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**The development of a new class of C-5' substituted
cinchona alkaloid derivatives as efficient
organocatalysts**



Trinity College Dublin

A thesis submitted to the University of Dublin for the degree of Doctor of
Philosophy

by
Carole Palacio

Under the supervision of
Prof. Stephen Connon

May 2013

Declaration

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C. Palacio, S. J. Connon, *Org. Lett.*, 2011, **13**, 1298

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Abstract

Over the past three decades, the synthesis of enantiomerically pure products became a major concern in modern research. In this context, organocatalysis has emerged as a viable method and interest in this field has intensified rapidly. In particular, cinchona alkaloids - incorporating two functionalities capable of the synergistic activation of two components of a reaction in a close and chiral environment - appeared as a valuable material in new organocatalysts design. Various cinchona alkaloid derivatives have been demonstrated to be capable of the bifunctional catalysis of a number of asymmetric reactions involving the addition of an acidic pronucleophile to an electrophile incorporating hydrogen-bond accepting functionality.

Our interest in these molecules led us to design and synthesise a library of new cinchona alkaloid derivatives, the first incorporating a urea moiety at the C-5' instead of the customary C-9 position. We proposed that placing the hydrogen bond donating group at this position would bring it closer to the quinuclidine base ring, leading to a tighter activation pocket that may provide a better fit for the transition states of some particular reaction(s). In addition, we studied the impact of the C-9 functionality on catalysis, in order to vary the distance between the two activating functions and thereby allowing the catalyst properties to be fine-tuned to meet the needs of individual reactions. The aim of this new library was to offer the practitioner more variation in the positioning of the catalyst's bifunctional components than was available with the widely employed C-9 substituted analogues.

Once these new promoters were prepared, the catalysis of efficient and highly enantioselective 1,2-addition of nitromethane to challenging trifluoromethylketones was studied. Excellent product yields and levels of enantiomeric excess have been obtained, using a diverse array of substrates. The most active catalyst promoted the Henry reaction involving alkyl trifluoromethylketones with unprecedented enantioselectivity.

These novel C-5'-substituted cinchona alkaloids were then evaluated in challenging 1,4-additions. The first general, highly efficient and enantioselective organocatalytic system for the addition of previously problematic alkane thiols to nitrostyrenes was developed. The process was of broad scope: a range of alkane thiols (including those containing

cleavable benzyl substituents) and a variety of electron deficient, electron rich and heterocyclic nitrostyrenes were compatible.

The promotion of the dynamic kinetic resolution (DKR) of azlactones by thiolysis was also investigated. Disappointingly, the C-5' urea-substituted cinchona alkaloids all performed poorly in this challenging process (from both enantioselectivity and activity standpoints). Therefore, a new class of C-5'-hydroxylated cinchona alkaloid catalysts were synthesised which were capable of considerably more effective catalysis in this reaction. Product yields were moderate. However, the most efficient catalyst could promote the thiolytic DKR of a wide range of azlactones, including the hitherto recalcitrant azlactones derived from branched chain amino acids, with excellent enantioselectivity for the first time.

Abbreviations

Å	Angstrom
Ac	Acetyl
AIBN	Azobisisobutyronitrile
app.	Apparent
Ar	Aryl
Atm	Atmosphere
Bn	Benzyl
BOC	<i>tert</i> -Butoxycarbonyl
br	Broad
Bu	Butyl
Bz	Benzoyl
cat.	Catalyst
Cbz	Carboxybenzyl
Conv.	Conversion
CPME	Cyclopentyl methyl ether
CSP	Chiral stationary phase
Cy	Cyclohexyl
d	Doublet
dd	Doublet of doublets
DABCO	1,4-diazabicyclo[2.2.2] octan
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIPEA	<i>N,N'</i> -Diisopropylethylamine
DKR	Dynamic Kinetic Resolution
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
d.r.	Diastereoisomeric ratio
<i>ee</i>	Enantiomeric excess
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq.	Equivalent
Et	Ethyl

EWG	Electron withdrawing group
FDA	Food and Drug Administration
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
IPA	<i>Iso</i> -propyl alcohol
IR	Infra red
J	Coupling constant
KR	Kinetic Resolution
k	Rate constant
lit.	Literature
LUMO	Lowest Unoccupied Molecular Orbital
<i>m</i>	<i>meta</i>
m	Multiplet
Me	Methyl
M.p.	Melting point
Ms	Mesyl
MS	Molecular sieves
MTBE	Methyl- <i>tert</i> -butyl ether
MVK	Methyl vinyl ketone
NCL	Native chemical ligation
NMR	Nuclear magnetic resonance
Np	Naphtyl
Ns	Nosyl
Nu	Nucleophile
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Ph	Phenyl
PHN	Phenanthrene
PMP	<i>para</i> -methoxyphenyl
q	Quartet
rac	Racemic
rt	Room temperature
s	Singlet
t	Triplet
TBAF	<i>tetra-n</i> -butylammonium fluoride

TBS	<i>tert</i> -Butylsilyl
TBDPSCI	<i>tert</i> -butylchlorodiphenylsilane
td	Triplet of doublet
TEA	Triethylamine
Temp.	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TS	Transition state
Ts	Tosyl
UV	Ultraviolet

1.1 Chiral compounds and organocatalysis

1.1.1 The importance of chirality

In 1848, Louis Pasteur made a discovery that has become a milestone in contemporary chemistry research. Studying the fermentation of wine, he first resolved a racemic mixture of sodium ammonium tartrate and gave clear evidence of chirality in matter.¹

A molecule is chiral if it cannot be superimposed on its own mirror image. In an achiral environment, these two mirror images (enantiomers) possess the same physical properties. However, if exposed to plane polarised light, two enantiomers rotate the light in opposite directions.² In an identical fashion, enantiomers will display different properties if placed in an asymmetric medium. This is of utmost importance since, like polarised light, biological targets (receptors, enzymes, *etc.*) in a human body are often asymmetric and their interactions, for instance with drugs, are often stereoselective.^{3,4} That explains why pairs of enantiomers may exhibit different biological properties.² For instance, the two enantiomeric forms of the natural molecule Limonene differ in the way that they interact with the scent receptor. The left-handed (*R*)-(+)-limonene (**1**) smells like oranges, the right-handed (*S*)-(-)-Limonene (**2**) offers a lemon smell (Figure 1.1).⁵

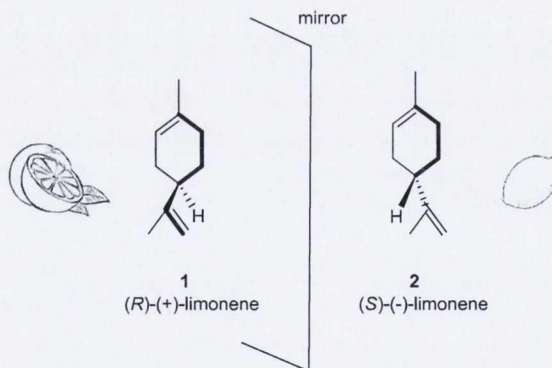


Figure 1.1 The two enantiomers of the natural molecule Limonene

Until the 1980's, racemic versions of drugs were commonly commercialised. The synthesis of racemates proved to be noticeably more facile to execute and less expensive. However, advances in the synthesis of enantiopure compounds and their bioanalysis highlighted that if one enantiomer in a racemic mixture did not exhibit the desired pharmacological activity, it could possess a separate activity which could be harmful for the human body.⁶

For instance, in 1961, it was proven that more than 10,000 cases of new born infants with gross deformities were caused by a drug that mothers would have been prescribed during their pregnancy: Contergan.³ Its active principal ingredient, Thalidomide (**3**, Figure 1.2), is a chiral molecule whose eutomer is a light sedative that treats morning sickness and aids sleep. In contrast, the dystomer (also present in the drug) was proved to be a potent teratogen. The drug was removed from the market and after other medical cases highlighted the danger of racemic drugs (*e.g.*, anti-Parkinsonian L-Dopa (**4**),² tuberculostatic ethambutol (**5**)⁷), the FDA set up more constrained regulations in 1992 in relation to chiral drugs in a 'Policy Statement for the Development of New Stereoisomeric Drugs'.⁸ Since then, companies are required to establish major justifications during their application to bring a molecule to the pharmaceutical market in its racemic version.

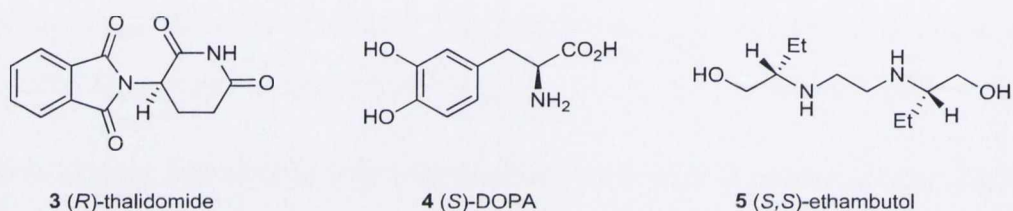


Figure 1.2 Examples of chiral drugs

As a consequence, the synthesis and evaluation of enantiomerically pure drugs has become an area of considerable interest.⁹ In 2006, 80% of the drugs approved by the FDA were chiral molecules, and 75% of these were single enantiomers.¹⁰ Facing those changes in the market profile,⁶ it was of major importance for synthetic chemists to develop better methods to allow access to enantiomerically pure molecules.

1.1.2 Different approaches toward the synthesis of enantiopure compounds

Three major routes have been developed to date (Figure 1.3).¹¹⁻¹³

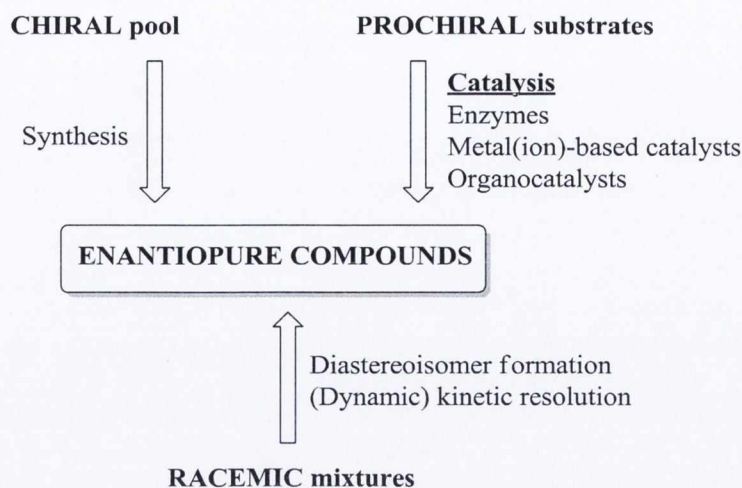


Figure 1.3 Routes towards the synthesis of enantiomerically pure compounds

1.1.2.1 The resolution of racemates

In this strategy, a single enantiomer is isolated from a racemic mixture.^{12,14} One such method is using a chiral resolving agent, where enantiomers can be derivatised into two separable diastereoisomers. For the method to be efficient, the diastereoisomer has to be easily transformed back into the desired enantiomer, without substantial loss of material, and the resolving agent has to undergo facile recycling during the process. This is an inexpensive and efficacious method. Nevertheless, the yield can only reach 50% at maximum.

1.1.2.2 Chiral pool-based method

Another approach is to utilise (enantiopure) starting materials belonging to the chiral pool.^{12,14,15} The chiral pool includes a plethora of molecules that are readily available from nature in only one enantiomeric form, such as amino acids or carbohydrates. They can be used as reagents in natural product synthesis and other synthetic strategies. *Via* this pathway, the preparation of high optical purity compounds in high yield is achievable and occurs through an intramolecular transfer of chiral information. The drawback of this approach is that the starting material utilised could be significantly expensive.

1.1.2.3 Asymmetric catalysis

Asymmetric synthesis¹⁶⁻¹⁸ can be achieved from prochiral substrates *via* catalysis using enzymes, metal(ion)-based catalysts or organocatalysts. In these methods, the chiral information is transferred intermolecularly (from the catalyst to the substrates) and is amplified: a single molecule of catalyst will be engaged in a number of cycles, generating each time an optically active product.¹¹ Providing that the catalyst is properly recycled and reusable after each cycle, this method (if well optimised) offers a highly attractive atom-economic pathway to prepare enantiomerically pure compounds from prochiral material.¹⁹ Typically 0.1-20 mol%²⁰ of catalyst is sufficient in an optimised process and high yield of highly enantioenriched products are often attained. The recent increased interest in catalysis relies on the fact that it broadens the scope of optically active molecules that can be produced.

1.1.2.3.1 Enzyme mediated catalysis

Biocatalysis^{21,22} involves multifunctional macromolecules (10^4 - 10^6 daltons) that are among the most efficient molecules that catalyse chemical reactions. Nevertheless, their substrate and reaction scope are often very limited. In addition, even though these bioprocesses occur under very mild conditions, these conditions can constitute a significant limitation to their activity. Since most of the interactions with the substrates are mediated by hydrogen-bonds²³ (as illustrated by the example of the carboxypeptidase A,²⁴ Figure 1.4), the pH will have a dramatic influence on the facile formation of enzyme-substrate complexes.

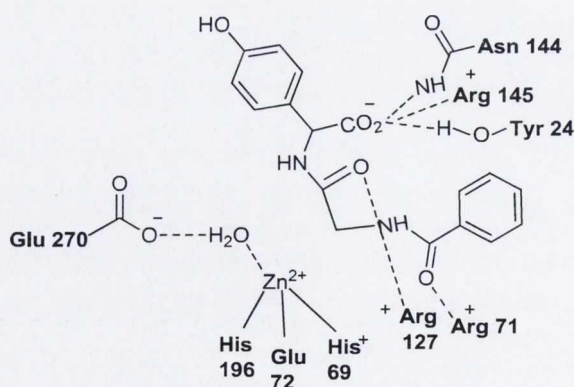


Figure 1.4 Enzyme-substrate complex associated with carboxypeptidase A

The temperature can also be of major significance since certain enzymes are denatured in too high temperatures, which changes the conformation of the protein (unwind) and, consequently, the conformation of their active site. However, if the conditions are well optimised, their astounding chemo- region- and stereoselectivity²⁵ make them an industrially viable technology.²⁶

1.1.2.3.2 Metal(ion)-based catalysis

This catalytic strategy relies on the use of a metal(ion) complex in a chiral environment to accelerate the rate of a reaction. During a catalytic cycle, a Lewis basic substrate coordinates to the metal(ion), decreasing the energy of its LUMO orbital and so enhancing its electrophilicity. The versatility of the geometry of the ligands, the nature of either the metal-ion or the counterion, introduced a great range of possibilities in terms of the tunability of the electronic and steric properties, enabling these catalysts to be used in an impressive range of reactions.¹³

Metal(ion)-based catalysis represents a powerful complementary method to enzymatic catalysis in a way that considerably extended the range of reactions that chemists can catalyse.²⁷ As William S. Knowles highlighted during his Nobel address: “When we started this work we expected these man-made systems to have a highly specific match between substrate and ligands, just like enzymes. Generally, in our hands and in the hands of those that followed us, a good candidate has been useful for quite a range of applications.”²⁷

For the development of methods for the formation of new C-C bonds by palladium-catalysed cross-coupling, Richard F. Heck, Ei-ichi Negishi and Akira Suzuki were awarded the Nobel Prize in Chemistry in 2010, demonstrating the importance of such catalytic systems in Organic Chemistry.²⁸

1.1.2.3.3 Organocatalysis

In organocatalysis (or metal-free organic catalysis), the acceleration of the rate of a reaction is induced by the addition, in a substoichiometric ratio, of a low molecular weight organic compound.²⁹⁻³³ These catalysts are generally naturally readily available as a single enantiomer (*e.g.* proline) and inexpensive. They are usually robust and stable to oxygen and moisture, which often enable chemists to use them without requiring strict reaction

conditions such as inert atmosphere or absolute solvents. ‘Metal-free’ catalysts are likely to be less toxic and environmental friendly which avoids the issue of pollution and waste treatments. These ‘green’ advantages make organocatalysis an alternative which seems to hold much promise in such areas as the synthesis of pharmaceutical or agrochemical products without possible heavy metal contamination.³⁴ Emerging as a practical method, interest in the organocatalysis field has intensified rapidly in the last decade.

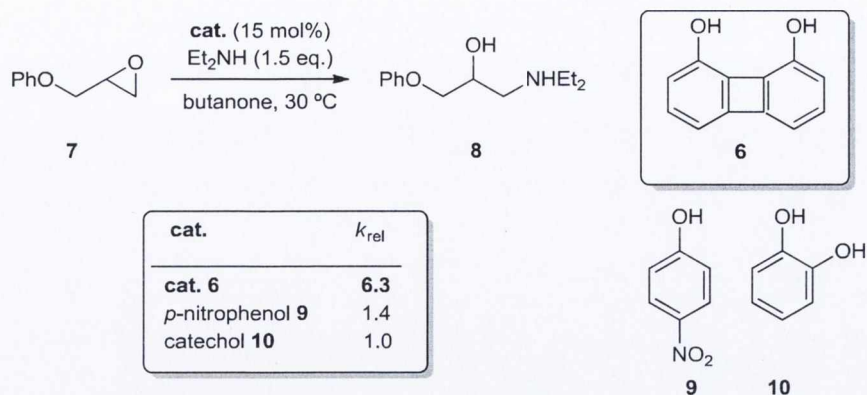
1.2 The development of (thio)urea-based catalysts

In this promising ‘metal-free’ method of catalysis, inspired by enzymatic mechanisms of action, rigid *bis*-hydrogen-bond donating molecule templates are in the center of new catalyst designs.^{35,36} In particular, urea and thiourea moieties play an important role and are widely used as a powerful tool for the activation of Lewis basic substrates as general acid catalysts.³⁷⁻³⁹ This has been elucidated as a result of various studies from the past two decades.

1.2.1 General principles

In the 1980’s, it was demonstrated that molecules incorporating appropriately positioned hydrogen donating groups, capable of electrophile activation, had great catalytic potential. This strategy was based on the use of conformationally restricted catalysts bearing two heteroatom-bond protons which would donate two strong hydrogen bonds to the same carbonyl functionality, through its oxygen atom’s lone pairs of electrons.⁴⁰

Hine et al.⁴¹ were the first to demonstrate the importance of using a rigid catalytic system (*i.e.* 1,8-biphenylenediol (**6**), Scheme 1.1) in the efficient promotion of the addition of secondary amines to glycidyl phenyl ether (**7**). The bis-phenolic catalyst **6** possesses two syn-periplanar hydrogen bond donating groups in a rigid catalyst framework, capable of interacting with both lone pairs of electrons of the epoxide oxygen atom. To test the validity of this hypothesis, Hine compared the catalytic activity of different phenolic systems in this reaction. Not only more acidic and monoprotic *p*-nitrophenol (**9**) revealed to be noticeably less efficient than **6**, but *bis*-hydroxyl functionalised catechol **10** exhibited even less activity.



Scheme 1.1 Evaluation of the catalytic properties of phenol derivatives for the promotion of ring opening glycidyl phenyl ether

Since hydrogen-bond donating solvents were already known to accelerate the rate of Diels Alder reactions,⁴² Kelly found an opportunity to use Hine's-type catalyst to study the promotion of such reactions. Based on the scaffold of Hine's most acidic bisphenylene diol (4,5-dinitro-1,8-biphenylenediol), he designed a more soluble biphenolic aromatic system (**11**, Figure 1.5) and successfully promoted Diels Alder reactions involving either aldehydic or ketonic dienophiles.⁴³ Once again, the significant rate acceleration of the reaction was explained *via* the bifurcated interaction between the hydroxyl groups of the catalyst and the carbonyl of the dienophile.

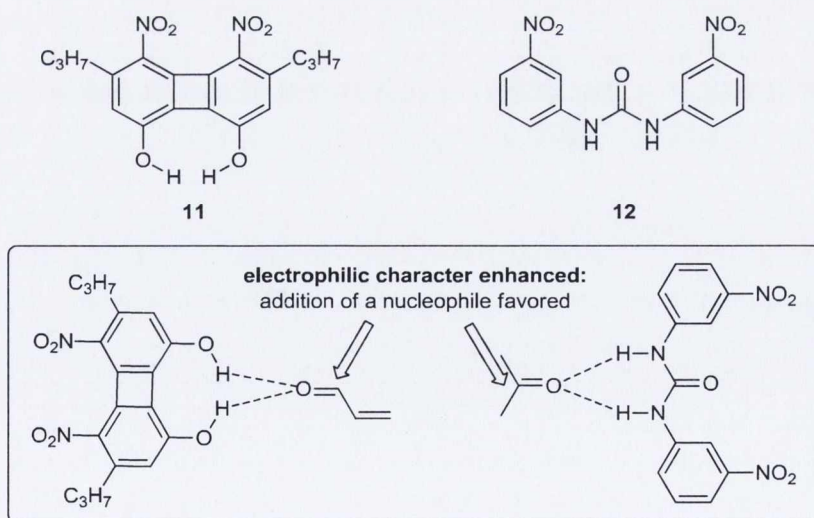


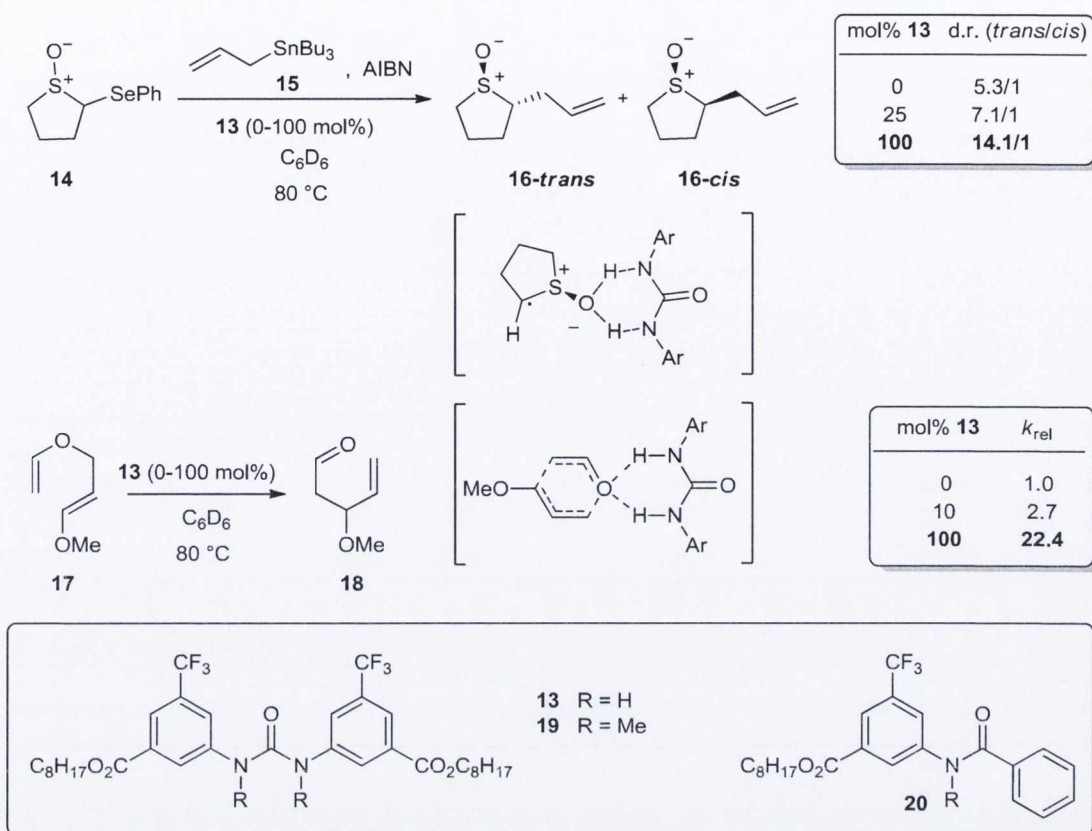
Figure 1.5 Hydrogen bond donating catalysts for the Diels-Alder reaction

Another discovery represented a major breakthrough for modern catalyst design. Etter *et al.*^{44,45} observed that *N,N'*-diaryl ureas bearing electron-withdrawing groups (*e.g.* **12**, Figure 1.5) readily formed cocrystals with various Lewis basic functional groups (*e.g.* carbonyl compounds) due to their ability to donate hydrogen bonds. This new discovery highlighted urea derivatives' potential to also promote - as general acid catalysts - the addition of a nucleophile to an electrophile, using hydrogen-bond donation to activate the reaction.

Nitro groups have been chosen as substituents for the aromatic ring due to their electron-withdrawing effect. Their location at the *meta* position has been found empirically to be the most suitable.^{44,45} If the nitro group is replaced by an electron donating group or is moved to another position on the aromatic ring, the complexing property of the urea core is noticeably weaker.

1.2.2 The (thio)urea moiety and its tunability

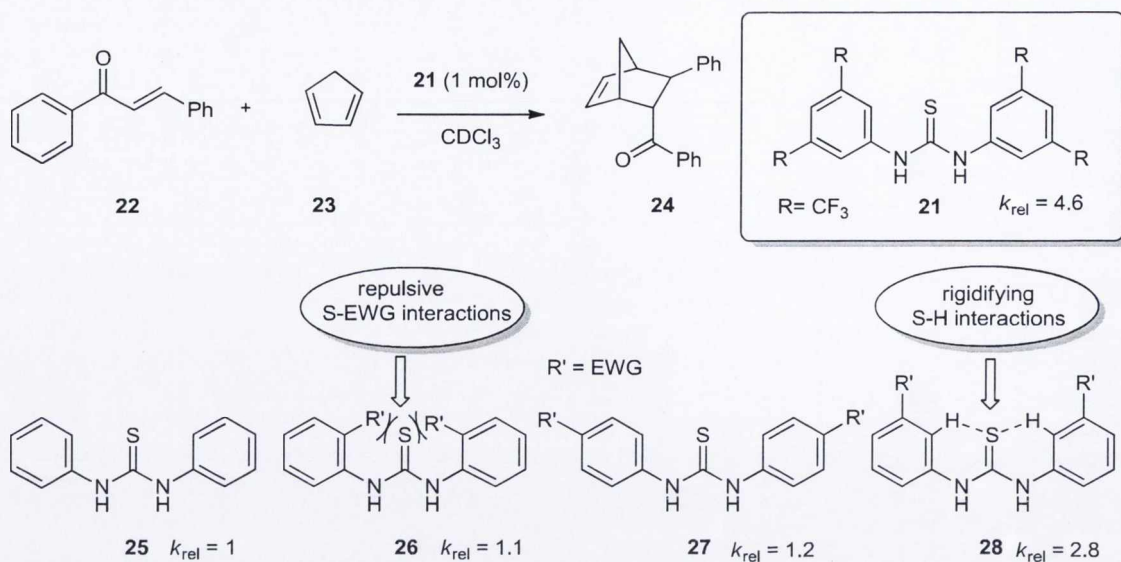
A few years later, in the light of these pioneering studies, Curran and Kuo reported the first examples of (thio)urea derivatives as efficient promoters for general acid catalysed reactions. Inspired by Etter's urea **12** and prompted by Kelly's success in promoting Diels Alder reactions using the bifurcated hydrogen-bond donor **11**, Curran designed a novel *N,N'*-diaryl(thio)urea **13** (Scheme 1.2) for the promotion of radical allylations. Since nitro groups were known to be radical inhibitors, he introduced onto Etter's scaffold trifluoromethyl groups that would have similar electron-withdrawing effects on the aromatic moiety. He also incorporated a lipophilic octyl ester functionality to increase its solubility in organic solvents. This new urea **13**, used in stoichiometric amount, proved to be an efficient additive in radical allylations of cyclic α -sulfinyl radicals **14** with allyltributylstannane **15**⁴⁶ and Claisen rearrangements of diene **17** (Scheme 1.2).⁴⁷



Scheme 1.2 The first examples of reactions promoted with a urea as a general acid catalyst

In line with Etter's results and supported by the failure of catalysts **19** and **20** (which are devoid of two coplanar N-H bonds available for hydrogen-bond donation) to promote the Claisen rearrangement, Curran *et al.* proposed a transition state model in which a bis-hydrogen-bond interaction between the urea and the lone pair of electrons of the oxygen atom was responsible for the efficient rate acceleration of these reactions (Scheme 1.2). Curran also theorised that, in the transition state of the radical allylation reaction, the urea moiety led to a better sulfinyl radical's facial differentiation resulting in a higher diastereocontrol of the addition.

The effect of trifluoromethyl substituents was further exploited in this catalyst class by Schreiner.^{48,49} Comparing the catalytic performance of a number of symmetrical thioureas bearing different substituents (Scheme 1.3), he confirmed that thioureas bearing electron-withdrawing substituents on the phenyl moieties were more efficient (especially *bis-meta*-substituted thiourea **21**) to promote the Diels Alder reaction of unsaturated ketone **22** with cyclopentadiene (**23**).



Scheme 1.3 The design of thiourea-based catalysts for the promotion of the Diels Alder reaction

This study also highlighted the fact that the choice of the substituent's positioning on the aromatic ring was fundamental in the catalyst design. Thioureas bearing a trifluoromethyl substituent in the *ortho* position (*i.e.* **26**) were found to be less active than if it was substituted in *para* (*i.e.* **27**) or, even better, *meta* position (*i.e.* **28**) of the phenyl ring. Schreiner *et al.* suggested that the trifluoromethyl group placed at *meta* position would enhance the acidity of the *ortho*-hydrogen atoms. This would result in an interaction between these protons and the (thio)urea oxygen/sulfur atom, hence constraining thiourea **28** into a planar conformation and rigidifying the catalyst's structure. This idea had a major impact on subsequent catalysts design. It should be added that trifluoromethyl groups also limited the self-association of the catalyst since it does not participate in hydrogen-bonding.

For this study, Schreiner selected thioureas in preference to their oxygenated derivatives for their higher acidity ($\text{p}K_{\text{a}}(\text{thiourea}) = 21$ in DMSO, $\text{p}K_{\text{a}}(\text{urea}) = 26.9$ in DMSO),⁵⁰ which he expected to lead to stronger hydrogen-bonding interactions with the substrates. Sulfur being less electronegative than oxygen, he also aimed at reducing the catalyst's tendency to self-associate. This logic will also be reused in future catalysts development, even though for some reactions ureas still remained a better promoter.⁵¹⁻⁵⁴

1.2.3 Chiral (thio)urea-based catalysts

In 1998, Sigman and Jacobsen discovered that it was possible to use (thio)urea catalophores to prepare optically active compounds. Thus, they disclosed the first examples of catalysts incorporating a (thio)urea functionality in close proximity to a chiral amino-acid-derived core, which role would be to transfer the chiral information during the transition state (**29** and **30**, Figure 1.6).⁵⁵

This (thio)urea scaffold revealed great potential, offering numerous possibilities to fine-tune - electronically and sterically - the catalyst structure to particular reaction demands.⁵⁶ Screening synthetic libraries of resin-bound catalyst candidates, they selected (thio)urea compounds **29** and **30**, incorporating a chiral cyclohexyl diamine moiety on one side and an enantiomerically pure *tert*-leucine amino acid on the other, as optimum promoters for the asymmetric Strecker reaction.

The two geometrically demanding *tert*-butyl groups at both extremities of the molecules (at the amino acid position and at the *meta*-position of the aromatic salicylimine) were proposed to be responsible for the high level of enantioselectivity. It was found that only 2 mol% of **29** was needed to efficiently prepare **31** and **32** *via* the addition of HCN to either aliphatic or aromatic substituted *N*-benzyl or *N*-allyl imines. Challenging aliphatic ketimines could also be used as substrates with excellent results (product **33**, Figure 1.6).^{51,52}

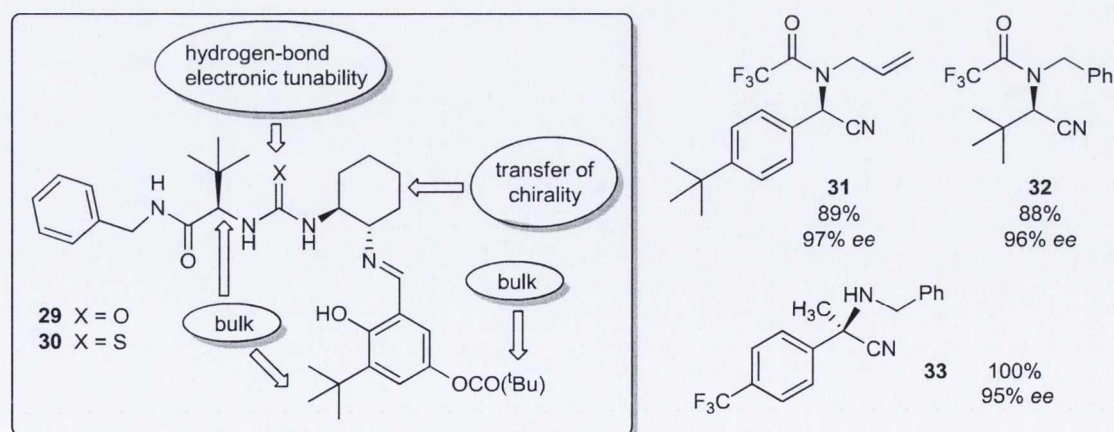


Figure 1.6 Chiral (thio)urea catalysts as efficient promoters of the Strecker reaction

A subsequent mechanistic and structural rational design study, based on computational modeling and NMR experiments, highlighted the importance of fine-tuning the steric bulk of the amide substituent of catalyst **29**.⁵⁷ Incorporating a tertiary amide onto urea's skeleton **34** (Figure 1.7) enabled Jacobsen *et al.* to achieve a better stereocontrol for some reactions. With these catalysts in hand, products **35** and **36** were generated with quantitative yields and excellent enantioselectivities (up to 99% *ee*).

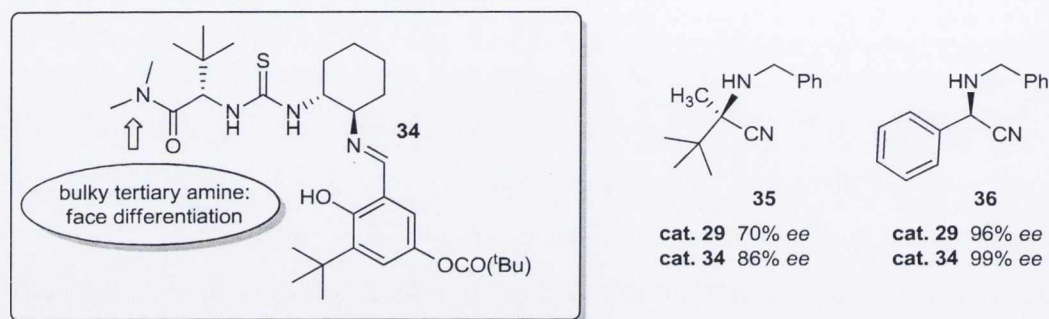
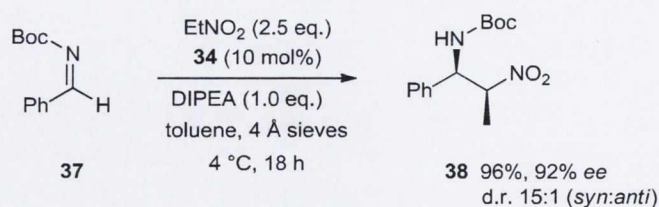


Figure 1.7 Sterically-tuned Jacobsen's catalyst for better face differentiation

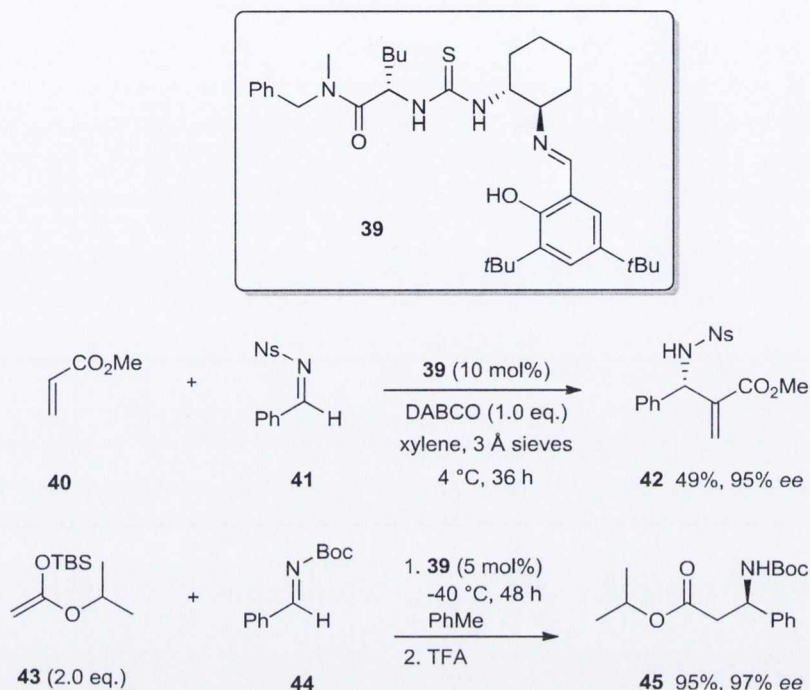
With such versatile and readily fine-tunable molecules, Jacobsen and coworkers were provided with catalytic systems that were efficacious for a wide scope of highly enantioselective reactions including aza-Henry reactions,⁵⁸ hydrophosphonylation of imines,⁵⁹ Mannich-type⁶⁰ and aza-Baylis-Hillman reactions.⁶¹

For instance, **34** was proved to be capable of the promotion of asymmetric aza-Henry reactions involving different nitroalkanes (nitroethane, nitropopane) with *N*-Boc-protected aromatic imines, such as **37**. Henry-adducts (*e.g.* **38**, Scheme 1.4) were obtained with excellent yields, enantioselectivities and with high diastereocontrols.⁵⁸



Scheme 1.4. Aza-Henry reaction catalysed by Jacobsen's thiourea **34**

Design of thiourea **39** (Scheme 1.5) gave access to the synthesis of Baylis-Hillman adducts (e.g. **42**), with moderate yields but high enantioselectivities (up to 99% *ee*), *via* the reaction of methylacrylate (**40**) with a series of aromatic imines such as **41**.⁶¹



Scheme 1.5 Highly enantioselective reactions catalysed by chiral thiourea **39**

It was found that 5 mol% loading of **39** was also highly catalytically efficient for the promotion of Mannich-type reactions (Scheme 1.5). Adding silyl ketene acetal **43** to aldimine **44** afforded β -aryl- β -amino acid **45** in excellent yield and enantioselectivity (95%, 97% *ee*).⁶⁰

1.2.4 Expanded reaction scope: bifunctionality

Following these discoveries and inspired by the enzymes' remarkable abilities to control the stereochemical outcome of the reactions they catalyse, which has (in part) been ascribed to their bifunctional activation pathway, Takemoto proposed to introduce the concept of bifunctionality into organocatalysis with the design of chiral thiourea **46** (Figure 1.8).⁶² Mimicking the synergistic activation mode used by enzymes, Takemoto's bifunctional catalyst possesses two catalytically active functional groups in close proximity to each other, capable of activating simultaneously the two substrates of a given reaction.

Therefore, in the transition state, the (thio)urea-bond-activated carbonyl group would be held in close proximity to the amine-activated pronucleophile in a defined controlled chiral environment.⁶³ For this purpose, Takemoto incorporated a chiral general base functionality (1,2-*trans*-cyclohexyldiamine) in close proximity to the aryl(thio)urea core.

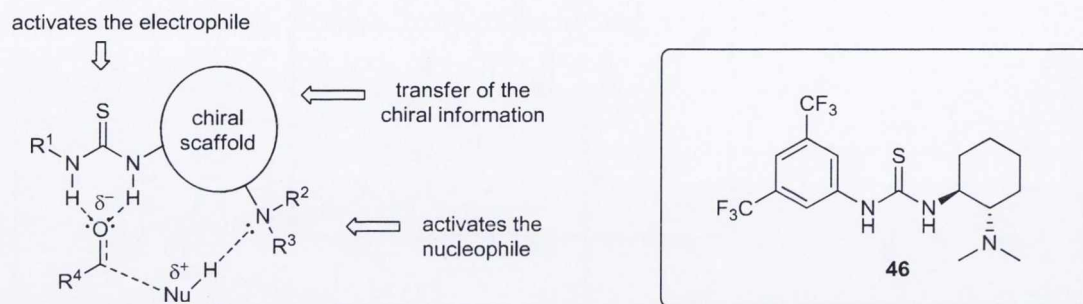


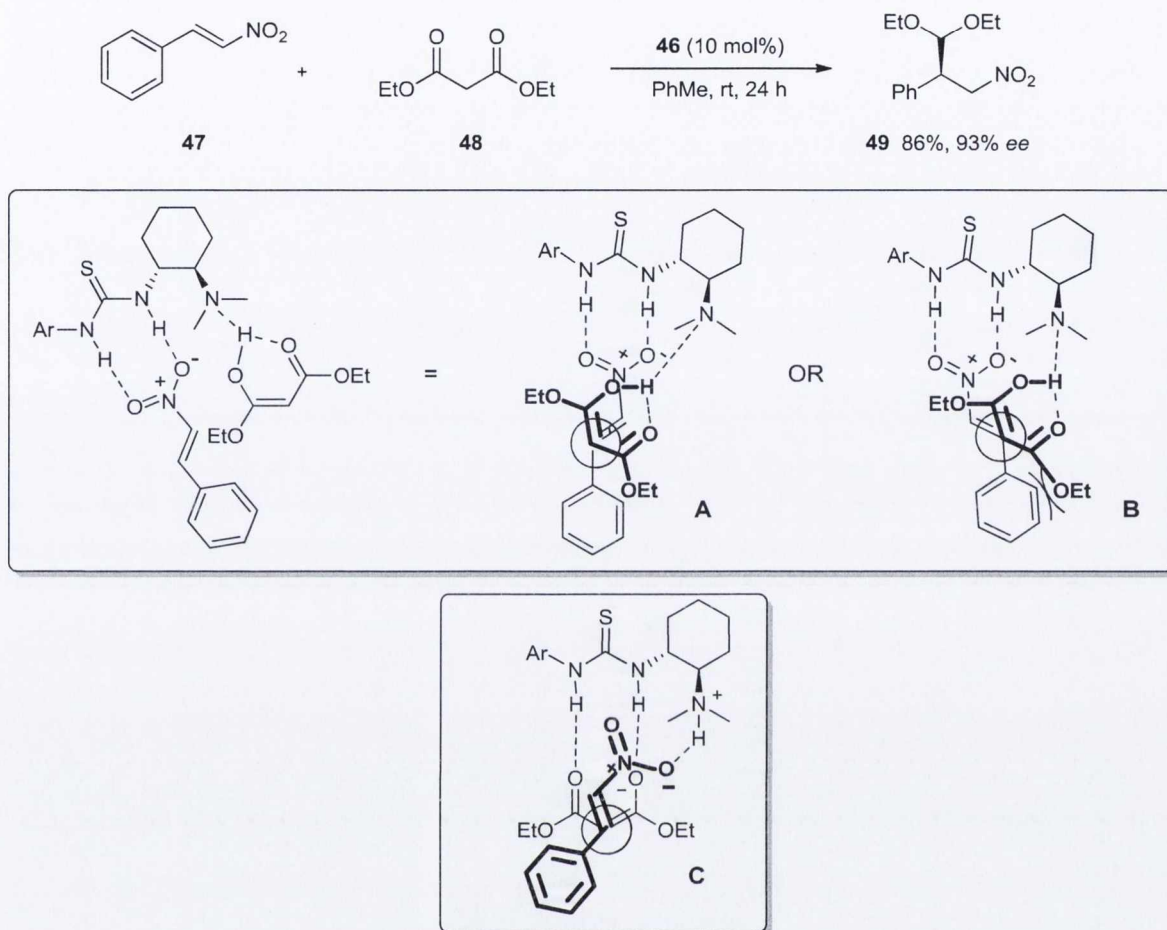
Figure 1.8 Takemoto's bifunctional catalyst

Thiourea **46** (Figure 1.8) was proved to offer enormous potential advantages over traditional strategies (*i.e.* monofunctional activation pathways using either basic triethylamine or general acidic Schreiner's ureas (*e.g.* **21**) as catalysts) in terms of both reaction rate and enantioselectivity.⁶⁴ For instance, it promoted the Michael addition of diethyl malonate (*e.g.* **48**) to (*E*)- β -nitroolefins (**47**), affording Michael adduct **49** with good yield and enantiomeric excess (Scheme 1.6), where either (thio)ureas or bases (triethylamine or DBU) used alone have been demonstrated to serve as poor catalysts, both conversion and selectivity-wise.^{62,63}

Takemoto *et al.* proposed a pre-transition state assembly **A** where the amine moiety would be responsible for the deprotonation of the malonate ester. Simultaneously, the thiourea would activate the nitroalkene and place it in an opportune position for the addition to occur selectively on one face of the electrophile.⁶³ According to Scheme 1.6, a steric clash between the ester group of the malonate and the phenyl moiety of the nitrostyrene would ensue in pre-transition state assembly **B**, making pre-transition state assembly **A** more likely to take place.

