UNIVERSITY OF KWAZULU-NATAL

SYNTHESIS AND EVALUATION OF NOVEL TETRAHYDROISOQUINOLINE ORGANOCATALYSTS IN ASYMMETRIC CATALYSIS

2012

TRICIA NAICKER

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2012

A thesis submitted to the School of Pharmacy and Pharmacology, Faculty of Health Science, University of KwaZulu-Natal, Westville, for the degree of Doctor of Philosophy.

This is a thesis in which the chapters are written as a set of discrete research papers, with an Overall Introduction and Final Discussion. Typically these chapters will have been published in internationally recognized, peer-reviewed journals.

As the candidate's supervisors, we have approved this thesis for submission.

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ABSTRACT

Organocatalysis has rapidly expanded in the last decade to encompass a wide variety of small organic molecules that are capable of either activating substrates or transforming them into more reactive forms. The aim of this study was to develop novel chiral organocatalysts based on the tetrahydroisoquinoline backbone and evaluate them on asymmetric reactions. Three organocatalytic modes of activation have been investigated for C-C bond forming asymmetric reactions. In chapter **2**, for the first time organocatalysts bearing a secondary nitrogen within a cyclohexane ring were evaluated in the asymmetric Diels–Alder reaction. These catalysts were tested over a range of dienes and dienophiles and displayed promising chemical conversions of up to 100 % with up to 64 % *ee* when triflic acid was employed as the cocatalyst. Density functional theory computational studies and 2D NMR spectroscopy were used to determine the structure of the intermediate iminium ion formed between the most efficient catalyst and cinnamaldehyde. Chapter **3** includes a series of novel tetrahydroisoquinoline chiral *N*-oxide organocatalysts and their evaluation in the asymmetric allylation reaction of aromatic and α-β-unsaturated aldehydes with allyltrichlorosilane. The chiral homoallyl products were obtained with good chemical efficiency (up to 93 % yield) and high enantioselectivity (up to 91 % *ee*) under mild reaction conditions (23 °C). Chapter **4** is the simple and practical microwave-assisted synthesis of new tetrahydroisquinoline guanidine organocatalysts and their evaluation in the asymmetric Michael addition reaction of malonates and β-ketoesters with nitro-olefins. In addition, a novel microwave assisted procedure of introducing the guanidine unit onto amino amide derivatives is reported. The chiral products were obtained with quantitative chemical efficiency (up to 99 % yield) and excellent enantioselectivity (up to 97 % *ee*). Chapter **5** is a collection of all X-ray crystal structures that were published from novel compounds synthesized pertaining to Chapters **2-4**, it contains 15 published crystal structures while Chapters **3-4** contain 3 other X-ray crystal structures.

It should be noted that with the exception of the introduction and Chapter **4** (submitted for publication), the remaining chapters of this thesis have been published in international peer reviewed journals. In the next section (DECLARATION 2 – PUBLICATIONS) a precise description of my contribution to each of the publications/chapters is provided.

DECLARATIONS

DECLARATION 1 – PLAGIARISM

I, **Tricia Naicker** declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.

2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Signed

DECLARATION 2 – PUBLICATIONS

DETAILS OF CONTRIBUTION TO PUBLICATIONS that form part and/or include research presented in this thesis (include publications in preparation, submitted, *in press* and published and give details of the contributions of each author to the experimental work and writing of each publication)

List of Publications

(1) Naicker, T.; Petzold, K.; Singh, T.; Arvidsson, P. I.; Kruger, H. G.; Maguire, G. E. M.; Govender, T. *Tetrahedron Asymmetry* **2010**, *21*, 2859.
Naicker T contributed to the design of the project, synthesised and characterised all compounds, performed the testing of the compounds and wrote the paper.
Petzold K assisted with setting up, acquiring and interpretating the ROESY NMR spectral data.
Singh T assisted with setting up and troubleshooting of the CHPC cluster used for the computational study as well as adjusting the structures accordingly in order to obtain the transiton states.
The remaining authors are supervisors.

(2) Naicker, T.; Arvidsson, P. I.; Kruger, H. G.; Maguire, G. E. M.; Govender, T. *European Journal of Organic Chemistry* **2011**, *34*, 6923.
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(3) Naicker, T.; Arvidsson, P. I.; Kruger, H. G.; Maguire, G. E. M.; Govender, T. *European Journal of Organic Chemistry* **2012**, *SUBMITTED*.
Naicker T contributed to the design of the project, synthesised and characterised all compounds, performed the testing of the compounds and wrote the paper.
The remaining authors are supervisors.

(4) Naicker, T.; Govender, T.; Kruger, H. G.; Maguire, G. E. M. *Acta Crystallogr., Sect. C Cryst. Struct. Commun.* **2011**, *C67*, o100.
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McKay M assisted with preparing the manuscript in the required format and generation of the figures.
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(6) Naicker, T.; Govender, T.; Kruger, H. G.; Maguire, G. E. M. *Acta Crystallogr., Sect. E Struct. Rep. Online* **2010**, *E66*, o3105.
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(9) Naicker, T.; Govender, T.; Kruger, H. G.; Maguire, G. E. M. *Acta Crystallogr., Sect. E Struct. Rep. Online* **2011**, *E67*, o1403.
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Madichaba C synthesised the compound.
The remaining authors are supervisors.

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Naicker T synthesised, characterised and grew the crystal of the compound as well as wrote the paper.

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Naicker T wrote the subsections entitled Asymmetric cyclopropanation reactions through organocatalytic hydrogen bond activation of electron-deficient olefin derivatives; Asymmetric cyclopropanation reactions through organocatalytic activation of ylides and Organocatalytic asymmetric cyclopropanation through chiral phase transfer catalysis.
Arvidsson and Bose wrote the remaining sections.

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~Om Shree Ganeshaya Namaha~

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TABLE OF CONTENTS

CHAPTER 1

1.1 Origin and Importance of Chirality

The pioneering work of scientists Hauy, Malus,[1] Biot,[2] Herschel[3] and Pasteur[4] during the nineteenth century led to an initial understanding of the concept of chirality. Thereafter, further enlightenment on stereochemistry[5,6] was brought about by Fisher, Van't Hoff[7] and Le Bel.[8] Today, we understand that stereoisomers which rotate plane-polarised light through equal angles but in opposite directions must be related to each other as an object and its non-superimposable mirror image. This phenomenon is attributed to the property possessed by all chiral molecules and the two forms of the optically active molecule are related to each other as three-dimensional non-superimposable mirror images (enantiomers) as illustrated with the example of the pair of human hands in Figure 1.[9,10]

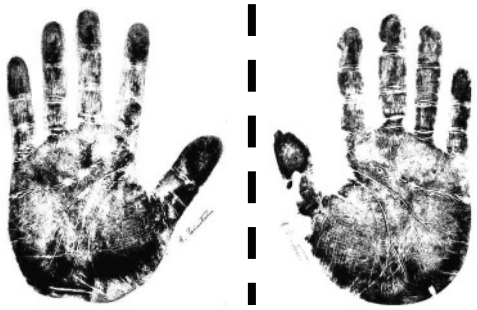
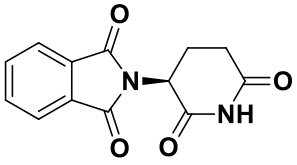
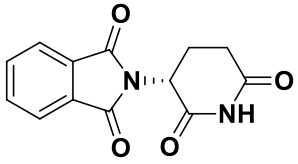


Figure 1. An example of enantiomers (handprints of Albert Einstein).[11]

Chirality is a key element in nature and plays a crucial role in science and technology.[12] Several biological and physical functions depend on the recognition of chiral molecules. In the human body, the majority of the vital building blocks that make up biological macromolecules (e.g. DNA, RNA, sugars and proteins) exist predominantly in one enantiomeric form. As a result, when a biologically active chiral compound such as a drug interacts with a chiral receptor site in biological systems the two enantiomers of the drug will interact differently and may lead to dissimilar biochemical effects.[6,13] There are several examples in literature showing the different effects of enantiomers.[6] One of the most cited examples was from the fatal drug thalidomide, which was used in the 1960s. Both enantiomers of the drug had the same sedative effect but only the (*S*)-(-) enantiomer resulted in death and deformities in foetuses when used by pregnant women.[14,15]

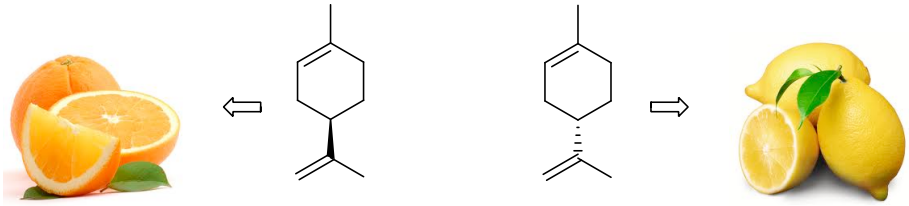


(*S*)-(-)-Thalidomide



(*R*)-(+)-Thalidomide

A further illustration of contrasting enantiomer properties comes from the markedly different scent of the terpene known as limonene, in which (*R*)-(+)-limonene and (*S*)-(−)-limonene have orange and lemon aromas respectively.[16]



(*R*)-(+)-Limonene (*S*)-(-)-Limonene

The synthesis of chiral molecules in optically pure form is not only imperative to the pharmaceutical industry but also in the generation of non-linear optical devices,[17] the control of polymer structure and properties,[18] the agrochemical industry,[19] flavours, fragrances,[20] the study of nearly all biochemical processes and the pursuit of understanding molecular recognition.[21] Therefore, chirality has been an important concept in various fields of chemistry and has been extensively studied. Today, the use and demand for optically active molecules is greater than ever, hence methodologies in asymmetric synthesis play a crucial role in science as they can provide materials and methods for various applications of chiral compounds.

1.2 Routes to Obtain Optically Pure Compounds

Amongst numerous routes to obtain optically pure or enriched compounds, the basic approaches can be divided into the following three classes as depicted in Figure 2:

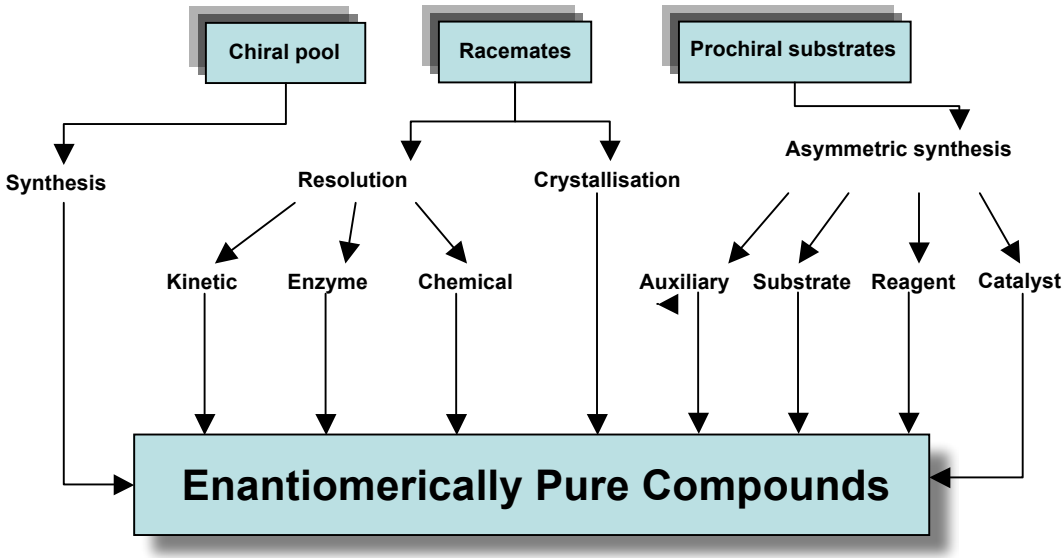


Figure 2. Methods to obtain enantiomerically pure compounds.

The chiral pool strategy involves the use of nature's 'limited' catalogue of enantiopure starting materials such as amino acids, carbohydrates, carboxylic acids, terpenes and related compounds.[22]

This serves as a convenient source to synthesize a vast range of enantiomerically pure compounds. Several pharmacologically relevant compounds have been obtained using this approach. Despite this fact it suffers severe potential drawbacks, which include the cost and availability of the stoichiometric amounts of the suitable chiral precursors along with more challenging multi-step synthetic routes. Nevertheless, this method of asymmetric synthesis is still frequently utilized. Chiral resolution is a process whereby racemic (equimolar) mixtures of the two enantiomers are separated.[12,23] These methods include enzymatic methods or more commonly diastereomer formation in which crystallization or chromatographic techniques are used to separate the diastereomers.[24,25] The major disadvantage of chiral resolution is that the theoretical yield is limited to 50 % unless alternative routes to convert the opposite enantiomer into the desired product (mainly enzymatic resolution) is further carried out.[26] Asymmetric synthesis involves the conversion of a prochiral starting material into a single enantiomer induced by a chiral environment. At present it is the most powerful and common approach to obtain optically active compounds. The basic strategies for asymmetric synthesis can be divided into four classes as shown in Figure 2.[6,12,23,27] Substrate-controlled catalysis utilizes a chiral starting substrate which serves to direct the formation of new chiral center/s on the product. Auxiliary-controlled involves the use of a chiral auxiliary which is deliberately attached to an achiral substrate. This serves to direct the diastereoselective reaction after which the auxiliary is removed or recycled and the enantiomerically pure compound is obtained when reacting with the reagent. Reagent-controlled makes use of an achiral substrate that is directly converted into a chiral product using a chiral reagent e.g. a chiral reducing agent. This is a relatively expensive option since reagents normally react in stoichiometric amounts. Finally, catalyst-controlled utilizes a substiochiometric amount of a chiral catalyst that promotes the conversion of an achiral substrate into a chiral product with preference for the formation of one of the enantiomers.[27] Remarkable progress has been made in this field resulting in several important asymmetric reactions primarily relying on this approach to generate chiral products.[23] The enormous practical potential of asymmetric catalysis makes it one the most widely explored areas for both industrial and academic fields of research.[6,12,23,28-30]

Asymmetric catalysis will now be described in more detail in the following section.

1.3 Asymmetric Catalysis

There are three main classes of asymmetric catalysts employed:

1.3.1 Biocatalysts

Biocatalysis makes use of enzymatic or microbial methods to effect stereoselective changes to unnatural substrates.[31] These methods include the use of hydrolases, lipases, lyases etc. The synthetic route of the antibiotic cefalexin has been shortened from ten to six steps using an enzymatic

procedure.[31] There are problems with this methodology, as biocatalysts cannot be applied to a wide range of asymmetric reactions. These methods are relatively expensive but recently a steady increase in research output in this field has emerged.[5,25]

1.3.2 Metal-ligand Complexes as Catalysts

These catalysts consist of metal-ligand complexes derived from chiral ligands. From the 1950's metal-ligand catalysts have had a significant impact on asymmetric catalysis.[23] It has been extensively studied and provides flexible methods for many types of organic reactions leading to some spectacular practical applications.[6,12,23] The tremendous progress in this field was illustrated in 2001 when the Nobel prize in chemistry was awarded to William R. Knowles, Ryoji Noyori and K. Barry Sharpless for their contribution to the development of transition metal-based asymmetric catalysis.

1.3.3 Organocatalysts

Chiral organocatalysis involves the use of organic molecules as catalysts to promote the conversion of achiral substrates into chiral products.[5] This type of catalysts had not attracted much attention in asymmetric synthesis since the last decade, which has had an explosive growth in the number of studies in this field and is currently on of the 'hottest' topics in organic synthetic research, see Figure 3.[5,25,29]

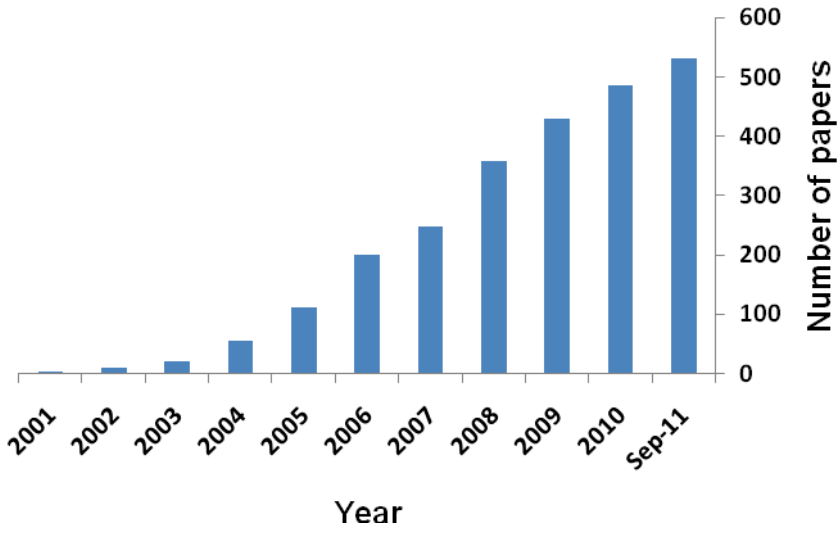


Figure 3. Growth in organocatalysis from 2001-2011.

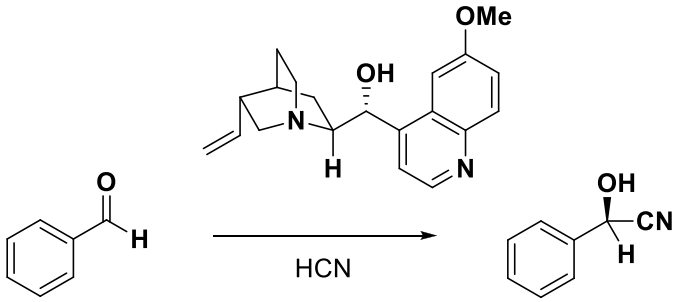
The data for the above statistical graph was obtained by performing a search using ISI Web of Knowledge in September 2011 for the keyword organocatalysis. This search is unlikely to have

found all publications on organocatalysis, and a conservative estimate is that more than 4,000 manuscripts have been published on this topic so far.

For the purpose of this project organocatalysis will be discussed in further detail.

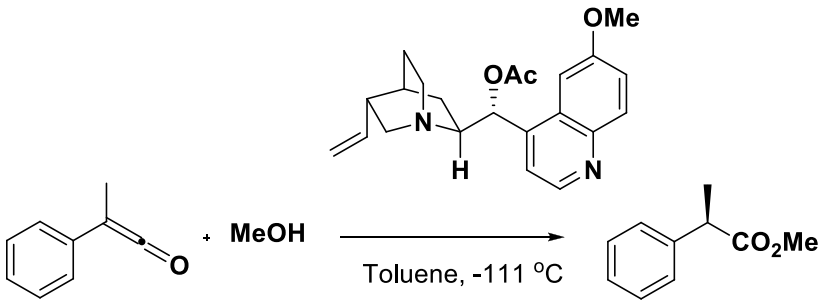
1.4 Organocatalytic systems

The use of organocatalysts has been known for more than a century but only during the last ten years has this 'new' field blossomed within the domain of asymmetric synthetic research.[32,33] In 1912, Bredig reported the first enantioselective alkaloid (quinine) catalyzed cyano-hydrin synthesis with an enantiomeric excess (*ee*) of less than 10 % for the reaction product. [34]



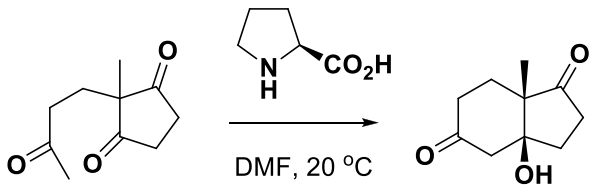
< 10 % ee

During the 1960's, Pracejus discovered that organocatalysts can give significant enantioselectivities when methyl phenyl ketene was converted to (-) Methyl 2-phenylpropionate in 74 % *ee* by using O-acetylquinine as a catalyst.[35]



74 % ee

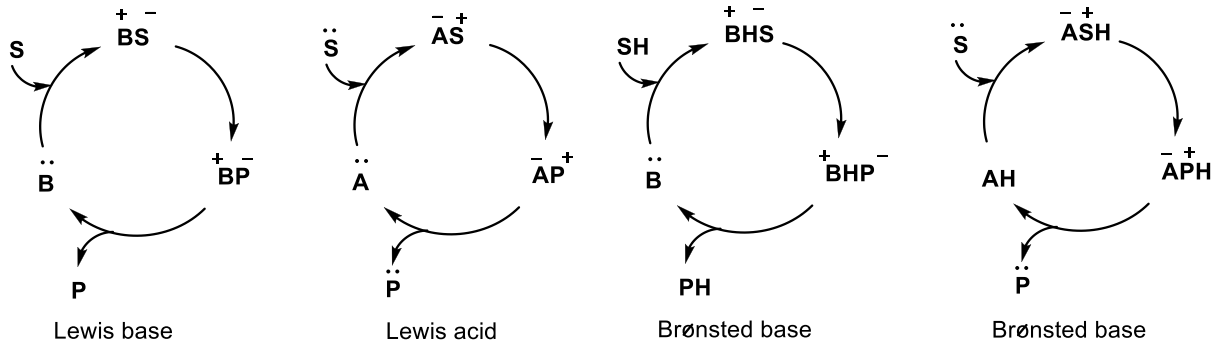
A milestone occurred in the 1970s when Hajos and Wiechert published the first highly enantioselective catalytic aldol reaction using the amino acid proline as the catalyst.[36]



93 % ee

For a long time it was generally accepted that only metal complexes and enzymes were the most efficient catalysts for asymmetric reactions. A change in perception occurred in the last decade when

several reports confirmed that relatively simple organic molecules could be highly efficient and selective catalysts for a variety of important asymmetric transformations.[37-41] The preparative advantages of organocatalysts over the metal-ligand complexes and biocatalysts are remarkable. These catalysts are often inexpensive to prepare and the reactions can be performed under aerobic environments and in wet organic solvents or aqueous media. They are usually more stable than both enzymes and organometallic catalysts and are less toxic to the environment. Today, the advent of organocatalysis has captured the attention of chemists around the world and has initiated an explosive growth of research activities in both industry and in academia.[5,32,33,42-52] Reactions that once needed metal-ligand catalysts can now be carried out with comparable efficiencies using organocatalysts that are more stable, cheaper and less toxic than their metal complex counterparts. Organocatalytic modes of activation can be broadly divided into Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids type catalysts. The corresponding catalytic cycles are shown in Scheme 1.



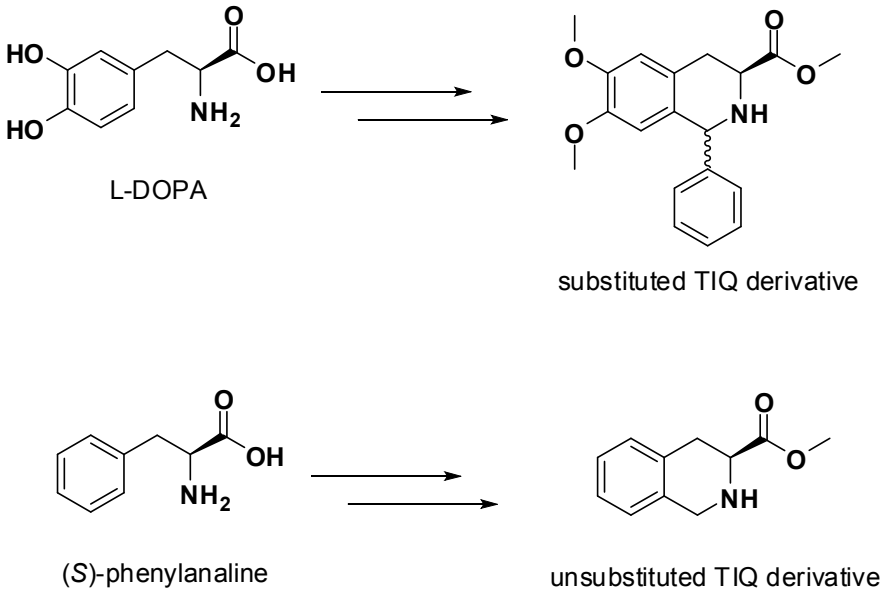
Scheme 1. Organocatalytic cycles.[41]

Lewis base catalysts (**B**) start the catalytic cycle via nucleophilic addition to the substrate (**S**). The resulting intermediate undergoes a reaction and then releases the product (**P**) and the catalyst. Lewis acid catalysts (**A**) activate nucleophilic substrates (**S**) in a similar way. The catalytic sequence for Brønsted base and acid catalysts commence *via* a deprotonation or protonation, respectively. Studies into the mechanistic details into these individual reaction pathways are continually growing and many unexplored modes of activation of organocatalysts are emerging.[32,33,49-53] The extent of organocatalytic reactions has significantly expanded; well known transition-metal mediated reactions such as Suzuki, Diels-Alder, Sonogashira, Michael additions, aldol reactions, hydrogenations and Heck-type coupling reactions can now be achieved under metal free conditions with the same reaction efficiency.[54]

For the purpose of this project only the following organocatalytic topics *i.e.* iminium catalysis, *N*-oxide type and guanidine organocatalysts will be further expanded upon, in this introductory chapter.

1.5 Tetrahydroisoquinoline compounds

The tetrahydroisoquinoline (TIQ) molecule and its derivatives have been widely investigated for their biological and pharmaceutical properties.[55-59] Due to our ongoing pursuit to establish novel chiral catalysts,[60-65] and L-DOPA/phenylanaline (Scheme 2) being commercially available, this class of compounds posed as an attractive skeleton for a source of chirality in asymmetric synthesis.

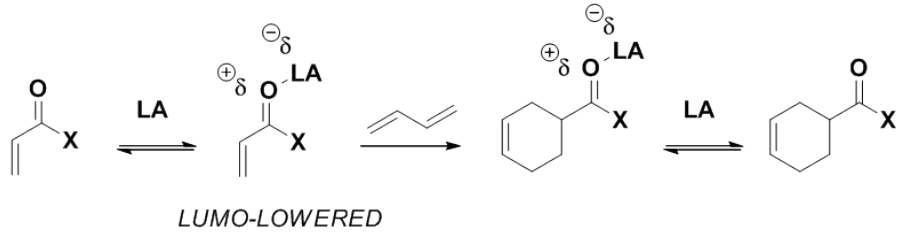


Scheme 2. TIQ based precursors.

Both substituted and unsubstituted TIQ derivatives served as the basic starting precursors for all compounds synthesized. These precursors' served as a readily tunable (both in terms of steric and electronic effects) backbone for the syntheses of a diverse range of catalysts that was made for the purpose of this project. Progress made in this area will be discussed in Chapters **2-5**.

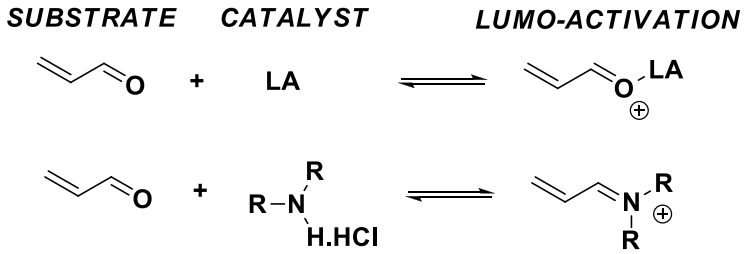
1.6 Iminium Catalysis

The first enantioselective example of this type of organocatalysis strategy was reported in 2000 by MacMillan and co-workers.[66] They took inspiration from conventional organometallic Lewis acid (LA) catalysts. Lewis acid catalysts have been used to activate various π-systems towards nucleophilic attack by the mechanism outlined in Scheme 3.



Scheme 3. Lewis acid catalysis.[66]

The Lewis acid reversible binds an electrophilic substrate, causing the π electron density of the substrate in the resulting adduct to shift towards the electron positive metal centre which lowers the energetic potential of the lowest unoccupied molecular orbital (LUMO). This electronic redistribution, in turn, decreases the energy gap between the LUMO of the electrophile and the highest occupied molecular orbital (HOMO) of the incoming nucleophile, thus facilitating the reaction between the two reacting partners. After bond formation occurs, the Lewis acid can then dissociate from the product to regenerate the catalyst. This strategy was then cleverly applied to α,β-unsaturated aldehydes with a chiral secondary amine salt to mimic the Lewis acid catalyst or LUMO-lowering catalyst (Scheme 4) in a Diels-Alder reaction.[66] This concept of LUMO-lowering catalysis using chiral secondary amines set the scene for an explosion of organocatalytic research into this area that is now referred to as amino-catalysis.

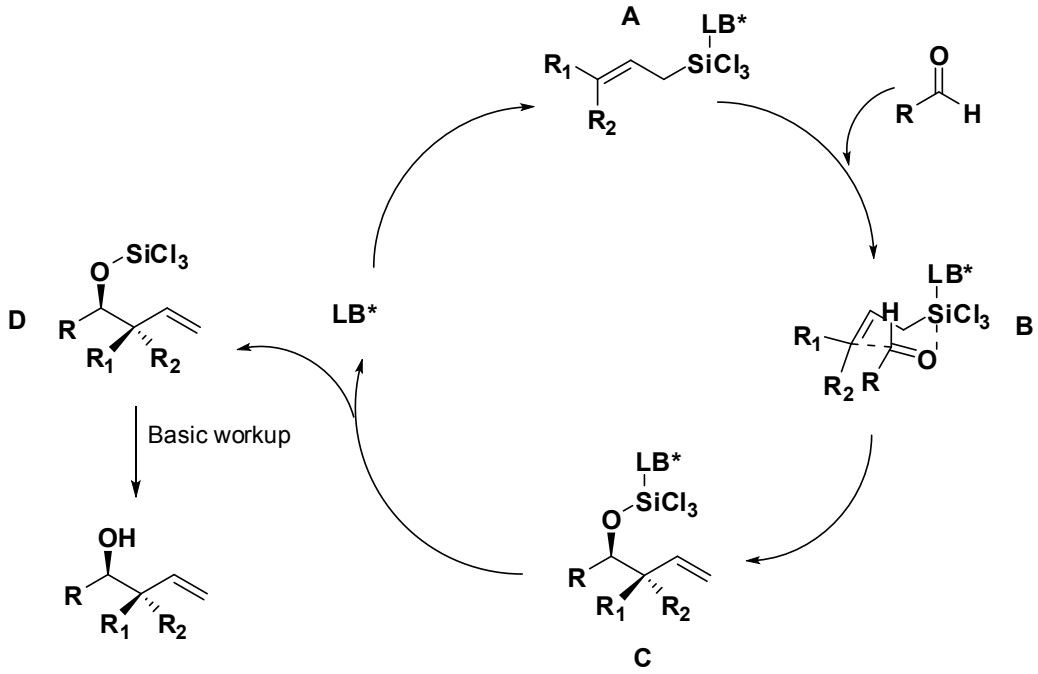


Scheme 4. LUMO-lowering organo catalysis with secondary amines.[66]

To date there are several examples of iminium catalysed reactions,[42,44] however for the purpose of this project only its application in the Diels-Alder reaction utilizing using chiral secondary amines as the organocatalyst will be discussed further in Chapter 2.

1.7 *N*-oxide type organocatalysts

The usefulness of heterocyclic *N*-oxides has attracted much attention in organic chemistry. These compounds have found applications as synthetic intermediates, protecting groups, oxidants, biological activity and more recently asymmetric catalysis (both metal-ligand[67,68] and organocatalysis[68-70]). The Nakajima group first developed a series of chiral Lewis basic *N*-oxide type organocatalysts for enantioselective allylation reactions.[71] This was based on the inherent nucleophilicity of *N*-oxides toward organosilicon reagents. The principle behind this mode of activation is based on the coordination of the *N*-oxide catalyst (which acts as a Lewis base) to a tetracoordinated silicon atom. This increases the Lewis acidity of the now hypervalent silicon centre. As a result, the organosilicon species becomes a highly reactive carbon nucleophile. The mechanism of the allylation reaction has been investigated by Denmark *et al.* (Scheme 5).[72,73]



Scheme 5. Lewis base catalyzed nucleophilic allylation.[72, 73]

The key step is the initial binding of the allylsilane to the Lewis base (**LB***) catalyst (chiral *N*-oxide) **A** to form the reactive species. The intermediate then reacts with incoming aldehyde, which is also coordinated to the silicon atom. This closed transition structure **B** provides dual activation of both substrates. The Lewis base catalyst dissociates from **C** to further react in the cycle. Upon completion of the reaction the trichlorosilane precursor **D** undergoes a basic workup to yield the chiral product. For the purpose of this project further information on *N*-oxide type organocatalysts will be discussed in Chapter 3.

1.8 Guanidine based organocatalysts

The guanidine moiety is well known in both chemistry and biology for its characteristic high pKa value and ability to form dual hydrogen bonds, which is used in molecular recognition.[74-76] Therefore, the guanidine functional group has been an attractive target incorporated into several chiral catalysts used for both metal-ligand and organocatalysis.[14,15,77-79] There is an array of excellent reviews highlighting the synthesis[30,80-82] and the other vast applications[16,83,84] of this remarkable functional group.

In the field of organocatalysis, guanidine type catalysts have become popular by acting as Brønsted bases in asymmetric transformations.[54]

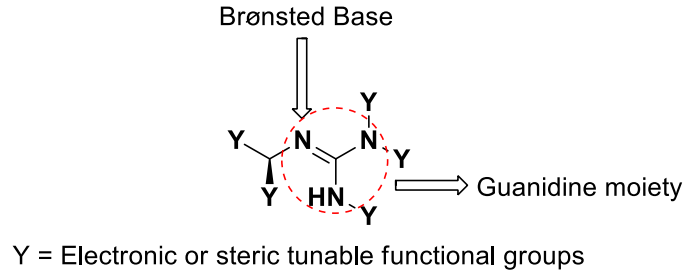
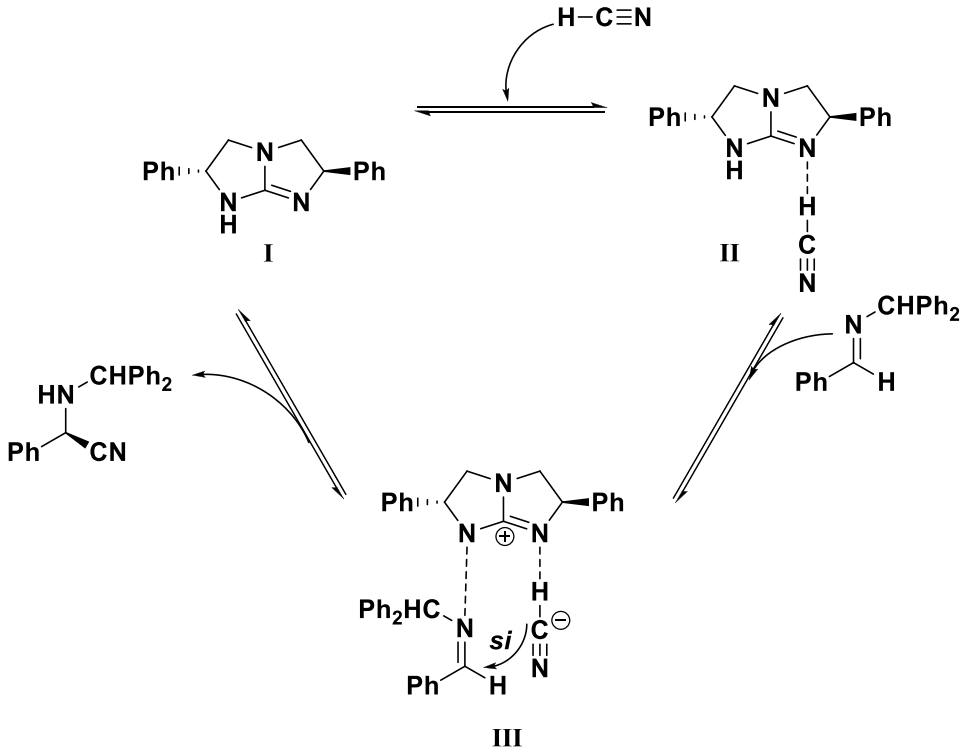


Figure 4. Guanidine type compound as a Brønsted base catalyst.[74]

This type of compound (Figure 4) has been classed as one of the strongest bases in organocatalysis due to the resonance stabilization of its conjugate acid. Since the discovery of the first chiral guanidine organocatalyst in 1994 which was demonstrated on a Henry reaction,[85] the scope of guanidine derived catalysts has been expanded to various other important asymmetric reactions.[74,77,78] The mechanism of guanidine was proposed in 1999 in the Strecker reaction for the addition of HCN to imines which was catalyzed by Corey's C_2 symmetric catalyst, **I** (Scheme 6).[28]



Scheme 6. Corey's proposed catalytic cycle for guanidine catalyzed hydrocyanation.[28]

The Corey group proposed that HCN underwent a Brønsted base interaction with the guanidine catalyst (**II**) allowing the activation of the nucleophile while simultaneously forming a hydrogen bond to the imine substrate that facilitates the attack (**III**).

For the purpose of this project further information on guanidine organocatalysts will be discussed in Chapter 4.

1.9 Outline of this Thesis

The development of novel TIQ based organocatalysts and their application in asymmetric reactions was the aim of this project. Three organocatalytic asymmetric transformations with novel catalysts bearing the TIQ framework have been investigated and make up subsequent Chapters *i.e* **2-4**.

Chapter **5** is a collection of all crystallographic papers published of compounds synthesized from the work pertaining to Chapters **2-4**.

Chapter **6** is a book chapter that was written in collaboration with Prof. Per Arvidsson (Astrazeneca, Sweden) and Dr Partha Bose (University of Uppsala, Sweden) on Asymmetric Organocatalytic Cyclopropane Formation for the Elsevier book entitled Comprehensive Chirality and is currently with the editors in its final proof stage after acceptance.

It must be noted that with the exception of Chapter **4** that has been submitted for publication, the remaining chapters of this thesis have already been published in international peer reviewed journals.

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CHAPTER 2

Novel tetrahydroisoquinoline based organocatalysts for asymmetric Diels-Alder reactions: insight into the catalytic mode using ROESY NMR and DFT studies

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ABSTRACT

For the first time an organocatalyst bearing a secondary nitrogen within a cyclohexane ring has been evaluated in the asymmetric Diels-Alder reaction. This organocatalyst is also the first of its kind based on a (1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline backbone. These catalysts were tested over a range of dienes and dienophiles and displayed promising chemical conversions up to 100 % with up to 64 % *ee* with triflic acid as the cocatalyst. Density functional theory computational studies and 2D NMR spectroscopy were used to determine the structure of the intermediate iminium ion formed between the most efficient catalyst and cinnamaldehyde. The reaction profile for each of the four possibilities in this reaction were calculated and it was found that the iminium intermediate leading to the major product is higher in energy but kinetically preferred. The activation energies of all possible reaction paths were calculated and the results correlated with the observed products. These experiments revealed that the presence of both (*E*)- and (*Z*)-isomers of the cinnamaldehyde were contributing factors for the low enantioselectivity of the reaction products.

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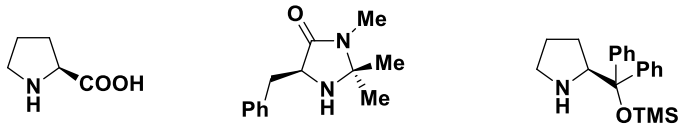
INTRODUCTION

In the last decade there has been an explosive growth in the field of organocatalysis and it has emerged as a powerful method for accelerating various asymmetric transformations.[1-3] Within this topic, the *in situ* generation of iminium and enamine intermediates using chiral amines (aminocatalysis) to facilitate the catalysis of carbonyl transformations has received a tremendous amount of interest from several research groups.[4-7] Significant contributions from the groups of List, MacMillan, and Jørgensen have reported the use of proline (i), imidazolinone (ii) and diaryl prolinols (iii) as successful chiral respectively.[8-10]



i ii iii

Figure 1. Some examples of successful secondary amine organocatalysts.

All of these organocatalysts consist of five membered hetero-atom rings and were evaluated for numerous important enantioselective reactions such as Diels-Alder cycloadditions, Michael additions, Mannich and Henry reactions. Iminium activation of carbonyl compounds using secondary amines (the organocatalyst) allows for lowering of the lowest unoccupied molecular orbital (LUMO), thus emulating classical Lewis acid catalysts.[8] The principle behind iminium activation is based on the reversible condensation between a secondary amine and an unsaturated aldehyde or ketone substrate to form a positively charged iminium intermediate. This results in a redistribution of the π–electron density from the double bond on the substrate towards the iminium cation. This lowers the energy of the LUMO on the unsaturated π-system and the iminium ion intermediate facilitates nucleophilic attack on the substrate.[5]

The tetrahydroisoquinoline (TIQ) molecule and its derivatives have been widely investigated due to their biological and pharmaceutical properties.[11-14] Due to our ongoing pursuit to establish novel chiral catalysts,[15-17] and *L*-DOPA being commercially available, this class of compounds posed as an attractive skeleton for a source of chirality. There are only a few reports that utilise the TIQ backbone as a catalyst precursor.[18-21] From these reports only studies done by Stingl *et al.*[21] and Basavaiah *et al.*[18] made use of a TIQ derivative as an organocatalyst in borane-mediated hydrogenation reactions. Given our recent success with TIQ based ligands for catalytic asymmetric transfer hydrogenation of prochiral ketones,[22,23] Henry reactions[24] and hydrogenation of olefins,[25] we decided to expand the potential of TIQ

derivatives as organocatalysts. On route to the synthesis of a novel organocatalyst bearing the TIQ framework that would potentially behave as a bifunctional organocatalyst we discovered that one of its precursors was able to form an iminium ion. This was unexpected; secondary amines that are part of five-, rather than six-, membered ring systems are known to be more efficient catalysts for enamine catalysis[26], and to the best of our knowledge no previous report has shown that six-membered ring amines are capable of activating α,β-unsaturated aldehydes or ketones through iminium ion formation. This sparked our interest to further investigate this compound and its derivatives for application on reactions known to proceed *via* iminium activation. Herein we report the evaluation of novel organocatalysts **1-9** in the asymmetric Diels-Alder cycloaddition between α,β-unsaturated aldehydes and cyclopentadiene. This is the first report of a chiral organocatalyst with the tetrahydroisoquinoline backbone that contains two chiral centres.

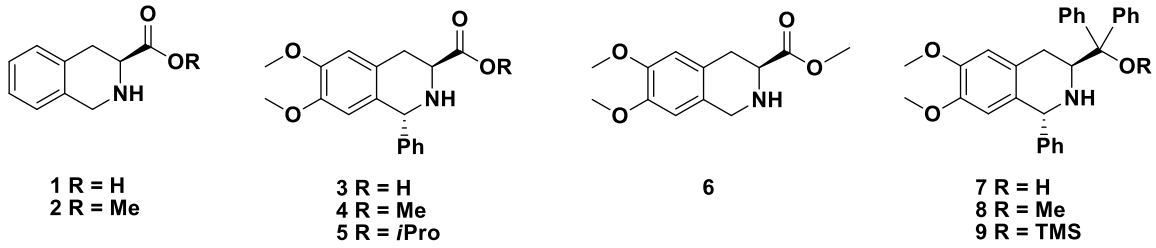
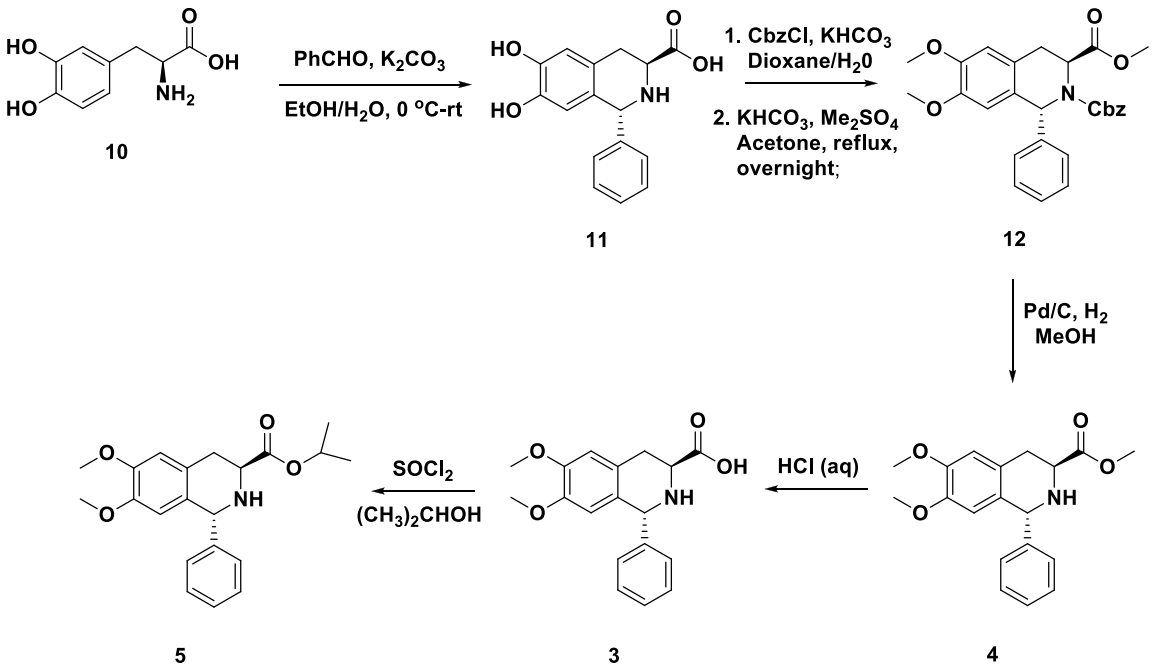


Figure 2. Catalysts evaluated for the Diels-Alder reaction.

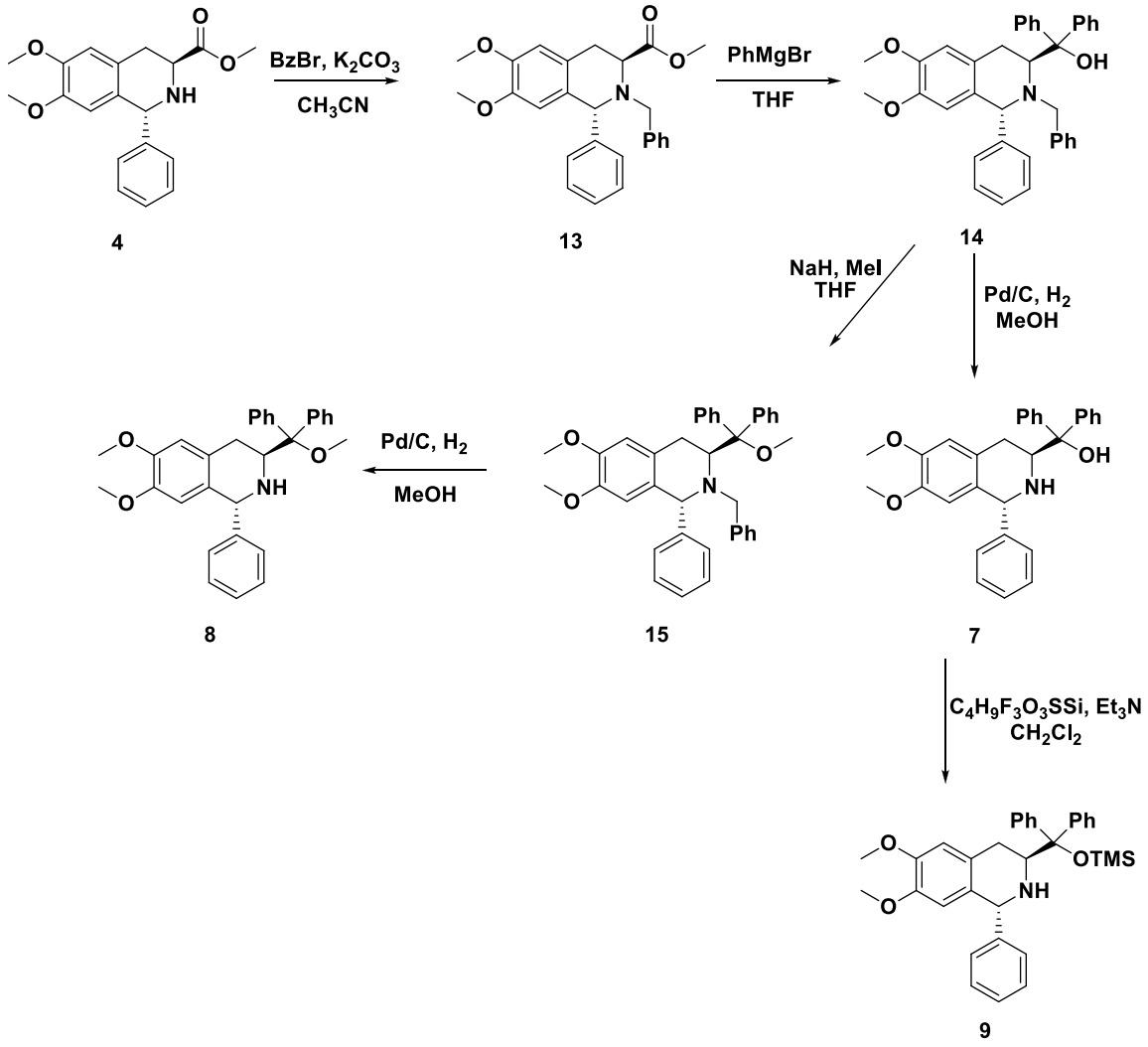
Catalyst Synthesis

Compounds **5**, **8** and **9** (Figure 2) are novel, whereas the syntheses of the remaining compounds have been reported in the literature for other applications. However, this is the first report of these derivatives as organocatalysts. Based on the simplicity of the structure, TIQ catalysts **1** and **2** were the first to be synthesized according to the literature procedure from (*S*)-phenylalanine.[27] Thereafter the more complex TIQ derivatives **3-5** were derived from *L*-DOPA **10** (Scheme 1). We recently reported a modification to the literature procedure for compound **11**.[22] *L*-DOPA **10** was treated with benzaldehyde in the presence of K_2CO_3 and aqueous ethanol to afford the *trans*-substituted derivative **11**. This compound was *N*-protected with benzyl chloroformate (Cbz) and then methylated at the phenolic and carboxylic acid positions to yield **12**. This was achieved by refluxing the compound in acetone in the presence of Me_2SO_4 and $KHCO_3$.[28] Deprotection of the Cbz group furnished catalyst **4**.



