stirred for 96 hours and then concentrated under reduced pressure. The residue was purified by flash chromatography (3: 1 hexane: diethyl ether) to afford the conjugate addition product.

Major Diastereomer:

^{1}H NMR ($CDCl_3$): δ 7.34-7.25 (m, 3H, ArH), 7.18-7.15 (m, 2H, ArH), 4.94 (dd, *J* = 12.4, 4.4 Hz, 1H, NO_2CH_2), 4.62 (dd, *J* = 12.4, 10.0 Hz, 1H, NO_2CH_2), 3.80–3.72 (m, NO_2-CH_2CH), 2.73–2.64 (m, 1H, CHCO), 2.49–2.33 (m, 2H, CH_2), 2.10-2.04 (m, 1H, CH_2), 1.80-1.53 (m, 4H, CH_2), 1.28-1.17 (m, 1H, CH_2).

^{13}C NMR ($CDCl_3$): δ 212.0 (C=O), 137.8 (Q ArC), 128.9, 128.3, 127.7 (3 x ArC), 78.9 (NO_2CH_2), 52.5 (NO_2-CH_2CH), 44.0 (CHC=O), 42.7 (CH_2), 33.2 (CH_2), 29.9 (CH_2), 27.4 (CH_2).

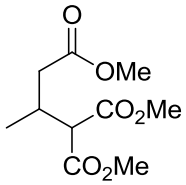
Minor Diastereomer:

^{1}H NMR ($CDCl_3$): δ 7.34-7.25 (m, 3H, ArH), 7.18-7.15 (m, 2H, ArH), 4.85 (dd, *J* = 12.1, 3.0 Hz, 1H, NO_2CH_2), 4.62 (dd, *J* = 12.1, 10.1 Hz, 1H, NO_2CH_2), 4.05–3.98 (m, NO_2-CH_2CH), 2.73–2.64 (m, 1H, CHCO), 2.49–2.33 (m, 2H, CH_2), 2.10-2.04 (m, 1H, CH_2), 1.80-1.53 (m, 4H, CH_2), 1.28-1.17 (m, 1H, CH_2).

^{13}C NMR ($CDCl_3$): δ 210.5 (C=O), 138.5 (Q ArC), 128.7, 128.3, 127.5 (3 x ArC), 76.6 (NO_2CH_2), 53.8 (NO_2-CH_2CH), 43.0 (CHC=O), 42.3 (CH_2), 33.2 (CH_2), 29.9 (CH_2), 28.5 (CH_2).

HPLC (Chiralpak IA, 20% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t_1 = 7.2 min, t_2 = 8.3 min.

6.4.8 Synthesis of trimethyl 2-methylpropane-1,1,3-tricarboxylate (79)



To a stirred solution of dimethyl ethylidenemalonate (0.15 mLs, 1 mmol) and dimethyl malonate (0.34 mLs, 3 mmol) in diethyl ether (2 mLs) was added base. The reaction was monitored by TLC. Upon consumption of the starting material, the solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (1: 1 hexane: diethyl ether) to afford the conjugate addition product as a colourless oil.

^{1}H NMR ($CDCl_3$): δ 3.74 (s, 6H, OMe), 3.68 (s, 3H, OMe), 3.46 (d, *J* = 7.2 Hz, 1H, $CH(COOMe)_2$), 2.82-2.68 (m, 1H, CH_3CH), 2.55 (dd, *J* = 15.8, 5.2 Hz, 1H,

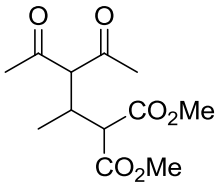
CH_2(COOMe)), 2.32 (dd, *J* = 15.8, 6.9 Hz, 1H, CH_2(COOMe)), 1.07 (d, *J* = 6.9 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ 172.5, 168.81, 168.83 (3 x C=O), 55.9 (*C*H$(COOMe)_2$), 52.4, 52.4, 51.6 (3 x OMe), 38.4 (*C*H_2(COOMe), 30.2 (*C*HCH_3), 17.6 (CH_3).

6.4.9 General procedure for conjugate addition reactions using dimethyl ethylidinemalonate as the Michael acceptor

To a stirred solution of dimethyl ethylidenemalonate (0.028 mL, 0.2 mmol) and pronucleophile (0.4 mmol) in toluene (0.8 mL) was added the chiral organocatalyst (0.02 mmol, 10 mol%). Upon consumption of the dimethyl ethylidenemalonate (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford the conjugate addition product.

6.4.9.1 Dimethyl 2-(3-acetyl-4-oxopentan-2-yl)malonate (68)



Acetylacetone was the pronucleophile in the synthesis of **68**. Flash column chromatography (1: 1 hexane: diethyl ether) afforded the product as a colourless liquid.

^{1}H NMR ($CDCl_3$): Keto: δ 3.97 (d, *J* = 9.5 Hz, 1H, HC$(COOMe)_2$), 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.52 (d, *J* = 5.3 Hz, 1H, HC$(COMe)_2$), 3.12-3.00 (m, 1H, C*H*CH_3), 2.23 (s, 3H, $COCH_3$), 2.19 (s, 3H, $COCH_3$), 1.03 (d, *J* = 7.1 Hz, 3H, CH_3).

Enol: δ 3.78 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 2.26 (s, 6H, $COCH_3$), 1.27 (d, *J* = 7.1 Hz, 3H, CH_3)

^{13}C NMR ($CDCl_3$): Keto: δ 203.5, 203.1 (2 x C=O), 168.7, 168.5 (2 x (MeO)C=O), 71.3, (*C*H$(COOMe)_2$), 53.1 (*C*H$(COMe)_2$), 52.5, 53.3 (2 x OMe), 32.7 (C*H*CH3), 30.2, 29.4 (2 x CO*C*H_3), 14.4 (CH_3).

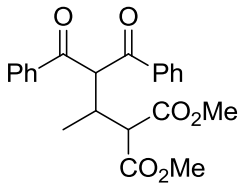
Enol: δ 196.4 (C=O), 168.6, 168.4 (2 x (MeO)C=O), 111.3 (C=C) 56.8 (*C*H$(COOMe)_2$), 53.4, 52.7 (2 x OMe), 32.0 (C*H*CH3), 24.5 ($COCH_3$), 18.3 (CH_3).

b.p.: 96-98 °C @ 5 x 10^{-2} torr.

HRMS: m/z 281.0987 [$C_{12}H_{18}O_6Na$ $(M + Na)^+$ requires 281.0996]

HPLC (Chirlapak IC, 2% isopropyl alcohol in hexane, 1 mL/min, 238 m): t_1 = 16.4 min, t_2 = 18.1 min.

6.4.9.2 Dimethyl 2-(3-benzoyl-4-oxo-phenylbutan-2-yl)malonate (69)



Dibenzoylmethane was the pronucleophile in the synthesis of **69**. Flash column chromatography (2: 1 hexane: diethyl ether) afforded the product as a colourless liquid.

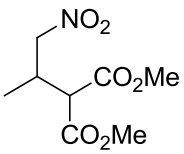
^{1}H NMR ($CDCl_3$): δ 8.06-7.99 (m, 4H, ArH), 7.55–7.39 (m, 6H, arH), 5.96 (d, *J* = 7.8 Hz, 1H, C*H*$(CO_2CH_3)_2$), 3.84 (d, *J* = 6.2 Hz, 1H, C*H*$(COPh)_2$), 3.68 (s, 6H, OCH_3), 3.47–3.35 (m, 1H, C*H*CH_3), 1.17 (d, *J* = 7.3 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ 195.4, 195.2 (2 x COPh), 169.2, 169.0 (2 x *C*O_2CH_3), 136.9, 136.0, 133.8, 133.6, 128.9, 128.7, 128.5 (7 x ArC), 57.5 (*C*H$(CO_2CH_3)_2$), 53.9 (*C*H$(COPh)_2$), 52.4, 52.3 (OCH_3), 34.2 (*C*HCH_3), 14.3 (CH_3).

HRMS: m/z 383.1412 [$C_{22}H_{23}O_6$ $(M + H)^+$ requires 383.140]

HPLC (Chirlapak IB, 60% isopropyl alcohol in hexane, 1 mL/min, 238 m): t_1 = 14.7 min, t_2 = 20.5 min.

Dimethyl 2-(1-nitropropan-2-yl)malonate (70)



Nitromethane was the pronucleophile in the synthesis of **70**. Flash column chromatography (2: 1 Hexane: diethyl ether) afforded the product as a colourless liquid.