Pápai *et al.*⁶⁵ proposed another pre-transition state assembly **C** for this reaction (Scheme 1.6), also involving a synergistic bifunctional activation of the two substrates. This assembly was based on the deprotonation of the malonate. The resulting enolate would

interact through hydrogen-bonding with the thiourea moiety, whereas the nitroolefin would be activated by the quinuclidinium moiety *via* another hydrogen-bond.



Scheme 1.6 The stereochemical rationale proposed to explain the outcome of the Michael addition of malonates to (*E*)-β-nitrostyrene catalysed by **46**

Following Curran and Takemoto's major discoveries, numerous research groups developed organocatalysts processes in which the (thio)urea *motif* had a central role. These systems were proved efficient for the promotion of various enantioselective reactions (including Michael-type additions, Friedel-Crafts reactions, Henry-type reactions, *etc.*).⁶⁶⁻⁷⁴

1.3 Cinchona alkaloids as useful catalyst scaffold

1.3.1 Structures of the molecules found in Cinchona bark

Cinchona alkaloids are natural molecules extracted from the bark of South-American trees of the genus *Cinchona*. From the extractions of these barks, around 30 different alkaloids could be isolated. Among them are found (in useful quantities) two pairs of *pseudoenantiomers*: quinine (**50**)/quinidine (**51**) and cinchonidine (**52**)/cinchonine (**53**) (Figure 1.9).

In 1912, Bredig and Fiske demonstrated the catalytic abilities of quinine and quinidine for the first time, when they were found to accelerate the addition of HCN to benzaldehyde.⁷⁵ The resulting cyanoanhydrides were optically active, however the obtained enantiomeric excess was low.

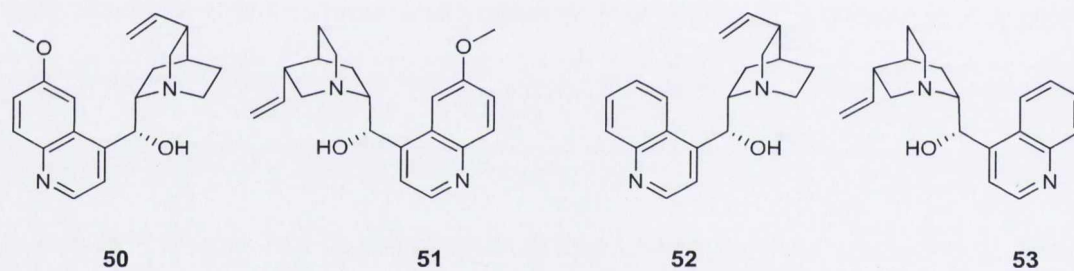


Figure 1.9 Cinchona alkaloids extracted from the bark of the *Cinchona* trees

1.3.2 Cinchona alkaloids as bifunctional catalysts

Since then, cinchona alkaloids have represented one of the most common templates used for organocatalyst design,^{11,76} mainly due to their bifunctional character. They incorporate two key functional groups, with complementary roles, which synergistically activate the two components of a reaction in a chiral environment (Figure 1.10).

In the transition state of an addition reaction involving an electrophile (with at least one Lewis-basic site near the electrophilic centre) and a pronucleophile which is deprotonated during the reaction, the quinuclidine ring, as a general base, creates and stabilises a negative charge on the nucleophilic substrate. Meanwhile, the hydroxyl group close by at the C-9 position, enhances the electrophilic character of the second substrate *via* hydrogen-

bonding. This simultaneous activation results often in a higher degree of selectivity during the reaction.³⁸ Another advantage of this bifunctional mechanism is that since both of the *pseudoenantiomeric* versions of these alkaloids are commercially available, it is often the case that the practitioner can conveniently access both enantiomers of a product in a catalytic process.⁷⁶

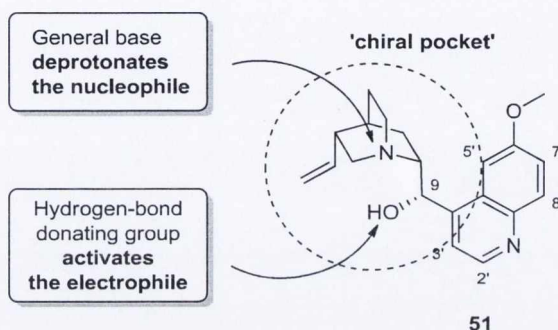
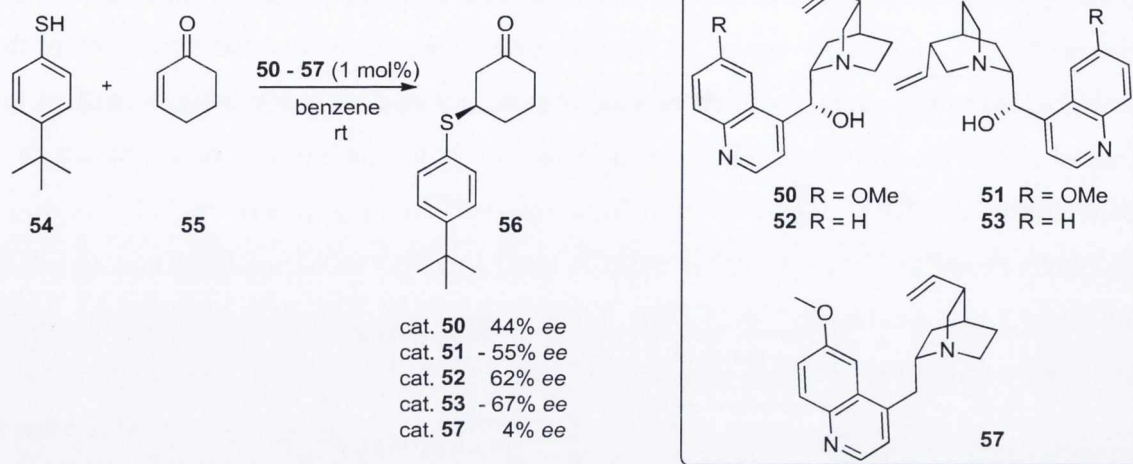


Figure 1.10 Quinidine: a bifunctional catalyst

1.3.3 Examples of reactions catalysed by natural cinchona alkaloids

1.3.3.1 Cinchona alkaloids as catalysts for the Michael-type addition: a seminal comprehensive study

In 1975, Wynberg investigated the Michael addition of activated nitroalkanes and β -ketoesters to methylvinylketone (MVK) using quinine (**50**) in catalytic amounts.⁷⁷ Following this study, Wynberg *et al.* extensively explored the possibility of obtaining an optically active product from two optically inactive substrates *via* the 1,4-additions of thiophenols (e.g. **54**) and selephenols to cyclohexenone (**55**). Enantiomeric excess up to 67% and quantitative chemical yields were obtained with only 1 mol% catalyst loading (e.g. adduct **56**, Scheme 1.7).⁷⁸⁻⁸⁰



Scheme 1.7 Asymmetric Michael addition catalysed by cinchona alkaloids

It is noteworthy that [2+2] cycloadditions (between ketene and chloral) could also be promoted by quinidine (**51**) with impressive stereoselectivities that reached 98% *ee*.⁸¹

1.3.3.3.1.1 Mechanistic and stereochemical rationale

In 1981, Wynberg published a landmark study: revisiting the investigation on the Michael-type addition of thiophenols onto cyclic enones, Wynberg and coworkers proposed a developed mechanistic insight of the reaction.⁸⁰

It was found that opposite enantiomers were preferentially obtained when catalysts with different β -hydroxyamine unit's stereochemical arrangement were involved in the catalysis (*i.e.* quinine/quinidine or cinchonidine/cinchonine, Scheme 1.7). Also, catalyst **57**, which included no hydroxyl group on its skeleton, failed to promote the Michael addition effectively, providing almost no enantiodiscrimination (4% *ee*). These results confirmed that cinchona alkaloids operated through a bifunctional mechanism and that the hydroxyl group had a central role in the catalyst's mode of action. Therefore, Wynberg proposed a transition state where the cycloalkenone and the thiol are simultaneously activated by the catalyst's hydroxyl and amine functionalities respectively (Figure 1.11).

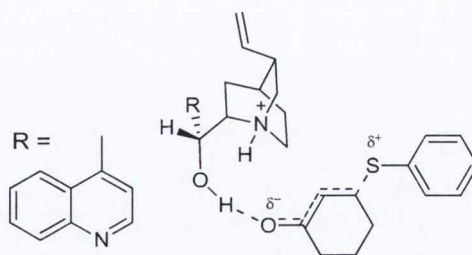


Figure 1.11 Proposed Michael-type addition transition state

Wynberg identified other important interactions that would occur during the transition state and which would have an influence on the transition state's stability (Figure 1.12). He postulated that the free catalyst would naturally adopt the conformation where its quinuclidine nitrogen's lone pair of electrons would be positioned away from the quinoline ring. Along with the formation of the ammonium-thiolate ion pair, the quinuclidine ring would rotate around its C8-C9 bond (Figure 1.12). Thus, in close proximity to its ammonium counter ion, the thiophenoxide would be positioned on top of the quinoline moiety, sharing an electrostatic interaction with the electron cloud of their aromatic system.

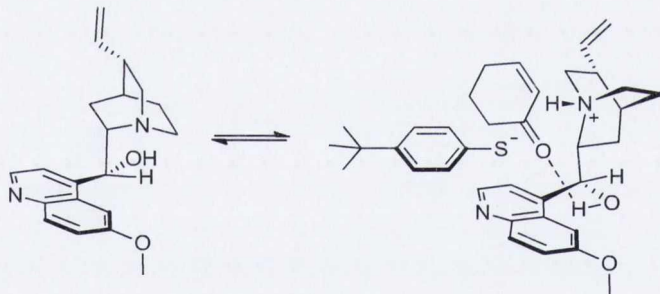


Figure 1.12 Conformation changes during the formation of the complex ammonium/thiophenoxide

Wynberg consequently established that the transition state was an arrangement of three entities, resulting from three interactions: the hydrogen-bonding and the two electrostatic interactions (the ions pair interaction and the last interaction described above). Thereby, the transition state would be well defined and not too many angles of approach would be possible for the two substrates, which would lead to high enantiocontrol during the reaction.

1.3.3.1.2 Influence of the reaction conditions

Wynberg, in the same seminal study, highlighted the importance of the choice of reaction conditions.

Solvents can have a major influence on the transition state stability. If the medium was too polar, the aforementioned ionic interactions would be considerably weakened. Moreover, if an alcoholic solvent was used, the hydrogen-bond between the C-9 hydroxyl group and the carbonyl substrate would likely face competition from the solvent.⁸⁰

Temperature was also proved to be an important factor. When the reaction was undertaken at lower temperature (-22 °C), in an attempt to achieve higher enantiocontrol, the reaction rate reduced significantly. Higher temperature (+60.5 °C) led to the production of less enantioenriched Michael adducts.

The substrates' structure had also a significant influence on the stereocontrol of the reaction. Sterically hindered cyclohexenones induced steric clashes with the catalyst's bulky bicyclic moiety which limit the possibilities of the angle of approach. For instance, the introduction of two methyl groups at the 5-position of the cyclohexenone led to better enantiocontrol.⁸⁰

1.3.3.1.3 Conformational studies

1.3.3.1.3.1 Background and theory

Since the late 1980's, numerous investigations into the conformation (in solution) of cinchona alkaloids and derivatives have been reported.⁸²⁻⁸⁵ These investigations have provided better insight into the pre-transition states of organocatalysed reactions. As stated before, the cinchona alkaloid backbone is constituted of two rigid moieties that rotate freely around two C-C bonds C8-C9 and C9-C4' (e.g. **52**, Figure 1.13). This dynamic environment is responsible for the existence of many conformational forms of these alkaloids. Their frequency of occurrence is variable, as is their ability to induce enantiocontrol in a given reaction.

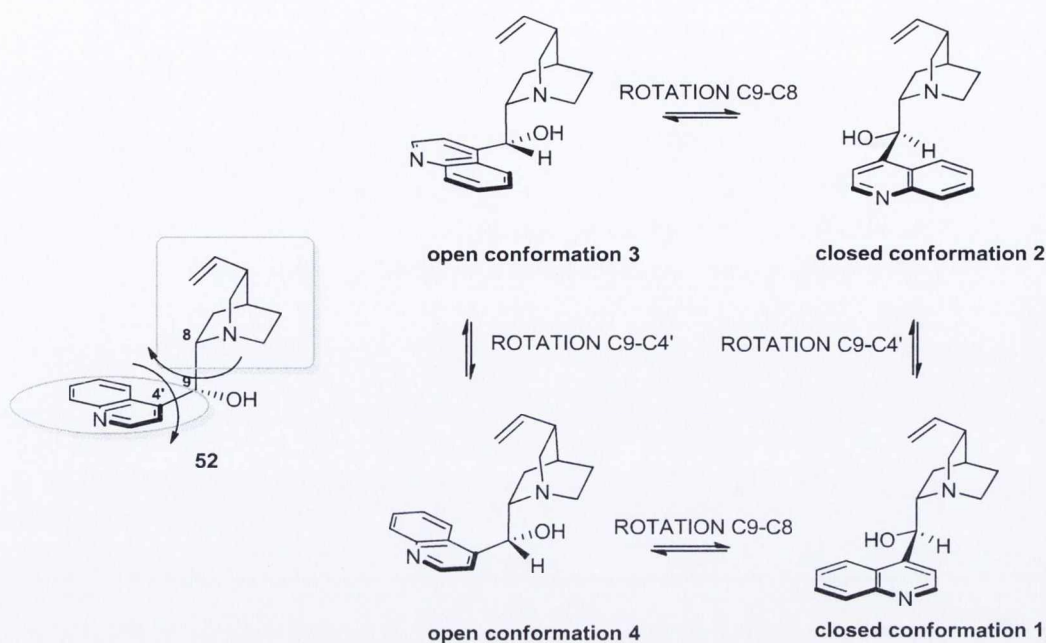


Figure 1.13 Four major conformations adopted by the cinchona alkaloids in solution

From computational modeling and MM2 calculations focusing on dihydroquinine and derivatives, four energy minima were identified associated with four conformers present in solution. They were each labeled open or closed depending on whether or not the lone pair of electrons of the nitrogen atom of the quinuclidine ring was facing the quinoline aromatic system (Figure 1.13).⁸⁵ Exhaustive NMR spectroscopic investigations (2D-NOESY and selective 1D-NOE) were undertaken to study the NOE contacts detectable between the protons of the quinoline ring and the quinuclidine moiety of a given alkaloid in solution (in particular H-3', H-5', H-6 α , H-7 α , H-8, H-9). Thus, the relative position in the space of the two rigid cyclic structures could be determined and the conformational preferences of these free alkaloids in solution could be clearly identified. The key NOE-contacts characterising each conformation are illustrated in Figure 1.14. They constitute the combined findings of studies independently reported by Wynberg's^{82,84} and Baiker's⁸⁵ research groups. For instance, NOE interactions between H-8 and H-9 would be representative of the open-type conformations adopted by the studied alkaloid, whereas interactions detected between H-9, H-6 α and H-7 α would prove that closed-type conformations were also present.

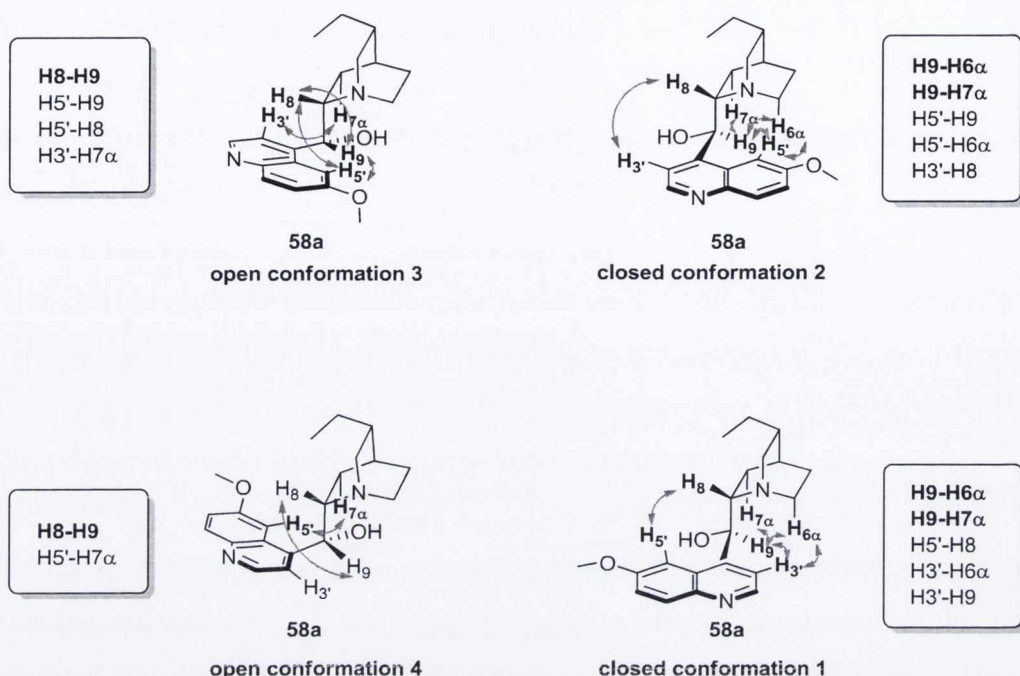


Figure 1.14 NOE contacts characteristic of the four conformations of dihydroquinine (58a)

Measurement of the J value between H-8 and H-9 was sometimes used as further evidence for the presence of preferred conformations.^{82,85} If a conformation was adopted in significant majority, this data, linked to the Karplus equation, could provide an indication on the H-8-C-8-H-9-C-9 dihedral angle value between those two protons, along with the relative position of the two rigid rings.

Once the conformations adopted by an alkaloid were identified, attention was then focused on the quantification of the population of the different conformations in a given sample.^{84,85} Several methods have been proposed in the literature. One of them was to undertake low temperature-NMR experiments. It was often the case that when studying a given alkaloid at 25 °C, a sharp set of average peaks could be obtained on the ^1H NMR spectrum, due to the fast rate of the conformational exchange occurring at this temperature in comparison to the time scale of the NMR experiment. By applying lower temperature, Baiker *et al.* aimed at slowing down the rate of these exchanges, enough to observe on the ^1H NMR spectrum separated sets of peaks (in different ratios) for the different conformations adopted by the studied alkaloid.⁸⁵

Another method was utilised by Wyndberg *et al.* when they investigated the conformational preferences of deoxycinchonidine **57** (*i.e.* a cinchonidine derivative devoid of a hydroxyl group at the C-9, Figure 1.15).⁸⁴ They found that NOE contacts could be observed between H-5' and respectively H-9 α (characteristic of open 3 conformation) and H-9 β (characteristic of closed 1 conformation) in CDCl₃. A computer modeling study demonstrated that the protons H-9 α and H-5' were positioned at 2.1 Å from each other when **57** adopted an open 3 conformation. Conveniently, the atomic distance between H-9 β and H-5' was also calculated to be 2.1 Å when **57** adopted the closed 1 conformation. Since these two atomic distances were equal, it was possible to directly compare the magnitude of the two Nuclear Overhauser enhancement observed for H-9 α and H-9 β upon irradiation of H-5' and thereby deduce that the conformations open 3 and closed 1 were present in a 60:40 ratio.

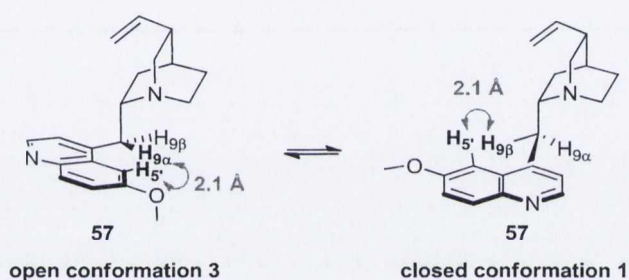


Figure 1.15 Comparison of H-5'-H-9 α and H-5'-H-9 β atomic distances in the two major conformations of deoxycinchonidine

1.3.3.1.3.2 Results

Wyndberg and Sharpless *et al.*^{82,84} demonstrated that dihydroquinine (**58a**) predominantly adopted the open 3 conformation in CDCl₃, with some additional conformational freedom that allowed closed conformation 1 and 2 to coexist at less than 10% (relative to conformation 3 levels). It was also found that the size of the substituent at the C-9 position (*i.e.* when the hydroxyl group was functionalised) significantly affected the conformational preferences of the alkaloid derivatives.

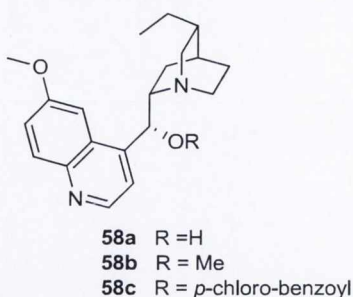


Figure 1.16 C-9 dihydroquinine derivatives used in Wyndberg's study

C-9-methoxy analogue **58b** (Figure 1.16) proved to exhibit the same conformational profile as dihydroquinine (**58a**) in CDCl_3 , whereas the C-9-*p*-chloro-benzoyl derivative **58c** was demonstrated to predominantly adopt the closed 2 conformation.

Importantly, the conformational equilibrium was found to be modified depending on the solvent utilised to perform the NMR experiments. Thus, alkaloid **58b** (which adopted the open 3 conformation in CDCl_3) was predominantly found in the closed 1 conformation when studied in CD_2Cl_2 . On the contrary, dihydroquinine (**58a**) preferentially remained in open 3 conformation when the solvent was changed to (deuterated) dichloromethane.⁸⁵

It is worth noting that in Wynberg's and Baiker's investigations, cinchona alkaloids (except deoxycinchonidine) were found to preferentially adopt either the closed 2 or open 3 conformations in most of the evaluated solvents. Baiker *et al.*⁸⁵ reasoned this to be due to a repulsive interaction occurring between H-5' and the oxygen atom of the C-9 hydroxyl group which destabilised the closed 1 and open 4 conformations. In the former conformations (2 and 3), molecular modeling studies⁸⁵ demonstrated that H-3' was further away from the same oxygen atom by 0.15 Å (Figure 1.17).

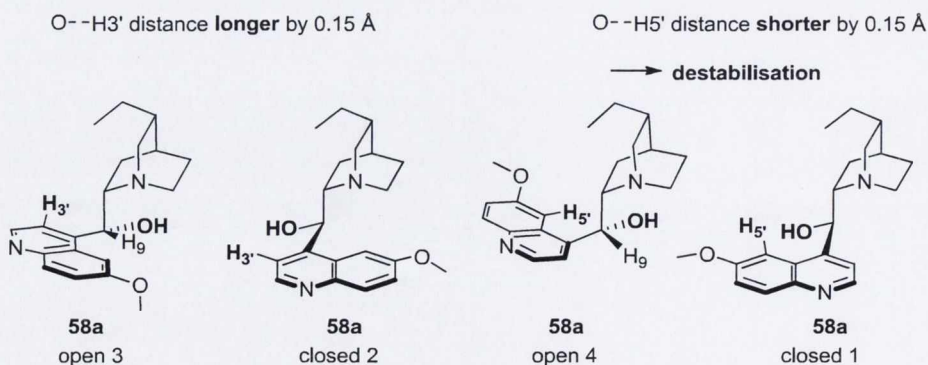


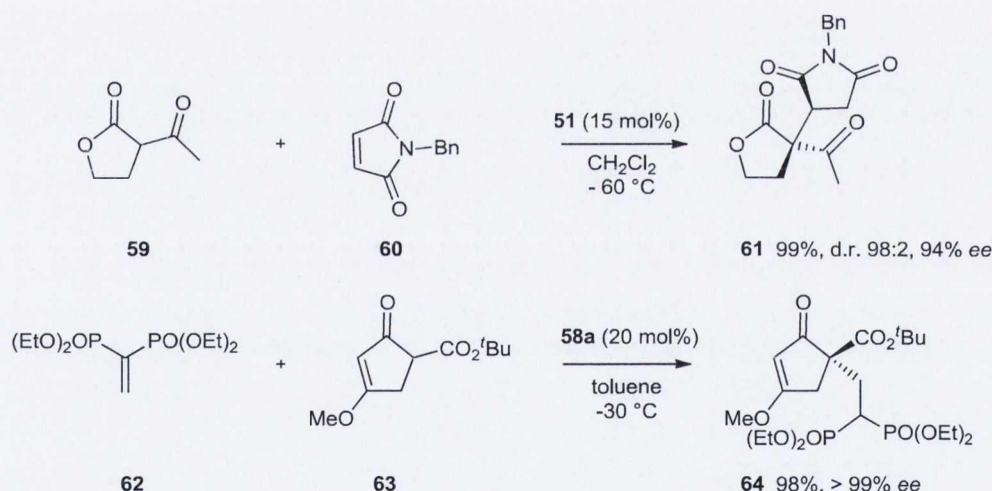
Figure 1.17 Comparison of O---H-3'/O---H-5' atomic distances in each conformation

Inspired by such results, several other groups used similar NMR spectroscopic techniques in an attempt to better understand these alkaloids' conformational preferences.⁸⁵⁻⁹¹

1.3.3.2 Other examples in the literature of the quinidine and quinidine's catalytic abilities

As Jacobsen highlighted in 2003, cinchona alkaloids are 'remarkable privileged chiral catalysts'⁹² which are capable of the bifunctional catalysis of a number of asymmetric reactions involving the addition of an acidic pronucleophile to an electrophile incorporating an hydrogen-bond accepting functionality.⁹³⁻⁹⁷

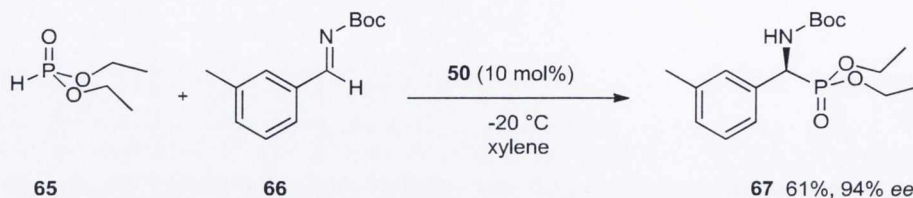
For instance, Melchiorre and coworkers found that the 1,4-conjugate addition of the β -ketoester **59** to maleimide **60** could be efficiently catalysed using 15 mol% of quinidine (**51**) to obtain the Michael adduct **61** in excellent yield and with high diastereo- and enantiocontrol (Scheme 1.8).⁹³



Scheme 1.8 Asymmetric Michael-type additions promoted by the natural cinchona alkaloids quinidine (**51**) and dihydroquinine (**58a**)

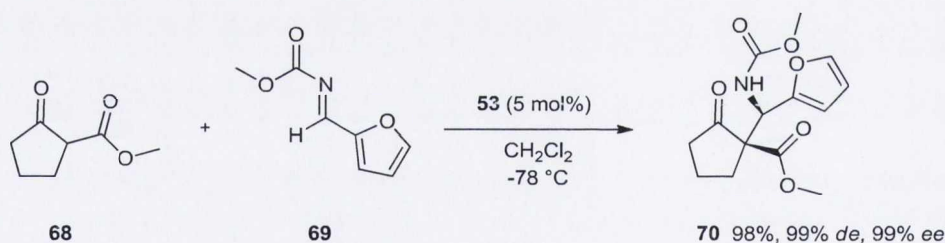
Jørgensen also studied the catalytic efficiency of natural cinchona alkaloids in Michael-type addition reactions (Scheme 1.8).⁹⁴ Dihydroquinine (**58a**), another natural molecule found in the bark of *Cinchona* trees, has demonstrated excellent activity and selectivity profile for the addition of ethylidene bisphosphonate (**62**) to β -ketoester **63**, leading to the formation of adduct **64** in 98% yield and > 99% ee.

Along similar lines, Ricci *et al.* demonstrated that quinine (**50**) was a valuable promoter for the asymmetric 1,2-addition of diethylphosphite (**65**) to a wide range of *N*-Boc protected aromatic imines (*e.g.* **66**) for the preparation of highly optically active adducts (*e.g.* **67**, Scheme 1.9).⁹⁵



Scheme 1.9 Hydrophosphonylation of *N*-Boc protected aromatic imines catalysed by quinine (**50**)

Cinchonine (**53**) was judiciously selected by Schaus and coworkers for the efficient promotion of diastereoselective Mannich-type addition of 1,3-dicarbonyl compounds with acyl imines (Scheme 1.10). Thus, as little as 5 mol% of **53** could promote the synthesis of **70** with excellent yield, enantioselectivity (99% *ee*) and diastereocontrol (99% *de*) via the addition of nucleophile **68** to acyl imine **69**.⁹⁶



Scheme 1.10 Use of cinchonine (**53**) in the highly efficient Mannich-addition of 1,3-dicarbonyl compounds with acyl imines

1.4 Cupreine/Cupreidine-based alternative catalyst systems

1.4.1 Cupreine and derivatives' structures and potentially advantageous properties

Wynberg concluded his systematic study on the mechanism of action of some cinchona alkaloids by writing: 'The scope of the utility of hydroxyl amines can perhaps be extended by constructing a catalyst containing a stronger base or a better hydrogen bond donor'.⁸² In

accordance with this statement, investigations on the use of both natural and synthetic derivatives of cinchona alkaloids incorporating a more acidic phenolic hydrogen-bond donor have emerged in the last 15 years. Three structures were initially proposed as potentially useful catalysts (Figure 1.18).

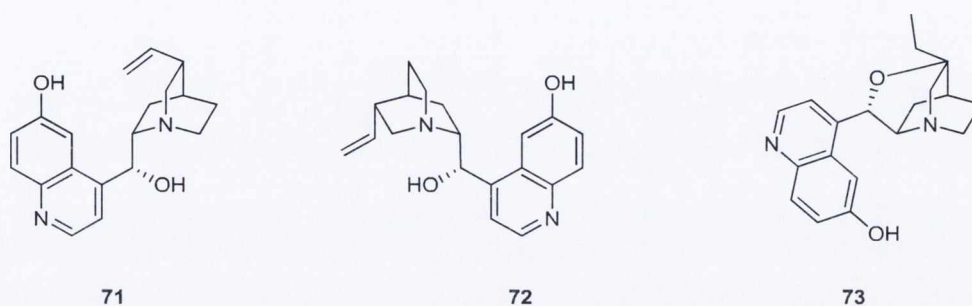


Figure 1.18 Cupreine/Cupreidine/β-isocupreidine

Phenolic hydrogen-bond donors cupreine (71), cupreidine (72) and β-isocupreidine (73) were also expected to be interesting structures for catalysis, due to the different relative spatial arrangement (position and orientation) on the alkaloid's backbone of their two catalytically active functional groups (compared to quinine and derivatives), leading to 'chiral activation pockets' with distinct steric and electronic characteristics (Figure 1.19).

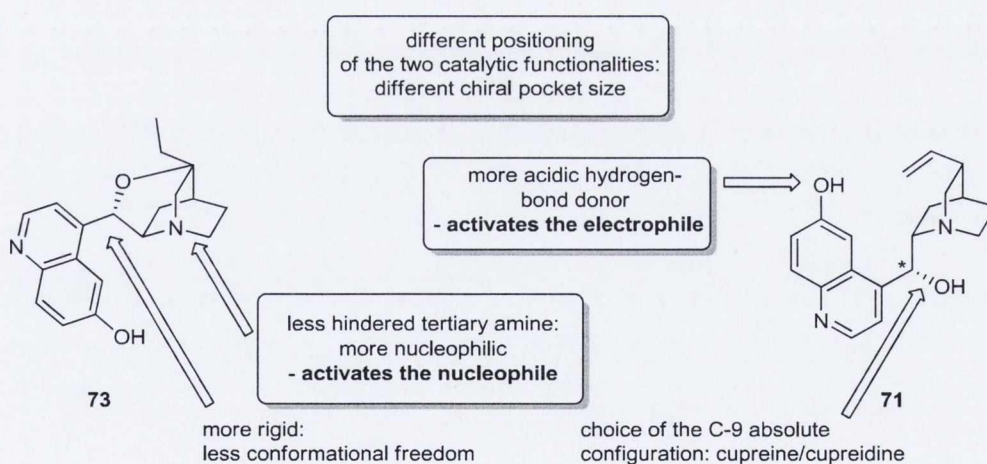


Figure 1.19 Concepts behind the use of cupreine/cupreidine scaffolds

Although cupreine (71) and cupreidine (72) could also be extracted from the bark of *Cinchona* trees, chemists were interested in the development of an efficient synthetic method to prepare them. Their synthesis was described by Stohs in 1979⁹⁸ in an efficient

one step-reaction involving the inexpensive and readily available quinine/quinidine. Thus, treatment of quinidine with boron tribromide led, after hydrolysis of the intermediate alkoxyborane, to **72** in 95% yield. Since their precursors are quinine and quinidine, alkaloids **71** and **72** could be advantageously prepared as a pair of *pseudoenantiomers*, often enabling the practitioner to independently access to the two enantioenriched antipodal products of an organocatalysed reaction.

The synthesis of β -isocupreidine (**73**) was less efficient. Compound **73** was obtained in moderate 61% yield from the reaction of quinidine with 10 equivalents of potassium bromide in 85% H_3PO_4 at 100 °C for 10 days.^{99,100} However this alkaloid still exhibited advantageous properties that motivated investigations towards its catalytic usage. The steric hindrance around the quinuclidine's nitrogen atom was reduced, which resulted in an increased nucleophilicity of the moiety (Figure 1.19).⁹¹ In addition, the tricyclic cage-like structure provided a more constrained skeleton, leading to limited conformational freedom.¹⁰¹ NMR spectroscopic experiments (Figure 1.20) undertaken to determine β -isocupreidine's conformational behavior confirmed that the phenolic hydroxyl group was in close proximity to the basic quinuclidine ring, resulting in the possible synergistic activation in a close environment of the both substrates of a given reaction.¹⁰⁰

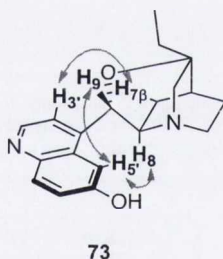


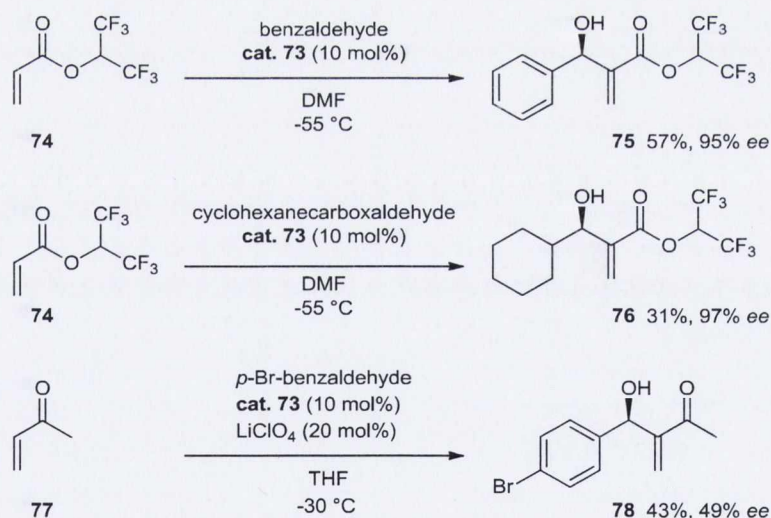
Figure 1.20 NOESY contacts detected that confirmed that β -ICD adopted an open 3 conformation in solution

1.4.2 Examples of the use of C-6' demethylated catalysts in asymmetric catalysis

These C-6'-demethylated analogues have proven to be powerful catalysts in a large range of asymmetric transformations where quinine/quinidine and their dihydro- derivatives were inefficient.¹⁰¹

Substantial improvements were afforded by these phenolic compounds in the Morita-Baylis-Hillman reaction. Hatakeyama demonstrated for the first time that β -ICD (**73**, 10 mol%) was an active catalyst for the highly enantioselective addition of various aromatic substituted aldehydes to activated 1,1,1,3,3,2-hexafluoroisopropyl acrylate (HFIPA **74**, Scheme 1.11).⁹¹ Under non-optimised conditions, the product of the addition of *p*-nitrobenzaldehyde to **74** (24 h at 2 °C) was generated in 12% yield when using quinidine as the catalyst, whereas the same product was afforded in 58% yield and 91% *ee* in the presence of a catalytic amount of β -ICD (after only 1 h at -55 °C). Following this encouraging result, several studies were reported in the literature (by Hatakeyama *et al.* and Shi *et al.*), involving a broad range of substrates.^{101,102}

Morita-Baylis-Hillman reactions could be promoted with enantioselectivities up to 99% *ee* (e.g. **75**, **76** and **78**, Scheme 1.11) using an activated acrylate (*i.e.* HFIPA, **74**) and a large range of aromatic aldehydes and cyclohexanecarboxaldehyde.^{91,103} Moderate enantioselectivities (up to 49% *ee*) were obtained with more challenging methyl vinyl ketone (MVK, Michael acceptor **77**).¹⁰⁴



Scheme 1.11 Examples of Morita-Baylis-Hillman reactionn catalysed by β -ICD

Aza-Morita-Baylis-Hillman reactions, promoted by β -ICD, provided access to products with high optical purity^{78,102,103,105} using acrylate **74**, methyl vinyl ketone (**77**, up to 99% *ee*) and other challenging substrates such as acrolein (**79**) and phenyl acrylate (**80**). Only *N*-tosyl or diphenylphosphinoyl protected imines were used as the ‘electrophilic’ component in these studies (e.g. adducts **81**, **82**, **83** and **84**, Figure 1.21).

Examples of Michael acceptors involved in efficient aza-Baylis-Hillman reactions (catalysed by alkaloid **73**):



Examples of the products formed:

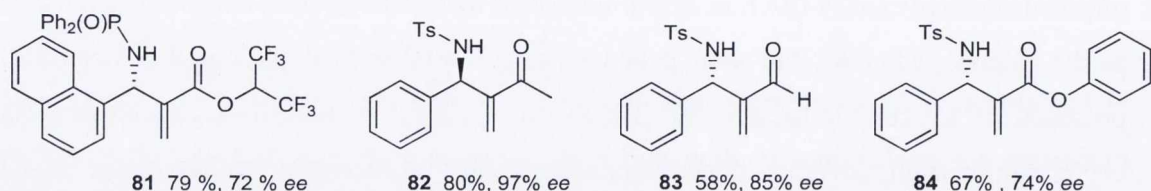
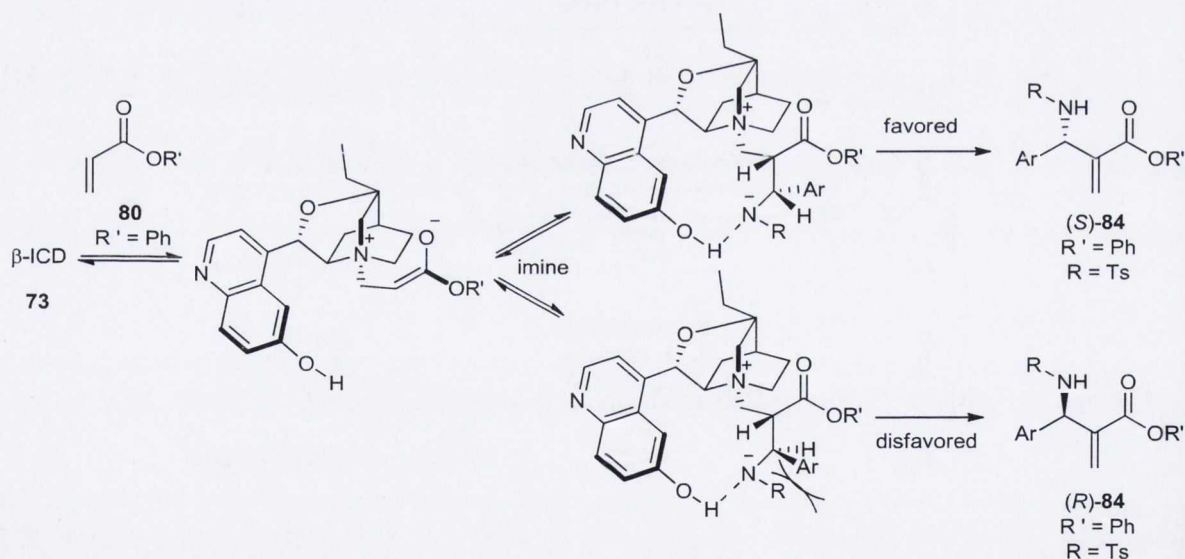


Figure 1.21 Examples of Michael acceptors efficiently utilised in the aza-Baylis-Hillman reaction catalysed by **73** and the corresponding products obtained

It was demonstrated that the promotion of these reactions was inefficient (especially from an enantioselectivity standpoint) if catalyst **73** was methylated at the C-6' position, which precluded the hydrogen-bond formation. This proved that the catalysis process operated *via* a bifunctional mechanism involving the C-6' hydroxyl group (Scheme 1.12).^{100,103,104}

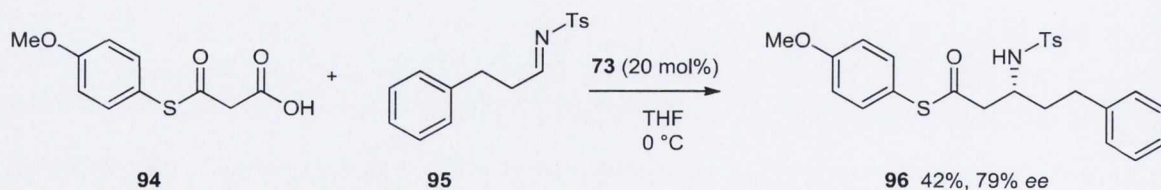
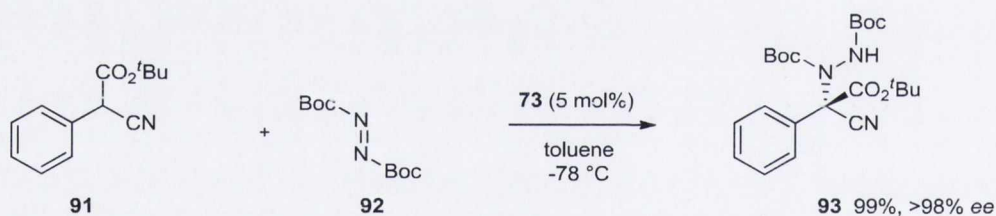
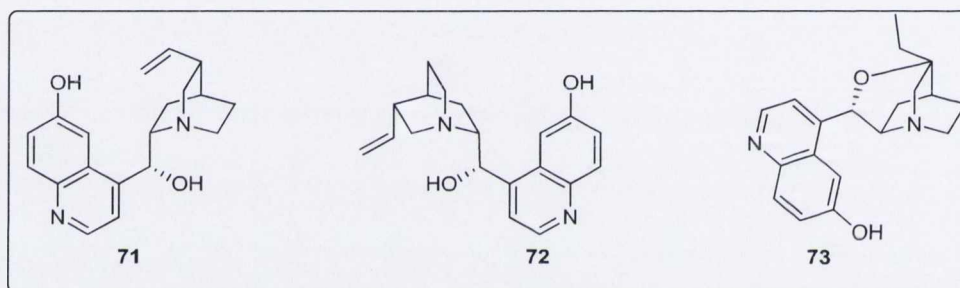
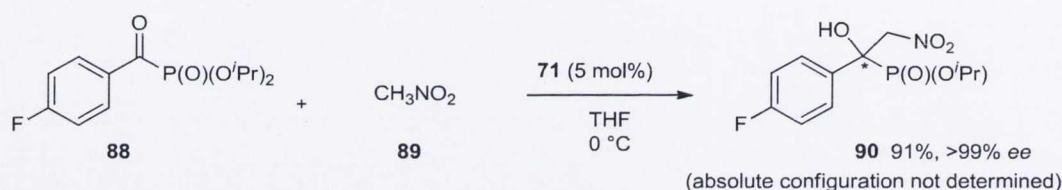
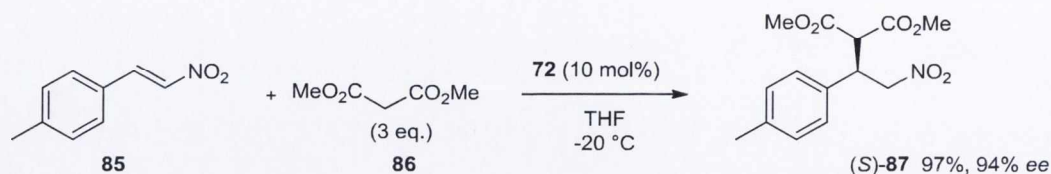
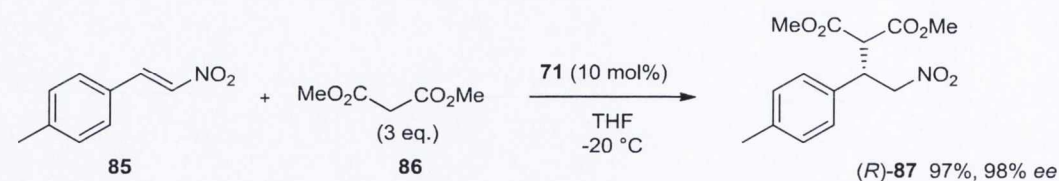


Scheme 1.12 Mechanism of the aza-Baylis-Hillman reaction catalysed by β -ICD proposed by Hatakeyama

Hatakeyama proposed a reaction mechanism where hydrogen-bonding would occupy a central role and which would explain the high enantiocontrol obtained during the aza-

Baylis-Hillman reaction: the steric clash between the *N*-protecting group and the aromatic substituent of the imines resulted in one of the two possible pathways to be disfavored (Scheme 1.12).¹⁰³

Several other reactions^{101,106-110} were also found to be efficiently catalysed by either β -ICD or cupreine/cupreidine: Michael-type conjugate-additions (*e.g.* nitroolefin **85** with malonate **86**, Scheme 1.13),¹⁰⁷ nitroaldol reactions (*e.g.* using α -ketophosphate **88** and nitromethane (**89**)),¹⁰⁸ electrophilic aminations (*e.g.* between α -cyanoacetate **91** and dialkyl azodicarboxylate **92**),¹⁰⁹ and decarboxylative additions (*e.g.* of malonic acid half thioester **94** to imine **95**).¹¹⁰



Scheme 1.13 Examples of organocatalysed reactions with cupreine/cupreidine/ β -ICD

1.4.3 Cupreine/cupreidine derivatives functionalised at the C-9 position

Wynberg's conformational studies (Section 1.3.3.1) demonstrated that dihydroquinine derivatives, bearing different functional groups at the C-9 position, would not all adopt the

same conformations in the same medium.^{82,84} In other words, the relative position/orientation of the two catalytically active functionalities of these alkaloids varied when changing the C-9 substituent's steric and electronic properties.