Scheme 1. Synthetic route to catalysts **3**-**5**.

Hydrolysis of the ester group in **4** afforded the acid derivative **3** and catalyst **5** was then obtained by simple esterification of **3** with thionyl chloride in isopropanol. Notably, catalysts **3-5** and **7-9** possess a second chiral centre and could not be synthesized from phenylalanine as it was essential to employ the activated aromatic group of *L*-DOPA to facilitate the cyclisation. Hence, methylation of the free phenolic hydroxyl groups had to be done after cyclization in order to simplify the synthesis. In order to test the effect of these methoxy groups on the reactivity of the catalysts, derivative **6** was synthesized by a literature procedure (scheme not shown) from *L*-DOPA and formaldehyde followed by our modified methylation procedure for the hydroxyl and acid positions.[29] Given the success of diaryl proline derivatives as organocatalysts[30] we synthesized the six membered ring TIQ analogues **7-9**. In order to introduce the phenyl groups, the secondary amine **4** was first benzyl protected to give **13**, after which a Grignard reaction with phenyl magnesium bromide afforded **14**. Deprotection of **14** (Scheme 2) resulted in the formation of catalyst **7**.



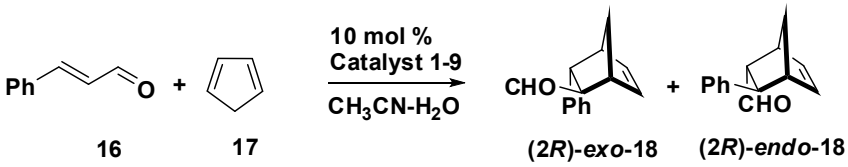
Scheme 2. Synthetic route for catalysts **7-9**.

Derivative **14** was then treated with NaH followed by MeI to yield the diphenyl methoxy *N*-benzyl protected compound **15** which underwent debenzylation to give catalyst **8**. Catalyst **9** was obtained by the hydroxyl protection of **7** using trimethylsilyl trifluoromethanesulfonate.[31]

RESULTS AND DISCUSSION

As a model, we investigated the reaction between cinnamaldehyde **16** and cyclopentadiene **17** in the presence of various tetrahydroisoquinoline derivatives **1-9** as potential catalysts (Table 1). Organocatalysts tested for this reaction have shown to react well in either methanol or acetonitrile/water mixtures.[8,32] Performing the reaction with our catalysts in methanol did show a slightly higher conversion than acetonitrile, nevertheless, acetonitrile was chosen as the solvent since it avoids hydrolysis of the dimethyl-acetal formed when methanol is used and thus, greatly simplifies the workup.

Table 1. Organocatalyzed [4+2] cycloaddition between *trans*-2-cinnamaldehdye **16** and cyclopentadiene **17** to give cycloaddition products *exo*- and *endo*-**18**.[a]



Entry	Catalyst	Conv. (%) 24 h	Conv. (%) 48 h	*ee* (%) *exo*-**18**[b]	*ee* (%) *endo*-**18**[b]	*exo:endo*[c]
1	**1**	53	78	47 (2*R*)	48 (2*R*)	2:1
2	**2**	67	94	43 (2*R*)	50 (2*R*)	2:1
3	**3**	67	90	44 (2*R*)	50 (2*R*)	2:1
4	**4**	73	94	45(2*R*)	51 (2*R*)	2:1
5	**5**	73	94	46 (2*R*)	57 (2*R*)	2:1
6	**6**	58	62	36 (2*R*)	36(2*R*)	2:1
7	**7**	< 5	-	-	-	2:1
8	**8**	< 5	-	-	-	2:1
9	**9**	< 5	-	-	-	2:1

[a]Conditions: 3.0 equiv of diene, 1.0 equiv of dienophile, 0.1 equiv of catalyst and 0.1 equiv of HCl (37%) in 475 μl of CH_3CN and 25 μl of H_20, all reactions were performed in duplicate. [b]Determined by GC analysis using a chiral capillary column and absolute and relative configurations were determined by correlation of GC retention times. The absolute and relative configurations were initially determined by correlation to known compounds. [c]The product ratios were determined by ^{1}H NMR recorded at ambient temperature.

From the TIQ catalysts **1** and **2** the ester derivative **2** showed a higher conversion than the acid derivative **1** (entries 1-2). Thereafter, it was decided to test the TIQ derivatives that contained a second chiral centre (entries 3-4). At that point, compound **4** emerged as the most reactive catalyst amongst **1-4** (entry 4). It appeared logical to substitute the methyl ester of compound **4** with a more bulky group in the hope of increasing the enantiomeric excess of the reaction products; in this case an isopropyl ester (**5**) was used (entry 5). However, this had an insignificant effect on the enantioselectivity. In order to evaluate if the higher conversion rate (*c.f.* the acid derivatives **1** and **3** (53 % and 67 % conversion after 24h, respectively) and the methyl esters **2** and **4** (67 % and 73 % conversion, respectively) was due to the introduction of the phenyl ring at the carbon adjacent to the nitrogen or the introduction

of the methoxy groups, catalyst **6** was synthesized and tested (entry 6). It was clear that the methoxy groups were not responsible for the increased conversion. The activity and selectivity of catalysts **3-5** compared to that of catalyst **1-2** were then attributed to the electron withdrawing nature of the phenyl ring, which increases the acidity of the nitrogen hence favoring iminium formation. To further establish if this was the case, we attempted the reaction with pipecolic acid as catalyst as well, but obtained only low (<10 %) conversions, even in the presence of an acidic co-catalyst (*vide supra*).

Given the success of the diaryl proline analogues as organocatalysts[30] we synthesized the TIQ derivatives **7-9** to be tested on the model reaction. The molecules showed very low conversion rates (entries 7-9). Evidence for iminium formation from catalysts **7-9** with cinnamaldehyde was confirmed with proton NMR spectroscopy. The low conversion could be due to one of two reasons, first, the diene could not attack the dienophile or second the reaction product is not released from the catalyst.

As with other organocatalysts tested for this reaction, an acid co-catalyst proved to be necessary. Therefore we investigated the effect of varying the type of acid with catalysts **2** and **4** (Table 2). The trend observed was that the conversion is proportional to the pKa of the acids. Using a sterically large acid did not influence the enantioselectivity (entry 2). The triflic counterion gave optimal conversion and enantioselectivity (entry 5). The possibility of such a strong acid catalyzing this Diels-Alder reaction and compromising the enantioselectivity by a competing achiral process has been thoroughly investigated by Lemay *et al.*[33] From their study it was concluded that triflic acid was not detrimental to the selectivity of the reaction.

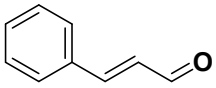
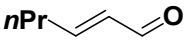
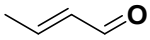
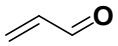
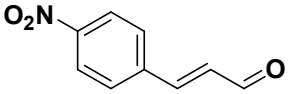
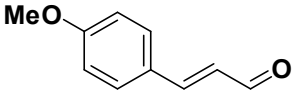
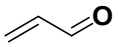
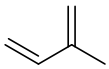
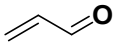
Table 2. Organocatalyzed [4+2] cycloaddition between *trans*-2-cinnamaldehdye **16** and cyclopentadiene **17** using catalyst **2** and **4** in CH_3CN with different acids.[a]

Entry	Catalyst.HCl	Acids	Conv. (%) 24 h	Conv. (%) 48 h	*ee* (%) *exo*-**18**[b]	*ee* (%) *endo*-**18**[b]	*exo:endo*[c]
1	**2**	HCl	71	93	47 (2*R*)	48 (2*R*)	2:1
2	**2**	*p*-TsOH	83	98	43 (2*R*)	50(2*R*)	2:1
3	**2**	TFA	75	92	43 (2*R*)	50(2*R*)	2:1
4	**2**	CH_3SO_2H	77	91	46 (2*R*)	46 (2*R*)	2:1
5	**2**	TfOH	100	-	43 (2*R*)	51 (2*R*)	2:1
6	**4**	HCl	73	90	45 (2*R*)	51(2*R*)	2:1
7	**4**	*p*-TsOH	72	90	48 (2*R*)	47 (2*R*)	2:1
8	**4**	TFA	65	90	49 (2*R*)	55(2*R*)	2:1
9	**4**	CH_3SO_2H	70	90	47 (2*R*)	42 (2*R*)	2:1
10	**4**	TfOH	95	-	47 (2*R*)	57 (2*R*)	2:1
11	**4**	TfOH	85 (12hr)	-	47 (2*R*)	57 (2*R*)	2:1

[a]Conditions: 3.0 equiv of diene, 1.0 equiv of dienophile, 0.1 equiv of catalyst and 0.1 equiv of acid in 475 μl of CH_3CN and 25 μl of H_20, all reactions were performed in duplicate. [b]Determined by GC analysis using a chiral capillary column and the absolute and relative configuration were determined by correlation of GC retention times. The absolute and relative configuration were initially determined by correlation to known compounds. [c]The product ratios were determined by ^1H NMR recorded at ambient temperature.

Having optimized the conditions for the system, the scope of these new TIQ based catalysts using various other dienophiles and dienes was investigated (Table 3).

Table 3. Organocatalyzed Diels-Alder cycloadditions between various dienophiles and dienes utilizing catalyst **4** and TfOH in CH_3CN.[a]

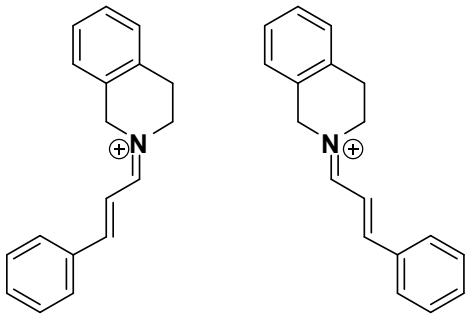
Entry	Dienophile	Diene	Conv. (%) 12h	*ee* (%) *exo*[b]	*ee* (%) *endo*[b]	*exo:endo*[c]
1			85 (55 [d])	47 (64[d])	57 (59)	2:1
2			100	22	*rac*	1:1
3			100	*rac*	4	1.2:1
4			100	5	10	3.5:1
5			100	35	42	2:1
6			40	52	4	1.6:1
7			100	30	-	-
8			100	*rac*	38	7:1

[a]Conditions: 3.0 equiv of diene, 1.0 equiv of dienophile, 0.1 equiv of catalyst and 0.1 equiv of acid in 475 µl of CH_3CN and 25 µl of H_20. [b]Determined by GC analysis using a chiral capillary column. [c]The product ratios were determined by ^1H NMR recorded at ambient temperature. [d]Reaction carried out at zero degrees Celsius and conversion tested after 36h.

A range of aliphatic dienophiles including electron-withdrawing and -donating group substituents on the cinnamaldehyde aryl ring was tested with cyclopentadiene (entries 1-6). All substrates gave excellent conversion with the exception of 4-methoxy cinnamaldehyde. The TIQ catalyst also proved to be efficient when varying the diene (entries 7-8) producing excellent conversion and facial selectivity (entry 8) but unfortunately poor enantioselectivity.

Structural elucidation of the iminium ion intermediate by NMR spectroscopy and computational chemistry

Seebach *et al.* have thoroughly investigated the structural characterization of reactive iminium ion intermediates derived from proline, diphenyl prolinol and imidazolidinones with cinnamaldehyde, employing X-Ray diffraction, NMR spectroscopy and Density Functional Theory (DFT) computational studies.[34-37] They have concluded that (*E*)- and (*Z*)-isomers are possible for the iminium ion intermediates as illustrated in Scheme 3.



Scheme 3. Possible isomers of the iminium ion formed between *trans*-2-cinnamaldehyde and tetrahydroisoquinoline.

We then decided to follow a similar methodology to elucidate the structure of the iminium ion formed between cinnamaldehyde and our catalyst **4**. We recently reported the X-ray crystal structures of precursors to catalyst **4** and **7** which revealed that the *N*-containing six membered ring could exist either as a half boat or half chair form respectively.[38,39] Based on these forms of the catalyst together with the possibility of the (*E*)- and (*Z*)-isomers of the reacting aldehyde, the structure of the iminium ion formed between cinnamaldehyde and catalyst **4** (Figure 3) were examined. The four possibilities A-D were computationally studied utilizing DFT calculations and are presented in Figure 3.

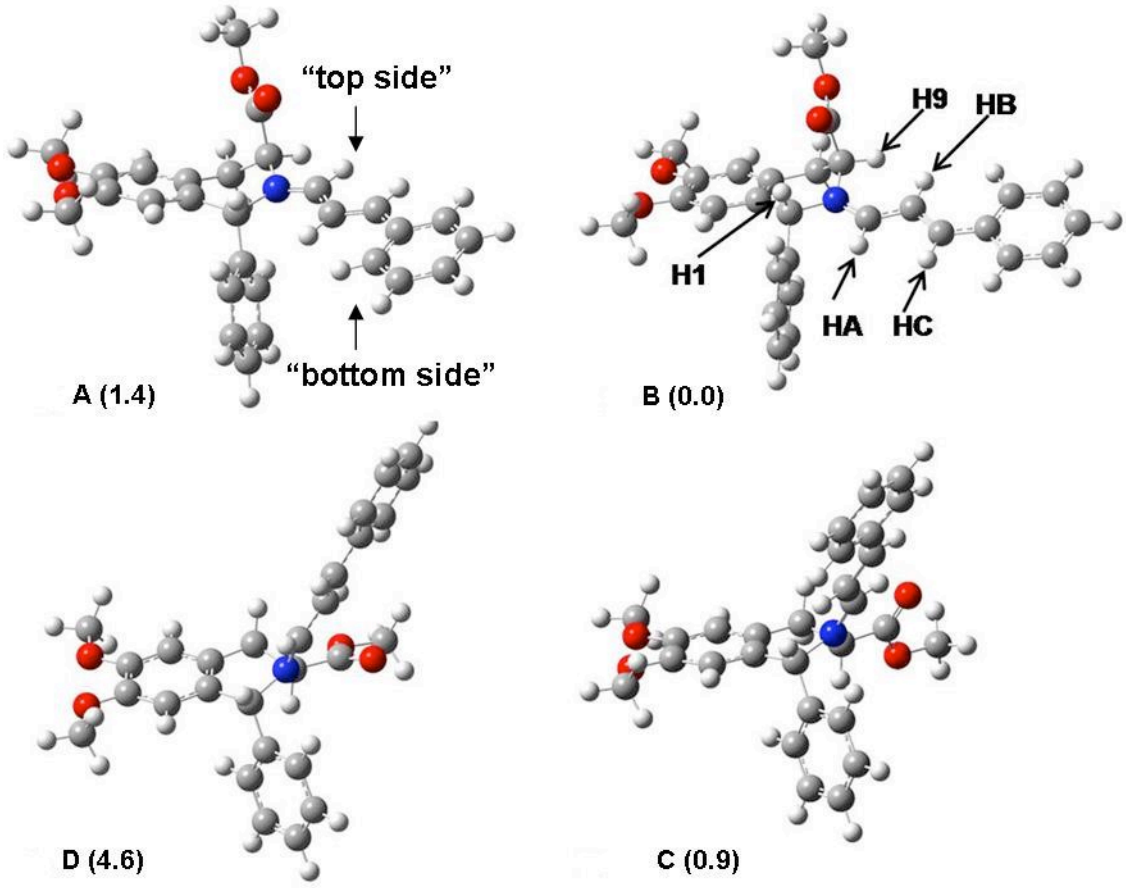


Figure 3. Optimized structures and relative energies (kcal mol-1) of the iminium ion formed between cinnamaldehyde and catalyst 4 at the B3LYP/6-31+G(d) level of theory. (The cartesian coordinates of these four structures are available as supplementary material).

The calculations indicated that intermediate B had the lowest energy conformation. NMR spectra of cinnamaldehyde in the presence of catalyst **4** were obtained to determine the geometry of cinnamaldehyde in the resulting complex. Specific features from the ROESY spectrum revealed that forms A and B coexist in the solution phase which corresponds to the (*E*)- and (*Z*)-isomers around the C=N bond respectively. Formation of imines are reversible at room temperature,[8] therefore it is possible for A and B to exist in equilibrium. The presence of these structures was inferred from the ROESY correlations of protons H1 and H9 to the HB protons on the substrate (see Figure 4).

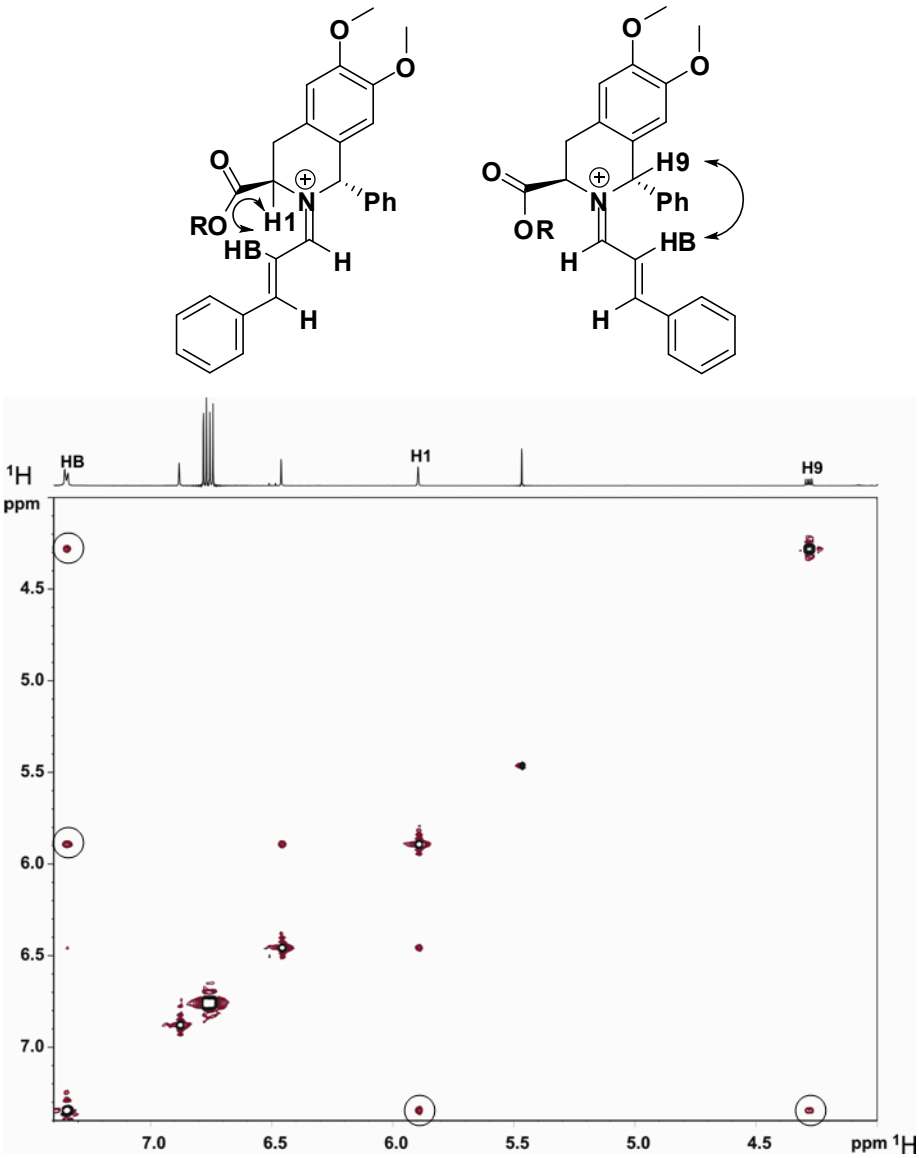


Figure 4. Expanded ROESY spectrum of catalyst **4** and cinnamaldehyde in CD_3CN at room temperature with characteristic cross-peaks marked.

There was no indication of intermediate structures C or D from the correlations in the ROESY spectrum. Peak integration[1] of the H1 and H9 to the HB correlations showed a ratio of 2:1 between intermediate A and B. However, the computational results reveal form A to be 1.45 kcal mol^{-1} higher in energy. The ratio of A:B will depend on the energy barrier leading to imine formation, suggesting that the product ratio (A:B) at room temperature is kinetically determined. Therefore based on the NMR evidence and the results of the iminium intermediate computations, it was concluded that both iminium structures A (*E*)-isomer and B

[1] Integration of the correlation dots on the ROESY spectrum was performed.

(*Z*)-isomer were present in solution at room temperature with the majority being the kinetically preferred structure A.

Another interesting observation from the NMR experiments was that the iminium proton HA was not seen at room temperature. However, proton signals HB and HC were clearly visible and confirmed using 2D NMR experiments that included HMBC, HSQC and COSY. These signals were clearly distinguished from the free form of cinnamaldehyde. Performing the ^{1}H NMR experiment at -38 ^{o}C showed the appearance of two broad peaks in the expected iminium proton region see Figure 5.

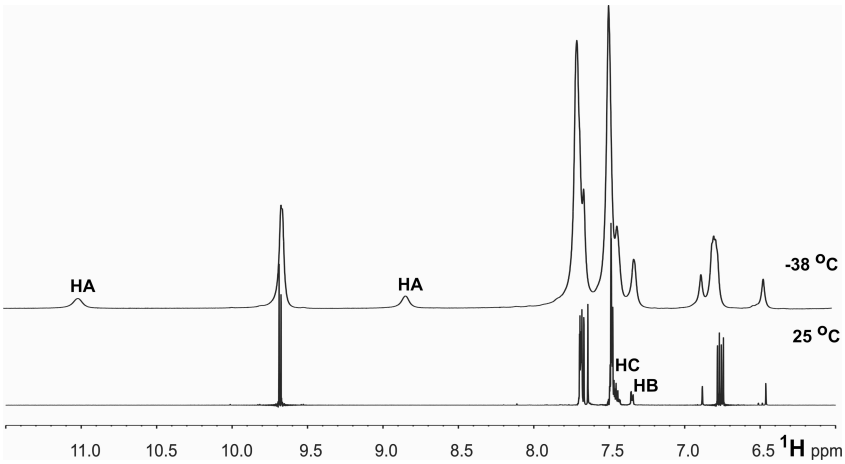


Figure 5. Expanded ^{1}H NMR spectrum of catalyst **4** and cinnamaldehyde in CD_3CN.

We concluded that the iminium proton was in the intermediate exchange regime (μs to ms timescale) of a two-site exchange at room temperature and therefore only observable at a lower temperature (in this case -38 ^{o}C). This confirmed our initial room temperature result of the interconversion between structures A and B.

From the imine intermediates A and B (see Figure 3), the course of the [2+4]-cycloaddition reaction was then studied computationally following the method reported by Houk *et al*.[40] Four possible modes of attack for the incoming cyclopentadiene on each imine intermediate exist. The first two products arise from "top side'' attack of cyclopentadiene on the imine (see Figure 3) where one CH_2 group of cyclopentadiene is pointing out of the plane of the page (indicated with the symbol **I**) and the other one with the CH_2 pointing into the plane of the page (indicated as **II**). The second pair of products arises from the corresponding "bottom side" attack. The eight transitions states were calculated and the energy profile for each intermediate is presented in Figure 6.

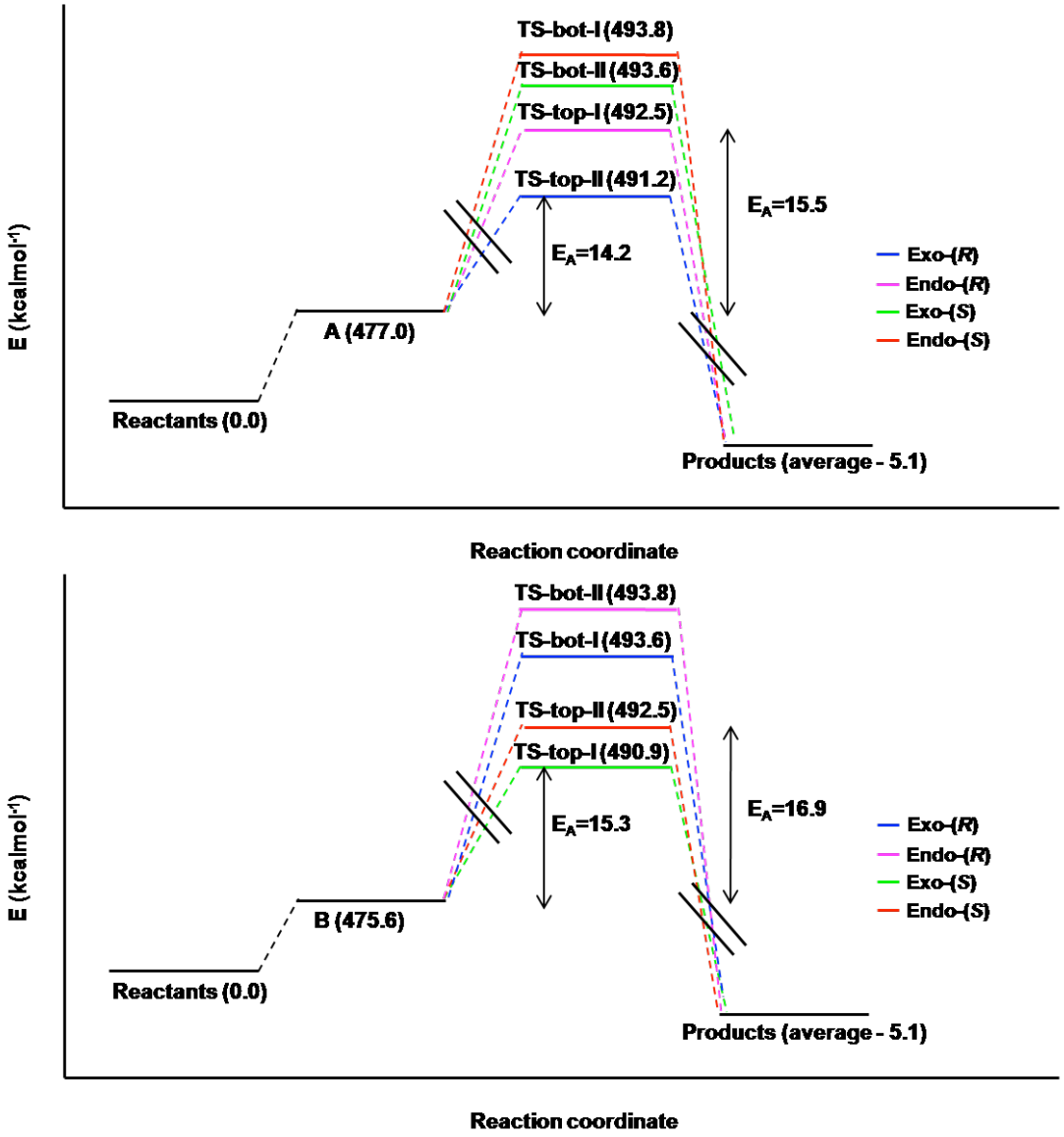


Figure 6. Calculated energy profiles for the catalyzed Diels-Alder reaction for the pathways corresponding to imine intermediate A (top) and B (bottom) respectively. (The Cartesian coordinates of the calculated structures are available as supplementary material).

The experimentally observed products are in the following order: exo-(*R*), endo-(*R*), exo (*S*) and endo-(*S*) (see Table 1 for the corresponding structures). It is clear from the activation energies that the reaction preferably proceeded through intermediate A. The transition state with the lowest energy barrier with respect to the imine intermediate A (TS-top-II) led to the major experimentally observed product. This observation agreed with our NMR study, which confirmed the dominant presence of intermediate A. The competing reaction product was the endo-(*R*)-adduct. The transition state leading to that (TS-Top-I) has the second lowest activation energy (15.5 kcal mol^{-1} – see Figure 6). The presence of both (*E*)- and (*Z*)-isomers

of the cinnamaldehyde/iminium ion complex is a contributing factor for the low enantioselectivity of the reaction products.

The theoretical observation that attack of the cyclopentadiene is from the top (A1-top-II) of the substrate, which corresponds to the lowest activation energy, enabled us to rationalize the results observed with catalysts **7-9** (Table 1, entries 7-9) as well. Although the iminium intermediate was forming with these catalysts (seen from ^{1}H NMR), the two phenyl rings at the C9 position will prevent attack of the diene from the top face, hence leading to the poor conversion.

CONCLUSIONS

For the first time an organocatalyst bearing a secondary nitrogen within a cyclohexane ring has been evaluated in the asymmetric Diels-Alder reaction, thus leading to a new class of TIQ based organocatalysts. Catalyst **4** afforded good to excellent chemical conversion but poor selectivity with the addition of TfOH as the cocatalyst. The poor selectivity was attributed to the presence of both (*E*)- and (*Z*)-isomers of the cinnamaldehyde, which was revealed, by both computational studies and 2D NMR spectroscopy. Catalysts **2** and **4** were identified as good starting points for further development; based on the computational model presented, we believe that this class of novel organocatalysts can be further refined for increased enantioselectivity. Studies into this class of organocatalysts are ongoing in our laboratory.

EXPERIMENTAL SECTION

General

Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instrument at room temperature unless otherwise stated. Chemical shifts are expressed in ppm relative to TMS unless otherwise stated and coupling constants are reported in Hz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254 plates. Crude compounds were purified with column chromatography using silica gel (60–200 mesh). All solvents were dried using standard procedures. All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded on a Perkin Elmer Polarimeter. High resolution mass spectrometric data was obtained using a Bruker microTOF-Q II instrument operating at ambient temperatures. All melting points are uncorrected. The enantiomeric excess of the chiral Diels-Alder products

were determined by gas chromatography Agilent 6890 GC-Ms with a Agilent 7683 auto injector system equipped with an Astec Chiraldex gamma-TA column (30m x 0.25mm), with helium gas as carrier gas and electron impact ionization (EI, 70 eV) or a Agilent 6820 capillary gas chromatograph with a CP-Chirasil-*β*-Dex column (25 m x 0.25 mm), nitrogen as carrier gas and a flame ionization detector.

Synthesis of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1)

This compound was prepared by following the literature procedure from (*S*)-phenylalanine.[27]

Synthesis of (*S*)-methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (2)

This compound was prepared by following the literature procedure from **1** which was in turn derived from (*S*)-phenylalanine.[27]

Synthesis of (1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (3)

This compound was prepared by following the literature procedure[41] from *L*-DOPA with slight modification that we have recently reported.[22]

Synthesis of (1*R*,3*S*)-methyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (4)

This compound was prepared by following the literature procedure from compound **3**.[41]

Synthesis of (1*R*,3*S*)-isopropyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5)

To a stirred solution of compound **3** (1.00 g, 3.2 mmol) in dry isopropanol (100 ml) at 0 ^{o}C, thionyl chloride (4.6 ml, 64.8 mmol) was added dropwise. The mixture was then allowed to warm up to room temperature and stirred overnight. The solution was then concentrated *in vacuo* and the residue washed with sodium bicarbonate solution (50 ml) and extracted with ethyl acetate (2 × 25 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.6) to afford the isopropyl TIQ ester 5 (0.95 g, 84 %) as a solid. Melting point 73-75 ^{o}C. $[\alpha]^{20}_{D}$ -70.0 (*c* 0.12 in $CHCl_3$). IR (neat) ν_{max}: 2938, 1724, 1512, 1246, 1218, 1103, 702 cm^{-1}. HRMS calculated for $C_{21}H_{25}NO_4$ $[M + H]^{1+}$ 356.1856, found 356.1856. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.11 (m, 5H), 6.67 (s, 1H), 6.34 (s, 1H), 5.26 (s, 1H), 5.02 (dq, *J* = 12.5, 6.3 Hz, 1H), 3.87 (s, 3H), 3.75 (dd, *J* = 8.6, 5.0 Hz, 1H), 3.68 (s, 3H), 3.14 (dd, *J* = 16.0, 5.0 Hz, 1H), 2.98 (dd, *J* = 16.0, 8.7 Hz, 1H),

1.37 – 1.09 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 147.8, 147.4, 144.6, 128.7, 128.3, 128.0, 127.3, 125.8, 111.1, 110.8, 68.4, 58.8, 55.8, 51.4, 31.1, 21.8, 21.7.

Synthesis of (*S*)-methyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (6)

This compound was prepared by following the literature procedure from L-DOPA.[29]

Synthesis of ((1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)diphenylmethanol (7)

We recently reported the synthesis of this compound that is derived from compound **3**.[22]

Synthesis of (1*R*,3*S*)-6,7-dimethoxy-3-(methoxydiphenylmethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (8)[31]

To a stirred solution of the *N*-benzyl protected derivative of compound **7** (0.50 g, 0.92 mmol) in dry THF (20 ml) was added sodium hydride (0.07 g, 3.0 mmol) at 0 ^{o}C under an inert atmosphere. The reaction mixture was then stirred for three hours at room temperature and then MeI (0.2 ml, 2.4 mmol) was added. The mixture was heated under reflux overnight. The excess NaH was hydrolysed with aqueous NH_4Cl solution. The organic layer separated and the aqueous layer extracted with ethyl acetate (2 × 10 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (30:70 EtOAc/Hexane, R_f 0.65) to afford the *N*-benzyl diphenyl methoxy derivative of compound **8** (0.40 g, 78 %) as a yellow oil. $[\alpha]^{20}_D$ -80.0 (*c* 0.10 in $CHCl_3$). IR (neat): 2939, 1509, 1446, 1241, 1093, 1079, 695 cm^{-1}. HRMS calculated for $C_{38}H_{37}NO_3$ (M + H$^+$) 556.2844, found 556.2846. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.00 (m, 18H), 6.96 – 6.89 (m, 2H), 6.77 (s, 1H), 6.31 (s, 1H), 4.68 (s, 1H), 4.22 (dd, *J* = 12.5, 3.4 Hz, 1H), 4.11 – 4.02 (m, 1H), 3.92 (s, 3H), 3.67 (s, 3H), 3.29 – 3.14 (m, 2H), 3.03 – 2.89 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.7, 147.5, 144.6, 143.4, 142.9, 141.0, 130.3, 129.1, 128.9, 128.6, 128.3, 128.0, 127.6, 127.5, 127.2, 126.9, 126.8, 126.5, 126.4, 125.9, 112.1, 111.5, 86.1, 65.2, 55.8, 55.8, 55.0, 53.1, 51.7, 24.9.

The benzyl group was then removed following a procedure we have recently reported for the analogous compound **7** to yield compound **8** (0.2 g, 60 %) as a white solid. Melting point 190-192 ^{o}C. $[\alpha]^{20}_D$ -10.0 (*c* 0.11 in $CHCl_3$). IR (neat): 2934, 1514, 1448, 1244, 1224, 1063, 698 cm^{-1}. HRMS calculated for $C_{31}H_{31}NO_3$ (M + H$^+$) 466.2377, found 466.2363. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.12 (m, 12H), 7.08 (t, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 2H), 6.65 (s, 1H), 6.40 (s, 1H), 5.23 (s, 1H), 3.95 (dd, *J* = 11.5, 3.6 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 2.92 – 2.75 (m, 4H), 2.52 (dd, *J* = 16.2, 11.5 Hz, 3H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ = 147.8, 147.1, 143.9, 141.6, 140.8, 129.6, 129.4, 129.0, 128.4, 128.0, 127.4, 127.3, 127.3, 127.1, 127.1, 111.6, 110.5, 84.6, 59.9, 55.9, 55.8, 51.1, 49.4, 29.5.

Synthesis of (1*R*,3*S*)-3-(diphenyl(trimethylsilyl)methyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (9)[31]

To a stirred solution of compound **7** (0.50 g, 1.1 mmol) and triethylamine (0.18 ml, 1.3 mmol) in dry dichloromethane (20 ml) trimethylsilyl triflate (0.24 ml, 1.33 mmol) was added dropwise at 0 ^oC under an inert atmosphere. The mixture was then allowed to warm up to room temperature and stirred overnight. The mixture was washed with water and the organic extracts were combined, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (20:80 EtOAc/Hexane, R_f 0.55) to afford the diphenyl trimethylsilyl derivative **9** (0.52 g, 86 %) as a white solid. Melting point 79-81 ^oC. $[\alpha]^{20}_D$ -30.0 (*c* 0.10 in $CHCl_3$). IR (neat): 2952, 1513, 1446, 1245, 1225, 1067, 834, 752, 698 cm^{-1}. HRMS calculated for $C_{33}H_{37}NO_3Si$ $[M + H]^{1+}$ 524.2615, found 524.2591. NMR chemical shifts are expressed in ppm relative to the $CHCl_3$ peak. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63 – 7.44 (m, 3H), 7.42 – 7.18 (m, 11H), 7.07 (d, *J* = 7.4 Hz, 2H), 6.73 (s, 1H), 6.58 (s, 1H), 5.40 (s, 1H), 4.08 – 3.92 (m, 4H), 3.85 (s, 3H), 2.71 (dd, *J* = 14.2, 11.1 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.6, 144.9, 143.0, 142.4, 142.0, 127.1, 126.4, 125.9, 125.8, 125.3, 125.2, 125.0, 124.7, 124.6, 109.4, 108.3, 80.6, 57.9, 53.7, 53.6, 49.6, 27.1, -0.00.

General procedure for Diels-Alder reaction

To a vial containing the catalyst (0.1 mmol) and the acid (0.1 mmol) in 457 μl of CH_3CN and 25 μl of H_2O was added the α,β-unsaturated aldehyde (1.0 mmol) followed by the diene (3.0 mmol). In the case of cyclopentadiene, it was freshly distilled before use. The reaction mixture was stirred for the time specified in the text. It was then was diluted with Et_2O and washed successively with H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography and analyzed as described in the supporting information according to the following references Table 3, entry 1[8], entry 2[8], entry 3[8], entry 4[42], entry 5[43], entry 6[44], entry 7[8], entry8[8]. Chromatographs and retention times for all chiral products were comparable to those reported.

NMR spectroscopy details

Study of the intermediate iminium ion structure.

To a solution of **4** (5.0 mg, 0.015 mmol) and TfOH (1.4 μl, 0.015 mmol) in 475 μl of CD_3CN and 25 μl of H_2O, (*E*)-cinnamaldehdye (9.6 μl, 0.075mmol) and was added. 1D ^1H and ^{13}C experiments were recorded according to the standard Bruker library, using 16 and 1024 scans, respectively. 2D homonuclear COSY experiments and heteronuclear HSQC and HMBC experiments were recorded according the standard Bruker library with 8 and 512; 8 and 256; and 16 and 512 scans and number of complex points in f1 dimension respectively. 2D homonuclear. ROESY experiments were recorded according to Thiele *et al.*, with 40 scans and 512 complex points.[45] A mixing time of 250 ms was applied to achieve proper transfer and a relaxation delay of 2s was applied, when distances where extracted. ROE distances were used as a range from 2.5 to 5 Å for calculations to restrain.

Computational details

Complexes **A-D** and transitions states were optimized in the gas phase using GAUSSIAN 09[46] at the at the density functional theory (DFT) level employing the B3LYP (Becke's three-parameter non-local exchange function[47-49] with the correlation functional of Lee, Yang and Par[50] in conjunction with the 6-31+G(d) basis set. set. Diffuse functions are typically used for a more accurate description where lone pair electrons are involved, while polarization functions remove some limitations of the basis set by expansion of the virtual space. Solvation effects were not considered in order to simplify the model. Cartesian coordinates of all the optimized structures are available as supporting information. Geometry optimizations were performed without restrictions in order to locate extrema presented herein. Frequency calculations were performed for all structures. Transitions states were characterized by a single imaginary frequency, which corresponds to the movement of atoms consistent with the expected reaction. To ensure that the lowest energy transition state for the first step (bond formation between atoms 1 and 2 in Figure 6) was found, a relaxed scan (using a semi-empirical calculation with Parameterized Model number 6)[51] was performed with the atom distance for atoms 1 and 2 kept fixed at about 1.89Å. The scan entailed a 360º rotation of the cyclopentadiene molecules in 15º steps. The structure corresponding to the lowest energy structure on the energy profile was used for a normal unconstrained transition state for the DFT calculation.

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SUPPORTING INFORMATION

See accompanying cd to this thesis.

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CHAPTER 3

Tetrahydroisoquinoline based *N*-oxides as chiral organocatalysts for the asymmetric allylation of aldehydes

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ABSTRACT

The short synthesis of a series of novel chiral *N*-oxide organocatalysts and their evaluation in the asymmetric allylation reaction of aromatic and α–β-unsaturated aldehydes with allytrichlorosilane is reported. These readily modifiable organocatalysts are the first of its kind based on a tetrahydroisoquinoline framework. The chiral homoallyl products were obtained with good chemical efficiency (up to 93 % yield) and high enantioselectivity (up to 91 % *ee*) under mild reaction conditions (23 °C).

INTRODUCTION

Organocatalysis has rapidly expanded in the last decade encompassing a wide variety of small organic molecules that are capable of either activating substrates or transforming them into more reactive forms.[1-5] Various fundamental asymmetric reactions that once required metal-ligand catalysts can now be conducted with comparable efficiencies using organocatalysts that are more stable, cheaper and less toxic than their metal complex counterparts.[6-8] A classic example is the promotion of the enantioselective allylation of aldehydes which was previously catalysed by Lewis acids (metal-complexes) to give chiral homoallylic alcohols. This can now be carried out in the presence of a range of organic Lewis bases in the form of chiral phosphoramides,

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formamides, imines, phosphine oxides, sulphoxides or *N*-oxides.[6,7,9] Homoallylic alcohol products are important building blocks for more complex molecules. One example, in which a homoallylic alcohol (*i.e* cinnamaldehdye as the substrate) is an important precursor, is in the synthesis of the natural product goniothalamin which exhibits antifungal[10], immunosuppressive and anti-inflammatory[11] activity as well as cytotoxic[12] and anti-tumor[13] properties. Nakajima and co-workers reported the first chiral heterocyclic *N*-oxide type organocatalysts capable of acting as Lewis bases for the enantioselective allylation reactions *via* the activation of allyltrichlorosilane and its derivatives.[9] This was based on the inherent nucleophilicity of *N*-oxides towards organosilicon reagents or substrates. The principle behind this mode of activation was based on the coordination of the *N*-oxide catalyst (which acts as a Lewis base) to a tetra-coordinated silicon atom. This increases the Lewis acidity of the now hypervalent silicon centre which becomes a highly reactive carbon nucleophile. Since Nakajima's report, various *N*-oxide based organocatalysts have been developed.[14,15] These can be largely classified into three types; the first being *N,N*-dioxides with two pyridine moieties bearing a stereogenic axis (**I**),[9] the second having *N*-oxides incorporated into a pyridine ring within a chiral framework (**II**),[16] and the third type in which the *N*-oxide is part of a pyrrolidine (**III**)[17] or piperidine ring.[18]

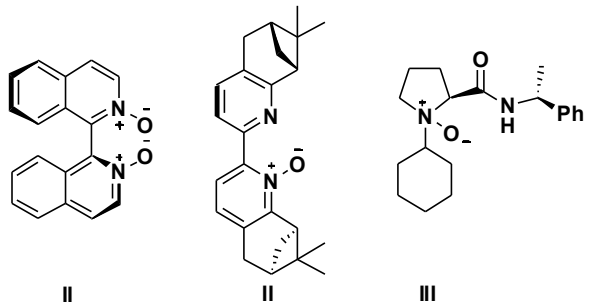


Figure 1. Examples of *N*-oxide based organocatalysts.

Amongst these, the catalysts possess either monodentate or bidentate *N*-oxide moieties. There are only a few examples of the third type of *N*-oxide catalysts with derivative (III) being currently the only example of a monodentate *N*-oxide bonded to an sp^3 nitrogen atom. With this in mind, we wanted to investigate catalysts derived from the tetrahydroisoquinoline (TIQ) backbone (**1-8**). This would constitute the second example of a monodentate *N*-oxide bonded to sp^3 nitrogen organocatalyst.

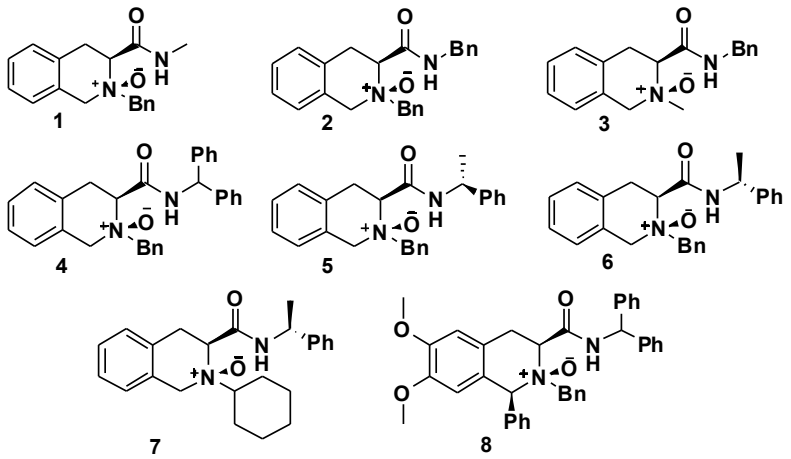


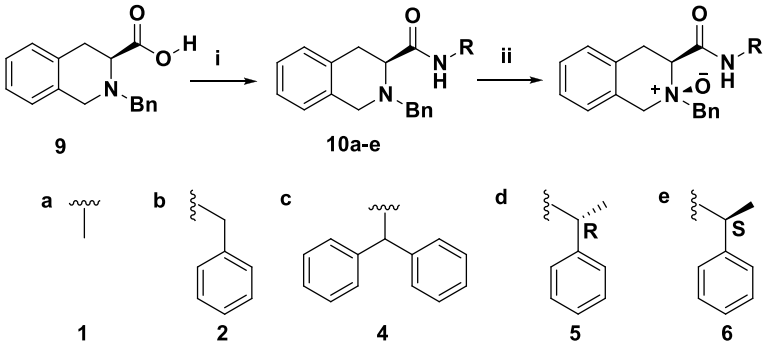
Figure 2. Catalysts evaluated for the allylation reaction.

In addition to the allylation of aldehydes, *N*-oxide organocatalysts have been shown to promote several other important asymmetric transformations.[14] However, preparation of these catalysts follows multi-step synthetic procedures and requires extensive optimization, such as low temperatures to ensure a high level of chiral induction. In this study, we have introduced a new class of easily accessible (four steps or less) TIQ based *N*-oxide organocatalysts that function under mild reaction conditions (23 ^{o}C). The TIQ molecule and its derivatives have been widely investigated due to their biological and pharmaceutical properties.[19-23] We have recently had much success with TIQ based ligands for catalytic asymmetric reactions such as: transfer hydrogenation of prochiral ketones,[24] Henry reaction,[25] hydrogenation of olefins,[26] and we also expanded the potential of these TIQ derivatives as organocatalysts in the Diels-Alder cycloaddition between α,β–unsaturated aldehydes and cyclopentadiene.[27] Herein we report a logical approach to the synthesis of novel Lewis base *N*-oxide organocatalysts (**1-8**) possessing the TIQ as a readily tunable backbone for the asymmetric reaction of allyltrichlorosilane with aryl and α,β–unsaturated aldehydes.