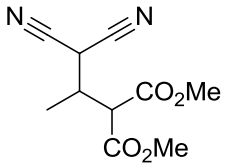
^{1}H NMR ($CDCl_3$): δ 4.65 (dd, *J* = 12.9, 5.1 Hz, 1H, NO_2CH_2), 4.47 (dd, *J* = 12.9, 7.7 Hz, 1H, NO_2CH_2), 3.78 (s, 6H, CO_2CH_3), 3.55 (d, *J* = 6.9 Hz, 1H, C*H*$(CO_2CH_3)_2$), 3.11-2.98 (m, 1H, NO_2CH_2CH), 1.14 (d, *J* = 6.7 Hz, 1H, CH_3).

^{13}C NMR ($CDCl_3$): δ 168.1, 168.1 (2 x C=O), 78.4 (CH_2NO_2), 53.8 (*C*H$(CO_2CH_3)_2$), 52.81, 52.82 (2 x OCH_3), 32.0 (*C*HCH_2NO_2), 15.5 (CH_3).

HRMS: m/z 220.0817 [$C_8H_{14}NO_6$ $(M + H)^+$ requires 220.0816]

HPLC (Chirlapak IC, 20% isopropyl alcohol in hexane, 1 mL/min, 238 m): t_1 = 8.4 min, t_2 = 9.6 min.

6.4.9.3 Dimethyl 2-(1,1-dicyanopropan-2-yl)malonate (71)



Malononitrile was the pronucleophile in the synthesis of **71**. Flash column chromatography (1: 1 Hexane: diethyl ether) afforded the product as a colourless liquid.

^{1}H NMR ($CDCl_3$): δ 4.53 (d, *J* = 5.0 Hz, 1H, $CH(CN)_2$), 3.81 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 3.53 (d, *J* = 8.4 Hz, 1H, C*H*$(CO_2CH_3)_2$), 2.95-2.84 (m, 1H, C*H*$CH_2(CN)_2$), 1.36 (d, *J* = 6.9 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ 167.5, 167.2 (2 x C=O), 111.2, 110.9 (2 x C≡N), 53.4 (*C*H$(CO_2CH_3)_2$), 53.3, 53.2 (2 x OCH_3), 34.9 (*C*H$CH_2(CN)_2$), 26.8 (*C*H$(CN)_2$), 15.0 (CH_3).

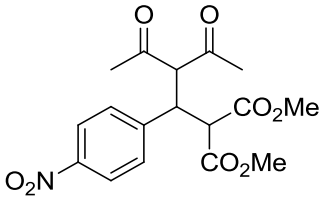
HRMS: m/z 225.088 [$C_{10}H_{13}N_2O_4$ $(M + H)^+$ requires 225.087]

HPLC (Chirlapak IB, 10% isopropyl alcohol in hexane, 1 mL/min, 238 m): t_1 = 12.6 min, t_2 = 13.6 min.

6.4.9.4 Synthesis of dimethyl 2-(2-acetyl-1-(4-nitrophenyl)-3-oxobutyl)malonate (72)

To a stirred solution of dimethyl (4-nitrobenzylidene)malonate (0.026 g, 0.1 mmol) and acetylacetone (0.02 mLs, 2 equiv, 0.2 mmol) in toluene (0.4 mL) was added the chiral organocatalyst (0.01 mmol, 10 mol%). Upon consumption of the dimethyl ethylidenemalonate (monitored by TLC), the reaction mixture was concentrated under

reduced pressure. The residue was purified by flash chromatography (1: 1 hexane: diethyl ether) to afford the conjugate addition product **72** as a white solid.



^{1}H NMR ($CDCl_3$): δ 8.14 (d, *J* = 8.8 Hz, 2H, ArH), 7.50 (d, *J* = 8.8 Hz, 2H, ArH), 4.73 (d, *J* = 10.9 Hz, 1H, *H*C$(CO_2CH_3)_2$), 4.42 (dd, *J* = 10.9, 6.8 Hz, 1H, ArCH), 3.81 (d, *J* = 6.8 Hz, 1H, *H*C$(COCH_3)_2$), 3.66 (s, 3H, CO_2CH_3), 3.60 (s, 3H, CO_2CH_3), 2.29 (s, 3H, $COCH_3$), 1.92 (s, 3H, $COCH_3$).

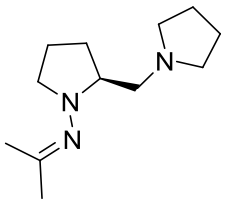
^{13}C NMR ($CDCl_3$): δ 201.7 (CH_3*C*=O), 201.4 (CH_3*C*=O), 167.9 (CH_3O*C*=O), 167.7 (CH_3O*C*=O), 147.4, 145.2, 130.4, 123.7 (4 x ArC), 71.3 (H*C*$(CO_2CH_3)_2$), 54.6 (H*C*$(COCH_3)_2$), 52.9 (CO_2*C*H_3), 52.7 (CO_2*C*H_3), 43.4 (ArCH), 30.4 (CO*C*H_3), 29.5 (CO*C*H_3).

HRMS: m/z 366.1183 [$C_{17}H_{20}NO_8$ $(M + H)^+$ requires 366.1183]

HPLC (Chirlapak IC, 30% isopropyl alcohol in hexane, 1 mL/min, 238 m): t_1 = 13.3 min, t_2 = 14.9 min.

6.5 Synthesis of imine derivatives and related compounds

6.5.1 Synthesis of (S)-N-(propan-2-ylidene)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-amine (74)



A mixture of (S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-amine (1.272g) and acetone (1 mL) was stirred at room temperature for 12 hours. The excess acetone was then removed *in vacuo*. The crude product was purified by Kugelrohr distillation to yield **74** (1.158 g, 74%) as a colourless oil.

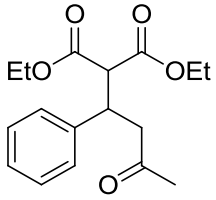
^{1}H NMR ($CDCl_3$): δ 3.17 – 3.04 (m, 2H, N-CH_2), 2.54 – 2.49 (m, 4H, CH_2), 2.47 – 2.33 (m, 4H, CH_2), 2.17 – 2.01 (m, 2H, CH_2), 1.94 (s, 3H, NC(CH_3)), 1.92 (s, 3H, NC(CH_3)), 1.85 – 1.69 (m, 4H, CH_2), 1.67 – 1.54 (m, 1H, CH).

^{13}C NMR ($CDCl_3$): δ 163.4 (C=N), 75.5 (N-C), 66.0 (N-C), 59.1 (OCH_3), 54.1 (CH_2), 26.6 (N=C(*C*H_3)), 25.1 (N=C(*C*H_3)), 22.0 (CH_2), 19.1 (CH_2).

HRMS: m/z 210.1974 [$C_{12}H_{24}N_3$ $(M + H)^+$ requires 210.1965]

b.p.: 62-64 °C @ 5.0 x 10^{-2} torr.

6.5.2 Synthesis of Ethyl-2-ethoxycarbonyl-5-oxo-3-phenylhexanoate (75)



Method 1: To a solution of **74** (0.54 mmol) in THF (0.6 mLs) at 0°C was added lithium diisopropylamide solution (0.166 mLs of a 1M solution, 1.1 eq.) dropwise at 0°C. The mixture was stirred for 2 hours, after which it was cooled to -78°C. Diethylbenzylidene malonate (0.062 mLs, 1eq.) was then added without solvent. Stirring was continued at this temperature for 2 hours and then it was allowed to warm up to 0°C, initially to -70°C and then by 10 degree increments per hour. The mixture was stirred at 0°C for a further 96 hours. It was then quenched with saturated ammonium chloride solution and extracted with diethyl ether (3 x 20 mL). After drying the organic layer with sodium sulphate and concentrating *in vacuo*, the crude oily product was purified by flash column chromatography (3:1 Hexane: Et_2O) to give the product as a clear oil. Yield (based on returned starting material): 85%. *ee*: 70%

Method 2: 4-phenyl-3-buten-2-one (0.73 g, 5 mmol) was added to a solution of $LiClO_4$ (0.27 g, 2.5 mmol) and pyrrolidine (0.04 mLs, 0.5 mmol) in diethyl malonate (2.2 mLs, 5 mmol). The mixture was stirred for 30 minutes, after which it was diluted with DCM (50 mLs) and washed with brine (30 mLs). The organic later was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography to give **75** as a colourless oil. Yield: 1.27 g (83%).