Placing the hydrogen-bond donor at the C-6' position on the cupreine/cupreidine framework conveniently renders the C-9 hydroxyl group available for modifications (with a view towards conformational control). Deng *et al.* designed a library of cupreine/cupreidine derivatives, keeping the two groups responsible for the catalytic activity at the same positions, but modifying the bulk around the C-9 position using different alkylating and esterifying agents (Figure 1.22). Thus, he obtained a series of molecules possessing various 'chiral pocket' sizes, potentially fine-tuned to the stereoelectronic demands of specific reactions' transition states. This was done in a combinational rather than in a 'rational design' context; *i.e.*, a suite of catalysts of variable bulk at C-9 were prepared and then these were tested in a range of reactions.

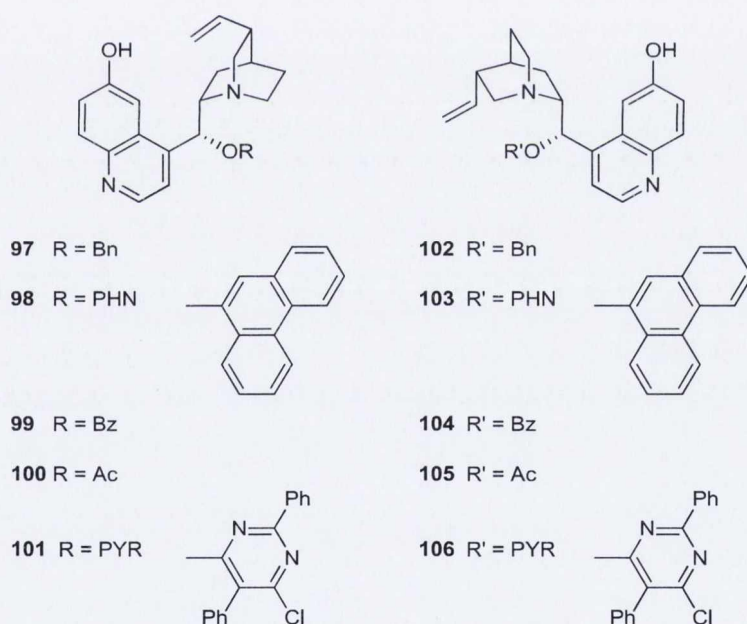
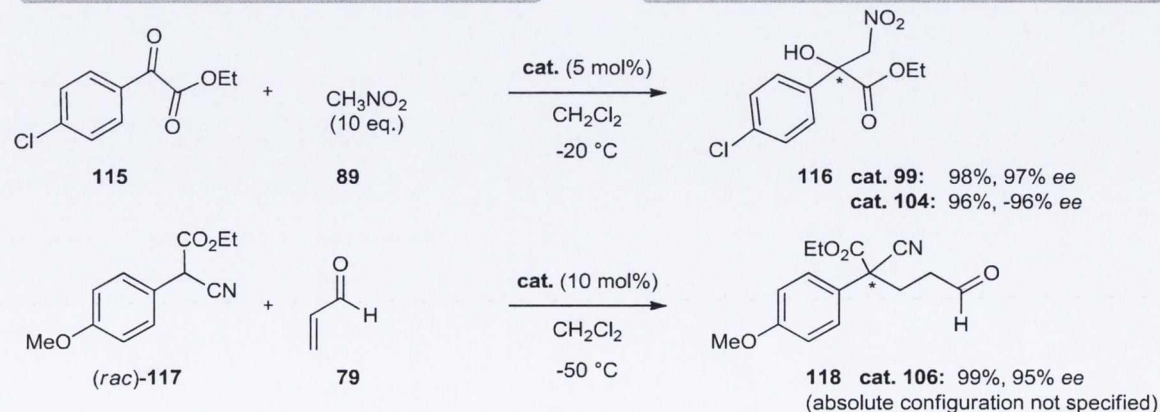
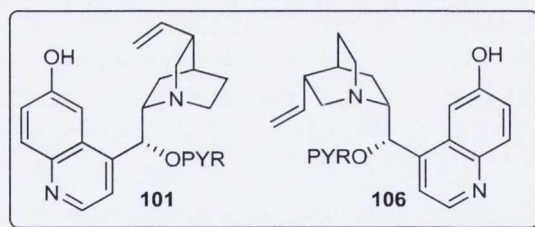
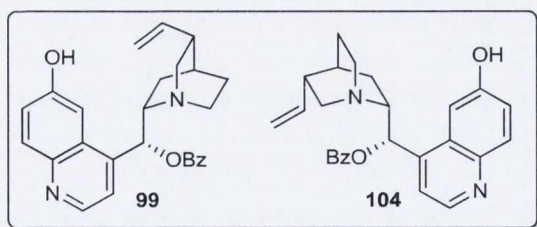
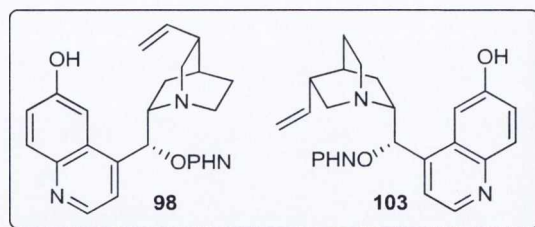


Figure 1.22 Cupreine/Cupreidine analogues designed by Deng

After an extensive screening of potentially interesting transformations to catalyse, each of these derivatives was proved efficient for the promotion of a (or several) particular reaction(s). In 2004, Deng *et al.* published the first paper¹¹¹ of a large series in which ether and ester derivatives of cupreine and cupreidine (**97-106**, Figure 1.22) were proven to efficiently catalyse a wide scope of reactions.¹¹²⁻¹¹⁹

Using cupreine-type analogues of considerable bulk at the C-9 position often led Deng and coworkers to a more efficient catalytic methodology. However, in the promotion of the asymmetric addition of malonate **86** to (*E*)- β -nitroolefin **85** (Scheme 1.13), cupreidine (possessing only a relatively small hydroxyl group at C-9) performed better as a catalyst than its more hindered derivatives **102** and **103**.¹⁰⁷ Therefore, the influence of the C-9 substituent on Deng's reactions' stereochemical outcomes is not easily predictable (*a priori*) and no systematic structural and mechanistic investigations has been undertaken to provide further explanations.

The variety of these alkaloids' 'chiral pocket' properties provided Deng's research group with a powerful and versatile library of catalysts capable of the promotion of an impressive range of reactions with high yields and enantioselectivities (products **108**, **109**, **112**, **114**, **116** and **118**, Scheme 1.14). Thus, electrophilic aminations¹¹¹ could be catalysed (*e.g.* using substrates **92** and **107**, Scheme 1.14) with high conversion rate and enantiocontrol (up to 99% *ee*). β -Ketoesters **68** and **113**^{112,114} and α -cyanoesters **110** and **117**^{113,116} served as substrates in Michael-type conjugate additions to nitroalkenes (*e.g.* **47**), vinyl sulfones (*e.g.* **111**), vinyl ketones (*e.g.* **77**)¹¹⁴ and acrolein (**79**).¹¹⁶ In 2006, Deng also described the challenging nitroaldol reaction of nitromethane (**89**) with α -ketoester **115**.¹¹⁵ With only 5 mol% of benzoyl-derivative **99** (or **104**), the latter reaction could be efficaciously promoted using a broad range of α -ketoesters, with various substituents, obtaining very good yields (up to 99%) and enantiomeric excess (up to 97%). Interestingly, cupreidine catalysed the generation of **116** (illustrated in Scheme 1.14) with only 86% *ee*, whereas alkaloid **104**, possessing identical catalytic groups at the same positions (the basic quinuclidine ring, and the C-6' hydroxyl group) and bearing a bulkier benzoyl group at the C-9 position, outperformed the parent alkaloid and mediated the formation of the same product with 96% *ee*.



35

1.5 Incorporation of a (thio)urea unit into the cinchona alkaloid skeleton

1.5.1 C-9 (Thio)urea substituted cinchona alkaloid derivatives

In 2005, the excellent results obtained using Takemoto's catalysts in the promotion of Michael additions prompted chemists to merge the best features of cinchona alkaloids with the rigid, tunable and robust (thio)urea hydrogen bond-donating moiety.³⁹

1.5.1.1 Design rationale

Novel cinchona alkaloid-derived frameworks were designed, where the hydroxyl group of the cinchona alkaloid backbone was replaced with more Lewis-acidic coplanar bifurcated hydrogen-bond donor (thio)ureas (Figure 1.23).

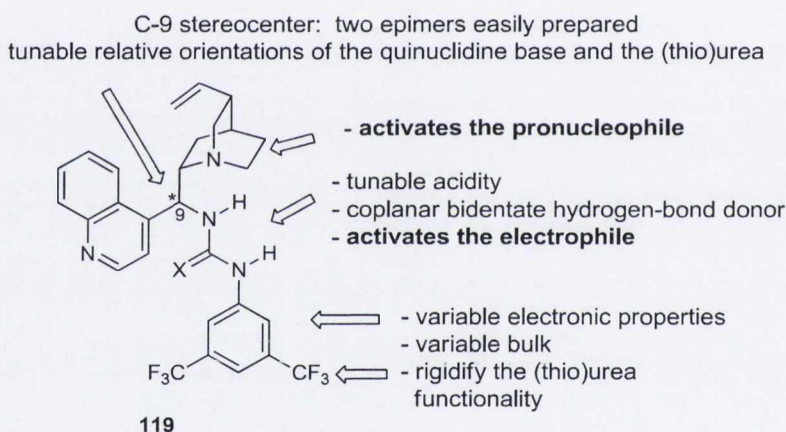


Figure 1.23 Catalyst design rationale: (thio)urea substituted cinchona alkaloids

Using this catalophore offered the practitioner additional possibilities in terms of fine-tuning its acidity (*i.e.* its binding abilities) by altering either the (thio)urea's heteroatom (*i.e.* using either urea or thiourea) or the electronic properties of the functional groups substituting its *N*-aryl ring.^{120,121} The (thio)urea's steric properties could also be advantageously modified through altering the same groups, allowing one to tune the steric bulk (and hopefully the conformations) of the resulting catalyst.¹²²

1.5.1.2 Discovery and use in organocatalysis

Initially, four research groups independently explored these (thio)urea-based cinchona alkaloids' catalytic abilities.^{67,120,121,123} They designed C-9-urea and thiourea cinchona alkaloid analogues bearing *bis*-trifluoromethyl groups at the two *meta*- positions of the *N*-aryl component, as this emerged as the most favorable substitution pattern in Schreiner's studies (Section 1.2.2)^{48,49} in terms of the solubility, acidity and rigidity of the resulting catalyst.

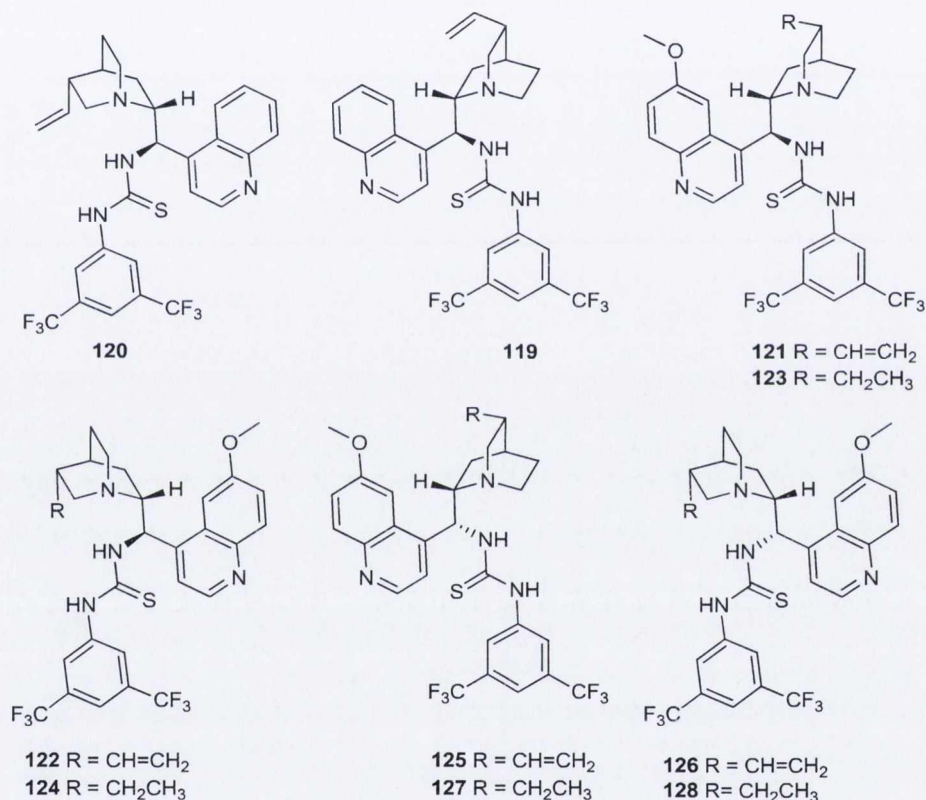
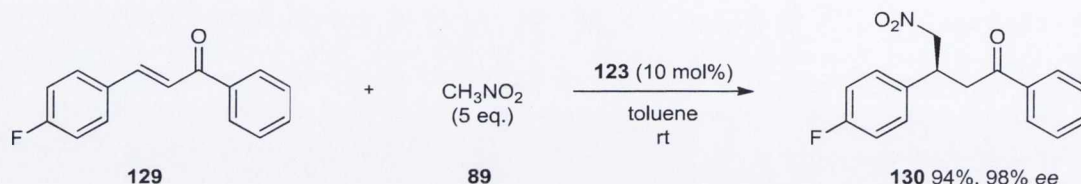


Figure 1.24 C-9 functionalised (thio)urea-based cinchona alkaloid derivatives

By inverting the absolute configuration of the C-9 hydroxy group associated with the *pseudoenantiomers* quinine (**50**) and quinidine (**51**), four different diastereomerically related catalysts (*e.g.* **121**, **122**, **125** and **126**, Figure 1.24) were accessible. This allowed the influence of the relative stereochemistry at C-8 and C-9 on catalysis to be unambiguously determined (from both activity and enantioselectivity standpoints).

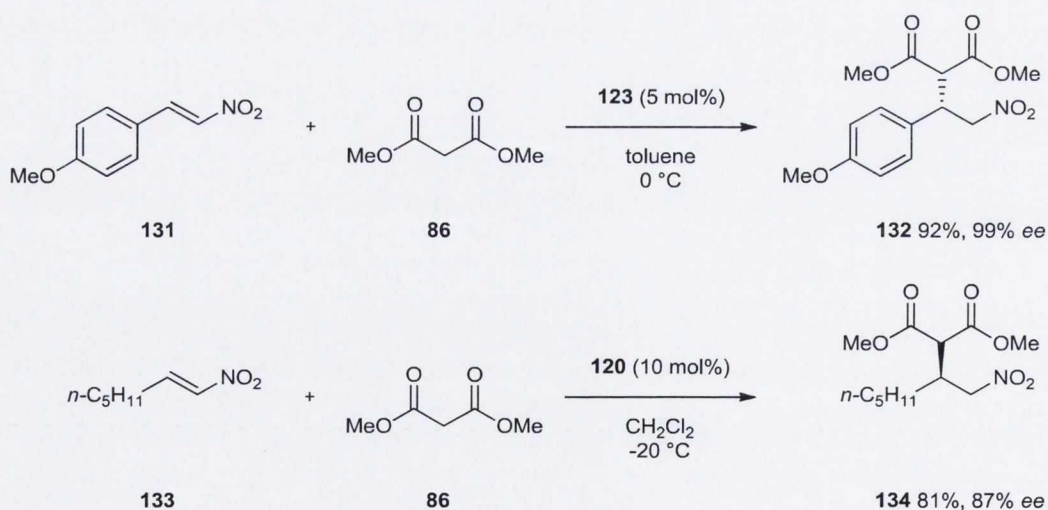
Chen was the first to report such catalysts.⁶⁷ He demonstrated that the cinchonidine- and cinchonine-based thioureas **119** and **120** were capable of promoting the Michael addition

of thiophenol to an α,β -unsaturated imide; unfortunately providing almost no stereocontrol. Shortly afterwards, Soós *et al.*¹²³ synthesised the thiourea-modified quinine-, quinidine- and dihydroquinine-analogues **121**, **122** and **123** (respectively) for the highly selective conjugate addition of nitromethane (**89**) to chalcones (89-98% *ee*, *e.g.* Henry-adduct **130**, Scheme 1.15).



Scheme 1.15 The highly enantioselective organocatalytic addition of nitromethane to chalcone

Connon¹²¹ and Dixon¹²⁰ both reported in complementary studies the catalytic capabilities of (respectively) the dihydroquinine-based thiourea **123** (of which only 0.5 mol% loading was needed) and the thiourea-modified cinchonine **120** to promote asymmetric Michael-type additions of malonate **86** to a wide range of nitroalkenes (such as **131**) with excellent product yields and enantiomeric excess (Scheme 1.16). More challenging aliphatic nitroalkene **133** could also be converted into the Michael adduct **134** with good enantiocontrol.



Scheme 1.16 Asymmetric conjugate addition of malonate **86** to nitroalkenes catalysed by C-9 thiourea-based **123** and **120**

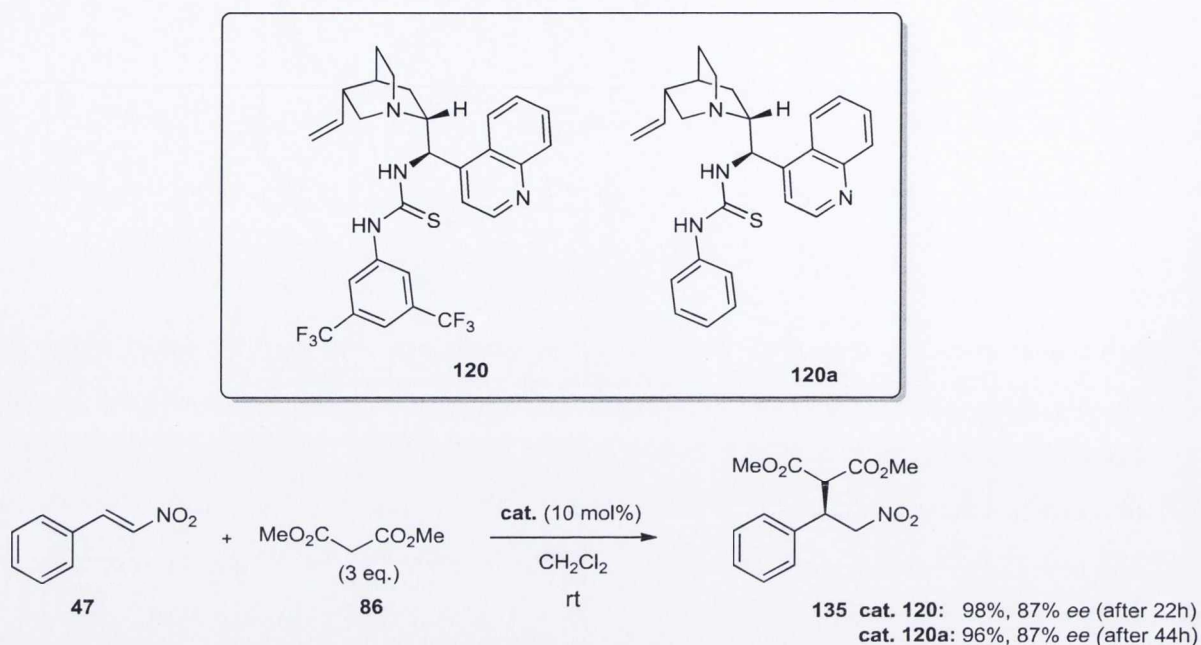
Later, Dixon *et al.* also used **120** for the highly enantioselective addition of malonate **86** to imines in a Mannich reaction process (described in further details in Section 1.5.1.2.3).

1.5.1.2.1 Design strategy: the use of either urea or (thio)urea moieties and the influence of the relative configuration at C-8 and C-9 on catalysis

In Cannon *et al.*'s study, it was proved that the less acidic urea version of **123** provided slightly less stereocontrolled Michael-type additions. Also, as it was found in Soós' study, Cannon and coworkers demonstrated the superiority of catalysts which possessed the opposite absolute configuration at C-9 to that associated with quinine and quinidine (*i.e.* **123** and **124**) over their C-9 epimers (*i.e.* **127** and **128**). As a result, in agreement with Takemoto's theory (Section 1.2), a transition state pre-assembly was proposed where the basic quinuclidine would deprotonate malonate **86** while, synergistically, the thiourea moiety was assumed to enhance the electrophilicity of the nitroalkene through a bifurcated hydrogen-bond interaction involving both oxygen atoms, holding the two substrates in a close and chiral environment.

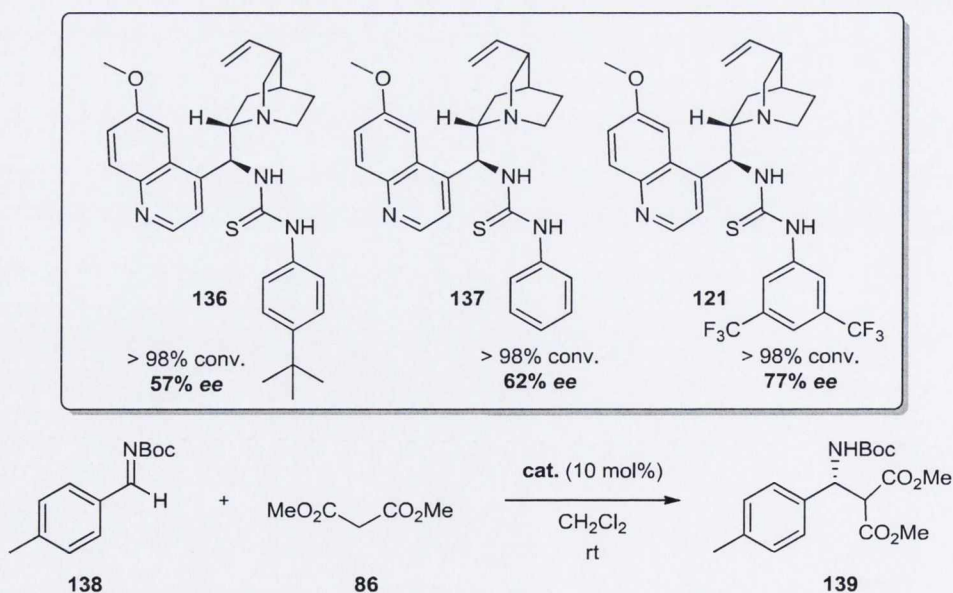
1.5.1.2.2 Design strategy: the influence of the *N*-aryl substituents on catalysis

In accordance with Schreiner's findings, Dixon and coworkers demonstrated the importance of the *bis*-trifluoromethyl *motif* in the design of the thiourea moiety. In the preliminary investigations of the Michael-type addition, they found that the addition of malonate **86** to (*E*)- β -nitrostyrene (**47**) would be complete after 22 hours when using catalyst **120** (87% *ee*), whereas the reaction could only reach completion after 44 hours when using a catalyst possessing an unfunctionalised *N*-aryl group (**120a**, Scheme 1.17). However, no effect was observed in this study on the enantioselectivity of the catalytic process.



Scheme 1.17 Influence of the thiourea's *N*-aryl core substituents on catalysis

Later, Deng *et al.*¹²² also examined the role of the *N*-aryl (thiourea) unit. In a systematic study, it was found that the 3,5-(bis-trifluoromethyl)phenyl unit was key to the promotion of highly enantioselective Mannich chemistry between imine **138** and malonate **86** in the presence of catalysts **121**, **136** and **137** (Scheme 1.18). Catalyst **121** promoted considerably more enantioselective 1,2-addition reactions than the more electron rich *para*- (*i.e.* **136**) or un-substituted (*i.e.* **137**) *N*-aryl thiourea analogues.

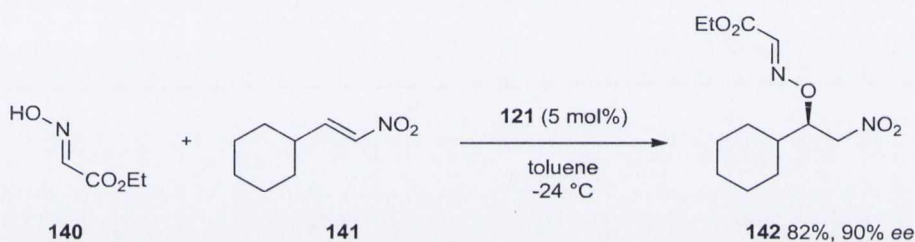


Scheme 1.18 Effect of the catalyst's *N*-aryl functionalities on the enantioselectivity of the organocatalysed Mannich reaction

1.5.1.3 Examples of highly selective transformations catalysed by thiourea-modified cinchona alkaloids

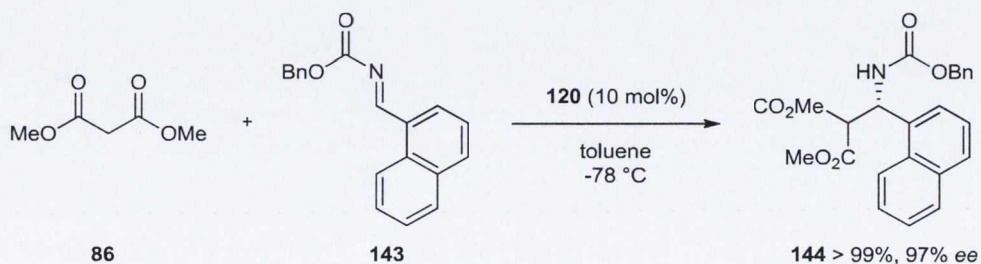
This new (thio)urea-based cinchona alkaloid library of catalysts were capable of the efficient promotion of an impressive amount of transformations, regarding both activity and enantioselectivity.¹²⁴⁻¹³³

Using alkaloids from the library illustrated in Figure 1.24, Jørgensen *et al.* reported the first enantioselective organocatalytic Michael-type addition of an alcohol (oxime **140**) to aliphatic nitroalkene **141** with good activity and enantioselectivity (90% *ee*, Scheme 1.19).¹³⁴



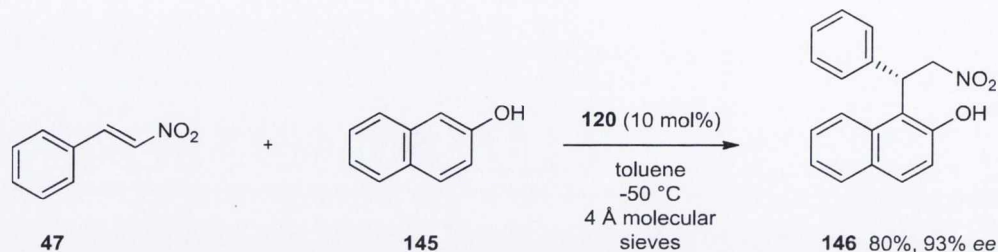
Scheme 1.19 First organocatalysed β -hydroxylation of nitroalkenes using **121**

Dixon *et al.* disclosed that asymmetric Mannich reactions could be efficiently catalysed by cinchonine-derived thiourea **120**.¹³⁵ For instance, the Cbz-protected imine **143** underwent smooth conversion to the corresponding protected amine **144** in excellent yield and *ee* in the presence of 1 equivalent of **86** and **120** at 10 mol% loading (Scheme 1.20). In the same study, it was also shown that other C-acidic pronucleophiles including β -diketones, β -ketoesters and β -diesters were also compatible with the methodology.



Scheme 1.20 Enantioselective Mannich reaction using **120** as efficient catalyst

Thiourea-modified cinchonine **120** also proved an active catalyst in the promotion of Friedel-Crafts reactions involving 2-naphthol (**145**) and nitroalkenes (e.g. **47**, Scheme 1.21).¹³⁶



Scheme 1.21 An asymmetric Friedel-Crafts reaction promoted by **120**

1.5.2 The C-6' substituted thiourea-based cinchona alkaloid

In 2006, inspired by the success of the use of C-9-thiourea cinchona alkaloid derivatives in several catalytic processes, Hiemstra decided to combine the efficiency as catalysts of the C-6'-demethylated cinchona alkaloids (cupreine/cupreidine, Section 1.4) with the (thio)urea's high activity as Lewis-acidic promoters.¹³⁷

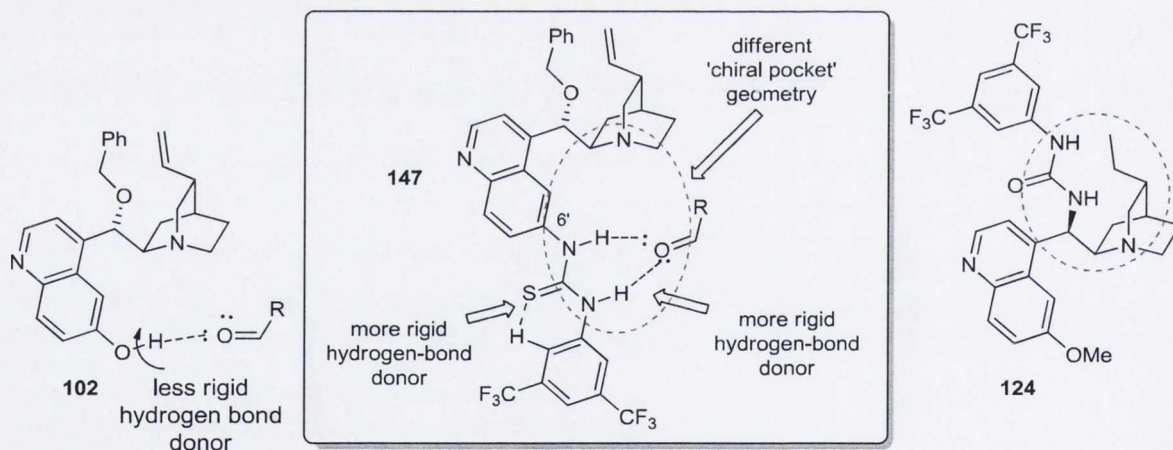


Figure 1.25 Rationale behind Hiemstra's design

Replacing the C-6' hydroxyl group of the quinoline ring by the (thio)urea catalophore (**147**, Figure 1.25) led to a catalyst incorporating a more rigid hydrogen-bond donor than in the case of cupreidine-derived **102**. Also, since the catalytically active functional groups of the molecule would be positioned differently on the catalyst's backbone than in the

powerful C-9 thiourea-based *epi*-dihydroquinidine **124**, alkaloid **147** would offer to the practitioner complementary alternatives, potentially leading to a wider range of possible organocatalysed reactions and/or more efficient asymmetric induction during the catalytic process.

Thus, Hiemstra *et al.* exploited the different properties (steric and electronic) of **147** to achieve, for the first time in the literature, the promotion of the highly enantioselective organocatalysed Henry reaction using various aromatic aldehydes as substrates (described later in Section 1.7).¹³⁷ In the only other report concerning the organocatalytic asymmetric Henry reaction, the same group had previously reported the obtention of almost racemic mixtures from the addition of nitromethane to the same aromatic-substituted aldehydes using catalyst **102**.¹³⁸

In 2008, triggered by the encouraging results provided by Hiemstra's catalyst, Deng designed an entire novel library of cinchona alkaloid analogues (Figure 1.26).¹³⁹ Applying his concept of modifying the C-9 ether/ester substituent in order to vary the bulk around the key bonds C4'-C9 and C9-C8, he modified the backbone of compound **147** to afford **148-152** (Figure 1.26), which exhibited versatile 'chiral pocket' sizes. This idea proved to be very fruitful in the case of the cupreine/cupreidine catalysts in a large scope of reactions (Section 1.4.3).

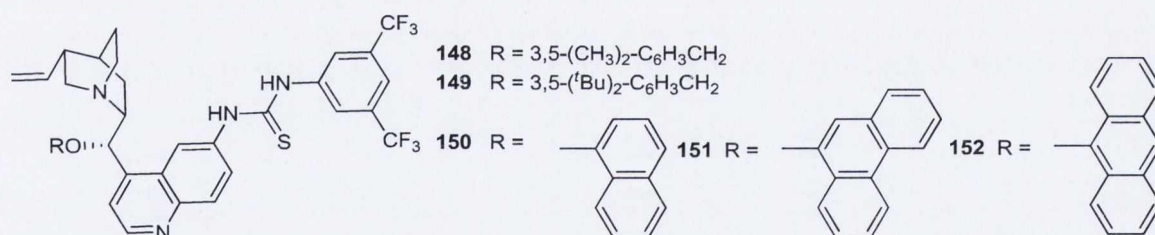


Figure 1.26 Deng's library of C-6'-thiourea-C-9-functionalised cinchona alkaloid derivatives

Using catalyst **152**, he could promote, for the first time in the literature, very efficient Michael-type organocatalysed additions of alkyl thiols to α,β -unsaturated *N*-acylated oxazolin-2-ones with excellent enantioselectivities (this reaction will be discussed further in Section 1.8). In the same reaction, the use of either C-9 hindered cupreidine derivatives **103-106** or the C-6'-thiourea-based **147** (less hindered at the C-9 position) led to only

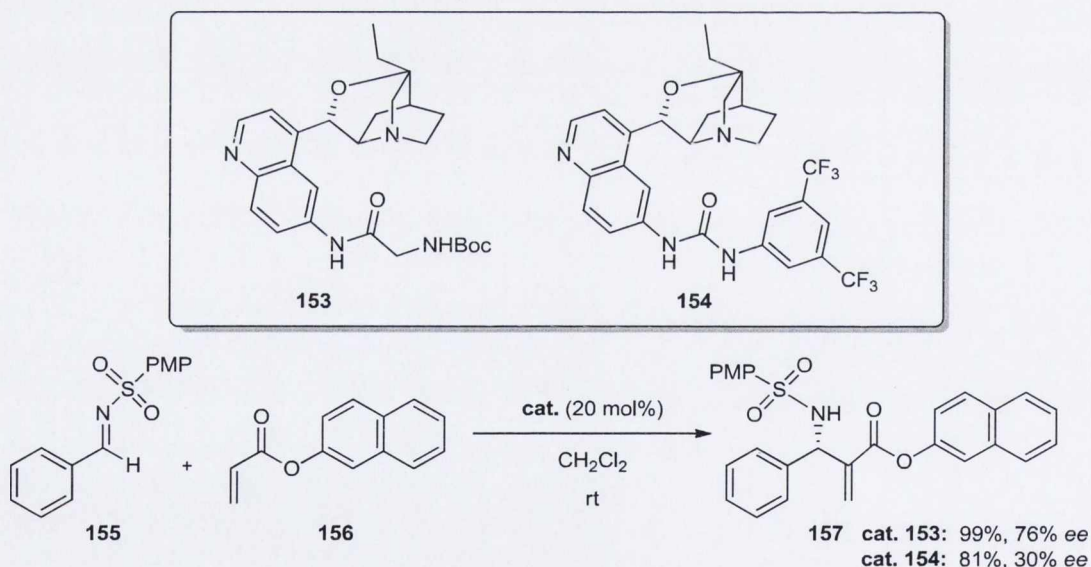
moderate enantiomeric excess. This proved again the benefit of using the more rigid and acidic thiourea catalophore in some catalyst design and the effectiveness of varying the bulk around the C-9 position in an attempt to increase the degree of tunability of a catalyst.

1.6 Other possibilities investigated to design cinchona alkaloids derivatives

1.6.1 Other *motifs* used as hydrogen-bond donors

Several alternatives to the (thio)urea moiety as a template for catalyst design appeared in the literature in the last few years, providing in some cases better results in terms of activity and/or enantioselectivity.

In line with Hiemstra's idea to use cupreine derivatives functionalised at the C-6' position with more acidic and tunable groups, Zhu *et al.* designed a series of C-6' functionalised β -ICD analogues.¹⁴⁰ Aiming at maintaining a certain degree of tunability of their catalysts, they introduced amide functionalities with different electronic and steric profiles onto the β -ICD scaffold.



Scheme 1.22 C-6'-substituted β -ICD-derived alkaloids used as catalysts for the asymmetric aza-Morita-Baylis-Hillman reaction

For example, during the asymmetric generation of **157** via an aza-Morita-Baylis-Hillman reaction (Scheme 1.22), the most efficient amide derivative of the library (*i.e.* **153**) was

significantly more active and led to a far more enantioselective outcome than the C-6'-thiourea-based β -ICD derivative **154**, even though **153**'s *modus operandi* involved a less rigid *monodentate* hydrogen-bond interaction (it was proven that the $\text{-NH}^t\text{Boc}$ functionality was not participating in the catalytic process).

Rawal introduced the even more rigid squaramide hydrogen-bond donor onto the cinchona alkaloid scaffold (Figure 1.27). The resulting cinchonine analogue **158** possessed excellent activity and selectivity profiles as a catalyst for the Michael addition of 2,4-pentanedione to a range of aromatic nitroalkenes with excellent yield and enantiocontrol (10 products prepared with enantioselectivities between 97% *ee* and >99% *ee*).¹⁴¹

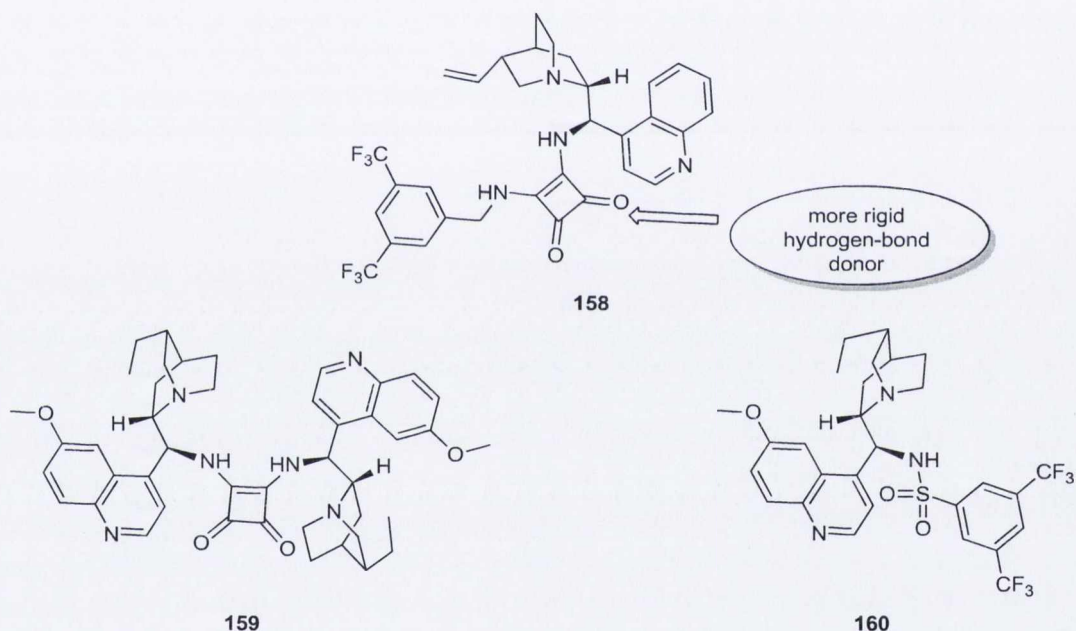


Figure 1.27 Other alternative cinchona alkaloid derivatives bearing different hydrogen-bond donors at the C-9 position

Investigating the dynamic kinetic resolution of racemic azlactones *via* alcoholysis (this reaction will be discussed in more details in Section 1.9), Song *et al.* designed a C2-symmetric version of squaramide-based cinchona alkaloid (*i.e.* **159** Figure 1.27) that proved superior to either the monomeric form **158** or the thiourea-substituted dihydroquinine analogue **123**. These results were reasoned to be due to the tendency of the latter to self-associate intermolecularly.¹⁴² One of the advantages behind the use of **159** was that this catalyst could be readily recovered, and therefore recycled, *via* a selective

precipitation in hexane, without any negative impact on reaction rates or enantioselectivities.