RESULTS AND DISCUSSION

SYNTHESIS

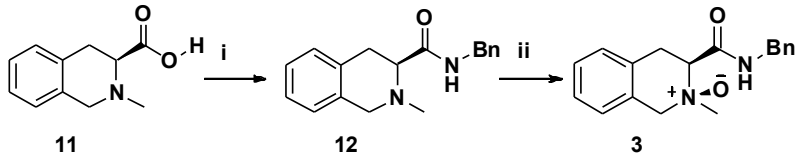
Catalysts **1-2** and **4-6** (Scheme 1) were synthesised from commercially available *N*-benzyl tetrahydroisoquinoline amino acid **9**. Amide bond formation of **9** with the respective amines yielded **10a–e**. Thereafter, oxidation of the tertiary amines with *m*-CPBA afforded the novel catalysts.



Scheme 1. Synthetic route to catalysts 1-2 and 4-6: (i) HBTU, DMF, respective amine, 4 hours at room temperature; (ii) *m*-CPBA, K_2CO_3, DCM, -78 ^oC, 3 hours.

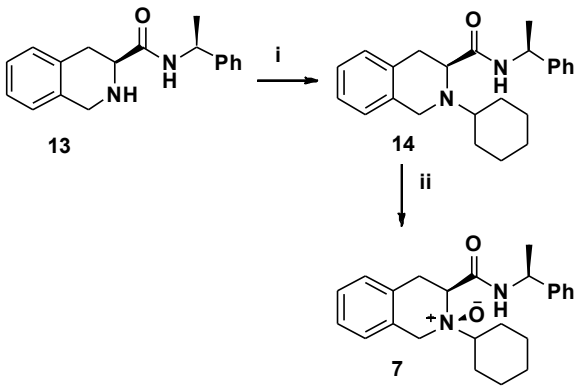
Once the *N*-oxide is formed the nitrogen atom becomes chiral and can form both diastereomers. It has been shown in literature with other pipecolic[28,29] and proline[30] derivatives that the *N*-oxide orientates *syn* (on the same side) to the hydrogen bond donor substituent and is stabilised by an intramolecular hydrogen bond. Our catalysts displayed the same orientation as can be seen from the X-ray crystal structures of **4** and **5**. For catalysts **5** and **6** which contain an additional chiral centre, a single diastereomer was observed after both, coupling of the amide and oxidation steps from proton NMR.

A similar procedure *i.e* for synthesis of catalysts **1-6** was followed for catalyst **3** except commercially available *N*-methyl tetrahydroisoquinoline amino acid **11** was used instead of **9**.



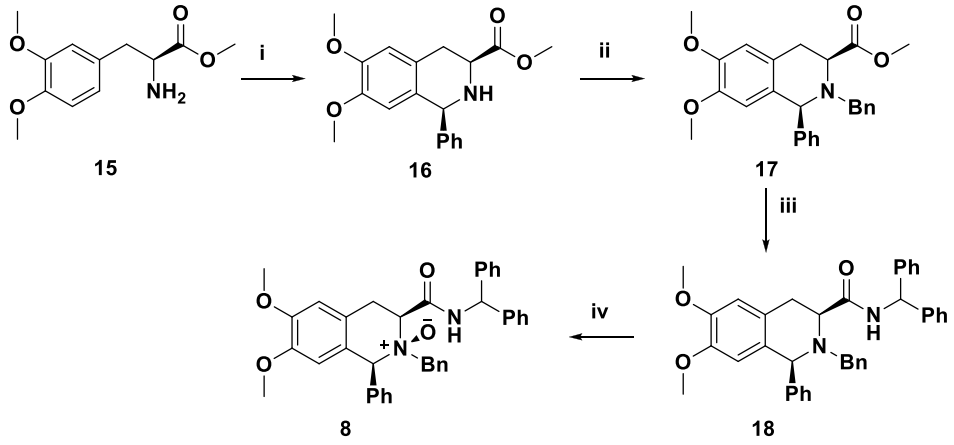
Scheme 2. Synthetic route to catalyst 3: (i) HBTU, DMF, benzyl amine, 4 hours at room temperature; (ii) *m*-CPBA, K_2CO_3, DCM, -78 ^oC, 3 hours.

We have previously reported the synthesis of compound **13** which upon protection of the secondary amine with bromocyclohexanone afforded derivative **14**. This underwent oxidation with *m*-CPBA to produce catalyst **7**. From proton NMR a single diastereomer was observed for compounds **14** and **7**.



Scheme 3. Synthetic route to catalyst 7: (i) Bromocyclohexane, K_2CO_3, DMSO, 70 ^oC, 48 hours.; (ii) *m*-CPBA, K_2CO_3, DCM, -78 ^oC, 3 hours.

Catalyst **8** was derived from commercially available amine **15**. Reductive amination of **15** with benzaldehyde followed by cyclisation of the imine yielded **16**. Diastereomers were obtained in a 90:10 ratio of the *cis:trans* isomers of **16** which were easily separated using silica gel chromatography. Thereafter the secondary amine underwent benzylation which was followed by microwave assisted acid hydrolysis of the ester. The acid was reacted with diphenylmethanamine to furnish the amide **18** (only the *cis* isomer was observed from proton NMR) which was oxidised with *m*-CPBA to produce catalyst **8**.



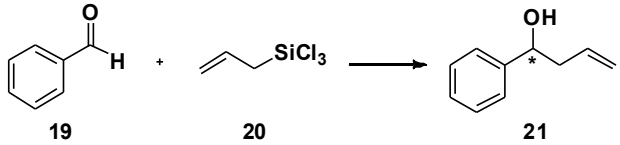
Scheme 4. Synthetic route to catalyst 3: (i) PhCHO, DCM/MeOH, molecular sieves, 1.5 hours, TFA reflux, 3 hours; (ii) BnBr, K_2CO_3, overnight at room temperature.; (iii) Microwave assisted acid hydrolysis, HBTU, DMF, diphenylmethanamine, 4 hours at room temperature; (iv) m-CPBA, K_2CO_3, DCM, -78 ^oC, 3 hours.

Notably, compounds **15-18** and **8** have a second chiral centre and could not be synthesized from phenylalanine as it was essential to employ the activated aromatic group **15** to facilitate the cyclization.

Catalyst Evaluation

The benchmark reaction for the evaluation of *N*-oxide type organocatalysts has been the asymmetric reaction between benzaldehyde (**19**) and allyltrichlorosilane (**20**).

Table 1. Allylation of benzaldehyde (**19**) and allyltrichlorosilane (**20**) facilitated by catalysts **1-8** at room temperature in DCM.



19 **20** **21**

Entry	Catalyst[a]	Yield (%)[b]	*ee*(%)[c,d]
1	1	81	<10
2	2	85	<10
3	3	80	<10
4	4	85	15 (*R*)
5	5	90	12 (*R*)
6	6	91	20 (*R*)
7	7	83	<10
8	8	86	44 (*R*)

[a]Reactions were carried out by using 10 mol-% of the organocatalyst; all reactions were performed in duplicate. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC; the values are an average of two measurements. [d]The configuration of the chiral product was established by the comparison of their HPLC retention times with the literature data.

Our study was initiated by examining the modification of the catalyst's C- and *N*-termini starting from the simple TIQ derivatives **1-3** (Table 1, entry 1-3). Although low selectivities were observed, there was substantial conversion to the allylation product **21**. Encouraged by these results we set out to introduce a more bulky group at the C-termini in the hope of increasing the enantiomeric excess (*ee*) with catalyst **4** (Table 1, entry 4). This moderately increased the *ee*, and we anticipated that another chiral centre at the amide position could enhance the selectivity (Table 1, entry 5-6). However, the 20 % *ee* remained the highest enantioselectivity obtained. Since the use of a chiral amide resulted in a slighty higher *ee*, it was then decided to synthesise the analogue of proline-derived catalyst (III), *i.e* a cyclohexyl group on the nitrogen in hope that this may affect the selectivity. Catalyst **7** displayed marginal difference on the enantioselectivity of the reaction product.

The X-ray crystal structures of catalyst **4** and **5** revealed further information on how the catalysts could be modified in order to enhance the enantiomeric excess as illustrated from the OLEX2[31] generated Figures 3 and 4.

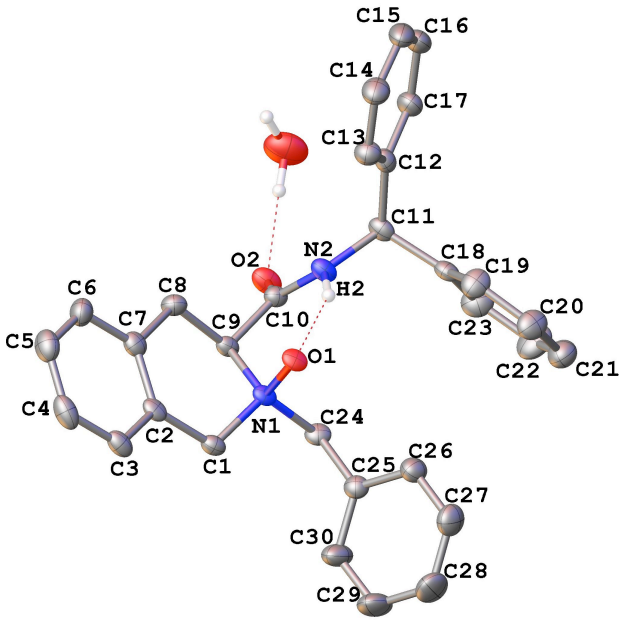


Figure 3. OLEX2 generated drawing of the X-ray structure of catalyst **4 (**CCDC-824790).

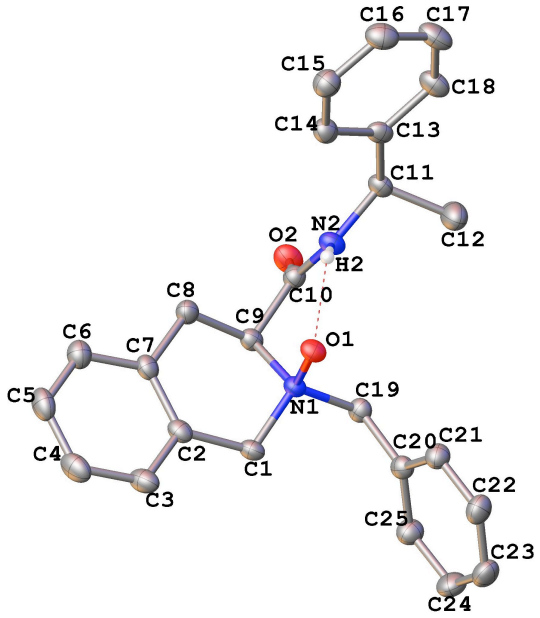


Figure 4. OLEX2 generated drawing of the X-ray structure of catalyst **5** (CCDC 824789).

It is evident from the crystal structures that the *N*-containing six membered ring assumes a half chair conformation with the *N*-oxide protruding up in order to hydrogen bond with the amide hydrogen. This observation explained why the *ee* was not influenced by changing groups on the

secondary amine. Catalysts **5** and **6** differ by the configuration at the chiral center in the coupled amine, and produced 12 % and 20 % *ee* respectively. The crystal structures also explains why the best asymmetric induction was obtained when a bulky diphenyl moiety is present at C11 (Figure 3), thereby creating a chiral pocket around the *N*-oxide functionality. Based on these findings we postulated that a diphenyl group on the amide and more steric bulk closer to the oxide moiety was required. It was synthetically possible to introduce a phenyl ring at C1 in either the *cis* or *trans* position. The *cis* position seemed more viable for chiral induction as it was closer to the oxide atom. Catalyst **8** was synthesised and significantly increased the selectively to 44 % (Table 1, entry 8).

It has been shown in the literature that the appropriate choice of solvent is crucial for asymmetric induction, rate and yield of the allylation reaction.[32] Therefore catalyst **8** was tested in the most common solvents used for this type of asymmetric reaction (Table 2). The change in solvent had a noteworthy effect on the enantiomeric excess of the reaction product (Table 2, entry 4).

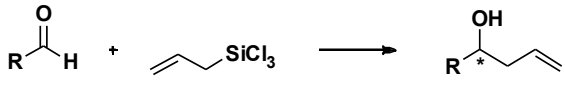
Table 2. Allylation of benzaldehyde (**19**) and allyltrichlorosilane (**20**) catalyzed by derivative **8** in different solvents (24 h) at room temperature.

Entry	Solvent[a]	Yield (%)[b]	*ee* (%)[c,d]
1	DCM[e]	85	44
2	DCE[f]	80	53
3	CH_3CN[g]	65	<10
4	THF[h]	85	65

[a]Reactions were carried out by using 10 mol-% of the organocatalyst; all reactions were performed in duplicate. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC; the values are an average of two measurements. [d]The configuration of the chiral product was established by the comparison of their HPLC retention times with the literature data. [e]Dichloromethane. [f]1,2-Dichloroethane. [g]Acetonitrile. [h]Tetrahydrofuran.

Having optimized the conditions for the system, the use of this new TIQ based organocatalyst **8** was extended by applying it to various aromatic aldehydes and allyltrichlorosilane (Table 3, entries 1-7) at room temperature (23 ^{o}C) in THF.

Table 3. Allylation of aldehydes and allyltrichlorosilane (**20**) catalyzed by derivative **8** in THF (24 h) at room temperature.



Entry	R	Yield (%)[a,b]	*ee* (%)[c,d]
1	Ph	80	65 (*R*)
2	4-$MeOC_6H_5$	87	60 (*R*)
3	4-$O_2NC_6H_5$	90	52 (*R*)
4	4-ClC_6H_5	89	55 (*R*)
5	4-FC_6H_5	93	65 (*R*)
6	2-Naphthyl	87	51 (*S*)
7	3,5-$(OMe)_2C_6H_3$	50	62 (*S*)
8	Ph-CH=CH	85	91 (*S*)

[a]Reactions were carried out by using 10 mol % of the organocatalyst; all reactions were performed in duplicate. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC; the values are an average of two measurements. [d]The configuration of the chiral products was established by the comparison of their HPLC retention times with the literature data.

All of the reactions proceeded with high conversions and reasonable selectivities. From Table 3, it may be concluded that the catalyst is highly sensitive to steric bulk, while electronic changes seems to have less influence on the chiral induction (*cf* Table 3, entries 1-5 vs entries 6-7). The configuration of the products changed from *R* to *S* upon increased steric bulk (Table 3, entries 6-7), suggesting such aldehydes orient themselves differently in the catalyst pocket before attack of the silyl substituent.

In order to evaluate if catalyst **8** was not limited to aromatic aldehydes, it was tested with an α,β–unsaturated aldehyde (*i.e.* cinnamaldehdye). The product from this reaction emerged with a high enantioselectivity of 91 % (Table 3, entry 8), again with opposite absolute configuration than the product originating from simple benzaldehyde substrates (i.e. Table 3, entries 1-5). This prompted us to re-examine the solvent choice for this substrate (Table 4).

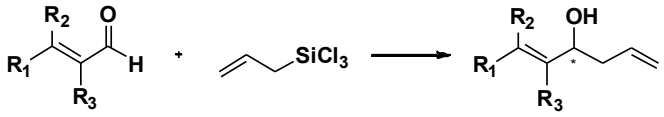
Table 4. Allylation of cinnamaldehyde and allyltrichlorosilane (**20)** catalyzed by derivative **8** in different solvents (24 h) at room temperature.

Entry	Solvent[a]	Yield (%)[b]	*ee* (%)[c,d]
1	DCM	80	75
2	DCE	75	87
3	CH_3CN	72	79
4	THF	85	91

[a]Reactions were carried out by using 10 mol-% of the organocatalyst; all reactions were performed in duplicate. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC; the values are an average of two measurements. [d]The configuration of the chiral product was established by the comparison of their HPLC retention times with the literature data.

Similar to the result for benzaldehyde, THF appeared to be the solvent of choice again as can be seen from Table 4. Based on this result and the fact that allylations of α,β−unsaturated aldehydes have been rather neglected,[33,34] it was decided to further expand the scope of this type of substrates with catalyst **8** (Table 5).

Table 5. Allylation of α,β unsaturated aldehydes and allyltrichlorosilane (**20**) catalyzed by derivative **8** in THF (24 h) at room temperature.



Entry	R_1	R_2	R_3	Yield (%)[a,b]	*ee* (%)[c,d]
1	Ph	H	H	85	91 (*S*)
2	4-$MeOC_6H_5$	H	H	85	50 (*S*)
3	2-$MeOC_6H_5$	H	H	86	42 (*S*)[e]
4	4-$O_2NC_6H_5$	H	H	90	30 (*S*)
5	2-$O_2NC_6H_5$	H	H	90	51 (*S*) [e]
6	4-BrC_6H_5	H	H	82	40 (*S*)
7	2-Furyl	H	H	87	43 (*S*)[e]
8	Me	H	H	65	<10 (*S*)
9	*n*Pro	H	H	0	-
10	Me	Me	H	55	17 (*S*)
11	Ph	H	Me	75	54 (*R*)

[a]Reactions were carried out by using 10 mol-% of the organocatalyst; all reactions were performed in duplicate. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC; the values are an average of two measurements. [d]The configuration of the chiral products was established by the compa rison of their HPLC or GC retention times with the literature data. [e]The absolute configuration was arbitrarily assigned based on the sign of optical rotation for known 1-phenyl-hexa-1,5-dien-3-ol (entry 1).

A range of aromatic α,β–unsaturated aldehydes including electron-withdrawing and -donating group substituents on the cinnamaldehyde aryl ring were employed with allyltrichlorosilane (Table 5, entries 1-7). All substrates displayed appreciable conversions, but moderate enantioselectivities. The large drop in stereoselectivity observed upon modest changes in the substrate structure (*cf.* Table 5, entries 1, 6, 7) is surprising and difficult to rationalize, but it again advocates that this catalyst system is highly sensitive to steric variations in the substrate.

In addition, aliphatic α,β–unsaturated aldehydes proved to have little or no activity (Table 5, entries 8-10). Lastly a hydrogen atom on the α position of cinnamaldehdye was replaced with a methyl group to determine if this increased bulk would have a considerable effect on the *ee* of the chiral product, but a decreased yield and poor selectivity was observed (Table 5, entry 11). In addition, the configuration of this product changed, suggesting that the orientation of the aldehyde with respect the catalyst changed. The best result observed from all of the substrates

screened with allyltrichlorosilane remained cinnamaldehyde (85 % yield, 91 % *ee*) at room temperature. As mentioned earlier, the chiral homoallylic product derived from cinnamaldehdye is a key precursor in the synthesis of the natural product goniothalamin. To the best of our knowledge, the highest *ee* reported to date for cinnamaldehdye is 79 % at room temperature when catalyst (**III**) was employed.[17]

CONCLUSIONS

In summary, we have identified a novel class of *N*-oxide TIQ organocatalysts that promotes the enantioselective allylation of both aromatic and α,β–unsaturated aldehydes. The catalysts are easily prepared from commercially available substrates, readily modifiable (displayed by the efforts to optimize the reaction's enantioselectivity) and the asymmetric allylation reaction can be done under mild reaction conditions (23 °C). The products were obtained in up to 91 % *ee* (cinnamaldehdye). Studies into this class of organocatalysts are ongoing in our laboratory.

EXPERIMENTAL SECTION

Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded on a Bruker AVANCE III 400 MHz instrument. Chemical shifts are expressed in ppm relative to $CDCl_3$ and coupling constants are reported in Hz. NMR Spectra were obtained at room temperature. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using Silica gel 60 mesh All solvents were dried using standard procedures. All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded on a Perkin Elmer Polarimeter. Microwave assisted reactions were carried out on a CEM Discover SP system. All melting points are uncorrected. High resolution mass spectrometric data was obtained using a Bruker microTOF-Q II instrument operating at ambient temperatures, using a sample concentration of approximately 1.0 ppm. The enantiomeric excess of the chiral allylation products were determined by either gas chromatography by using an Agilent 6820 capillary gas chromatograph with a CP-Chirasil-β-Dex column (25 m × 0.25 mm), nitrogen as the carrier gas and a flame ionization detector or on an Agilent 1100 HPLC with either a Chiralpak IA, IB or AS-H column.

Representative procedure for the synthesis of TIQ based amides

(*S*)-2-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**9**) or (*S*)-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**11**) (4.8 mmol) was dissolved in DMF (15 ml) and THF (5.0 ml) followed by addition of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium

hexafluorophosphate (HBTU, 5.8 mmol), *N,N*-diisopropylethylamine (DIPEA, 9.6 mmol) and the appropriate amine (5.3 mmol). The reaction mixture was then stirred at room temperature until no more starting material could be detected by TLC analysis (approximately 4 hours). The reaction mixture was poured into 30 volumes of chilled water; the mixture was then extracted thrice with ethyl acetate (20 ml). The extracts were dried over anhydrous Na_2SO_4 and then concentrated to dryness affording the crude product which was purified by column chromatography.

(*S*)-*N*,2-dibenzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (10a)

The crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.50) to afford the product 1.20 g (92 %) as a yellow oil. $[\alpha]^{20}_D$ -25.00 (*c* 0.16 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 6H), 7.23 – 7.11 (m, 3H), 7.00 (d, J = 7.2 Hz, 1H), 3.80 (d, J = 15.2 Hz, 1H), 3.65 (dt, J = 13.3, 10.6 Hz, 3H), 3.52 (t, J = 6.8 Hz, 1H), 3.21 – 3.05 (m, 2H), 2.78 (d, J = 5.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.68, 138.21, 134.62, 134.36, 128.86, 128.82, 128.60, 128.56, 128.23, 127.50, 127.00, 126.45, 126.27, 62.18, 58.55, 51.12, 28.01, 25.94. IR (neat): 3322, 2937, 1654, 1524, 731, 698 cm^{-1}. HRMS calculated for $C_{18}H_{21}N_2O$ $[M + H]^{1+}$ 281.1648, found 281.1664.

(*S*)-*N*,2-dibenzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (10b)

The crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.45) to afford the product 1.50 g (88 %) as a yellow oil. $[\alpha]^{20}_D$ 10.00 (*c* 0.10 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.11 (m, 11H), 7.11 – 6.90 (m, 3H), 4.52 – 4.41 (dd, J = 15.0, 6.4 Hz, 1H), 4.37 (dd, J = 15.0, 5.5 Hz, 1H), 3.85 – 3.55 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.11, 138.30, 137.98, 134.99, 134.52, 129.07, 128.95, 128.63, 128.59, 128.39, 128.19, 127.51, 127.35, 127.26, 127.13, 126.48, 126.40, 62.17, 59.00, 51.42, 43.05, 28.59. IR (neat): 3301, 2929, 1654, 1264, 731, 696 cm^{-1}. HRMS calculated for $C_{24}H_{25}N_2O$ $[M + H]^{1+}$ 357.1961, found 357.1971.

(*S*)-*N*-benzhydryl-2-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (10c)

The crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.45) to afford the product 1.88 g (91 %) as a colourless oil. $[\alpha]^{20}_D$ 5.263 (*c* 0.19 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.6 Hz, 1H), 7.36 – 6.68 (m, 20H), 6.11 (d, J = 8.7 Hz, 1H), 3.84 – 3.53 (m, 5H), 3.21 (dd, J = 15.7, 5.2 Hz, 1H), 3.11 (dd, J = 15.7, 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.39, 141.99, 141.35, 137.90, 135.50, 134.80, 129.00, 128.96, 128.74, 128.59, 128.45, 128.20, 128.16, 127.78, 127.52, 127.47, 127.35, 127.01, 126.82, 126.52, 126.44, 126.08, 62.30, 60.41, 59.66, 56.49, 51.65, 29.76, 29.36, 21.05, 14.25. IR (neat): 3319, 2919,

1663, 1493, 745, 697 cm^{-1}. HRMS calculated for $C_{30}H_{29}N_2O$ $[M + H]^{1+}$ 433.2274, found 433.2297.

(*S*)-2-benzyl-*N*-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (10d)

The crude product was purified by column chromatography (30:70 EtOAc/Hexane, R_f 0.30) to afford the product 1.88 g (91 %) as a brown solid. Melting point 96-99 ^oC. $[\alpha]^{20}_D$ 11.36 (c 0.22 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.7 Hz, 1H), 7.37 – 7.12 (m, 11H), 7.05 (d, J = 6.5 Hz, 1H), 6.88 (dd, J = 6.7, 2.6 Hz, 2H), 5.08 – 4.94 (m, 1H), 3.90 – 3.54 (m, 5H), 3.12 (dd, J = 6.3, 2.2 Hz, 2H), 1.39 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.10, 143.16, 138.16, 134.73, 134.49, 128.99, 128.79, 128.72, 128.66, 128.58, 128.38, 128.22, 127.44, 127.32, 127.05, 126.45, 126.34, 126.19, 77.39, 62.15, 58.45, 51.45, 48.36, 28.38, 21.76. IR (neat) : 3302, 2924, 1651, 1651, 1494, 743, 698 cm^{-1}. HRMS calculated $C_{25}H_{27}N_2O$ $[M + H]^{1+}$ 371.2118, found 371.2134.

(*S*)-2-benzyl-*N*-((*S*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (10e)

The crude product was purified by column chromatography (30:70 EtOAc/Hexane, R_f 0.30) to afford the product 1.88 g (91 %) as a brown solid. Melting point 96-99 ^oC. $[\alpha]^{20}_D$ -12.20 (c 0.41 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 1H), 7.42 – 7.10 (m, 13H), 7.02 (d, J = 7.2 Hz, 1H), 5.12 – 4.90 (m, 1H), 3.89 – 3.53 (m, 4H), 3.53 (t, J = 6.7 Hz, 1H), 3.14 (d, J = 6.7 Hz, 2H), 1.54 (d, J = 12.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.26, 143.24, 138.08, 135.21, 134.65, 129.14, 128.95, 128.79, 128.64, 128.58, 128.49, 128.37, 128.23, 128.16, 127.54, 127.20, 126.90, 126.40, 125.67, 125.04, 62.25, 59.13, 51.86, 47.93, 29.72, 28.95, 22.07. IR (neat) : 3302, 2924, 1651, 1651, 1494, 743, 698 cm^{-1}. HRMS calculated for $C_{25}H_{27}N_2O$ $[M + H]^{1+}$ 371.2118, found 371.2134.

(*S*)-*N*-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (12)

The crude product was purified by column chromatography (100 % EtOAc, R_f 0.50) to afford the product 1.00 g (77 %) as a brown solid. Melting point 91-95 ^oC. $[\alpha]^{20}_D$ -7.93 (c 0.21 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 7H), 7.04 (dd, J = 32.3, 6.5 Hz, 3H), 4.56 – 4.45 (m, 1H), 4.30 (dd, J = 15.0, 5.2 Hz, 1H), 3.90 – 3.74 (m, 2H), 3.64 (d, J = 14.2 Hz, 1H), 3.11 (d, J = 6.4 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.29, 138.33, 135.35, 133.96, 128.79, 128.57, 128.03, 127.82, 127.48, 127.25, 127.18, 127.05, 126.32, 126.12, 63.87, 55.09, 42.92, 42.89, 42.16, 29.43, 23.50. IR (neat): 3302, 2924, 1651, 1651, 1494, 743, 698 cm^{-1}. HRMS calculated for $C_{18}H_{21}N_2O$ $[M + H]^{1+}$ 281.1648, found 281.1668.

(*S*)-2-cyclohexyl-*N*-((S)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) (14)

To a stirred solution of (*S*)-*N*-((*S*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**13**) (1.0 g, 3.6 mmol) in dry DMSO (50 ml), potassium bicarbonate (1.5 eq.) was added

followed by bromocyclohexane (2.5 eq.). The reaction mixture was allowed to stir for 48 hours at 70 ^{o}C. Thereafter, water (50 ml) was added to the reaction. The aqueous layer was extracted with ethyl acetate (3 × 20 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to yield the unpurified amide which was carried to the oxidation step.

(1*S*,3*S*)-methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (16)

To a stirred solution of 1:1 methanol: methylene chloride (6.0 ml) with 4 Å molecular sieves, (S)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate **15** (1.0 g, 4.2 mmol) and benzaldehdye (1.1 eq.) was added under an inert atmosphere. The reaction mixture was allowed to stir for 1.5 hours. Thereafter the reaction mixture was filtered and the solvents were removed *in vacuo* to yield the intermediate imine which was left on a high vaccum pump to remove any residual water for 2 hours. The residue was then dissolved in trifluoroacetic acid (20 ml) and refluxed for 3 hours. The reaction mixture was then neutralised with a saturated sodium bicarbonate solution and extracted with ethyl acetate (4 × 20ml). The organic extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product (diastereomers) was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.5) to afford the product 1.20 g (88 %) as a white solid. Melting point 97-99 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.11 (m, 5H), 6.57 (s, 1H), 6.10 (s, 1H), 5.02 (s, 1H), 3.79 (s, 4H), 3.70 (s, 3H), 3.52 (s, 3H), 3.01 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.96, 147.76, 147.41, 143.87, 130.22, 129.04, 128.59, 127.84, 126.07, 111.31, 110.56, 62.85, 56.54, 55.89, 55.84, 52.18, 32.22.

(1*S*,3*S*)-methyl-2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (17)

To a stirred solution of **16** (1.5 g, 4.5 mmol) in acetonitrile (30 ml), potassium carbonate (1.5 eq.) and benzylbromide (1.1 eq.) was added. The reaction mixture was allowed to stir overnight at room temperature. Thereafter, water (30 ml) and ethyl acetate (30 ml) was added to the reaction. The organic layer separated and the aqueous layer extracted with ethyl acetate (3 × 20 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (20:80 EtOAc/Hexane, R_f 0.50) to afford the product 1.80 g (95 %) as a white solid. Melting point 146-148 ^{o}C. $[\alpha]^{20}_{D}$ 3.030 (*c* 0.10 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.7 Hz, 4H), 7.22 (ddt, J = 14.3, 12.9, 7.1 Hz, 6H), 6.65 (s, 1H), 6.30 (s, 1H), 4.75 (s, 1H), 3.92 (d, J = 14.2 Hz, 1H), 3.86 – 3.78 (m, 4H), 3.68 – 3.55 (m, 4H), 3.37 (s, 3H), 3.08 (dd, J = 15.3, 7.4 Hz, 1H), 2.88 (dd, J = 15.3, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.02, 147.81, 147.39,

143.22, 138.71, 129.63, 129.14, 129.12, 128.14, 127.98, 127.09, 126.98, 125.94, 111.44, 110.71, 64.79, 60.69, 59.07, 55.93, 55.90, 51.53, 30.55. IR (neat): 2944, 1729, 1511, 1152, 753, 699 cm^{-1}; HRMS calculated for $C_{26}H_{28}NO_4$ $[M + H]^{1+}$ 418.2018, found 418.2012.

(1*S*,3*S*)-*N*-benzhydryl-2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (18)

Derivative **17** (0.30 g) was dissolved in 10 % aqueous HCl (5.0 ml) and underwent microwave assisted hydrolysis for 2 hours at 120 ^oC. The reaction mixture was then concentrated *in vacuo*, co-evapourated with toluene to ensure all water had been removed and used for the next coupling reaction. The acid was dissolved (1.9 g, 4.7 mmol) was dissolved in DMF (15 ml) and THF (5.0 ml) followed by addition of HBTU (5.2 mmol), DIPEA (9.6 mmol) and diphenylmethanamine (5.2 mmol). The reaction mixture was then stirred at room temperature until no more starting material could be detected by TLC analysis (approximately 4 hours). The reaction mixture was poured into 30 volumes of chilled water; the mixture was then extracted thrice with ethyl acetate (20 ml). The extracts were dried over anhydrous Na_2SO_4 and then concentrated to dryness affording the crude product. This crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.6) to afford the product 2.50 g (92 %) as a brown oil. $[\alpha]^{20}_D$ -1.389 (c 0.24 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 1H), 7.37 – 7.13 (m, 15H), 6.99 – 7.12 (m, 6H), 6.78 (s, 1H), 6.41 (s, 1H), 6.23 (s, 1H), 4.84 (s, 1H), 3.92 (s, 3H), 3.80 (m, 1H), 3.72 (m, 4H), 3.50 (d, J = 13.4 Hz, 1H), 3.12 (dd, J = 17.3, 11.8 Hz, 1H), 3.02 (dd, J = 17.4, 5.5 Hz ,1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.59, 148.23, 147.75, 143.54, 138.48, 129.05, 128.93, 128.68, 128.14, 127.56, 127.39, 127.26, 126.58, 126.32, 124.74, 116.87, 112.00, 111.80, 62.73, 55.91, 55.90, 55.37, 52.20, 23.43. IR (neat): 3026, 1681, 1493, 1241, 751, 698 cm^{-1}. HRMS calculated for $C_{38}H_{37}N_2O_3$ $[M + H]^{1+}$ 569.2820, found 569.2799.

Representative procedure for the synthesis of TIQ based *N*-oxides.

The TIQ amide (0.50 g) was dissolved in dry methylene chloride (20 ml). Potassium carbonate (2.0 eq.) was added and the reaction cooled to -78 °C. Meta-chloroperbenzoic acid (*m*-CPBA, 1.2 eq.) was then added, and the reaction was allowed to stir at -78 °C for 3 hours. At this time, the reaction was allowed to warm to room temperature. After stirring for 2 hours at room temperature, methylene chloride (20 ml) was added to dilute the reaction and celite (200 mg) was added to aid filtration. The reaction was filtered, and methylene chloride concentrated to dryness affording the crude product which was purified by column chromatography.

(3*S*)-2-benzyl-3-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide (1)

The crude product was purified by column chromatography (10:90 MeOH/DCM, R_f 0.25) to afford the product 0.44 g (85 %) as a white solid. Melting point 146-148 ^oC. $[\alpha]^{20}_D$ 8.642 (*c*

0.27 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.49 – 7.10 (m, 8H), 6.96 (d, J = 7.4 Hz, 1H), 4.71 (d, J = 12.9 Hz, 1H), 4.59 (d, J = 12.9 Hz, 1H), 4.43 (d, J = 15.1 Hz, 1H), 4.34 – 4.20 (m, 2H), 4.03 (dd, J = 9.5, 5.1 Hz, 1H), 3.83 (dd, J = 17.1, 9.6 Hz, 1H), 3.23 (dd, J = 17.1, 5.0 Hz, 1H), 2.94 (d, J = 4.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.79, 132.59, 130.91, 130.19, 130.05, 129.35, 128.97, 128.83, 128.11, 127.83, 126.92, 126.76, 73.56, 70.08, 65.03, 30.15, 25.75. IR (neat): 2928, 1670, 1271, 736, 703 cm^{-1}. HRMS calculated for $C_{18}H_{21}N_2O_2$ $[M + H]^{1+}$ 297.1598, found 297.1592.

(3*S*)-2-benzyl-3-(benzylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide (2)

The crude product was purified by column chromatography (2:98 MeOH/DCM, R_f 0.20) to afford the product 0.50 g (96 %) as a white solid. Melting point 155-157 ^oC. $[\alpha]^{20}_D$ 10.00 (*c* 0.10 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.52 (dd, J = 7.1, 2.3 Hz, 2H), 7.47 – 7.11 (m, 12H), 6.94 (d, J = 7.3 Hz, 1H), 4.68 (d, J = 12.9 Hz, 1H), 4.61 – 4.38 (m, 4H), 4.21 (d, J = 15.0 Hz, 1H), 4.01 (dd, J = 9.9, 4.9 Hz, 1H), 3.92 – 3.76 (m, 1H), 3.24 (dd, J = 17.0, 4.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.28, 132.58, 130.19, 129.99, 129.42, 128.95, 128.71, 128.10, 127.80, 127.36, 126.91, 126.74, 73.64, 69.96, 65.28, 43.10, 30.18. IR (neat): 3031, 1671, 1542, 734, 700 cm-1. HRMS calculated for $C_{24}H_{25}N_2O_2$ $[M + H]^{1+}$ 373.1911, found 373.1919.

(3*S*)-3-(benzylcarbamoyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline 2-oxide (3)

The crude product was purified by column chromatography (5:95 MeOH/DCM, R_f 0.25) to afford the product 0.45 g (86 %) as a white solid. Melting point 108-110 ^oC. $[\alpha]^{20}_D$ -5.556 (*c* 0.18 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 7.43 – 7.13 (m, 9H), 7.02 (d, J = 7.1 Hz, 1H), 4.70 – 4.36 (m, 4H), 4.02 (dd, J = 10.1, 4.4 Hz, 1H), 3.78 (dd, J = 17.0, 10.3 Hz, 1H), 3.39 (s, 3H), 3.26 – 3.11 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.61, 137.99, 130.15, 128.82, 128.76, 128.70, 128.61, 128.30, 128.02, 127.87, 127.70, 127.66, 127.38, 127.09, 126.53, 126.23, 72.91, 69.92, 58.18, 43.60, 43.03, 30.14. IR (neat): 3029, 1670, 1544, 736, 699 cm^{-1}. HRMS calculated for $C_{18}H_{21}N_2O_2$ $[M + H]^{1+}$ 297.1634, found 297.1598.

(3*S*)-3-(benzhydrylcarbamoyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline 2-oxide(4)

The crude product was purified by column chromatography (2:98 MeOH/DCM, R_f 0.25) to afford the product 0.48 g (94 %) as a white solid. Melting point 157-158 ^oC. $[\alpha]^{20}_D$ -5.263 (*c* 0.19 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 11.74 (s, 1H), 7.05-7.40 (m, 18H) 6.86 (d, J = 7.4 Hz, 1H), 6.30 (d, J = 8.8 Hz, 1H), 4.59 – 4.31 (m, 3H), 4.15 (d, J = 14.7 Hz, 1H), 3.77 (dd, J = 16.9, 10.0 Hz, 1H), 3.19 (dd, J = 17.1, 4.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.35, 141.75, 141.50, 132.64, 130.05, 129.98, 128.91, 128.85, 128.67, 128.12, 127.90, 127.56, 127.50,

127.26, 127.07, 126.99, 126.74, 73.43, 65.39, 69.81, 56.83, 30.17. IR (neat): 2918, 1677, 1545, 749, 699 cm^{-1}. HRMS calculated for $C_{30}H_{29}N_2O_2$ $[M + H]^{1+}$ 449.2224, found 449.2250.

(3*S*)-2-benzyl-3-((*R*)-1-phenylethylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide (5)

The crude product was purified by column chromatography (2:98 MeOH/DCM, R_f 0.25) to afford the product 0.49 g (94 %) as a white solid. Melting point 163-165 ^oC. $[\alpha]^{20}_D$ 66.67 (*c* 0.12 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 11.29 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 6.5, 3.0 Hz, 2H), 7.52 – 7.29 (m, 7H), 7.29 – 7.03 (m, 4H), 6.94 (d, J = 7.2 Hz, 1H), 5.29 – 5.14 (m, 1H), 4.80 (d, J = 13.0 Hz, 1H), 4.64 (d, J = 13.0 Hz, 1H), 4.46 (d, J = 14.9 Hz, 1H), 4.18 (d, J = 15.0 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.86 – 3.68 (m, 1H), 3.17 (dd, J = 17.0, 4.8 Hz, 1H), 1.58 (dd, J = 18.6, 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.37, 143.31, 132.62, 130.22, 130.03, 129.52, 129.03, 128.70, 128.10, 127.72, 127.18, 126.87, 126.72, 126.05, 73.78, 69.76, 65.35, 48.83, 30.12, 22.92. IR (neat): 2924, 1671, 1540, 736, 699 cm^{-1}. HRMS calculated for $C_{25}H_{27}N_2O_2$ $[M + H]^{1+}$ 387.2084, found 387.2067.

(3*S*)-2-benzyl-3-((*S*)-1-phenylethylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide (6)

The crude product was purified by column chromatography (2:98 MeOH/DCM, R_f 0.25) to afford the product 0.50 g (96 %) as a white solid. Melting point 163-165 ^oC. $[\alpha]^{20}_D$ 66.67 (*c* 0.12 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 11.23 (d, J = 7.8 Hz, 1H), 7.52 – 7.25 (m, 10H), 7.29 – 7.11 (m, 5H), 6.95 (d, J = 7.3 Hz, 1H), 5.29 – 5.13 (m, 1H), 4.57 – 4.36 (m, 3H), 4.17 (d, J = 14.9 Hz, 1H), 3.87 (dd, J = 26.3, 9.9 Hz, 2H), 3.26 (dd, J = 16.4, 4.1 Hz, 1H) 1.58 (dd, J = 18.6, 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.41, 143.37, 132.55, 130.27, 129.88, 129.38, 128.86, 128.75, 128.11, 128.07, 127.77, 127.31, 126.87, 126.77, 126.32, 73.35, 69.82, 65.32, 48.95, 30.32, 22.55. IR (neat): 2924, 1671, 1540, 736, 699 cm^{-1}. HRMS calculated for $C_{25}H_{27}N_2O_2$ $[M + H]^{1+}$ 387.2084, found 387.2067.

(3*S*)-2-cyclohexyl-3-((*S*)-1-phenylethylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide (7)

The crude product was purified by column chromatography (3:97 MeOH/DCM, R_f 0.25) to afford the product 0.47 g (90 %) as a yellow oil. $[\alpha]^{20}_D$ -69.05 (*c* 0.14 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 10.57 (d, J = 8.5 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.35 (dd, J = 10.3, 4.8 Hz, 2H), 7.28 – 7.13 (m, 5H), 7.00 (d, J = 6.5 Hz, 1H), 5.14 (dd, J = 8.8, 7.1 Hz, 1H), 4.38 (d, J = 15.0 Hz, 1H), 4.21 (d, J = 15.1 Hz, 1H), 3.99 (d, J = 3.8 Hz, 1H), 3.93 – 3.79 (m, 1H), 3.22 – 3.08 (m, 1H), 2.72 (d, J = 11.7 Hz, 1H), 1.59 – 1.14 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.36, 143.47, 131.01, 128.67, 128.30, 127.96, 127.46, 127.22, 126.87, 126.80, 126.64, 76.70, 69.35, 60.60, 48.58, 30.54, 29.70, 28.04, 26.09, 25.52, 25.41, 25.26, 21.72. IR (neat): 2923, 1670, 1532, 1454, 739 cm^{-1}. HRMS calculated for $C_{24}H_{25}N_2O_2$ $[M + H]^{1+}$ 379.2367, found 379.2401.

(1*S*,3*S*)-3-(benzhydrylcarbamoyl)-2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline 2-oxide (8)

The crude product was purified by column chromatography (3:97 MeOH/DCM, R_f 0.25) to afford the product 0.25 g (50 %) as a white solid. Melting point 180-182 ^oC. $[\alpha]^{20}_D$ -100.00 (*c* 0.11 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 12.38 (d, J = 8.7 Hz, 1H), 7.43 (dd, J = 13.4, 7.3 Hz, 3H), 7.38 – 7.14 (m, 16H), 7.11 – 7.01 (m, 2H), 6.87 (s, 1H), 6.34 (d, J = 8.8 Hz, 1H), 6.16 (s, 1H), 4.90 (s, 1H), 4.32 (ddd, J = 29.1, 16.5, 9.7 Hz, 3H), 3.95 (s, 3H), 3.85 – 3.66 (m, 4H), 3.58 – 3.45 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.65, 149.48, 148.53, 142.42, 141.56, 135.21, 133.08, 132.90, 129.64, 129.49, 128.89, 128.65, 128.43, 128.07, 127.69, 127.45, 127.20, 127.07, 124.73, 123.62, 110.57, 109.89, 76.62, 66.04, 64.47, 57.28, 56.02, 56.00, 29.05. IR (neat): 2924, 1667, 1531, 1228, 696 cm^{-1}. HRMS calculated for $C_{38}H_{37}N_2O_4$ $[M + H]^{1+}$ 585.2856, found 585.2748.

General procedure for allylation reactions

To an oven dried schlenck tube purging with argon, the catalyst (0.03 mmol) followed by dry THF (1.0 ml) and the aldehyde (0.3 mmol) was added, thereafter 156 μl of DIPEA (3.0 eq.) followed by allyltrichlorosilane (3.6 mmol) was added. The reaction was sealed with a septum and kept under an argon atmosphere while stirring for 24 hours at room temperature (23 °C). To quench, saturated aqueous $NaHCO_3$ (1.0 ml) was then added and the reaction was vigorously stirred for 1 hour. The reaction was then extracted with ethyl acetate (2 × 5 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography and analyzed as described below. Chromatographs and retention times for all chiral products were comparable to the racemic samples. NMR data for all racemic samples synthesised were in agreement with previously reported data.

(*R*)-1-Phenyl-3-buten-3-ol (Table 3, entry 1)[17]

^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 5.82 (ddt, J = 17.2, 10.0, 7.2 Hz ,1H), 5.17 (dd, J = 17.2, 1.2 Hz, 1H), 5.15 (dd, J = 10.4, 1.2 Hz, 1H), 4.74 (dt, J = 6.4, 2.4 Hz, 1H), 2.58-2.6 (m, 2H), 2.06 (d, J = 2.8 Hz, 1H).

Optical purity was established by chiral HPLC analysis (Chiralpak IB, 99:1 Hexane:Isopropanol, 0.8 mL/min, λ = 220 nm.)

(*R*)-1-(4-methoxyphenyl)but-3-en-1-ol (Table 3, entry 2)[17]

^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H), 6.84 (t, J = 5.7 Hz, 2H), 5.87 – 5.65 (m, 1H), 5.18 – 4.94 (m, 2H), 4.62 (t, J = 6.6 Hz, 1H), 3.76 (s, 3H), 2.39 (ddd, J = 70.6, 14.1, 9.3 Hz, 2H).

Optical purity was established by chiral HPLC analysis (Chiralpak IB, 99:1 Hexane:Isopropanol, 0.8 mL/min, λ = 220 nm

(*R*)-1-(4-nitrophenyl)but-3-en-1-ol (Table 3, entry 3)[35]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 5.79 (d, J = 7.8 Hz, 1H), 5.20 (ddd, J = 11.1, 6.3, 1.0 Hz, 2H), 4.94 – 4.75 (m, 1H), 2.51 (ddd, J = 22.0, 10.1, 5.6 Hz, 2H), 2.13 (d, J = 71.3 Hz, 1H).

Optical purity was established by chiral HPLC analysis (Chiralpak IA, 97:3 Hexane:Isopropanol, 0.7 mL/min, λ = 220 nm.)

(*R*)-1-(4-chlorophenyl)but-3-en-1-ol (Table 3, entry 4)[17]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.06 (m, 4H), 5.93 – 5.62 (m, 1H), 5.28 – 4.91 (m, 2H), 4.75 – 4.52 (m, 1H), 2.46 (dt, J = 14.0, 6.5 Hz, 2H), 2.13 (s, 1H).

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 99:1 Hexane:Isopropanol, 0.7 mL/min, λ = 220 nm.)

(*R*)-1-(4-fluorophenyl)but-3-en-1-ol (Table 3, entry 5)[36]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, J = 8.4 Hz, 4H), 5.77 (qt, J = 52.1, 26.0 Hz, 1H), 4.92 (ddd, J = 97.4, 16.5, 8.8 Hz, 2H), 4.11 (d, J = 7.1 Hz, 1H), 2.58 (t, J = 32.0 Hz, 2H), 2.38 – 2.13 (m, 1H).

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 99:1 Hexane:Isopropanol, 0.8 mL/min, λ = 220 nm.)

(*S*)-1-(naphthalen-1-yl)but-3-en-1-ol (Table 3, entry 6)[17]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.75 (m, 4H), 7.59 (dt, J = 14.9, 7.1 Hz, 3H), 7.51 – 7.37 (m, 1H), 5.93 – 5.63 (m, 1H), 5.22 – 4.79 (m, 3H), 4.10 (q, J = 7.1 Hz, 1H), 2.25 (ddd, J = 42.5, 19.9, 16.0 Hz, 2H).

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 99:1 Hexane:Isopropanol, 0.8 mL/min, λ = 220 nm.)