^{1}H NMR ($CDCl_3$): δ 7.23 – 7.17 (m, 4H, ArH), 7.15 – 7.08 (m, 1H, ArH), 4.12 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.95 – 3.89 (m, 1H, PhCH), 3.86 (q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 3.65 (d, *J* = 9.9 Hz, 1H, HC(COOEt)$_2$), 2.95 – 2.80 (m, 2H, CH$_3$COC*H*$_2$), 1.94 (CH$_3$CO), 1.18 (t, J = 7.1 Hz, OCH$_2$C*H*$_3$), 0.93 (t, J = 7.1 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 205.9 (CH$_3$*C*=O), 168.1, 167.6 2 x EtOC=O), 140.5, 128.4, 128.1, 127.1 (4 x ArC), 61.5, 61.2 (2 x O*C*H$_2$CH$_3$), 57.3 (PhCH), 47.3 (H*C*(COOEt)$_2$), 40.4 (CH$_2$CO), 30.2 (*C*OCH$_3$), 13.9, 13.7 (2 x OCH$_2$*C*H$_3$).

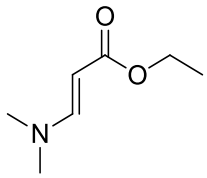
HPLC (Chiralpak IA, 15% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t_1 = 7.3 min, t_2 = 10.6 min.

6.6 Synthesis of β-substituted α,β-unsaturated esters

6.6.1 General procedure for the preparation of of β-substituted aminoacrylates:

To a round-bottomed flask containing ethyl propiolate (0.5 mL, 5 mmol) was added the appropriate secondary amine (5 mmol) at 0 °C . The solution was allowed to warm to room temperature, stirred for 4 hours, diluted with $CHCl_3$ (30 mLs) and washed with water (2 x 15 mL portions). The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by Kugelrohr distillation.

6.6.1.1 Ethyl-3-(dimethylamino)acrylate (76)[267]



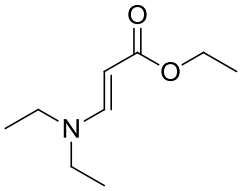
Ethyl-3-(dimethylamino)acrylate was prepared using 40% aqueous solution of dimethylamine. This reaction was worked up by separation of the aqueous layer with $CHCl_3$ (20 mLs), followed by washing with $CHCl_3$ (2 x 10 mLs). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Kugelrohr distillation yielded **76** (0.6 g, 84%) as a colourless oil.

^{1}H NMR ($CDCl_3$): δ 7.41 (d, *J* = 12.9 Hz, 1H, CH=CH), 4.47 (d, *J* = 12.9 Hz, 1H, $CH=CH_2$), 4.08 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 2.88 (br s, 6H, $N(CH_3)_2$), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3)

^{13}C NMR ($CDCl_3$): δ 169 (C=O), 152.5 (CH=CH), 83.9 (CH=CH), 58.2 (CH_2CH_3), 43.1 (NCH_3), 36.8 (NCH_3), 14.3 (CH_2CH_3).

b.p.: 52-54 °C @ 4.2 x 10^{-2} torr. Lit: 83-84.5 @ 1 torr.[268]

6.6.1.2 Ethyl-3-(diethylamino)acrylate (77)[267]



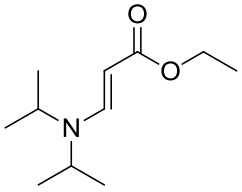
Ethyl-3-(diethylamino)acrylate was prepared using a 20% aqueous solution of diethylamine. This reaction was worked up by separation of the aqueous layer with $CHCl_3$ (20 mLs), followed by washing with $CHCl_3$ (2 x 10 mLs). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Kugelrohr distillation yielded **78** (0.74 g, 86%) as a colourless oil.

^{1}H NMR ($CDCl_3$): δ 7.43 (d, *J* = 13.1 Hz, 1H, CH=CH), 4.47 (d, *J* = 13.1 Hz, 1H, CH=CH), 4.12 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.19 (q, *J* = 7 Hz, 4H, NCH_2CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.16 (t, *J* = 7 Hz, 6H, NCH_2CH_3).

^{13}C NMR ($CDCl_3$): δ 169.5 (C=O), 150.5 (CH=CH), 83.1 (CH=CH), 58.3 (OCH_2CH_3), 48.9 (NCH_2CH_3), 42.6 (NCH_2CH_3), 14.4 (OCH_2CH_3), 12.8 (NCH_2CH_3).

b.p.: 70-72 °C @ 4.2 x 10^{-2} torr. Lit: 97-98 @ 1.3 torr.[267]

6.6.1.3 Ethyl-3-(diisopropylamino)acrylate (78)



Ethyl-3-(diisopropylamino)acrylate was prepared from diisopropylamine. Kugelrohr distillation yielded **78** (0.86 g, 87%) as a colourless oil which solidified overnight to form white crystals.

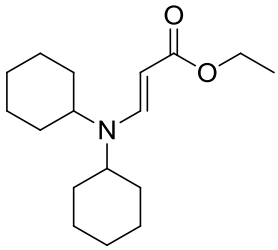
^{1}H NMR ($CDCl_3$): δ 7.47 (d, *J* = 13.2 Hz, 1H, CH=CH), 4.56 (d, *J* = 13.2 Hz, 1H, CH=CH), 4.02 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.55 (br s, 2H, $NCH(CH_3)_2$), 1.22 – 1.0 (m, 15H, OCH_2CH_3 and $NCH(CH_3)_2$).

^{13}C NMR ($CDCl_3$): δ 169.7 (C=O), 146.7 (CH=CH), 83.2 (CH=CH), 58.2 ((OCH_2CH_3)), 47.6 ($NCH(CH_3)_2$), 21.3 ($NCH(CH_3)_2$), 14.4 (OCH_2CH_3).

b.p.: 72-74 °C @ 8 x 10^{-2} torr.

HRMS: m/z 200.1645 [$C_{11}H_{22}NO_2$ $(M + H)^+$ requires 200.1645]

6.6.1.4 Ethyl-3-(dicyclohexylamino)acrylate (79)



Ethyl-3-dicyclohexylamino)acrylate was prepared from dicyclohexylamine. Kugelrohr distillation yielded **79** (1.2 g, 86%) as white crystals.

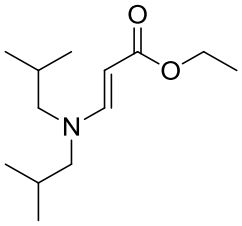
^{1}H NMR ($CDCl_3$): δ 7.57 (d, *J* = 13 Hz, 1H, CH=CH), 4.65 (d, *J* = 13 Hz, 1H, CH=CH), 4.13 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.17 (br s, 2H, NCH), 2.0 – 1.58 (m, 10H*), 1.57 – 1.03 (m, 10H* and 3H (OCH_2CH_3)). *Cyclohexyl ring.

^{13}C NMR ($CDCl_3$): δ 170.1 (C=O), 147.8 (CH=CH), 82.6 (CH=CH), 58.6 (OCH_2CH_3), 56.9 (NCH), 34.0 ($NCHCH_2$), 30.2 ($NCHCH_2$), 26.0 (CH_2), 25.3 (CH_2), 14.7 (OCH_2CH_3).

b.p.: 114-116 °C @ 3.9 x 10^{-2} torr.

HRMS: m/z 280.2267 [$C_{17}H_{30}NO_2$ $(M + H)^+$ requires 280.2271]

6.6.1.5 Ethyl-3-(diisobutylamino)acrylate (80)



Ethyl-3-(diisobutylamino)acrylate was prepared from diisobutylamine. Kugelrohr distillation yielded **80** (1.1 g, 93%) as a colourless liquid.

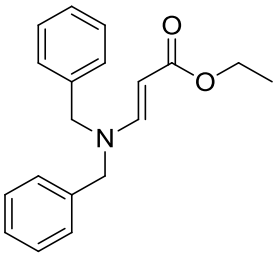
^{1}H NMR ($CDCl_3$): δ 7.37 (d, *J* = 13.1 Hz, CH=CH), 4.48 (d, *J* = 13.1 Hz, 1H, CH=CH), 4.06 (q, *J* = 7.1 Hz, 2H, O*C*$H_2$$CH_3$), 2.87 (d, *J* = 7.3 Hz, 4H, NCH_2), 1.93 (br s, 2H, NCH_2C*H*$(CH_3)_2$), 1.19 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$), 0.82 (d, *J* = 6.7 Hz, 12H, $NCH_2CH(C$*H*$_3)_2$).

^{13}C NMR ($CDCl_3$): δ 169.9 (C=O), 152.4 (CH=CH), 83.7 (CH=CH), 64.1 (NCH_2), 58.6 (O*C*$H_2$$CH_3$), 56.5 ($NCH_2$), 26.7 ($NCH_2$*C*$H(CH_3)_2$), 20.0 ($NCH_2CH($*C*$H_3)_2$), 14.6 ($OCH_2$*C*$H_3$).

b.p.: 128-130 °C @ 8 x 10^{-2} torr.