Shortly afterwards, Song and coworkers synthesised the monodentate 9-sulfonamide-*epi*-dihydroquinine derivative **160** (Figure 1.27), which was capable of highly efficient and selective catalysis of methanolic desymmetrisations of cyclic anhydrides, outperforming the benchmark thiourea-based catalyst **121** in the same reaction.¹⁴³

1.6.2 Early investigations of the C-5' position on the cinchona alkaloid scaffold

Since altering the C-9 and the C-6' positions of the parent natural cinchona alkaloid scaffold led to very efficient alternative catalysts for the promotion of some asymmetric transformations,¹²⁰⁻¹⁴³ it seemed opportune to consider the modification of other positions on the scaffold to push even further the catalytic limits of the so called 'privileged',⁹² cinchona alkaloids.

Before the discoveries described in this thesis, only two reports mentioned the installation of catalytically useful functionalities at the C-5' position of the cinchona alkaloid framework. Jørgensen^{144,145} and Deng¹⁴⁶ have independently developed hydrazide-substituted catalysts **161-163** and **164-165** (respectively) which exploited the reaction between cupreines/cupreidines and diazodicarboxylate esters at C-5' (Figure 1.28).

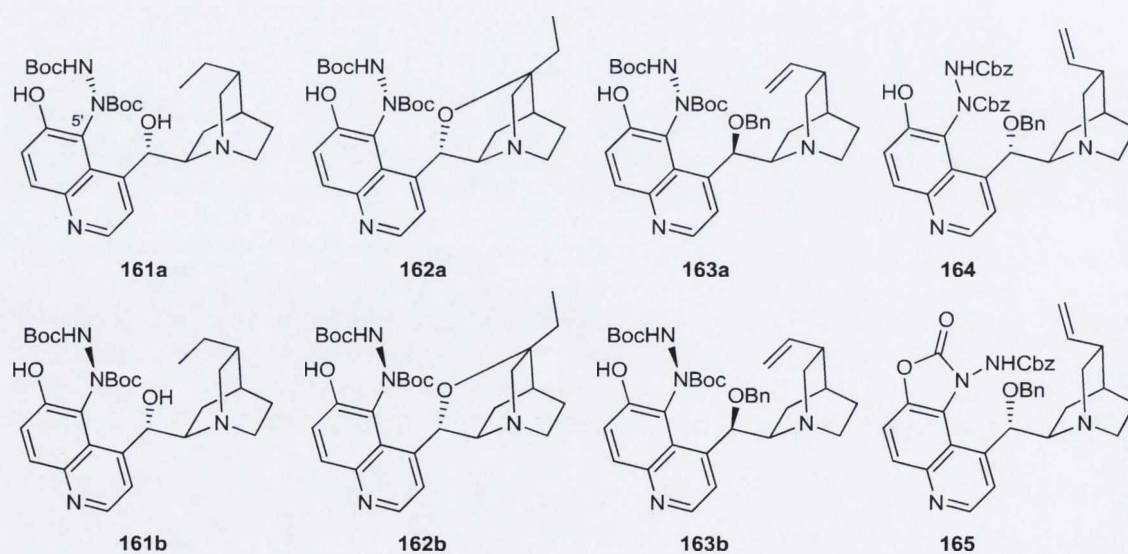
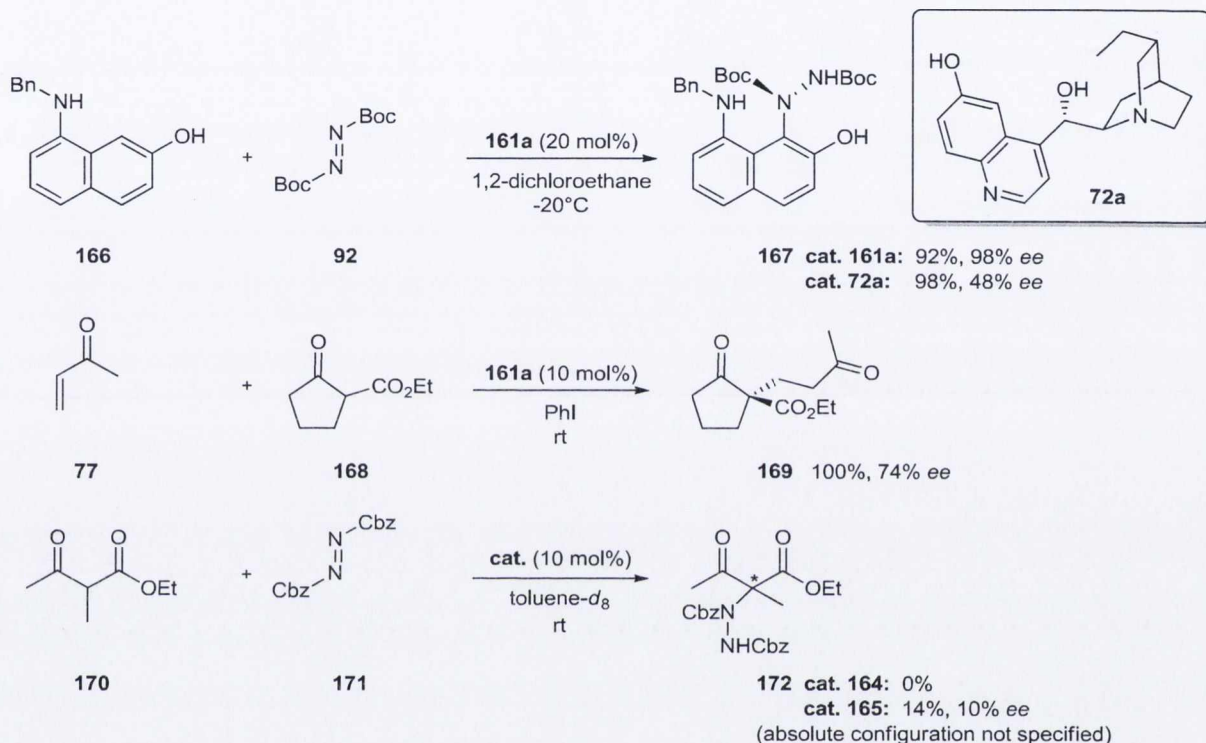


Figure 1.28 The first reported C-5' substituted cinchona alkaloid catalysts

Jørgensen demonstrated that **161a** (most efficient catalyst of his library) could promote the amination of 2-naphthol derivative **166** (using **92**, Scheme 1.23) and the Michael addition of β -ketoester **168** to methylvinylketone (**77**) with good to excellent enantiocontrol. However, Deng found that **164** failed to promote the α -amination of β -ketoester malonate **170** (using **171**), while the use of **165** in the same reaction resulted in poor yield and low levels of product enantiomeric excess.



Scheme 1.23 First reported reactions catalysed by the C-5' substituted cinchona alkaloids

Even though the introduction of the hydrazide group at C-5' on alkaloid **161a** provided Jørgensen and coworkers with a significantly more selective catalyst than dihydrocupreidine (**72a**, Scheme 1.23), they theorised that this functionality would not be directly involved in the catalytic process of the amination of **166** (*via* hydrogen-bond donation for instance). It would only have an influence on the selective guiding of the azodicarboxylate approach towards one face of the naphthol-derived zwitterionic species (due to steric clashes induced by the hydrazide functionality, Figure 1.29).

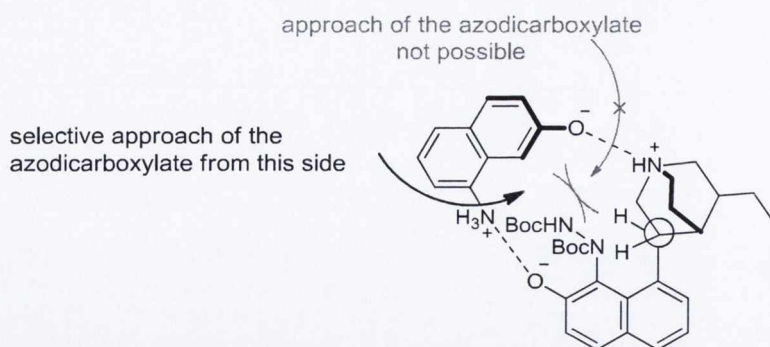


Figure 1.29 Ion pair formed during the interaction of substrate **165** with catalyst **161a** and the resulting face-selective approach of the azodicarboxylate

No further development of these types of catalysts has been reported since.

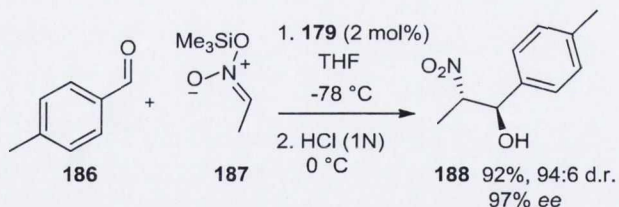
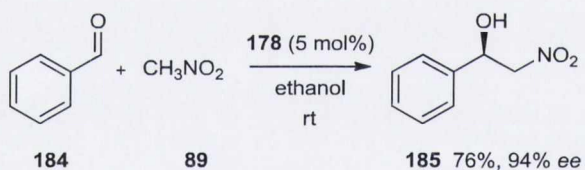
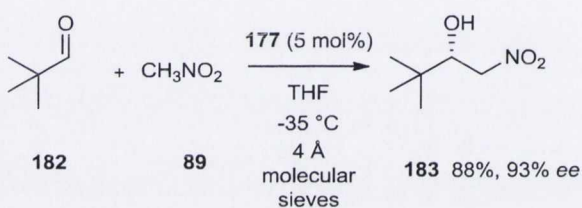
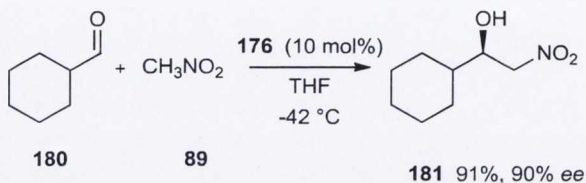
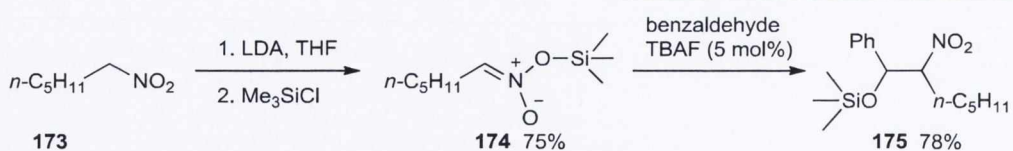
1.7 Organocatalysis of the enantioselective Henry reaction

1.7.1 Historical perspectives and synthetic importance

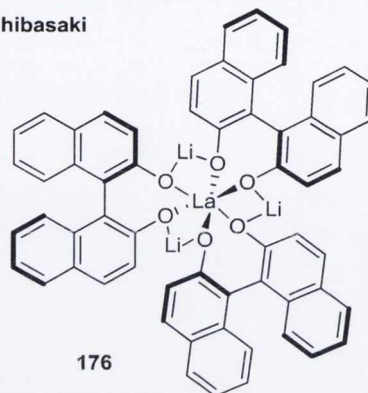
The nitroaldol reaction,^{147,148} also called the Henry reaction, was described for the first time by Henry *et al.* in 1895.¹⁴⁹ This transformation, involving a carbonyl group (aldehyde or ketone) and a nitroalkane, represents a powerful strategy in organic chemistry: a novel C-C bond and a quaternary stereocenter (if the substrate is a ketone) are created along with the generation of an enantioenriched β -nitroalcohol adduct. These products constitute a synthetically useful class of compounds that can be easily derivatised (through oxidations, reductions, eliminations) and provides easy access to β -aminoalcohols.¹⁵⁰

After the first example in 1895, no other effective reaction of this kind was reported until the 1970's. Since then, several different metal(ion)-based complexes have been demonstrated as efficient catalysts for this transformation. First, Seebach and Colvin reported the racemic aldol addition of silyl nitronates (*e.g.* **174**, synthesised from nitroalkane **173**) on aryl- and alkyl-substituted aldehydes catalysed by *tetra-n*-butylammonium fluoride (TBAF),¹⁵¹ obtaining adducts such as **175** with excellent yields (up to 91% yield, Scheme 1.24). Later, several catalysts (metal/chiral ligand complexes) were proposed in the literature to promote the enantioselective catalytic nitroaldol addition of nitromethane on various aldehydes. Thus, a lithium/lanthanum bimetallic catalyst **176** (Scheme 1.24, Shibasaki¹⁵²) and a dinuclear zinc-based catalyst with a chiral diarylcarbinol

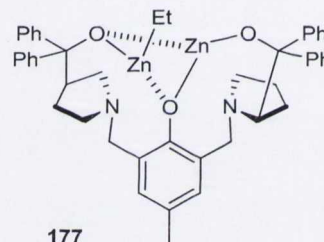
ligand **177** (Trost^{153,154}) were shown to possess excellent activity and selectivity profiles as promoters for the asymmetric addition of nitromethane (**89**) to aldehydes (*e.g.* carboxaldehyde **180** and *tert*-butyl substituted aldehyde **182**, see products **181** and **183**). A copper complex with (bis)oxazoline ligands **178** (Evans¹⁵⁵) was also successfully investigated. High yields and *ee* (73-94% *ee*) were obtained (*e.g.* **185**) on a large range of aldehydes, aryl- and alkyl-substituted, using 5-10 mol% of catalyst loading and 10 equivalents of nitromethane (**89**). Finally, Maruoka demonstrated the efficient use of a chiral quaternary ammonium bifluoride salt **179** to mediate the asymmetric version of the addition of trimethyl silyl nitronates (*e.g.* **187**) on (strictly aromatic) aldehydes (*e.g.* **186**).¹⁵⁶ The use of only 2 mol% of this catalyst led to high conversion and *ee* (*e.g.* **188**).



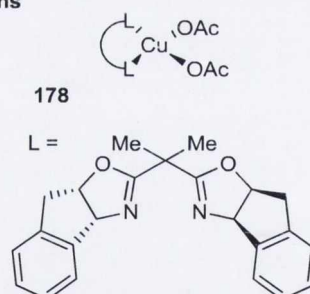
Shibasaki



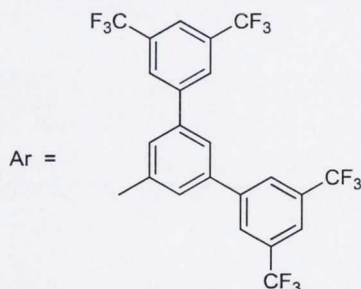
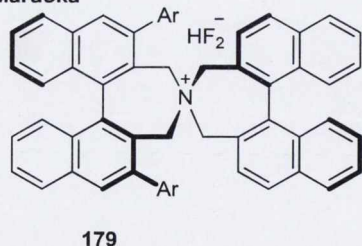
Trost



Evans

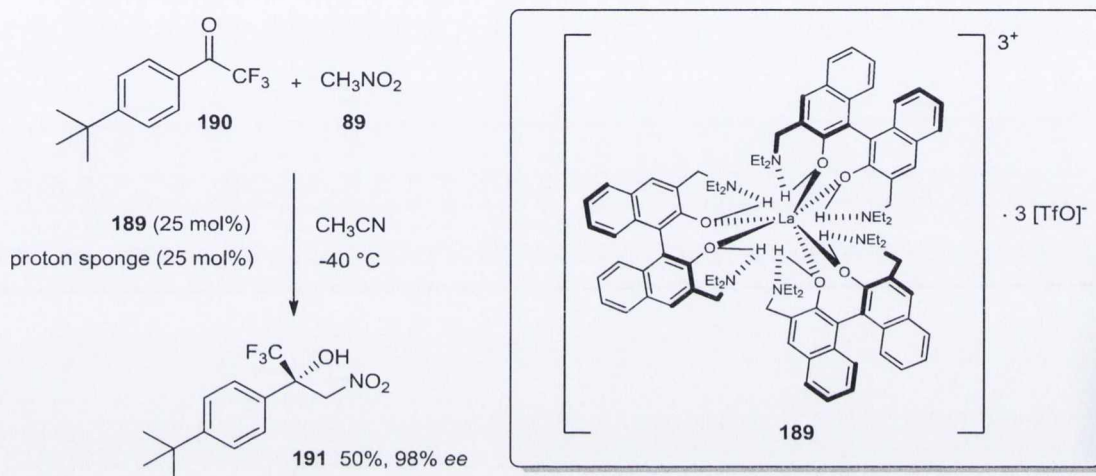


Maruoka



Scheme 1.24 Efficient Henry reactions catalysed by metal(ion)-based catalysts

Due to the significantly lower reactivity of simple ketones, no examples of enantioselective Henry reaction using them as substrates had been reported in the literature prior to 2008. However, several groups proposed to perform asymmetric versions of this reaction using activated ketones, such as α -ketoesters.^{157,158} The nitroaldol reaction involving α -trifluoromethyl substituted ketones as substrates were of particular interest, since the resulting trifluoromethylated tetrasubstituted chiral products are of pharmaceutical/agrochemical relevance.^{159,160}



Scheme 1.25 Enantioselective Henry reaction of trifluoromethylketones catalysed by a chiral La-complex

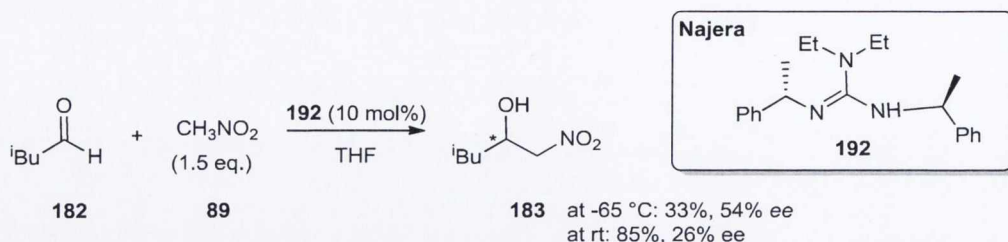
At the outset of the study described in this thesis, only one highly enantioselective catalytic methodology (*i.e.* $ee > 90\%$) for the Henry reaction of such substrates was reported (by Saá *et al.*) utilising 25 mol% of a chiral La-complex **189** (*e.g.* synthesis of adduct **191**, Scheme 1.25).¹⁶¹ Only aromatic ketones (*e.g.* **190**) were involved in this study.

1.7.2 Organocatalysed Henry reactions: scope and limitations

1.7.2.1 Aldehyde substrates

Novel metal-free systems appeared as promising new alternatives for the promotion of the Henry reaction, the most investigated being guanidine and cinchona alkaloid derivatives. In 1994, Najera *et al.*¹⁶² reported an example of the addition of nitromethane (**89**) to both benzaldehyde (31%, 13% *ee*) and isopentanal (**182**, 33%, 54% *ee*, Scheme 1.26) catalysed

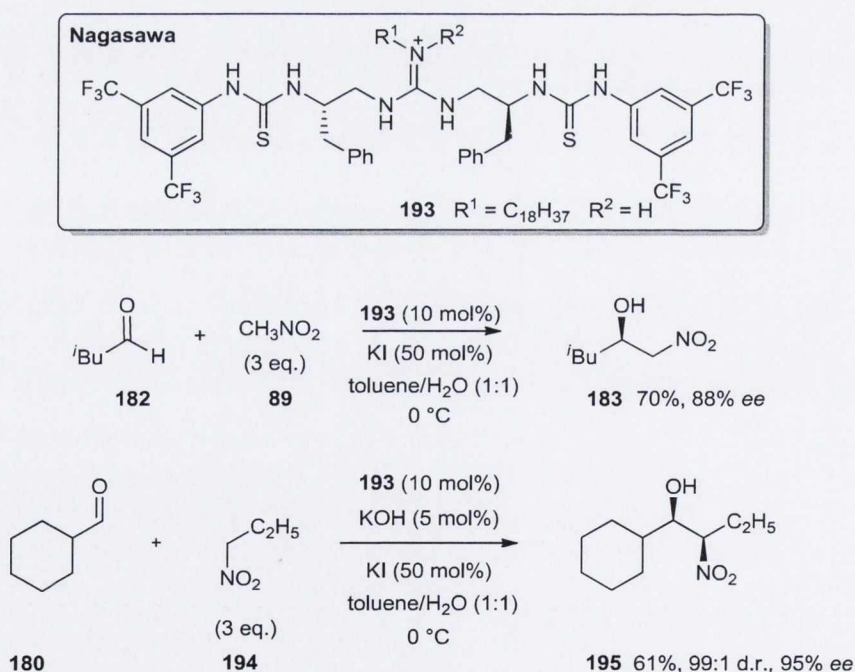
by the guanidine analogue **192**. Only 1.5 equivalents of nitromethane were required in this reaction.



Scheme 1.26 Guanidine derivative used as organocatalyst for the Henry reaction

Five different guanidine derivatives were screened as catalysts in the reaction. The best catalyst **192** could provide high conversion at room temperature (up to 85%), but low enantiocontrol (product **183**, 26% ee). Lowering the temperature afforded moderate enantioselectivity, however, at the expense of the reaction rate.

Since this initial report, research groups have further developed this class of catalysts, resulting in significant improvements in enantiocontrol. Nagasawa published several studies on the development of guanidine-thiourea bifunctional catalysts (Scheme 1.27).

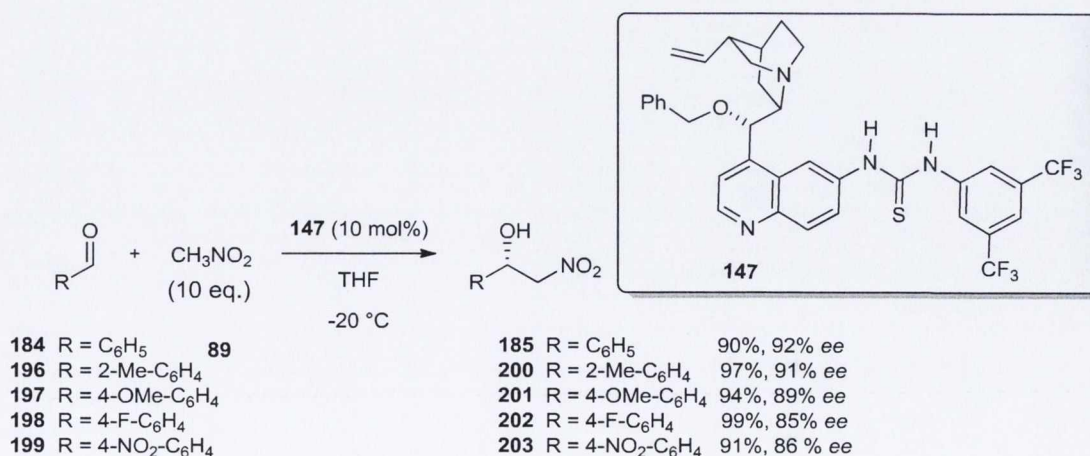


Scheme 1.27 A guanidine-thiourea derivative as an efficient bifunctional catalyst for the promotion of Henry reactions using nitromethane and other nitroalkanes

In 2005, one of his catalysts (*i.e.* **193**) was demonstrated to serve as a highly efficient promoter of the addition of nitromethane (**89**) to aliphatic aldehydes. In the presence of 50 mol% of potassium iodide at 0 °C, guanidine-derived catalyst **193** gave access to Henry adduct **183** from aldehyde **182** with an enantioselectivity reaching 88% *ee* (compared with 54% *ee* using Najera's catalyst **192**, Scheme 1.26).¹⁶³

One year later, the same catalyst system was applied to the promotion of the highly selective addition of other non-methyl nitroalkanes (*e.g.* **194**, Scheme 1.27) to aliphatic-substituted aldehydes (*e.g.* **180**), leading this time to products with *syn*-diastereoselectivity as high as 99:1, coupled with product enantiomeric excess up to 95% (*e.g.* **195**).¹⁶⁴

Along with the development of guanidine-based catalysts, the design of (thio)urea-based cinchona alkaloids analogues provided chemists with complementary catalytic methods which led to major advances in the development of the asymmetric Henry reaction. As discussed previously, Hiemstra and Deng played an important role in these improvements. The C-9-benzylated cupreidine-modified **102** (Figure 1.22, Section 1.4.3) was firstly investigated by Hiemstra and coworkers to promote the Henry reaction of benzaldehyde and activated aromatic derivatives (such as *p*-nitrobenzaldehyde). The reaction proceeded with very high yields but low enantiocontrol.¹³⁸ In 2006, Hiemstra designed the C-6'-(thio)urea cupreidine-derived alkaloid **147** (Section 1.5.2) and found that it was capable of the catalysis of highly enantioselective addition of nitromethane (**89**) to a broad range of aromatic aldehydes (**184** and **196-199**, Scheme 1.28).



Scheme 1.28 Highly enantioselective nitroaldol reaction catalysed by alkaloid **147**

These alkaloid **147**-catalysed Henry reactions all proceeded with high yields and good stereocontrol (adducts **185** and **200-203**).¹³⁷

In agreement with the bifunctional character of cinchona alkaloid derivatives, Hiemstra proposed a pre-transition state assembly where nitromethane could be deprotonated by the general base quinuclidine while the aldehyde would be simultaneously activated by the hydrogen-bond donor thiourea (assembly **A**, Figure 1.30).

A different coordination pathway (assembly **B**, Figure 1.30) has also been identified as a possibility by Hiemstra and coworkers in DFT calculation-based studies.¹⁶⁵ It involved hydrogen-bond interactions between the quinuclidinium species and the aldehyde and between the nitromethide anion with the thiourea core (analogous to the findings of Papai *et al.*'s⁶⁵ computational study of Michael additions catalysed by bifunctional thioureas, Section 1.2). Both pathways appeared viable, however the former assembly envisioned was calculated to be slightly energetically more favorable.

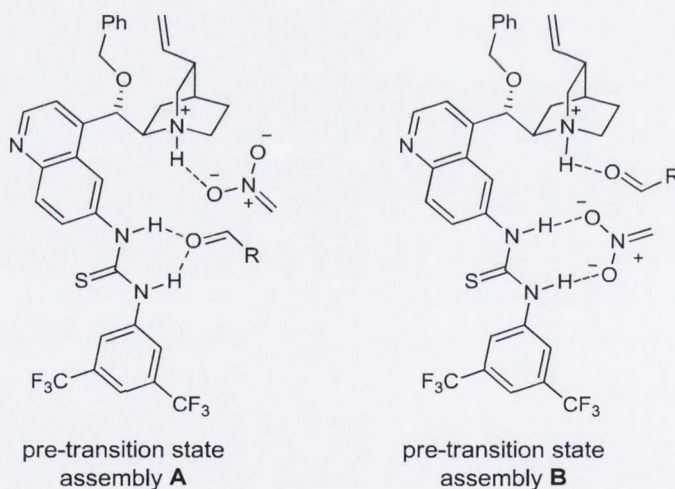
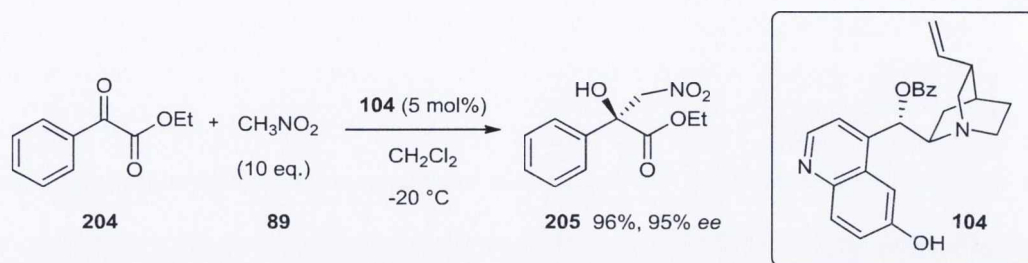


Figure 1.30 Pre-transition state assembly proposed by Hiemstra for the organocatalysed Henry reaction using **147**

1.7.2.2 Ketone substrates

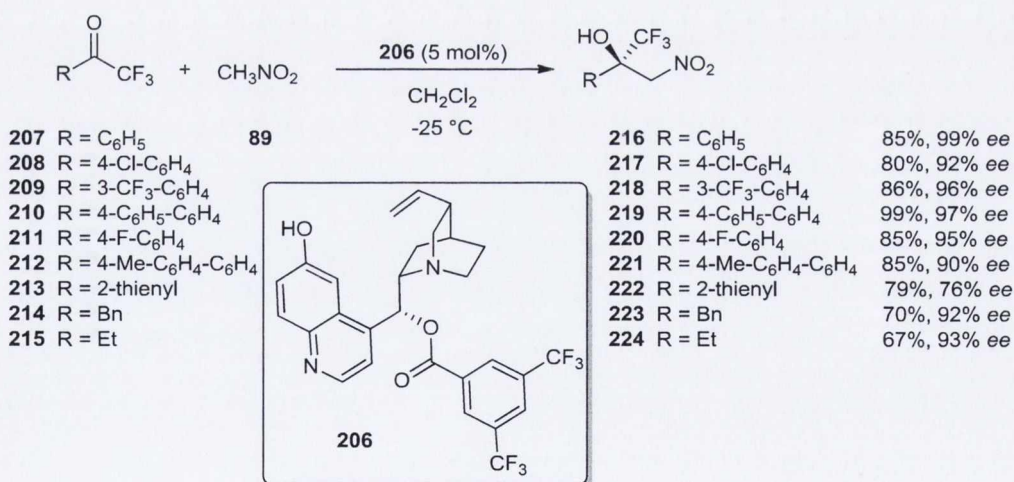
Meanwhile, Deng demonstrated that it was possible to promote the challenging asymmetric addition of nitromethane to β -ketoesters (aromatic- and alkyl-substituted) using cupreine- and cupreidine-derived ether and ester analogues (**97-99** and **102-104**, Figure 1.22, Section

1.4.3).¹¹⁵ Thus, with 10 mol% of alkaloid **104** and 10 equivalents of nitromethane (**89**), nitroalcohol **205** (Scheme 1.29) was produced with 96% yield and 95% *ee* at -20 °C utilising β -ketoester **204** as substrate.



Scheme 1.29 Highly enantioselective Henry reaction involving an α -ketoester

As the study described in this thesis was being initiated, the first organocatalysed nitroaldol reaction involving challenging trifluoromethylketones as substrates was reported by Bandini *et al.*¹⁶⁶ Using 5 mol% of the C-9-benzoyl substituted cupreine-modified **206** (Scheme 1.30), nitroalcohols incorporating a quaternary stereocenter were obtained from a broad range of aromatic trifluoromethyl ketones (*e.g.* **207-214**) and an aliphatic analogue (*i.e.* **215**) with excellent yield and enantiomeric excess that could reach 99% under optimal conditions (Henry-adducts **216-224**).



Scheme 1.30 The organocatalysed asymmetric Henry reaction involving trifluoromethyl ketones

1.7.3 Scope limitations: conclusions on the organocatalytic Henry reaction

Over the last ten years, the organocatalytic promotion of the Henry reaction has constituted a great endeavor in the field of asymmetric catalysis. Impressive progress has been made in terms of substrate scope and obtainable enantioselectivities, driven by the development of (*inter alia*) tunable cinchona alkaloid derivatives. The recently designed libraries of cupreidine-derived alkaloids (combined findings of independently reported studies by Hiemstra, Deng and Bandini) provided highly efficient promoters for the unprecedented organocatalysed nitroaldol reactions of a significantly broad range of electrophiles: aromatic-substituted aldehydes and activated ketones (*i.e.* α -ketoesters and trifluoromethyl ketones).

However, improvements are still possible. Thus far, only one study on the organocatalysed Henry reaction of trifluoromethylketones has been published. In this report, heterocyclic-substituted trifluoromethylketone **213** led to only moderate enantioselectivity (*i.e.* 76% *ee*). Bandini's cinchona alkaloid derivative could also tolerate the ethyl-substituted trifluoromethylketone **215**. However, the resulting adduct was produced in only 67% yield and no other example involving the use of bulkier alkyl-substituted substrate has been provided. This dearth in the literature was also present in the field of metal(ion)-based catalysis where no example of a catalytic system has been devised to promote the highly enantioselective Henry reaction of aliphatic trifluoromethylketones. As a consequence, the development of a general catalytic method leading to high asymmetric induction was needed, enabling the use of a broader range of trifluoromethylketones with various steric and electronic profiles, and especially a larger range of aliphatic trifluoromethylketones.

Moreover, no organocatalytic systems involving cinchona alkaloids has been proved active in the Henry reaction with aliphatic aldehydes to date. For this purpose, thiourea-guanidine catalysts constitute a great alternative. Nevertheless, even though these molecules have been demonstrated to be capable of the efficacious promotion of Henry reactions involving branched alkyl-substituted aldehydes, this transformation remains challenging in respect of the use of unbranched aldehydes.

1.8 Catalysis of the sulfa-Michael addition of alkyl thiols to nitroolefins

1.8.1 Overview of the Michael addition of thiols to nitroalkenes and metal(ion)-based catalytic methods

The sulfa-Michael addition¹⁶⁷ is typically the reaction of a thiol with a C-C multiple bond electrophile. A new C-S bond is formed along with the creation of up to two new stereogenic centers. The study developed in this thesis focused on the addition of alkane thiols to (*E*)- β -nitrostyrene derivatives. This is a reaction of major interest, since the resulting enantioenriched products are highly versatile potential synthetic building blocks, incorporating both a sulfur atom and a nitro functionality in a chiral environment. These moieties can be readily transformed into other synthetically useful functionalities, such as amines, sulfoxides and disulfides.¹⁶⁷

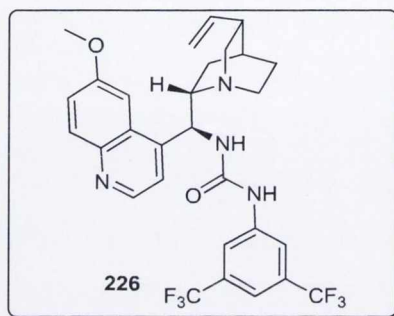
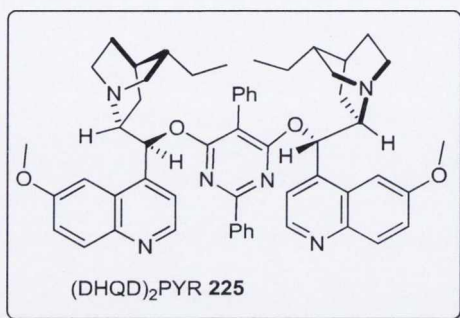
So far, no examples of catalytic systems including a metal(ion) species has been proposed to promote such addition (*i.e.* alkyl thiols to nitroalkenes reactions). However, metal(ion)-based methodologies have been reported for the efficacious additions of alkyl thiols to other electrophiles, such as α,β -unsaturated carbonyl compounds, oxazolidinone and trifluoromethyl-substituted propaonates.¹⁶⁸⁻¹⁷² As these reports had no influence on the study described herein, they will not be discussed in this introduction. The description of useful catalytic processes for the sulfa-Michael addition will be confined to organocatalysis alone.

1.8.2 Organocatalysed variants: scope and limitations

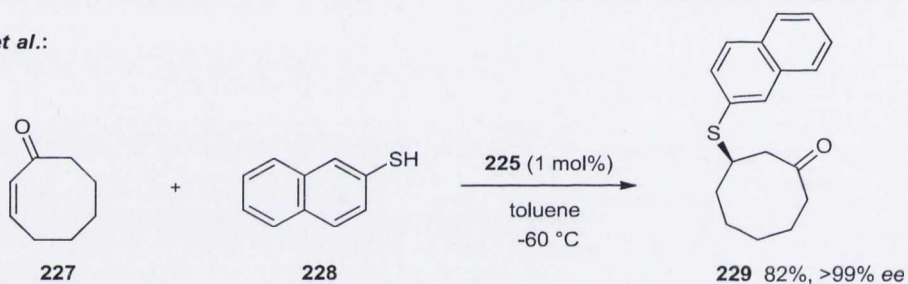
Recently, there has been a great deal of interest in the catalytic asymmetric addition of thiols to Michael acceptors. Much of this attention has been focused on the organocatalytic variant of the process. However, despite considerable endeavor, the scope of these reactions remains reasonably narrow.

Several very efficient catalytic processes have been reported in the literature since the first organocatalysed additions of 4-*t*Bu-thiophenol with cyclohexenone (up to 75% *ee*)^{78,80} and more challenging benzyl mercaptan with (*E*)- β -nitrostyrene (up to 28% *ee*),¹⁷³ studied by Wyndberg and Pracejus (respectively). Specifically, the asymmetric addition of thiophenols to a range of Michael acceptors promoted by bifunctional tertiary amine-based

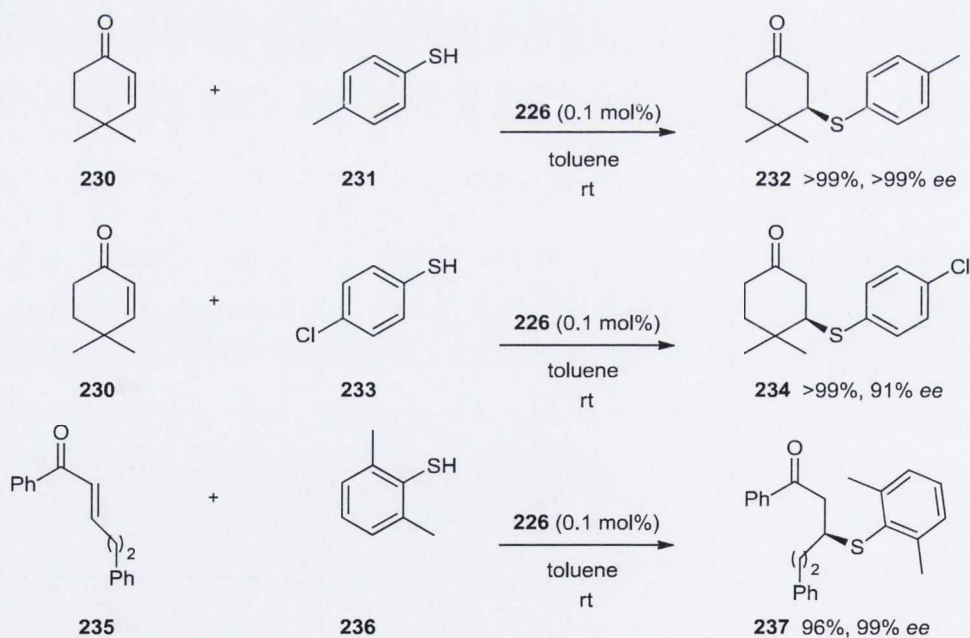
catalysts is now relatively straightforward. For instance, Deng and Singh developed highly efficient catalytic processes leading to high asymmetric induction for the sulfa-Michael addition of a wide range of thiophenol derivatives of variable electronic characteristics (*e.g.* **228**, **231**, **233** and **236**, Scheme 1.31) to both acyclic (*e.g.* **235**) and cyclic (5 to 9-membered rings, *e.g.* **227** and **230**) enones.