(*S*)-1-(3,5-dimethoxyphenyl)but-3-en-1-ol (Table 3, entry 7)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 2.3 Hz, 2H), 6.70 (dd, J = 8.1, 5.9 Hz, 1H), 5.91 – 5.71 (m, 1H), 5.25 – 5.02 (m, 2H), 4.74 – 4.58 (m, 1H), 3.82 (d, J = 21.6 Hz, 6H), 2.49 (dd, J = 13.7, 6.7 Hz, 2H).

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 97:3 Hexane:Isopropanol, 0.7 mL/min, λ = 220 nm.)

(1*E*,3*S*)-1-phenylhexa-1,5-dien-3-ol (Table 3, entry 8)[17]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dddd, J = 13.7, 9.4, 5.2, 3.2 Hz, 5H), 6.59 (d, J = 15.9 Hz, 1H), 6.23 (dd, J = 15.9, 6.3 Hz, 1H), 5.96 – 5.76 (m, 1H), 5.24 – 5.07 (m, 2H), 4.34 (d, J = 6.3 Hz, 1H), 4.10 (q, J = 7.1 Hz, 1H), 2.41 (ddd, J = 14.5, 6.3, 4.3 Hz, 2H).

Optical purity was established by chiral HPLC analysis (Chiralpak IB, 90:10 Hexane:Isopropanol, 0.8 mL/min, λ = 220 nm.)

(1*E*,3*S*)-1-(4-methoxyphenyl)hexa-1,5-dien-3-ol (Table 5, entry 2)[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.51 (d, J = 15.9 Hz, 1H), 6.08 (dd, J = 15.9, 6.6 Hz, 1H), 5.94 – 5.73 (m, 1H), 5.14 (dd, J = 12.1, 11.3 Hz, 1H), 4.29 (d, J = 5.5 Hz, 1H), 4.10 (d, J = 7.1 Hz, 1H), 3.77 (s, 3H), 2.47 – 2.16 (m, 2H).

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 90:10 Hexane:Isopropanol, 0.8 mL/min, λ = 220 nm.)

(1*E*,3*R*)-1-(2-methoxyphenyl)hexa-1,5-dien-3-ol (Table 5, entry 3)

$[\alpha]^{20}_D$ -3.889 (*c* 1.2 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.5 Hz, 1H), 7.23 (dd, J = 14.3, 6.3 Hz, 1H), 6.98 – 6.79 (m, 3H), 6.26 (dd, J = 16.1, 6.6 Hz, 1H), 5.97 – 5.75 (m, 1H), 5.25 – 5.07 (m, 2H), 4.45 – 4.29 (m, 1H), 4.12 (q, J = 7.1 Hz, 1H), 3.83 (d, J = 10.3 Hz, 3H). HRMS calculated for $C_{13}H_{16}O_2$ $[M - H2O + H]^{1+}$ 187.1117, found 187.1172.

Optical purity was established by chiral HPLC analysis (Chiralpak IB, 97:3 Hexane:Isopropanol, 0.7 mL/min, λ = 220 nm.)

(1*E*,3*S*)-1-(4-nitrophenyl)hexa-1,5-dien-3-ol (Table 5, entry 4)[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.6 Hz, 1H), 8.18 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 1H), 7.52 (dd, J = 12.1, 10.0 Hz, 1H), 6.81 (dd, J = 16.1, 7.4 Hz, 1H), 6.71 (d, J = 16.0 Hz, 1H), 6.44 (dd, J = 15.9, 5.6 Hz, 1H), 5.98 – 5.72 (m, 1H), 5.30 – 5.11 (m, 2H), 4.43 (d, J = 5.8 Hz, 1H), 2.57 – 2.07 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.33, 132.27, 128.74, 126.91, 126.04, 125.30, 120.65, 118.19, 110.87, 72.29, 55.43, 42.04. IR (neat): 3418, 2931, 1489, 1243, 781 cm^{-1}

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 90:10 Hexane:Isopropanol, 0.65 mL/min, λ = 230 nm.)

(1*E*,3*S*)-1-(2-nitrophenyl)hexa-1,5-dien-3-ol (Table 5, entry 5)

$[\alpha]^{20}_D$ -5.556 (*c* 1.2 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 -7.93 (d, J = 8.2 Hz, 5H), 7.40 (t, J = 7.5 Hz, 1H), 6.22 (dd, J = 15.8, 6.0 Hz, 1H), 5.87 (dd, J = 17.0, 10.2 Hz, 1H), 5.31 – 5.13 (m, 2H), 4.95 (s, 1H), 4.42 (d, J = 6.3 Hz, 1H), 2.43 (dt, J = 13.9, 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.30, 133.82, 132.66, 131.14, 129.08, 128.15, 125.23, 118.87, 41.77,

36.86. IR (neat) : 3329, 2843, 1681, 1312, 737 cm^{-1}. HRMS calculated for $C_{12}H_{13}NO_3$ [M – C_3H_5 + H]$^{1+}$ 180.0655, found 180.1315.

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 90:10 Hexane:Isopropanol, 0.65 mL/min, λ = 230 nm.)

(1*E*,3*S*)-1-(4-bromophenyl)hexa-1,5-dien-3-ol (Table 5, entry 6)[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 1H), 7.43 – 7.29 (m, 2H), 7.24 (t, J = 7.0 Hz, 3H), 6.55 (d, J = 15.9 Hz, 1H), 6.23 (dd, J = 15.9, 6.1 Hz, 1H), 5.84 (ddd, J = 14.3, 10.1, 7.2 Hz, 1H), 5.29 – 5.03 (m, 2H), 4.35 (dd, J = 12.2, 6.1 Hz, 1H), 2.51 – 2.13 (m, 2H).

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 97:3 Hexane:Isopropanol, 0.60 mL/min, λ = 220 nm.)

(1*E*,3*S*)-1-(furan-2-yl)hexa-1,5-dien-3-ol (Table 5, entry 7)

$[\alpha]^{20}_D$ -0.909 (*c* 1.1 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 – 6.23 (m, 3H), 6.17 – 6.00 (m, 2H), 5.84 – 5.60 (m, 1H), 5.06 (dd, J = 14.2, 5.6 Hz, 2H), 4.21 (d, J = 5.3 Hz, 1H), 2.27 (qd, J = 14.3, 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.36, 141.97, 133.96, 130.18, 118.60, 118.56, 111.29, 108.09, 71.23, 41.97. IR (neat) : 3378, 2908, 1640, 1012, 733 cm^{-1}. HRMS calculated for $C_{10}H_{12}O_2$ [M + Na]$^{1+}$ 187.0729, found 187.1168.

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 90:10 Hexane:Isopropanol, 0.80 mL/min, λ = 220 nm.)

(*S*,*E*)-hepta-1,5-dien-4-ol (Table 5, entry 8)[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dddd, J = 34.5, 21.6, 11.6, 6.7 Hz, 2H), 5.51 (dd, J = 15.3, 6.8 Hz, 1H), 5.23 – 4.99 (m, 2H), 4.10 (dd, J = 12.5, 6.3 Hz, 1H), 2.44 – 2.11 (m, 5H).

Optical purity was established by chiral GC analysis (80 °C for 1 min, then 1 °C/min to 160 °C, 5 min at that temperature)

(1*E*,3*S*)-6-methylhepta-1,5-dien-4-ol (Table 5, entry 10)[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 5.92 – 5.67 (m, 1H), 5.28 – 4.93 (m, 3H), 4.38 (d, J = 8.1 Hz, 1H), 2.37 – 2.12 (m, 2H), 1.86 – 1.48 (m, 6).

Optical purity was established by chiral GC analysis (80 °C for 1 min, then 1 °C/min to 160 °C, 5 min at that temperature)

(1*E*,3*R*)-2-methyl-1-phenylhexa-1,5-dien-3-ol (Table 5, entry 11)[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (ddd, J = 19.9, 14.3, 7.6 Hz, 5H), 6.52 (s, 1H), 5.84 (d, J = 7.0 Hz, 1H), 5.16 (t, J = 14.0 Hz, 2H), 4.22 (s, 1H), 2.52 – 2.33 (m, 2H).

Optical purity was established by chiral HPLC analysis (Chiralpak AS-H, 90:10 Hexane:Isopropanol, 0.8 mL/min, λ = 220 nm.)

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SUPPORTING INFORMATION

See accompanying cd to this thesis.

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CHAPTER 4

Microwave-assisted synthesis of guanidine organocatalysts bearing a tetrahydroisoquinoline framework and their evaluation on the 1,4 Michael addition

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ABSTRACT

The simple and practical syntheses of a novel class of chiral guanidine organocatalysts and their evaluation in the asymmetric Michael addition reaction of malonates and β-ketoesters with nitro-olefins is reported. These organocatalysts are the first of its kind based on a tetrahydroisoquinoline framework. In addition, a new microwave assisted procedure of introducing the guanidine unit onto amino amide derivatives is included. The chiral products were obtained with quantitative chemical efficiency (up to 99 % yield) and excellent enantioselectivity (up to 97 % *ee*).

INTRODUCTION

The guanidine moiety has become well known in both chemistry and biology for its characteristic high pKa value and ability to form dual hydrogen bonds.[1-3] Therefore, this functional group has been an attractive target incorporated into several chiral catalysts used for both metal-ligand[4,5] and organocatalysis.[6,7] It has been successfully employed as both Brønsted base/acid and phase transfer catalysts for several important asymmetric reactions such as the

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Henry,[8] Strecker[9], Mannich, Diels-Alder, Michael and Claisen rearrangement.[7,10] As a result, the roles of guanidine-based catalysts are steadily increasing in asymmetric synthesis. Some excellent reviews on guanidine chemistry have emerged during the last decade.[2,3,5-7,10-18]

Amino acid based organocatalysts have arisen as versatile and efficient candidates that promote a wide range of enantioselective transformations.[19-22] The incorporation of naturally occurring α- amino acids as a source for chirality into guanidine organocatalysts however has not been widely investigated (Figure 1).[23-25] As illustrated only a few organocatalysts have taken advantage of including guanidines into readily available amino acids.

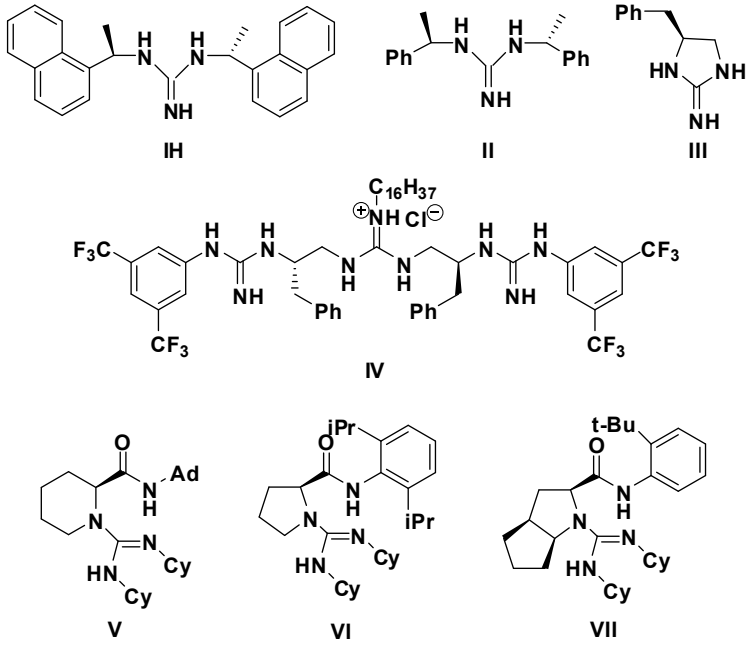


Figure 1. Examples of chiral guanidine organocatalysts derived from α-amino acids (I-II[23], IV[24] and V-VII[25]).

Furthermore, the amino acid based guanidine catalysts developed thus far are molecules that are prepared through nontrivial syntheses. Hence the development of a simple route to prepare other chiral guanidine's is still of great interest. We have set out to introduce a new class of easily accessible amino acid-based guanidine organocatalysts bearing a tetrahydroisoquinoline (TIQ) backbone.

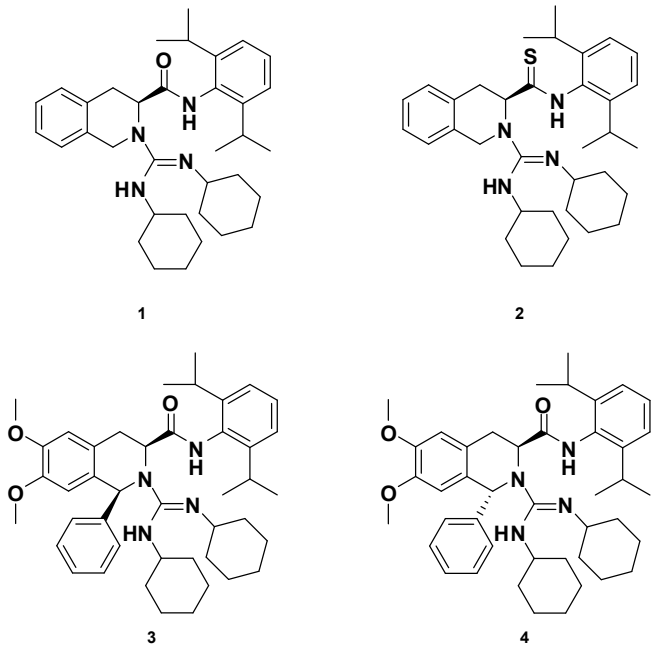


Figure 2. TIQ guanidine organocatalysts evaluated in this study.

This initiative was also partly encouraged by the observation that chiral pipecolic and pyrrole acid derived guanidines (Fig. 1) with an amide functional group (**V-VII)** have been shown to promote synthetically useful transformations such as the Michael addition[25] and Domino reaction.[26] The TIQ molecule and its derivatives have been extensively studied due to their biological and pharmaceutical properties.[27-29] However, it has been sparsely used as a source for chirality in asymmetric catalysis. Recently, we have made much progress with TIQ based ligands for catalytic asymmetric reactions such as: transfer hydrogenation of prochiral ketones[30], Henry reaction[31], hydrogenation of olefins[32], and expanded the potential of these TIQ derivatives as organocatalysts for the Diels-Alder reaction[33] and allylation of aldehydes.[34]

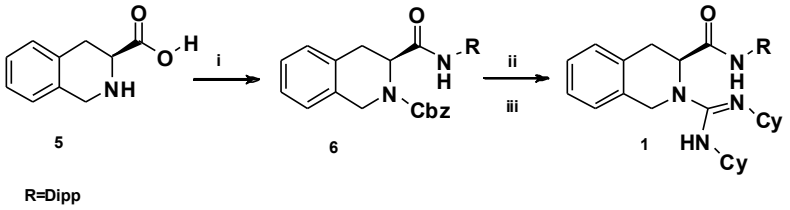
Herein, we report the microwave assisted synthesis and catalytic activity of TIQ-based guanidines that promote the asymmetric 1,4-addition of β-ketoesters or malonates to nitro-olefins in up to 97 % enantiomeric excess (*ee*). The catalysts are insensitive to moisture or oxygen and are easily prepared from commercially available starting materials in three straightforward steps with 90-95 % isolated yield.

RESULTS AND DISCUSSION

Catalyst Synthesis

As a preliminary study we chose the diisopropylphenyl (dipp) amide and dicyclohexylcarbodiimide (DCC) functional groups to be used on the TIQ skeleton. These moieties proved to be optimal when used by Feng *et al.* on pipecolic acid for application as an

organocatalyst for Michael addition reactions.[25] Catalyst **1** (Scheme 1) was synthesised in 95 % overall yield from commercially available tetrahydroisoquinoline amino acid **5** (phenylalanine derived).



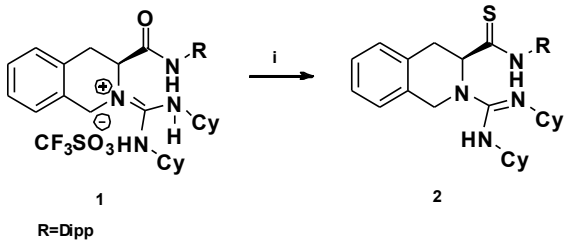
Scheme 1. Synthetic route to catalysts **1**: (i) $KHCO_3$, Cbz-Cl, dioxane/water *in situ* solvent evaporation DIPEA, ethyl chloroformate, diisopropylphenyl amine, dichloromethane, 0 °C-r.t, 12 hours; (ii) 10 wt.-% Pd/C, H_2 (1 atm), methanol, r.t, 1 hour; (iii) $Yb(OTf)_3$, DCC, microwave irradiation, toluene, 120 °C, 3hours.

The secondary amine **5** was protected by performing an *in situ* reaction with benzyl chloroformate (Cbz)[30] followed by amide bond formation with diisopropylamine to yield compound **6**. Thereafter the amide was deprotected through hydrogenation. This reaction was monitored by TLC until no starting material could be detected. Upon filtration of the palladium on carbon and evaporation of the solvent the product was used directly for the next step. In order to synthesize the guanidine unit, we applied the lithiation and subsequent addition of DCC procedure as done with pipecolic and pyrrole acid derivatives.[25] However even after several attempts, the reaction resulted in many side products and proved difficult to purify. Next we attempted the one pot procedure by Shen *et al.* which reported the catalytic use of $Yb(OTf)_3$ for the addition of carbodiimides to non-chiral amines under solvent free conditions utilising conventional heating.[35] However, low product yields (40 % isolated) and long reaction times (> 24 hours) led us to modify this procedure making use of microwave irradiation. Initially the reaction was carried out under neat conditions in the microwave (Table 1, entries 1-3). An increase in temperature resulted in higher yields of the product however for reactions greater than 100 °C charring of the reagents occurred. Next we investigated adding a solvent to the reaction mixture (Table 1, entries 4-6). Toluene proved to be optimal in the microwave at 120 °C for three hours (Table 1, entry 8) with a 95 % isolated yield. This is one of only few procedures employing microwave irradiation for guanidine attachment to chiral auxillaries.[36-38]

Table 1. Optimisation of microwave conditions for guanidine formation on TIQ derivatives.

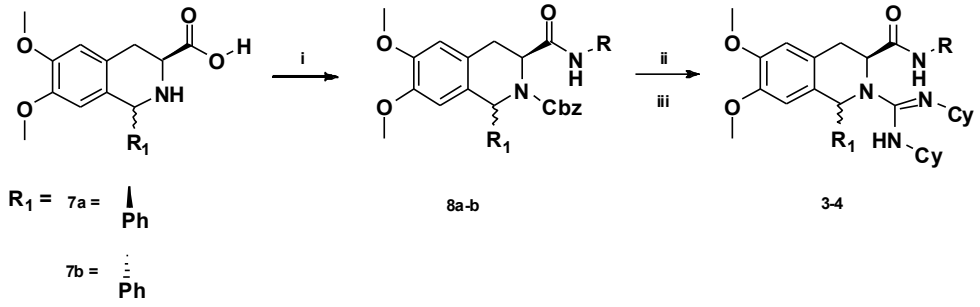
Entry	Solvent	Time (hours)	Temperature (°C)	Yield (%)
1	Neat	3	80	20
2	Neat	6	80	34
3	Neat	1	100	41
4	THF	1	80	35
5	CH_3CN	1	80	32
6	Toluene	1	80	40
7	Toluene	1	100	55
8	Toluene	3	120	95

A similar synthetic route (as that of catalyst 1) was followed for 2 except that the triflate salt of the final product was treated with Lawesson's reagent to yield the TIQ thioamide guanidine organocatalyst.



Scheme 2. Synthetic route to catalyst 2: (i) Lawesson's reagent, toluene, reflux, 12 hours.

We have previously reported the synthesis of both *cis* and *trans* substituted TIQ acid **7a-b**.[31,34] The *N*-Cbz protected acid was reacted with diisopropylamine to furnish the amide **8a-b**. The protecting group was then removed and the guanidine moiety was attached following the same microwave procedure as that for the unsubstituted organocatalysts to furnish compounds **3-4**.



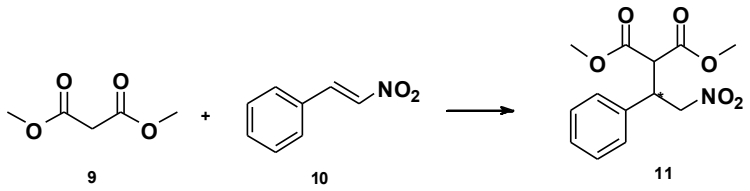
Scheme 3. Synthetic route to catalyst 3-4:(i) $KHCO_3$, Cbz-Cl, dioxane/water *in situ* solvent evaporation DIPEA, ethylchloroformate, diisopropylphenyl amine, dichloromethane, 0 °C-r.t, 12 hours; (ii) 10 wt.-% Pd/C, H_2 (1 atm), methanol, r.t, 1 hour; (iii) $Yb(OTf)_3$, DCC, microwave irradiation, toluene, 120 °C, 3 hours.

Notably, all compounds in Scheme 3 have a second chiral centre and could not be synthesized from a phenylalanine derivative since it was essential to employ the activated aromatic group **7a-b**(derived from L-DOPA) to facilitate the cyclization and in order to introduce the additional chiral group. Moreover, for catalysts **3-4**, a single diastereomer was observed from proton NMR after both coupling of the amide and carbodiimide groups.

Catalyst Evaluation

The TIQ guanidine organocatalysts was evaluated on the asymmetric 1,4 Michael addition reaction between dimethylmalonate (**9)** and nitrostyrene (**10)**. It has been shown in the literature that the appropriate choice of solvent was crucial for asymmetric induction.[18,25,39-41] Therefore catalyst **1** was tested in the most common solvents used for this type of asymmetric reaction (Table 2). The change in solvent had a noteworthy effect on the enantiomeric excess of the reaction product **11** (Table 2, entry 6).

Table 2. Michael addition between dimethylmalonate (**9**) and nitrostyrene (**10**) with catalyst **1** at 0 °C.



9 10 11

Entry	Solvent[a]	Yield (%)[b]	*ee* (%)[c,d]
1	Et_2O	93	21(*R*)
2	EtOAc	90	22(*R*)
3	THF	92	23(*R*)
4	DCM	90	5(*R*)
5	MeOH	99	2(*R*)
6	Toluene	99	45(*R*)
7	CH_3CN	95	3(*R*)

[a]Reactions were carried out by using 10 mol-% of the organocatalysts **1** for 12 hours. [b]Isolated yield after column chromatography.[c]Determined by chiral HPLC. [d]The configuration of the chiral product was established by the comparison of their HPLC retention times with the literature data.

Although moderate selectivity was observed, there was excellent reactivity to the Michael addition product **11**. Encouraged by these results we set out to modify our catalyst in the hope of increasing the enantiomeric excess. Feng and co-workers have reported that the amide hydrogen was imperative for both selectivity and conversion with their pipecolic

organocatalysts.[25] It has been shown in literature, for some organocatalysts in which the amide group played a significant role, that replacement of this group with a more acidic thioamide functionality could be beneficial.[42-44] Hence catalyst **2** was synthesised; however, this change decreased both selectivity and yield of the reaction product (Table 3, entry 2). This result indicated that the amide hydrogen was also important in our system for conversion and asymmetric induction.

Table 3. Michael addition between dimethylmalonate (**9**) and nitrostyrene (**10**) with catalysts **1-4** in toluene at 0 °C.

Entry	Catalyst[a]	Yield (%)[b]	*ee* (%)[c,d]
1	1	99	45
2	2	90	20
3	3	91	2
4	4	95	31

[a]Reactions were carried out by using 10 mol-% of the organocatalyst for 12 hours. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC. [d]The configuration of the chiral product was established by the comparison of their HPLC retention times with the literature data.

Next we looked at the X-ray crystal structure of catalyst **1** for further information on how the catalyst could be modified in order to enhance the enantiomeric excess as illustrated from the OLEX2 generated Figure 3.

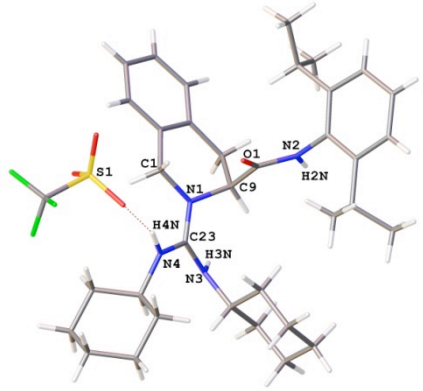


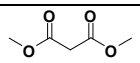
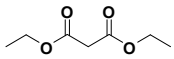
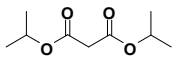
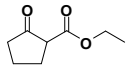
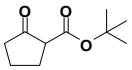
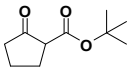
Figure 3. OLEX2[45]generated drawing of the X-ray structure of catalyst 1as the triflate salt(CCDC 860511).

It is evident from the crystal structures that the *N*-containing six membered ring assumes a half boat conformation with the guanidine moiety tilted downwards. It is synthetically possible to introduce a phenyl ring at the C1 atom in either the *cis* or *trans* position in hope that this would have an effect on the chiral induction of the catalyst. Derivatives **3-4** were synthesised and

tested, however marginal difference in enantiomeric excess was observed (Table 3, entries 3-4). It was optimal to proceed with catalyst **1** and toluene as the solvent of choice.

This new TIQ based organocatalyst **1** was extended by applying it to other malonates or β-ketoesters and nitrostyrene (Table 4, entries 1-6).

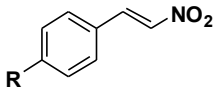
Table 4. Michael addition between different malonates or β-ketoesters and nitrostyrene (**10)** with catalyst **1** at 0 °C in toluene.

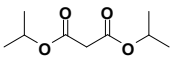
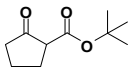
Entry	Substrate[a]	Yield (%)[b]	*ee* (%)[c,d]	Syn:Anti[c]
1		99	45(*R*)	-
2		99	50(*R*)	-
3		99	68(*S*)	-
4		99	63	99:1
5		99	78	99:1
6		99	82d	99:1

[a]Reactions were carried out by using 10 mol % of the organocatalyst **1** for 12 hours.[b]Isolated yield after column chromatography.[c] Determined by chiral HPLC. [d]The configuration of the chiral products was established by the comparison of their HPLC retention times with the literature data.[d]Reaction carried out at -15 °C, after 20 hours (further decrease of the temperature did not increase the selectivity).

All of the reactions proceeded with quantitative yields and reasonable increase in selectivities was observed. This illustrated that catalyst 1 could be applied to both linear and cyclic esters. The cyclic esters gave rise to chiral products containing an additional stereogenic centre with excellent diasteromeric ratios (Table 4, entries 4-6). The tert-butyl 2-oxocyclopentanecarboxylate ester gave the highest selectivity (Table 4, entry 6) at -15 °C. It was then decided to vary the nitro-olefin for both diisopropyl malonate and tert-butyl 2-oxocyclopentanecarboxylate ester (Table 5).

Table 5. Michael addition between diisopropyl malonate or *tert*-butyl 2-oxocyclopentanecarboxylate ester and different nitrostyrene derivatives with catalyst **1** at -15 °C in toluene.



Entry	Substrate[a]	R	Yield (%)[b]	*ee* (%)[c,d]	Syn:Anti[c]
1		H	99	73(*S*)	-
2		Me	94	92(*S*)[e]	-
3		NO_2	92	77(*S*)[e]	-
4		OMe	85	97(*S*)[e]	-
5		H	99	82	99:1
6		Me	99	71	99:1
7		NO_2	95	72	96:4
8		OMe	82	60	97:3

[a]Reactions were carried out by using 10 mol-% of the organocatalyst **1** after 20 hours. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC. [d]The configuration of the chiral product was established by the comparison of their HPLC retention times with the literature data. [e]The absolute configuration was arbitrarily assigned based on the sign of the optical rotation for known diisopropyl 2-(2-nitro-1-phenylethyl)malonate (Entry 1).

Nitro-olefins including electron-withdrawing and -donating group substituents on the aryl ring of nitrostyrene were employed with both linear and cyclic esters (Table 5). All substrates displayed very good conversions. A decrease in activity for both ester systems was observed when 4-OMe was used as the substituent on the nitro-olefin suggesting electronics plays a role in this substrate's reactivity. For linear diisopropyl malonate substrate, in general, an increase of electron density from the 4- position of the aryl ring on the nitro-olefin resulted in an increase in stereoselectivity. However this effect appears less pronounced when the *tert*-butyl 2-oxocyclopentanecarboxylate ester was employed. The best result observed from all of the substrates screened was with diisopropyl malonate and 4-OMe-nitrosytrene and (85 % yield, 97 % *ee*).

CONCLUSIONS

We have identified a novel class of TIQ based guanidine organocatalysts that promotes the enantioselective Michael addition of malonates and β-ketoesters with nitro-olefins. The catalysts are easily prepared from commercially available substrates and are insensitive to moisture or oxygen. Furthermore, a new microwave assisted procedure of introducing the guanidine unit on to amino amide derivatives is reported. The chiral products were obtained with quantitative chemical efficiency up to 99 % yield and excellent enantioselectivity up to 97 % *ee*. Further studies of this class of organocatalysts are ongoing in our laboratory.

EXPERIMENTAL SECTION

Reagents and solvents were purchased from Aldrich, Merck or Fluka suppliers. All solvents were dried prior to use according to standard procedures. All NMR spectra were recorded on a Bruker AVANCE III 400 MHz instrument. Chemical shifts are expressed in ppm relative to $CDCl_3$ and coupling constants are reported in Hz. NMR spectra were obtained at room temperature. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using Silica gel 60 mesh. All solvents were dried using standard procedures. All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded on a Perkin Elmer Polarimeter. Microwave assisted reactions were carried out on a CEM Discover SP system.All melting points are uncorrected. High resolution mass spectrometric data was obtained using a Bruker microTOF-Q II instrument. The enantiomeric excess of the chiral products were determined on a Shimadzu Prominence HPLC with either a Chiralpak IA or IB column.

Representative procedure for the Cbz protection and synthesis of TIQ based amides

To a solution of TIQ carboxylic acid (1.0 g) in dioxane (20 mL) and water (10 mL) at 0 °C a solution of potassium hydrogen carbonate (5.0 eq.) was added dropwise for 15 minutes followed by addition of Cbz-Cl (1.1 eq.). The solution was stirred for 1.5 hours at 0 °C and then at ambient temperature for a further 1.5 hours. The reaction was monitored with LC-MS (by neutralizing the reaction mixture with 10 % HCl and extraction with ethyl acetate). The solvent was evaporated under reduced pressure and dried under high vacuum. The solid *N*-Cbz TIQ acid product (2.0 g) was dissolved in dichloromethane (20 mL), *N,N*-diisopropylethylamine (DIPEA, 1.5 eq.) and ethyl chloroformate (1.5 eq.) was added at 0 °C. After 1 hour, the diisopropylamine (1.1 eq.) was added and stirred at ambient temperature for 18 h. Completion of the reaction was

monitored by TLC. The reaction mixture was washed with saturated sodium hydrogen carbonate (20 mL) followed by brine (10 mL). The organic layer was separated, dried over anhydrous magnesium sulfate and purified through using silca gel column chromatography using hexane/ethyl acetate as themobile phase.

Representative procedure for deprotection of Cbz and guanidine formation

A solution of the *N*-Cbz protected TIQ amide (1.0 g) in MeOH (20 mL) was added to a suspension of activated 10 wt.-% Pd/C (250 mg) in MeOH (5 mL). The mixture was supplied with H_2 under atmospheric pressure and stirred at room temperature for 1 hour. The reaction was monitored with TLC in hexane/ethyl acetate as the mobile phase. The Pd/C was filtered through a celite pad and washed with methanol (20 mL). The filtrate was then evaporated under reduced pressure affording the deprotected TIQ amide derivatives. In a 10 mL microwave vessel, the TIQ amide (300 mg) was dissolved in toluene (5 mL) and $Yb(OTf)_3$ (0.4 eq.) and DCC (1.1 eq.) was added. The vessel was then placed in the microwave reactor and heated to 120 °C for 3 hours. The toluene was then evaporated under reduced pressure and the residue passed through a short plug of silica with 50:50 hexane/ethyl acetate (100 mL) as the mobile phase. The solvent was then evaporated under reduced pressure and dissolved in a minimum amount of ethyl acetate and left in the refrigerator overnight. This mixture was then filtered and the filtrate evaporated under reduced pressure to yield a residue that was purified through using silica gel column chromatography using hexane/ethyl acetate as the mobile phase. The white foam product (triflate salt) was dissolved in dichloromethane and an equal amount of saturated aqueous NaOH was added in a separation flask which was shaken for 2 minutes. The organic phase was dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure to yield solids for all TIQ guanidine organocatalysts.

(*S*)-benzyl3-(2,6-diisopropylphenylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6)

The crude product was purified by column chromatography (30:70 EtOAc/Hexane, R_f 0.40) to afford the product (51 %) as a yellow solid. Melting point 60-62 °C. $[\alpha]^{20}_D$-11.32 (*c* 0.53 in $CHCl_3$). (NMR spectra are reported for a mixture of two rotamers due to the Cbz group).[30,46] ^{1}H NMR (400 MHz, CDCl3) δ 7.52 – 6.93 (m, 12H), 5.58 – 5.00 (m, 3H), 4.93 – 4.52 (m, 2H), 3.53 (m, 1H), 3.12 (m, 1H), 1.22 (m, 2H), 0.88 (m, 12H).^{13}C NMR (101 MHz, $CDCl_3$)): δ 170.6, 146.1, 132.6, 128.7, 128.4, 127.9, 123.2, 68.2, 56.6, 45.9, 32.2, 28.2, 23.6; IR ν_{max}/cm^{-1} (neat): 3280, 1643, 1547, 1453, 1222, 1029, 963, 755, 694;IR (neat) : 3280, 1643, 1547, 1453, 1222, 1029, 963, 755, 694cm^{-1}. HRMS calculated for $C_{30}H_{35}N_2O3$ $[M + H]^{1+}$471.2642, found 471.2639.

(1*S*,3*S*)-benzyl3-(2,6-diisopropylphenylcarbamoyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate (8a)

The crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.55) to afford the product (55 %) as a yellow oil.$[\alpha]^{20}_D$-5.26 (*c* 0.19 in $CHCl_3$). (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 6.69 (m, 16), 6.63 (s, 1H), 6.30-6.11 (s, 0.5H), 5.49 (m, 0.5H), 5.26 – 4.85 (m, 2.3H), 4.52 – 4.28 (m, 0.5H), 3.92 – 3.68 (m, 8H), 3.32 – 2.75 (m, 2H), 1.35 – 1.01 (m, 12H).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.36, 156,13, 148.98, 148.90, 146.40, 141.01, 135.71, 129.46, 128.72, 128.65, 128.58, 127.85, 127.82, 126.95, 125.71, 125.37, 125.21, 123.45, 123.34, 123.26, 110.87,110.01, 110.46, 68.35, 68.02, 60.11, 59.55, 58.45, 57.88, 56.15, 56.09, 55.77, 53.65, 31.00, 27.99, 23.93, 23.58, 22.95.IR (neat) : 3298, 2962, 1688, 1513, 1224, 698 cm^{-1}. HRMS calculated for $C_{24}H_{25}N_2O$ $[M + H]^{1+}$607.3166, found 607.3215.

(1*R*,3*S*)-benzyl3-(2,6-diisopropylphenylcarbamoyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate (8b)

The crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.55) to afford the product (58 %) as a yellow oil. $[\alpha]^{20}_D$+8.19 (*c* 0.23 in $CHCl_3$). (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 6.69 (m, 16), 6.63 (s, 1H), 6.30-6.11 (s, 0.5H), 5.49 (m, 0.5H), 5.26 – 4.85 (m, 2.3H), 4.52 – 4.28 (m, 0.5H), 3.92 – 3.68 (m, 8H), 3.32 – 2.75 (m, 2H), 1.35 – 1.01 (m, 12H).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.36, 156,13, 148.98, 148.90, 146.40, 141.01, 135.71, 129.46, 128.72, 128.65, 128.58, 127.85, 127.82, 126.95, 125.71, 125.37, 125.21, 123.45, 123.34, 123.26, 110.87,110.01, 110.46, 68.35, 68.02, 60.11, 59.55, 58.45, 57.88, 56.15, 56.09, 55.77, 53.65, 31.00, 27.99, 23.93, 23.58, 22.95.

(*S*,*E*)-2-(*N*,*N'*-dicyclohexylcarbamimidoyl)-N-(2,6-diisopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide(1)

The crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.20) to afford the product (95 %) as a whitesolid. Melting point 82-83°C.$[\alpha]^{20}_D$ -70.71 (*c* 0.66 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 7.32 – 6.72 (m, 8H), 4.98 (s, 1H), 4.43 (q, J = 16.5 Hz, 2H), 3.42 (t, J = 13.3 Hz, 1H), 2.88 (m, 5H), 1.92 – 1.32 (m, 12H), 1.32 – 0.55 (m, 20H).^{13}C NMR (101 MHz, $CDCl_3$) δ 170.25, 158.55, 145.84, 131.69, 131.31, 130.08, 128.48, 128.36, 127.98, 127.48, 126.04, 123.37, 122.01, 118.83, 77.36, 77.04, 76.72, 57.54, 55.56, 48.89, 33.52, 33.20, 32.43, 29.70, 28.75, 28.49, 25.08, 24.81, 23.62.IR (neat) : 2926, 2853, 1613, 799cm-^{1}. HRMS calculated $C_{35}H_{51}N_4O$ $[M + H]^{1+}$543.4059, found 543.4057.

(*S*,*E*)-2-(*N*,*N*′-dicyclohexylcarbamimidoyl)-N-(2,6-diisopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carbothioamide (2)

The triflate salt (white foam) of compound **1** (0.1g, 0.3 mmol) was dissolved in dry toluene (20 mL) and Lawesson's reagent (0.5 eq., 0.06 g) was added under a nitrogen atmosphere. The mixture was gently refluxed under nitrogen for 12 hours. Thereafter the solvent was evaporated under reduced pressure to yield a residue that was purified through using silca gel column chromatography, (50:50 EtOAc/Hexane, R_f 0.15) to afford the product (92 %) as a yellow solid. Melting point 100-102 °C. $[\alpha]^{20}_D$ -100.00 (*c* 0.20 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 6.67 (m, 8H), 5.15 (s, 1H), 4.37 (s, 2H), 4.00 (d, J = 16.2 Hz, 1H), 3.18 – 2.67 (m, 6H), 2.32 – 1.95 (m, 4H), 1.61 (t, J = 42.6 Hz, 10H), 1.36 – 0.84 (m, 18H).^{13}C NMR (101 MHz, $CDCl_3$) δ 143.91, 132.77, 128.96, 127.25, 126.92, 125.36, 125.14, 123.40, 123.12, 77.33, 59.73, 54.73, 46.85, 35.35, 34.17, 31.93, 30.93, 28.73, 28.52, 25.42, 25.06, 24.88, 24.43, 24.34, 23.57, 23.13.IR (neat) : 3302, 2924, 1651, 1651, 1494, 743, 698 cm-1. HRMS calculated for $C_{35}H_{51}N_4S$ $[M + H]^{1+}$ 559.3829, found 559.3840.

(1*S*,3*S*)-2-((*E*)-*N*,*N*′-dicyclohexylcarbamimidoyl)-N-(2,6-diisopropylphenyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (3)

The crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.20) to afford the product (90 %) as a white solid. Melting point 100-103 °C. $[\alpha]^{20}_D$ -44.09 (*c* 0.93 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.29 – 6.88 (m, 9H), 6.60 (s, 1H), 6.33 (s, 1H), 6.16 (s, 1H), 4.58 (s, 1H), 3.85 – 3.46 (m, 7H), 3.34 (d, J = 10.0 Hz, 2H), 3.13 (s, 1H), 2.80 (d, J = 32.8 Hz, 2H), 1.70 – 0.86 (m, 16H).^{13}C NMR (101 MHz, $CDCl_3$) δ 173.08, 153.99, 147.87, 147.54, 146.29, 146.13, 145.70, 131.45, 129.59, 129.17, 127.81, 127.69, 126.66, 124.67, 123.12, 111.56, 110.76, 59.94, 58.93, 55.79, 55.68, 53.36, 49.10, 36.34, 34.50, 34.05, 33.96, 32.48, 28.67, 28.09, 25.98, 25.74, 25.63, 25.38, 24.95, 24.78, 24.07, 23.35, 22.74.IR (neat) : 3349, 2926, 2852, 1629, 1254, 699 cm-1. HRMS calculated for $C_{43}H_{59}N_4O_3$ $[M + H]^{1+}$ 679.4582, found 679.4564.

(1*R*,3*S*)-2-((*E*)-*N*,*N*′-dicyclohexylcarbamimidoyl)-N-(2,6-diisopropylphenyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (4)

The crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f 0.20) to afford the product (95 %) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.34 – 6.82 (m, 9H), 6.60 (s, 1H), 6.33 (s, 1H), 6.18 (s, 1H), 4.59 (s, 1H), 3.87 – 3.43 (m, 7H), 3.29 (d, J = 63.6 Hz, 2H), 3.13 (s, 1H), 2.80 (d, J = 20.6 Hz, 2H), 1.59 – 0.86 (m, 17H).^{13}C NMR (101 MHz, $CDCl_3$) δ 173.01, 154.06, 147.90, 147.59, 146.30, 146.12, 145.65, 131.44, 129.53, 129.12, 128.23, 127.82, 127.75, 126.72, 124.62, 124.47, 123.98, 123.45, 123.13, 119.09, 111.55, 110.75,

59.99, 58.98, 55.80, 55.71, 53.39, 36.29, 34.47, 34.02, 32.50, 31.93, 31.44, 30.20, 28.66, 28.10, 25.95, 25.70, 25.36, 24.96, 24.75, 24.03, 23.40.

General procedure for Micheal addition reactions

To a 10 mL microwave vial, the catalyst (0.02 mmol) followed bytoluene(1.0 mL) and the nitro-olefin (0.20 mmol) was added, thereafter the malonate (0.20mmol.) was added. The reaction was kept at the specified temperature while stirring for 12 hours (or some cases 20 hours). The toluene was directly evaporated under vaccum and resulting residue was purified by silica gel chromatography (40:60 Et_2O/Hexane) and analyzed as described below. NMR data and retention times for all chiral products were in agreement to the racemic samples or previously reported literature data. Chiral products are listed in order of how it has been reported in the Tables 2-5.

(*R*)-dimethyl 2-(2-nitro-1-phenylethyl)malonate

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.38 (5H, m),4.92 (1H, dd, J = 13.0, 5.7 Hz), 4.89 (1H, dd, J = 13.0, 8.6 Hz), 4.25 (1H, td, J = 8.6, 5.7 Hz), 3.87 (1H, d, J = 8.6 Hz), 3.77 (3H, s), 3.56 (3H, s). The *ee* was determined by HPLC analysis using a chiralpak IA column, hexane/2-propanol 90:10, flow rate = 0.9 mL/min 210 nm (major enantiomer 15.2 min and minor enantiomer 20.0 min).

(*R*)-diethyl 2-(2-nitro-1-phenylethyl)malonate

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.36 (5H, m), 4.95 (1H, dd, J = 13.1, 5.3 Hz), 4.87 (2H, dd, J = 13.1, 8.1 Hz), 4.17-4.34 (3H, m), 4.01 (2H, q, J = 7.2 Hz), 3.83 (1H, d, J = 9.5 Hz), 1.27 (3H, t, J = 1.2 1.05 Hz), (3H, t, J = 7.2 Hz). The *ee* was determined by HPLC analysis using a chiralpak IA column, hexane/2-propanol 90:10, flow rate = 0.9 mL/min 210 nm (major enantiomer 12.8 min and minor enantiomer 16.8 min).

(*R*)-diisopropyl 2-(2-nitro-1-phenylethyl)malonate

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.35 (5H, m), 5.09 (1H, septet, J = 6.2 Hz), 4.93 (1H, dd, J = 12.7, 9.5 Hz), 4.84 (1H, dd, J = 12.7, 9.5 Hz), 4.82 (1H, septet, J = 6.2 Hz), 4.21 (1H, td, J = 9.5, 4.9 Hz), 3.76 (1H, d, J = 9.5 Hz), 1.24 (6H, d, J = 6.2 Hz), 1.07 (3H, d, J = 6.2 Hz), 1.02 (3H, d, J = 6.2 Hz). The *ee* was determined by HPLC analysis using a chiralpak IA column, hexane/2-propanol 90:10, flow rate = 0.9 mL/min 210 nm (major enantiomer 11.4 min and minor enantiomer 24.0 min).

ethyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.32 (m, 5H), 4.75-4.87 (m, 2H), 4.11-4.20 (m,3H), 4.02 (q, J=6.8 Hz, 1H), 3.83 (d, J=9.6 Hz, 1H), 1.25 (t, J=7.2 Hz, 3H), 1.05 (t, J=7.2 Hz,3H). The *ee* was

determined by HPLC analysis using a chiralpak IB column, hexane/2-propanol 95:5, flow rate = 0.9 mL/min 210 nm (syn; major enantiomer11.9 min and minor enantiomer 24.5 min).

***tert*-butyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.24 (m, 5 H), 5.16 (dd, J = 13.44, 3.76 Hz, 1 H), 4.98 (dd, J = 13.28, 11.16 Hz, 1 H), 4.04 (dd, J = 11.12, 3.72 Hz, 1 H), 2.38-2.25 (m, 2 H), 2.02-1.74 (m, 4 H), 1.44 (s, 9 H) ppm. The *ee* was determined by HPLC analysis using a chiralpak IA column, hexane/2-propanol 99:1, flow rate = 0.9 mL/min 210 nm (syn; major enantiomer12.8 min and minor enantiomer 15.1 min).

diisopropyl 2-(2-nitro-1-p-tolylethyl)malonate

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (s, 1H), 7.01 (m, 3H), 5.01 (q, J = 6.64, 12.611,1H), 4.80 (m, , 3H), 4.09 (m, 1H), 3.66 (d, J = 8.77, 1H), 2.10 (s, 3H), 1.17 (m, 6H), 0.98 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.1, 133.2, 129.5, 127.9, 78.10, 69.8, 69.4, 55.3, 42.5, 21.6, 21.4, 21.3, 21.2. The *ee* was determined by HPLC analysis using a chiralpak IA column, hexane/2-propanol 90:10, flow rate = 0.9 mL/min 210 nm (major enantiomer 24.9 min and minor enantiomer 23.5 min).

diisopropyl 2-(2-nitro-1-(4-nitrophenyl)ethyl)malonate

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (d, J = 8.75 Hz, 2H), 7.48 (d, J = 8.75 Hz, 2H), 5.10 (q, J = 6.06, 12.12 Hz, 1H), 4.92 (m, 3H), 4.35 (m, 1H), 3.78 9d, J= 9.3 Hz, 1H), 1.26 (m, 6H), 1.10 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.0, 143.9, 137.4, 129.5, 124.2, 70.4, 70.2, 54.6, 42.5, 21.5, 21.4,21.36, 21.33. The *ee* was determined by HPLC analysis using a chiralpak IA column, hexane/2-propanol 90:10, flow rate = 0.9 mL/min 210 nm (major enantiomer 18.6 min and minor enantiomer 17.4 min).

diisopropyl 2-(1-(4-methoxyphenyl)-2-nitroethyl)malonate

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, J = 8.36 Hz, 2H), 6.75 (d, J = 8.36 Hz, 2H), 5.10 (q, J = 7.76, 13.5 Hz, 1H), 4.77 (m, 3H), 4.08 (m, 1H), 3.69 (s, 3H), 3.65(d, J= 9.52 Hz, 1H), 1.16 (m, 6H), 0.99 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.5, 142.1, 136.6, 129.3, 114,26, 78.2, 69.8, 69.5, 55.3, 55.2, 21.6, 21.4, 21.34, 21.32. The *ee* was determined by HPLC analysis using a chiralpak IA column, hexane/2-propanol 90:10, flow rate = 0.9 mL/min 210 nm (major enantiomer 11.1 min and minor enantiomer 9.7 min).

***tert*-butyl 1-(2-nitro-1-p-tolylethyl)-2-oxocyclopentanecarboxylate**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18-7.16 (m, 2 H), 7.12-7.10 (m, 2 H), 5.16 (dd, J = 13.28, 3.76 Hz, 1 H), 4.97 (dd, J = 13.32, 11.20 Hz, 1 H), 4.03 (dd, J = 11.16, 3.76 Hz, 1 H), 2.32 (s, 3 H), 2.38-2.29 (m, 3 H), 2.02-1.77 (m, 4 H), 1.47 (s, 9 H) ppm. The *ee* was determined by HPLC

analysis using a chiralpak IB column, hexane/2-propanol 98:2, flow rate = 1.0 mL/min 210 nm (syn; major enantiomer 12.0 min and minor enantiomer 16.9 min).