HRMS: m/z 228.1958 [$C_{13}H_{26}NO_2$ $(M + H)^+$ requires 228.1956]

6.6.1.6 Ethyl-3-(dibenzylamino)acrylate (81)



Ethyl-3-(dibenzylamino)acrylate prepared from dibenzylamine. Kugelrohr distillation yielded **81** (1.18 g, 88%) as a yellow oil.

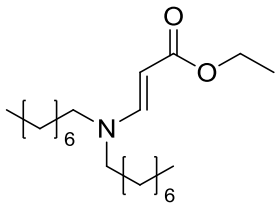
^{1}H NMR ($CDCl_3$): δ 7.78 (d, *J* = 13.1 Hz, 1H, CH=CH), 7.32 – 7.18 (m, 6H, ArH), 7.10 – 7.08 (m, 4H, ArH), 4.78 (d, *J* = 7.1 Hz, 1H, CH=CH), 4.18 (br s, 4H, CH_2Ph), 4.08 (q, *J* = 7.1 Hz, 2H, O*C*$H_2$$CH_3$), 1.19 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$)

^{13}C NMR ($CDCl_3$): δ 169.6 (C=O), 152.6 (CH=CH), 51.5 (NCH_2), 136.1 (Q ArC), 128.8 , 127.8, 127.5 (3 x ArC), 85.9 (CH=CH), 58.9 (O*C*$H_2$$CH_3$), 14.7 ($OCH_2$*C*$H_3$).

b.p.: 156-158 °C @ 6 x 10^{-2} torr.

HRMS: m/z 318.1465 [$C_{19}H_{22}NO_2$ $(M + Na)^+$ requires 318.1473]

6.6.1.7 Ethyl-3-(dioctylamino)acrylate (82)



Ethyl-3-(dioctylamino)acrylate was prepared from dioctylamine. Kugelrohr distillation yielded **82** (1.46 g, 86%) as a yellow oil.

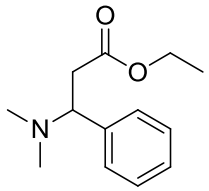
^{1}H NMR ($CDCl_3$): δ 7.28 (d, *J* = 13 Hz, 1H, CH=CH), 4.39 (d, *J* = 13 Hz, 1H, CH=CH), 3.98 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.96 (t, *J* = 6.8 Hz, 2H, NCH_2), 1.41 (app. t, 4H, NCH_2CH_2), 1.20 – 1.09 (m, 24H, $N(C_8H_{17})$), 0.77 – 0.73 (m, 6H, $N(C_8H_{17})$).

^{13}C NMR ($CDCl_3$): δ 169.6 (C=O), 151.4 (CH=CH), 83.3 (CH=CH), 58.4 (OCH_2CH_3), 55.7 (NCH_2), 48.5 (NCH_2), 31.6, 29.1, 29.1, 26.7 (4 x $N(C_8H_{17})$), 14.5 (OCH_2CH_3), 13.9 ($N(C_8H_{17})_2$).

b.p.: 140-142 °C @ 6 x 10^{-2} torr.

HRMS: m/z 340.321 [$C_{21}H_{42}NO_2$ $(M + H)^+$ requires 340.322]

6.6.2 Synthesis of Ethyl-3-(dimethylamino)-3-phenylpropanoate (83)



Phenyllithium solution (1.8 mol dm^{-3}, 2 mL, 3.6 mmol of phenyllithium) was slowly added to a solution of **76** (0.32 g, 2.24 mmol) in dry diethyl ether (5 mL) under an argon atmosphere at −15 °C. The mixture was stirred for 30 mins, keeping the temperature below −10 °C. It was then stirred at room temperature for a further 3 hours, after which it was quenched with saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (3x5 mL). The combined

organic layers were washed with aqueous HCl (3 M, 20 mL). The aqueous layer was extracted with diethyl ether (3x20 mL) and then basified to pH 11 with aqueous NaOH solution (10% w/v). The aqueous layer was extracted with diethyl ether (3x20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude amine was purified by kugelrohr distillation to yield ethyl-3-(dimethylamino)-3-phenylpropanoate (**83**) as a clear oil (0.32 g, 64%).

^{1}H NMR ($CDCl_3$): δ 7.34 - 7.22 (m, 5H, ArH), 4.02 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.86 (dd, *J* = 7.0 Hz, 1H, CHPh), 2.95 (dd, *J* = 7.0 Hz, 1H, CH_2), 2.68 (dd, *J* = 8.2 Hz, 1H, CH_2), 2.18 (s, 6H, $N(CH_3)_2$), 1.11 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 171.7 (C=O), 138.8 (Q ArC), 128.4, 128.0, 127.4 (3 x ArC), 66.4 (Me_2NCH), 60.2 (OCH_2CH_3), 42.3 (NMe_2), 38.6 (CH_2CO_2Et), 14.0 (OCH_2CH_3).
b.p.: 140-142 °C @ 6 x 10^{-2} torr. Lit: 83-84.5 @ 1 torr.[236]

Bibliography

1. Vicario, J. L. B., Dolores; Carrillo, Luisa; Reyes, Efraim, *Organocatalytic Enantioselective Conjugate Addition Reactions*. The Royal Society of Chemistry: Cambridge, **2010**.
2. Jamali, F.; Mehvar, R.; Pasutto, F. M., *J. Pharm. Sci.* **1989**, *78*, 695-715.
3. Lu, H., *Expert Opinion on Drug Metabolism #26; Toxicology* **2007**, *3*, 149-158.
4. Ramón, D. J.; Yus, M., *Chem. Rev.* **2006**, *106*, 2126-2208.
5. Bolm, C.; Gladysz, J. A., *Chem. Rev.* **2003**, *103*, 2761-2762; Williams, J. M. J., *Catalysis in Asymmetric Synthesis*. Sheffield Academic Press Ltd.: Sheffield, **1999**.
6. Reetz, M. T., *Angew. Chem., Int. Ed.* **2011**, *50*, 138-174.
7. Burns, N. Z.; Baran, P. S.; Hoffmann, R. W., *Angew. Chem., Int. Ed.* **2009**, *48*, 2854-2867; Peterson, E. A.; Overman, L. E., *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943-11948; Nicolaou, K. C.; Snyder, S. A., *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11929-11936.
8. Garrett, C. E.; Prasad, K., *Adv. Synth. Catal.* **2004**, *346*, 889-900.
9. Vicario, J. L.; Badía, D.; Carrillo, L., *Synthesis* **2007**, 2062-2092.
10. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
11. Dalko, P. I.; Moisan, L., *Angew. Chem., Int. Ed.* **2004**, *43*, 5138-5175.
12. Berkessel, A., *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis* Wiley-VCH: Weinheim, **2005**.
13. MacMillan, D. W. C., *Nature* **2008**, *455*, 304-308.
14. Hiemstra, H.; Wynberg, H., *J. Am. Chem. Soc.* **1981**, *103*, 417-430.
15. Hermann, K.; Wynberg, H., *J. Org. Chem.* **1979**, *44*, 2238-2244.
16. Schreiner, P. R., *Chem. Soc. Rev.* **2003**, *32*, 289-296.
17. Dalko, P. I., *Enantioselective Organocatalysis*. Wiley-VCH: Weinheim, **2007**.
18. Stork, G.; Terrell, R.; Szmuszkovicz, J., *J. Am. Chem. Soc.* **1954**, *76*, 2029-2030.
19. Heine, A.; DeSantis, G.; Luz, J. G.; Mitchell, M.; Wong, C.-H.; Wilson, I. A., *Science* **2001**, *294*, 369-374.
20. List, B., *Tetrahedron* **2002**, *58*, 5573-5590.
21. Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M., *J. Am. Chem. Soc.* **1996**, *118*, 4910-4911.