Deng *et al.*:



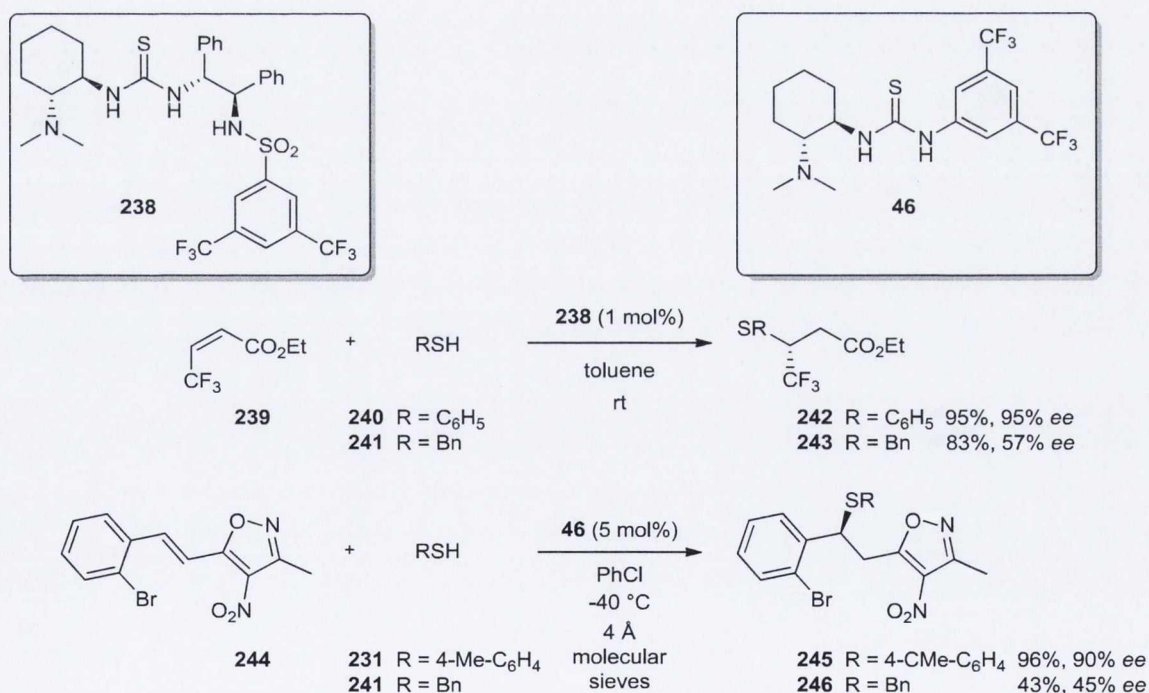
Singh *et al.*:



Scheme 1.31 Examples of the highly enantioselective organocatalytic sulfa-Michael additions with thiophenols

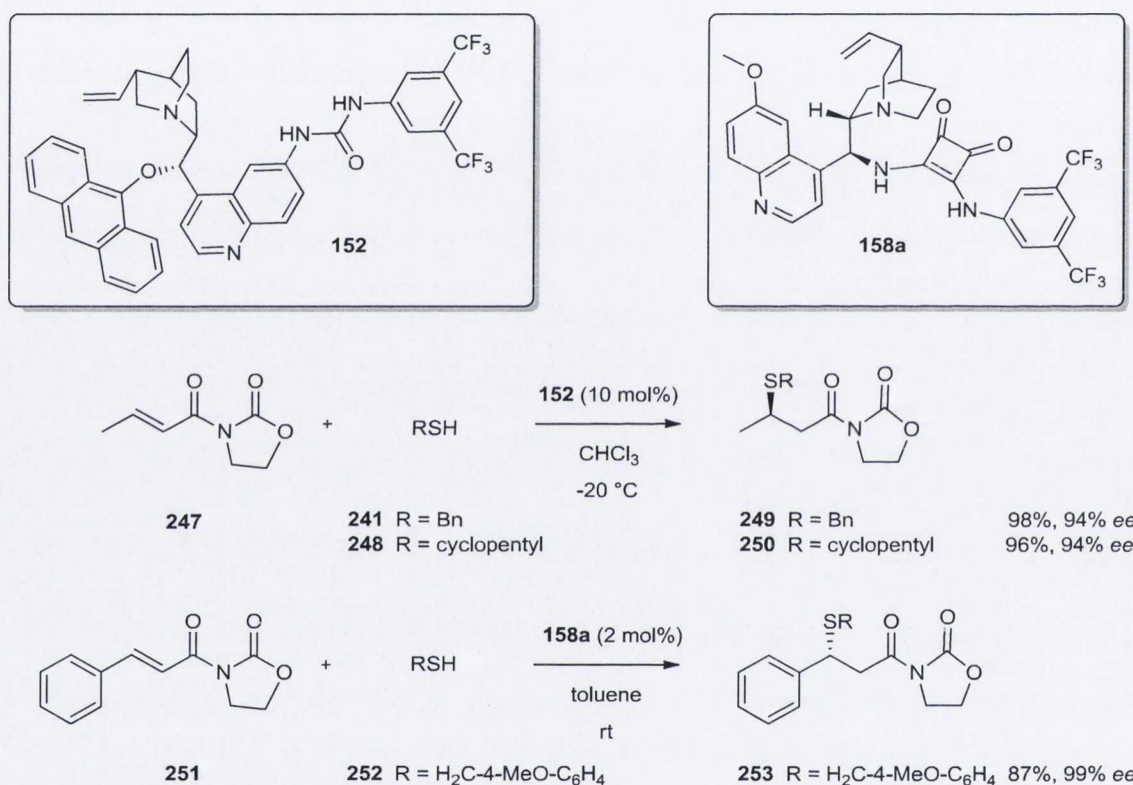
These catalytic processes employed either 1 mol% of the C2-symmetric quinine analogue **225** or only 0.1 mol% of the C-9-urea-based **226** and led to the generation of Michael-adducts (*e.g.* products **229**, **232**, **234**, **237**) with excellent yields and enantioselectivities (up to >99% *ee*).^{174,175}

However, in the majority of studies, the less reactive yet considerably more versatile aliphatic thiols are either not utilised or are reported to undergo considerably less selective addition than their aromatic counterparts. Wang *et al.* demonstrated the remarkable capability of thiourea **238** (Scheme 1.32) to catalyse the Michael addition of thiophenol (**240**) to (*Z*)-ethyl 4,4,4-trifluorocrotonate (**239**) with excellent yield and enantioselectivities (*e.g.* Michael adduct **242**, 95% *ee*). The same reaction using benzyl mercaptan (**241**) resulted in the generation of Michael adduct **243** with only 57% *ee*.¹⁷⁶ The same could be observed in the asymmetric addition of thiols to 3-methyl-4-nitro-5-alkenyl-isoxazole (**244**) catalysed by thiourea **46**. While the reaction using 4-methylthiophenol (**231**) proceeded smoothly with 90% *ee*, only moderate enantiocontrol could be obtained in the same conditions using benzyl mercaptan (**241**, see products **245** and **246**).¹⁷⁷



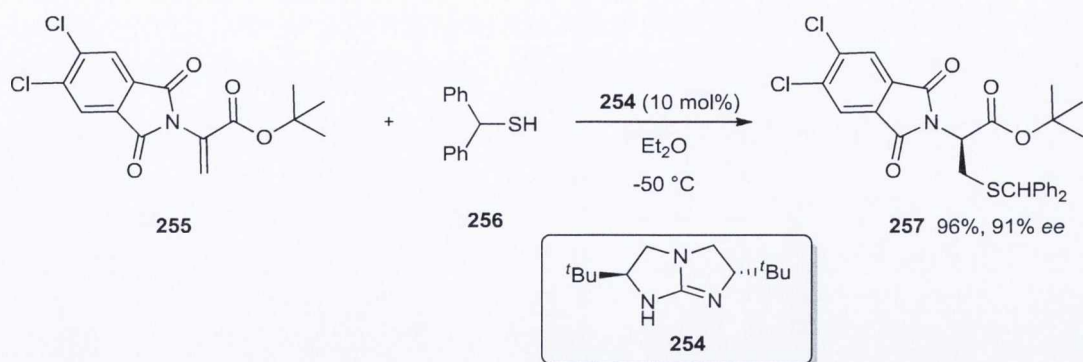
Scheme 1.32 Lower enantioselectivity associated with organocatalytic Michael additions using alkyl thiols compared to the reactions using thiophenols

Examples of the enantioselective addition of aliphatic thiols to Michael acceptors, with a view to preparing chiral organosulfur compounds with high optical activity, are very rare. Thiourea and squaramide substituted cinchona alkaloids **152** and **158a** demonstrated high activity and selectivity in the addition of aliphatic thiols onto α,β -unsaturated *N*-acylated oxazolidinones (e.g. **247** and **251**) in two separate reports from Deng and Chen (Scheme 1.33).^{139,178} A wide range of alkyl thiols (such as **241**, **248** and **252**) have been involved, their steric and electronic variety exhibiting no influence on either the efficiency or the enantioselectivity of the reaction.



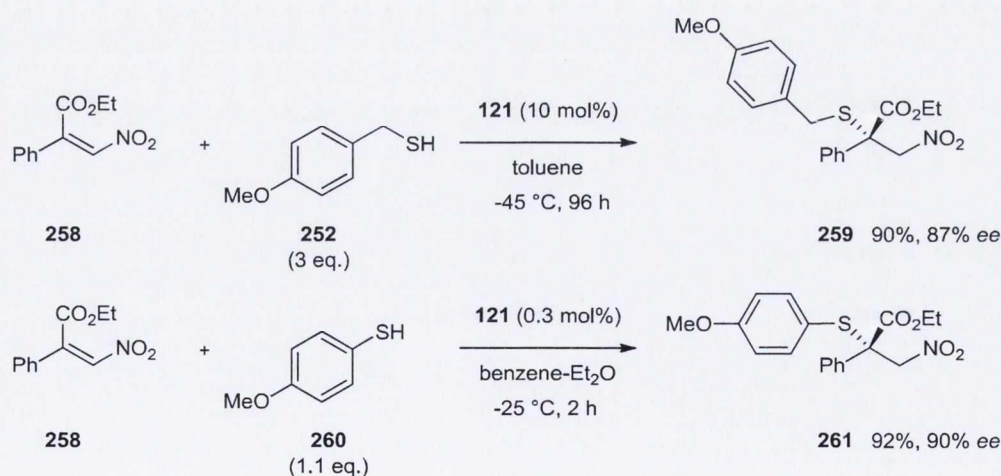
Scheme 1.33 Highly enantioselective sulfa-Michael addition using alkyl thiols

Guanidine derivative **254** (Scheme 1.34) could also mediate the promotion of highly enantiocontrolled tandem sulfa-Michael addition/protonation reactions involving the alkyl thiol **256** and *tert*-butyl-2-phthalimidoacrylate **255**, producing adduct **257** with 96% yield and 91% ee.¹⁷⁹



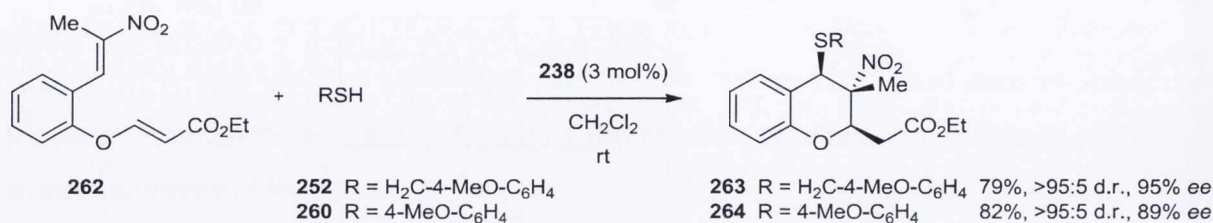
Scheme 1.34 Enantioselective sulfa-Michael addition/protonation catalysed by the guanidine derivative **254**

In the case of the highly synthetically malleable 1,2-disubstituted nitroalkenes, no examples are known. It is noteworthy that an organocatalytic asymmetric addition of benzyl mercaptan derivative **252** to a β,β -disubstituted nitroalkene **258** (mediated by C-9-*epi*-thiourea quinine derivative **121**) has been reported by Xia and coworkers.¹⁸⁰ This addition proceeded at a slower rate (96 h versus 2 h) and was less enantioselective (87% *ee*) than the corresponding addition of thiophenol analogue **260** to the same electrophile **258** (adducts **259** and **261**, Scheme 1.35). The reaction also required increased nucleophile and catalyst loadings.



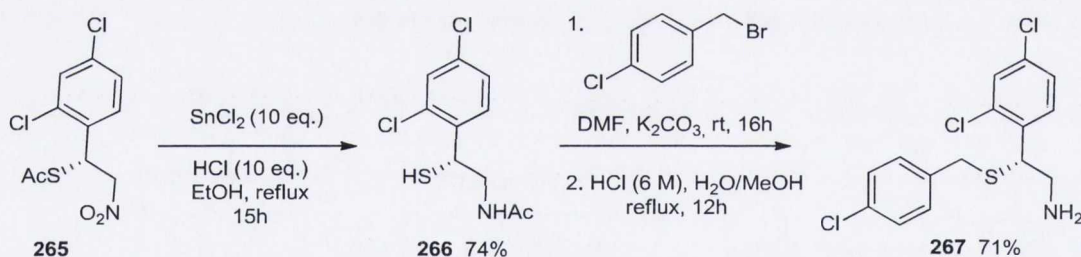
Scheme 1.35 Sulfa-Michael addition of alkyl and aromatic thiols to β,β -disubstituted nitroalkenes

In contrast, the thiourea molecule **238** proved an active catalyst for the highly diastereo- and enantioselective promotion of the sulfa-Michael/Michael addition of alkyl thiol **252** (and thiophenol **260**) to nitroolefin enoate **262** (*i.e.* adducts **263** and **264**, Scheme 1.36).¹⁸¹



Scheme 1.36 Very efficient Sulfa-Michael/Michael addition using alkyls/aryls thiols

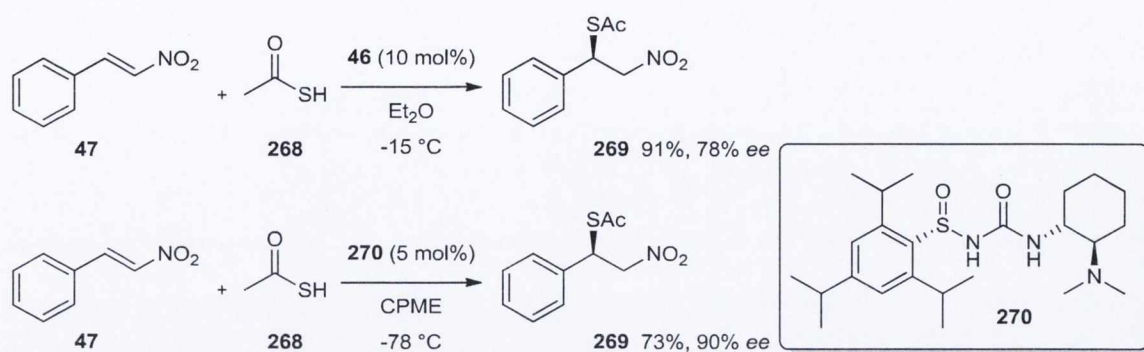
However, this successful extension of the reaction scope to alkyl thiols is rare and has never been observed in reactions where (*E*)- β -nitrostyrene derivatives are involved as the acceptor. An indirect solution to circumvent this problem has been identified independently by Wang and Ellman: use of thioacetic acid (2.0 eq.) as the nucleophile allows the possibility of later cleaving the thioester adduct (*e.g.* **265**, Scheme 1.37) hydrolytically, followed by an alkylation to give the product formally derived from the addition of an aliphatic thiol to the nitroalkene (*e.g.* **267**).⁷³



Scheme 1.37 Cleavage of the optically active thioester followed by an alkylation of the resulting thiol

In 2006, Wang devised a protocol using Takemoto's catalyst **46** (Section 1.2) for the catalytic asymmetric addition of thioacetic acid (**268**) to (*E*)- β -nitrostyrene (**47**), with a level of product enantiomeric excess up to 78% *ee* (adduct **269**, Scheme 1.38).¹⁸² Later, Ellman *et al.*⁷³ developed the chiral *N*-sulfinyl urea-based catalyst **270** capable of promoting the same reaction with 90% product *ee* at -78°C . The process was complicated by product consuming Baylis-Hillman-type chemistry under the reaction conditions, which limited the product yields to 63–88% when using aromatic nitrostyrenes. Higher yields (up

to 95%) were achievable when aliphatic nitroolefins were employed. Excellent enantioselectivities up to 96% were obtained *via* this catalytic pathway.



Scheme 1.38 Protocols for the enantioselective Michael addition of thioacetic acid to nitroalkenes

1.8.3 Conclusion on the organocatalytic sulfa-Michael additions involving nitroalkenes

Due to the development of new catalyst libraries (*i.e.* cinchona alkaloids and amino thioureas), significant improvements have been recorded in the highly enantioselective promotion of sulfa-Michael additions. While various promoters have been investigated for the efficient addition of thiophenol derivatives to Michael acceptors, there has been a significant dearth of literature examples of the use of less reactive yet considerably more versatile aliphatic thiols, especially regarding conjugate additions to (*E*)- β -nitroalkenes.

The catalytic process using the C-9-*epi*-thiourea-modified cinchona derivative **121** for the addition of alkyl thiol **252** to β,β -disubstituted nitroolefin **258** gave satisfying results, but this reaction required the use of a considerable amount of mercaptan (3 eq.) and relatively long reaction times.

Ellman's urea-based catalyst **270** was highly enantioselective and tolerated a broad range of aryl- and alkyl-substituted nitroolefins. However, this catalytic system afforded Michael adducts in only moderate yields and was limited to the use of thioacetic acid (with 2 eq. required). The hydrolysis of the optically active thioester followed by the alkylation of the resulting organosulfur compound was demonstrated as an efficient method in obtaining alkylated-sulfur Michael adducts. However, this process was step-consuming and required

consecutive acidic and basic reaction conditions (with the use of HCl and K₂CO₃ solutions). This could be limiting in some total synthesis strategies that would not be compatible with such pH variations. Finally, benzylic thioethers are less labile than their thioester counterparts and are cleaved under specific conditions depending on their aryl substituents (discussed in Section 3.2.5.2). Therefore, they could be imagined to serve as synthetic equivalents for H₂S in a total synthesis strategy where the thioether would need to be orthogonally cleaved at a key moment of the synthesis.

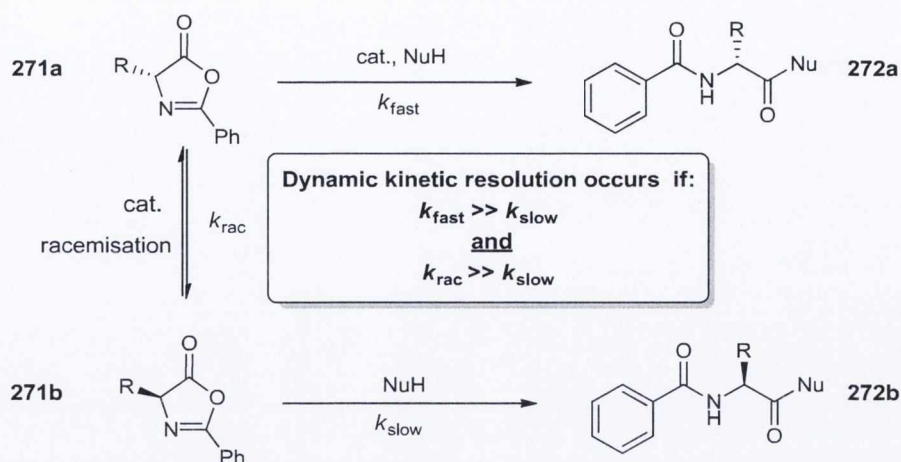
For these reasons, it would be of significant importance to develop a catalytic system that would provide a general highly efficient and enantioselective pathway for the addition of problematic alkane thiols to nitrostyrenes.

1.9 The dynamic kinetic resolution of azlactones

1.9.1 Alcoholysis

The Dynamic Kinetic Resolution (DKR) of azlactones by alcoholysis^{183,184} is now a mature technology involving the catalytic addition of a primary alcohol to one enantiomer of the readily racemisable (pK_a ca. 9 in H₂O)¹⁸⁵ racemic electrophile. This strategy is of high synthetic utility since it generates an orthogonally protected and enantioenriched α -amino-acid product.⁵³

The DKR of azlactones is an example of a complex process where, even though a mixture of the two enantiomers of the substrate are present in the reaction, only one asymmetric product is expected (Scheme 1.39).¹⁸⁶⁻¹⁸⁸ One enantiomer (**271a**) will react preferentially with the nucleophile in the presence of a chiral catalyst. If the rate of the reaction of the fast-reacting enantiomer (k_{fast}) is considerably greater than that associated with the slower-reacting antipode (k_{slow}), then kinetic resolution results (*i.e.* $k_{fast} \gg k_{slow}$). However, in the case of DKR, a successful catalyst must not only bring about a selective kinetic resolution, it must also be of sufficient basicity to catalyse the epimerisation equilibrium of the azlactone with an efficiency that ensures that racemisation occurs at a considerably faster rate than the addition of the alcohol to the less preferred substrate enantiomer (*i.e.* $k_{rac} \gg k_{slow}$).

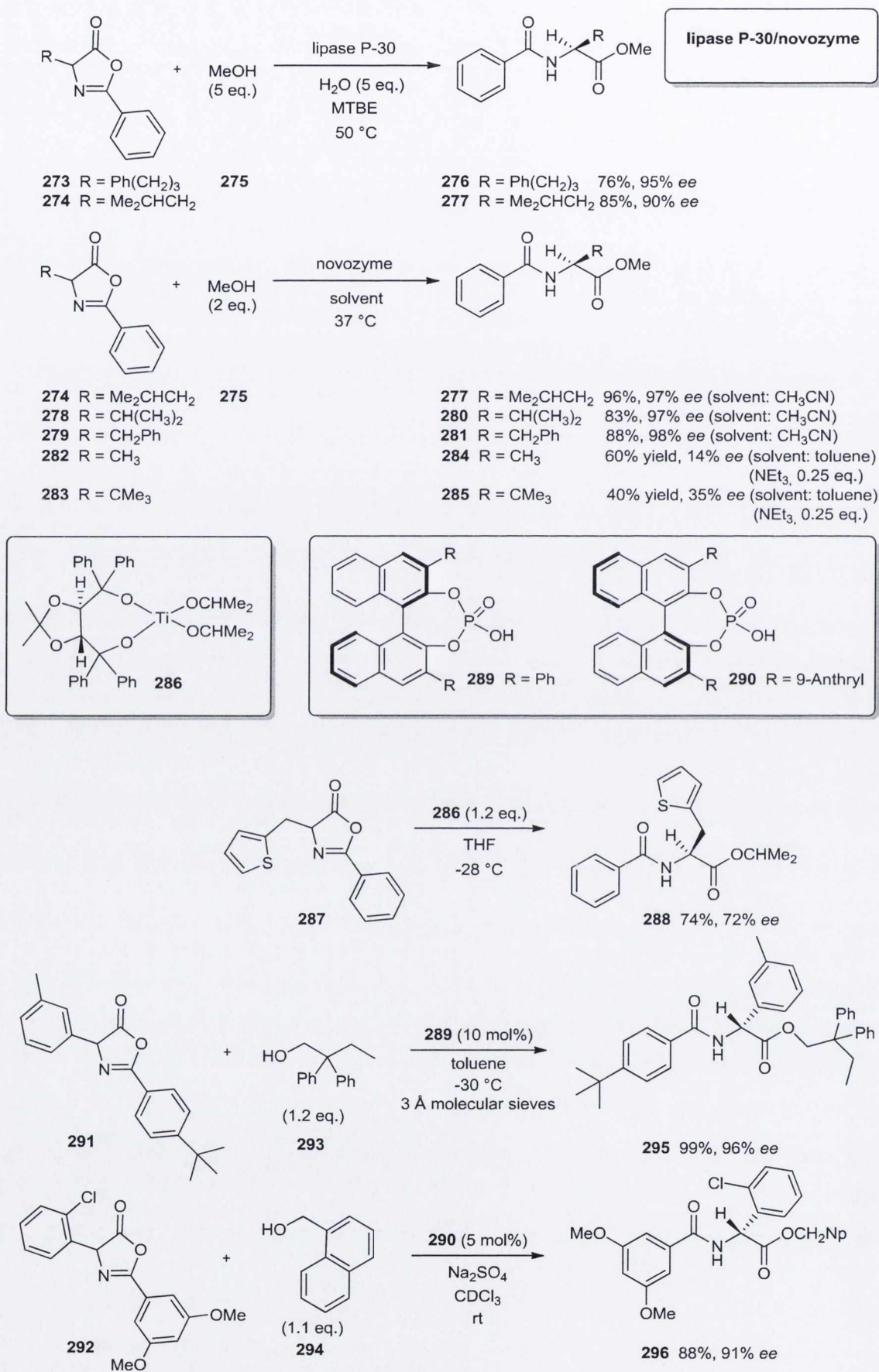


Scheme 1.39 The dynamic kinetic resolution of azlactones

In this scenario, the product can be theoretically obtained as a single enantiomer in quantitative yield due to the continuous regeneration of the faster reacting enantiomer as the reaction progresses.

Several catalytic strategies capable of delivering high product yields and enantioselectivities have appeared for the DKR of azlactones *via* alcoholysis. For instance, enzymes,¹⁸⁹⁻¹⁹¹ Ti-complexes,¹⁹² and chiral Brønsted acids^{193,194} have been employed (Scheme 1.40).

In 1993, Sih *et al.* developed several lipase-based catalytic protocols to promote the ring opening of *N*-benzoyl protected azlactones *via* methanolysis with moderate to high yields and enantioselectivities (Scheme 1.40).^{189,190} For example, *pseudomonas* lipase P-30 could promote the ring opening of azlactone **273** and leucine-derived azlactone **274** using methanol (**275**) to afford benzoyl protected methyl esters **276** and **277** in 76% and 85% yield (respectively) and 90-95% *ee*. Lower enantioselectivities were obtained using valine- (77% *ee*), phenyl glycine- (75% *ee*), phenylalanine- (78% *ee*) and alanine-derived (59% *ee*) azlactones. It was found (without further explanation) that adding 5 equivalents of water was beneficial for the enantiocontrol of some of the DKR studied, at the expense of the product yield.



Turner *et al.* reported a complementary catalytic alternative for the same reaction using lipase B from *candida antarctica* (novozyme) which was proved to be very efficient, especially in the methanolysis of leucine- **274**, valine- **278**, and phenylalanine-derived **279** azlactones (97-98% *ee*, Scheme 1.40).¹⁹¹ The ring opening of alanine analogue **282** occurred with almost no enantiocontrol (14% *ee*) and the *tert*-leucine azlactone derivative **283** could be used as a substrate, albeit with low enantiocontrol (40% yield and 35% *ee*). These last two substrates (**282** and **283**) proved very challenging.

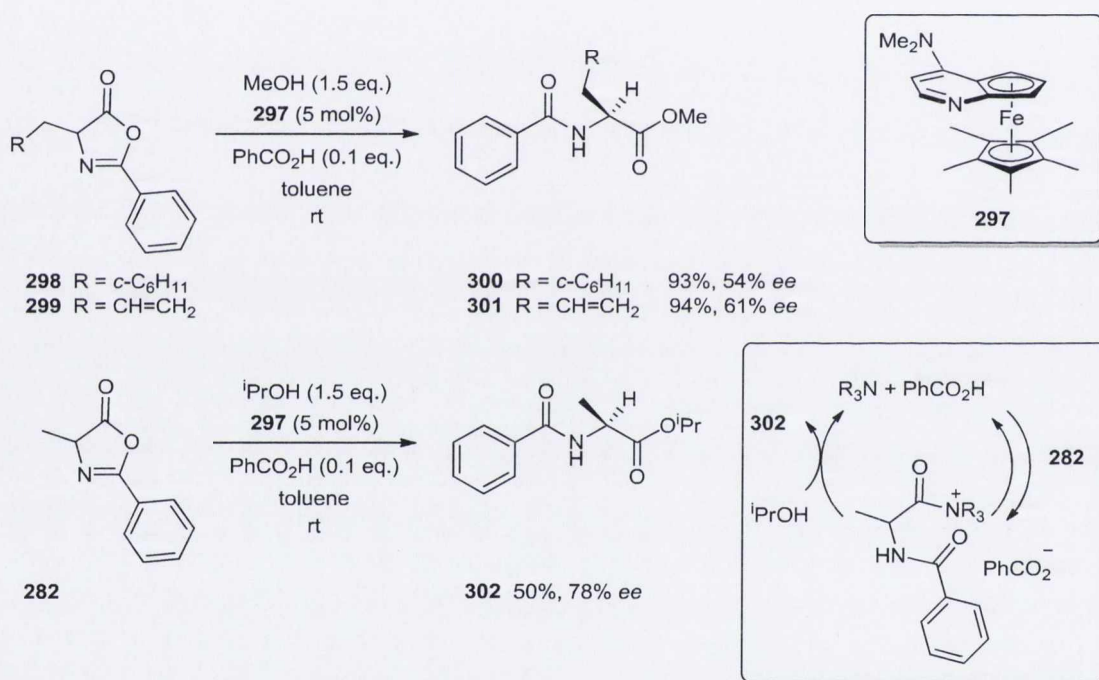
Metal(ion)-based catalysis also provided alternative methodologies. Ti-TADDOLate **286** (Scheme 1.40) was demonstrated by Seebach *et al.* to be capable of the promotion of the ring cleavage of phenylalanine azlactone derivatives (*e.g.* **287**) *via* the transfer of an isopropoxide from the complex's ligand sphere to the carbonyl group of the azlactone. Moderate yields and enantiomeric excess were obtained using a stoichiometric amount of the promoter (1.2 eq.).¹⁹²

Recently, Brønsted acids were used as highly efficient complementary catalytic systems for this process. In 2011, Gong¹⁹³ and Birman¹⁹⁴ independently reported the use of 3,3'-aryl-substituted-BINOL phosphoric acid **289** (10 mol%) and **290** (5 mol%) to promote the DKR of aryl-substituted azlactones with excellent activities and selectivities (*e.g.* **295** and **296**, Scheme 1.40). They postulated that these chiral phosphoric acids were acidic enough (pK_a *ca.* 1 in H₂O) to activate the azlactone directly *via* protonation. Various aryl-substituted azlactones (*e.g.* **291** and **292**), with different electronic and steric properties, could be involved in the DKR without altering the reaction rate or the enantioselectivity of the outcome. Both studies highlighted the advantage of using β -substituted primary alcohols (*i.e.* either **293** or **294**), instead of methanol (**275**). This limits the utility of the process, as one is confined to the use of large, relatively expensive, alcohol nucleophiles.

Since the late 1990's, several other organocatalytic processes were developed as efficient strategies for the DKR of azlactones previously described as challenging in the literature (*e.g.* the DKR of either *tert*-leucine derivative **283** or alanine analogue **282**).

Fu *et al.* disclosed the first selective DKR of azlactones catalysed by a planar-chiral DMAP derivative **297** (Scheme 1.41) as a nucleophilic organocatalyst operating *via* an acyl transfer mechanism (the ferrocene core is not involved in the catalytic process).¹⁹⁵ It was found that the addition of a catalytic amount of benzoic acid (10 mol%) increased the

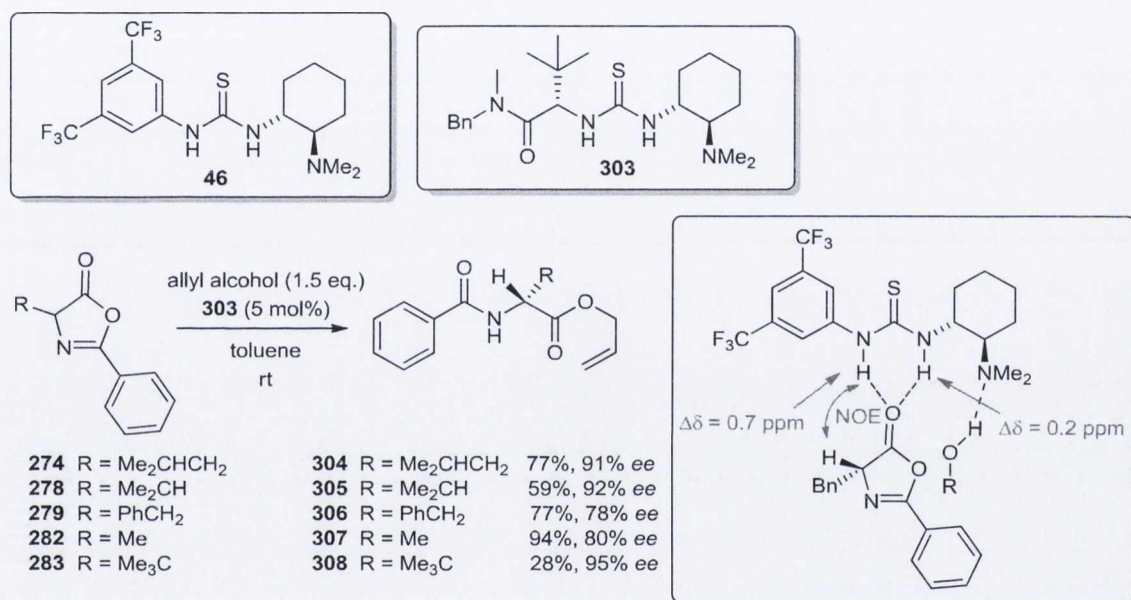
rate and the stereoselectivity, as its carboxylate counterion was involved in the proposed mechanism to activate the alcohol (Scheme 1.41). Only azlactones bearing aliphatic side chains were used as substrates. Orthogonally protected L-amino acids (*e.g.* cyclohexyl- or allyl glycine-derivatives **300** and **301** respectively) were synthesised with excellent yields (93-94%) but only moderate enantioselectivities (54-61% *ee*, Scheme 1.41). It is worth noting that the challenging alanine amino acid derivative **302** could be generated with an unprecedented 78% *ee* (relatively to the previous benchmark enzymatic processes considered) when the more sterically demanding isopropanol was involved in the process, however at the expense of the reaction rate (50% yield obtained after 1 week, Scheme 1.41).



Scheme 1.41 Nucleophilic catalysis of DKR of azlactones

The first examples of bifunctional organocatalysed systems for this reaction were reported by Berkessel and coworkers in 2005-2006. Takemoto's bifunctional (thio)urea/Brønsted-basic tertiary amine catalyst (*e.g.* **46**) was utilised as a promoter.¹⁹⁶ The proposed mechanism, supported by NMR spectroscopic experiments, involved the synergistic activation of the alcohol by the general base moiety, whereas the (thio)urea catalophore would interact with the azlactone through hydrogen-bond donation (leading to both its epimerisation *via* enolisation and its electrophilicity enhancement, Scheme 1.42). To support this theory, it was demonstrated that the use of either a base (triethylamine) or a

(thio)urea moiety as sole catalyst failed to promote the reaction.^{196,197} Thus, the DKR *via* allyl alcohol addition of various azalactones, with a broad range of steric profiles, was reported. Moderate to good yields and good enantioselectivities were obtained. For instance, azlactones derived from leucine (*i.e.* **274**), valine (*i.e.* **278**) and phenylalanine (*i.e.* **279**) could be resolved with good product enantiopurities (73-85% *ee*). The preparation of a novel thiourea-based catalyst **303**, which possessed an additional stereocenter,¹⁹⁷ provided Berkessel *et al.* with better enantiocontrol. Product enantiomeric excess reached 95% *ee*, with yields between 28 to 94% (*e.g.* allyl esters **304-308**, Scheme 1.42).¹⁹⁸

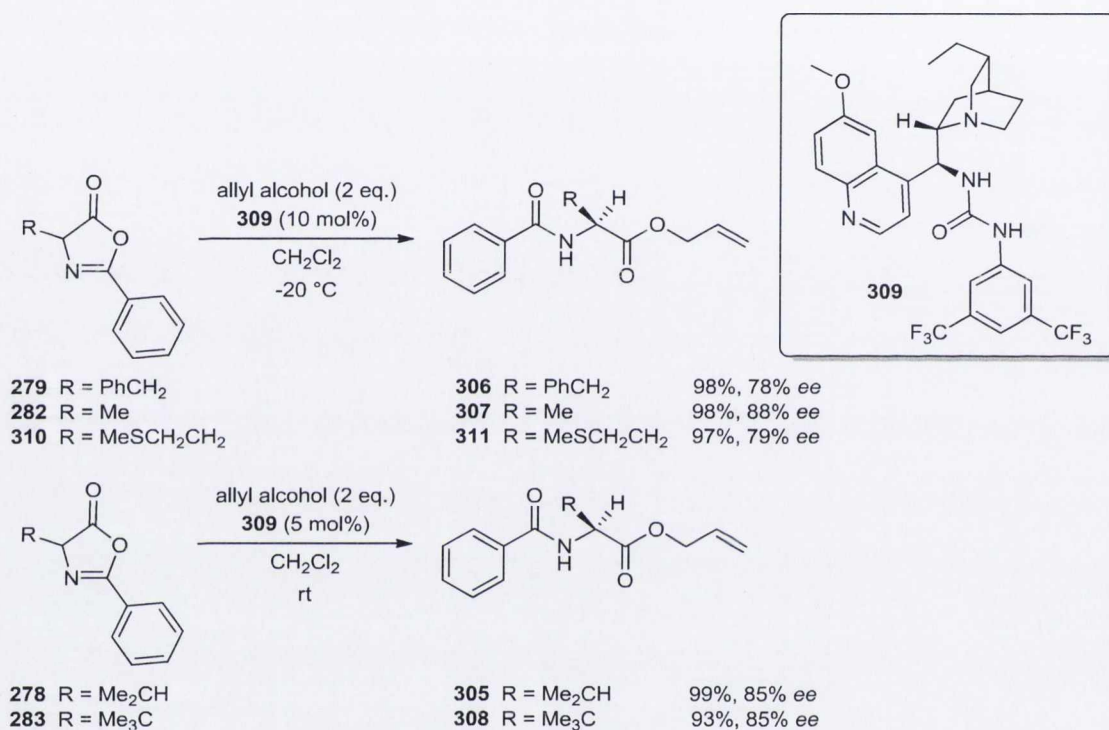


Scheme 1.42 The DKR of azlactones catalysed by (thio)urea-based bifunctional catalysts

Importantly, Berkessel reported in this study the highest enantioselectivity achieved at the time for the DKR of the *tert*-leucine-derived azlactone substrate **283** (95% *ee*), outperforming even the enzymatic catalytic systems. The difficult alanine azlactone analogue **282** (from an enantioselectivity standpoint) was opened with similar enantioselectivity (80% *ee*) as that obtained using Fu's previous catalyst (78% *ee*), albeit providing a much better conversion rate (94% conversion after 24 h). It should also be noted that the use of **303** led to the production of unnatural D-amino acid allyl esters.

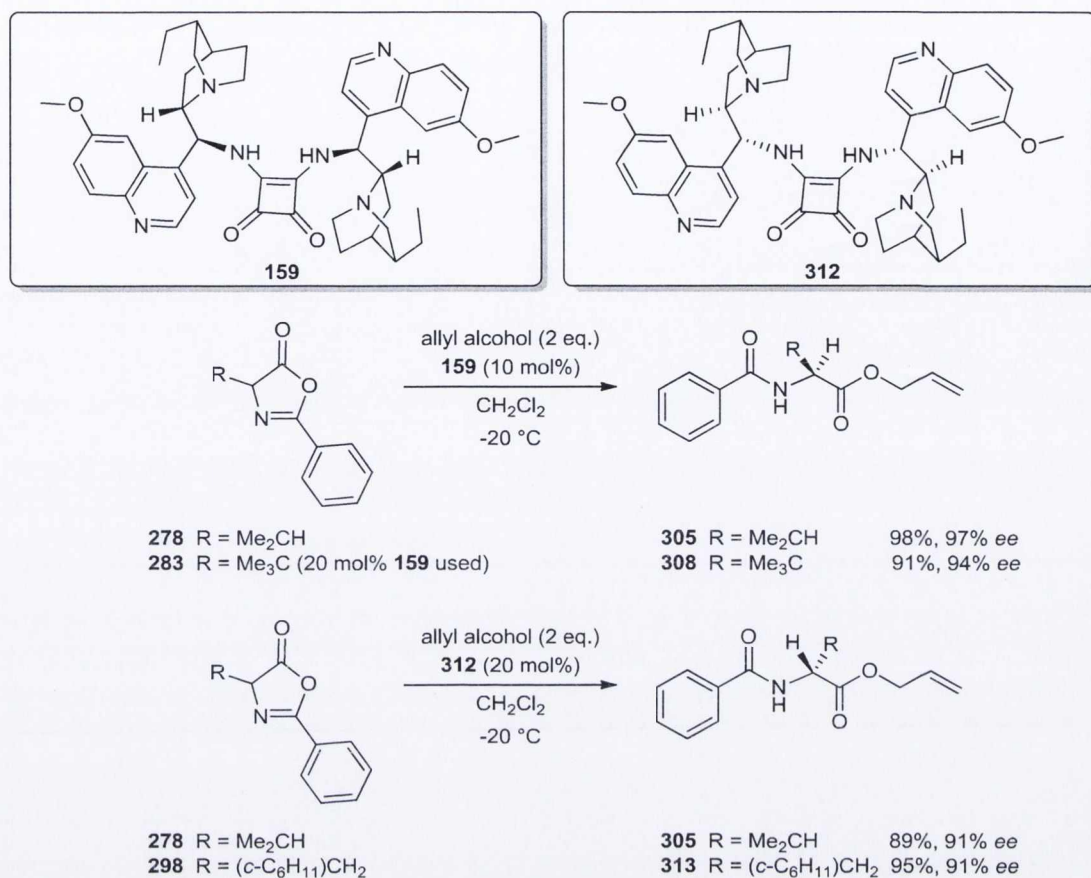
In 2008, Cannon *et al.*⁵³ reported the use of cinchona alkaloid derivatives in this transformation, especially urea-based C-9-*epi*-dihydroquinine **309** (Scheme 1.43). The DKR of azlactones possessing very different side chains was efficiently conducted, with

slightly less enantiopurities (78-88% *ee*) than described in previous studies, but with excellent yields (93-99% yield). In particular, orthogonally *N*-protected alanine allyl ester **307** could be produced in 98% yield with an unprecedented enantioselectivity of 88% *ee* and *tert*-leucine analogue **308** was also prepared in excellent yield (93%). It should be noted that the urea derivative **309** outperformed the thiourea analogue **123** in this reaction (Figure 1.24, Section 1.5.1.2).



Scheme 1.43 Use of the highly active *C*-9-*epi*-urea cinchona derivative **309** in the DKR of azlactones

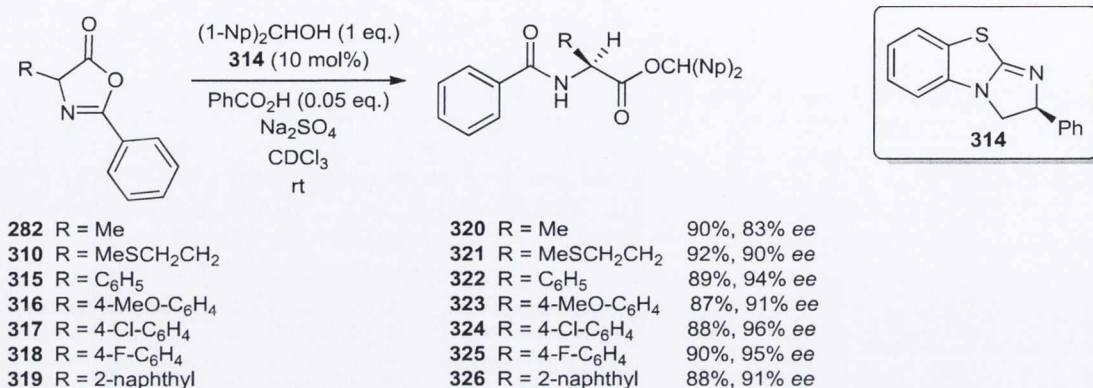
Song *et al.*¹⁴² designed and prepared the C2-symmetric squaramide-based dihydroquinine derivative **159** and dihydroquinidine analogue **312**. These were capable of the very efficient DKR of azlactones, in particular the valine analogue **278** (ester **305** was generated with 97% *ee* and 98% yield after only 8 h using catalyst **159**, Scheme 1.44). This catalytic process led to L-amino acid allyl esters when promoted by **159**, as well as the enantioenriched artificial D-amino acid analogues when **312** was involved in the catalysis. **159** Proved a powerful catalyst which facilitated the efficient preparation of *tert*-leucine amino acid allyl ester **308** with a yield and enantiopurity both superior to 90% *ee*; hence **308** represented no longer a catalytic challenge.



Scheme 1.44 D- and L-protected amino acid allyl esters prepared using the C2-symmetric squaramide-based catalysts **159** and **312**

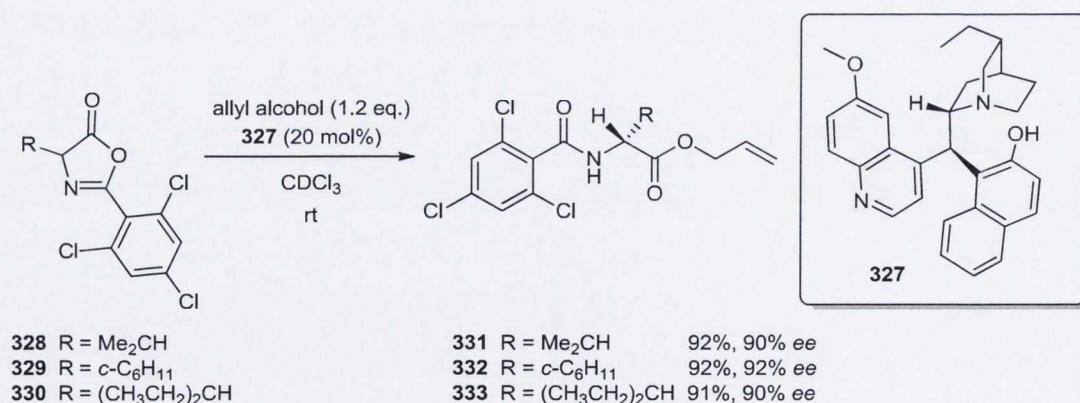
In 2010, Birman *et al.* employed the nucleophilic aminidine-based catalyst **314** (benzotetramisole, Scheme 1.45) to promote the ring-opening of a broad range of alkyl- and aryl-substituted azlactones. Using the bulky *bis*-(1-naphtyl)methanol and 5 mol% of benzoic acid in the presence of **314** led to excellent yields (e.g. **320-326** produced in 86-97% yield) and enantioselectivities (83-96% ee).¹⁹⁹ The catalytic process operated through the same acyl transfer mechanism described in Fu's study (Scheme 1.41). The challenging L-alanine protected amino acid **320** was efficiently prepared with 90% yield and 83% ee (Scheme 1.45). The efficiency of this catalytic system was especially illustrated in the promotion of the opening of phenyl glycine-derived azlactone **315** and other arylated azlactone derivatives **316-319** which afforded arylated compounds **322-326** with excellent enantiocontrol (91-96% ee). Overall, this catalytic method provided Birman *et al.* with access to the DKR of a wide range of azlactones (using 16 alkyl- and aryl-substituted azlactones) with high enantiocontrol (76-97% ee) and excellent yields (86-97%). However, **314** failed to promote the DKR of relatively hindered substrates, such as valine derivative

278 (<5% yield under optimised conditions). Also, the use of a specific, large and expensive alcohol was required, which limits the broad applicability of this method.