***tert*-butyl1-(2-nitro-1-(4-nitrophenyl)ethyl)-2-oxocyclopentanecarboxylate**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19-8.17 (m, 2 H), 7.59-7.55 (m, 2 H), 5.23 (dd, J = 13.84, 3.56 Hz, 1 H), 5.02 (dd, J = 13.84, 11.20 Hz, 1 H), 4.09 (dd, J = 11.20, 3.56 Hz, 1 H), 2.49-2.40 (m, 1 H), 2.34-2.25 (m, 1 H), 2.14-1.84 (m, 4 H), 1.44 (s, 9 H) ppm. The *ee* was determined by HPLC analysis using a chiralpak IB column, hexane/2-propanol 95:5, flow rate = 1.0 mL/min 254 nm (syn; major enantiomer 22.9 min and minor enantiomer 49.5 min).

***tert*-butyl1-(1-(4-methoxyphenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.21 (m, 2 H), 6.86-6.82 (m, 2 H), 5.14 (dd, J = 13.20, 3.80 Hz, 1 H), 4.95 (dd, J = 13.20, 11.28 Hz, 1 H), 3.93 (dd, J = 13.20, 3.80 Hz, 1 H), 3.79 (s, 3 H), 2.39-2.29 (m, 2 H), 2.02-1.77 (m, 4 H), 1.47 (s, 9 H) ppm. The *ee* was determined by HPLC analysis using a chiralpak IB column, hexane/2-propanol 95:5, flow rate = 1.0 mL/min 210 nm (syn; major enantiomer 9.2 min and minor enantiomer 10.1 min).

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SUPPORTING INFORMATION

See accompanying cd to this thesis.

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CHAPTER 5

CRYSTALLOGRAPHIC PAPERS

DESCRIPTION

This chapter is a collection of all X-ray crystal structures that were published from novel compounds synthesized pertaining to Chapters **2-4** and were published in either journal *i.e* Acta Crystallographica Section C or Acta Crystallographica Section E. It must be noted that only the title page and comment section of each paper is included. For further supplementary information on these papers please refer to the copies that are on the cd accompanying this thesis. This chapters contains 15 published crystal structures (excluding the 2 crystals currently submitted) while Chapters **3-4** contain 3 other X-ray crystal structures.

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Optically active diaryl tetrahydroisoquinoline derivatives

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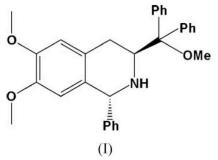
In (1*R*,3*S*)-6,7-dimethoxy-3-(methoxydiphenylmethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, $C_{31}H_{31}NO_3$, (I), and (1*R*,3*S*)-2-benzyl-3-[diphenyl(trimethylsiloxy)methyl]-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline, $C_{40}H_{43}NO_3Si$, (II), the absolute configurations have been confirmed to be *R* and *S* at the isoquinoline 1- and 3-positions, respectively, by NMR spectroscopy experiments. Both structures have monoclinic ($P2_1$) symmetry and the N-containing six-membered ring assumes a half-chair conformation. The asymmetric unit of (I) contains one molecule, while (II) has two molecules within the asymmetric unit. These structures are of interest with respect to the conformation around the exocyclic C—C bond: (I) displays an *ap* (antiperiplanar) conformation, while (II) displays an *sc-exo* (synclinal) conformation around this bond. These conformations are significant for stereocontrol when these compounds are used as catalysts. Various C—H$\cdots\pi$ and C—H$\cdots$O bonds link the molecules together in the crystal structure of (I). In the crystal structure of (II), three intermolecular C—H$\cdots\pi$ hydrogen bonds help to establish the packing.

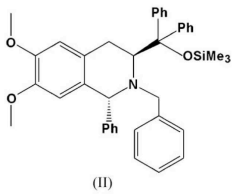
Comment

The tetrahydroisoquinoline (TIQ) molecule and its derivatives have been widely investigated due to their biological and pharmaceutical properties. Given our recent success with TIQ-based ligands for catalytic asymmetric transfer hydrogenation of prochiral ketones, Henry reactions and hydrogenation of olefins (Peters *et al.*, 2010). We decided to investigate the potential of TIQ derivatives as organocatalysts. Compound (I) has recently been synthesized and evaluated as a novel iminium-activated organocatalyst in an asymmetric Diels–Alder reaction (Naicker, Petzold *et al.*, 2010). Compound (II) is novel and is the precursor to the same class of organocatalysts based on a (1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline backbone.

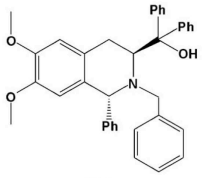
Derived from commercially available L-DOPA, the absolute stereochemistry of (I) and (II) was confirmed to be *R* and *S* at the C1 and C9 positions by ^{1}H NMR, as shown in Figs. 1 and 2, respectively.



(I)



(II)



(III)

Both structures have monoclinic ($P2_1$) symmetry. Compound (I) has a single molecule in the asymmetric unit, while (II) has two molecules within the asymmetric unit. Molecule (I) has a methyl group at the O3 position, whilst (II) has a trimethylsilyl group in this position. In addition, (II) has a benzyl group on the N atom.

In the structure of (I), intermolecular C—H$\cdots\pi$ and C—H$\cdots$O interactions involving atoms O1 and O2 link the molecules into extended chains which run parallel to the *b* axis (Table 1 and Fig. 3). In the chain, the molecules are arranged so that their tails, linked by the C—H$\cdots$O interactions, point towards the core of the chain and their heads protrude to the outer edges of the chain, with adjacent molecules alternating from side-to-side. The C—H$\cdots\pi$ interactions link the heads of those molecules lying on the same side of the chain core.

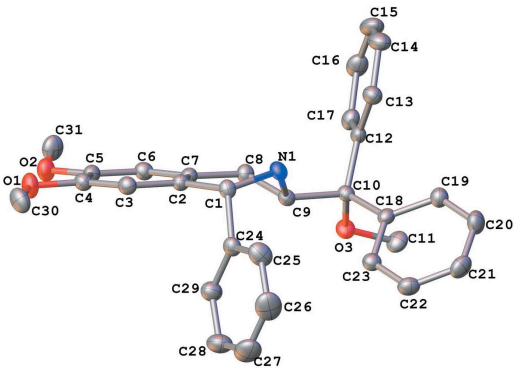


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

  doi:10.1107/S0108270110053357

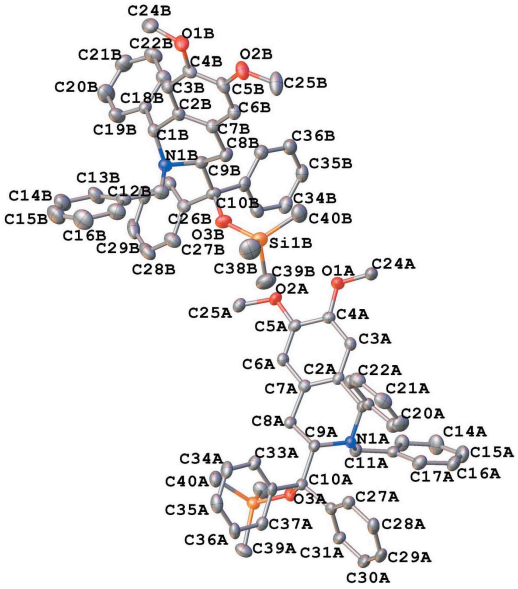


Figure 2
The molecular structure of (II), showing the atom-numbering scheme. There are two molecules in the asymmetric unit, labelled with suffixes *A* and *B*. Displacement ellipsoids are drawn at the 50% probability level. H atoms and some atom labels have been omitted for clarity.

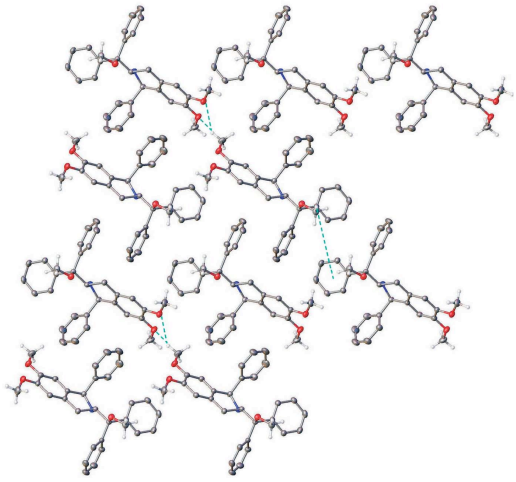


Figure 3
A partial projection of the structure of (I), viewed along [010]. Dashed lines indicate intermolecular interactions. H atoms not involved in intermolecular interactions have been omitted for clarity.

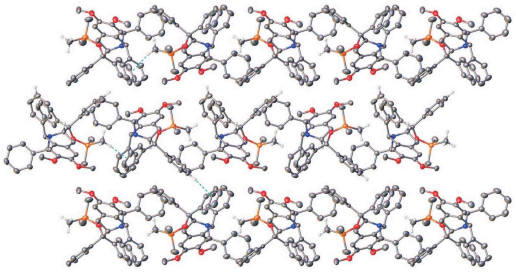


Figure 4
A partial projection of the structure of (II), viewed along [100]. The top and bottom layers contain only *B* molecules, while the central layer contains *A* molecules. Dashed lines indicate intermolecular interactions. H atoms not involved in intermolecular interactions have been omitted for clarity.

In the structure of (II), each independent molecule displays an intramolecular C—H$\cdots\pi$ interaction, while a single intermolecular C—H$\cdots\pi$ interaction involving C35*A*—H links just the two independent molecules (Table 2). An extended network of interactions is not present. The crystal packing of (II) reveals that the pseudosymmetry relates the two independent molecules within the asymmetric unit resulting in a layered packing along the *a* axis (Fig. 4).

From the crystal structures, it is evident that the N-containing six-membered rings assume half-chair conformations (Figs. 1 and 2). This result differs from two analogous compounds, namely (1*R*,3*S*)-methyl 2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate and (1*R*,3*S*)-methyl 6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, which assume half-boat conformations (Naicker *et al.*, 2009; Naicker, Govender *et al.*, 2010*a*). The current study confirms our previous postulation that the change in conformation is a result of the introduction of the phenyl groups at the C1 position.

According to the Cambridge Structural Database (Version 5.31; Allen, 2002), the only other crystal structure of a tetrahydroisoquinoline derivative with diaryl substitution at the C10 position is compound (III) (see Scheme), which we reported recently (Naicker, Govender *et al.*, 2010*b*). In this crystal structure, the methanol O atom is a free OH group. Due to the lack of analogous structures, these diaryl tetrahydroisoquinoline alcohols were compared with proline diaryl alcohols (Seebach *et al.*, 2008). Compound (III) displays a similar conformation to its proline analogue, which displays a *gauche* or *sc-endo* (synclinal) conformation around the O3—C10—C9—N1 bond, with the OH group partially covering the piperidine ring with a torsion angle of −77.0 (2)°.

Compound (I) displays an *ap* (antiperiplanar) conformation around the exocyclic C9—C10 bond, with an O3—C10—C9—N1 torsion angle of 171.5 (1)°. This conformation has only been found in a few examples of *N*-amino prolinol methyl esters (Seebach *et al.*, 2008).

Proline diphenyl OTMS (OTMS is trimethylsiloxy) analogues exhibit an *sc-exo* conformation around the exocyclic ethane bond, with a torsion angle of 61.0°. Both molecules of (II) (Fig. 2) display an *sc-endo* conformation, with torsion angles of −81.1 (3) and −84.8 (2)°. A possible reason for this

change could be that the benzyl group on the N atom forces the phenyl rings at the C10 atom to be the furthest away from it, hence adopting the *sc-endo* conformation.

Proline diaryl alcohols have been used as successful chiral catalysts by exploiting the same rotation along the C9—C10 bond (Diner *et al.*, 2008). This change, which is brought about by different groups on the methanol O atom, makes the current study particularly useful. This feature is found in (I) which, when tested for its catalytic activity in the Diels–Alder reaction, showed poor yields. The structural data demonstrated how we could improve the catalytic reactivity by reducing the steric bulk of the ligand. A successful catalyst was obtained by removing the phenyl moieties from (I) (Naicker, Petzold *et al.*, 2010).

Experimental

To (1*R*,3*S*)-2-benzyl-3-(1,1-diphenylethyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (0.4 g, 0.72 mmol), derived from L-DOPA (Naicker, Petzold *et al.*, 2010), in MeOH–THF (1:1 *v*/*v*, 20 ml) was added half an equivalent by mass of 10% palladium on carbon Pd/C under hydrogen (approximately 1 atm). The reaction was stirred for 2 h. The crude product was obtained by filtering the Pd/C through a plug of Celite and the filtrate was then concentrated to dryness. The resulting residue was purified by column chromatography (50:50 EtOAc–hexane, R_F = 0.6) to yield (I) as a white solid [yield 0.2 g, 60%; m.p. 463–465 K; $[\alpha]_D^{20}$ −10.0 (*c* 0.11 in $CHCl_3$)]. Recrystallization from ethyl acetate afforded colourless crystals suitable for X-ray analysis. IR (neat, ν_{max}, cm ^{1}): 2934, 1514, 1448, 1244, 1224, 1063, 698; ^{1}H NMR (400 MHz, $CDCl_3$, δ, p.p.m.): 7.47–7.12 (*m*, 12H), 7.08 (*t*, *J* = 7.6 Hz, 2H), 6.92 (*d*, *J* = 7.6 Hz, 2H), 6.65 (*s*, 1H), 6.40 (*s*, 1H), 5.23 (*s*, 1H), 3.95 (*dd*, *J* = 11.5 and 3.6 Hz, 1H), 3.86 (*s*, 3H), 3.70 (*s*, 3H), 2.92–2.75 (*m*, 4H), 2.52 (*dd*, *J* = 16.2 and 11.5 Hz, 3H).

To a stirred solution of [(1*R*,3*S*)-3-(hydroxydiphenylmethyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-2-yl](phenyl)-methanone (0.6 g, 1.1 mmol), derived from L-DOPA (Naicker, Petzold *et al.*, 2010), in dry dichloromethane (20 ml) and triethylamine (0.18 ml, 1.3 mmol), trimethylsilyl trifluoromethanesulfonate (0.24 ml, 1.33 mmol) was added dropwise at 273 K under an inert atmosphere. The mixture was allowed to warm to room temperature and was stirred overnight. The mixture was washed with water, the organic extracts were combined and dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (20:80 EtOAc–hexane, R_F = 0.55) to afford (II) as a white solid [yield 0.5 g, 75%; m.p. 458–460 K; $[\alpha]_D^{20}$ 57.58 (*c* 0.33 in $CHCl_3$)]. Recrystallization from acetone afforded colourless crystals suitable for X-ray analysis. IR (neat, ν_{max}, cm ^{1}): 2956, 1513, 1245, 839, 696; ^{1}H NMR (400 MHz, $CDCl_3$, δ, p.p.m.): 7.17 (*m*, 14H), 6.84 (*m*, 5H), 6.63 (*m*, 2H), 6.36 (*s*, 1H), 4.57 (*s*, 1H), 4.38 (*d*, *J* = 13.63 Hz, 1H), 4.24 (*dd*, *J* = 3.38 and 12.13 Hz, 1H), 4.00 (*s*, 3H), 3.73 (*s*, 3H), 3.39 (*dd*, *J* = 4.32 and 12.58 Hz, 1H), 3.31 (*d*, *J* = 13.85 Hz, 1H), 2.29 (*dd*, *J* = 3.38 and 16.88 Hz, 1H), 0.0 (*s*, 9H).

Table 1
Hydrogen-bond geometry (Å, °) for (I).

Cg is the centroid of the C18–C23 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C11—H11*A*···*Cg*^{i}	0.98	2.57	3.45 (2)	150
C30—H30*A*···O1^{ii}	0.98	2.54	3.356 (2)	140
C30—H30*A*···O2^{ii}	0.98	2.59	3.400 (2)	140

Symmetry codes: (i) $x, y+1, z$; (ii) $-x, y-\frac{1}{2}, -z+1$.

Compound (I)

Crystal data

$C_{31}H_{31}NO_3$
M_r = 465.57
Monoclinic, $P2_1$
a = 11.4071 (14) Å
b = 6.4750 (8) Å
c = 16.961 (2) Å
β = 101.707 (2)°
V = 1226.7 (3) Å^3
Z = 2
Mo *K*α radiation
μ = 0.08 mm^{-1}
T = 173 K
0.22 × 0.14 × 0.09 mm

Data collection

Bruker APEXII DUO diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2008)
T_{min} = 0.645, T_{max} = 0.746
11498 measured reflections
3737 independent reflections
3191 reflections with $I > 2\sigma(I)$
R_{int} = 0.051

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.108
S = 1.05
3737 reflections
320 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Compound (II)

Crystal data

$C_{40}H_{43}NO_3Si$
M_r = 613.84
Monoclinic, $P2_1$
a = 11.045 (10) Å
b = 17.008 (15) Å
c = 18.489 (15) Å
β = 105.287 (15)°
V = 3350 (5) Å^3
Z = 4
Mo *K*α radiation
μ = 0.11 mm^{-1}
T = 100 K
0.22 × 0.12 × 0.10 mm

Data collection

Bruker APEXII DUO diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2008)
T_{min} = 0.976, T_{max} = 0.989
37993 measured reflections
17263 independent reflections
11255 reflections with $I > 2\sigma(I)$
R_{int} = 0.064

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.124
S = 0.99
17263 reflections
812 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.41 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter: 0.00 (10), 8119 Friedel pairs

Atom H1N on N1 of (I) was located in a difference electron-density map and refined isotropically with a simple bond-length restraint of N1—H1N = 0.96 (1) Å. All remaining H atoms were positioned geometrically, with C—H = 0.95 (aromatic), 0.98 (methyl), 0.99 (methylene) or 1.00 Å (methine), and refined as riding on their

Table 2
Hydrogen-bond geometry (Å, °) for (II).

*Cg*1, *Cg*2, *Cg*3 and the centroids of the C26*B*–C31*B*, C32*A*–C37*A* and C32*B*–C37*B* rings, respectively.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C35*A*—H35*A*···*Cg*1^{i}	0.95	2.80	3.669 (3)	152
C40*A*—H40*A*···*Cg*2	0.98	2.71	3.540 (3)	143
C40*B*—H40*D*···*Cg*3	0.98	2.64	3.449 (4)	140

Symmetry code: (i) $x+1, y, z+1$.

parent atoms, with U_{iso}(H) = 1.5U_{eq}(C) for methyl groups or 1.2U_{eq}(C) otherwise. For (I), the Flack *x* parameter (Flack, 1983) based on refinement with 3080 Friedel pairs was −0.5 (10), which indicated that no conclusions can be drawn regarding the absolute structure. Consequently, the Friedel pairs were merged before the final refinement. For (II), the Flack parameter refined to 0.00 (10) using 8119 Friedel pairs, which indicated that the refined model represents the true absolute configuration and is in accordance with expectation from the known chirality of the starting material in the synthesis.

For both compounds, data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors thank Dr Hong Su of the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3143). Services for accessing these data are described at the back of the journal.

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Structure Reports Online
ISSN 1600-5368

(3*S*)-2-Benzyl-3-carboxy-1,2,3,4-tetrahydroisoquinolinium chloride monohydrate

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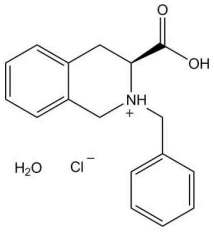
Key indicators: single-crystal X-ray study; T = 193 K; mean σ(C–C) = 0.003 Å; R factor = 0.036; wR factor = 0.082; data-to-parameter ratio = 19.5.

In the title compound, $C_{17}H_{18}NO_2^+\cdot Cl^-\cdot H_2O$, a precursor to novel asymmetric catalysts, the N-containing six-membered ring of the tetrahydroquinolinium unit assumes a half-boat conformation. In the crystal, intermolecular O—H···O, O—H···Cl, N—H···Cl and C—H···O hydrogen bonds and C—H···π interactions link the molecules into a three-dimensional network.

Related literature

For related structures of tetrahydroisoquinoline derivatives, see: Naicker, Petzold *et al.* (2010); Naicker, Govender *et al.* (2010, 2011); Peters *et al.* (2010). For related structures with the same chiral centre and conformation of the six-membered ring, see: Naicker *et al.* (2009); Chakka *et al.* (2010).



Experimental

Crystal data

$C_{17}H_{18}NO_2^+\cdot Cl^-\cdot H_2O$
M_r = 321.79
Monoclinic, $P2_1$
a = 8.6159 (8) Å
b = 10.0670 (9) Å
c = 10.1392 (9) Å
β = 108.686 (2)°
V = 833.08 (13) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.24 mm^{-1}
T = 193 K
0.30 × 0.11 × 0.02 mm

Data collection

Bruker Kappa DUO APEXII diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2008*a*)
T_{min} = 0.931, T_{max} = 0.995
9083 measured reflections
4158 independent reflections
3414 reflections with $I > 2\sigma(I)$
R_{int} = 0.024

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.082
S = 1.04
4158 reflections
213 parameters
5 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Absolute structure: Flack (1983), 1961 Friedel pairs
Flack parameter: −0.01 (5)

Table 1
Hydrogen-bond geometry (Å, °).

Cg is the centroid of the C12–C17 ring.

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···Cl1^{i}	0.97 (2)	2.09 (2)	3.0521 (15)	176 (1)
O2—H2···O3^{ii}	0.96 (2)	1.59 (2)	2.533 (2)	167 (3)
O3—H3*A*···Cl1^{i}	0.96 (2)	2.21 (2)	3.1615 (15)	172 (2)
O3—H3*B*···Cl1	0.96 (2)	2.20 (2)	3.1434 (16)	165 (2)
C9—H9···O1^{iii}	1.00	2.30	3.169 (2)	145
C15—H15···*Cg*^{iii}	0.95	2.78	3.386 (3)	122

Symmetry codes: (i) $-x+1, y+\frac{1}{2}, -z+1$; (ii) $x, y, z-1$; (iii) $-x+1, y+\frac{1}{2}, -z$.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008*b*); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008*b*); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su of the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: IS2635).

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Acta Cryst. (2011). E**67**, o228 [doi:10.1107/S1600536810053122]

(3*S*)-2-Benzyl-3-carboxy-1,2,3,4-tetrahydroisoquinolinium chloride monohydrate

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The tetrahydroisoquinoline (TIQ) molecule and its derivatives have been widely investigated due to their biological and pharmaceutical properties. We have recently had much success with TIQ based ligands for both metal ligand (Peters *et al.*, 2010) and organocatalysis (Naicker, Petzold *et al.*, 2010). Bearing an acid functional group, the title compound is a useful precursor to many of these novel asymmetric catalysts. The neutral form of this compound is commercially available but there has been no report of its single X-ray crystal structure.

The structure has monoclinic ($P2_1$) symmetry with a single molecule in the asymmetric unit together with a water molecule (Fig. 1). Various intra- and intermolecular short contact interactions (2.87–3.14 Å) occur but only one C15—H···π (C12—C17 ring) is observed within the crystal packing (Table 1). The most significant feature of the structure is the intermolecular hydrogen bonding array. The carboxylic acid functional group (O2—H) hydrogen bonds to the water molecule which in turn interacts with two chloride ions. These ions interact further with another water molecule but also with the protonated tertiary amine nitrogen. This series of interactions helps to construct the three-dimensional network (Fig. 2 and Table 1).

From the crystal structure it is evident that the *N*-containing six membered ring assumes a half boat conformation (Fig. 1), this observation is similar to analogous structures that we have recently reported (Naicker *et al.*, 2009; Naicker, Govender *et al.*, 2010).

Experimental

(*S*)-Methyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate was added to a 10% (v/v) solution of HCl in water (5 mL). The mixture was then microwaved for 2 h at 120 °C, thereafter the reaction mixture was evaporated under reduced pressure to afford the title compound as a white solid.

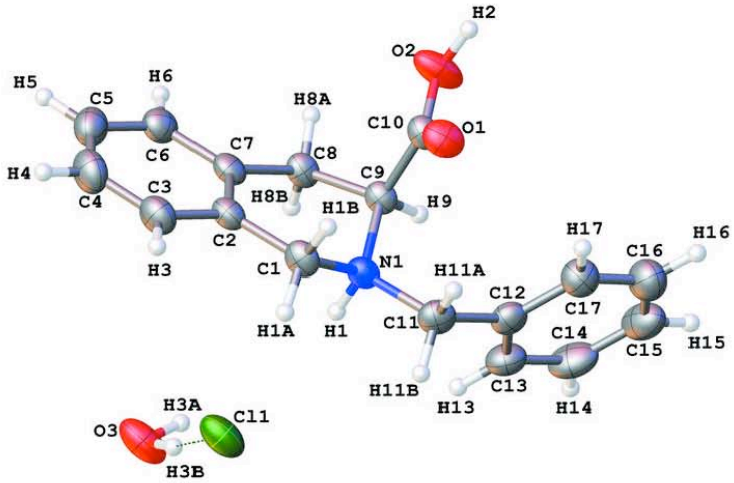
Melting point 205–208 °C. IR (neat): 3339, 2501, 1712, 1224, 754, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.28 (d, 1H), 3.36 (d, 1H), 4.37 (m, 5H), 7.13 (d, 1H), 7.25 (m, 3H) and 7.39 (m, 5H).

Recrystallization from 10% HCl in water afforded colourless crystals suitable for X-ray analysis.

Refinement

All H atoms on carbons were positioned geometrically with C—H distances ranging from 0.95 to 1.00 Å and refined as riding on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C)$. Atoms H1, H2, H3A and H3B were located in a difference Fourier map. The distances of N1—H1, O2—H2, O3—H3A and O3—H3B were restrained to 0.97 (1) Å and the U_{iso} values of H3A and H3B were assigned as $1.2U_{eq}(O3)$.

Fig. 1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O2
H5
C5
H6
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C6
C7
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H4
C4
C3
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H1B
H9
H17
H16
C2
C16
H3
C1
N1
H11A
C12
C17
H1A
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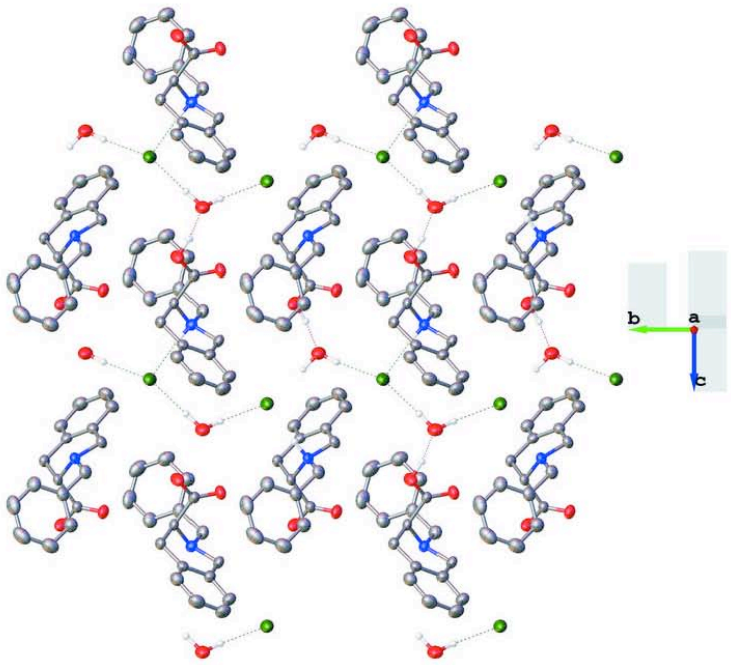
O3
H3B

Fig. 2



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(*S*)-*N*-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

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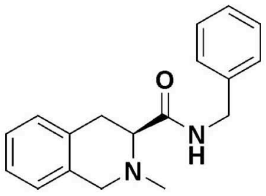
Received 12 November 2010; accepted 1 December 2010

Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.005 Å; R factor = 0.036; wR factor = 0.088; data-to-parameter ratio = 9.0.

The structure of the title compound, $C_{18}H_{20}N_2O$, at 173 K has hexagonal ($P6_1$) symmetry. The *N*-containing six-membered ring assumes a half-chair conformation. In the crystal, intermolecular N—H···O hydrogen bonding *via* the amide groups cross-link the molecules along the *a* axis. The absolute configuration was confirmed by 2D NMR studies.

Related literature

The title compound is a precursor to chiral ligands involving a tetrahydroisoquinoline backbone. For the application of these ligands as catalysts, see: Chakka *et al.* (2009); Peters *et al.* (2010); Naicker *et al.* (2010*a*). For related structures, see: Chakka *et al.* (2010). For a related structure with the same chiral centre and conformation of the six-membered ring, see: Naicker *et al.* (2010*b*).



Experimental

Crystal data

$C_{18}H_{20}N_2O$ M_r = 280.36
Hexagonal, $P6_1$
a = 10.1838 (13) Å
c = 25.965 (3) Å
V = 2332.1 (5) Å^3
Z = 6
Mo $K\alpha$ radiation
μ = 0.08 mm^{-1}
T = 173 K
0.22 × 0.12 × 0.03 mm

Data collection

Bruker Kappa DUO APEXII diffractometer
18777 measured reflections
1759 independent reflections
1358 reflections with $I > 2\sigma(I)$
R_{int} = 0.059

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.088
S = 1.05
1759 reflections
195 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O1^{i}	0.96 (2)	1.92 (2)	2.852 (3)	165 (3)

Symmetry code: (i) $y, -x+y+1, z-\frac{1}{6}$.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su of the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG2752).

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Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

Acta Cryst. (2011). E**67**, o67 [**doi:10.1107/S1600536810050361**]

(*S*)-*N*-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound (Fig. 1) is a precursor in the synthesis of novel chiral ligands involving a tetrahydroisoquinoline backbone. Recently, we have reported the application of these ligands as useful catalysts for transfer hydrogenation of prochiral ketones (Chakka *et al.*, 2009), Henry reactions, hydrogenation of olefins (Peters *et al.* 2010) and Diels-Alder reactions (Naicker *et al.*, 2010*a*).

Compound 1 was derived from commercially available *S*-phenyl glycine and formaldehyde. The absolute stereochemistry was confirmed to be S at the C9 position from proton NMR spectroscopy. (Peters *et al.* 2010).

From the crystal structure it is evident that the *N*-containing six membered ring assumes a half chair conformation (Fig. 1), in which the 1—N1—C9—C8 bond has a torsion angle of 68.7 (3)°. This observation is similar to analogous structures that we have reported recently (Chakka *et al.*, 2010) and (Naicker *et al.*, 2010*b*).

The molecule exhibits intermolecular hydrogen bonding, which involves the atom O1 which links the molecules together see Table 1 and Fig. 2.

Experimental

(*S*)-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1.5 g, 7.8 mmol) was dissolved in DMF (15 ml) followed by addition of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) hydrochloride (8.8 mmol), hydroxybenzotriazole (0.81 g, 8.3 mmol), a catalytic amount of 4-dimethylaminopyridine and benzyl amine (8.3 mmol). The reaction mixture was then stirred at room temperature until no more starting material could be detected by TLC analysis (approximately 1 h). The reaction mixture was poured into 30 volumes of chilled water; the mixture was then extracted twice with ethyl acetate. The extracts were combined, washed with 5% HCl (aq) to remove latent EDC urea, dried over anhydrous magnesium sulfate and then concentrated to dryness affording the crude product which was purified by column chromatography.

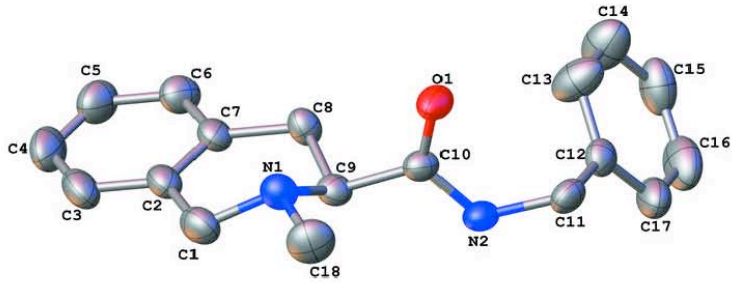
Melting point 91–95 ^{o}C. $[\alpha]^{20}_{D}$ -7.93 (*c* 0.21 in $CHCl_3$).

IR (neat) n_{max}: 3281, 2923, 1646, 1548, 1454, 1240, 739, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.78 (d, 3H), 3.12 (m, 2), 3.52 (t, 1H), 3.66 (m, 3H), 3.78 (d, 1H), 6.99 (d, 1H), 7.19 (m, 3H), 7.30 (m, 6H)

Recrystallization from EtOAc afforded colourless crystals suitable for X-ray analysis.

Fig. 1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C5
C6
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C13
C15
C7
C8
C4
C10
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C9
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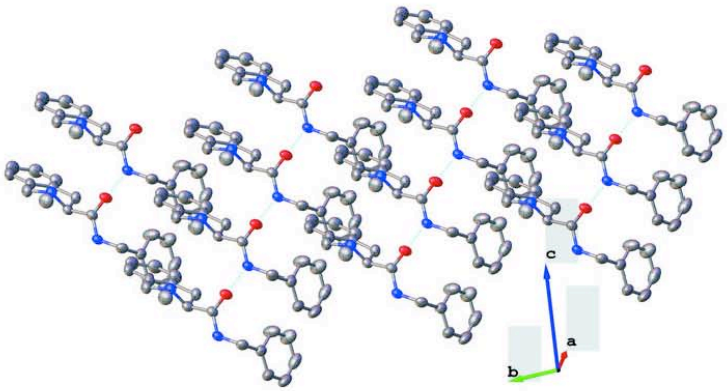
C3
C11
C17
C1
N2
C18

Fig. 2



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(*S*)-2-Benzyl-*N*-(2,6-diisopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

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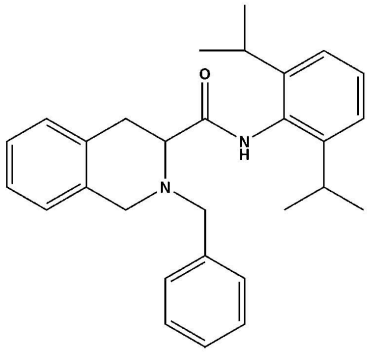
Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.009 Å; R factor = 0.057; wR factor = 0.146; data-to-parameter ratio = 8.5.

The asymmetric unit of the title compound, $C_{29}H_{34}N_2O$, contains two molecules in which the N-containing six-membered rings assume different conformations *viz.* half-chair and envelope. Intermolecular N—H···O hydrogen bonding *via* the amide groups cross-link the molecules in the crystal structure.

Related literature

The title compound is a precursor to novel *N*-oxide type organocatalysts, see: Naicker *et al.* (2010). For a related structure, see: Naicker *et al.* (2011).



Experimental

Crystal data

$C_{29}H_{34}N_2O$
M_r = 426.58
Monoclinic, $P2_1$
a = 9.493 (3) Å
b = 12.459 (5) Å
c = 21.280 (8) Å
β = 102.241 (7)°
V = 2459.8 (16) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.07 mm^{-1}
T = 173 K
0.35 × 0.06 × 0.05 mm

Data collection

Bruker Kappa DUO APEXII diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2006)
T_{min} = 0.976, T_{max} = 0.997
16565 measured reflections
4932 independent reflections
2620 reflections with $I > 2\sigma(I)$
R_{int} = 0.093

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.146
S = 0.98
4932 reflections
577 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N2A—H2A···O1B^{i}	0.88	2.15	2.900 (6)	142

Symmetry code: (i) $x-1, y, z$.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su of the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG5021).

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Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

Acta Cryst. (2011). E**67**, o1106 [**doi:10.1107/S1600536811012554**]

(*S*)-2-Benzyl-*N*-(2,6-diisopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound is a precursor in the synthesis of novel chiral catalysts containing a tetrahydroisoquinoline framework (TIQ). Upon oxidation of the secondary amine, the *N*-oxide form of this compound and its derivatives are currently being tested as novel organocatalysts for asymmetric allylation reactions (Naicker *et al.* 2010).

The structure has two molecules in the asymmetric unit (Fig. 1). These molecules are linked *via* various intermolecular short contact interactions (2.01–2.83 Å). The crystal packing reveals that a hydrogen bond *via* the amide groups N2A—H2A···O1B link the molecules together resulting in a one-dimensional sheet along the *c* axis (Fig. 2), also see (Naicker *et al.* 2011)

From the crystal structure it is evident that the *N*-containing six membered rings assume different conformations for the two molecules in the asymmetric unit (Fig. 1). The ring containing N1A adopts a half chair conformation while N1B exists as a half boat conformation.

Experimental

(*S*)-2-Benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1.5 g, 3.4 mmol) was dissolved in dry dichloromethane (15 ml) followed by the addition of triethylamine (2.0 eq.) and ethylchloroformate (1.2 eq.) which was stirred for 1 h at 0 degrees followed by the addition of 2,6-diisopropylaniline (1.1 eq.). The reaction mixture was then stirred at room temperature until no more starting material could be detected by TLC analysis (approximately 3 h). The reaction mixture was poured into water (30 equivalent volumes); the mixture was then extracted twice with dichloromethane (20 ml). The extracts were combined, dried over anhydrous magnesium sulfate and then concentrated to dryness affording the crude product which was purified by silica column chromatography (hexane:ethylacetate 80:20 R_f =0.6).

Melting point 418–420 K. $[\alpha]^{20}_D$ +4.762 (*c* 0.14 in $CHCl_3$).

IR (neat): 3286, 2961, 1676,1488, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.45 – 7.32 (m, 5H), 7.27 – 7.16 (m, 5H), 7.09 (t, *J* = 5.8 Hz, 3H), 3.92 (dt, *J* = 16.1, 13.2 Hz, 3H), 3.80 (dd, *J* = 7.2, 4.2 Hz, 1H), 3.68 (d, *J* = 13.7 Hz, 1H), 3.33 (dd, *J* = 15.4, 4.2 Hz, 1H), 3.18 (dd, *J* = 15.4, 7.2 Hz, 1H), 1.59 (s, 4H), 1.00 (dd, *J* = 20.3, 6.2 Hz, 13H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.91, 145.83, 137.71, 135.85, 134.98, 131.15, 128.96, 128.76, 127.93, 127.90, 127.71, 127.43, 126.55, 126.17, 123.28, 77.34, 77.02, 76.70, 62.42, 60.85, 51.60, 29.76, 28.50, 23.72, 23.64.

Recrystallization from dichloromethane at room temperature afforded colourless crystals suitable for X-ray analysis.

Fig. 1

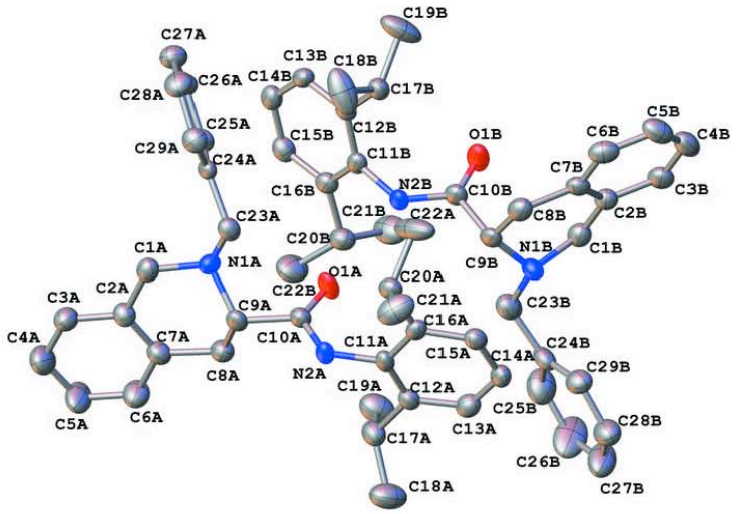
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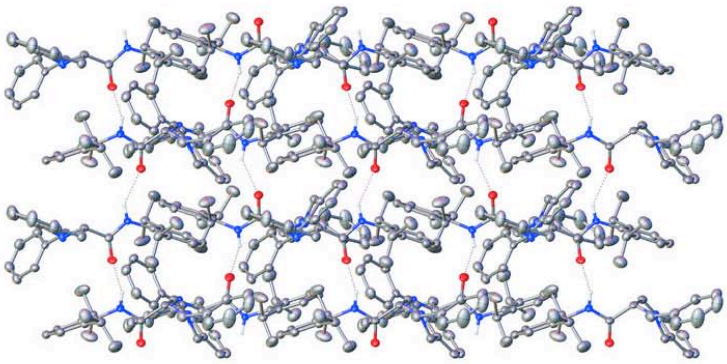
Fig. 2



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(1*S*,3*S*)-Methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

Tricia Naicker,[a] Thavendran Govender,[a] Hendrik G. Kruger[b] and Glenn E. M. Maguire[b]*

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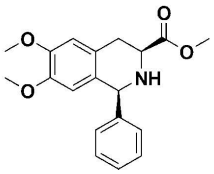
Received 15 May 2011; accepted 17 May 2011

Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.002 Å; R factor = 0.030; wR factor = 0.082; data-to-parameter ratio = 10.2.

In the title compound, $C_{19}H_{21}NO_4$, an organocatalyst with a tetrahydroisoquinoline backbone, the heterocyclic ring assumes a half-boat conformation. The dihedral angle between the aromatic rings is 82.93 (8)°. In the crystal, molecules are linked *via* N—H···O and C—H···O hydrogen bonds, forming a layer parallel to (10$\bar{1}$).

Related literature

For related structures, see: Naicker *et al.* (2010, 2011).



Experimental

Crystal data

$C_{19}H_{21}NO_4$
M_r = 327.37
Monoclinic, $P2_1$
a = 9.3841 (3) Å
b = 6.3453 (2) Å
c = 14.2048 (4) Å
β = 94.475 (2)°
V = 843.25 (4) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 173 K
0.90 × 0.07 × 0.06 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.923, T_{max} = 0.995
4184 measured reflections
2275 independent reflections
2138 reflections with $I > 2\sigma(I)$
R_{int} = 0.010

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.030
$wR(F^2)$ = 0.082
S = 1.05
2275 reflections
222 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.13 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1*N*···O3^{i}	0.91 (2)	2.27 (1)	3.0918 (17)	149 (2)
C1—H1···O3^{ii}	1.00	2.55	3.503 (2)	160
C19—H19*B*···O2^{iii}	0.98	2.53	3.270 (2)	132

Symmetry codes: (i) $-x+1, y+\frac{1}{2}, -z+2$; (ii) $x, y+1, z$; (iii) $-x, y-\frac{1}{2}, -z+1$.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su from the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: IS2714).

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Acta Cryst. (2011). E**67**, o1501 [**doi:10.1107/S1600536811018782**]

(1*S*,3*S*)-Methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound is a novel chiral organocatalyst containing a tetrahydroisoquinoline (TIQ) framework. We have recently reported the use of similar TIQ derivatives as organocatalysts in the Diels-Alder cycloaddition between alpha, beta-unsaturated aldehydes and cyclopentadiene (Naicker *et al.*, 2010).

Diastereomers formed during the synthesis of the title compound were easily separated using column chromatography to yield the TIQ derivative with the stereochemistry as illustrated in Fig. 1. The absolute stereochemistry was confirmed to be *S*,*S* at the C1 and C9 positions, respectively, by proton NMR spectroscopy.

The *N*-containing six-membered ring assumes a half-boat conformation [Q = 0.5537 (16) Å, θ = 53.94 (16)° and φ = 335.3 (2)°]. This observation is similar to a related structure that we recently reported (Naicker *et al.*, 2011). The molecules are linked through N1—H1N···O3^{i} and C1—H1···O3^{ii} hydrogen bonds (Table 1) into a column stacked along the *b* axis. The columns are further connected by C19—H19B···O2^{iii} hydrogen bonds, forming a layer parallel to the (10$\bar{1}$) plane (Fig. 2).

Experimental

To a stirred solution of 1:1 methanol: methylene chloride (6.0 ml) with 4 Å molecular sieves, (*S*)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate (1.0 g, 4.2 mmol) and benzaldehdye (1.1 eq.) was added under an inert atmosphere. The reaction mixture was allowed to stir for 1.5 h. Thereafter the reaction mixture was filtered and the solvents was removed *in vacuo* to yield the intermediate imine which was left on a high vacuum pump to remove any residual water for 2 h. The residue was then dissolved in trifluoroacetic acid (20 ml) and refluxed for 3 h. The reaction mixture was then neutralized with a saturated sodium bicarbonate solution and extracted with ethylacetate (4 × 20 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product (diastereomers) was purified by column chromatography (50:50 EtOAc/Hexane, R_f 1/2) to afford the product 1.20 g (88%) as a white solid. Melting point 370–372 K. IR (neat): 2928, 2600, 1746, 1516, 1250, 1123, 727 cm^{-1} $[\alpha]^{20}_D$ = +15.38 (*c* 0.26 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.11 (m, 5H), 6.57 (s, 1H), 6.10 (s, 1H), 5.02 (s, 1H), 3.79 (s, 4H), 3.70 (s, 3H), 3.52 (s, 3H), 3.01 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.96, 147.76, 147.41, 143.87, 130.22, 129.04, 128.59, 127.84, 126.07, 111.31, 110.56, 62.85, 56.54, 55.89, 55.84, 52.18, 32.22.

Recrystallization from ethyl acetate at room temperature afforded crystals suitable for X-ray analysis.

Refinement

All hydrogen atoms, except H1N on N1, were placed in idealized positions and refined as riding, with U_{iso}(H) = 1.2 or 1.5U_{eq}(C). The position of H1N was located in a difference electron density map and refined with a bond length restraint

Fig. 1

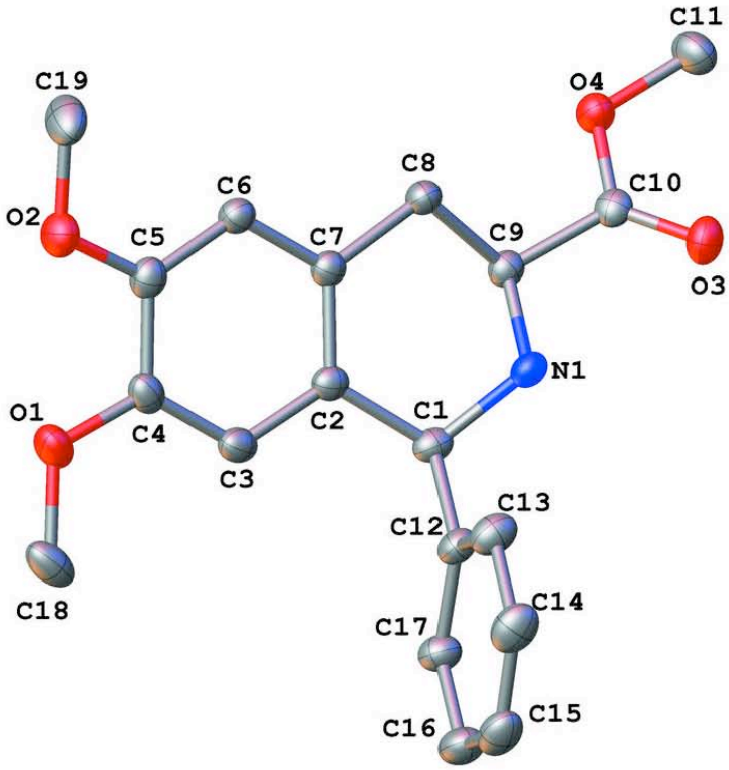
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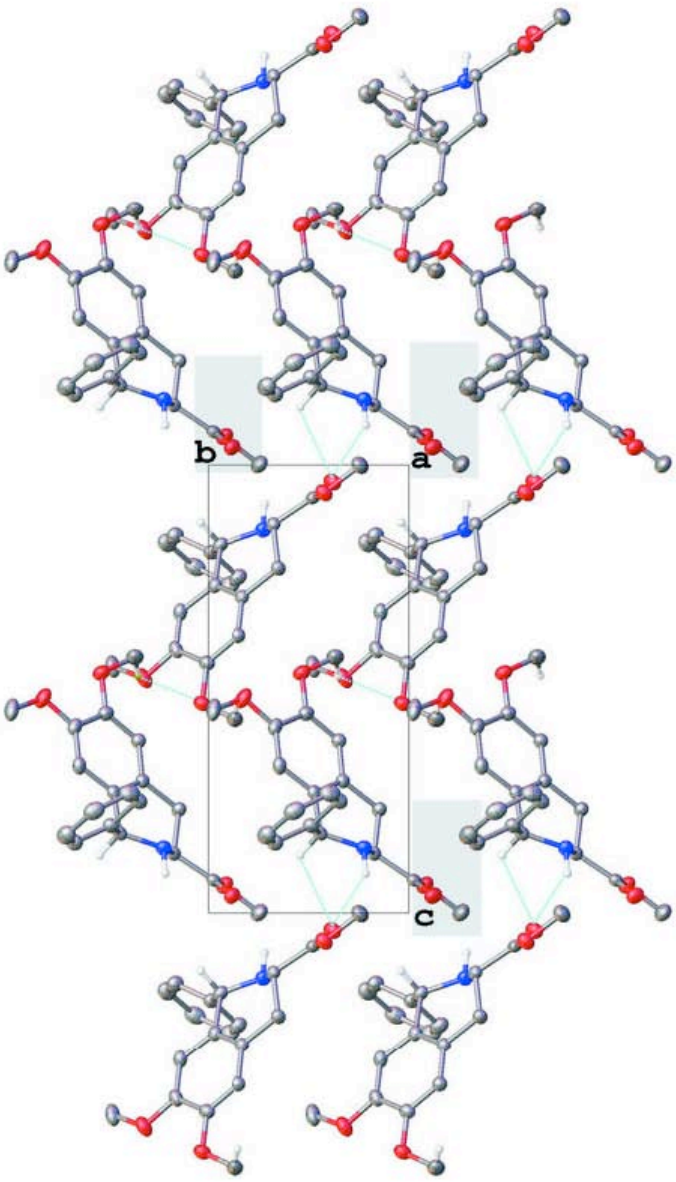
Fig. 2



organic compounds

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6,7-Dimethoxy-3-methoxycarbonyl-1-(2-methoxyphenyl)-3,4-dihydroisoquinoline 2-oxide

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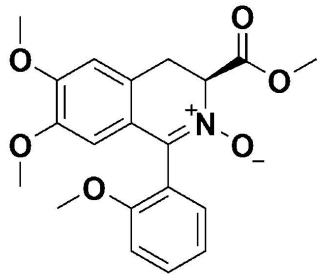
Received 26 April 2011; accepted 2 May 2011

Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.002 Å; R factor = 0.053; wR factor = 0.157; data-to-parameter ratio = 16.2.