22. Sigman, M. S.; Jacobsen, E. N., *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.
23. Dolling, U. H.; Davis, P.; Grabowski, E. J. J., *J. Am. Chem. Soc.* **1984**, *106*, 446-447.
24. Hughes, D. L.; Dolling, U. H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J., *J. Org. Chem.* **1987**, *52*, 4745-4752.
25. List, B.; Lerner, R. A.; Barbas, C. F., *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.
26. Barbas, C. F., *Angew. Chem., Int. Ed.* **2008**, *47*, 42-47.
27. Almasi, D.; Alonso, D. A.; Nájera, C., *Tetrahedron: Asymmetry* **2007**, *18*, 299-365.
28. France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T., *Chem. Rev.* **2003**, *103*, 2985-3012.
29. Enders, D.; Grondal, C.; Hüttl, M. R. M., *Angew. Chem., Int. Ed.* **2007**, *46*, 1570-1581.
30. Kelleher, F.; Kelly, S.; Watts, J.; McKee, V., *Tetrahedron* **2010**, *66*, 3525-3536.
31. Seebach, D.; Grošelj, U.; Schweizer, W. B.; Grimme, S.; Mück-Lichtenfeld, C., *Helvetica Chimica Acta* **2010**, *93*, 1-16; Seebach, D.; Gilmour, R.; Grošelj, U.; Deniau, G.; Sparr, C.; Ebert, M.-O.; Beck, A. K.; McCusker, L. B.; Šišak, D.; Uchimaru, T., *Helvetica Chimica Acta* **2010**, *93*, 603-634.
32. List, B., *Acc. Chem. Res.* **2004**, *37*, 548-557.
33. List, B., *Chem. Commun.* **2006**, 819-824.
34. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B., *Chem. Rev.* **2007**, *107*, 5471-5569.
35. Layer, R. W., *Chem. Rev.* **1963**, *63*, 489-510.
36. Erkkilä, A.; Majander, I.; Pihko, P. M., *Chem. Rev.* **2007**, *107*, 5416-5470.
37. Bertelsen, S.; Nielsen, M.; Jørgensen, K. A., *Angew. Chem., Int. Ed.* **2007**, *46*, 7356-7359.
38. Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C., *Science* **2007**, *316*, 582-585.
39. Renaud, P.; Leong, P., *Science* **2008**, *322*, 55-56; Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2009**, *131*, 10875-10877.
40. Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A., *Chem. Commun.* **2011**, *47*, 632-649.

41. Beel, R.; Kobialka, S.; Schmidt, M. L.; Engeser, M., *Chem. Commun.* **2011**, *47*, 3293-3295.
42. Pellissier, H., *Recent developments in Asymmetric Organocatalysis*. The Royal Society of Chemistry: Cambridge, **2010**.
43. Kuehne, M. E.; DiVincenzo, G., *J. Org. Chem.* **1972**, *37*, 1023-1028.
44. Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A., *J. Am. Chem. Soc.* **2006**, *128*, 12973-12980.
45. Bergonzini, G.; Vera, S.; Melchiorre, P., *Angew. Chem., Int. Ed.* **2010**, *49*, 9685-9688.
46. Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C., *Angew. Chem., Int. Ed.* **2010**, *49*, 6418-6420.
47. Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P., *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642-20647.
48. Jew, S.-s.; Park, H.-g., *Chem. Commun.* **2009**, 7090-7103.
49. Ooi, T.; Maruoka, K., *Angew. Chem., Int. Ed.* **2007**, *46*, 4222-4266.
50. Shen, J.; Tan, C.-H., *Org. Biomol. Chem.* **2008**, *6*, 3229-3236.
51. Palomo, C.; Oiarbide, M.; Lopez, R., *Chem. Soc. Rev.* **2009**, *38*, 632-653.
52. Knowles, R. R.; Jacobsen, E. N., *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678-20685.
53. Taylor, M. S.; Jacobsen, E. N., *Angew. Chem., Int. Ed.* **2006**, *45*, 1520-1543.
54. Starks, C. M., *J. Am. Chem. Soc.* **1971**, *93*, 195-199.
55. Hashimoto, T.; Maruoka, K., *Chem. Rev.* **2007**, *107*, 5656-5682.
56. Woodward, S., *Chem. Soc. Rev.* **2000**, *29*, 393-401; P. Sibi, M.; Manyem, S., *Tetrahedron* **2000**, *56*, 8033-8061.
57. Tsogoeva, S. B., *Eur. J. Org. Chem.* **2007**, 1701-1716.
58. Sulzer-Mossé, S.; Alexakis, A., *Chem. Commun.* **2007**, 3123-3135.
59. List, B.; Pojarliev, P.; Martin, H. J., *Org. Lett.* **2001**, *3*, 2423-2425.
60. Ni, B.; Zhang, Q.; Headley, A. D., *Tetrahedron: Asymmetry* **2007**, *18*, 1443-1447.
61. Cao, C.-L.; Sun, X.-L.; Zhou, J.-L.; Tang, Y., *J. Org. Chem.* **2007**, *72*, 4073-4076.
62. Almasi, D.; Alonso, D. A.; Nájera, C., *Tetrahedron: Asymmetry* **2006**, *17*, 2064-2068.
63. McCooey, S. H.; Connon, S. J., *Org. Lett.* **2007**, *9*, 599-602.

64. Betancort, J. M.; Barbas, C. F., *Org. Lett.* **2001**, *3*, 3737-3740.
65. Wang, W.; Wang, J.; Li, H., *Angew. Chem., Int. Ed.* **2005**, *44*, 1369-1371.
66. Wang, W.; Wang, J.; Li, H.; Liao, L., *Tetrahedron Lett.* **2004**, *45*, 7235-7238; Wang, W.; Wang, J.; Li, H., *Tetrahedron Lett.* **2004**, *45*, 7243-7246.
67. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A., *Angew. Chem., Int. Ed.* **2005**, *44*, 794-797.
68. Zhao, G.-L.; Vesely, J.; Sun, J.; Christensen, K. E.; Bonneau, C.; Córdova, A., *Adv. Synth. Catal.* **2008**, *350*, 657-661.
69. Zhu, Q.; Lu, Y., *Org. Lett.* **2008**, *10*, 4803-4806.
70. Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Jørgensen, K. A., *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304.
71. Zhao, G.-L.; Dziedzic, P.; Ullah, F.; Eriksson, L.; Córdova, A., *Tetrahedron Lett.* **2009**, *50*, 3458-3462; Yu, X.; Wang, W., *Org. Biomol. Chem.* **2008**, *6*, 2037-2046.
72. Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figueiredo, R. M.; Christmann, M., *Org. Lett.* **2009**, *11*, 4116-4119.
73. Murphy, J. J.; Quintard, A.; McArdle, P.; Alexakis, A.; Stephens, J. C., *Angew. Chem., Int. Ed.* **2011**, *50*, 5095-5098.
74. Halland, N.; Aburel, P. S.; Jørgensen, K. A., *Angew. Chem., Int. Ed.* **2003**, *42*, 661-665.
75. Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V., *Chem. Commun.* **2006**, 66-68.
76. Prieto, A.; Halland, N.; Jørgensen, K. A., *Org. Lett.* **2005**, *7*, 3897-3900.
77. Mei, K.; Jin, M.; Zhang, S.; Li, P.; Liu, W.; Chen, X.; Xue, F.; Duan, W.; Wang, W., *Org. Lett.* **2009**, *11*, 2864-2867.
78. Xu, L.-W.; Xia, C.-G., *Eur. J. Org. Chem.* **2005**, 633-639.
79. Lu, X.; Deng, L., *Angew. Chem., Int. Ed.* **2008**, *47*, 7710-7713.
80. Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L., *Acc. Chem. Res.* **2004**, *37*, 621-631.
81. Marcelli, T.; Hiemstra, H., *Synthesis* **2010**, 1229-1279.
82. Li, H.; Wang, Y.; Tang, L.; Deng, L., *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907.
83. Corey, E. J.; Noe, M. C.; Xu, F., *Tetrahedron Lett.* **1998**, *39*, 5347-5350.
84. Okino, T.; Hoashi, Y.; Takemoto, Y., *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673.

85. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y., *J. Am. Chem. Soc.* **2005**, *127*, 119-125.

86. Bui, T.; Syed, S.; Barbas, C. F., *J. Am. Chem. Soc.* **2009**, *131*, 8758-8759.

87. Jiang, L.; Zheng, H.-T.; Liu, T.-Y.; Yue, L.; Chen, Y.-C., *Tetrahedron* **2007**, *63*, 5123-5128.

88. Zhou, W.-M.; Liu, H.; Du, D.-M., *Org. Lett.* **2008**, *10*, 2817-2820.

89. McCooey, S. H.; Connon, S. J., *Angew. Chem., Int. Ed.* **2005**, *44*, 6367-6370.

90. Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T., *Org. Lett.* **2005**, *7*, 1967-1969.

91. Ye, J.; Dixon, D. J.; Hynes, P. S., *Chem. Commun.* **2005**, 4481-4483.

92. Doyle, A. G.; Jacobsen, E. N., *Chem. Rev.* **2007**, *107*, 5713-5743.

93. Akiyama, T.; Katoh, T.; Mori, K., *Angew. Chem., Int. Ed.* **2009**, *48*, 4226-4228.

94. He, R.; Ding, C.; Maruoka, K., *Angew. Chem., Int. Ed.* **2009**, *48*, 4559-4561.

95. Guillena, G.; Nájera, C.; Ramón, D. J., *Tetrahedron: Asymmetry* **2007**, *18*, 2249-2293; Mlynarski, J.; Paradowska, J., *Chem. Soc. Rev.* **2008**, *37*, 1502-1511.