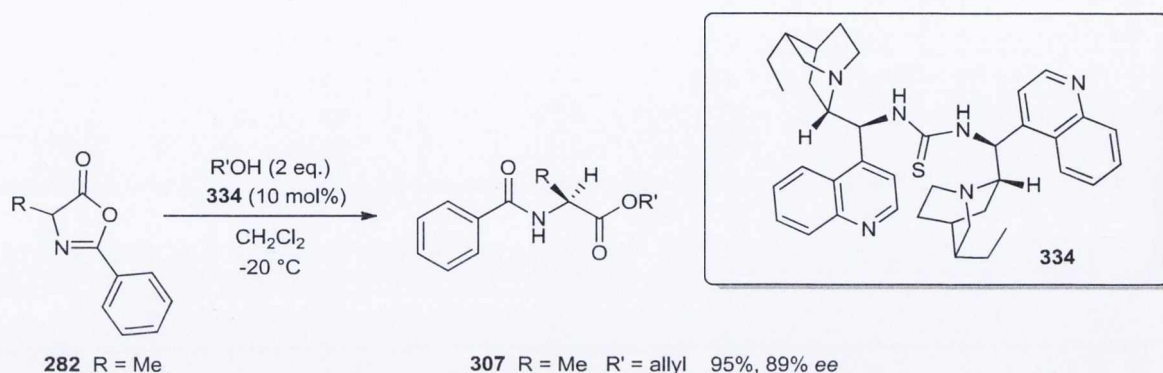
Scheme 1.45 Efficient and highly selective DKR of alkyl- and aryl-substituted azlactones catalysed by benzotetramisole (**314**)

High levels of enantioselectivity were also achieved this year by a different bifunctional catalytic system based on a readily prepared C-9 arylated cinchona alkaloid **327** (Scheme 1.46) designed by Cannon *et al.*²⁰⁰ The significantly bulky nature of the enantioenriched protected D-amino acids prepared (valine, cyclohexyl glycine and diethyl glycine analogues **331**, **332** and **333**) had no impact on the excellent conversion rate (91-92%) and enantiocontrol (90-92% *ee*) obtained.



Scheme 1.46 Highly enantioselective and efficient DKR of hindered azlactones catalysed by **327**

Very recently, Song and coworkers developed another C2-symmetric thiourea **334** (Scheme 1.47) also capable of the efficient resolutions of azlactone **282** with good level of product enantiopurity (95% *ee*) and conversion (89%).²⁰¹

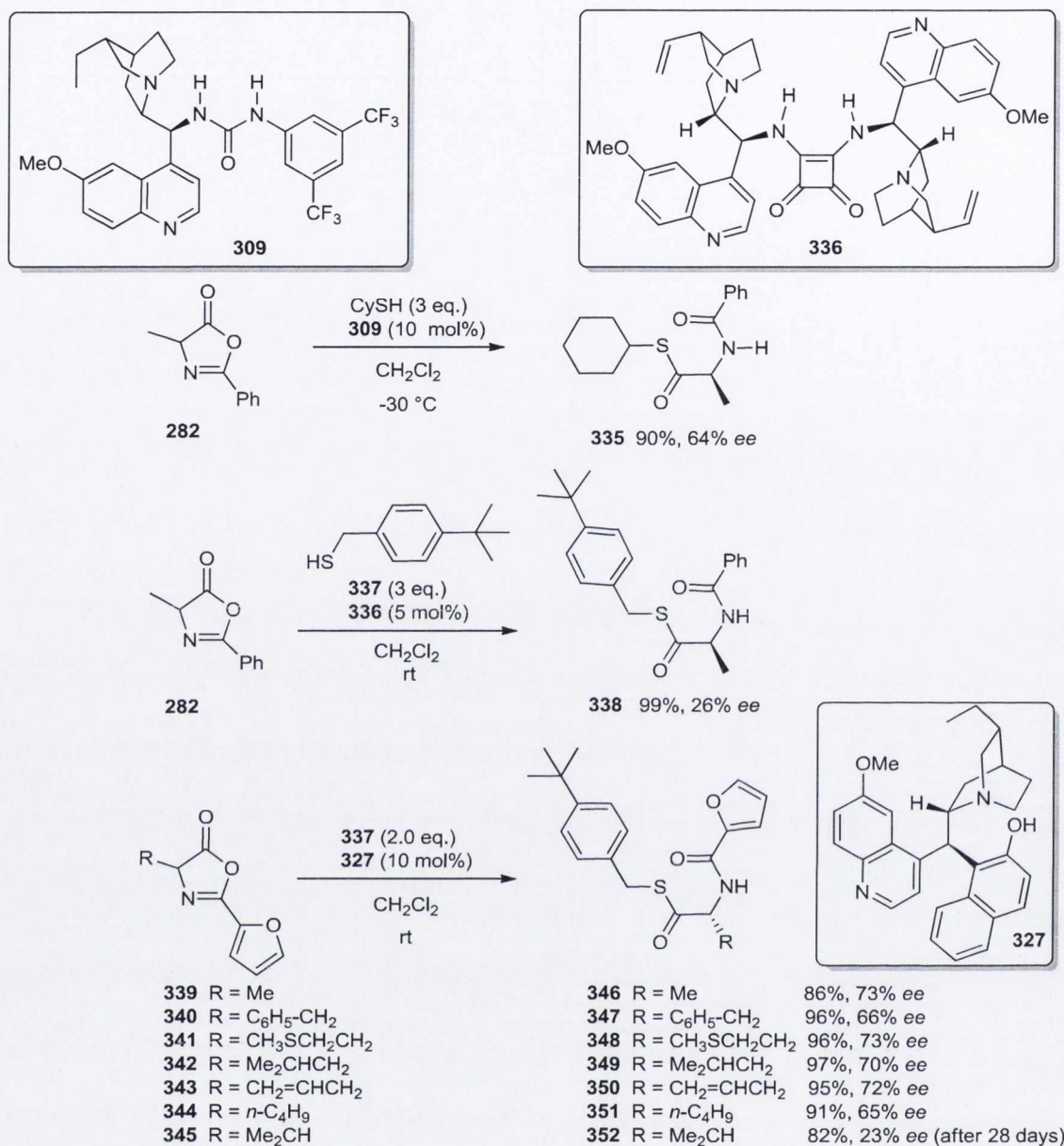


Scheme 1.47 Efficient DKR of azlactones **282** and **333** catalysed by **332**

1.9.2 Thiolysis

While there are now several complementary catalytic options to carry out effective (>90% *ee*) DKR of azlactones by alcoholysis, the corresponding reaction involving thiol nucleophiles remains considerably more difficult.¹⁸³ A selective variant of such a reaction is an attractive catalytic target which would provide direct access to enantioenriched thioesters potentially valuable in native chemical ligation (NCL)^{202,203} a powerful peptide coupling process.^{204,205}

Connon and coworkers first reported this reaction as part of a study focused on the corresponding alcoholysis reaction in 2008.⁵³ Cyclohexane thiol could be added to the alanine-derived azlactone **282** in the presence of the bifunctional urea-based cinchona alkaloid catalyst **309** to give the *N*-benzoyl amino acid thioester **335** in excellent yield and moderate *ee* (Scheme 1.48). It is noteworthy that when a less hindered primary thiol nucleophile (which generates thioester products of far greater utility in NCL processes) was utilised, the level of product *ee* was considerably lower.



Scheme 1.48 Only reported examples of the DKR of azlactones *via* thiolysis

The C2-symmetric squaramide catalyst **336** (developed by Song *et al.*, *vide supra*) is one of the current benchmark systems for the catalysis of the analogous alcoholysis chemistry.¹⁴² However, in the thiol-based variant of this process using the primary thiol nucleophile **337**, catalysis was efficient but relatively unselective (*i.e.* thioester **338**, Scheme 1.48).²⁰⁶

This year, C-9 arylated cinchona alkaloid **327** proved to be significantly more efficient in the catalysis of the DKR of furyl-substituted azlactones **339-345** through thiolysis (Scheme 1.48). *N*-protected D-amino acid thioesters **346-352** were generated with up to 73% product

*ee.*²⁰⁶ This catalyst could operate at room temperature and accepted a range of azlactone substrates derived from unhindered amino-acids. However both activity and selectivity were markedly diminished in the presence of the valine-derived substrate **345**.

1.9.3 Conclusion on the organocatalytic DKR of azlactones

While very efficient methods of DKR of azlactones *via* alcoholysis have been described in the literature, considerable scope for improvement remains when considering the thiolysis version of the reaction, in particular from an enantioselectivity standpoint. The state of the art in this reaction is the catalytic system involving C-9 arylated cinchona alkaloid **327**, which mediated the synthesis of protected D-amino acids with excellent yields but levels of product enantiomeric excess only up to 73% *ee*. It should be noted that only unhindered amino acid-derived azlactones are compatible with **327**, more hindered azlactones (*i.e.* those derived from α -branched amino acids) are converted at an impractically slow rate.

Modification of the C-9 cinchona alkaloid substituent (*i.e.* catalysts **309**, **327** and **336**) has led to steady yet ultimately unsatisfactory progress, from a synthetic utility perspective. The design of different catalytic architectures, resulting from the modification of the cinchona alkaloid framework at different positions (than C-9), may be beneficial to allow further enantioenrichment of the subsequent amino-acids.

2.0 Highly enantioselective nitroaldol reactions promoted by a new class of cinchona alkaloid derivatives

As previously mentioned in Section 1.7, organocatalytic systems capable of the highly enantioselective promotion of nitroaldol reactions are rare. While several efficient metal(ion)-based catalytic processes have been reported in the literature for the Henry reaction, such additions proved to be particularly difficult to catalyse in a ‘metal-free’ fashion. Thus, Hiemstra *et al.* encountered major difficulties when investigating the use of cinchona alkaloid derivatives to mediate the addition of nitromethane to (activated) *para*-nitro-benzaldehyde (**199**, Section 1.7.2.1). Using the cupreine-derived catalyst **102**, the obtained levels of product enantiomeric excess were very modest.¹³⁸ The design of catalyst **147** (Section 1.5.2), possessing the bifurcated, rigid and more Lewis acidic *bis*-hydrogen-bond donor thiourea unit at the C-6' position (instead of the hydroxyl group), was necessary for Hiemstra and coworkers to achieve better enantiocontrol. Even then, the scope of this organocatalytic 1,2-addition remained noticeably narrow since only aromatic aldehydes could be efficiently used as substrates. In this context, we were intrigued as to how a catalyst characterised by bifunctional components in closer proximity would fare in an analogous 1,2-addition reaction.

2.1 Design and synthesis of a novel library of catalysts: C-5' substituted systems

2.1.1 Rationale

Over the past 7 years, cinchona alkaloid derivatives incorporating a C-9-(thio)urea component (*e.g.* molecules **119-128**) have emerged as powerful catalysts for a range of asymmetric transformations susceptible to the influence of general acid-base catalysis (Section 1.5.1). While the success of these systems is undoubtedly related to the proximity of the mutually compatible bifunctional components in a well-defined chiral environment, from a design perspective, one is limited in what can be achieved in terms of tunability. While the (thio)urea component can be modified/replaced (as elegantly demonstrated by Rawal for example¹⁴¹), the relative positioning of the nucleophile- and electrophile-activating components (a key feature of any bifunctional catalyst) remains relatively fixed in all such systems. Therefore if the stereoelectronic demands of a particular general acid/base catalysed reaction happen not to overlay neatly with the distance between the C-9 substituted catalyst's bifunctional components, it is unlikely that any amount of

modification of the (thio)urea substituent will result in efficient catalysis. With this in mind, and inspired by Hiemstra's findings, we became interested in developing catalysts which retain the essential elements of the successful bifunctional system **147**, yet in which the distance between the bifunctional components has been varied.

As mentioned in Section 1.6.2, the installation of catalytically useful functionalities at C-5' have not been extensively explored yet. Jørgensen demonstrated interesting catalytic activities of alkaloids **161-163** in Michael additions and amination reactions (Section 1.6.2). However, these studies did not have any impact on the research work presented in this thesis, since it was postulated that the C-5' hydrazide group of these systems was not directly involved in the catalytic process.

We therefore embarked upon the development of a novel library of cinchona alkaloids substituted at C-5' with variable functionalities capable of hydrogen-bond donation. We speculated that positioning the hydrogen-bond donating group at C-5' (instead of the customary C-9 or C-6' position) would place it closer to the quinuclidine base ring, leading to a 'tighter activation pocket' that may provide a better fit for the transition states of 1,2-additions (Figure 2.1).

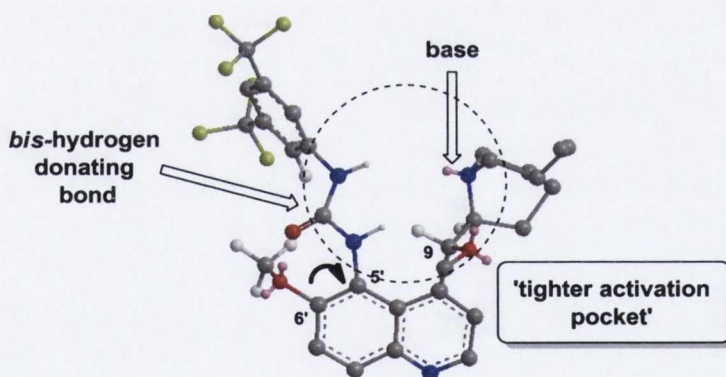


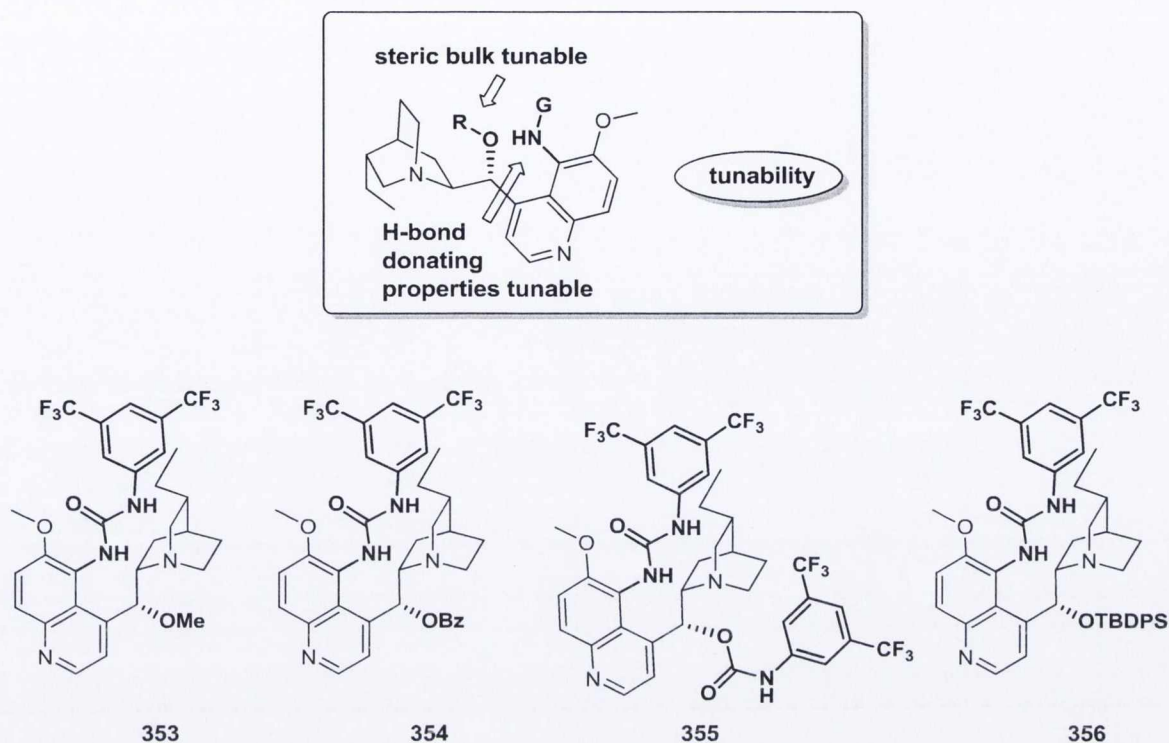
Figure 2.1 Structure of the novel C-5'-substituted catalytic systems

With this aim, we decided to install an amine functionality at C-5' on the dihydroquinine scaffold, offering a wide range of possibilities to readily modify the properties of the hydrogen-bond donating group.

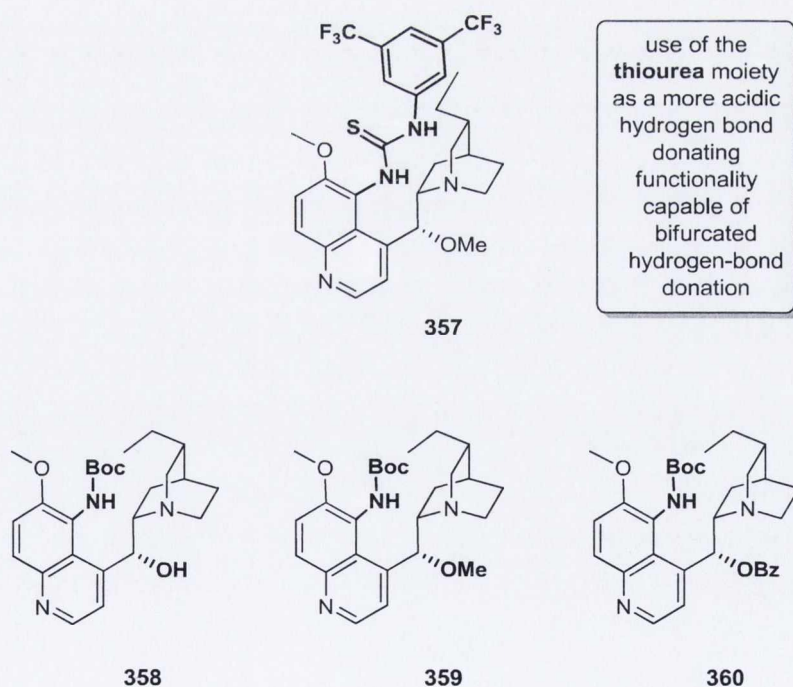
Conformational studies demonstrated that the size of the substituent at the C-9 position of dihydroquinine analogues (*i.e.* alkaloids **58a-c**, Section 1.3.3.1.3) significantly affected the

conformational preferences of the alkaloid derivatives.⁸² Changing the position of the urea moiety from the C-9 to the C-5' position conveniently rendered the C-9 hydroxyl group available for modifications (with a view towards conformational control). Encouraged by Deng's results obtained with his fruitful library of C-9 derivatives (*i.e.* catalysts **97-106** Section 1.4.3 and alkaloids **148-152** Section 1.5.2), we wished to design systems incorporating variable substituents at C-5' and C-9, so that the steric requirement and electronic/hydrogen bond donating properties of the catalyst could be systematically modulated. We proposed that the steric bulk variation of the functionalities at these positions (C-5' and C-9) could lead to more conformationally restricted catalysts capable of improved performance, providing alkaloids with various 'activation pocket' sizes and consequently with different catalytic profiles.

Thus, to test our theory, a selection of alkaloids that could serve as potential promoters were designed (Figure 2.2). The preparation of dihydroquinine derivatives **353-360**, possessing different C-9-substituents, would provide catalysts with varied degrees of framework rigidity. It seemed also opportune to synthesise the thiourea-based dihydroquinine analogue **357** in order to determine whether or not this more acidic hydrogen-bond donor would be superior to its urea counterpart in the specific promotion of the Henry reaction. Finally, to evaluate the effect of the use of a bifurcated *bis*-hydrogen bonding system on catalysis (*i.e.* **353-356**), we wished to prepare alkaloids **358-360** possessing a *mono*-hydrogen bond donor at the C-5' position.



variation of the **size of the substituent at the C-9 position** to vary the rigidity of the alkaloid's framework



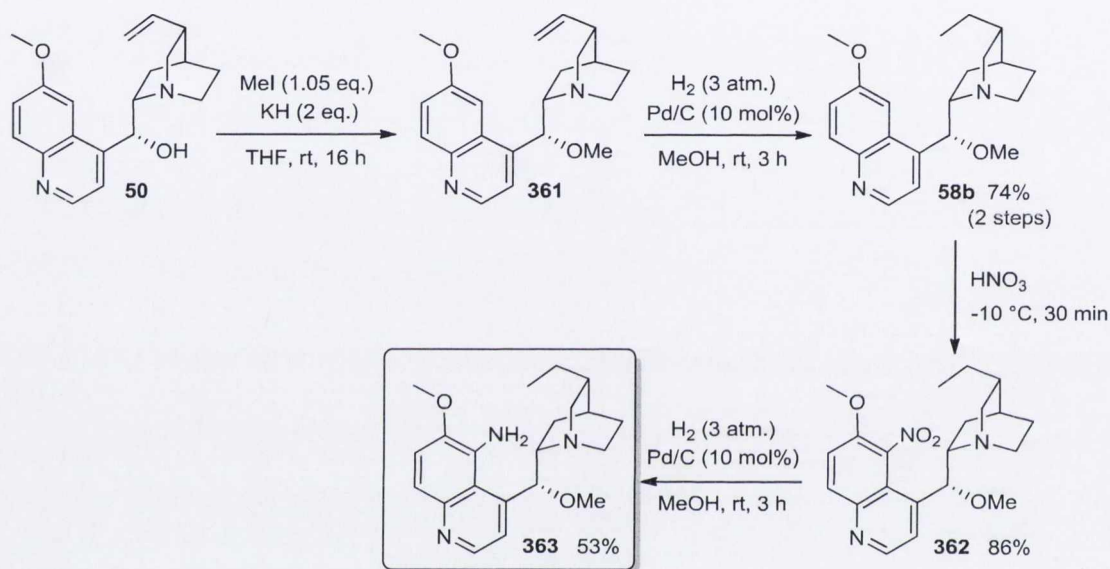
installation of a **mono-hydrogen bond donating functionality** in conjunction with the **variation of the substituent at the C-9 position**

Figure 2.2 Readily tunable C-5' substituted cinchona alkaloid organocatalysts: targets

2.1.2 Synthesis of the library

2.1.2.1 Preparation of the C-9 methoxy-substituted catalysts **353**, **357** and **359**

From a retrosynthesis analysis, it was speculated that catalysts **353**, **357** and **359** could be obtained from the key intermediate amino-derivative **363**. The synthetic route utilised to produce this intermediate is outlined in Scheme 2.1.

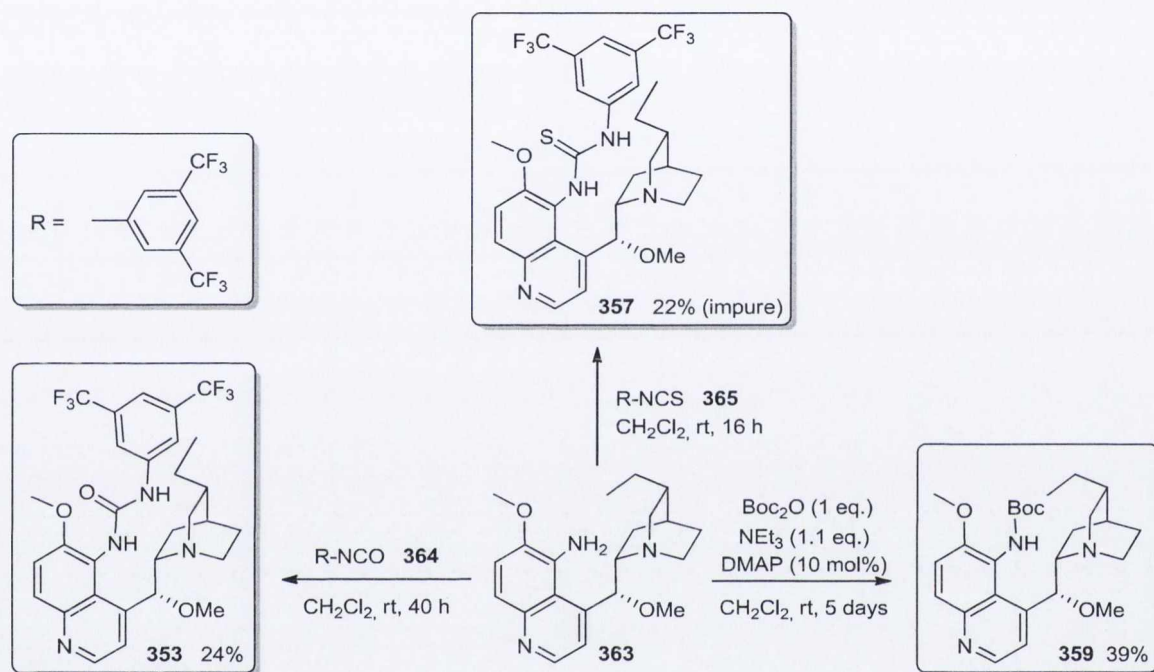


Scheme 2.1 Synthetic route towards the preparation of the key amino-derivative **363**

In the presence of two equivalents of potassium hydride, the inexpensive and readily available quinine (**50**) was alkylated using methyl iodide in THF overnight. To avoid any loss of material during the following nitration step due to side reactions at the vinylic position, it was decided to firstly hydrogenate this alkene. Compound **361** was directly hydrogenated as a crude material, using 10 mol% of palladium on charcoal under a hydrogen atmosphere (3 atm.) in methanol for 3 h. After purification by column chromatography, the C-9-modified dihydroquinine **58b** was obtained in 74% yield over two steps. Employing a synthetic methodology described by Giemsa and Halberkann in 1920,²⁰⁷ **58b** was then treated with fuming nitric acid at -10 °C, producing **362** in 86% yield after 30 min. The nitro group of **362** was subsequently reduced by hydrogenation, using 10 mol% of palladium on charcoal, to afford the marginally stable **363** (which can be stored in the dark at -6 °C) in moderate yield. This reaction requires the use of 3 atm. of

hydrogen; preliminary experiments demonstrated that hydrogenation at atmospheric pressure produced **363** only in poor yields.

Once available, **363** could be treated with 3,5-bis(trifluoromethyl)phenyl isocyanate (**364**) at ambient temperature to afford the targeted catalyst **353** after purification by column chromatography (Scheme 2.2).



Scheme 2.2 Convergent synthesis of catalysts **353**, **357** and **359**

In parallel, the C-5' amino derivative **363** was reacted with isothiocyanate **365** (1.05 eq.) at ambient temperature overnight (Scheme 2.2). Analysis of the crude mixture by ^1H NMR spectroscopy after 16 h confirmed the formation of **357**. However, despite the various attempts undertaken to purify this compound (using column chromatography, recrystallisation techniques and preparative TLC), only degraded material could be isolated, shedding some light on the alkaloid's unstability. We reasoned this to be possibly due to the hydrolysis of the thiourea functionality catalysed by the proximal general base (*i.e.* the quinuclidine ring). Such an unstable molecule would not be of particular interest for organocatalytic purposes. For this reason its preparation was abandoned.

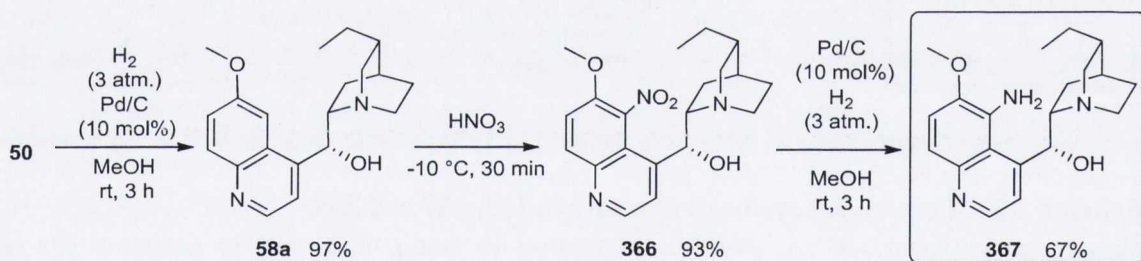
Subsequently, **363** was added to Boc_2O at room temperature in the presence of triethylamine (NEt_3 , 1.3 eq.) and 10 mol% of dimethylaminopyridine (DMAP) used as a

catalyst (in the absence of DMAP no trace of the expected product was found), providing **359** in 39% yield (Scheme 2.2).

This synthetic strategy was found very convenient since different alkaloids of interest (possessing potential catalytic abilities) were accessible in only one step from the key intermediate. This intermediate could be synthesised on 8 g scale in good yields (Scheme 2.1). However, the last step of each catalyst synthesis (Scheme 2.2) was marked by low conversions. This may be due to the significant hindrance around the amino group, surrounded by the methoxy group at C-6' and the ether substituent at C-9 (in certain conformations possible to adopt by the alkaloid).

2.1.2.2 Synthesis of alkaloids **354**, **355**, **356**, **358** and **360**

The most effective method to synthesise these alkaloids was to find a key intermediate from which all the targeted alkaloids could be prepared by a convergent synthetic strategy: dihydroquinine derivative **367**, possessing an hydroxyl group at the C-9 position and an amino functionality at the C-5' (Scheme 2.3).

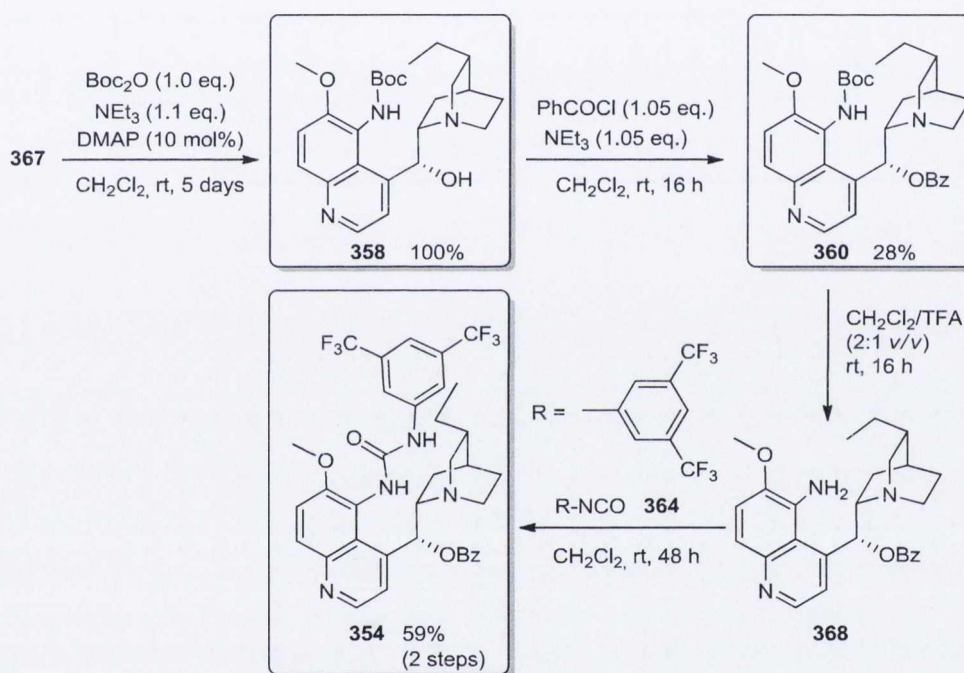


Scheme 2.3 Efficient synthesis of key intermediate **367**

The key intermediate **367** was conveniently prepared from inexpensive quinine (**50**), using the same synthetic route as for the preparation of **363** (Scheme 2.1), in only three steps and 60% overall yield. Quinine was hydrogenated for 3 h under 3 atm. of hydrogen in the presence of 10 mol% of palladium on charcoal. The resulting dihydroquinine (**58a**) was then directly engaged in the nitration step without further purification. Alkaloid **58a** was treated with fuming nitric acid for 30 min at -10 °C to obtain **366** in 93% yield after selective precipitation from ethyl acetate. Subsequent hydrogenation of the nitro-substituted intermediate, using the same reaction conditions as these outlined above,

furnished the amino derivative **367** in 67% yield after another selective precipitation from ethyl acetate.

With the intermediate **367** in hand, the synthesis of the last class of targeted dihydroquinine derivatives began. Alkaloid **367** was reacted with Boc anhydride in the presence of NEt₃ and DMAP (Scheme 2.4), affording the Boc-protected dihydroquinine derivative **358** in quantitative yield after 16 h. This compound was then treated with benzoylchloride (1.05 eq.) and NEt₃ (1.05 eq.) to produce potential catalyst **360** in 28% yield.

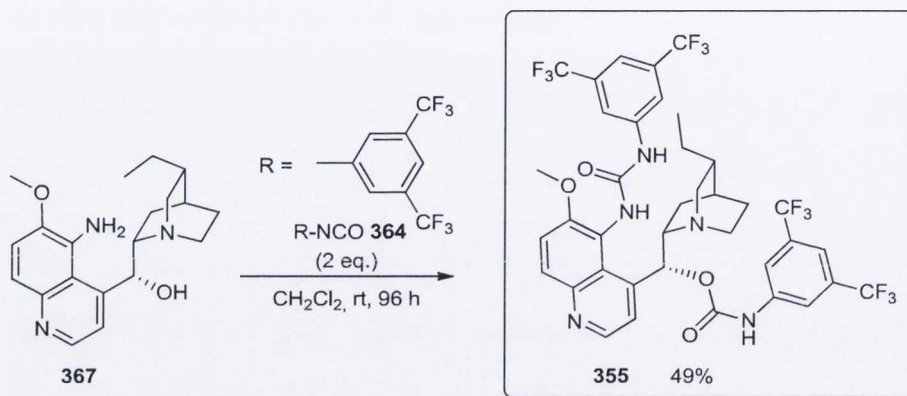


Scheme 2.4 Preparation of the dihydroquinine derivatives **354**, **358** and **360**

This benzoylation process was not efficient, leading to the production in larger amount (60% yield) of a side product that was suspected to result from the double benzoylation of the C-9 hydroxyl group and the C-5' amide functionality. This side product, exhibiting no potential catalytic properties, was not investigated further. Despite the substantial loss of material, it was decided to continue this synthetic route since it would conveniently lead to the generation of three of our targets (**354**, **358** and **360**) in one synthetic sequence. Thus, **360** was deprotected using trifluoroacetic acid (TFA), leading to the amino derivative **368**. In the final step, this intermediate was reacted with the isocyanate **364** in order to provide

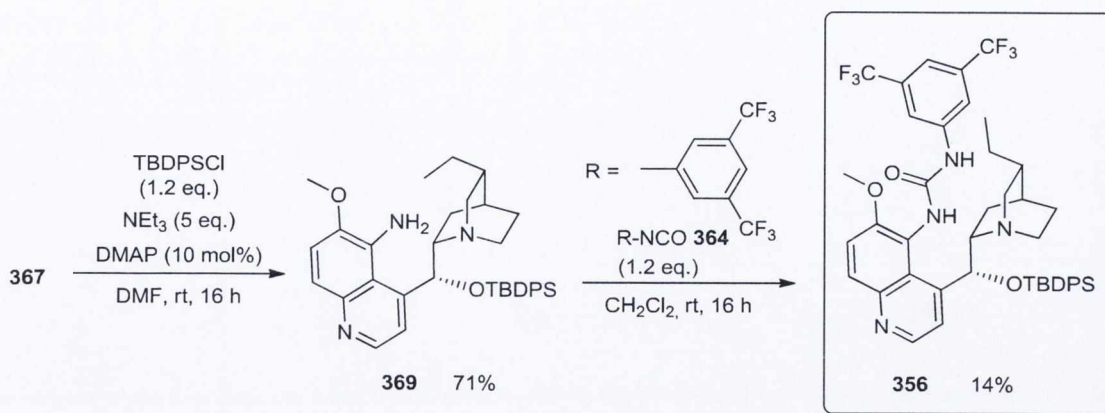
the desired catalyst **354** in 59% yield (over the last two steps) after purification by column chromatography.

Subsequently, the facile synthesis of the C-9-carbamoyl-based **355** was achieved in moderate yield (49%, Scheme 2.5), *via* the reaction of **367** with 2 equivalents of isocyanate **364**.



Scheme 2.5 Synthesis of the C-5'-urea-based C-9-carbamoyl-modified derivative **355**

To finish our first library of cinchona alkaloid derivatives, we directed our effort towards the synthesis of dihydroquine analogue **356**, which is characterised by an augmented steric bulk at the C-9 position (Scheme 2.6). The direct silylation of **367** was attempted to form the silyl ether **369**, using 1.2 equivalents of *tert*-butylchlorodiphenylsilane (TBDPSCl) in the presence of NEt_3 (5 eq.) and a catalytic amount of DMAP (10 mol%) in DMF. Thus, **369** was successfully prepared in 71% yield after purification by column chromatography. It should be noted that this compound was also accessible, in slightly lower yield (52%), by treatment of **367** with potassium hydride (2 eq.) in THF followed by the addition of the same TBDPSCl reagent (1.2 eq.) in the reaction medium. A subsequent addition of the amino derivative **369** to the isocyanate **364** at ambient temperature provided the urea-based catalyst **356** after purification by column chromatography.



Scheme 2.6 Synthesis of C-5'-urea-C-9-sylilated dihydroquinine derivative **356**

2.2 The Henry reaction: preliminary investigations

Intrigued by the considerably narrow scope of the organocatalysed nitroaldol reaction (only the use of aromatic aldehydes was described in the literature when using a ‘metal free’ process) and driven by a desire to expand the scope of this challenging transformation, we wished to evaluate the catalytic performance of our new class of cinchona alkaloids in the Henry reaction of trifluoromethylketone substrates. This reaction is synthetically useful, generating trifluoromethylated^{159,208} chiral products which incorporate a quaternary stereocenter. We postulated that these C-5'-substituted dihydroquinine derivatives would act as efficient promoters for some Henry reactions whose transition state demands may be beyond the abilities of existing bifunctional C-9 or C-6' (thio)urea-based catalytic systems.

Focusing our attention on the reaction of ketone **207** (Table 2.1) with nitromethane (**89**), we decided first to assess the catalytic performance of the parent alkaloids quinine (**50**)/quinidine (**51**) and of the benchmark C-9-*epi*-thiourea derivatives **123** and **124** (prepared by Dr. Aldo Pesciulli) in this transformation (Figure 2.3). The results of these preliminary experiments are tabulated below (Table 2.1). The reaction conditions initially decided upon were genuinely low loadings of catalyst (2 mol%), 10 equivalents of nitromethane (**89**) and 1 equivalent of α,α,α -trifluoroacetophenone (**207**), in THF at ambient temperature. The parent alkaloids quinine (**50**) and quinidine (**51**) proved efficient catalysts of the reaction, however the β -nitroalcohol product **216** was formed with very low levels of enantiomeric excess (entries 1 and 2). The benchmark C-9-*epi*-thiourea-

modified catalysts **123** and **124** also promoted the smooth formation of **216**, with significantly higher levels of enantiomeric excess (*ca.* 50% *ee*, entries 3 and 4).

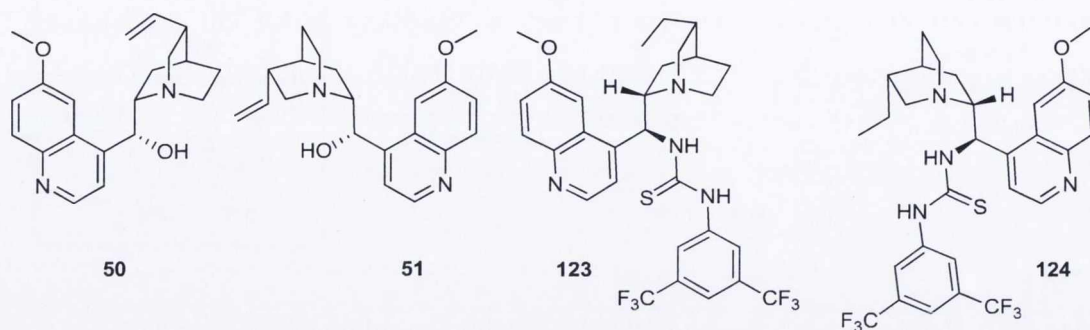
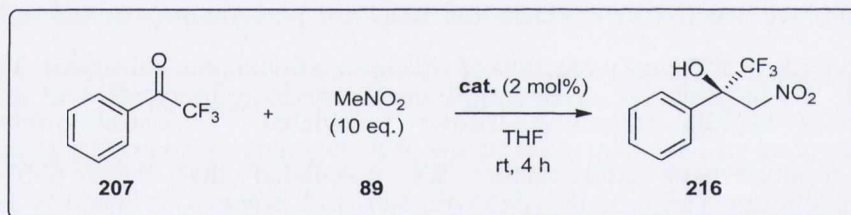


Figure 2.3 Catalysts evaluated as promoters of the addition of **89** to **207**

Table 2.1 Preliminary evaluation of the parent cinchona alkaloids and the thiourea-modified derivatives as promoters for the Henry reaction involving ketone **207**



entry	cat.	yield (%) ^a	<i>ee</i> (%) ^b
1	50	70	6
2	51	96	5
3	123	>98	-54
4	124	76	52

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

With these results in hand, the next step was to evaluate the C-5'-modified cinchona alkaloid derivatives (Figure 2.4) as promoters for the same 1,2-addition (Table 2.2).

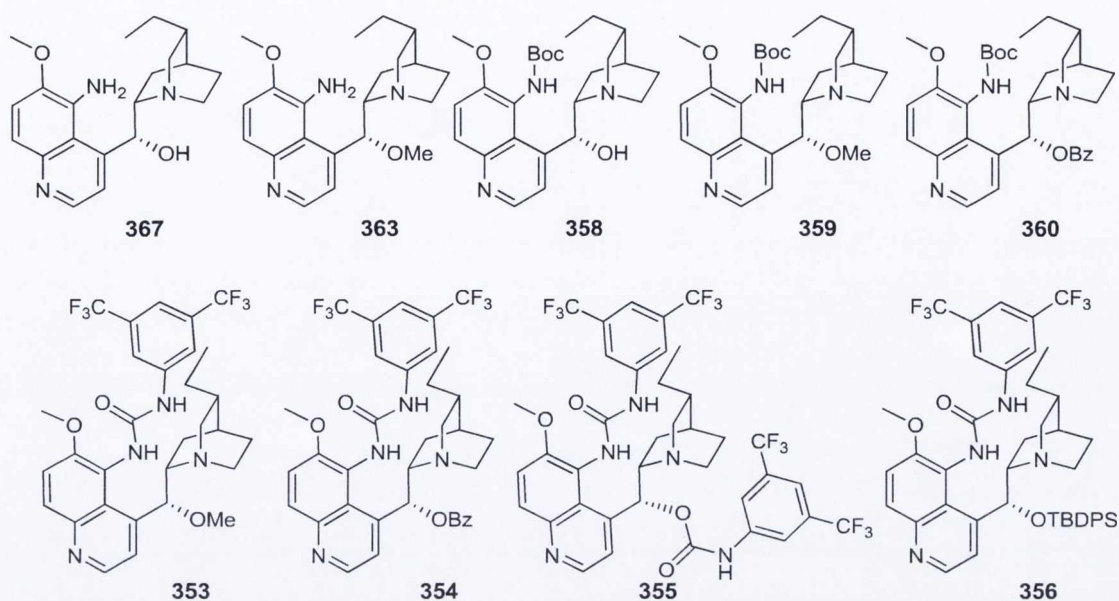
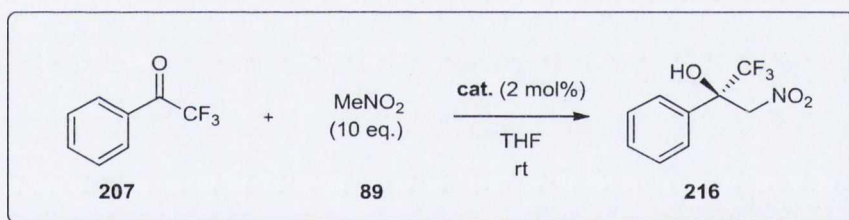


Figure 2.4 C-5' modified alkaloids evaluated in the addition of **89** to **207**

Table 2.2 Evaluation of the catalytic performance of the C-5' substituted dihydroquinine derivatives **353-360**, **363** and **367** in the Henry reaction



entry	cat.	time (h)	yield (%) ^a	ee (%) ^b
1	367	18	88	7
2	363	18	75	13
3	358	22	22	10
4	359	22	91	20
5	360	64	22	7
6	353	21	66	39
7	354	21	2	nd ^c
8	355	21	>98	62
9	356	21	93	10

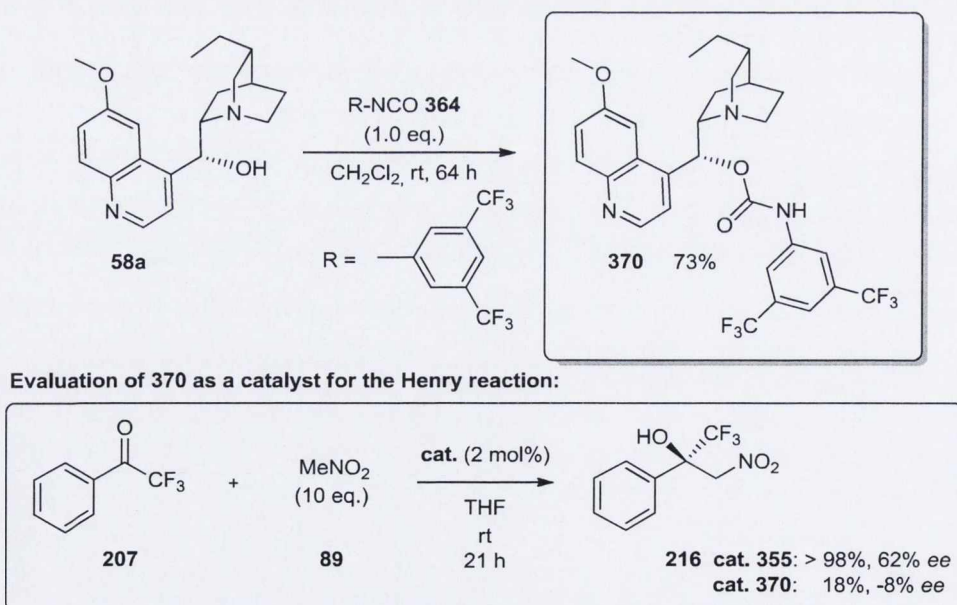
^aDetermined by ¹H NMR spectroscopy using an internal standard.