In the title compound, $C_{20}H_{21}NO_6$, an N-oxide-based organocatalyst, the N-containing six-membered ring adopts a twisted half-chair conformation. No hydrogen bonding or π–π stacking was found within the crystal structure.

Related literature

For related structures, see: Naicker *et al.* (2010, 2011).



Experimental

Crystal data

$C_{20}H_{21}NO_6$
M_r = 371.38
Monoclinic, $P2_1/n$
a = 5.4765 (1) Å
b = 21.9984 (6) Å
c = 15.0007 (4) Å
β = 92.774 (2)°
V = 1805.08 (8) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 173 K
0.25 × 0.18 × 0.15 mm

Data collection

Bruker APEXII diffractometer
7815 measured reflections
3959 independent reflections
3092 reflections with $I > 2\sigma(I)$
R_{int} = 0.016

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.157
S = 1.06
3959 reflections
245 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.92 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su of the Chemistry Department, University of Cape Town, for her assistance with the crystallographic data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG5031).

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Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

Acta Cryst. (2011). E**67**, o1352 [**doi:10.1107/S1600536811016539**]

6,7-Dimethoxy-3-methoxycarbonyl-1-(2-methoxyphenyl)-3,4-dihydroisoquinoline 2-oxide

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound is a novel *N*-oxide based catalyst containing a tetrahydroisoquinoline (TIQ) backbone. This is the first X-ray crystal structure report of this type of organocatalyst within this TIQ class of molecules. This compound and its derivatives are currently being tested in our laboratory as novel organocatalysts for asymmetric allylation reactions (Naicker *et al.* 2010).

From the crystal structure it is evident that the *N*-containing six membered ring assumes a twisted half chair conformation (Fig. 1). This differs from a similar structure that we recently reported which displays a twisted half boat conformation (Naicker *et al.* 2011). A possible reason for the change is the introduction of the oxygen atom O2 onto the sp2 hybridized nitrogen atom. All our previous examples have either a hydrogen or methyl group at that position.

Interestingly there is no classic hydrogen bonding within the crystal packing however, there are various intermolecular and intramolecular short contact interactions that link the molecules together within the crystal lattice. The *N*-oxide oxygen O2 displays two potential hydrogen bond interactions to C16—H16 and C20A—H20A which are 3.36 Å and 3.34 Å respectively. These interactions result in a layered packing within the crystal stucture as shown along the (100) axis in Fig. 2. A centroid distance of 7.156 Å indicated that there is no π-π stacking within the crystal matrix.

Experimental

(*S*)-methyl 6,7-dimethoxy-1-(2-methoxyphenyl)-3,4-dihydroisoquinoline-3-carboxylate (1.30 g, 3.7 mmol) was dissolved in dry methylene chloride (50 ml). Potassium carbonate (1.0 g, 7.5 mmol) was added and the reaction cooled to −78 °C. Meta-chloroperbenzoic acid (0.86 g of 75% pure, net 0.65 g, 3.7 mmol) was then added, and the reaction was allowed to stir at −78 °C for 3 h. At this time, the reaction was allowed to warm to room temperature. After stirring for a further 2 h at room temperature, methylene chloride (50 ml) was added to dilute the reaction and celite (500 mg) was added to aid filtration. The reaction was filtered, and the methylene chloride concentrated to dryness affording the crude product which was purified by column chromatography (methylene chloride:methanol, 99:1, R_f = 1/5) (1.20 g, 87% yield).

Melting point 423 K. $[\alpha]^{20}_D$ 5.128 (c 0.13 in $CHCl_3$).

IR (neat): 2923, 1742, 1508, 1285, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.20 – 6.97 (m, 3H), 6.74 (d, *J* = 6.5 Hz, 1H), 6.27 (d, *J* = 13.6 Hz, 1H), 4.94 (dt, *J* = 5.8, 2.9 Hz, 1H), 3.90 (d, *J* = 1.8 Hz, 4H), 3.77 (d, *J* = 4.3 Hz, 3H), 3.73 – 3.54 (m, 6H), 3.49 – 3.33 (m, 1H).

Fig. 1

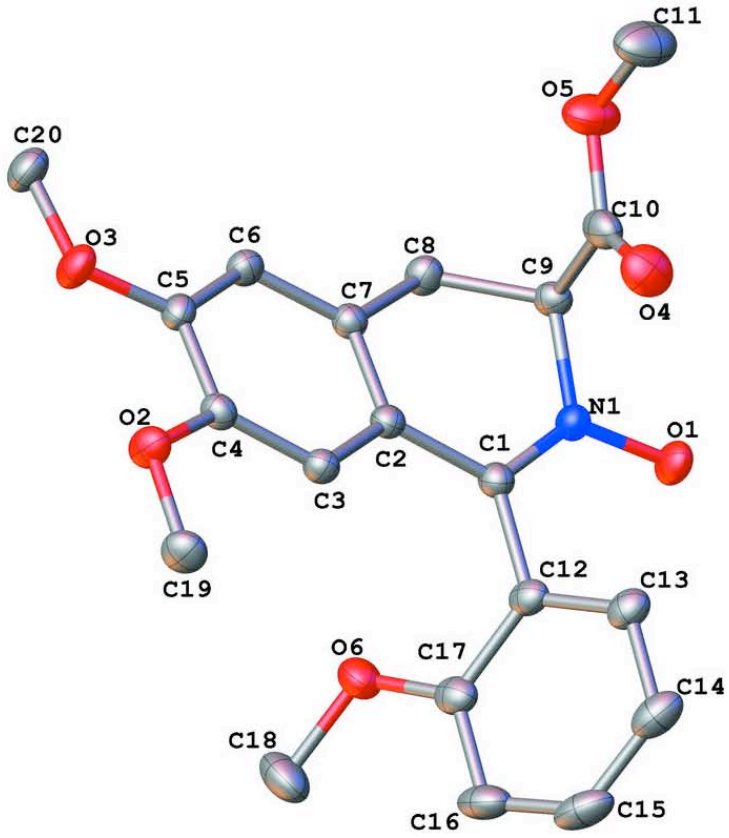
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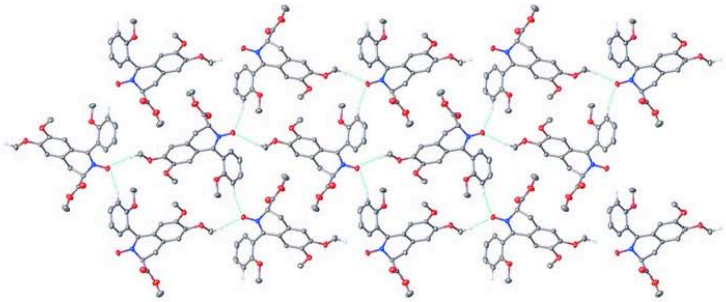
Fig. 2



Acta Crystallographica Section E
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(1*S*,3*S*)-Methyl 2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

Tricia Naicker,[a] Thavendran Govender,[a] Hendrik. G. Kruger[b] and Glenn. E. M. Maguire[b]*

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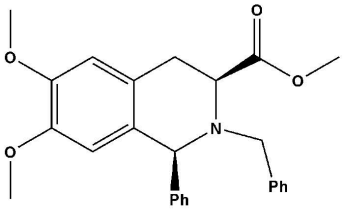
Received 4 March 2011; accepted 9 May 2011

Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.002 Å; R factor = 0.031; wR factor = 0.087; data-to-parameter ratio = 10.8.

In the title compound, $C_{26}H_{27}NO_4$, the heterocyclic ring assumes a half-chair conformation and intermolecular C—H···O interactions help to construct the three-dimensional network within the crystal packing.

Related literature

The title compound is a precursor to chiral catalysts bearing a tetrahydroisoquinoline (TIQ) backbone. TIQ catalyst precursors have shown to be efficient for several asymmetric transformations, see: Chakka *et al.* (2010); Kawthekar *et al.* (2010). For related structures, see: Naicker *et al.* (2009, 2010, 2011). For the assignment of the absolute stereochemisty by NMR, see: Aubry *et al.* (2006).



Experimental

Crystal data

$C_{26}H_{27}NO_4$
M_r = 417.49
Monoclinic, $P2_1$
a = 9.7797 (7) Å
b = 5.4646 (4) Å
c = 20.6959 (15) Å
β = 96.986 (1)°
V = 1097.82 (14) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 173 K
0.85 × 0.07 × 0.06 mm

Data collection

Bruker Kappa DUO APEXII diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2008*a*)
T_{min} = 0.931, T_{max} = 0.995
20624 measured reflections
3032 independent reflections
2764 reflections with $I > 2\sigma(I)$
R_{int} = 0.030

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.087
S = 1.05
3032 reflections
280 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C18—H18···O3^{i}	0.95	2.51	3.445 (2)	168
C25—H25A···O1^{ii}	0.98	2.43	3.183 (2)	133

Symmetry codes: (i) $x, y+1, z$; (ii) $-x+1, y+\frac{1}{2}, -z$.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008*b*); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008*b*); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su from the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: GW2101).

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Acta Cryst. (2011). E**67**, o1403 [**doi:10.1107/S1600536811017430**]

(1*S*,3*S*)-Methyl 2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

Chiral catalysts containing a tetrahydroisoquinoline (TIQ) backbone have proven to be very successful in our research group. These TIQ catalyst precursors have shown to be efficient for several asymmetric transformations. (Chakka *et al.*, 2010, Kawthekar *et al.*,2010 and Naicker *et al.*, 2010) The title compound (Fig. 1) is a precursor in the synthesis of several novel chiral ligands containing the TIQ framework.

The absolute stereochemistry of the crystal was confirmed to be S,*S* at C1 and C9 positions respectively by proton NMR spectroscopy. We recently reported the crystal structure of the *R*,*S* diastereomer at the C1 and C9 positions respectively. (Naicker *et al.*, 2009)

Interestingly, there are several significant differences between these diasteromeric crystals. The title compound crystallizes with monoclinic (P21) symmetry while its diastereomer has triclinic (P1)symmetry. Also the *N*-containing six membered ring assumes a half chair conformation [Q=0.5312 (16) Å, θ= 53.39 (17)° and φ=324.7 (2)°] as apposed to a half boat conformation (Fig. 1). This heterocyclic ring shape affects the position of the ester moiety relative to the phenyl ring at the C1 position. The torsion angle for C1—N1—C9—C10 is -171.7 (1)° while for the diastereomer this angle was 66.0 (2)°. In addition, the *N*-benzyl and phenyl ring at C1 exisit in a *cis* orientation along the N1—C9 bond with a dihedral angle of 70.2 (2)° while for the diasteromer they are *trans* to each other with a dihedral angle of -64.7 (1)°. From the plain formed by the atoms C1—C2—C7—C8—N1—C9 the maximum displacement from planarity for N1 is 0.334 Å and for C9 0.360 Å.

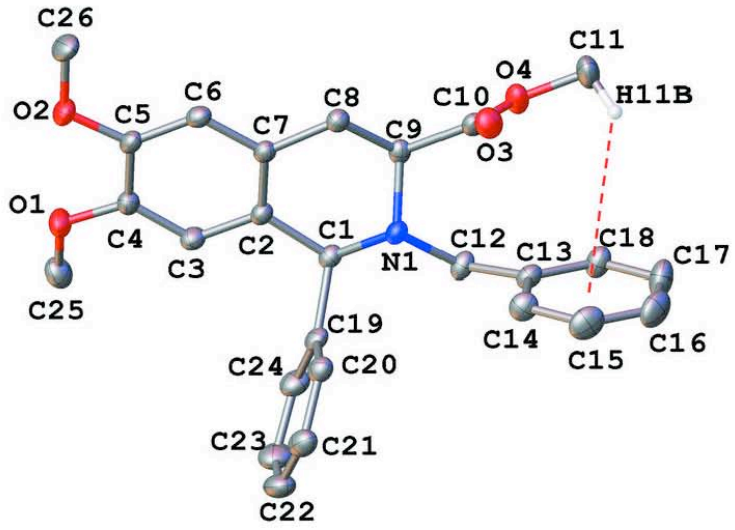
A single intramolecular interaction between H11B and the phenyl ring attached to C12 (2.862 Å) is evident (Fig. 1). Two specific intermolecular short contacts originating from methoxy O1 and the ester O3 to different C–H groups (Fig. 2) link the molecules together in the crystal (Table 1). This arrangement results in chains parallel to the *a* axis. In the chain, the molecules are arranged so that their tails, linked by these C—H···O interactions, protrude to the outer edges of the chain, and their heads point towards the core of the chain.

Experimental

To a solution of (1*S*,3*S*)-methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (500 mg, 1.52 mmol) in acetonitrile (20 ml), solid K_2CO_3 (635 mg, 4.58 mmol) was added followed by benzyl bromide (286 mg, 1.67 mmol) at ambient temperature. There after the reaction mixture was refluxed for 3 h. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (60:40, R_f =0.5). The solvent was evaporated and 30 ml of ethylacetate was added, washed with 2 × 10 ml of water, the organic layer was separated, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford crude product, which was purified by column chromatography using hexane:ethyl acetate (60:40) as the eluent to yield pure product. (0.44 g, 90%) as a white solid.

Melting point: 420 K. $[\alpha]^{20}_D$ +3.03 (c 0.1 in $CHCl_3$).

Fig. 1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C6
C8
C10
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C5
C7
C9
O3
O1
C4
C2
C1
C12
C13
C18
C17
C3
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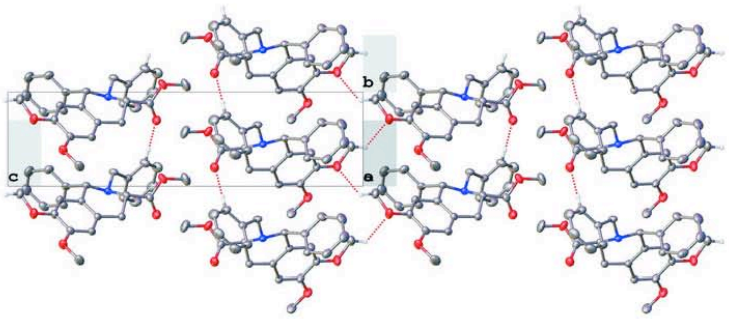
C25
C19
C14
C16
C24
C20
C15
C23
C21
C22

Fig. 2



Acta Crystallographica Section E
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Methyl 1-cyclohexyl-6,7-dimethoxy-3,4-dihydroisoquinoline-3-carboxylate

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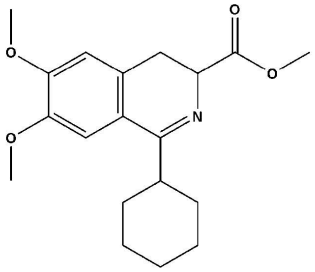
Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.002 Å; R factor = 0.040; wR factor = 0.110; data-to-parameter ratio = 17.7.

There are two independent molecules in the asymmetric unit of the title compound, $C_{19}H_{25}NO_4$. A single C—H$\cdots\pi$ interaction and various intermolecular contacts (2.65–2.83 Å) link the independent molecules in the crystal structure. The N-containing six-membered ring assumes a twisted half-boat conformation.

Related literature

For related structures, see: Naicker *et al.* (2010*a*,*b*, 2011).



Experimental

Crystal data

$C_{19}H_{25}NO_4$
M_r = 331.40
Triclinic, $P\overline{1}$
a = 9.5720 (2) Å
b = 10.8441 (4) Å
c = 17.5925 (6) Å
α = 80.941 (1)°
β = 75.267 (2)°
γ = 89.343 (2)°
V = 1743.25 (9) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 173 K
0.44 × 0.38 × 0.35 mm

Data collection

Bruker Kappa DUO APEXII diffractometer
15272 measured reflections
7670 independent reflections
6167 reflections with $I > 2\sigma(I)$
R_{int} = 0.014

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.110
S = 1.05
7670 reflections
433 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

Cg is the centroid of the C2*B*–C7*B* ring.

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
C8*A*—H8*A*1$\cdots Cg^{i}$	0.99	2.96	3.9272 (13)	167

Symmetry code: (i) $x-1, y, z$.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su from the Chemistry Department of the University of Cape Town for her assistance with the data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG5002).

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Methyl 1-cyclohexyl-6,7-dimethoxy-3,4-dihydroisoquinoline-3-carboxylate

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound is a precursor in the synthesis of novel chiral catalysts containing a tetrahydroisoquinoline framework. Upon oxidation of the sp2 hybridized nitrogen, the oxide form of this compound and derivatives are currently being tested in our laboratory as novel organocatalysts for asymmetric allylation reactions (Naicker *et al.* 2010*a*).

The structure has triclinic (*P*T) symmetry with two molecules in the asymmetric unit (Fig. 1). These two molecules are linked by various intermolecular short contact interactions and one C—H··· π (C2B—C7B ring) bond (Table 1). The crystal packing reveals that *via* the centre of symmetry operation the enantiomer generates its mirror image. This results in a layered packing along the *a* axis (Fig. 2).

From the crystal structure it is evident that the *N*-containing six membered ring assumes a twisted half boat conformation (Fig. 1). This heterocyclic ring within similar structures displays either a half chair ((Naicker *et al.* 2010*b*) or half boat (Naicker *et al.* 2011) conformation. A possible reason for the change is the introduction of the sp2 hybrized nitrogen atom.

As anticipated the cyclohexane moieties adopt chair conformations.

Experimental

To a solution of methyl 2-(cyclohexanecarboxamido)-3-(3,4-dimethoxyphenyl)propanoate (0.30 g, 0.86 mmol) in toluene (20 ml), phosphoryl trichloride (8.7 eq, 0.68 ml) was added. The mixture was refluxed for 4 h. Thereafter the toluene was evapourated under reduced pressure and the resulting residue treated with aqueous saturated potassium carbonate (15 ml) and extracted with ethyl acetate (2 *x* 10 ml). The organic extracts were combined and dried over anhydrous magnesium sulfate and then concentrated to dryness affording the crude product which was purified by column chromatography, (1:1 ethyl acetate, hexane), R_f = 0.5. Recrystallization from chloroform at room temperrature afforded colourless crystals suitable for X-ray analysis.

Melting point 377–379 K.

IR (neat) ν_{max}: 2928, 1738, 1514, 1249, 1149, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.70 (s, 1H), 4.29 (t, *J* = 8.4 Hz, 1H), 3.91 (s, 6H), 3.75 (s, 3H), 2.87 (m, 2H), 1.87–1.21 (m, 11H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.57, 151.04, 147.77, 129.82, 121.36, 110.60, 108.80, 59.40, 56.33, 55.98, 52.25, 42.67, 31.44, 30.80, 28.55, 26.55, 26.42, 26.14.

Symmetry codes: (i) $x-1, y, z$.

Fig. 1

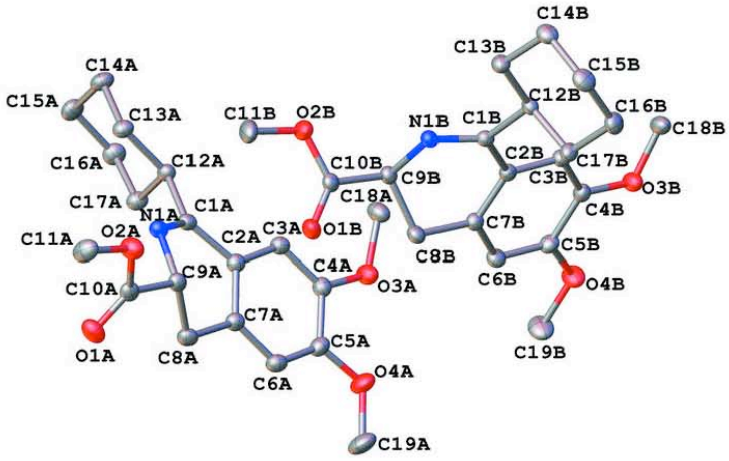
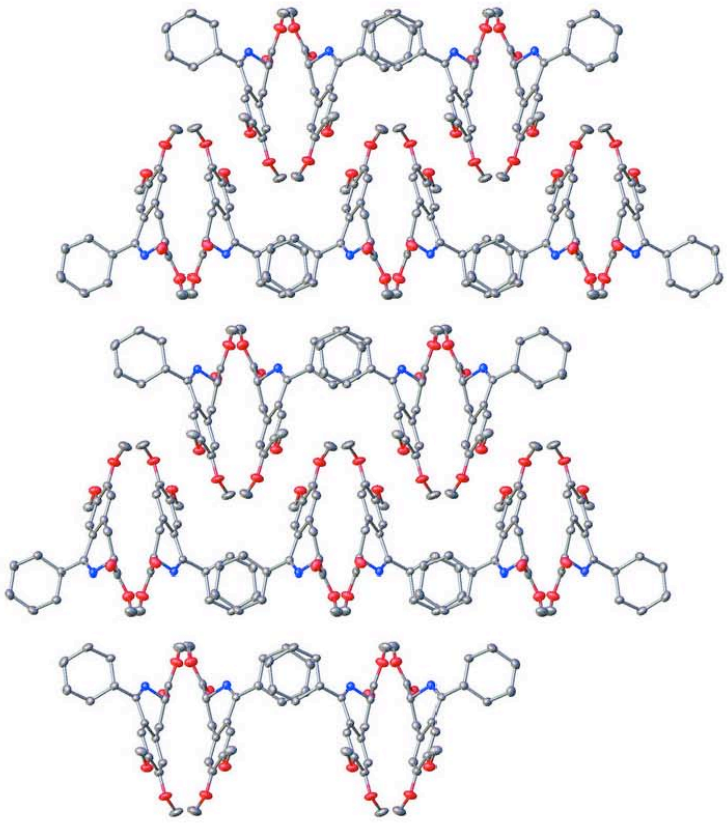


Fig. 2



Acta Crystallographica Section E
Structure Reports Online
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{(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl}diphenylmethanol

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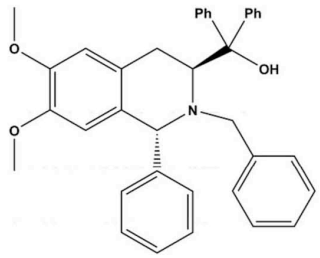
Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.003 Å; R factor = 0.025; wR factor = 0.068; data-to-parameter ratio = 6.7.

In the title compound, $C_{37}H_{35}NO_3$, a precursor to novel chiral catalysts, the N-containing six-membered ring assumes a half-chair conformation. Intermolecular C—H···O hydrogen bonds link the molecules in the crystal structure.

Related literature

For the synthesis of the title compound, see: Chakka *et al.* (2010). For related structures, see: Aubry *et al.* (2006). For a related structure with the same chiral centres and configuration, see: Naicker *et al.* (2009). For proline diaryl alcohols, see: Diner *et al.* (2008); Seebach *et al.* (2008).



Experimental

Crystal data

$C_{37}H_{35}NO_3$
M_r = 541.66
Monoclinic, $P2_1$
a = 11.9706 (5) Å
b = 10.1934 (4) Å
c = 13.1515 (5) Å
β = 116.546 (2)°
V = 1435.58 (10) Å^3
Z = 2
Cu $K\alpha$ radiation
μ = 0.62 mm^{-1}
T = 173 K
0.22 × 0.14 × 0.12 mm

Data collection

Bruker Kappa Duo APEXII diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2006)
T_{min} = 0.876, T_{max} = 0.930
15262 measured reflections
2514 independent reflections
2451 reflections with $I > 2\sigma(I)$
R_{int} = 0.025

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.025
$wR(F^2)$ = 0.068
S = 1.10
2514 reflections
375 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C15—H15···O2^{i}	0.95	2.44	3.385 (2)	171

Symmetry code: (i) $x, y, z-1$.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997) and *DIAMOND* (Brandenburg, 1998); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su of the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection and Dr M Bala of the School of Chemistry at University of KwaZulu-Natal for his assistance with preparation of this manuscript.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: LX2135).

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Acta Cryst. (2010). E**66**, o638 [doi:10.1107/S1600536810005295]

{(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl}diphenylmethanol

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound (**2**, Fig. 3) is a precursor in the synthesis of novel chiral ligands involving a tetrahydroisoquinoline backbone. Recently, we have reported the application of these ligands as useful catalysts for transfer hydrogenation reactions (Chakka *et al.*, 2010).

Compound 2 contains four phenyl rings and the absolute stereochemistry was confirmed to be *R,S* at C1 and C9 positions as shown in Fig. 1, respectively (Aubry *et al.*, 2006). The crystal packing is stabilized by intermolecular C—H···O hydrogen bonds. The H atom of methanol does not form hydrogen bonds (Table 1 & Fig. 2). According to the Cambridge structural data base this is the first tetrahydroisoquinoline derivative with diaryl substitution at the C10 position. The structure displays a *gauche* or sc (synclinal) conformation around the O3—C10—C9—N1 bond with the OH group almost over the piperidine ring with a torsion angle of -77.0 (2)°. Due to the lack of analogous structures this observation was compared to proline diaryl alcohols (Seebach *et al.*, 2008) which display a similar conformation around the exocyclic C9—C10 bond. Given the success of proline diaryl alcohols as a chiral catalyst (Diner *et al.*, 2008) this comparison is particularly useful for catalysts bearing a tetrahydroisoquinoline framework as this feature could have a significant effect on the stereocontrol of the catalyst.

We recently reported a crystal structure of a similar molecule to the title compound (Naicker *et al.*, 2009) which has an ester moiety at the C10 position and the N-containing six membered ring assumes a half boat conformation. The N-containing six membered ring in the title compound exists in a half chair conformation (see Fig. 1). A possible reason for this difference in conformation could be the introduction of large phenyl ring substitiuents at the C10 position. The efficiency of these tetrahydroisoquinoline catalysts is currently being tested in our laboratory.

Experimental

To a solution of compound **1** (Fig. 3) (500 mg, 1.19 mmol) in THF (10 ml), freshly prepared Grignard reagent of phenyl magnesium bromide (2.17 g, 11.9 mmol) was added under a nitrogen atmosphere at ambient temperature. Completion of the reaction was monitored with TLC by quenching 0.1 ml aliquots of the reaction mixture with saturated ammonium chloride solution at 0 °C using ethyl acetate/hexane as the solvent (40 : 60 R_f 0.5). Thereafter the reaction mixture was filtered and the solvent was evaporated under reduced pressure to afford the crude product. This was purified by column chromatography using ethyl acetate/hexane (40:60) as the eluent to yield 80 % (0.52 g) pure tetrahydroisoquinoline diphenyl alcohol **2** as a white solid. ^{1}H NMR (600 MHz,$CDCl_3$,δ, p.p.m): 7.38 (d, *J* = 7.26 Hz, 2H), 7.32–7.16 (m, 9H), 6.54 (s, 1H), 6.26 (s, 1H), 5.19 (s, 1H), 3.85–3.72 (m, 6H), 3.61 (s,6*H*), 3.23 (dd, *J* = 5.10, 15.66 Hz, 1H), 2.98 (dd, *J* = 3.00, 15.72, Hz, 1H). Light yellow crystals suitable for X-ray diffraction were obtained by slow evaporation of **2** in dichloromethane at room temperature.

Fig. 1

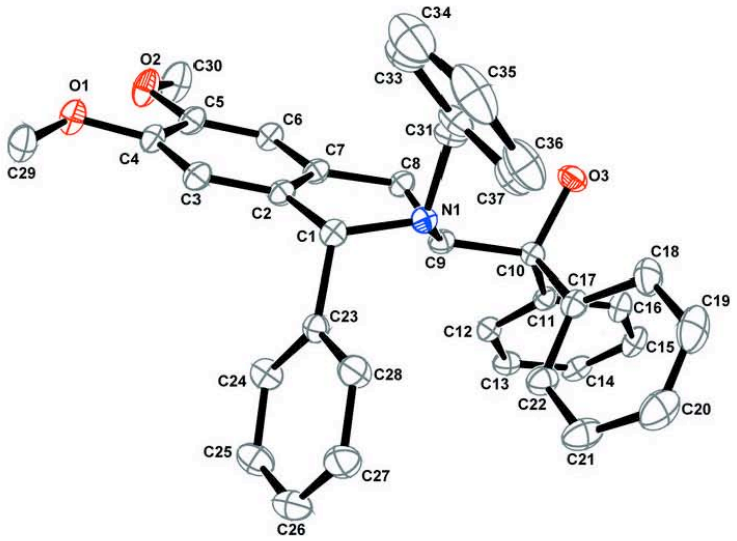
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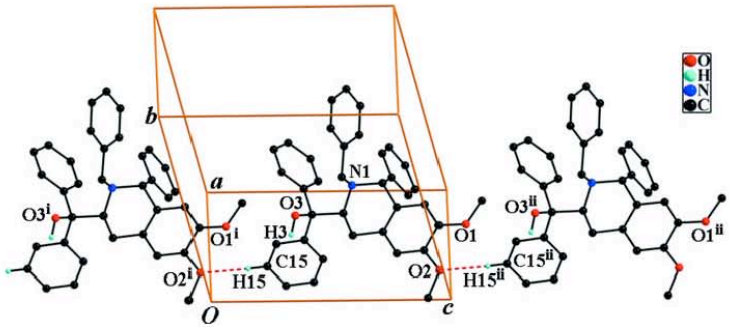
Fig. 2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(1*R*,3*S*)-Methyl 6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

Tricia Naicker,[a] Thavendran Govender,[b] Hendrik G. Kruger[a] and Glenn E. M. Maguire[a]*

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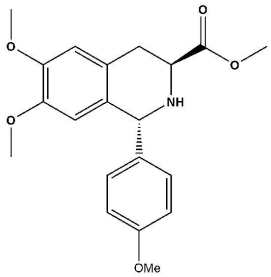
Received 8 September 2010; accepted 2 November 2010

Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.002 Å; R factor = 0.036; wR factor = 0.090; data-to-parameter ratio = 12.0.

The title compound, $C_{20}H_{23}NO_5$, is the third in a series of tetrahydoisoquinoline (TIQ) compounds that are precursors to novel chiral catalysts. The N-containing six-membered ring assumes a half-boat conformation. No hydrogen bonding is observed in the crystal structure.

Related literature

For related structures, see: Naicker *et al.* (2009, 2010); Alberach *et al.* (2004). For the synthesis of the title compound, see: Aubry *et al.* (2006).



Experimental

Crystal data

$C_{20}H_{23}NO_5$
M_r = 357.39
Orthorhombic, $P2_12_12_1$
a = 5.3719 (7) Å
b = 12.1726 (14) Å
c = 27.021 (3) Å
V = 1766.9 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 173 K
0.20 × 0.12 × 0.12 mm

Data collection

Bruker Kappa DUO APEXII diffractometer
13619 measured reflections
2878 independent reflections
2538 reflections with $I > 2\sigma(I)$
R_{int} = 0.032

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.090
S = 1.04
2878 reflections
239 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors thank Dr Hong Su of the University of Capetown for the data collection and structure refinement.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG2711).

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Acta Cryst. (2010). E**66**, o3105 [doi:10.1107/S1600536810044909]

(1*R*,3*S*)-Methyl 6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound was derived from commercially available *L*-DOPA and anisaldehyde. Diastereomers formed during the first step of the synthesis were separated to yield subsequent derivatives and the title compound with the stereochemistry as illustrated in Fig. 1. The title compound is the third report in a series of molecules containing a tetrahydroisoquinoline backbone and is a precursor to one of the molecules that we previously reported ((1*R*,3*S*)-methyl 2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate), (Naicker *et al.*, 2009). The molecule has been reported previously and the absolute stereochemistry of the diastereomer was confirmed to be *R,S* at C4 and C2 positions respectively by proton NMR (Aubry *et al.*, 2006).

There are a number of common features found in this structure and that of the the unprotected secondary amine system. First, the *N*-containing six membered ring assumes a half boat conformation. This differs from last report for the (1*R*,3S)-2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4 tetrahydroisoquinolin-3-yl diphenylmethanol structure (Naicker *et al.*, 2010) and previous reports by Alberach *et al.* (2004) and Aubry *et al.* (2006) where the heteroatomic ring adopted a half chair conformation. Second, given the presence of the secondary amine, ether and in this example ester functional groups, no hydrogen bonding is observed in any of the structures of this series, (see Fig. 2).

Experimental

A solution of the Cbz protected *trans*-6,7-dimethoxy-1-(4-methoxyphenyl)-TIQ methyl ester (1.0 g, 0.21 mmol) in THF (20 ml) was added to a suspension of activated 10 wt% Pd/C (500 mg) in dry MeOH (20 ml). The mixture was connected to a hydrogen source at one atmosphere and stirred at room temperature for 1 h. Completion of the reaction was monitored through TLC in hexane/ethyl acetate (50/50, R_f = 0.6). The Pd/C was filtered through a Celite pad and washed with methanol (20 ml). The filtrate was evaporated under reduced pressure affording the crude amino ester, which was purified by column chromatography using ethyl acetate/hexane (50:50) as the eluent to yield pure title compound (0.70 g, 93%) as a yellow solid. m.p. = 392–393 K. Crystals suitable for X-ray diffraction were obtained by slow evaporation of the title compound in MeOH at room temperature.

^{1}H NMR (600 MHz, $CdCl_3$, d, p.p.m.): 1.58 (broad s, 1H), 2.99 (dd, 1H), 3.09 (dd, 1H), 3.60 (s, 3H), 3.66 (s, 3H) 3.67(s, 3H), 3.78 (m, 1H), 3.88 (s, 3H), 5.23 (s, 1H), 6.30(s, 1H), 6.61 (s, 1H), 6.82 (d, 2H), 7.09 (d, 2H).

IR: 2946 (w), 1700 (w), 1507 (*s*), 1223 (*vs*), 832 (*s*), 563 (w)

Refinement

All H atoms, except H1N, were positioned geometrically with C—H distances ranging from 0.95 Å to 1.00 Å and refined as riding on their parent atoms, with U_{iso} (H) = 1.2–1.5U_{eq} (C).

Fig. 1

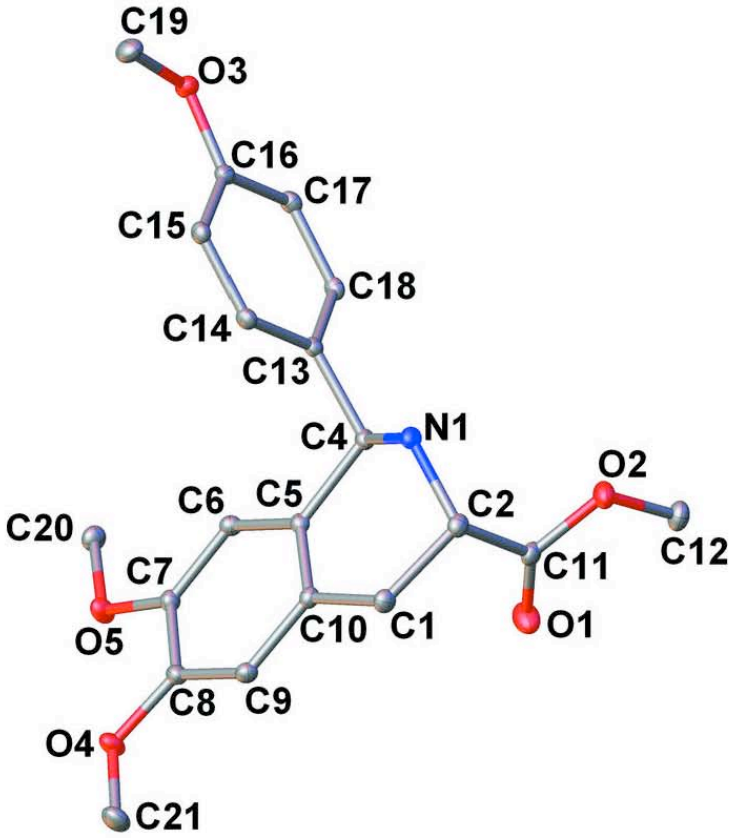
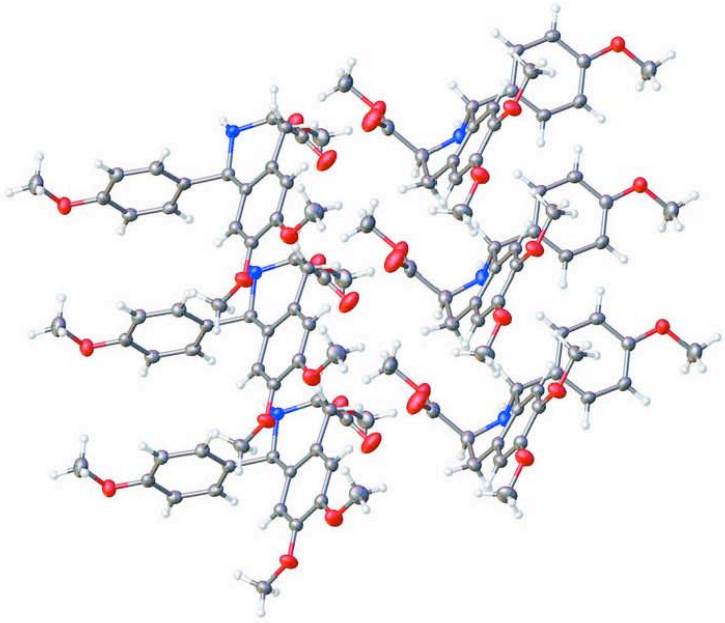

C19
O3
C16
C17
C15
C18
C14
C13
C4
N1
O2
C6
C5
C2
C20
C12
C7
C11
O5
C10
C1
O1
C8
C9
O4
C21

Fig. 2



organic compounds

Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

(1*R*,3*S*)-Methyl 2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

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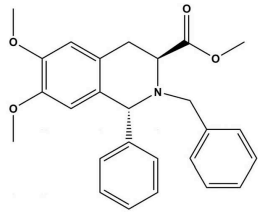
Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.002 Å; R factor = 0.028; wR factor = 0.077; data-to-parameter ratio = 12.7.

In the title compound, $C_{26}H_{27}NO_4$, a precursor to novel chiral catalysts, the N-containing six-membered ring assumes a half-boat conformation. Various C—H$\cdots\pi$ interactions and intermolecular short contacts (C$\cdots$H = 2.81–2.90 Å) link the molecules together in the crystal structure.

Related literature

For the synthesis, see: Chakka *et al.* (2009). For crystallograhic details of analogous molecules, see Alberch *et al.* (2004); Aubry *et al.* (2006).



Experimental

Crystal data

$C_{26}H_{27}NO_4$
M_r = 417.49
Triclinic, $P1$
a = 6.0199 (1) Å
b = 9.2592 (2) Å
c = 11.0429 (2) Å
α = 73.365 (1)°
β = 74.694 (1)°
γ = 75.737 (1)°
V = 559.05 (2) Å^3
Z = 1
Cu $K\alpha$ radiation
μ = 0.67 mm^{-1}
T = 173 K
0.22 × 0.12 × 0.08 mm

Data collection

Bruker Kappa Duo APEXII diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1997)
T_{min} = 0.692, T_{max} = 0.753
7546 measured reflections
3561 independent reflections
3536 reflections with $I > 2\sigma(I)$
R_{int} = 0.012

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.028
$wR(F^2)$ = 0.077
S = 1.07
3561 reflections
281 parameters
3 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Absolute structure: Flack (1983), 1483 Friedel pairs
Flack parameter: −0.01 (14)

Table 1
C—H$\cdots\pi$ interaction (Å, °).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
C19—H19$A\cdots Cg^{i}$	0.98	2.82	3.639 (2)	148

Symmetry code: (i) $x+1, y+1, z-1$. Cg is the centroid of the C21–C26 ring.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008) and *X-SEED* (Barbour, 2001); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *ORTEP-3*.

The authors wish to thank Dr Hong Su of the Chemistry Department at the University of Cape Town for his assistance with the crystallographic data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG2607).

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Acta Cryst. (2009). E**65**, o3278 [doi:10.1107/S1600536809050521]

(1*R*,3*S*)-Methyl 2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

T. Naicker, M. McKay, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound (2, Scheme 1) is a precursor in the synthesis of novel chiral ligands containing a tetrahydroisoquinoline backbone. We have recently reported the use of these ligands as successful catalysts for transfer hydrogenations reactions (Chakka *et al.*, 2009).

Compound 2 was derived from commercially available *L*-DOPA and benzaldehyde. Diastereomers formed during the first step of the synthesis were separated to yield subsequent derivatives and the title compound and with the stereochemistry as illustrated in Figure 1. The absolute stereochemistry was confirmed to be *R,S* at C1 and C9 positions respectively.

From the crystal structure it is evident that the N-containing six membered ring assumes a half boat conformation (Figure 1). This differs from an analogous structure which assumes a half chair conformation (Aubry *et al.*, 2006 and Alberch *et al.*, 2004). A possible reason for this change in conformation could be either the introduction of a substitutent on the nitrogen or the *trans* position of the phenyl ring at the C1 position.

The molecule exhibits various intermolecular short contacts *i.e.* between the methyl ester hydrogen (H11C) and phenyl ring (C14) of a neighbouring molecule; H15 to C6 and C7 and H24 to C14 and C15.

The methoxy groups display different interactions. The first methoxy group at C4 position displays one interaction between H18B and O2, which is the ether oxygen of the other methoxy group. The second methoxy group at C5 position displays three interactions; the first being the above mentioned interaction with H18B and O2, the second being a short contact between O2 and H25, and the third being another CH-π the interaction between H19A and C25. The atoms involved in these short contacts are shown in Figure 2.

Experimental

To a solution of **1** (Scheme 1) (500 mg, 1.52 mmol) in acetonitrile (20 ml), solid K_2CO_3 (635 mg, 4.58 mmol) was added followed by benzyl bromide (286 mg, 1.67 mmol) at ambient temperature. There after the reaction mixture was refluxed for 3 h. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (60:40, R_f 1/2). The solvent was evaporated and 30 ml of ethylacetate was added, washed with 2 × 10 ml of water, the organic layer was separated, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford crude product, which was purified by column chromatography using hexane/ethyl acetate (60:40) as the eluent to yield pure benzyl ester **2** (0.44 g, 90%) as a white solid.

^{1}H NMR (400 MHz/$CDCl_3$): δ = 7.44 (d, *J* = 1.16 Hz, 2H), 7.32–7.10 (m, 14H), 7.0–6.88 (m, 6H), 6.69 (s, 1H), 6.38 (s, 1H), 4.74 (s,1*H*), 4.21 (d, *J* = 13.60 Hz, 1H), 4.14 (q, *J* = 3.70, 12.74 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H), 3.57 (s, 1H), 3.30–3.18 (m, 2H), 2.60 (dd, *J* = 3.60, 16.48 Hz, 1H).

Fig. 1

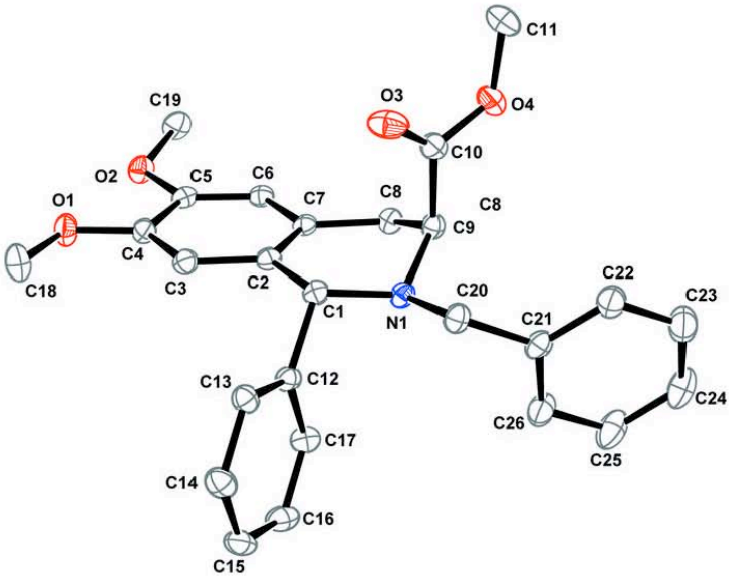
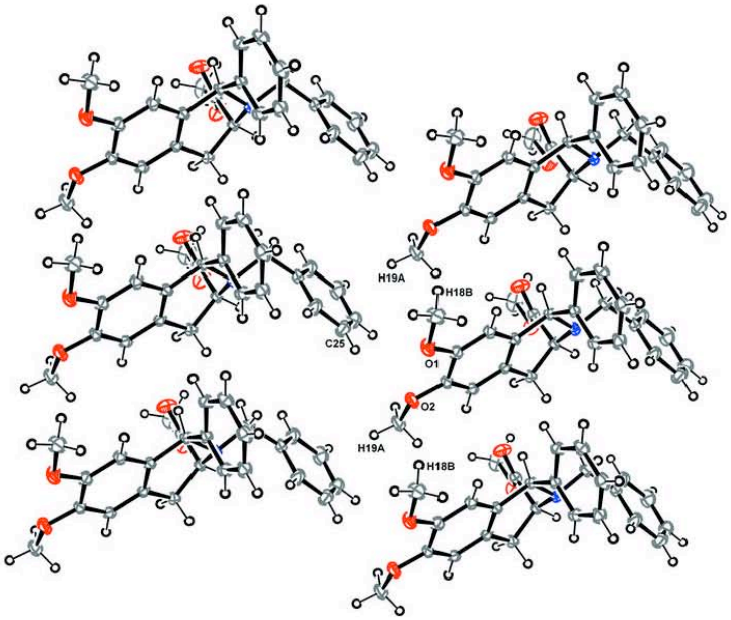

C11
O3
O4
C19
C10
O2
C5
C6
C8
C7
C8
O1
C9
C4
C2
C22
C3
C20
C23
C1
N1
C21
C13
C12
C24
C26
C17
C25
C14
C16
C15
C18

Fig. 2



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(1*R*,3*S*)-*N*-Benzhydryl-2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carbothioamide

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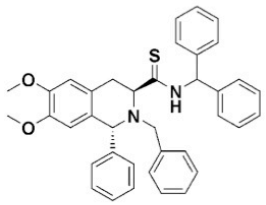
Received 4 November 2011; accepted 18 November 2011

Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.002 Å; R factor = 0.033; wR factor = 0.090; data-to-parameter ratio = 18.9.