96. Geary, L. M.; Hultin, P. G., *Tetrahedron: Asymmetry* **2009**, *20*, 131-173.

97. List, B.; Pojarliev, P.; Castello, C., *Org. Lett.* **2001**, *3*, 573-575; Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267.

98. Enders, D.; Grondal, C., *Angew. Chem., Int. Ed.* **2005**, *44*, 1210-1212.

99. Kazmaier, U., *Angew. Chem., Int. Ed.* **2005**, *44*, 2186-2188.

100. Zheng, C.; Wu, Y.; Wang, X.; Zhao, G., *Adv. Synth. Catal.* **2008**, *350*, 2690-2694; Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y., *Tetrahedron* **2008**, *64*, 9585-9591; Gandhi, S.; Singh, V. K., *J. Org. Chem.* **2008**, *73*, 9411-9416; Zhang, S.-p.; Fu, X.-k.; Fu, S.-d.; Pan, J.-f., *Catal. Comm.* **2009**, *10*, 401-405.

101. Tzeng, Z.-H.; Chen, H.-Y.; Huang, C.-T.; Chen, K., *Tetrahedron Lett.* **2008**, *49*, 4134-4137.

102. Xu, L.-W.; Lu, Y., *Org. Biomol. Chem.* **2008**, *6*, 2047-2053.

103. Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J.-P., *Org. Lett.* **2008**, *10*, 653-656; Luo, S.; Xu, H.; Chen, L.; Cheng, J.-P., *Org. Lett.* **2008**, *10*, 1775-1778.

104. Luo, S.; Zheng, X.; Cheng, J.-P., *Chem. Commun.* **2008**, 5719-5721.

105. Zhou, J.; Wakchaure, V.; Kraft, P.; List, B., *Angew. Chem., Int. Ed.* **2008**, *47*, 7656-7658.

106. Alvarez-Casao, Y.; Marques-Lopez, E.; Herrera, R. P., *Symmetry* **2011**, *3*, 220-245.

107. Sohtome, Y.; Hashimoto, Y.; Nagasawa, K., *Eur. J. Org. Chem.* **2006**, 2894-2897.

108. Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K., *Tetrahedron Lett.* **2008**, *49*, 1623-1626.

109. Wang, F.; Liu, X.; Cui, X.; Xiong, Y.; Zhou, X.; Feng, X., *Chem. Eur. J.* **2009**, *15*, 589-592.

110. Lou, S.; Schaus, S. E., *J. Am. Chem. Soc.* **2008**, *130*, 6922-6923.

111. Wu, Y.-Y.; Chai, Z.; Liu, X.-Y.; Zhao, G.; Wang, S.-W., *Eur. J. Org. Chem.* **2009**, 904-911.

112. Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K., *Angew. Chem., Int. Ed.* **2006**, *45*, 3492-3494.

113. Masson, G.; Housseman, C.; Zhu, J., *Angew. Chem., Int. Ed.* **2007**, *46*, 4614-4628; Basavaiah, D.; Reddy, B. S.; Badsara, S. S., *Chem. Rev.* **2010**, *110*, 5447-5674; Radha Krishna, P.; Sachwani, R.; Srinivas Reddy, P., *Synlett* **2008**, 2897-2912.

114. Friestad, G. K.; Mathies, A. K., *Tetrahedron* **2007**, *63*, 2541-2569.

115. Córdova, A., *Acc. Chem. Res.* **2004**, *37*, 102-112.

116. Verkade, J. M. M.; Hemert, L. J. C. v.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T., *Chem. Soc. Rev.* **2008**, *37*, 29-41.

117. Miyabe, H.; Takemoto, Y., *Bulletin of the Chemical Society of Japan* **2008**, *81*, 785-795.

118. Yalalov, D. A.; Tsogoeva, S. B.; Shubina, T. E.; Martynova, I. M.; Clark, T., *Angew. Chem., Int. Ed.* **2008**, *47*, 6624-6628.

119. Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C., *J. Am. Chem. Soc.* **2008**, *130*, 7955-7966.

120. Pan, S. C.; List, B., *Chemistry – An Asian Journal* **2008**, *3*, 430-437; Abermil, N.; Masson, G.; Zhu, J., *J. Am. Chem. Soc.* **2008**, *130*, 12596-12597.

121. Corey, E. J., *Angew. Chem., Int. Ed.* **2002**, *41*, 1650-1667.

122. Moyano, A.; Rios, R., *Chem. Rev.* **2011**, *111*, 4703-4832.

123. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G., *Angew. Chem., Int. Ed.* **2002**, *41*, 1668-1698.

124. Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P., *Synthesis* **2011**, 1-26.

125. Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2005**, *127*, 11616-11617.

126. Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L., *J. Am. Chem. Soc.* **2008**, *130*, 2422-2423.

127. Fang, Y.-Q.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2008**, *130*, 5660-5661.

128. Wynberg, H.; Staring, E. G. J., *J. Am. Chem. Soc.* **1982**, *104*, 166-168.

129. Ma, J.-A.; Cahard, D., *Chem. Rev.* **2004**, *104*, 6119-6146.

130. Brunet, V. A.; O'Hagan, D., *Angew. Chem., Int. Ed.* **2008**, *47*, 1179-1182.

131. Ueda, M.; Kano, T.; Maruoka, K., *Org. Biomol. Chem.* **2009**, *7*, 2005-2012.

132. Beeson, T. D.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828.

133. Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A., *Angew. Chem., Int. Ed.* **2005**, *44*, 3703-3706.

134. Steiner, D. D.; Mase, N.; Barbas, C. F., *Angew. Chem., Int. Ed.* **2005**, *44*, 3706-3710.

135. Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M., *Angew. Chem., Int. Ed.* **2008**, *47*, 4157-4161.

136. Vedejs, E.; Jure, M., *Angew. Chem., Int. Ed.* **2005**, *44*, 3974-4001.

137. Berkessel, A.; Mukherjee, S.; Cleemann, F.; Muller, T. N.; Lex, J., *Chem. Commun.* **2005**, 1898-1900.

138. Peschiulli, A.; Quigley, C.; Tallon, S. n.; Gun'ko, Y. K.; Connon, S. J., *J. Org. Chem.* **2008**, *73*, 6409-6412.

139. Peschiulli, A.; Procuranti, B.; O' Connor, C. J.; Connon, S. J., *Nature Chemistry* **2010**, *2*, 380-384.

140. Marcia de Figueiredo, R.; Christmann, M., *Eur. J. Org. Chem.* **2007**, 2575-2600.

141. Erkkilä, A.; Majander, I.; Pihko, P. M., *Chemical Reviews* **2007**, *107*, 5416-5470; Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M., *Chem. Rev.* **2008**, *108*, 2796-2823.

142. Ramãn, D. J.; Yus, M., *Chem. Rev.* **2006**, *106*, 2126-2208.

143. Pellissier, H., *Tetrahedron* **2007**, *63*, 9267-9331.

144. Sykes, P., *Mechanism in Organic Chemistry*. 6th ed.; Pearson Education Limited: London, **1986**.

145. Clayden, J., Greaves, N., Warren, S., Wothers, P., *Organic Chemistry*. Oxford University Press: New York, **2001**.

146. Feringa, B. L., *Acc. Chem. Res.* **2000**, *33*, 346-353.

147. Zenz, I.; Mayr, H., *J. Org. Chem.* **2011**, *76*, 9370-9378.

148. Berner, Otto M.; Tedeschi, L.; Enders, D., *Eur. J. Org. Chem.* **2002**, 1877-1894.

149. Ballini, R.; Petrini, M., *Tetrahedron* **2004**, *60*, 1017-1047.

150. Tamura, R.; Kamimura, A.; Ono, N., *Synthesis* **1991**, *1991*, 423,434.

151. Lloyd, D. H.; Nichols, D. E., *J. Org. Chem.* **1986**, *51*, 4294-4295.

152. Kamlet, M. J.; Kaplan, L. A.; Dacons, J. C., *J. Org. Chem.* **1961**, *26*, 4371-4375.

153. Mukaiyama, T.; Hoshino, T., *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.

154. Li, H.; Wang, B.; Deng, L., *J. Am. Chem. Soc.* **2005**, *128*, 732-733.

155. Kel'in, A., *Current Organic Chemistry* **2003**, *7*, 1855-1886.

156. Brunner, H.; Kimel, B., *Monatshefte für Chemie / Chemical Monthly* **1996**, *127*, 1063-1072.

157. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y., *J. Am. Chem. Soc.* **2004**, *127*, 119-125.

158. Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W., *Org. Lett.* **2005**, *7*, 4713-4716.