^bDetermined by CSP-HPLC. ^cnd: not determined.

The C-5'-amino-dihydroquinine **367** catalysed rapid 1,2-addition relatively unselectively, as did its C-9 methylated analogue **363** (entries 1 and 2 respectively). Conversion of the C-5'-amino group to a Boc moiety (to augment its hydrogen-bond donating characteristics) led to significant improvement in catalyst performance (entries 3 and 4); however, product *ee* remained modest. Benzoylation of **358** at C-9 (*i.e.* catalyst **360**, entry 5) resulted in a dramatic loss of catalyst activity.

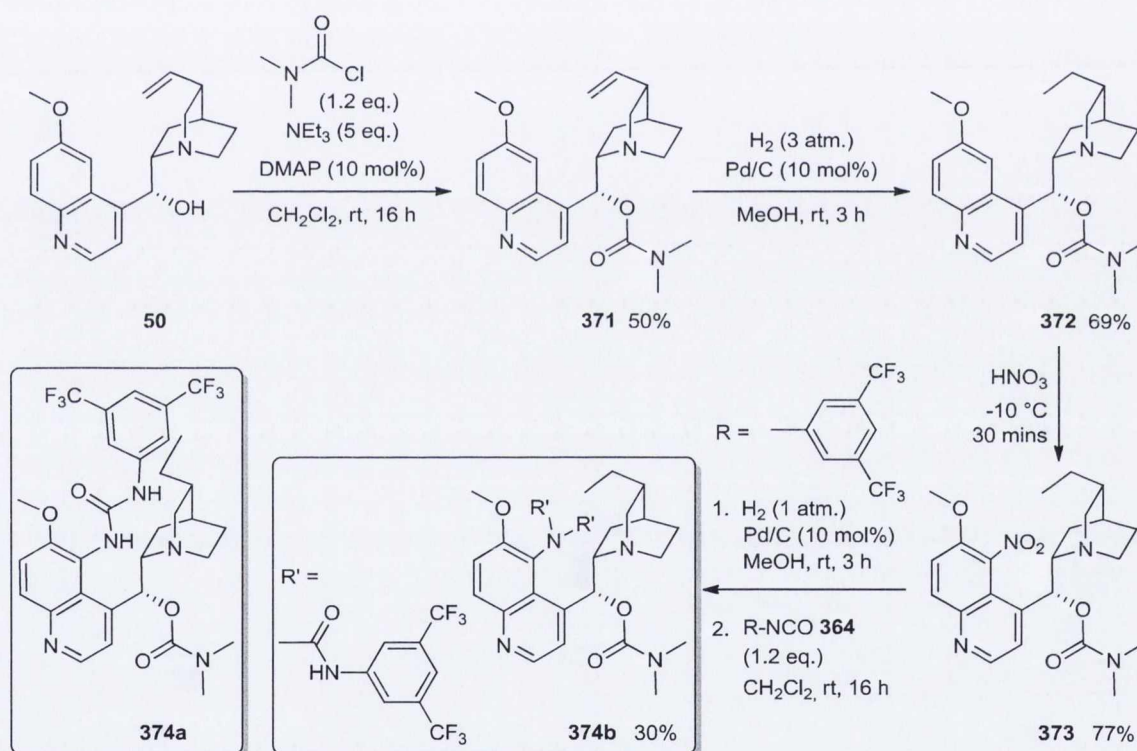
Gratifyingly, the conversion of alkaloid **363** to the corresponding urea derivative **353** resulted in a catalyst capable of promoting the reaction with significantly higher enantioselectivity (39% *ee*, entry 6), while again installation of a benzoyl unit at C-9 proved unhelpful (*i.e.* catalyst **354**, entry 7). Given the deleterious effect of acylation at C-9 on catalyst performance, we were surprised to observe that the C-9 carbamoyl derivative **355** possessed excellent catalytic activity and could promote the reaction with superior product enantiomeric excess (quantitative conversion, 62% *ee* at 2 mol% catalyst loading, entry 8) to that obtained using any of the other catalysts in this study. In contrast, the silyl ether derivative **356** promoted the smooth formation of **216** with almost no asymmetric induction (10% *ee*, entry 9).

To shed some light on the influence of the carbamoyl group on catalyst efficacy we prepared **370**, an analogue of **355** devoid of the C-5' urea (Scheme 2.7).



Scheme 2.7 Synthesis of carbamate **370** and its evaluation as a catalyst for the enantioselective synthesis of β -nitroalcohol **216**

Dihydroquinine (**58a**) was reacted with 1 equivalent of isocyanate **364** for 64 h to give **370** with 73% yield after purification by column chromatography. This catalyst was both relatively inactive and unselective (Scheme 2.7). It also promoted the formation of the opposite enantiomer to that observed in the reaction mediated by **355**. We would therefore suggest that the superiority of **355** to **353** and the inferiority of **370** to **355** signaled that the C-9 carbamoyl moiety was not directly involved in the catalysis by hydrogen-bond donation. It was obvious however, that its presence in conjunction with the C-5' urea was advantageous. Since different enantiomers were obtained when the synthesis of β -nitroalcohol **216** was catalysed by either **370** (-8% *ee*) or **355** (62% *ee*), we wished to prepare the analogue **374a** (possessing a C-9 carbamoyl functionality incapable of hydrogen bond donation) with a view to avoiding any disadvantageous side catalysis (Scheme 2.8).



Scheme 2.8 Synthesis of the C-9 carbamoyl-functionalised cinchona alkaloid derivative **374b** and its evaluation in the promotion of the Henry reaction with **207**

Surprisingly, the devised synthetic pathway (*via* the generation of the C-9-carbamoyl-functionalised alkaloids **371** and **372**, followed by the preparation of the C-5'-nitro substituted **373**) led to the formation of the *N*-acyl urea **374b** as the major product. This catalyst promoted the nitroaldol reaction with a respectable enantioselectivity, albeit at a considerably slower rate than **355** (Scheme 2.8).

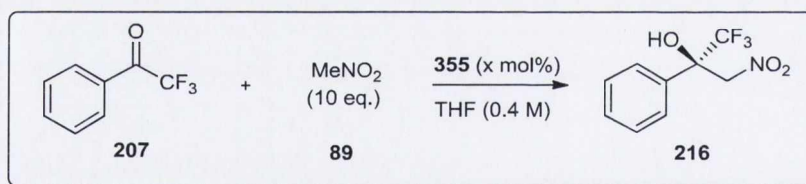
Since **370** and **374b** failed to promote the synthesis of β -nitroalcohol **216** in satisfying yields, we identified **355** as the optimum catalyst for the studied reaction.

2.3 The Henry reaction: optimisation of the conditions

With the identification of the best catalyst complete, we next proceeded to optimise the reaction conditions. As demonstrated by Wynberg *et al.*,⁸⁰ a careful determination of these conditions is important to achieve satisfying enantiocontrol of the transformation (Section 1.3.3.1.2).

We first decided to examine the effect of lower temperatures on catalysis efficacy (Table 2.3).

Table 2.3 Optimisation of the reaction conditions: the effect of temperature



entry	temp. (°C)	x (mol%)	time (h)	yield (%) ^a	ee (%) ^b
1	rt	2	21	>98	62
2	-25	2	21	77	87
3	-50	5	21	54	91
4	-30	10	21	65	88

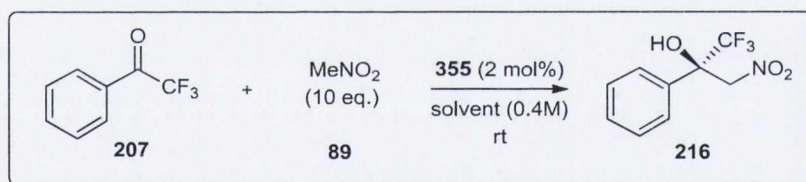
^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

The results previously obtained at ambient temperature are shown for comparison purposes (entry 1). Conducting the reaction at -25 °C resulted in the formation of **216** with

significantly higher enantiocontrol (87% *ee*, entry 2). Lowering the temperature to -50 °C led to excellent enantioselectivity (91% *ee*, entry 3), however at the expense of the yield, even using a 2.5-fold increase in catalyst loading. Attempting the reaction at -30 °C in conjunction with a 10 mol% catalyst loading did not provide a satisfying result regarding the rate of the reaction (entry 4). Hence, -25 °C seemed to be the temperature of choice to pursue our investigation.

In an attempt to improve our protocol, a solvent screen was then completed. Undertaking this assessment using a fixed concentration (0.4 M) of the activated ketone in the reaction medium (solvent + nitromethane), it was found that the use of MTBE as the reaction medium facilitated the 1,2-addition, leading to similar yield and levels of product *ee* to those observed when using THF (entries 1-2, Table 2.4). Product levels of enantiomeric excess diminished when the reactions were conducted in either toluene or CH₂Cl₂ (entries 3-4). MTBE, which was more convenient to use, was chosen as the optimum solvent for this reaction.

Table 2.4 Determination of the optimum solvent



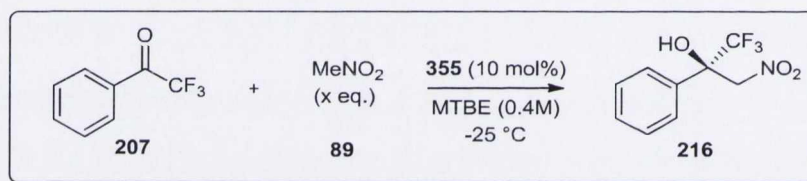
entry	solvent	time (h)	yield (%) ^a	<i>ee</i> (%) ^b
1	THF	21	>98	62
2	MTBE	21	99	56
3	toluene	21	90	12
4	CH ₂ Cl ₂	21	80	10

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

We then focused on the influence of the polarity of the reaction medium. The conditions used so far involved the employment of a significant excess of nitromethane, which represented one sixth of the volume of liquid present in the entire reaction (entry 1, Table

2.5). Concerned that some of the catalyst might be protonated (and so inactivated) under such conditions, loadings of the nucleophile were lowered (7 and 5 equivalents). In an attempt to avoid a drop of the product yield under such reaction conditions, 10 mol% of alkaloid **355** was employed in these reaction. Gratifyingly, the use of 7 equivalents of nitromethane at -25 °C led to a substantial improvement in selectivity (90% *ee*, entry 2) and a good yield. However, the β -nitroalcohol **216** could only be obtained in 60% yield when 5 equivalents of nitromethane were involved in the reaction (91% *ee*, entry 3). As predicted, **216** was generated with excellent yield but with an unsatisfactory enantioselectivity (77% *ee*, entry 4) when a large amount of nitromethane was used for the reaction (16 eq.).

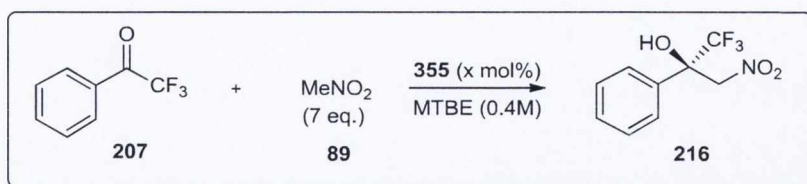
Table 2.5 Influence of the polarity of the medium on catalysis



Entry	x (eq.)	time (h)	yield (%) ^a	<i>ee</i> (%) ^b
1	10	21	70	84
2	7	21	69	90
3	5	21	56	91
4	16	21	93	77

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

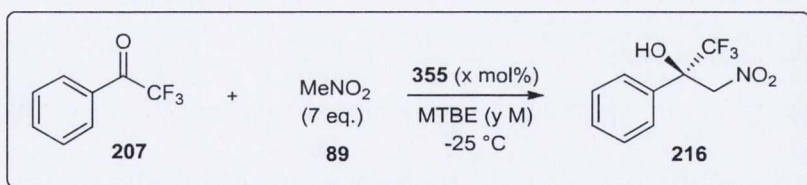
Employing 7 equivalents of nitromethane in conjunction with the use of 10 mol% catalyst and a longer reaction time (72 h) resulted in the production of **216** in moderate yield (72%) and in 90% *ee* (entry 1 Table 2.6). Ketone **207** underwent faster conversion when increased catalyst loading (20 mol%) was utilised (81% after 72 h, entry 2) at -25 °C, albeit with disappointing enantioselectivity (<90% *ee*). We were pleased with the result recorded in entry 3: product **216** was obtained with acceptable yield (62%) and excellent enantioselectivity (91%) when the reaction was conducted at -30 °C with 10 mol% of alkaloid **355**. However, utilising increased catalyst loading (20 mol%) at -30 °C did not lead to a better product *ee* to that obtained at -25 °C (entry 4).

Table 2.6 Variation of the catalyst loading and the temperature

Entry	x (mol%)	temp.	time (h)	yield (%) ^a	ee (%) ^b
1	10	-25	72	72	90
2	20	-25	72	81	88
3	10	-30	72	62	91
4	20	-30	72	70	88

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

No other alteration of the reaction conditions were found to provide better yields while maintaining enantioselectivities above 90% *ee*. The best condition set available thusfar is shown in entry 1 (Table 2.7). Increasing the concentration of the reaction medium (0.6 M) provided excellent conversion of **207** (89% yield, entry 2) but again with less enantiocontrol (85% *ee*).

Table 2.7 Influence of the concentration of the reaction medium on catalysis

Entry	x (mol%)	y (M)	time (h)	yield (%) ^a	ee (%) ^b
1	10	0.4	72	72	90
2	10	0.6	72	89	85
3	5	0.6	72	82	86
4	20	0.2	72	43	92

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

Using a smaller amount of catalyst (5 mol%) with the same high concentration (0.6 M, entry 3) did not lead to better asymmetric induction (86% *ee*). Alternatively, the use of more diluted conditions (0.2 M, entry 4) with a higher catalyst loading (20 mol%) provided the best enantiocontrol obtained thus far, however with a yield too low to be acceptable (43%).

To conclude, the reaction conditions used in the experiment described in entry 3 of Table 2.6 were identified as the optimum conditions for the nitroaldol reaction of ketone **207** with nitromethane (**89**) catalysed by **355**.

2.4 The Henry reaction: Reaction scope

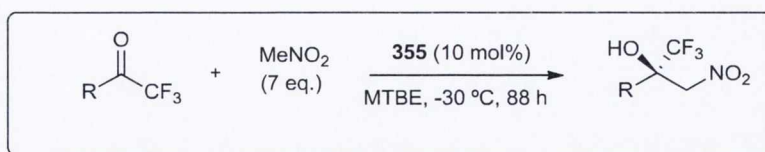
2.4.1 The use of various trifluoromethylketones as electrophiles

With a readily available organocatalyst and optimised reaction conditions leading to the highly enantioenriched Henry adduct **216**, our attention turned to the key question of the reaction scope. With this aim, a selection of commercially available trifluoromethylketones, with different steric and electronic characteristics, were reacted with nitromethane (**89**) in the presence of alkaloid **355** (Table 2.8).

We were pleased to find that *p*-fluoro- α,α,α -trifluoroacetophenone (**211**) could be converted to the β -nitroalcohol **220** in good yield (78%) and excellent enantiomeric excess (90% *ee*, entry 1). The *p*-bromo and *p*-methyl analogues **375** and **377** (entries 2-3) afforded **376** and **378** in slightly lower *ee* (83-85% *ee*) but still with satisfactory yields (69-77%). The use of more hindered *m*-fluoro- α,α,α -trifluoroacetophenone **379** (entry 4) led to the production of the corresponding adduct in comparable yields (76%) as the one obtained with the *p*-isomer **211** (entry 1), however with somewhat less selectivity (85% *ee*). Disappointingly, applying the optimised protocol to sterically demanding **381** did not lead to any product formation (entry 5).

The thienyl substituted alcohol **222** was formed in 82% *ee*, which, while lower than that obtained using non-heterocyclic acetophenone derivatives, represented a significant improvement over the previous literature benchmark (Section 1.7.2.2)¹⁶⁶ for substrate **213** (entry 6).

Table 2.8 Henry reactions using trifluoromethylketones under optimised conditions



entry	ketone	product	yield (%) ^a	ee (%) ^b
1	 211	 220	78	90
2	 375	 376	77	85
3 ^c	 377	 378	69	83
4 ^d	 379	 380	76	85
5 ^e	 381	 382	0	-
6 ^c	 213	 222	85	82
7	 215	 224	73	95
8	 214	 223	78	96
9	 383	 384	70	96

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC. ^cReaction at -25 °C. ^d7 days reaction time. ^eReaction at ambient temperature.

Gratifyingly, alkyl trifluoromethylketones (*i.e.* **214**, **215** and **383**) – a substrate class which has more proven problematic in previous studies¹⁶⁶ – was found particularly susceptible to the influence of catalyst **355**. Good yields (70-78%) and excellent levels of product *ee* ($\geq 95\%$) were recorded in all cases (*i.e.* β -nitroalcohols **223**, **224** and unprecedented **384**, entries 7-9).

Alkaloid **355** provided better results (in terms of both selectivity and activity) in the nitroaldol reaction of ethyl-substituted trifluoromethylketone **215** (73%, 95% *ee*, entry 7) than the catalytic systems previously described in the literature (*i.e.* metal-free catalyst **206** (67%, 93% *ee*) and metal(ion)-based catalyst **189** (55%, 85% *ee*, Section 1.7).^{161,166} The β -nitroalcohol **223** was synthesised with an excellent asymmetric induction (96% *ee*, entry 8) which was also superior to the results previously reported in the literature (*i.e.* metal-free catalyst **206** (92% *ee*) and metal(ion)-based catalyst **189** (93% *ee*)).

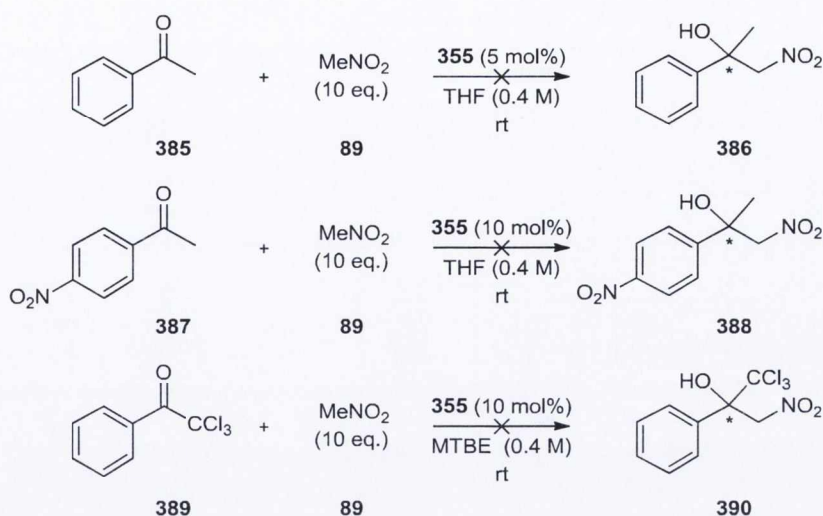
To the best of our knowledge this represents the most enantioselective general process for the catalytic asymmetric Henry reaction involving this substrate class to date.

It should be noted that the absolute configuration of the obtained Henry-adducts was assigned by comparison with the literature specific rotation data^{161,166} and was determined to be *R*.

2.4.2 The use of other electrophiles

Encouraged by such findings, we were curious to evaluate the catalytic profile of the alkaloid **355** in unprecedented nitroaldol reactions.

We first turned our attention towards the use of other (activated and non-activated) ketones (Scheme 2.9). When reacting acetophenone (**385**) with nitromethane (in a ratio 1:10) at room temperature in the presence of **355** (5 mol%), no trace of product could be detected after 112 h by analysis of the reaction mixture *via* ¹H NMR spectroscopy. In an attempt to provide more energy to the reaction, the same mixture was heated at 45 °C for 16 h, which unfortunately did not lead to a better result. The considerably more activated *p*-NO₂-acetophenone (**387**) and trichloromethylketone analogue **389** (prepared by Mr. Simon Curran) were also employed as an electrophile for the Henry reaction catalysed by alkaloid **355**. However, both the reactions failed to deliver any product after 4 days.



Scheme 2.9 Nitroaldol reactions using different electrophiles

Further investigations evaluated the possibility of using benzaldehyde (**184**) and challenging alkyl-substituted aldehydes as substrates in the Henry reaction catalysed by alkaloid **355** (Table 2.9).

Table 2.9 Henry reactions using aldehydes as electrophiles

entry	ketone	product	yield (%) ^a	ee (%) ^b
1			80	77
2			93	4
3			89	9

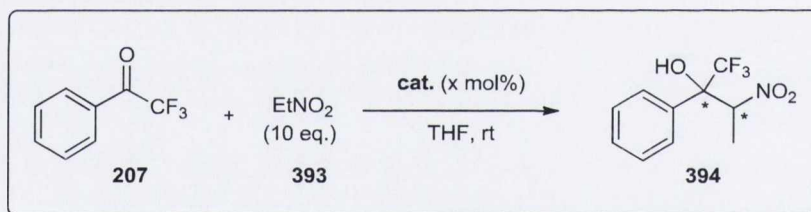
^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC.

Gratifyingly, catalyst **355** was found highly efficient in the Henry reaction of benzaldehyde **184**, producing the targeted adduct **185** with satisfying yield and enantioselectivity using non-optimised conditions (80% yield, 77% *ee*, entry 1 Table 2.9). The same catalyst **355** also proved capable of the smooth conversion of alkyl-substituted aldehydes **391** and **180** (89-93% yield, entry 2 and 3), however with almost no enantiocontrol (4-9% *ee*).

2.4.3 The use of other nucleophiles

To date, no organocatalytic process was described active in the promotion of the asymmetric nitroaldol reaction of other nitroalkanes (than nitromethane) when trifluoromethylketones were involved as the electrophile. We decided to investigate the possibility of carrying out such reactions using the C-5' urea-based catalysts **355**, **353** and C-9 thiourea-based alkaloid **123** (Table 2.10).

Table 2.10 Henry reactions using nitroethane as nucleophile



entry	cat.	x (mol%)	time (h)	yield (%) ^a	d.r. ^a	<i>ee</i> (%) ^b
1	355	10	63	59	2:1	12%
2	123	2	4	17	1.4:1	22%
3	353	5	89	35	7:1	33%

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC.

We were pleased to find that **355** catalysed the synthesis of **394** in moderate yields (59% after 63 h). However, the enantio- and the diastereocontrol were disappointing (entry 1). The use of C-9 thiourea-based **123** did not lead to either better activity or selectivity (entry 2). Interestingly, the addition of nitroethane (**393**) was more enantioselective when promoted by alkaloid **353** (entry 3) than when alkaloid **355** was utilised. The diastereoselectivity and the enantioselectivity obtained with this promoter was encouraging,

considering that this experiment was conducted under non-optimised conditions (7:1 d.r., 33% *ee*). However, this catalyst proved a poor promoter from an activity standpoint. The obtained conversion after 89 h (33%) was judged too low to warrant further investigations.

2.5 Proposed selectivity model for the cinchona alkaloid **355**-catalysed addition of nitromethane to trifluoromethylketones

In order to understand the novel C-5' urea-substituted cinchona alkaloid **355** *modus operandi*, an examination of models and MM2 calculations was undertaken. We firstly proposed that **A** was a sensible representation of the most stable conformation adopted by alkaloid **355** conducive to bifunctional catalysis (Figure 2.5). In this scenario, the left side of catalyst **355** (as drawn) is significantly more crowded than its right side. Therefore, in the pre-transition state **B** (Figures 2.6), the ketone is expected to selectively bind to the catalyst's urea functionality in such a way as to direct its (sterically more demanding)²⁰⁹ trifluoromethyl group towards the less bulky catalyst hemisphere (*i. e.* directed into the solvent). Thus, the nitronate (enol form) would be delivered selectively to the *re* face of the electrophile, while interacting *via* hydrogen bonding with the basic quinuclidine.

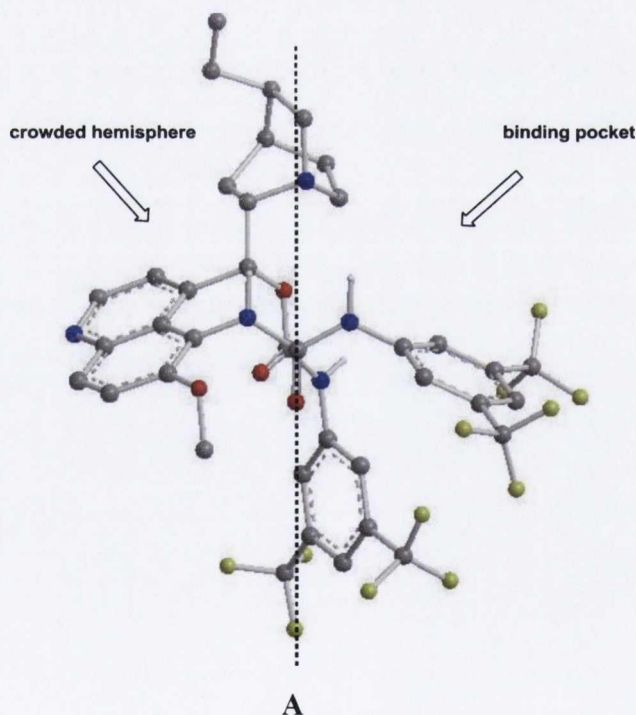
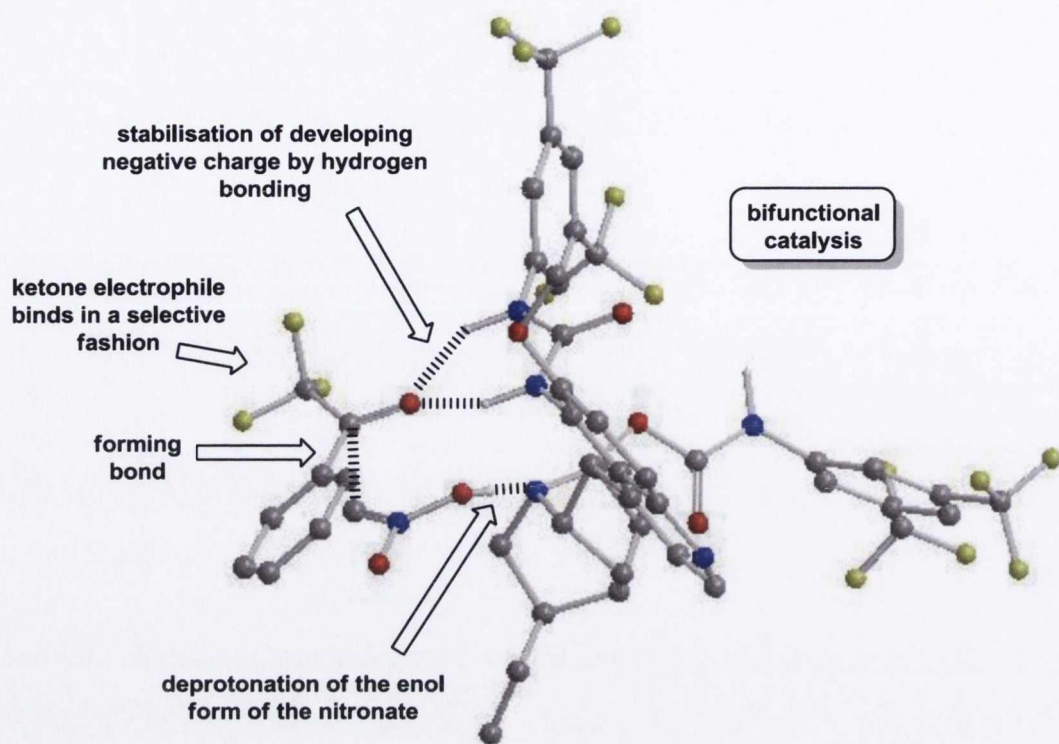
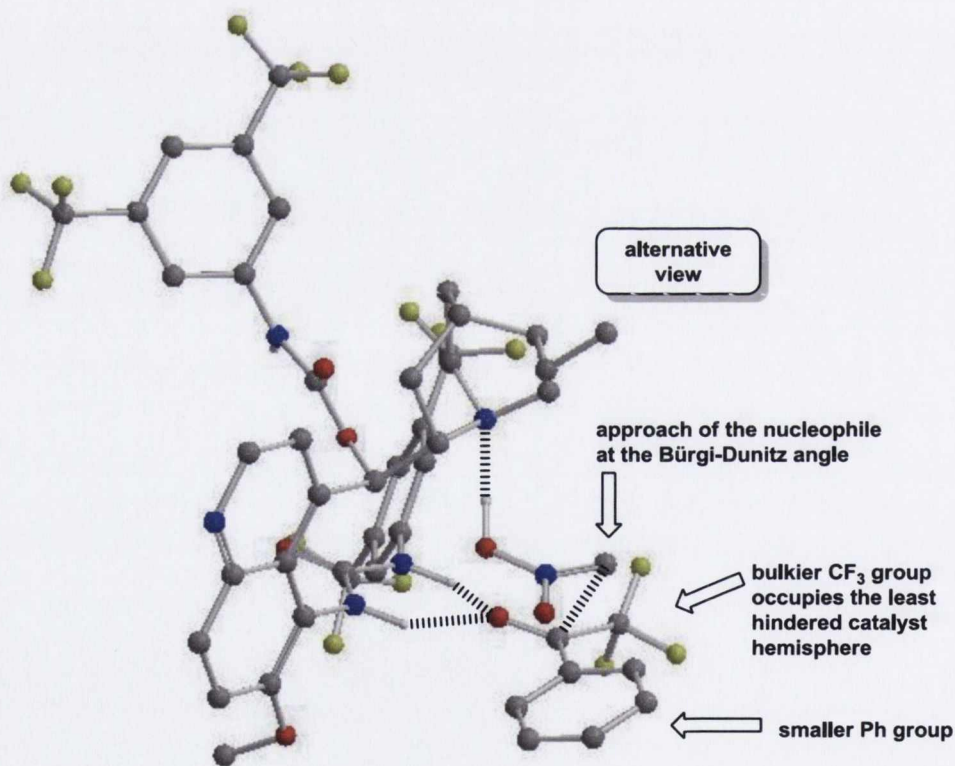


Figure 2.5 Proposed catalytically active conformation adopted by alkaloid **355**



B (right side view)



B (left side view)

Figure 2.6 The alkaloid 355-catalysed Henry reaction between nitromethane (89) and trifluoromethylketone 207: stereochemical rationale

2.6 Conclusion for Chapter 2

In summary, we have developed a new class of cinchona alkaloid-based organocatalysts characterised by the presence of a C-5' urea moiety, which an examination of models suggests is in very close proximity to the quinuclidine ring nitrogen atom. In a challenging nitroaldol reaction process the most useful of these materials (catalyst **355**) outperformed the traditional C-9 thiourea-substituted catalysts **123** and **124** from both catalyst activity and product enantioselectivity standpoints. Under optimised conditions **355** could promote the formation of the products of significant potential synthetic utility possessing quaternary stereocenters in good yields and excellent enantiomeric excess. Alkyl-substituted trifluoromethylketone substrates were converted to the corresponding nitroaldol products with the highest levels of enantiomeric excess recorded in the literature thus far.

3.0 Organocatalysed Michael additions

In the previous Section, we described the design of a library of C-5'-substituted cinchona alkaloid-derived catalysts devised to introduce some variation in the positioning of the key bifunctional components. We demonstrated their usefulness (especially **355**) in the enantioselective promotion of Henry reactions involving nitromethane and trifluoromethylketones. Encouraged by these findings, we were curious to evaluate the potential of this new library of alkaloids as promoters of other asymmetric transformations, and in particular, to determine whether or not these new systems would meet the stereoelectronic requirements of some 1,4-conjugate additions.

3.1 The addition of nitroalkanes to (*E*)- β -nitrostyrene

The Michael-type addition of disubstituted (branched) nitroalkanes to nitroalkenes is a synthetic strategy that can lead to the production of 1,3-dinitro-functionalised molecules possessing two contiguous quaternary stereocenters.²¹⁰ Despite several recent contributions in this area (Section 1.4.3),^{112,211,210} considerable scope for improvement remains, in particular from the nitroalkane structure standpoint.

3.1.1 Preliminary study: The addition of unbranched nitroethane

In 2011, Du *et al.* demonstrated that several cinchona alkaloid derivatives possessing a squaramide hydrogen-bond donor at C-9 (in particular the C2-symmetric alkaloid **159** Figure 1.27) were efficient catalysts for the asymmetric addition of nitroethane to (*E*)- β -nitrostyrene (**47**).²¹² We were intrigued as to how catalysts characterised by bifunctional components in a different spatial arrangement (*i.e.* bearing a hydrogen-bond donor at C-5') would fare in an analogous reaction. Therefore, before investigating the conjugate addition of more challenging disubstituted nitroalkanes, we decided to verify (in a short preliminary study) the efficacy of our C-5'-modified systems (Figure 3.1) in the addition of monosubstituted nitroethane to nitroolefins. The reaction conditions initially decided upon were room temperature, 5 mol% of catalyst loading and 1 equivalent of (*E*)- β -nitrostyrene (**47**) for 10 equivalents of nitroethane (**393**, Table 3.1).

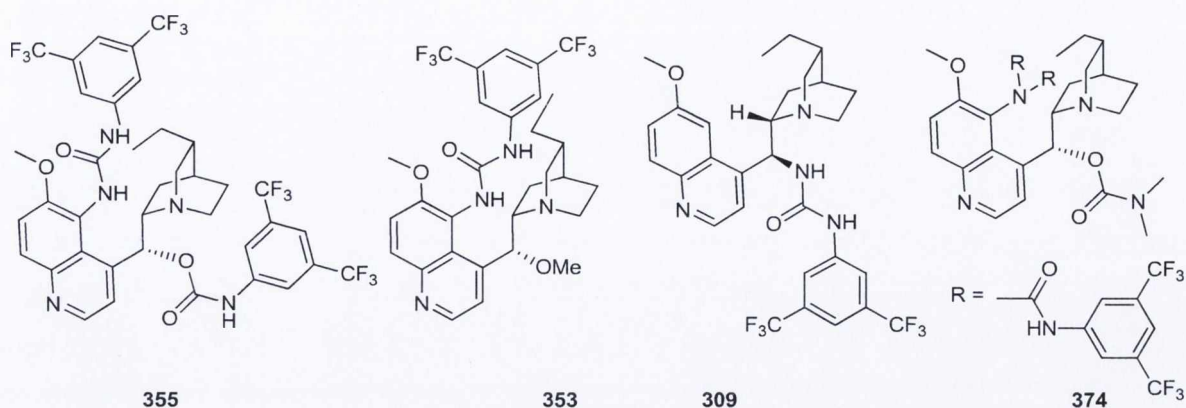
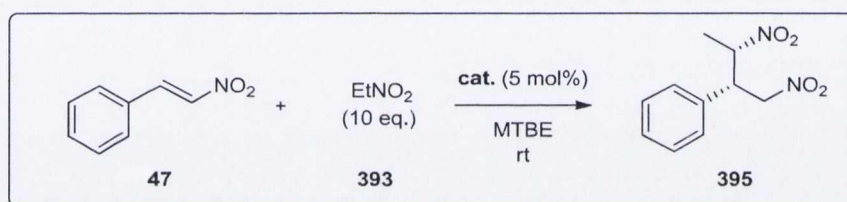


Figure 3.1 Catalysts evaluated in the asymmetric 1,4-addition of nitroethane to **47**

Table 3.1 Evaluation of a selection of dihydroquinine derivatives as catalysts for the Michael addition of nitroethane (**393**) to (*E*)- β -nitrostyrene (**47**)



entry	cat.	time (h)	yield (%) ^a	d.r. ^a	ee (%) ^b
1	355	20	83	1:1.3	86, 70
2 ^c	353	16	98	1:1.3	69, 62
3	309	20	90	1:1.2	-55, -59
4 ^c	374	16	37	1:2.3	54, 72

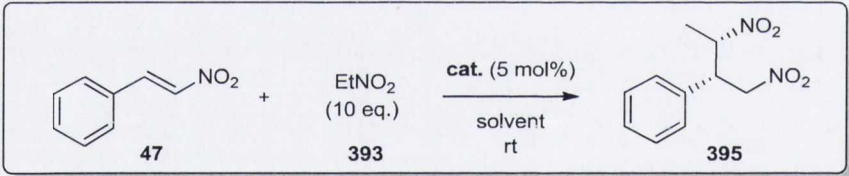
^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC. ^cThe reaction was undertaken using 10 mol% of catalyst.

We were pleased to find that the urea-based dihydroquinine **355** (determined as the best catalyst from our library of C-5'-modified alkaloids in the Henry reaction) held promise as an efficient promoter for the addition of **393** to nitroalkene **47**. Under non-optimised conditions, the Michael adduct **395** could be generated with good yield (83%) and enantioselectivity (86% and 70% *ee*, entry 1, Table 3.1) using only 5 mol% of **355**. However, the diastereoselectivity was disappointing. The C-5'-urea substituted **353** and C-9 urea-based **309** (entries 2-3) also proved active in this addition, however they provided markedly less enantiocontrol. Finally, alkaloid **374** catalysed the reaction with a

respectable enantioselectivity, albeit at a considerably slower rate (entry 4). Since the adduct **395** was obtained with satisfying yield and enantioselectivity when **355** was involved in the catalytic process, this alkaloid was identified as the optimal catalyst system for this addition. The low diastereoselectivity associated with the reaction catalysed by **355** was reasoned to be due to a non-selective binding of the promoter with one of the substrates. However, if both the diastereoisomers of **395** can be isolated with excellent enantioselectivity at the outset of the study, the development of a catalytic system providing such results is still of significant interest.

Next, our attention shifted to the determination of the optimum solvent (Table 3.2). Replacing MTBE (entry 1) by THF was not conclusive, since it led to the formation of **395** with comparable selectivity but lower activity (increased reaction time was required to achieve the same yield 83%, entry 2). In contrast, when the reaction was conducted in toluene, the Michael adduct **395** was obtained quantitatively after only 16 h, however with less efficient asymmetric induction (entry 3).

Table 3.2 Determination of the optimal solvent for the studied conjugate addition

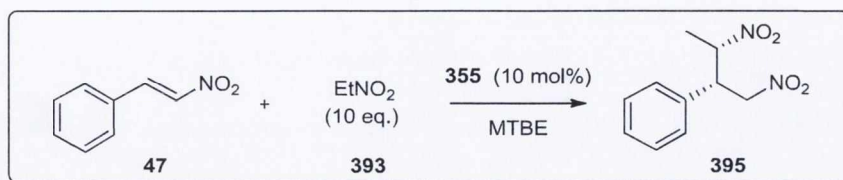
					
entry	solvent	time (h)	yield (%) ^a	d.r. ^a	ee (%) ^b
1	MTBE	19	83	1:1.3	86, 70
2	THF	40	83	1:1.3	83, 69
3	toluene	16	100	1:1.3	83, 59

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

Finally, the effect of lower temperatures on catalysis was examined. While **395** was already generated with an interesting enantiocontrol at ambient temperature (86 and 70% ee, entry 1, Table 3.3), no improvement was recorded at 0 °C (entry 2). However, substantial improvements in selectivity were observed when undertaking the reaction at -

30 °C (entry 3). Product *ee* as high as 94% and 81% was obtained and a satisfactory level of activity was maintained (65%, entry 3).

Table 3.3 Effect of the temperature on catalysis



Entry	temp. (°C)	time (h)	yield (%) ^a	d.r. ^a	<i>ee</i> (%) ^b
1 ^c	<i>rt</i>	19	83	1:1.3	86, 70
2	0	88	100	1:1.5	86, 68
3	-30	88	65	1:1.5	94, 81

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

^cReaction conducted using 5 mol% of catalyst.

3.1.2 The addition of a disubstituted nitroalkane to (*E*)-β-nitrostyrene

Since it was confirmed that the C-5' urea-based catalysts **353** and **355** (in particular) promoted efficient and selective Michael addition of nitroethane to nitroolefin **47**, we wondered if these alkaloids would remain efficient in the mediation of the unprecedented asymmetric addition of hindered disubstituted nitroalkane **396** (synthesised by Mr. Emiliano Sorrentino) to the same nitroolefin **47**.

With this aim, a preliminary evaluation of the catalytic performance of a selection of C-5'-modified alkaloids and of the literature benchmark catalysts **158a** and **309** (Figure 3.2) in the Michael addition of nitroalkane **396** to **47** was undertaken.