The title compound, $C_{38}H_{36}N_2O_2S$, has a heterocyclic ring that assumes a half-chair conformation. The phenyl rings of neighbouring molecules align forming alternating chains parallel to [100] within the crystal packing. The absolute stereochemistry of the crystal was confirmed to be *R*,*S* at the 1- and 3-positions, respectively, by proton NMR spectroscopy. A single intramolecular N—H···N hydrogen bond is observed.

Related literature

For background to chiral organocatalysts bearing a tetrahydroisoquinoline framework and for related structures, see: Naicker *et al.* (2010, 2011*a*,*b*).



Experimental

Crystal data

$C_{38}H_{36}N_2O_2S$ M_r = 584.75
Orthorhombic, $P2_12_12_1$
a = 9.0463 (1) Å
b = 17.6687 (2) Å
c = 19.6178 (2) Å
V = 3135.64 (6) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.14 mm^{-1}
T = 173 K
0.34 × 0.32 × 0.30 mm

Data collection

Nonius KappaCCD diffractometer
7464 measured reflections
7464 independent reflections
6545 reflections with $I > 2\sigma(I)$
R_{int} = 0.013

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.090
S = 1.06
7464 reflections
394 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Absolute structure: Flack (1983), 3271 Friedel pairs
Flack parameter: −0.07 (5)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H1*N*···N1	0.903 (17)	2.139 (16)	2.6548 (15)	115.4 (12)

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su from the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection and refinement.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG5134).

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Acta Cryst. (2011). E**67**, o3441 [**doi:10.1107/S1600536811049324**]

(1*R*,3*S*)-*N*-Benzhydryl-2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carbothioamide

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

Chiral organocatalysts bearing a tetrahydroisoquinoline (TIQ) framework have proven to be very successful by our research group (Naicker *et al.*, 2010 and 2011*a*). The title compound (Fig. 1) is a precursor in the synthesis of these novel chiral organocatalysts. The crystal structure contains a thioamide moiety at the C10 position making it the first example in this class to be reported.

The absolute stereochemistry of the molecule was confirmed to be *R,S* at C1 and C9 positions respectively by proton NMR spectroscopy.

The *N*-containing six membered ring assumes a half chair conformation [Q=0.5212 (12) Å, θ= 50.52 (14)° and φ=325.8 (18)°] similar to an analogous structure which has a methyl ester at the C10 position (Naicker *et al.*, 2011*b*). This heterocyclic ring shape affects the position of the thioamide moiety relative to the phenyl ring at the C1 position. The torsion angle for C1—N1—C9—C10 is -157.6 (1)°. Also, in the analogous structure the torsion angle between C8—N1—C9—C10 is 44.1 (2)° while in the title structure this angle is -18.3 (2)°. This is probably due to the C═S bond which adopts a more planar orientation relative to the TIQ backbone as compared to the C═O bond orientation previously reported in this family of molecules (Naicker *et al.*, 2011*b*). In addition, the *N*-benzyl and phenyl ring at C1 exist in a *trans* orientation along the N1—C9 bond with a dihedral angle of -153.3 (1)°.

The title compound contains four phenyl rings however, no intermolecular C—H···π or π···π interactions are evident. A single intramolecular hydrogen bond between atoms N2—H1N···N1 can be observed. The molecules within the crystal structure line up such that the phenyl rings face each other, this forms alternating chains parallel to the [100] plane (Fig. 2).

Experimental

To a solution of (1*R*,3*S*)-*N*-benzhydryl-2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (0.1 g, 0.02 mmol) in dry THF (20 ml), Lawssons reagent (0.06 g, 0.15 mmol) was added. The mixture was allowed to stir at 50 °C for 16 h under a nitrogen atmosphere. Thereafter the solvent was evaporated *in vacuo* and the residue purified using silica column chromatography (hexane: ethyl acetate, 50:50, R_f = 0.8) to yield the pure product (0.1 g, 90%) as a yellow solid. *M*.p. = 458 K

Recrystallization from ethyl acetate at room temperature afforded crystals suitable for X-ray analysis.

Refinement

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms could be found in the difference electron density maps. H1N was thus positioned and refined freely with independent isotropic temperature factors. The other hydrogen atoms were placed with idealized positions and refined as riding on their parents atoms with U_{iso} = 1.2 or 1.5 *x* U_{eq} (C).

Fig. 1

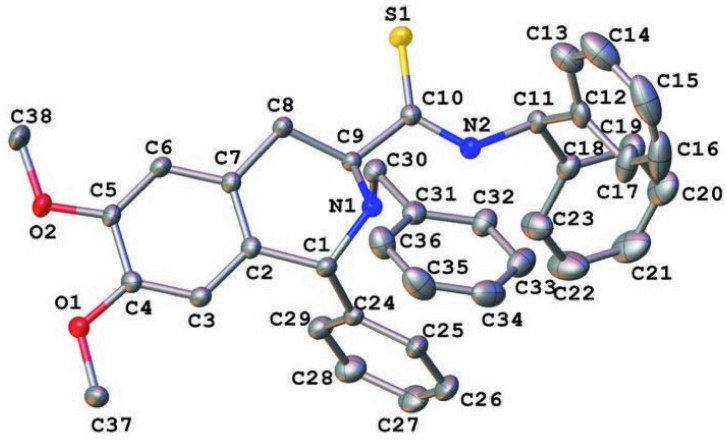
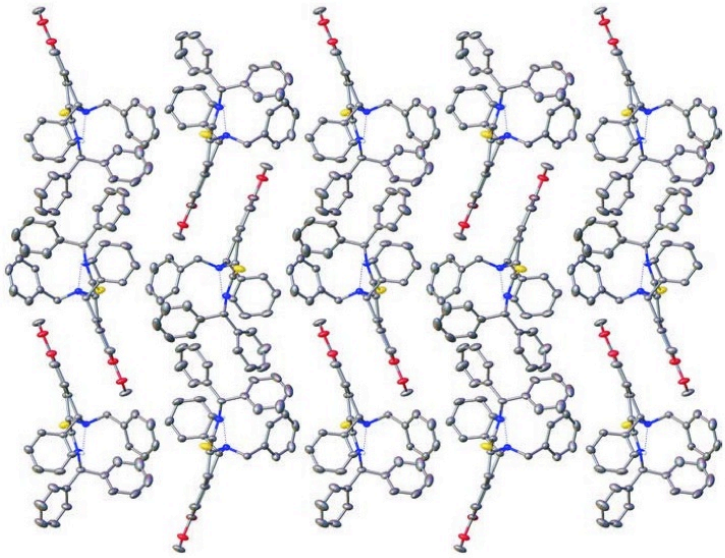


Fig. 2



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(*S*)-Methyl 3-(3,4-dimethoxyphenyl)-2-[2-(diphenylphosphanyl)benzamido]-propanoate

Tricia Naicker,[a] Thavendran Govender,[a] Hendrick G. Kruger[b] and Glenn E. M. Maguire[b]*

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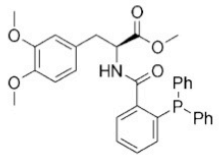
Received 12 October 2011; accepted 8 November 2011

Key indicators: single-crystal X-ray study; T = 173 K; mean σ(C–C) = 0.002 Å; R factor = 0.034; wR factor = 0.079; data-to-parameter ratio = 19.0.

Molecules of the title compound, $C_{31}H_{30}NO_5P$, show a sttagered conformation about the C—C bond joining the dimethoxybenzene group to the chiral centre, with the dimethoxybenzene ring *gauche* to the amide group and *anti* to the ester group. In the crystal, weak intermolecular N—H···O and C—H···O hydrogen bonds form layers parallel to (110).

Related literature

For related structures, see: Clegg & Elsegood, (2003). For organocatalysts prepared from a related precursor, see: Naicker *et al.* (2010, 2011). For analogous precusors to several biologically active compounds, see: Zalán *et al.* (2006).



Experimental

Crystal data

$C_{31}H_{30}NO_5P$
M_r = 527.53
Monoclinic, $P2_1$
a = 10.2218 (3) Å
b = 8.4535 (2) Å
c = 15.7633 (4) Å
β = 100.300 (2)°
V = 1340.16 (6) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.14 mm^{-1}
T = 173 K
0.18 × 0.15 × 0.14 mm

Data collection

Nonius KappaCCD diffractometer
6654 measured reflections
6654 independent reflections
5550 reflections with $I > 2\sigma(I)$

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.079
S = 1.04
6654 reflections
350 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Absolute structure: Flack (1983), 3108 Friedel pairs
Flack parameter: −0.08 (6)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1*N*···O2^{i}	0.816 (17)	2.345 (17)	3.1428 (17)	166 (15)
C10—H10*A*···O3^{i}	0.98	2.56	3.371 (2)	140
C21—H21···O4^{ii}	0.95	2.58	3.279 (2)	131

Symmetry codes: (i) $-x+1, y+\frac{1}{2}, -z$; (ii) $-x+2, y+\frac{1}{2}, -z+1$.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Dr Hong Su of the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: LR2034).

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Acta Cryst. (2011). E**67**, o3285 [**doi:10.1107/S1600536811047179**]

(*S*)-Methyl 3-(3,4-dimethoxyphenyl)-2-[2-(diphenylphosphanyl)benzamido]propanoate

T. Naicker, T. Govender, H. G. Kruger and G. E. M. Maguire

Comment

The title compound is being used as a precusor to novel chiral organocatalysts (Naicker *et al.* 2010 and 2011). Analogous structures are well known precusors to several biologically active compounds (Zalán *et al.*, 2006).

There is an analogous X-ray crystal structure reported (Clegg and Elsegood, 2003), which has a *tert*-butoxy group at the ester carboxyl carbon and a (9-*H*-Fluoren-9-yl)-methoxy group attached to the amide carboxyl carbon. The title compound has a methoxy and a 2-diphenylphoshinobenzene group at the these positions respectively.

The title compound exists in a well ordered staggered conformation about the C7—C8 bond (Fig. 1). As in the analogous X-ray structure, the dimethoxybenzene ring is *gauche* to the amide group and *anti* to the ester group. The configuration at C8 was confirmed to be *S*, on the basis of anomalous scaterring effects, Flack *x* parameter = -0.08 (6).

The molecules in the crystal are connected by relatively weak hydrogen bond interactions (Fig. 2) in which the N1—H1···O2 and the C10—H10A···O3 interactions give chains along the *b* axis. These chains are interconnected *via* the C21—H21···O4 interaction giving a layered packing system.

Experimental

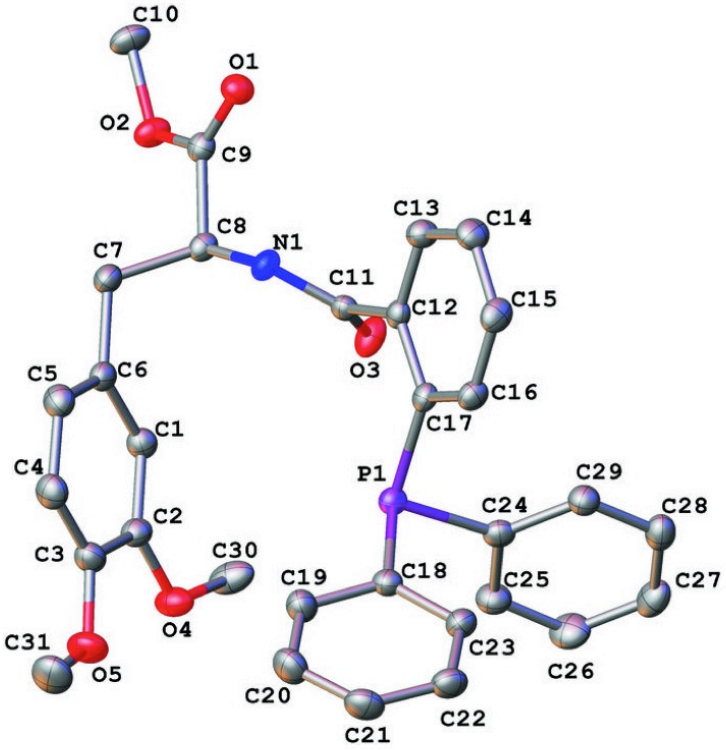
2-(diphenylphosphanyl)benzoic acid (1.3 g, 4.2 mmol) was dissolved was dissolved in DMF (15 ml) and THF (5 ml) followed by addition of HBTU (4.6 mmol), DIPEA (8.4 mmol) and (*S*)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate (1.0 g, 4.2 mmol). The reaction mixture was then stirred at room temperature until no more starting material could be detected by TLC analysis. The reaction mixture was poured into 30 volumes of chilled water; the mixture was then extracted thrice with ethyl acetate (20 ml). The combined extracts were dried over anhydrous sodium sulfate and then concentrated to dryness affording the crude product. This crude product was purified by column chromatography (50:50 EtOAc/Hexane, R_f = 0.6) to afford the product 2.20 g (98%) as a white solid. *M*.p. = 420 K.

Recrystallization from ethyl acetate at room temperature afforded crystals suitable for X-ray analysis.

Refinement

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms could be found in the difference electron density maps. H1N was thus positioned and refined freely with independent isotropic temperature factors. The other hydrogen atoms were placed with idealized positions and refined as riding on their parents atoms with U_{iso} = 1.2 or 1.5 times U_{eq} (C).

Fig. 1


C10
O1
O2
C9
C8
N1
C7
C13
C14
C11
C12
C15
O3
C5
C6
C16
C17
C1
C4
P1
C29
C24
C28
C2
C3
C30
C19
C18
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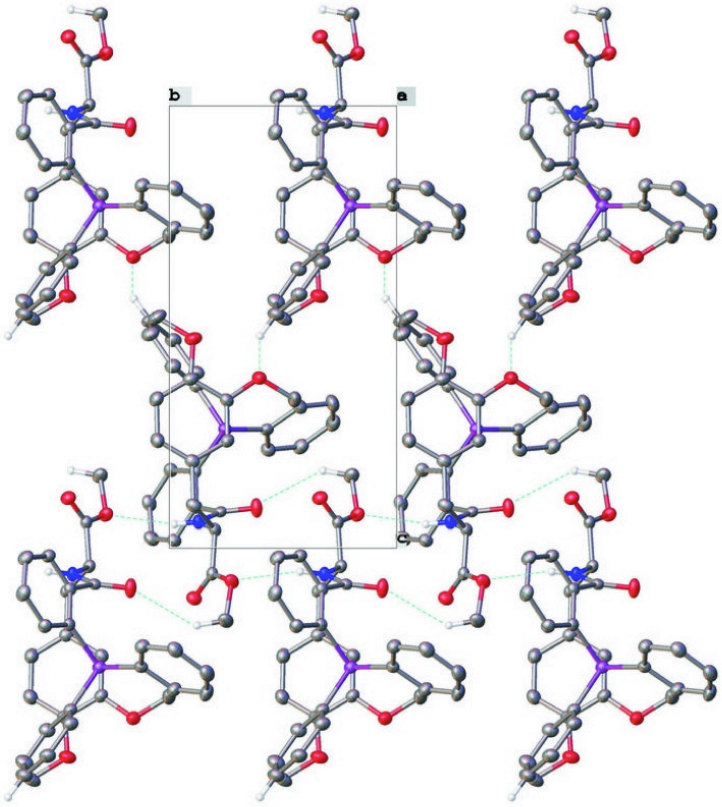
C27
O4
C31
O5
C23
C26
C20
C22
C21

Fig. 2



CHAPTER 6

BOOK CHAPTER

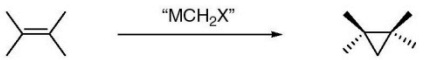
This is a book chapter that was written in collaboration with Prof. Per Arvidsson (Astrazeneca, Sweden) and Dr Partha Bose (University of Uppsala, Sweden) on Asymmetric Organocatalytic Cyclopropane Formation for the Elsevier book entitled Comprehensive Chirality and is currently with the editors in its final proof stage after acceptance.

I (Tricia Naicker) wrote the subsections entitled Asymmetric cyclopropanation reactions through organocatalytic hydrogen bond activation of electron-deficient olefin derivatives, Asymmetric cyclopropanation reactions through organocatalytic activation of ylides and Organocatalytic asymmetric cyclopropanation through chiral phase transfer catalysis (6.11.4-6.11.6).

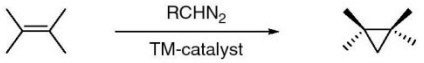
6.11.2 Background to Cyclopropane Synthesis

As a consequence of the importance of the cyclopropane motif in organic chemistry, a range of synthetic methods have been explored for the asymmetric synthesis of chiral cyclopropane analogs.[2,5,16–20] Two comprehensive reviews summarizing these developments over the last 10 years deserves special attention,[9,21] as they are not restricted to (organo)catalytic procedures.

The cyclopropane motif is traditionally prepared from olefins using one of six basic kinds of reactions. Both the halomethylmetal-mediated reaction (equation 1), in which the classical Simmons-Smith reaction[22–24] represents the archetypical example, and the transition metal catalyzed decomposition of diazo compounds (for reviews see Refs. 25–28) (equation 2) converts alkenes into cyclopropane derivatives. Nowadays, useful asymmetric versions of these reactions exist, either using chiral auxiliaries or employing chiral catalysis; however, as both these reaction classes use metal catalysis they are out of scope for the present text, and the reader is referred to the key review articles describing the recent development in this area.[9,19]

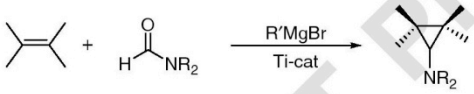


(1)



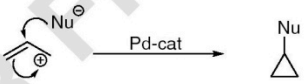
(2)

Likewise, alternative routes to the cyclopropane motif, such as the Kulinkovich-de Meijere reaction (equation 3),[29–31] and the recent examples of epoxide methylene-transfer cyclopropanation (equation 4),[32–34] and nucleophile-promoted intramolecular cycloadditions (equation 5)[35–37] are excluded from the present summary as these reactions rely on transition metal catalysis.



(3)

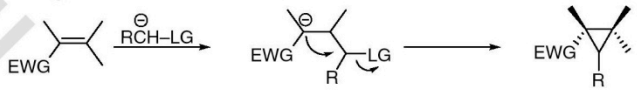
(4)



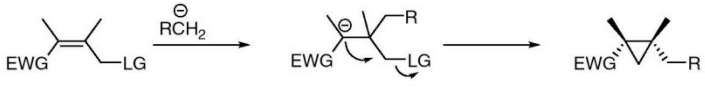
(5)

Also excluded from the present coverage are enzymatic routes to chiral cyclopropanes, as all these examples relie on desymmetrization or kinetic resolution of *meso*- or racemic-cyclopropane derivatives, respectively, and thus do not involve an organocatalyzed carbon–carbon bond forming step.[9,19]

The other two main approaches for synthesizing the cyclopropane motif starting from olefins rely on nucleophilic ring closure sequences (equations 6 and 7):



(6)



(7)

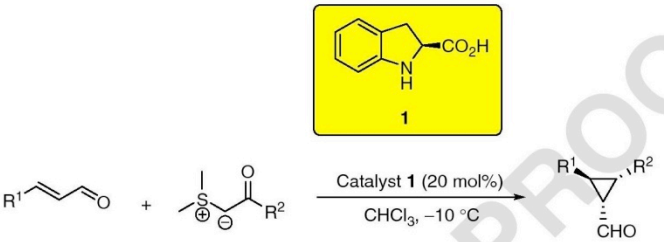
All, but one, examples of organocatalyzed asymmetric cyclopropanation reactions reported until today operate through these so-called Michael-initiated ring closure (MIRC) reactions, either with the leaving group present on the nucleophilic reagent (equation 6) or on the olefin part (equation 7).

In order to induce chirality in these reactions, the chiral organocatalyst interacts with an electrophilic olefin derivative, the nucleophilic reagent, or a combination of both. We have chosen to partition the presentation below by how the catalyst is proposed to act. Although this division is somewhat arbitrary as the exact mechanisms by which these catalysts operate is, at best,

speculative, we begin by presenting reactions that activate the electrophilic olefin derivative and finish with reactions where the catalyst is more likely to operate on the initial nucleophile reagent.

6.11.3 Asymmetric Cyclopropanation Reactions through Organocatalytic Iminium Ion Activation of α,β-Unsaturated Aldehydes and Ketones

Building on their seminal work on increasing the reactivity of α,β-unsaturated aldehydes and ketones through organocatalytic LUMO lowering activation,[38,39] MacMillan's group reported the first enantioselective cyclopropanation based on this concept in 2005.[40] In an organocatalytic implementation of the MIRC reaction (equation 6, above), the double bond is activated through iminium-ion formation with the catalyst, which facilitates attack by nucleophilic sulfonium ketone ylides. Commercially available (2*S*)-dihydroindole-2-carboxylic acid **1** was introduced as a novel organocatalyst for this reaction. This novel reaction sequence provided the corresponding cyclopropane derivatives with excellent levels of enantio enrichment and yields, Scheme 1.



R^1	R^2	*Yield (%)*	*de %*	*ee %*
n-Pr	Bz	85	94	95
CH_2Oallyl	Bz	77	90	91
Me	Bz	67	90	90
Ph	Bz	73	94	89

Scheme 1 Asymmetric organocatalytic cyclopropanation of α,β-unsaturated aldehydes as reported by MacMillan and co-workers (representative data shown; R^1 = Me, R^2 = Bz was carried out at 4 °C).

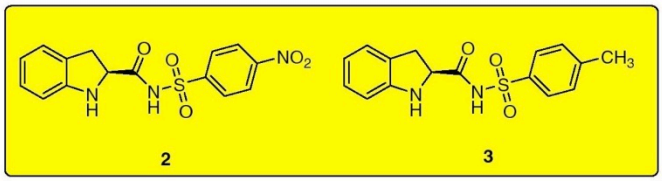
As part of the mechanistic rationale for this highly stereoselective reaction they put forward a new stereoinduction concept for organocatalysis termed directed electrostatic activation (DEA), Figure 2. They reasoned that the catalyst-derived iminium-ion and the ylide engage in electrostatic association *via* their pendant carboxylate and thionium substituents. In doing so, the ylide carbanion and the iminium β-carbon are transiently activated while in close proximity, thereby facilitating the carbon–carbon bond formation. Within this mechanistic framework the (2*S*)-dihydroindole-2-carboxylic acid scaffold proved to be the best DEA cyclopropanation catalyst, specifically because the catalyst-derived zwitterion would predominately populate the (*Z*)-iminium isomer to minimize van der Waals interactions between the substrate olefin and the aryl hydrogen. As a result, the carboxylate group on the catalyst framework directs ylide addition selectively to the *Re*-face of the activated olefin, thereby ensuring enantiocontrol in the reaction. Evidently, this catalyst design was successful furnishing the corresponding cyclopropanes with excellent levels of stereoinduction (up to 95% *ee*; up to 94% diastereomeric excess (*de*)) and reaction yield up to 85%.

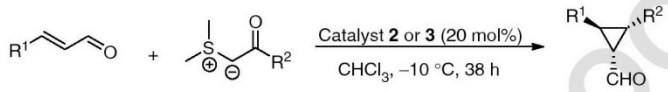
In the following years, substitution of the crucial carboxylic acid functionality of (2*S*)-dihydroindole-2-carboxylic acid paved the way for the development of new catalysts. In 2007, Arvidsson's group reported the synthesis of novel chiral arylsulfonamides **2**

E-isomer *Z*-isomer

Figure 2 Rationale for the observed diastereo- and enantioselectivity seen with dihydroindole-based catalyst **1**. Steric repulsion forces the iminium-on to adopt the Z-isomer, and direct electrostatic activation between the catalyst's carboxylic acid function and the ylide's thionium function certify high level of sterochemical control.

and **3** derived from (2*S*)-dihydroindole-2-carboxylic acid (Scheme 2), and employed these organocatalysts for similar enantioselective cyclopropanations of α,β-unsaturated aldehydes with sulfur ylides as those described above.[41] These catalysts were designed to allow fine tuning of the catalyst structure by varying the substitution on the phenyl ring of the aryl sulphonamide. Although these new catalysts performed the cyclopropanation reactions in worse yields than the chiral indoline-2-carboxylic acid used by MacMillan, these sulfonamide-modified dihydroindole derivatives produced high level of stereochemical induction, as seen in Scheme 2.

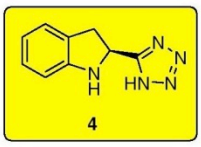


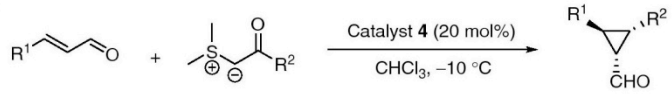


R^1	R^2	Catalyst	Yield (%)	de %	ee %
Me	Ph	**2**	45	95	88
n-Pr	Ph	**2**	25	96	94
Ph	Ph	**2**	20	95	92
Me	Ph	**3**	55	95	88
n-Pr	Ph	**3**	52	97	98
Ph	Ph	**3**	28	94	97

Scheme 2 Sulfonamide-based organocatalysts for asymmetric cyclopropanation reported by Arvidsson and co-workers (representative data shown; R^1 = Me, R^2 = Ph was carried out at 4 °C).

In the same year Arvidsson and co-worker developed another new chiral organocatalyst, a tetrazolic acid-functionalized dihydroindole, that is, **4**, for the enantioselective cyclopropanation of α,β-unsaturated aldehydes with sulfur ylides, Scheme 3[42]. Excellent diastereoselectivities ranging from 96% to 98% *de*, along with enantioselectivities exceeding 99% *ee*, for all reacted α,β-unsaturated aldehydes were observed. Clearly, replacing the carboxylic acid of catalyst **1** with the corresponding tetrazolic acid in catalyst **4** proved beneficial in terms of asymmetric induction.

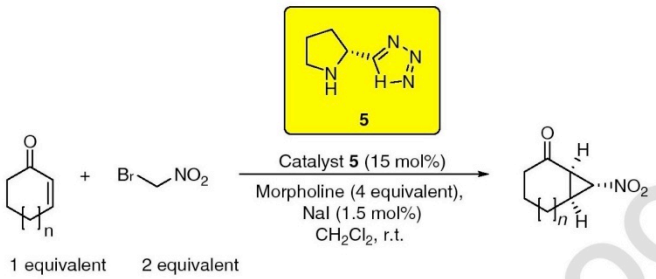




R^1	R^2	Yield (%)	de %	ee %
n-Pr	Ph	82	97	99
n-Pr	*p*-BrC_6H_4	74	97	99
Me	Ph	85	96	99
Ph	Ph	74	97	99

Scheme 3 Tetrazole-based catalyst for asymmetric organocatalytic cyclopropanation of α,β-unsaturated aldehydes as reported by Arvidsson and co-worker (representative data shown; R^1 = Me, R^2 = Ph was carried out at 4 °C).

Reagents containing both an acidic proton and a good leaving group attached to the same carbon atom represent alternative nucleophiles than sulfonium ylides for the iminium-ion activated cyclopropanation reaction. Ley's group was the first to illustrate this concept by employing bromonitromethane as a nucleophile in an asymmetric organocatalytic nitro-cyclopropanation in 2006.[43] Following the concept of tetrazolic acid substitution at the crucial 2 position of pyrrolidine motif, they used (*R*)-5-(pyrrolidin-2-yl)-1H-tetrazole **5** as an organocatalyst for activation of 2-cyclohexen-1-one followed by addition of bromonitromethane, Scheme 4. The original protocol was subsequently evolved by modifying the reaction conditions, which opened for a more general nitrocyclopropanation for both cyclic and acyclic α,β-unsaturated ketones.[44]



n	*Time (h)*	*Yield (%)*	*ee %*
0	2	87	48
1	2	87	90
2	16	91	70

Scheme 4 Asymmetric organocatalytic cyclopropanation of cyclic enones with bromonitromethane as nucleophile as reported by Ley and co-workers. Nitrocyclopropanation of acyclic α,β-unsaturated ketones was also reported, but gave modest results.

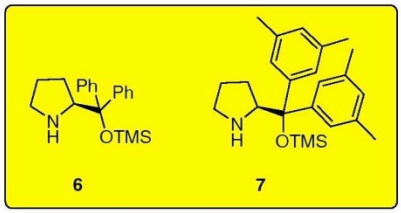
As seen in Scheme 4, the improved process yields bicyclic nitrocyclopropanes in high yield, full diastereoselectivity, and with good enantioselective control. Acylic α,β-unsaturated enones were also employed as electrophiles, and provided the corresponding straight-chain nitrocyclopropanes in good yields, but with modest degree of diastereoselectivity and enantiomeric excesses (*ee*'s). Chiral nitrocyclopropanes are useful building blocks, which may be converted to a wide range of functionalities, for example, reduction to aminocyclopropanes that are often found in biologically active derivatives.

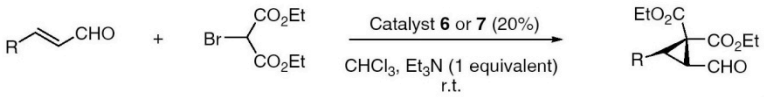
Using bromomalonates as nucleophile, the groups of Cordova [45,46] and Wang [47] independently reported novel examples of highly chemo- and enantioselective organocatalytic cyclopropanation of α,β-unsaturated aldehydes. The reaction was efficiently catalyzed by readily available chiral diarylprolinol TMS ether derivatives **6** and **7** and gave the corresponding 2-formylcyclopropanes in high yields with up to >25:1 diastereomeric ratio (*dr*) and 93–99% *ee*, Scheme 5.

This highly efficient reaction process produces synthetically and biologically important cyclopropanes in high levels of enantio- and diastereoselectivities from readily available starting materials. In contrast to the dihydroindole-based catalysts **1**–**4**, which restrict the *E*/*Z*-isomerization of the iminium-ion intermediate to the *Z*-isomer and use directed electrostatic activation to direct the nucleophiles attack from the top (*Re*-face), the diarylprolinol-based catalysts **6** and **7** use primarily steric shielding to enforce adoption of the *E*-isomer of the iminium-ion and nucleophilic attack from the bottom (also *Re*-face), Scheme 6.

Cordova and Wang also applied unsymmetrical 2-bromo-3-keto esters as nucleophiles, instead of the symmetric bromomalonates used above, thereby producing chiral cyclopropanes with three stereogenic centers. These studies were later expanded by Rios and co-workers [48] to include a variety of highly functionalized cyclopropanes in high diastereoselectivity and excellent enantioselectivities and yields, Scheme 7.

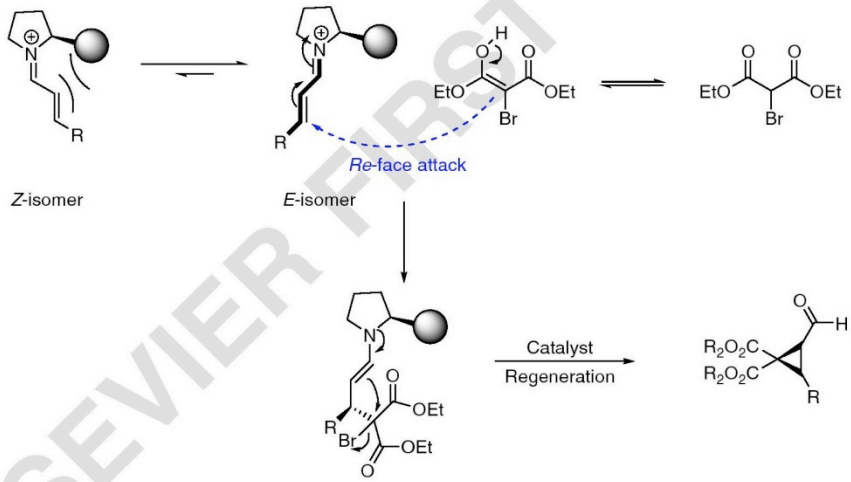
In 2010 Vicario and co-workers showed that the chiral amine-catalyzed enantioselective cyclopropanation of α,β-unsaturated aldehydes with diethyl bromomalonate, originally reported by Cordova and Wang, could be carried out without adding one equivalent of an external base, provided that the reaction proceed under iminium activation 'on water', Scheme 8.[49] Under the optimized conditions, the reaction proceeded in an efficient way when β-aryl-substituted α,β-unsaturated aldehydes were employed; however, it failed when aliphatic enals were used. For this reason, a new catalyst was designed and prepared, that is, catalyst **8**, in which the proline skeleton has been modified by incorporating a long hydrophobic alkyl side chain. The new catalyst **8** showed somewhat improved performance in the reaction of β-alkyl substituted α,β-unsaturated aldehydes, such as pent-2-enal. Although the yield of the reaction in this case was still rather low, the result suggests that the concept behind this catalyst design was functional.





R	*Catalyst*	*Yield (%)*	*de %*	*ee %*
Me	**6**	88	80	94
n-Pr	**6**	80	88	99
Ph	**6**	83	>92	99
Ph	**7**	87	>92	99
p-$NO_2C_6H_4$	**7**	81	81	98
2-Naph	**7**	80	>92	93

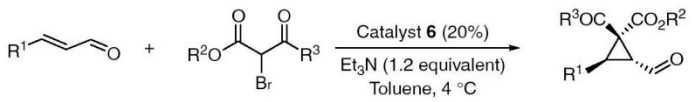
Scheme 5 Asymmetric organocatalyzed cyclopropanation of α,β-unsaturated aldehydes as reported by the groups of Cordova and Wang (representative data shown).



Scheme 6 Rationale for the observed diastereo- and enantioselectivity seen with diarylprolinol based catalysts **6** and **7**. Steric repulsion forces the iminium-ion to adopt the *E*-isomer form and the nucleophile to attack from below (*Re*-face).

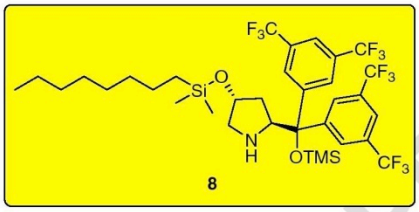
Cordova and co-workers extended the scope of the diarylprolinol TMS ether catalysts to the enantioselective synthesis of nitrocyclopropanes from α,β-unsaturated aldehydes,[50] using the bromonitromethane nucleophile pioneered by Ley's group for cyclic α,β-unsaturated ketones (see Scheme 4). Cordova's approach furnished 1-nitro-2-formylcyclopropanes in very high enantiomeric excesses (91–99% *ee*), Scheme 9, and represented the first example of a highly enantioselective organocatalytic nitrocyclopropanation of α,β-unsaturated aldehydes.

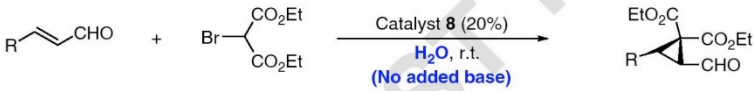
The low diastereoselectivity observed in this reaction was rationalized mechanistically. As shown in Scheme 10, the reaction is believed to proceed similarly to the proposed mechanism for the bromomalonate cyclopropanation depicted in Scheme 6. The bulky aryl groups of the pyrrolidine catalyst leads to stereoselective *Re*-facial nucleophilic conjugate addition by the 2-bromonitromethane on the chiral iminium intermediate. Next, the generated chiral enamine intermediate undergoes intramolecular



R^1	R^2	R^3	Yield (%)	dr	ee %
Ph	Et	Me	90	10:1	94
4-CN-C_6H_4	Me	Me	93	10:1	98
n-Bu	Et	Me	95	2.4:1	90
Ph	Et	*t*-Bu	76	>25:1	96

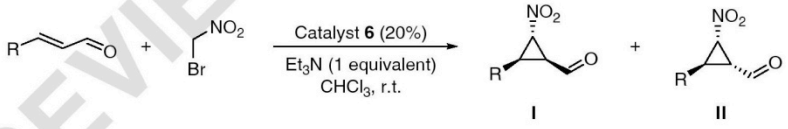
Scheme 7 Asymmetric organocatalyzed cyclopropanation of α,β-unsaturated aldehydes with unsymmetrical 2-bromo-3-keto esters as reported by Rios and co-workers (representative data shown).





R	Yield (%)	dr	ee %
Ph	78	>10:1	88
Et	28	>10:1	84

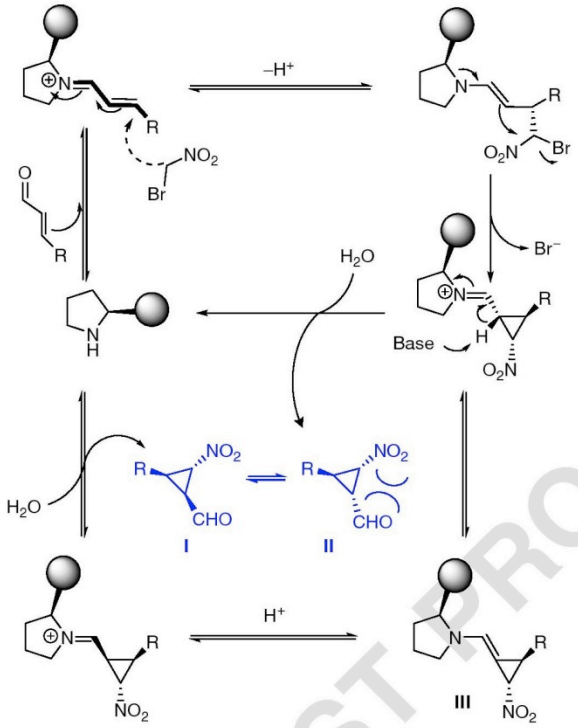
Scheme 8 Asymmetric organocatalyzed cyclopropanation of α,β-unsaturated aldehydes 'on water' with novel catalyst **8** do not require addition of external base (representative data shown).



R	Yield (%)	dr (I:II)	ee % (I:II)
Ph	63	1:1	95:95
2-Naph	56	3:2	98:99
n-Pr	42	1:1	91:92

Scheme 9 Asymmetric organocatalyzed cyclopropanation of α,β-unsaturated aldehydes with bromonitromethane as reported by Cordova et al. (representative data shown).

3-exo-tert nucleophilic attack to form the cyclopropane ring. The intramolecular ring-closure pushes the equilibrium forward and makes this step irreversible. Hydrolysis of iminium intermediate releases the catalyst and gives the corresponding 2-formyl cyclopropane **I**. However, epimerization may occur before catalyst regeneration *via* intermediate **III**, thus forming the diastereomer **II** (Scheme 10).



Scheme 10 Proposed mechanism for the organocatalyzed asymmetric nitrocyclopropanation reaction catalyzed by diphenylprolinol silylether catalyst **6**. The low diastereoselectivity in this reaction is rationalized by catalyst mediated epimerization between **I** and **II** *via* intermediate **III**.

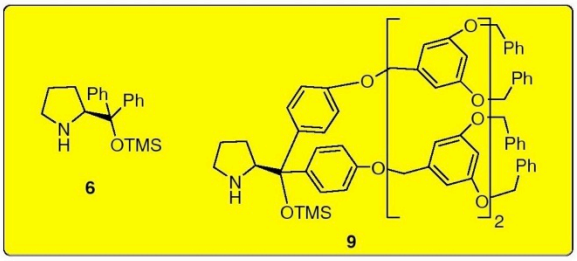
It is interesting to note that Cordova et al. also screened MacMillan's indole-based catalyst **1** (see Scheme 1) in the nitrocyclopropanation reaction and obtained the diastereomeric products **I** and **II** (Scheme 9) in a 1:1 ratio, but with impressive enantioselectivities (− 91% and − 86% *ee*, respectively). The opposite asymmetric induction observed with catalysts **1** and **6** reflects the different preference in iminium-ion geometry for these catalysts, and the low conversions and diastereoselectivity observed with catalyst **1** reflects the lack of the direct electrostatic activation when **1** is used with the bromonitromethane nucleophile instead of the sulfur ylides, as it was originally designed for.

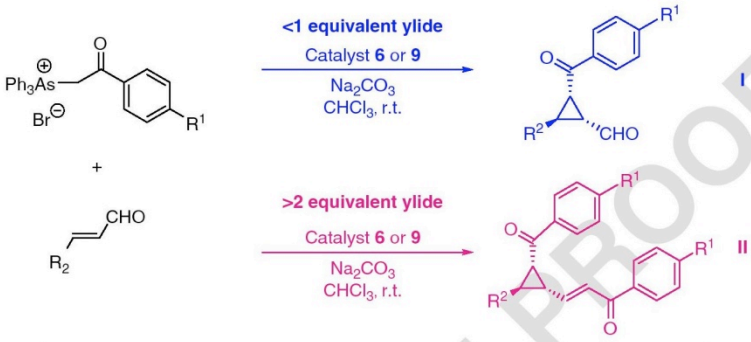
Yan's group recently reported that slight modifications of Cordova's conditions, that is, sodium acetate instead of triethylamine as base, methanol instead of chloroform as solvent, and use of triethylsilyl diphenylprolinol instead of the trimethylsubstituted catalyst **6**, gave better results in this reaction.[51] Although few direct examples allow for a direct comparison to solidify this claim, several substituted 1-bromonitromethanes, such as 1-bromonitroethane and 1-phenyl-1-bromonitromethane, were employed and provided excellent enantioselectivities and improved diastereoselectivities.

Cao and co-workers reported that the diphenylprolinol silylether catalyst **6** could also be used for the organocatalytic asymmetric cyclopropanation of α,β-unsaturated aldehydes with arsonium ylides as nucleophiles, Scheme 12. A variety of chiral cyclopropyl aldehydes were obtained in moderate to good yields with up to 99:1 *dr* and 99% *ee* under simple and mild reaction conditions.[52] In the following year the same group utilized a dendritic modification of the catalyst (i.e. catalyst **9**) and employed it for tandem cyclopropanation–Wittig reactions, Scheme 11.[53] The dendritic catalyst offered the products in moderate yield and with high diastereoselectivities (up to 99:1 *dr*) and enantioselectivities (up to 99% *ee*). The catalyst could be recycled without any loss in activity.

The stereochemical outcome of the diphenylprolinol silylether catalyst **6** catalyzed cyclopropanation with the arsonium ylide nucleophile (Scheme 11) is the same as that obtained with the dihydroindole-based catalysts **1**–**4** (Schemes 1–3), but for different reasons. Catalyst **6** enforces the *E*-configured iminium ion isomer in combination with nucleophilic attack of the ylide from below the plane (*Re*-face), whereas catalysts **1**–**4** enforce the *Z*-iminium ion isomer and utilize direct electrostatic activation to direct the ylide attack from the top (also *Re*-face).

Recently, Wang and co-workers expanded the scope of the nitro-cyclopropanation with bromonitromethane as nucleophile to include both cyclic and straight-chain α,β-unsaturated ketones. [54] Instead of the secondary amine based catalysts previously used, they employed a primary amine catalyst based on the cinchona alkaloid scaffold, that is, catalyst **10** (Scheme 12) to activate the





R^1	R^2	Catalyst	Product	Yield (%)	dr	ee %
H	Ph	**6**	**I**	80	38:1	98
F	Ph	**6**	**I**	73	11:1	97
Cl	Ph	**6**	**I**	65	25:1	96
OMe	Ph	**6**	**I**	55	>99:1	98
H	Ph	**9**	**II**	60	99:1	98
F	Ph	**9**	**II**	56	91:1	97
Cl	Ph	**9**	**II**	64	80:20	96
OMe	Ph	**9**	**II**	68	95:5	94

Scheme 11 Asymmetric organocatalyzed cyclopropanation of α,β-unsaturated aldehydes with arsonium ylides catalyzed by diphenylprolinol silylether catalyst **6** and tandem cyclopropanation–Wittig reaction catalyzed by dendritic catalyst **9** (representative data shown).

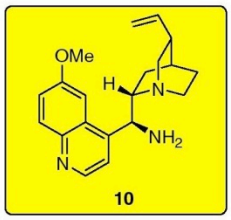
electrophile. An acidic co-catalyst was needed in order to obtain high conversion; however as the acids impact on enantioselectivity was minute *rac*-4-methyl-mandelic acid was chosen for cyclic substrates.

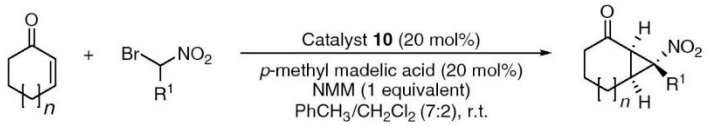
As can be seen in Scheme 12, this reaction produces 5-, 6-, and 7-membered bicyclic cyclopropanes in high yields and excellent enantioselectivities when bromonitromethane is employed as nucleophile. 1-Bromonitroethane also worked, albeit with a lower yield (entry 4) – phenyl substituted nitromethane (R^1 = Ph) did not give any product. Notably, by employing a sub-stoichiometric amount of bromonitromethane and *N*-methylmorpholine (NMM) a highly efficient kinetic resolution if 4-substituted 2-cyclohexenones could be realized when large substituent were in the 4-position (e.g. *t*-amyl, *t*-Bu, and Ph).

The reaction demanded a two-step procedure in order to achieve high diastereoselectivity when straight-chain α,β-unsaturated ketones were used as electrophiles, Scheme 13. The acid co-catalyst and base was also replaced to trifluoroacetic acid and dimethylpiperazine, respectively.

A 'one-pot' procedure, in which the base was added after 72 h, was also developed. This procedure provided slightly higher yields, but at the expense of lower diastereoselectivities and a modest decrease in enantiomeric excesses.

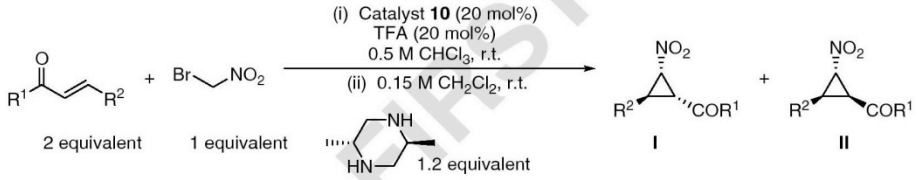
The reaction mechanism is proposed to involve activation of the α,β-unsaturated electrophile through iminium ion formation between the catalyst's secondary amine function and the carbonyl of the enone. The catalyst's tertiary nitrogen is expected to help direct the nucleophilic bromonitromethane attack to ensure enantiocontrol in the addition. The intermediate enamine then makes an internal 3-exo-tert nucleophilic attack to form the cyclopropane. In the one-mixture reaction in Scheme 12, it is reasonable to assume that the acid co-catalyst serves to help form the iminium-ion intermediate, whereas the base helps deprotonate the bromonitromethane and assists in the cyclopropanation step by sequestering the bromide ion formed. However,





Entry	*n*	*R*^{1}	*Time (h)*	*Yield (%)*	*ee %*
1	0	H	24	94	83
2	1	H	12	99	98
3	2	H	16	85	99
4	1	Me	48	54	97

Scheme 12 Asymmetric organocatalyzed nitrocyclopropanation of cyclic enones with the cinchona alkaloid based catalyst **10**, having a primary amine functionality for activation of the α,β-unsaturated enone.



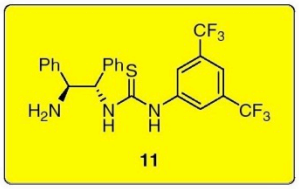
R^1	*R*^{2}	*Yield (%)*	*dr (**I**:**II**)*	*ee %*
Ph	Ph	70	94:6	>99
Ph	4-Cl-C_6H_4	66	95:5	98
Ph	4-Me-C_6H_4	63	90:10	99
Ph	3-Furyl	60	92:8	98
4-Cl-C_6H_4	Ph	77	69:31	97
2-Naphtyl	Ph	76	87:13	96

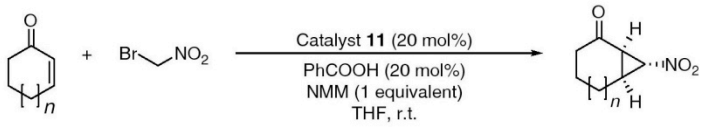
Scheme 13 Asymmetric organocatalyzed nitrocyclopropanation of enones catalyzed by **10**. Straight-chain α,β-ketones demanded modification of the reaction conditions, as compared to cyclic enones reported above. The results shown are from the optimized 2-step reaction sequence; a 'one-pot' procedure, where the dimethylpiperazine base was added after 72 h, was also reported with slightly lower diasteromeric ratios and enantioselectivities, but approximately 5% higher yields.

as the Michael addition step can be divided from the cyclopropanation step by omitting the base, the need for a base to deprotonate the bromonitromethane is questionable with this catalyst.