159. Terada, M.; Ube, H.; Yaguchi, Y., *J. Am. Chem. Soc.* **2006**, *128*, 1454-1455.

160. Pu, X.; Li, P.; Peng, F.; Li, X.; Zhang, H.; Shao, Z., *Eur. J. Org. Chem.* **2009**, *2009*, 4622-4626; Pu, X.-W.; Peng, F.-Z.; Zhang, H.-B.; Shao, Z.-H., *Tetrahedron* **2010**, *66*, 3655-3661; Almaşi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C., *J. Org. Chem.* **2009**, *74*, 6163-6168; Jiang, X.; Zhang, Y.; Liu, X.; Zhang, G.; Lai, L.; Wu, L.; Zhang, J.; Wang, R., *J. Org. Chem.* **2009**, *74*, 5562-5567; Malerich, J. P.; Hagihara, K.; Rawal, V. H., *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417; Nemoto, T.; Obuchi, K.; Tamura, S.; Fukuyama, T.; Hamada, Y., *Tetrahedron Lett.* **2011**, *52*, 987-991.

161. Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H., *Angew. Chem., Int. Ed.* **2006**, *45*, 7496-7504.

162. Dranz, K., *Enzymatic Catalysis in Organic Synthesis*. Wiley-VCH: Weinheim, **1995**.

163. Marcus, Y., *Chem. Soc. Rev.* **1993**, *22*, 409-416.

164. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B., *J. Am. Chem. Soc.* **1989**, *111*, 8069-8076.

165. Lee, Y.-J.; Park, Y.; Kim, M.-h.; Jew, S.-s.; Park, H.-g., *J. Org. Chem.* **2011**, *76*, 740-743.

166. Tian, S.-K.; Deng, L., *J. Am. Chem. Soc.* **2001**, *123*, 6195-6196.

167. Bella, M.; Jørgensen, K. A., *J. Am. Chem. Soc.* **2004**, *126*, 5672-5673.

168. Poulsen, T. B.; Bell, M.; Jørgensen, K. A., *Org. Biomol. Chem.* **2006**, *4*, 63-70.

169. Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-F.; Zhu, J.; Deng, J.-G., *Org. Lett.* **2005**, *7*, 5293-5296.

170. McDaid, P.; Chen, Y.; Deng, L., *Angew. Chem., Int. Ed.* **2002**, *41*, 338-340.

171. Calter, M. A.; Phillips, R. M.; Flaschenriem, C., *J. Am. Chem. Soc.* **2005**, *127*, 14566-14567.

172. Tang, L.; Deng, L., *J. Am. Chem. Soc.* **2002**, *124*, 2870-2871.

173. Cucinotta, C. S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. L., *Chem. Eur. J.* **2009**, *15*, 7913-7921.

174. Connon, S. J., *Synlett* **2009**, 354,376.

175. Curran, D. P.; Kuo, L. H., *Tetrahedron Lett.* **1995**, *36*, 6647-6650.

176. Sigman, M. S.; Vachal, P.; Jacobsen, E. N., *Angew. Chem., Int. Ed.* **2000**, *39*, 1279-1281; Su, J. T.; Vachal, P.; Jacobsen, E. N., *Adv. Synth. Catal.* **2001**, *343*, 197-200; Vachal, P.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2002**, *124*, 10012-10014.

177. Wittkopp, A.; Schreiner, P. R., *Chem. Eur. J.* **2003**, *9*, 407-414.

178. Schreiner, P. R.; Wittkopp, A., *Org. Lett.* **2002**, *4*, 217-220.

179. Bordwell, F. G., *Acc. Chem. Res.* **1988**, *21*, 456-463.

180. Huisgen, R.; Steiner, G., *J. Am. Chem. Soc.* **1973**, *95*, 5055-5056.

181. Wolff, H., *Org. React.* **1946**, *III*, 327.

182. Bassas, O.; Huuskonen, J.; Rissanen, K.; Koskinen, A. M. P., *Eur. J. Org. Chem.* **2009**, 1340-1351.

183. Oliva, C. G.; Silva, A. M. S.; Resende, D. I. S. P.; Paz, F. A. A.; Cavaleiro, J. A. S., *Eur. J. Org. Chem.* **2010**, *2010*, 3449-3458.

184. Kacprzak, K.; Gierczyk, B., *Tetrahedron: Asymmetry* **2010**, *21*, 2740-2745.

185. Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Adler, A., *Eur. J. Org. Chem.* **2004**, *2004*, 1577-1583.

186. Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F., *Adv. Synth. Catal.* **2007**, *349*, 2537-2548; Zuend, S. J.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2007**, *129*, 15872-15883.

187. Kelly, T. R.; Kim, M. H., *J. Am. Chem. Soc.* **1994**, *116*, 7072-7080.

188. Hamza, A.; Schubert, G.; Sóos, T.; Pápai, I., *J. Am. Chem. Soc.* **2006**, *128*, 13151-13160.

189. Evans, D. A.; Mito, S.; Seidel, D., *J. Am. Chem. Soc.* **2007**, *129*, 11583-11592.

190. Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T., *J. Am. Chem. Soc.* **2004**, *126*, 11148-11149.

191. Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J., *Chem. Commun.* **2008**, 1431-1433.

192. Charton, M., *J. Am. Chem. Soc.* **1975**, *97*, 1552-1556.

193. Bordwell, F. G.; Fried, H. E., *J. Org. Chem.* **1981**, *46*, 4327-4331.

194. Jacob, K.; Sigalov, M.; Becker, James Y.; Ellern, A.; Khodorkovsky, V., *Eur. J. Org. Chem.* **2000**, *2000*, 2047-2055.

195. Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W., *J. Am. Chem. Soc.* **2006**, *128*, 12652-12653.

196. Chi, Y.; Gellman, S. H., *Org. Lett.* **2005**, *7*, 4253-4256; Maher, D. J.; Connon, S. J., *Tetrahedron Lett.* **2004**, *45*, 1301-1305.

197. Xu, L.-W.; Li, L.; Shi, Z.-H., *Adv. Synth. Catal.* **2011**, *352*, 243-279.

198. Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., *J. Am. Chem. Soc.* **2006**, *128*, 4966-4967; Zheng, Z.; Perkins, B. L.; Ni, B., *J. Am. Chem. Soc.* **2009**, *132*, 50-51.

199. Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A., *Acc. Chem. Res.* **2011**, 248-264.

200. Liu, F.; Wang, S.; Wang, N.; Peng, Y., *Synlett* **2007**, *2007*, 2415,2419.

201. Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E., *Angew. Chem., Int. Ed.* **2006**, *45*, 5984-5987.

202. Wang, C.; Yu, C.; Liu, C.; Peng, Y., *Tetrahedron Lett.* **2009**, *50*, 2363-2366.

203. Tan, B.; Zeng, X.; Lu, Y.; Chua, P. J.; Zhong, G., *Org. Lett.* **2009**, *11*, 1927-1930; Xu, Y.; Zou, W.; Sundén, H.; Ibrahem, I.; Córdova, A., *Adv. Synth. Catal.* **2006**, *348*, 418-424; Xiong, Y.; Wen, Y.; Wang, F.; Gao, B.; Liu, X.; Huang, X.; Feng, X., *Adv. Synth. Catal.* **2007**, *349*, 2156-2166.

204. Chuan, Y.-M.; Chen, G.-H.; Gao, J.-Z.; Zhang, H.; Peng, Y.-G., *Chem. Commun.* **2011**, *47*, 3260-3262.

205. Seebach, D.; Goliński, J., *Helvetica Chimica Acta* **1981**, *64*, 1413-1423.

206. Mossé, S.; Alexakis, A., *Org. Lett.* **2005**, *7*, 4361-4364.

207. Wang, J.; Zhang, M.-M.; Zhang, S.; Xu, Z.-A.; Li, H.; Yu, X.-H.; Wang, W., *Synlett* **2011**, *2011*, 473,476; Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P., *Angew. Chem., Int. Ed.* **2006**, *45*, 4966-4970.

208. Alemán, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A., *Angew. Chem., Int. Ed.* **2007**, *46*, 5520-5523.

209. Melchiorre, P.; Jørgensen, K. A., *J. Org. Chem.* **2003**, *68*, 4151-4157.

210. Sulzer-Mossé, S.; Tissot, M.; Alexakis, A., *Org. Lett.* **2007**, *9*, 3749-3752.

211. Johnson, J. S.; Evans, D. A., *Acc. Chem. Res.* **2000**, *33*, 325-335.

212. Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S., *J. Am. Chem. Soc.* **2000**, *122*, 9134-9142; Alexakis, A.; Benhaim, C., *Tetrahedron: Asymmetry* **2001**, *12*, 1151-1157; Zhuang, W.; Hansen, T.; Jørgensen, K. A., *Chem. Commun.* **2001**, 347-348; Zhou, J.; Tang, Y., *Chem. Commun.* **2004**, 432-433; Zhou, J.; Tang, Y., *J. Am. Chem. Soc.* **2002**, *124*, 9030-9031; Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O., *Org. Lett.* **2006**, *8*, 6099-6102.

213. Wen, L.; Shen, Q.; Lu, L., *Org. Lett.* **2010**, *12*, 4655-4657.

214. Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., *Tetrahedron Lett.* **2001**, *42*, 4441-4444.

215. Liu, J.; Yang, Z.; Liu, X.; Wang, Z.; Liu, Y.; Bai, S.; Lin, L.; Feng, X., *Org. Biomol. Chem.* **2009**, *7*, 4120-4127.

216. Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H., *J. Am. Chem. Soc.* **2001**, *123*, 9500-9512.

217. Mayr, H.; Kempf, B.; Ofial, A. R., *Acc. Chem. Res.* **2002**, *36*, 66-77.

218. Kaumanns, O.; Lucius, R.; Mayr, H., *Chem. Eur. J.* **2008**, *14*, 9675-9682.

219. Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F., *Chem. Rev.* **2011**, *111*, 3076-3154; Aléman, J.; Jacobsen, C. B.; Frisch, K.; Overgaard, J.; Jørgensen, K. A., *Chem. Commun.* **2008**, 632-634.

220. Cook, A. G.; Feltman, P. M., *J. Chem. Ed.* **2007**, *84*, 1827.

221. Reichardt, C., *Solvents and Solvent Effects in Organic Chemistry*. Wiley-VCH: Weinheim, **2003**.

222. Zhu, Q.; Lu, Y., *Org. Lett.* **2009**, *11*, 1721-1724.

223. Guo, H.-M.; Li, J.-G.; Qu, G.-R.; Zhang, X.-M.; Yuan, W.-C., *Chirality* **2011**, *23*, 514-518.

224. Magar, D. R.; Chang, C.; Ting, Y.-F.; Chen, K., *Eur. J. Org. Chem.* ***2010***, 2062-2066.

225. Paquette, L. A., *Chiral Reagents for Asymmetric Synthesis*. John Wiley & Sons Ltd.: Chichester, **2003**.

226. Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D., *Tetrahedron* **2002**, *58*, 2253-2329.

227. Okano, T.; Fumoto, M.; Kusukawa, T.; Fujita, M., *Org. Lett.* **2002**, *4*, 1571-1573.

228. Coates, R. M., Denmark, S. E., *Reagents, Auxiliaries and Catalysts for C-C bonds*. John Wiley & Sons Ltd.: Chichester, **1999**.

229. Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D., *Org. Lett.* **2002**, *4*, 1023-1026.

230. Enders, D.; Demir, A. S.; Rendenbach, B. E. M., *Chem. Ber.* **1987**, *120*, 1731-1735.

231. Aryanasab, F.; Saidi, M. R., *Synthetic Commun.* **2008**, *38*, 4036-4044.

232. Sankararaman, S.; Nesakumar, J. E., *Eur. J. Org. Chem.* **2000**, *2000*, 2003-2011.

233. Laurence, C.; Graton, J.; Gal, J.-F., *J. Chem. Ed.* **2011**, *88*, 1651-1657.

234. Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2006**, *128*, 9328-9329; Boezio, A. A.; Charette, A. B., *J. Am. Chem. Soc.* **2003**, *125*, 1692-1693.

235. Ma, J.-A., *Angew. Chem., Int. Ed.* **2003**, *42*, 4290-4299.

236. Fleming, I.; Marangon, E.; Roni, C.; Russell, M. G.; Chamudis, S. T., *Chem. Commun.* **2003**, 200-201.

237. Stewart, W. E.; Siddall, T. H., *Chem. Rev.* **1970**, *70*, 517-551.

238. Cox, C.; Ferraris, D.; Murthy, N. N.; Lectka, T., *J. Am. Chem. Soc.* **1996**, *118*, 5332-5333; Cox, C.; Young, V. G.; Lectka, T., *J. Am. Chem. Soc.* **1997**, *119*, 2307-2308.

239. Neugebauer Crawford, S. M.; Taha, A. N.; True, N. S.; LeMaster, C. B., *J. Phys. Chem. A* **1997**, *101*, 4699-4706.

240. Eberhardt, E. S.; Loh, S. N.; Hinck, A. P.; Raines, R. T., *J. Am. Chem. Soc.* **1992**, *114*, 5437-5439.

241. Fischer, G.; Schmid, F. X., *Biochemistry* **1990**, *29*, 2205-2212.

242. Kemnitz, C. R.; Loewen, M. J., *J. Am. Chem. Soc.* **2007**, *129*, 2521-2528.

243. Moore, J.; Mehta, P.; Breneman, C., *Structural Chemistry* **1997**, *8*, 21-37; Kaur, S.; Eberhardt, E. S.; Doucette, A.; Chase, A.; Dalby, C., *J. Org. Chem.* **2002**, *67*, 3937-3940.

244. Dabrowski, J.; Kozerski, L., *JCS Chem. Commun.* **1968**, 586-587; Dabrowski, J.; Kozerski, L., *J. Chem. Soc. B.: Phys. Org.* **1971**, 345-348.

245. Kemp, W., *NMR in Chemistry; A Multinuclear Introduction*. The MacMillan Press Ltd.: Hong Kong, **1986**.

246. Freibolin, H., *Basic One- and Two-Dimensional NMR Spectroscopy*. Wiley-VCH: Weinheim, **1991**.

247. Charton, M., *J. Am. Chem. Soc.* **1975**, *97*, 3691-3693.

248. Charton, M., *J. Am. Chem. Soc.* **1975**, *97*, 3694-3697; Charton, M., *J. Am. Chem. Soc.* **1975**, *97*, 6159-6161.

249. Charton, M.; Charton, B., *J. Am. Chem. Soc.* **1975**, *97*, 6472-6473.

250. Charton, M., *J. Org. Chem.* **1976**, *41*, 2217-2220.

251. Patrick, G. L., *An Introduction to Medicinal Chemistry*. 3rd ed.; Oxford University Press: Oxford, **2005**.

252. Saeed, S.; Rashid, N.; Jones, P. G.; Ali, M.; Hussain, R., *Eur. J. Med. Chem.* **2010**, *45*, 1323-1331.

253. Kharal, S. A., Hussain, Qurban, Ali, Shujat, *J. Pak. Med. Assoc.* **2009**, *4*, 208-211.

254. Wolf, R.; Baroni, A.; Greco, R.; Donnarumma, G.; Ruocco, E.; Tufano, M. A.; Ruocco, V., *Ann. Clin. Microbiol. Antimicrob.* **2002**, *1*, 5.

255. Rádl, S., *Arch. Pharm. (Weinheim)* **1996**, *329*, 115-119.

256. Ramadas, K.; Suresh, G.; Janarthanan, N.; Masilamani, S., *Pest. Sci.* **1998**, *52*, 145-151; Klayman, D. L.; Griffin, T. S.; Bower, J. D.; Page, S. W., *J. Med. Chem.* **1973**, *16*, 1042-1043.

257. Schroeder, D. C., *Chem. Rev.* **1955**, *55*, 181-228.

258. Yan, Z.; Cai, X.; Yang, X.; Song, B.; Chen, Z.; Bhadury, S. P.; Hu, D.; Jin, L.; Xue, W.; Lu, P., *Chin. J. Chem.* **2009**, *27*, 593-601.

259. Patel, N. B., Patel, S. D., Patel, J. N., Patel, J. S., Gorgamwala, Y. S. , *Int. J. Biol. Chem.* **2011**, *5*, 37-45.

260. Cullen, P., "State has EU's highest rate of E. coli infection, study finds". *The Irish Times.* **2010**.

261. Donnellan, E., "Fatal hospital infections increasing, says specialist". *The Irish Times.* **2010**.

262. Perrin, D., Armarego, W., *Purification of Laboratory Chemicals*. 3rd ed.; Pergamon Press: Oxford, **1980**.

263. Kelly, J.; Rowan, R.; McCann, M.; Kavanagh, K., *Med. Mycol.* **2009**, *47*, 697-706.

264. Barry, A. L.; Fuchs, P. C., *Antimicrob. Agents Chemother.* **1991**, *35*, 955-960.

265. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J., *Adv. Drug Deliv. Rev.* **1997**, *23*, 3-25; Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J., *Adv. Drug Deliv. Rev.* **2001**, *46*, 3-26.

266. Kasmi-Mir, S.; Djafri, A.; Paquin, L.; Hamelin, J.; Rahmouni, M., *Molecules* **2006**, *11*, 597-602.

267. Truce, W. E.; Brady, D. G., *J. Org. Chem.* **1966**, *31*, 3543-3550.

268. Lang, S. A.; Cohen, E., *J. Med. Chem.* **1975**, *18*, 441-443.