Subsequently, also Yan and co-workers utilized primary amine based catalysts for the nitrocyclopropanation of cyclic enones.[55] Instead of the tertiary base in catalyst **10**, they used catalyst **11** with a pending thiourea function as a mean to direct the bromonitromethane attack, Scheme 14.

Optimization of the reaction conditions for this catalyst proved benzoic acid to be the best co-catalyst and NMM to be the base of choice. The results obtained with **10** are inferior to those obtained with catalyst **11** in Scheme 12, and demands longer reaction time than Ley's improved conditions (Scheme 4).





n	*Time (h)*	*Yield (%)*	*ee %*
0	32	32	88
1	24	98	99
2	32	51	96

Scheme 14 Asymmetric organocatalyzed nitrocyclopropanation of cyclic enones catalyzed by **11**, as recently reported by Yan and co-workers. Similarly to catalyst **10** (Scheme 12) this catalyst uses a primary amine group for iminium ion activation, but in contrast to **10**, catalyst **11** has a thiourea function for directing the bromonitromethane nucleophile.

6.11.4 Asymmetric Cyclopropanation Reactions through Organocatalytic Hydrogen bond Activation of Electron-deficient Olefin Derivatives

Hydrogen bond formation represents a complimentary approach for electrophilic activation than iminium ion formation, and is a major area of asymmetric organocatalysis in itself. (For recent reviews see: Refs. 56,57. Among the most widely used catalysts are chiral (thio)ureas, chiral diols, chiral phosphoric acids, and various chinchona based catalysts.[58]

Connon and co-workers were the first to report an asymmetric organocatalytic nitrocyclopropanation reaction based on hydrogen bond activation in 2006.[59] The modified cinchona alkaloid **12** was developed to catalyze the addition of dimethyl chloromalonate to nitroolefins, followed by a DBU-mediated cyclization in the presence of hexamethylphosphoramide (HMPA) (Scheme 15).

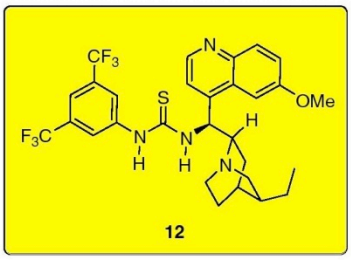
This procedure allowed for convenient synthesis of nitrocyclopropanes in high yields, and with very high diasteromeric excesses (>98% *de*), but with modest levels of enantiomeric excess (maximum 47% *ee*).

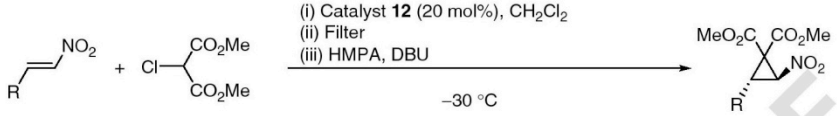
Building on the finding of Deng and co-workers,[60] who showed that 6′-demethyl cinchona alkaloids were highly enantioselective organocatalysts for addition of malonates to nitroalkenes, and the report by Connon's group above, Yan and co-workers recently reported a highly practical route to chiral nitrocyclopropanes.[61] They utilized 6′-demethyl quinine **13**, which does not contain a thiourea moiety, to affect the Michael addition of dimethyl bromomalonate to nitroolefins. This addition was followed by a base mediated intramolecular cyclization to furnish only *trans*-nitrocyclopropanation products in excellent enantiomeric excesses and good yields, Scheme 16.

This organocatalyst rely on simultaneous hydrogen bond activation of both the nitro-olefin electrophile (through the phenolic hydroxyl group) and the bromomalonate nucleophile (through the amine), in analogy to the malonate addition originally described by Li et al.[60] DABCO in DMF was shown to be the base and solvent of choice, respectively, to mediate the intramolecular cyclization. Notably, catalyst **13** also mediated the addition of dimethyl chloromalonate to *β*-nitrostyrene in good yield, but cyclization using the DABCO/DMF system was not efficient, and the Connon's DBU/HMPA system gave poor enantioselectivity of the resulting nitrocyclopropane.

Along the same lines, Fan and co-workers reported the asymmetric synthesis of nitrocyclopropanes *via* oxidative cyclization of the Michael adducts of malonates with nitroalkenes.[62] The Michael adducts were obtained by the asymmetric addition of malonates to nitroolefins catalyzed by the bifunctional thiourea catalyst **14** as previously described by the group of Takemoto[63]; these intermediates were then subjected to oxidative cyclization mediated by hypervalent iodine formed by addition of iodobenzene diacetate and tetrabutylammonium iodide. Highly substituted nitrocyclopropanes were obtained in good yields with high enantioselectivities and diastereoselectivity (>95% *de* in all cases), Scheme 17.

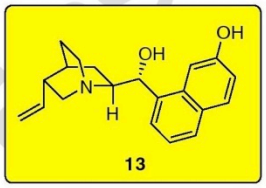
The key chirality inducing step in this reaction is the organocatalyzed addition of diethyl malonate to the *β*-nitroolefin, mediated by the bifunctional thiourea catalyst **14**. This reaction is postulated to proceed through dual activation by the catalyst; the thiourea function activates the nitroolefin through hydrogen bond donation, thus making the double bond more electrophilic, whereas the amine function activates the malonate by accepting a hydrogen bond. The chiral framework of the catalyst

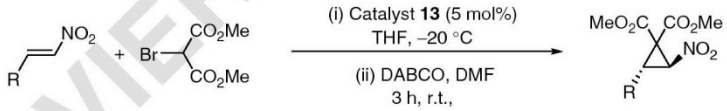




R	*Time (h)*	*Yield (%)*	*de %*	*ee %*
Phenyl	22	69	>98	38
4-Br-C_6H_4	25	67	>98	47
2-NO_2-C_6H_4	24	64	>98	18
n-C_6H_{13}	24	66	>98	17
2-Methylthiophene	22	65	>98	31

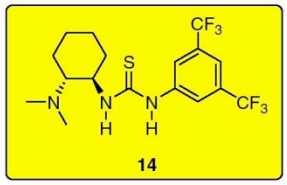
Scheme 15 Two-step enantioselective nitrocyclopropanation through chloromalonate addition to nitro olefins catalyzed by the cinchona alkaloid derived thiourea catalyst **12**, as reported by Connon's group.

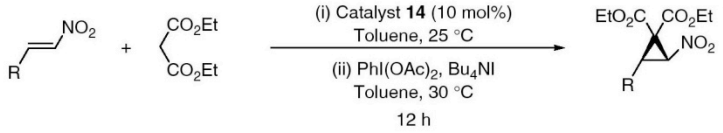




R	*Time (h)*	*Yield (%)*	*ee %*
Phenyl	24	78	>99
4-Br-C_6H_4	24	68	94
2-NO_2-C_6H_4	66	73	95
2-Thienyl	24	69	98
3-Cl-C_6H_4	24	72	>99
2-Furyl	24	47	99

Scheme 16 Two-step enantioselective nitrocyclopropanation as reported by Yan's group. The known 6′-demethyl quinine catalyst **13** was used to activate the nitroolefin through hydrogen bond donation from the phenolic hydroxyl group, possibly combined with hydrogen bond accepting of the bromomalonate by the tertiary nitrogen atom. The DABCO/DMF system for cyclization is crucial for obtaining good yields and high stereoselectivities. The reaction is completely diastereoselective, only forming the *trans*-cyclopropane adducts.





R	*Yield (%)*	*ee %*
Phenyl	73	87
2-Br-C_6H_4	81	94
2-CH_3O-C_6H_4	52	89
4-F-C_6H_4	71	93
4-Cl-C_6H_4	87	90
1-Naphthyl	80	93

Scheme 17 Two-step enantioselective nitrocyclopropanation as reported by Fan and co-workers. The bifunctional thiourea catalyst **14** was known to mediate highly enantioselective addition of malonates to nitroolefins. Hypervalent iodine was used to carry out oxidative cyclization of the intermediate Michael adducts to afford nitrocyclopropanes in high enantiomeric excess and >95% *de* for all products.

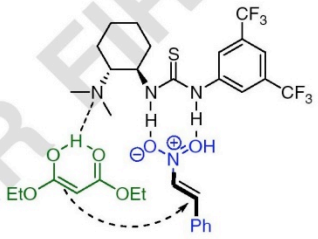


Figure 3 Proposed transition state for the organocatalyzed addition of diethylmalonate to β-nitrostyrene mediated by **14**. The obtained Michael adducts have (*R*)-configuration, suggesting orientation and attack by the reaction partners as indicated.

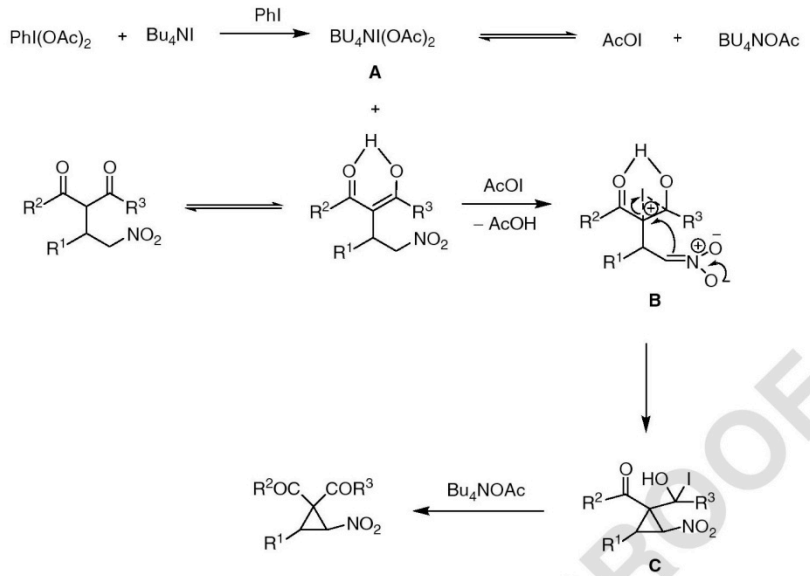
assures enantiocontrol in the addition. Based on the experimental outcome, the malonate attacks the nitroolefin from the *Re*-face (when R = Ph) as illustrated in Figure 3.[64]

The proposed oxidative cyclopropanation mechanism is outlined in Scheme 18.

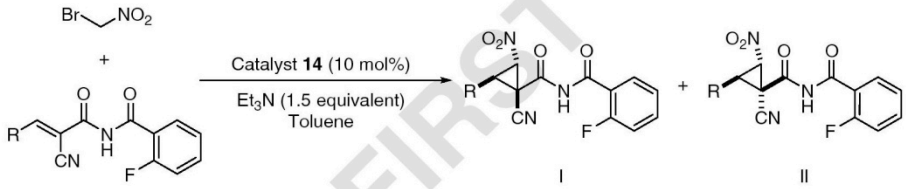
In the presence of $PhI(OAc)_2$ and Bu_4NI, the tetrabutylammonium salt of diacetoxyiodine **A** is formed. The enolate forms of the Michael adduct and **A** facilitates the formation of intermediate **B** which undergoes an intramolecular cyclization to **C**. Elimination of HI in the presence of Bu_4NOAc affords the chiral nitrocyclopropane product.

Takemoto's group subsequently used their bifunctional thiourea catalyst **14** for a one-pot nitrocyclopropanation reaction, similar to those reported with iminium ion activation of α,β-unsaturated aldehydes above. In this case, Michael addition of bromonitromethane onto α,β-unsaturated α-cyanoimides followed by an intramolecular S_N2 reaction gave the cyclopropane products,[65] Scheme 19.

Several aryl derivatives of the Michael acceptors and bromonitromethane gave the highly functionalized cyclopropane type products as shown in Scheme 19 in high yield, moderate diastereoselectivity, and excellent enantioselectivity. Notably the reaction was completely diastereoselective when the reaction was performed at room temperature (r.t.) (R = Ph) and produced **I** in Scheme 19 with 96% *ee*, albeit with a lower yield (55%).



Scheme 18 Proposed reaction pathway for oxidative cyclopropanation of Michael adducts formed by hydrogen bond catalyzed addition of malonates to nitroolefins.

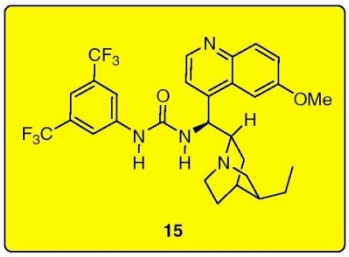


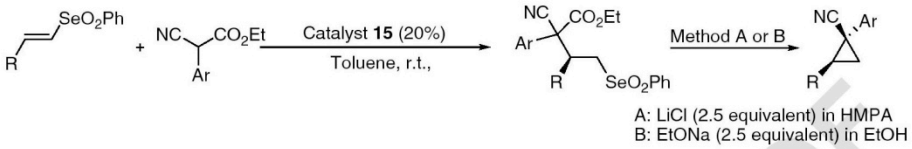
R	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*dr* (***I:II***)	*ee %*
4-MeC_6H_4	–60	24	81	62:38	99
4-ClC_6H_4	–20	4	75	60:40	98
3-ClC_6H_4	–20	2	80	50:50	98
2-ClC_6H_4	–20	1	79	63:37	98
4-BrC_6H_4	–20	5	76	58:42	98
1-Naphthyl	–20	1	81	73:27	98

Scheme 19 Asymmetric organocatalytic nitrocyclopropanation with α,β-unsaturated α-cyanoimides, catalyzed by bi-functional thiourea catalyst **14**, proceeding *via* a tandem Michael-nucleophilic displacement reaction within the same reaction solution.

It was envisioned that the thiourea catalyst again functioned through dual activation of both the nucleophile and the electrophile similarly as depicted in Figure 3; that is, the thiourea motif activates the electrophilic α,β-unsaturated α-cyanoimides through hydrogen bond donation, and the catalyst's basic nitrogen atom is increasing the nucleophilicity of the bromonitromethane through deprotonation. Although cyclization of the intermediate Michael adduct was hypothesized to take place with the help of the catalyst, optimization showed that addition of triethyl amine was needed to increase the yield of the cyclopropanation product.

Recently, the first asymmetric organocatalytic synthesis of cyclopropanes *via* Michael addition to vinyl selenones was developed by Marini et al.[66] Although this reaction sequence utilizes alkalimetal salts for the cyclopropanation step, and consequently are





Entry	Ar	R	Method A		Method B	
			Yield (%)	ee %	Yield (%)	ee %
1	Ph	Ph	65	66	54	76
2	Ph	4-MeO-C_6H_4	64	66	40	74
3	Ph	4-Cl-C_6H_4	40	72	40	72
4	4-Br-C_6H_4	Ph	52	61	50	70
5	4-F-C_6H_4	4-Cl-C_6H_4	42	74	66	66
6	4-MeO-C_6H_4	C_6H_{13}	91	52	–	–

Scheme 20 Enantioselective cyclopropanation *via* Michael addition to vinyl selenones as reported by Marini et al. (representative data shown).

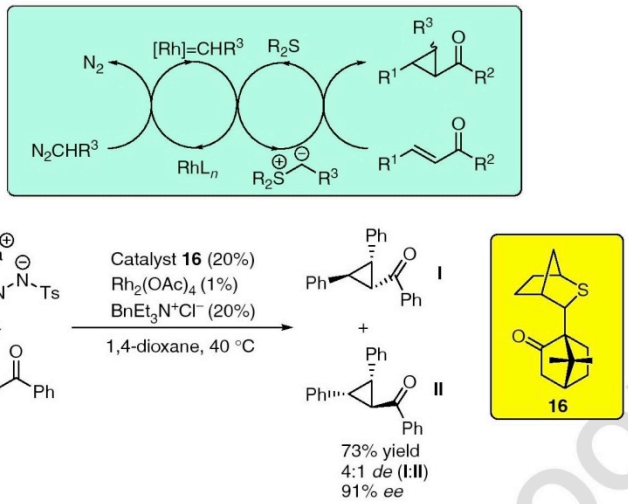
not organocatalytic in the most conservative sense, it will be summarized here as the key asymmetric step is based on an organocatalytic Michael addition of (*E*)-vinylselenones to ethylphenylcyanoacetates in the presence of urea catalyst **15**, Scheme 20.

Interestingly, thiourea catalysts **12** and **14** were also evaluated, but none of these provided the Michael adduct in equally high enantiomeric excess as **15**. Two different protocols (method A: LiCl in HMPA; method B: NaOEt in EtOH) were used to displace the ester group, which through the nitrile enolate displace the selenonyl group through a 3-exo-tert cyclization. Reactions proceeded with complete diastereoselectivity, but with moderate enantiomeric excess and yields, despite long reaction times (90–144 h). The stereochemistry of products from entries 1 and 6 (Scheme 20) suggested that in presence of catalyst **15**, preferential attack on the *Re* face of the unsaturated selenone was favored. This facial selectivity was different to that observed in similar reactions with Michael acceptors that contain either a nitro or carbonyl group, suggesting that the selenoyl group alters the spatial orientation of the ternary complex formed by the catalyst and the substrate.

6.11.5 Asymmetric Cyclopropanation Reactions through Organocatalytic Activation of Ylides

The organocatalytic activation strategies reviewed above relies on that the chiral catalyst is temporary being attached to the electrophile (either covalently as in the case of iminium ion catalysis, or as a hydrogen bonded complex as in the case of hydrogen bond catalysts), and thus dictates the stereochemical outcome of the reaction by directing the incoming nucleophilic reagent through steric and electronic interactions. An alternative strategy for inducing stereochemical control in the reaction would be by temporarily modifying the nucleophile with a chiral catalyst. One way to accomplish this is through chiral modification of an ylide nucleophile.

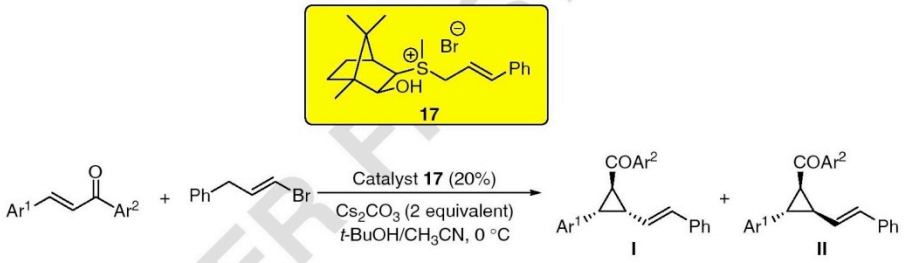
Aggarwal and co-workers pioneered the use of chiral sulfur-ylides for stoichiometric epoxidation-, aziridination-, and cyclopropanation-reactions,[67,68] and also reported the first catalytic asymmetric cyclopropanation using an ylide as catalyst in 1997[69,70] and disclosed an improved protocol in 2001.[70] The improved process is a true extravagance in catalysis, combining metal catalysis, phase-transfer catalysis, and organocatalysis to produce cyclopropanes from α,β-unsaturated carbonyl compounds and tosyl hydrazone salts, Scheme 21. The final cyclopropanation step utilizes the chiral sulfide **16** as an organocatalyst.



Scheme 21 Example of asymmetric cyclopropanation with chiral sulfide **16** as organocatalyst in the final cyclopropanation step, as reported by Aggarwal et al. Rh-catalysis, combined with phase-transfer catalysis, is used to regenerate the chiral sulfur ylide from tosyl hydrazone salts.

Unfortunately, even the improved protocol was limited under catalytic conditions, primarily being of practical utility for phenyl ketones and α-amino-substituted acrylates.

Recently, Tang and co-workers[71] reported an alternative catalytic cycle for sulfur ylide catalyzed cyclopropanations, Scheme 22.



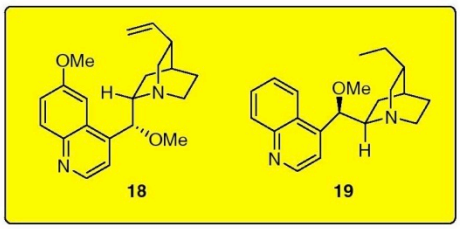
Ar^1	Ar^2	Yield (%)	dr (**I**:**II**)	ee % (**I**)
Ph	Ph	92	86:14	82
p-Br-C_6H_4	Ph	89	75:25	78
p-OMe-C_6H_4	Ph	66	86:14	80
Ph	*p*-Me-C_6H_4	87	87:13	81

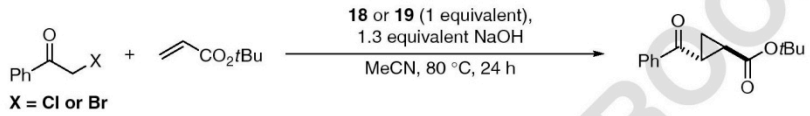
Scheme 22 Asymmetric organocatalyzed cyclopropanation of α,β-unsaturated ketones with sulfur ylide catalyst **17**, as reported by Tang and co-workers (representative data shown).

The chiral camphor-derived sulfonium salt **17** functioned as the organocatalyst, by being deprotonated by Cs_2CO_3 to form the ylide that reacts with α,β-unsaturated ketones to yield cyclopropanation products with fair diastereoselectivity, good yield, and high enantiomeric excesses. The sulfonium salt of the catalyst was regenerated *in situ* by reaction with the allylic bromine shown. Tang previously reported a similar cyclopropanation using a chiral tellurium ylide as catalyst, although most reactions in that report were stoichiometric in the ylide.[72]

The major breakthrough in the area of asymmetric organocatalyzed activation of ylides came in 2003, when Gaunt and co-workers employed tertiary amines as organocatalysts.[73] In the original study, the ammonium ylide was first generated *in situ* by the addition of a stoichiometric amount of a non-chiral tertiary base (DABCO) to phenacyl chloride followed by addition of the α,β-

unsaturated carbonyl compound. After stirring the reaction mixture for 18 h at 80 °C, the cyclopropane product was isolated in 79% yield as a single diastereoisomer. The methodology was then applied with a stoichiometric amount of the two cinchona alkaloid derivatives **18** and **19** as the tertiary base, to promote the cyclopropanation shown in Scheme 23, providing the cyclopropanation product in fair yield, and with very high levels of sterocontrol (up to 94% *ee*).

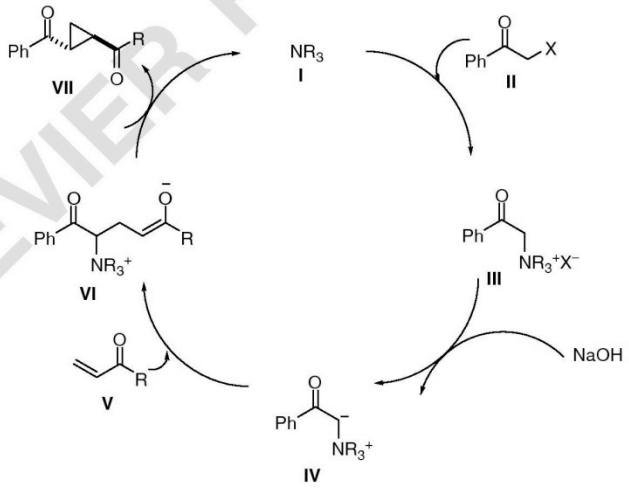




Chiral Amine	*Yield %*	*ee %*
18	57	94 (+)
19	58	94 (–)

Scheme 23 One pot enantioselective cyclopropanation promoted by a stoichiometric amount of the pseudoenantiomeric cinchona alkaloids **18** and **19** used as nucleophilic reagents to form temporary ammonium ylides that promote cyclopropanation of *t*-Bu acrylate.

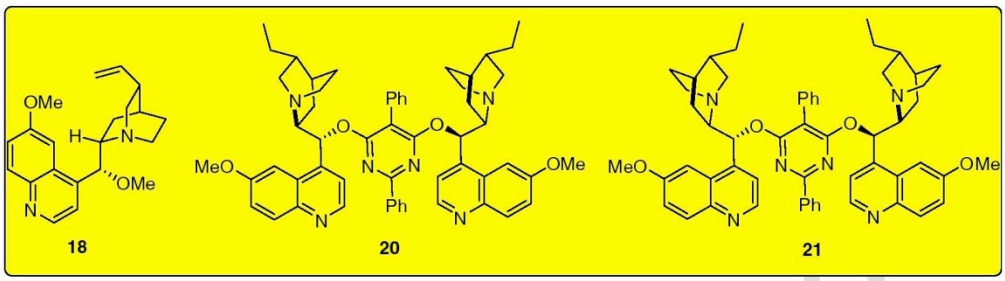
With these results in hand, the authors investigated the catalytic process for this reaction based on the proposed mechanism, Scheme 24.

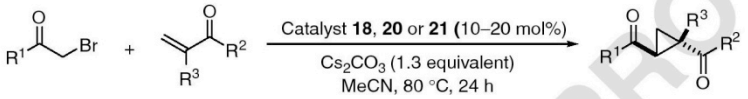


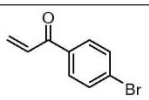
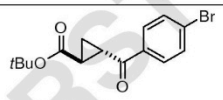
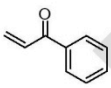
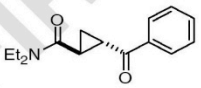
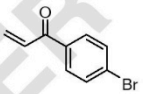
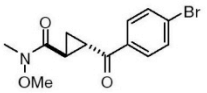
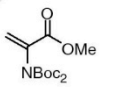
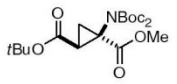
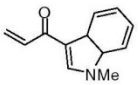
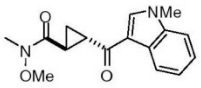
Scheme 24 Proposed catalytic cycle for organocatalyzed cyclopropanations *via in situ* generated ammonium ylides.

The mechanism proposed by the authors suggested that the α-halo carbonyl compound **II** undergoes an S_N2 displacement reaction with the tertiary amine **I** to form a quaternary ammonium salt **III**. Deprotonation with a mild base afforded the ylide **IV**,

which undergoes a conjugate addition to the alkene **V** to yield **VI**. Cyclization generates the cyclopropane product **VII** and the amine **I** which should be regenerated at the end of the reaction. Based on this mechanism the tertiary amine should be possible to use in catalytic quantities without the possibility of a competing background reaction. Consequently, in 2004, Gaunt's group reported an organocatalytic asymmetric intermolecular cyclopropanation between α-bromo carbonyl compounds and electron deficient alkenes using cinchona derivatives **18**, **20** and **21**,[64] using a slightly modified protocol, Scheme 25.



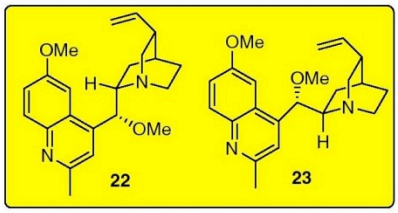


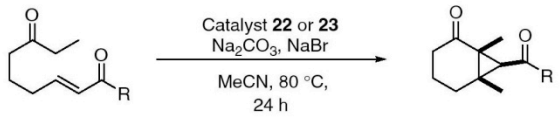
Entry	R^1	Alkene	Product	Catalyst	Yield (%)	ee %
1	O*t*Bu			**18**	83	85 (+)
2	NEt_2			**18**	94	97 (+)
3	NMe(OMe)			**20** **21**	67 74	96(+) 97(–)
4	O*t*Bu			**18**	90	97 (+)
5	NMe(OMe)			**20** **21**	74 84	95 (+) 94(–)

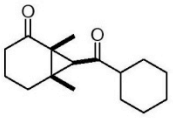
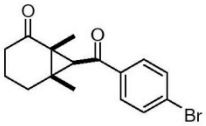
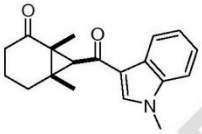
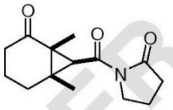
Scheme 25 Intermolecular organocatalytic asymmetric cyclopropanation as reported by Gaunt and co-workers (representative data shown).

The pseudoenantiomeric relationship of cinchona derived organocatalysts **20** and **21** allows either enantiomer of the cyclopropane product to be accessed (entries 3–5, Scheme 25).

In another study, Gaunt and co-workers [74] expanded the concept of *in situ* generated ammonium ylide formation to a new organocatalytic intramolecular cyclopropanation reaction; this reaction was subsequently evolved by developing two new organocatalysts, that is, **22** and **23**, that experienced less of the undesirable quinoline *N*-alkylation and promoted the desired quinuclidine alkylation,[75] Scheme 26.





Cyclopropane product	*Yield (%)*	*ee %*
	79	95
	83	96
	95	98
	77	99

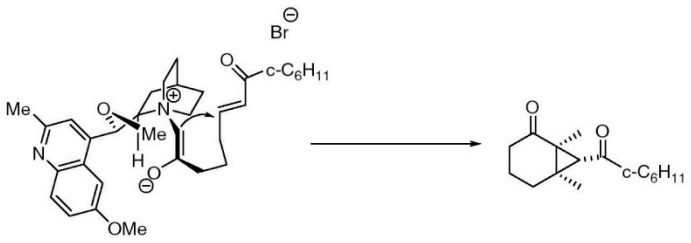
Scheme 26 Intramolecular organocatalyzed asymmetric cyclopropanation reaction catalyzed by the second generation catalysts **22** and **23** from Gaunt and co-workers (representative data shown).

Addition of either NaBr or NaI (40 mol%) facilitated formation of the quaternary ammonium salt, and decreased the reaction time from 4–5 days to 1 day and provided higher enantioselectivities. The modified catalysts worked on a range of substrates for intramolecular cyclopropanation reactions as shown with some representative examples in Scheme 26.

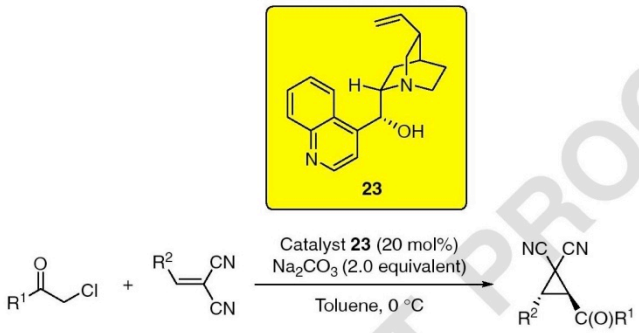
Upon investigation on the origin of the enantioselectivity, it was suggested from the transition state model of a derivative of catalyst **23** and a ketone (Scheme 15) that the ammonium salt orientates itself such that the *Z*-enolate of the nucleophile is favored upon deprotonation with the base and intramolecular conjugate addition takes place *via* a boat-type transition state, Scheme 27.

Kojima and co-workers reported the use of the natural cinchona alkaloid cinchonidine **23** as organocatalysts for the cyclopropanation of chloromethyl ketones and *β*-substituted methylidenemalononitriles to yield tetrasubstitued cyclopropane products.[76] From an initial screening of cinchona derivatives as catalysts, **23** emerged as the best catalyst and was used on a variety of substrates (Scheme 28).

Moderate selectivity was achieved with fairly mild (0 °C) conditions although long reaction times were required. Interestingly, these non-*O*-methylated cinchona catalysts did not follow the proposed mechanism by Gaunt et al. The expected quaternary ammonium salt intermediate formed between phenacyl bromide and the tertiary amine catalyst did not form under these reaction conditions in absence of the acceptor. This led to the assumption that a Brønsted base mechanism was taking place. In addition,



Scheme 27 Proposed transition state model for intramolecular conjugate addition forming a 6-membered ring intermediate, which subsequently undergoes a second intramolecular cyclization leading to the cyclopropane ring.



R^1	R^2	Time (days)	Yield (%)	ee %
Ph	Ph	4	78	56
Ph	2-ClC_6H_4	2	81	44
Ph	*t*-Bu	3	27	66
2-ClC_6H_4	Ph	7	19	33
t-Bu	Ph	7	22	56

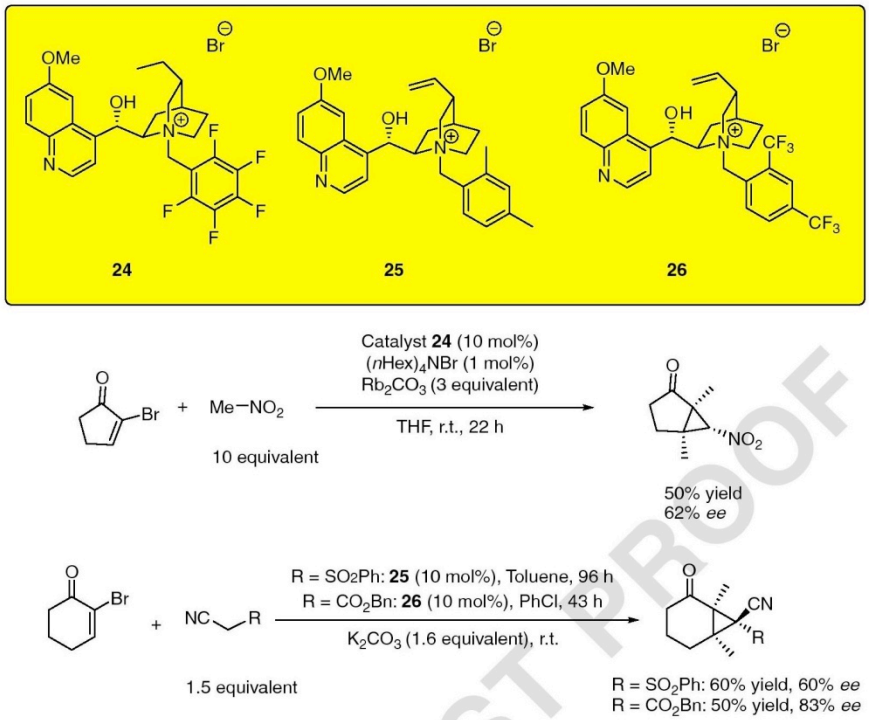
Scheme 28 Enantioselective intermolecular cyclopropanation with β-substituted methylidene malononitriles catalyzed by cinchonidine. Interestingly, Brønsted base catalysis, and not nucleophilic catalysis *via* ammonium ylides, was proposed to operate in this reaction.

hydrogen bonding seemed to be necessary for asymmetric induction. Unfortunately, no further mechanistic insight into these findings have been so far reported.

6.11.6 Organocatalytic Asymmetric Cyclopropanation through Chiral PTC

In addition to the "traditional" modes of organocatalyzed activation, that is, iminium ion formation, hydrogen bond formation, nucleophilic catalysis, and acid–base catalysis, a few reports exploiting phase-transfer catalysis for asymmetric cyclopropanation have been described. Application of phase transfer catalysis (PTC) for cyclopropropanations remained unexplored until Merz and Mark reported the first PTC cyclopropanation in 1973 using a nonchiral catalyst.[77] During the course of the next 25 years a steady interest in this field occurred; however, it took until 1999 when Arai et al. developed the first enantioselective PTC cyclopropanation reaction.[78] The cyclopropanation of α-bromocycloenones with either nitromethane, cyanomethyl phenyl sulfone, or cyanoacetate in the presence of cinchona derived catalysts **24–26** was achieved under phase transfer conditions, Scheme 29.

This reaction sequence involves an enantioselective Michael addition followed by proton transfer and an intramolecular alkylation step. The addition of nitromethane to 2-bromo-3-cyclopentenone in presence of catalyst **24** was found to proceed with optimum yield and enantioselectivity by the addition of 1 mol% of tetrahexylammonium bromide as an achiral co-PTC and by



Scheme 29 Asymmetric organocatalyzed cyclopropanation of cyclic α-bromoenones under phase-transfer conditions, as reported by Arai and co-workers (best results shown).

using Rb_2CO_3 instead K_2CO_3. These modifications were not needed when the more acidic nucleophiles cyanomethyl phenyl sulfone or cyanoacetate were used. Although the yields and enantioselectivities obtained with this procedure were modest, it represents the only example of organocatalyzed cyclopropanation reaction in which the leaving group is part of the electrophilic reactant (i.e. equation 7 in the introduction section).

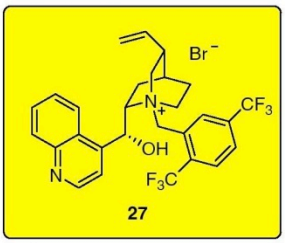
Surprisingly, the next enantioselective PTC cyclopropanation has only been recently reported by Belyk et al.[79] In effort to minimize the production cost of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid (vinyl-ACCA), which is a key building block in several hepatitis C virus (HCV) NS3/4a protease inhibitors, these Merck scientists developed a scalable organocatalytic asymmetric PTC cyclopropanation procedure to this derivative, Scheme 30.

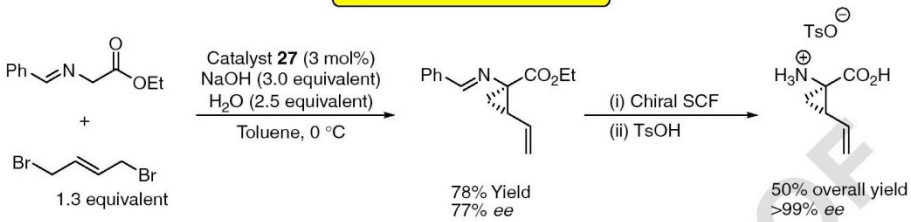
An extensive study using more than 100 cinchona derived PTC catalysts for the reaction between imine protected glycine derivative and *trans*-1,4-dibromo-2-butene under various reaction conditions was investigated. Catalyst **27** emerged as the best furnishing the desired product in 78% yield and 77% *ee*. After enhancement of the optical purity by supercritical fluid chromatography on a chiral stationary phase, and deprotection, they obtained the desired product in 50% overall yield and with >99% enantiomeric excess.

6.11.7 Conclusion and Outlook

The cyclopropane structural element continues to fascinate chemists. The importance of chiral cyclopropane derivatives in organic chemistry, natural product chemistry, and medicinal chemistry continues to rise, as witnessed by an expansion of commercially manufactured cyclopropane derivatives, for example, as part of pharmaceutical agents. Over the past decades, the evolving field of organocatalysis has significantly expanded the methods available for asymmetric synthesis. Consequently, asymmetric organocatalysis has also contributed with a number of environmentally friendly, high yielding, and highly stereoselective methods for the preparation of chiral cyclopropane derivatives, as illustrated in this chapter. We have tried to summarize the contributions made to the area, and, as stated in the introduction, we have limited ourselves to catalytic processes and omitted enzyme catalyzed processes. Upon concluding, we allow ourselves a few reflections on the topic reviewed:

All examples of organocatalyzed asymmetric cyclopropanation rely on the concept of Michael-initiated ring-closure (MIRC) reactions of the general kind illustrated in equations 6 and 7 in the introduction. A few new organocatalysts have been specifically



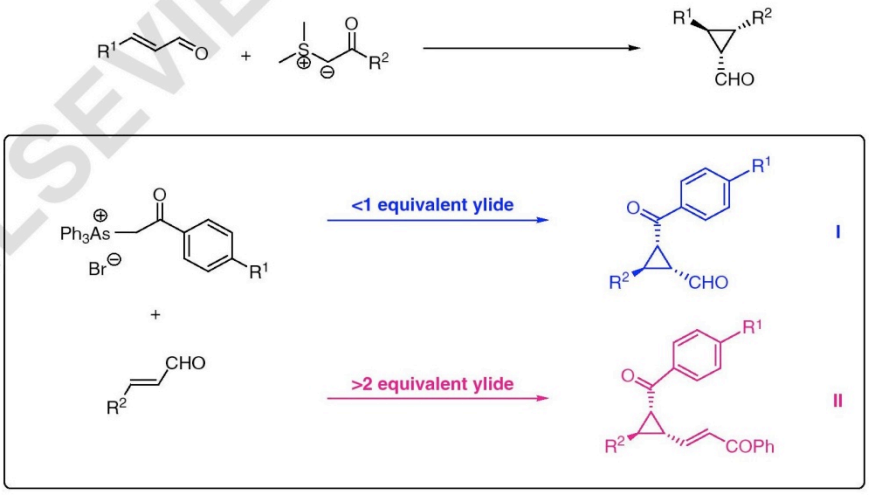


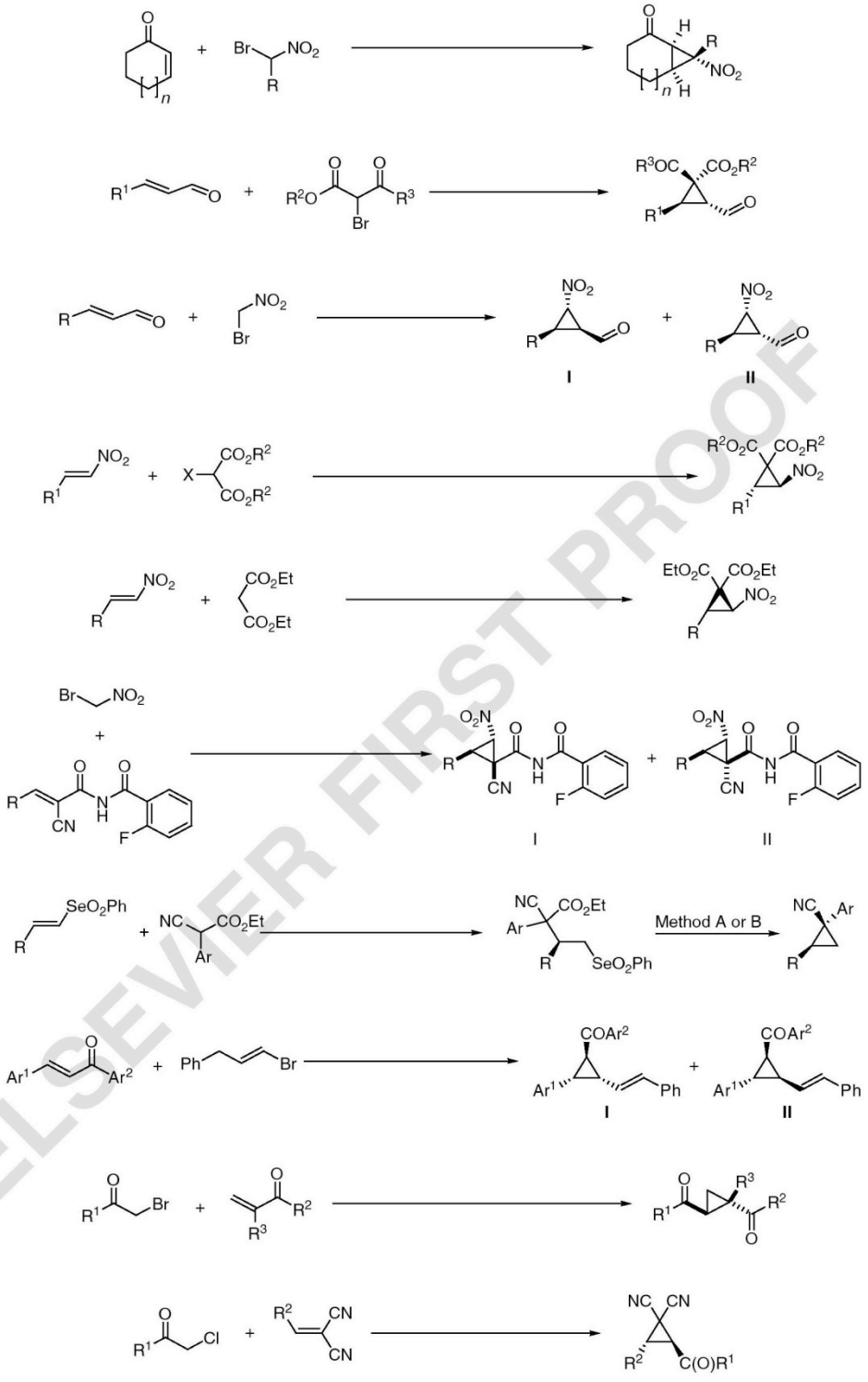
Scheme 30 Asymmetric organocatalyzed cyclopropanation under phase transfer conditions, as reported by Belyk et al. for the manufacture of a key intermediate found in protease inhibitors.

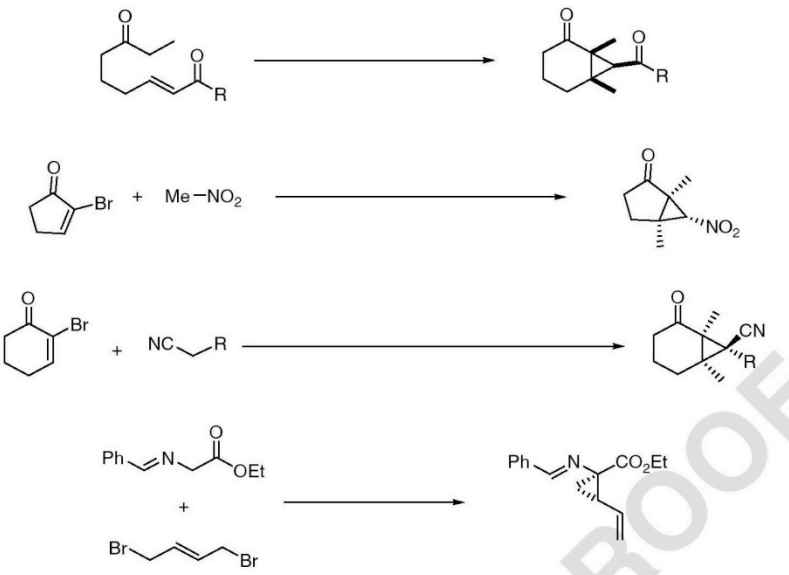
developed for asymmetric cyclopropanation reactions, whereas most catalyst have been utilized for various other organocatalyzed processes before, and proven successfully also for the MIRC process. The reported catalysts operate through either of two main modes of activation, that is, activation of α,β-unsaturated electrophiles *via* iminium ion formation or through hydrogen bond formation; or, alternatively, activation of the nucleophile *via* ammonium ylide formation or through chiral counter ion formation in case of PTC. Only a handful of reagents have so far been employed as nucleophiles for addition to the activated electrophiles, for example, chalcogen ylides, bromomalonates, and bromonitroalkanes; likewise the substrate scope for catalysis *via* ammonium ylides is somewhat restricted. Almost all examples reported proceed *via* a process where the nucleophile contains the leaving group that departs when the 3-membered ring is formed. The only exceptions to this are the two phase-transfer catalyzed processes described in the last section of this review.

The purpose of these reflections were not to diminish the important contributions made in the area of organocatalytic asymmetric synthesis of cyclopropane derivatives, but rather to (hopefully) spark an interest that there are more discoveries to be made in this rapidly evolving field!

Table Summary of Transformations







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CHAPTER 7

SUMMARY

The development of novel chiral organocatalysts based on the tetrahydroisoquinoline backbone and their evaluation on asymmetric reactions was successfully achieved. Three organocatalytic modes of activation have been investigated for C-C bond forming asymmetric reactions. For the first time organocatalysts bearing a secondary nitrogen within a cyclohexane ring were evaluated in the asymmetric Diels–Alder reaction. These catalysts were tested over a range of dienes and dienophiles and displayed promising chemical conversions of up to 100 % with up to 64 % *ee* when triflic acid was employed as the cocatalyst. Density functional theory computational studies and 2D NMR spectroscopy were used to determine the structure of the intermediate iminium ion formed between the most efficient catalyst and cinnamaldehyde. The reaction profile for each of the four possibilities in this reaction were calculated and it was found that the iminium intermediate leading to the major product is higher in energy but kinetically preferred. The activation energies of all possible reaction paths were calculated and the results correlated with the observed products. These experiments revealed that the presence of both (*E*)- and (*Z*)-isomers of the cinnamaldehyde were contributing factors for the low enantioselectivity of the reaction products. Thereafter, a series of novel tetrahydroisoquinoline chiral *N*-oxide organocatalysts and their evaluation in the asymmetric allylation reaction of aromatic and α-β-unsaturated aldehydes with allyltrichlorosilane was carried out. The chiral homoallyl products were obtained with good chemical efficiency (up to 93 % yield) and high enantioselectivity (up to 91 % *ee*) under mild reaction conditions (23 °C). Lastly, the simple and practical syntheses of new tetrahydroisquinoline guanidine organocatalysts and their evaluation in the asymmetric Michael addition reaction of malonates and β-ketoesters with nitro-olefins were performed. In addition, a novel microwave assisted procedure of introducing the guanidine unit onto amino amide derivatives is reported. The chiral products were obtained with quantitative chemical efficiency (up to 99 % yield) and excellent enantioselectivity (up to 97 % *ee*). Furthermore, 18 X-ray crystal structures pertaining to Chapters **2-4** were published from this project.