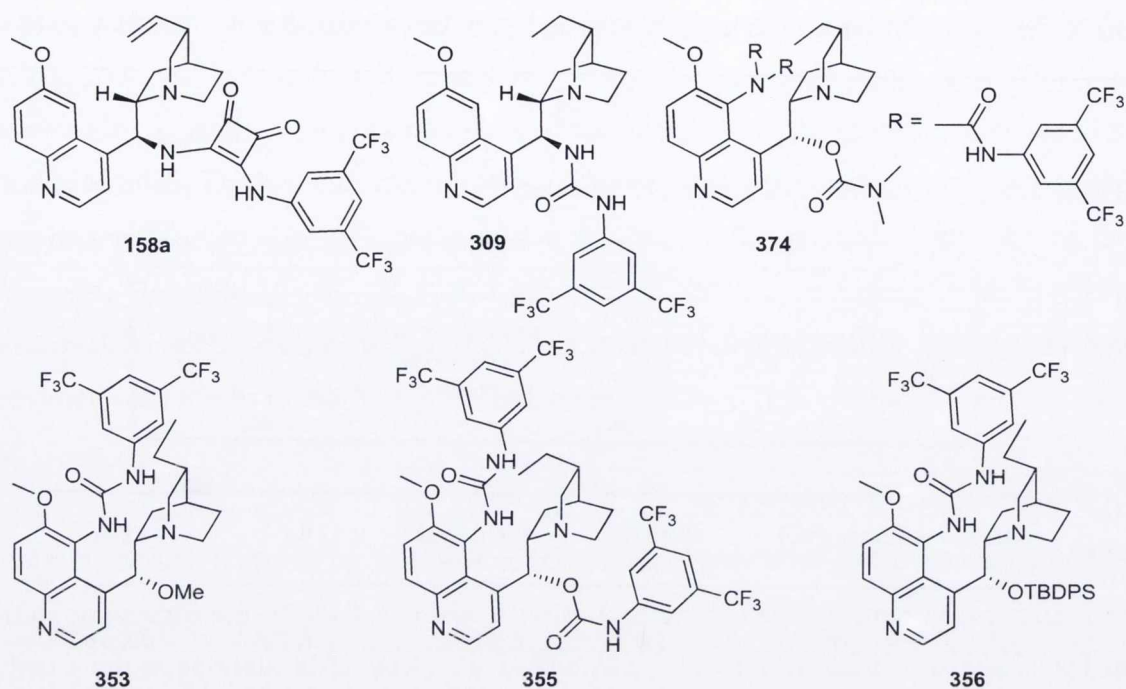
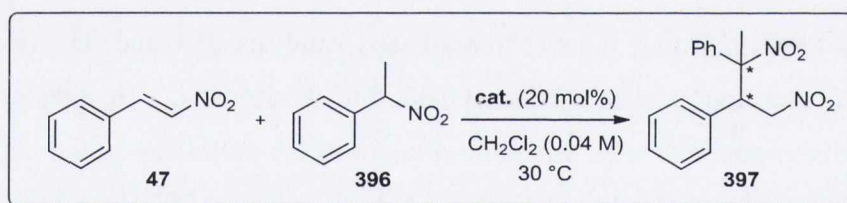


Figure 3.2 Alkaloids evaluated as catalysts in the 1,4-addition of **396** to **47**

Table 3.4 Evaluation of catalysts for the promotion of the asymmetric Michael addition of nitroalkane **396** to (*E*)- β -nitrostyrene



Entry	cat.	yield (%) ^a	d.r. ^a	ee (%) ^b
1	158a	14	1:1.5	nd ^c
2	309	9	1:1.5	nd
3	353	0	nd	nd
4	355	17	1:1.5	59, 58
5	374	1	nd	Nd
6	356	31	1:1.5	90, 85

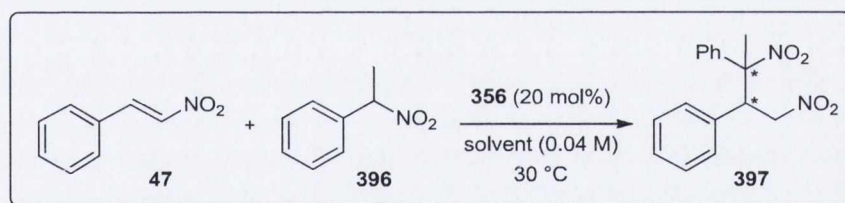
^aDetermined by ^1H NMR spectroscopy using an internal standard.

^bDetermined by CSP-HPLC. ^cnd: not determined.

Since the nitroalkane required to be synthesised prior to the Michael addition, it was decided to commence the study using the two substrates (*i.e.* **396**/*(E)*- β -nitrostyrene) in a 1:1 ratio. To avoid any polymerisation of the nitroolefin, the conditions initially chosen involved a very dilute medium (0.04 M) and a high catalyst loading (20 mol%). The results of these preliminary findings are tabulated above (Table 3.4). Disappointingly, the C-9 and C-5'-modified cinchona alkaloid derivatives **158a**, **309**, **353**, **355** and **374** proved to be very poor catalysts for this transformation (entries 1-5, Table 3.4). Even the C-9-carbamoyl-derived **355**, which was highly active in the addition of nitroethane to the same Michael acceptor **47**, catalysed the reaction with only 17% yield after 112 h and moderate enantioselectivity (59%, 58% *ee*, entry 4). However, silyl ether **356** was found promising in this reaction, leading to the generation of adduct **397** with a low yield (31% after 112 h) but excellent enantioselectivity (90% and 85% *ee*, entry 6). As in the addition of nitroethane, the diastereocontrol of the reaction was very poor (1:1.5).

Subsequent experiments identified C₂Cl₄ as the optimum solvent (Table 3.5).

Table 3.5 Determination of the optimum solvent for the conjugate addition using **396** as nucleophile



entry	solvent	yield (%) ^a	d.r. ^a	<i>ee</i> (%) ^b
1	CH ₂ Cl ₂	31	1:1.5	90, 85
2	THF	0	-	-
3	MTBE	6	Nd	nd ^c
4	toluene	20	1:1.5	70, 63
5	CHCl ₃	37	1:2	76, 66
6	C ₂ Cl ₄	46	1:1.5	88, 90
7	C ₂ H ₄ Cl ₂	23	1:1.5	89, 83

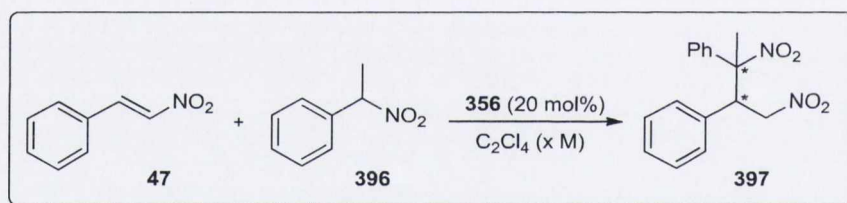
^aDetermined by ¹H NMR spectroscopy using an internal standard.

^bDetermined by CSP-HPLC. ^cnd: not determined.

Replacing DCM (entry 1) by ethereal solvents led to remarkably poor activity (*vide supra*, entries 2 and 3, Table 3.5). When the reaction was conducted in toluene, Michael adduct **397** was afforded with slightly lower activity and selectivity to those observed in CH₂Cl₂ (entry 4). Chlorinated solvents were determined as the medium of choice. The use of either CHCl₃ or C₂Cl₄ provided higher yields and enantioselectivity (entry 5 and 6). However, when C₂H₄Cl₂ was utilised as the solvent, the transformation proceeded slowly (entry 7).

In an attempt to improve our protocol, we then examined the effect of the temperature, the loading of nitroalkane utilised and the concentration of the reaction medium on catalysis (Table 3.6). The best condition set available thusfar is shown for comparison purposes (entry 1).

Table 3.6 Investigations towards the determination of the optimum reaction conditions for the conjugate addition of nitroalkane **396** to nitroalkene **47**



entry	temp. (°C)	nitroalkane (eq.)	x (M)	yield (%) ^a	d.r. ^a	ee (%) ^b
1	30	1	0.04	46	1:1.5	88, 90
2	35	1	0.04	49	1:2.5	75, 81
3	40	1	0.04	53	1:2.5	66, 71
4	30	2	0.04	81	1:2	74, 87
5	30	1	0.08	64	1:2.3	68, 70

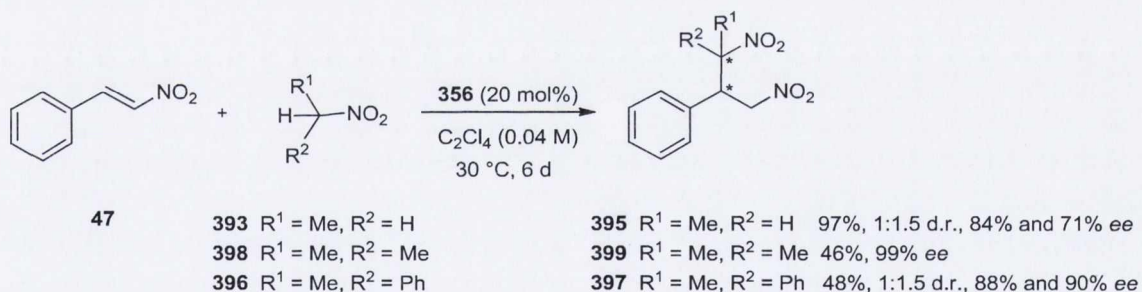
^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.
^cnd: not determined.

Surprisingly, increasing the temperature by only 5 °C led to a considerable decrease in the enantioselectivity, with almost no improvement observed in product yield (entries 1-3). In an attempt to increase the yield of the reaction, the loading of nitroalkane utilised was increased (2 eq., entry 4). Under these conditions, catalyst **356** could promote the addition

of **396** with high activity (81%), albeit at the expense of the enantioselectivity (74%, 87% *ee*). Comparable results were obtained when the concentration of the medium was increased (*i.e.* 0.08 M, 64% yield, 68% and 70% *ee* entry 5).

Despite our efforts, the level of activity obtained remained synthetically useless under reaction conditions that allowed the retention of satisfying selectivity. We postulated first that these low yields could be attributed in part to the likely rather crowded nature of the catalyst's active site (in which bifunctional catalysis must occur). If this were of insufficient volume to accommodate both substrates, then the efficiency of the bifunctional catalysis would be dependent of the size of the nitroalkane involved. Consequently, this would limit the scope of the Michael-type addition to relatively non-hindered nitroalkanes. Such reactions would not be interesting to investigate since several efficient catalytic systems for the conjugate addition of non-hindered nitroalkanes have already been reported in the literature.²¹⁰⁻²¹⁶

To ascertain whether or not the slow reaction rate of the reaction is linked to the change of structure of the nucleophile, we undertook a comparative study of Michael additions of various nitroalkanes of variable steric bulk to **47** (Scheme 3.1).



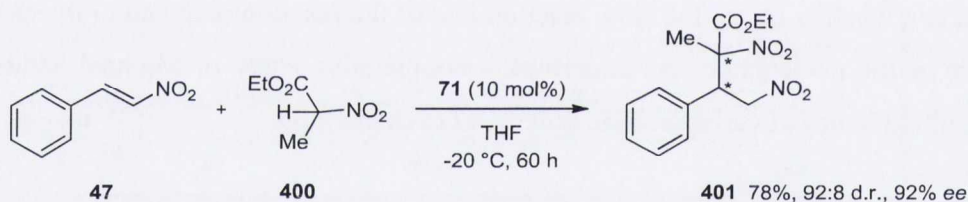
Scheme 3.1 The influence of the nitroalkane's bulk on the efficacy of catalysis

After 136 h, adduct **395** (obtained after the addition of monosubstituted nitroethane to (*E*)- β -nitrostyrene) was obtained with excellent yield (97%, Scheme 3.1), whereas products **397** and **399** (derived from the addition of bulkier disubstituted **396** and **398**) were formed with significantly lower yields (46%-48%) under the same reaction conditions.

However, if the bulk of the nucleophile was the only factor limiting the catalytic efficiency, it is likely that the cinchona alkaloid derivative would still promote the reaction

via monofunctional base catalysis. This would result in higher yields and lower selectivity, which was not the case in our study.

Another plausible explanation would involve the intrinsic properties of nitroalkanes. It has been found in the literature that the more alkyl substituents present at the α -position of the nitro group, the slower the deprotonation of the nitroalkane by general base catalysis would occur. This phenomena was explained by a destabilising polar interaction appearing between the alkyl substituents (due to their inductive donating effect) and the negative charge created when deprotonation takes place.^{217,218} The veracity of this theory here would be supported by the possible efficient addition of the bulky disubstituted nitroalkane **400** to (*E*)- β -nitrostyrene (**47**) catalysed by cupreine (**71**) as described by Deng *et al.*¹¹² in 2005 (Scheme 3.2). This disubstituted nucleophile (since it possesses an ester substituent) would be less likely to experience a destabilising interaction involving the negative charge build up at the α -position during deprotonation.



Scheme 3.2 Efficient cupreine-catalysed addition of disubstituted nitroalkane **400** to **47**

This theory would then explain the low yields obtained when using nitroalkane **396**. In this case, it is likely that no alterations of either the steric or the electronic properties of the C-5' urea-based cinchona alkaloid analogue **356** would lead to a successful outcome in the development of this reaction.

3.2 The Michael-type addition of alkyl thiols to nitroolefins

Faced with this failure, we decided to attempt other Michael-type additions with different nucleophiles. After a careful study of the literature, we were intrigued by and drawn to the curious general inferiority of synthetically relevant alkyl thiols in the organocatalysed Michael-type processes compared to their aromatic analogues (thiophenols). While it was tempting to attribute this to the lower activity of alkyl thiols due to their reduced acidity, pronucleophiles of both similar and higher acidity have been shown to add to nitroolefins

enantioselectively under similar conditions in the presence of cinchona alkaloid-based bifunctional catalysts.^{120,121,136} We therefore postulated that the dearth of literature examples may be related to a combination of mechanistic and stereoelectronic factors. It is likely that catalysis by tertiary amines involving thiophenol ($pK_a = 6.52^{219}$ in H_2O) occurs largely through specific base catalysis, while the less acidic alkane thiols (pK_a (benzyl mercaptan) = 9.43^{219} in H_2O) would require proton transfer in the transition state (*i.e.* general base catalysis, Figure 3.3). In this case, the stereocontrol over the formation and cleavage of longer bonds to a 2nd row element (relative to either carbon or other first row element based pronucleophiles) may be beyond the abilities of previously evaluated bifunctional catalyst systems (the relative positioning of the bifunctional components in which are reasonably invariant) such as C-9 thiourea-based dihydroquinine-derived **123** (Section 1.5.1.2).

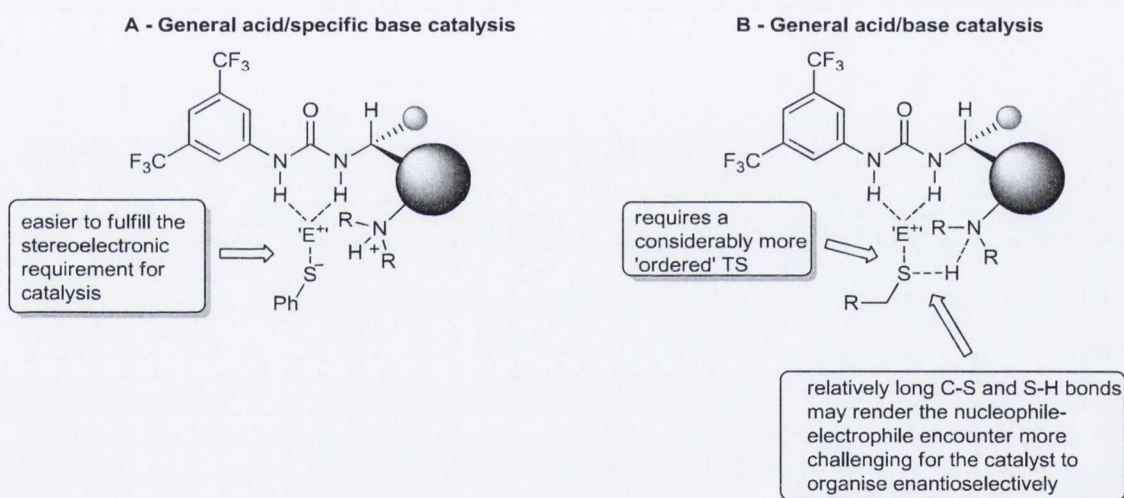
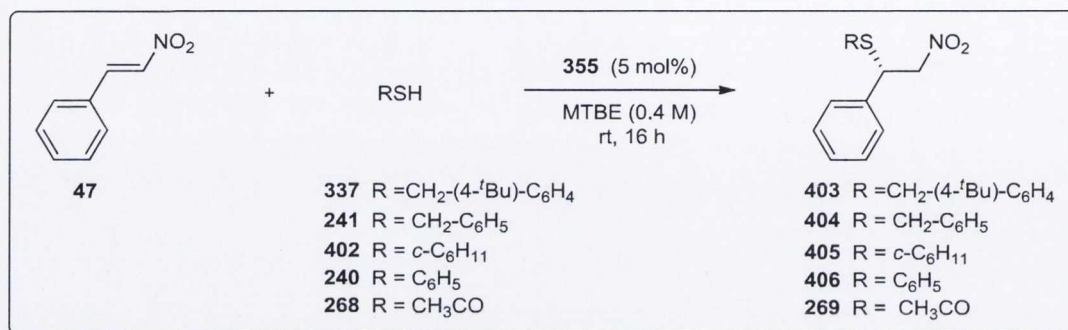


Figure 3.3 Stereoelectronic requirements of organocatalytic Michael-type additions involving thiols

In Section 2.0, was described the preparation and the use of a range of C-5'-substituted cinchona alkaloid-derived catalysts devised to introduce some variation in this key catalyst attribute (*i.e.* the positioning of the bifunctional components). We were naturally interested in evaluating their potential as catalysts for the problematic process outlined above.

3.2.1 Preliminary studies: evaluation of several thiols as nucleophiles in the Michael-type addition using (*E*)- β -nitrostyrene (**47**)

Table 3.7 Evaluation of the catalytic profile of **355** in the addition of different thiols



entry	thiol	yield (%) ^a	ee (%) ^b
1 ^c	337	0	0
2	337	>98	32
3	241	>98	25
4	402	>98	4
5	240	>98	3
6	268	85	0

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC. ^cThis experiment was undertaken in the absence of catalyst.

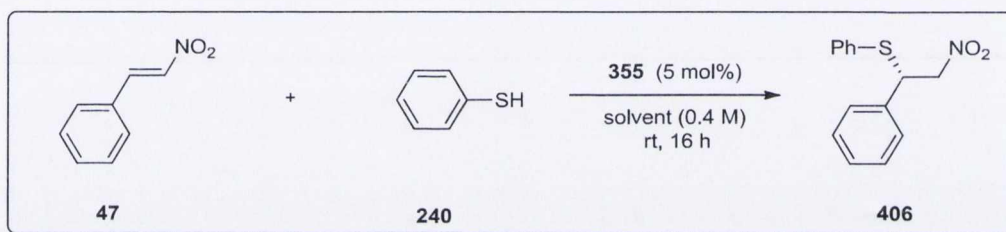
Beginning with the optimum catalyst for the Henry reaction study described in Section 2.0 (*i.e.* **355**) at 5 mol% levels in MTBE, we evaluated the addition of a range of thiols (**240**, **241**, **268**, **337** and **402**) of variable acidity to (*E*)- β -nitrostyrene (**47**). The results of this preliminary survey are presented in Table 3.7.

First it was confirmed that no background reaction occurred between (*E*)- β -nitrostyrene (**47**) and 4-*tert*-butyl benzyl mercaptan (**337**) in the absence of catalyst (entry 1). Then, the study of the addition of thiols **240**, **241**, **268**, **337** and **402**, in the presence of alkaloid **355** began. The general trend observed in previous studies reported in the literature was reversed in the presence of the C-5'-modified dihydroquinine derivative: alkyl thiols **337**

and **241** underwent moderately selective reaction (entries 2-3). Interestingly the hindered thiol **402** proved a poor substrate (entry 4), while more acidic thiols **240** and **268** furnished either racemic or almost racemic products (entries 5-6). This was quite surprising since in the literature **268** consistently proved less challenging than **337** to react with **47** in organocatalytic reactions.

To verify that the failure of thiophenol to add enantioselectively to **47** was not solvent-specific, the same reaction (*i.e.* entry 5, Table 3.7) was carried out using different solvents (Table 3.8). However no improvement in asymmetric induction was observed (entries 1-4).

Table 3.8 Influence of the solvent on the addition of thiophenol (**240**) to **47**



entry	solvent	yield (%) ^a	ee (%) ^b
1	MTBE	>98	3
2	THF	>98	5
3	CH ₂ Cl ₂	>98	4
4	toluene	>98	7

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC

Conveniently, 4-*tert*-butyl benzyl mercaptan (**337**, considerably less malodorous than the other thiols tested) was identified as the nucleophile of choice.

3.2.2 The addition of 4-*tert*-butyl benzyl mercaptan to (*E*)- β -nitrostyrene: determination of the optimum catalyst

Next, a catalyst screen for the addition of **337** to nitroolefin **47** was undertaken involving catalysis by a selection of C-5'-modified dihydroquinine derivatives and C-9-hydrogen bond donor-substituted quinine and dihydroquinine derivatives (Figure 3.4). It was decided to only use 1 equivalent of alkyl thiol for each equivalent of nitrostyrene involved in the reaction. Organocatalytic systems proposed so far in the literature required increased amount of alkyl thiol to achieve efficient catalysis, which could represent a limitation of the process if the reaction is conducted in larger scale (Section 1.8).

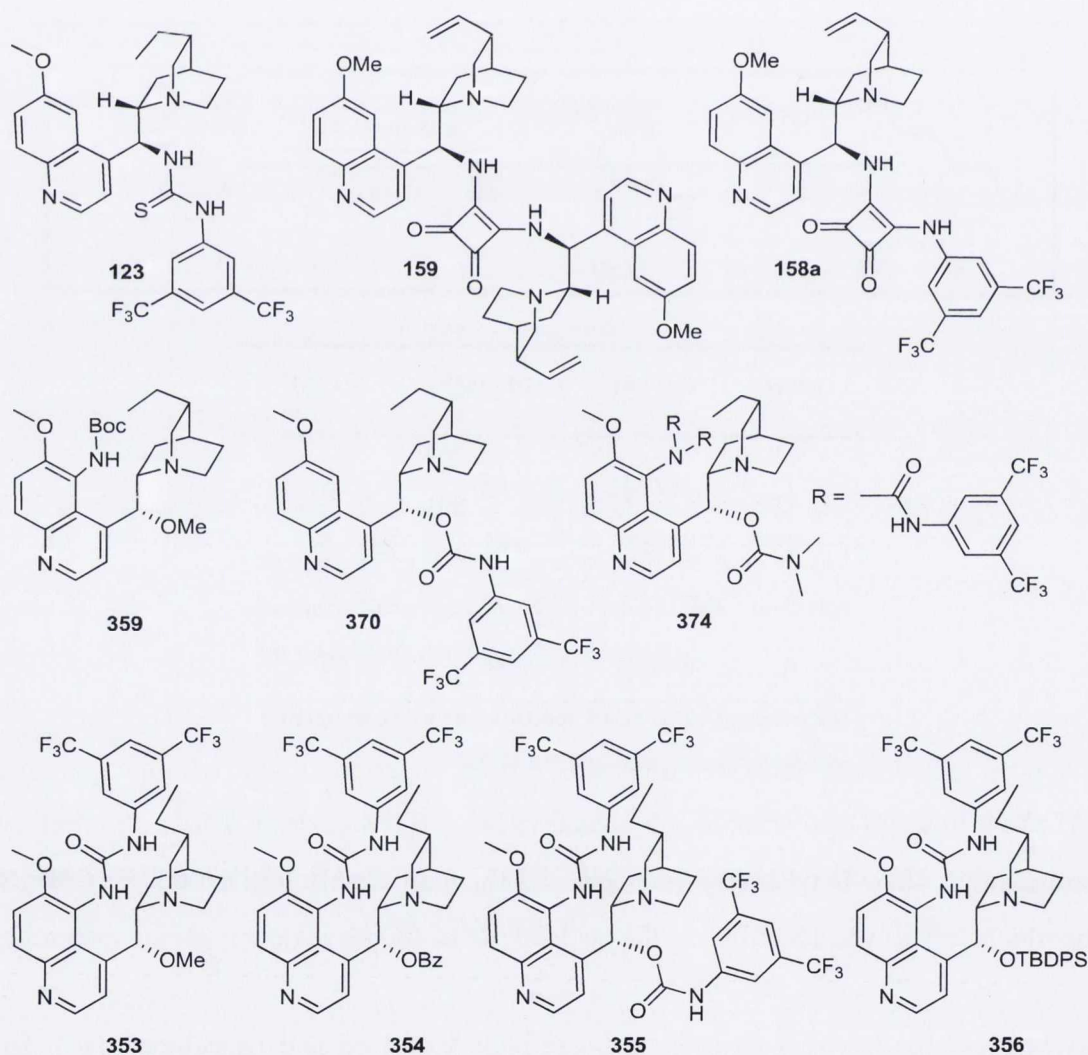
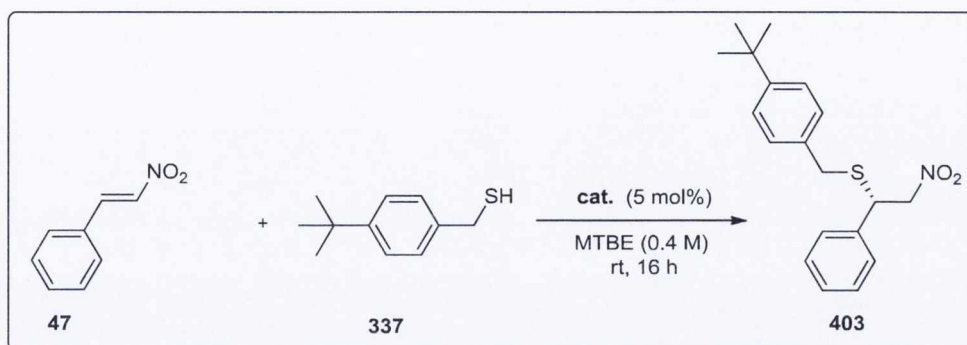


Figure 3.4 Catalysts assessed in the sulfa-Michael addition of **337** to **47**

Table 3.9 Evaluation of some cinchona alkaloid derivatives in the sulfa-Michael addition of **337** to **47**



entry	cat.	yield (%) ^a	ee (%) ^b
1	123	>98	-1
2	159	>98	4
3	158a	>98	-8
4	359	>98	1
5	370	>98	8
6	374	>98	17
7	355	>98	32
8	353	>98	33
9	354	>98	-8
10	356	>98	51

^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

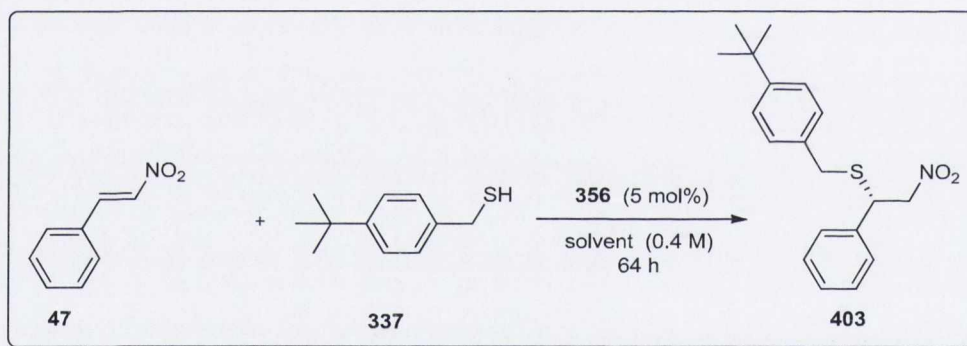
As expected, representative traditional literature catalyst systems characterised by functionalities capable of donating two hydrogen bonds at C-9 (*i.e.* **123**, **159** and **158a** entries 1-3 respectively, Table 3.9) failed to promote enantioselectively this reaction involving an alkyl thiol. Catalysts devoid of the C-5' urea (*i.e.* **359** and **370**, entries 4 and 5) promoted efficient but unselective reactions. While the C-5'-*bis*-urea substituted catalyst **374** fared marginally better (entry 6), it represented no improvement upon **355** (entry 7). Variation of the C-9 substituent of catalyst **355** proved instructive: use of the methoxy-substituted catalyst **353** (entry 8) led to slightly higher product *ee*, whereas the

corresponding benzoyl analogue **354** was a poor catalyst from a stereoselectivity standpoint (entry 9). Gratifyingly, catalyst **356** (characterised by a large (TBDPS) silyl-group at C-9) was capable of generating **403** in significantly improved enantiomeric excess (entry 10).

3.2.3 The addition of 4-*tert*-butyl benzyl mercaptan to (*E*)- β -nitrostyrene: optimisation of the reaction conditions

We next proceeded to study the effect of solvent variations in association with lower temperatures on the catalysis efficacy.

Table 3.10 Evaluation of the influence of temperature in conjunction with various solvents



entry	temp. (°C)	solvent	time (h)	yield (%) ^a	ee (%) ^b
1	rt	MTBE	16	>98	51
2	-30	MTBE	64	>98	71
3	-30	CHCl ₃	64	>98	75
4	-30	CH ₂ Cl ₂	64	>98	78
5	-30	Et ₂ O	64	>98	69
6	-30	toluene	64	>98	63
7	-78	CH ₂ Cl ₂	64	>98	83
8	-78	CHCl ₃	64	>98	81

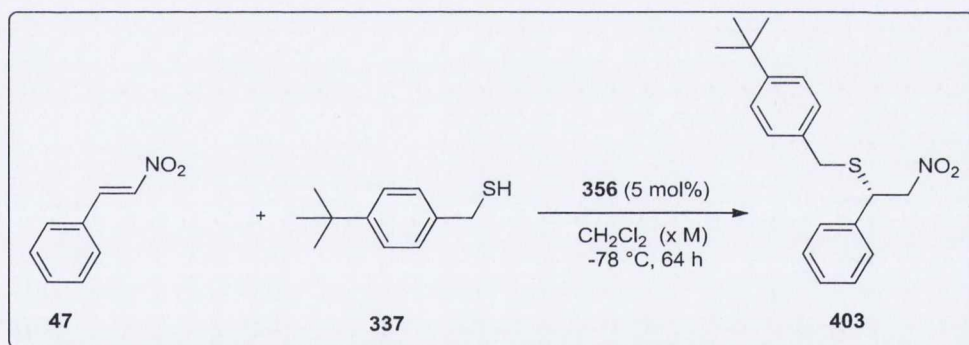
^aDetermined by ¹H NMR spectroscopy using an internal standard. ^bDetermined by CSP-HPLC.

As anticipated, compared to the results obtained previously (entry 1, Table 3.10), the enantioselectivity increased further at -30 °C (entry 2).

A subsequent screening of a variety of solvents (entries 3-6) revealed that chlorinated solvents (*i.e.* CH₂Cl₂ and CHCl₃, entries 3 and 4) were superior to both ethereal solvents (entry 2 and 5) and toluene (entry 6) with respect to product enantioselectivity. Further experiments at -78 °C in CH₂Cl₂ provided substantial improvement of selectivity (83% *ee*, entry 7) and proved this solvent to be slightly superior to CHCl₃ (81% *ee*, entry 8) at the same temperature.

In an attempt to improve our sulfa-Michael addition protocol, we decided to examine whether or not conducting the addition at lower concentrations would have a positive effect on the enantiomeric excess.

Table 3.11 Evaluation of the influence of concentration on the enantiomeric excess



entry	x (M)	time (h)	yield (%) ^a	<i>ee</i> (%) ^b
1	0.4	64	>98	83
2	0.04	64	>98	88
3	0.02	24	>98	92
4	0.008	64	80	74
5	0.004	64	79	63

^aDetermined by ¹H NMR spectroscopy using an internal standard.

^bDetermined by CSP-HPLC.

Dilute conditions (compared to previous best condition set entry 1, Table 3.11) allowed the formation of **403** in 88% *ee* (0.04 M, entry 2) and 92% *ee* (0.02 M, entry 3). Further dilutions (0.008 M and 0.004 M) unfortunately led to lower yields and enantiomeric excess (entries 4 and 5).

To conclude, solvent/temperature/concentration optimisation experiments (Table 3.10 and 3.11) allowed conditions to be identified under which **356** (at 5 mol% loading) could promote the clean formation of **403** in quantitative yield and 92% *ee* in 24 h using only 1 equivalent of alkyl thiol **337**.

3.2.4 Optimisation of the synthesis of catalyst **356**

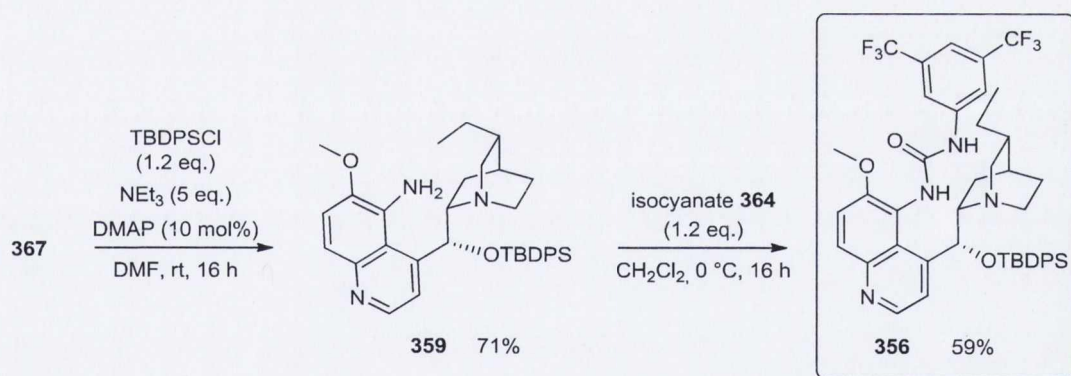
According to the results presented above, **356** was found the optimum catalyst for the addition of alkyl thiol **337** to nitroolefin **47**. However, the synthetic pathway described in the previous section for the preparation of this material was particularly inefficient, delivering this derivative of dihydroquinine with an overall yield of 14% after only two steps (Section 2.1). It seemed clear, that the synthesis of **356** needed to be optimised before carrying our investigation of the sulfa-Michael addition on further.

The second step (*i.e.* the addition of the C-9 silyl ether derivative **369** to the isocyanate) was principally responsible for the low product yield. Two major products were obtained during this transformation in a ratio 1:3 - the targeted alkaloid **356** (14%) and another alkaloid **356a** (48%). The characterisation of these two molecules by ¹H NMR spectroscopy and mass spectroscopy (identical mass and fragments were detected for both molecules *via* HRMS and MALDI experiments) led us to the conclusion that these two molecules were atropoisomers. This was not surprising since Jørgensen already reported the formation of two atropoisomers (**161a-161b**, Section 1.6.2) when adding the bulky azodicarboxylate **92** to cupreidine **72**. Inspired by this discovery, we postulated that **356** and **356a** would be characterised by a different relative orientation of the *N*-aryl group of the urea and the quinoline moiety (which unfortunately we were not able to specifically assign). We reasoned that the presence of the very bulky silyl ether in close proximity to the urea moiety may increase the rigidity of the molecule backbone which would allow the isolation of two atropoisomers.

Interestingly, when both alkaloids were utilised to promote the sulfa-Michael addition, only **356** proved to be active. Consequently, we wished to unbalance the ratio of the two products obtained during the addition of the amino-substituted **359** to the isocyanate **364** towards the selective formation of **356**.

We speculated that if **356a** was more stable than **356**, it may constitute the thermodynamic product of the transformation and would be generated as the major product at ambient temperature. Consequently, if we succeeded in altering the reaction conditions so that the kinetic reaction control would prevail, the generation of **356** might be favoured over its isomer **356a**.

Gratifyingly, when the addition of the amino derivative **359** to the isocyanate **364** was undertaken at 0 °C (instead of ambient temperature as was described in Section 2.1.2.2), the desired atropoisomer **356** was obtained in a considerably better yield (59%) after 16 h, whereas the other atropoisomer was only afforded in less than 10% yield. The synthetic pathway towards the preparation of **356** was then markedly more efficient with an overall yield of 42% (instead of the previous 14%, Scheme 3.3).



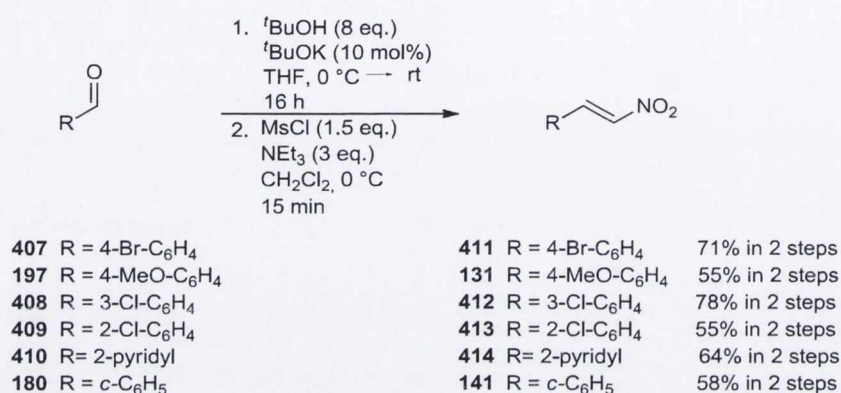
Scheme 3.3 Optimised synthetic pathway towards the preparation of alkaloid **356**

3.2.5 The sulfa-Michael addition of alkyl thiols to (*E*)- β -nitrostyrene: reaction scope

With a readily available organocatalyst and a useful protocol in hand for the highly enantioselective addition of alkyl thiol **337** to (*E*)- β -nitrostyrene (**47**), attention turned to the question of substrate scope.

3.2.5.1 Evaluation of the reaction scope with respect to nitroalkenes

We decided first to evaluate the scope of our asymmetric reaction with respect to the Michael-acceptors. With this aim, a range of representative nitroalkenes were prepared starting from the corresponding aldehydes (Scheme 3.4).



Scheme 3.4 Synthesis of the nitroolefins used as substrates in the organocatalysed sulfa-Michael addition

Each aldehyde (*i.e.* **180**, **197** and **407-410**) underwent a Henry reaction with nitromethane in the presence of *tert*-butanol and potassium *tert*-butoxide. After volatiles were removed (under reduced pressure), the resulting nitroaldol crude residue was dissolved in CH₂Cl₂ and was directly utilised in an elimination process *via* the addition of methanesulfonyl chloride and NEt₃ at 0 °C (Scheme 3.4). All nitroalkenes were readily prepared in two steps, in moderate to good yields (55-71%), after purification *via* column chromatography. It should be noted that the nitroolefin **414** was highly unstable (even at low temperatures) due to its rapid polymerisation. Therefore, it was necessary to use **414** immediately following its synthesis from the nitroaldol intermediate (which could be stored at -6 °C).

In addition, *p*-NO₂-C₆H₄- and furyl-substituted nitroalkenes (**415** and **416**) were already available within the group (prepared by Dr. Eimear Fleming) and the thienyl-substituted analogue **417** was sourced commercially.

Once prepared, these nitroalkenes could be evaluated in our optimised protocol of the sulfa-Michael addition using alkyl thiol **337** (10 mol% of **356**, CH₂Cl₂ (0.02 M), -78 °C).

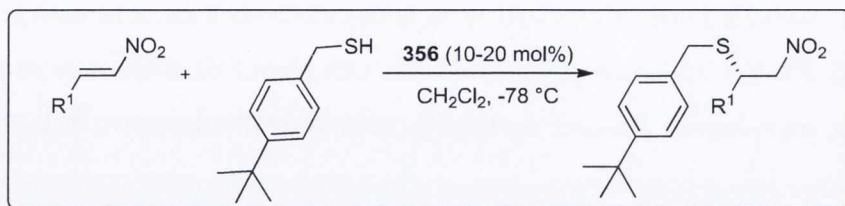
Investigating the influence of the electronic and steric profiles of the nitroalkene substituents on catalysis, we were pleased to find that products derived from the addition of **337** to both activated and deactivated nitroolefins (**131**, **411** and **415** entries 1-3, Table 3.12) were obtained in excellent yields and with a degree of enantiocontrol that could be maintained at high levels. Product *ee* was $\geq 90\%$ in all cases save that of the nitro-substituted **419**.

A slight variation of the steric bulk (*i.e.* substrate **412**) was well tolerated by the catalyst (entry 4). However, when applying sterically demanding substrate **413**, the procedure failed to deliver a satisfactory outcome (entry 5). The resulting adduct **422** was obtained in good yield (94%) but with only 34% *ee*.

The reaction scope could also be broadened to include heterocyclic-derived nitroalkenes (both π -excessive and π -deficient, **416**, **417** and **414**, entries 1-3 respectively, Table 3.13), with the production of the corresponding adducts with excellent results (91-99%, 90-96% *ee*).

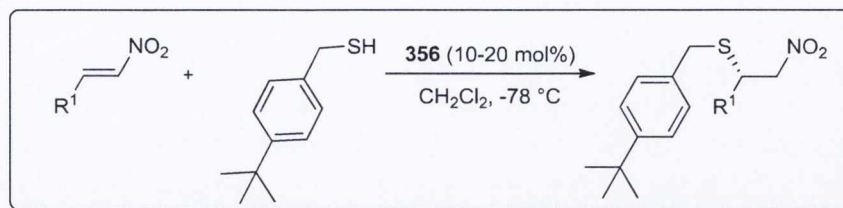
Disappointingly, our catalytic method was not compatible with the aliphatic-substituted nitroolefin **141** (entry 4). Using this substrate, catalyst **356** failed to deliver any product. The same experiment at a higher temperature (-30 °C) led to the generation of adduct **426** with an excellent yield of 98% after 20 h; however highly reduced selectivity was observed (32% *ee*).

Table 3.12 Sulfa-Michael addition catalysed by **356**: reaction scope



entry	nitroolefin	Products	cat. (mol%)	conc. (M)	time (h)	yield (%) ^a	ee (%) ^b
1			10	0.02	20	96	90
2			20	0.01	68	98	86
3			20	0.01	68	97	90
4			20	0.007	68	84	91
5			10	0.02	20	94	34

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC.

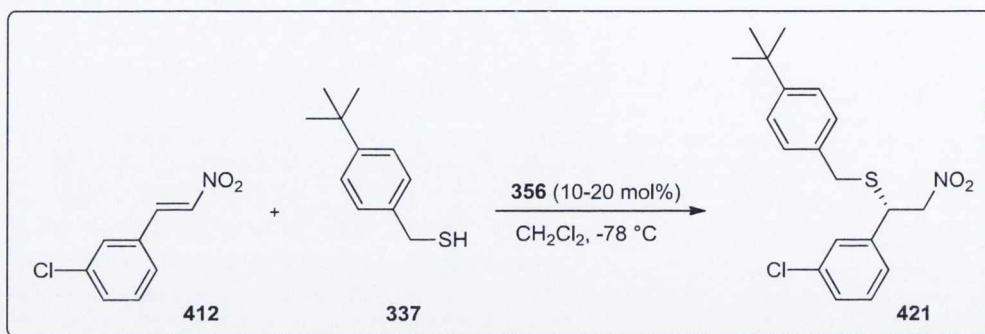
Table 3.13 Sulfa-Michael addition catalysed by **356**: reaction scope

entry	nitroolefin	products	cat. (mol%)	conc. (M)	time (h)	yield (%) ^a	ee (%) ^b
1			20	0.01	68	99	90
2			10	0.02	20	93	92
3			10	0.02	20	91	96
4 ^c			10	0.02	20	98	32

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC. ^cReaction conducted at -30 °C.

A set of two slightly modified protocols needed to be devised to adapt the reaction to particular substrates. Medium dilution (0.01 M or 0.007 M) in association with an increased catalyst loading (20 mol%) was required in some cases to access Michael adducts with products of *ee* >90%. This is well illustrated by the case of nitroalkene **412** (Table 3.14). Entry 1 shows the product yield and *ee* obtained (94%, 88% *ee*) with the optimum conditions previously determined in Section 3.2.3. A 2-fold decrease of the concentration accompanied by a 2-fold increase of the catalyst loading (entry 2) led to a slightly better enantiocontrol (89% *ee*) and almost quantitative yield after 68 h. Further dilution of the reaction medium (0.007 M, entry 3), allowed access to excellent enantiocontrol (91% *ee*) without altering the reaction yield (93%).

Table 3.14 Increased enantiocontrol of the sulfa-Michael addition when **412** was used along with catalyst loading/concentration modifications

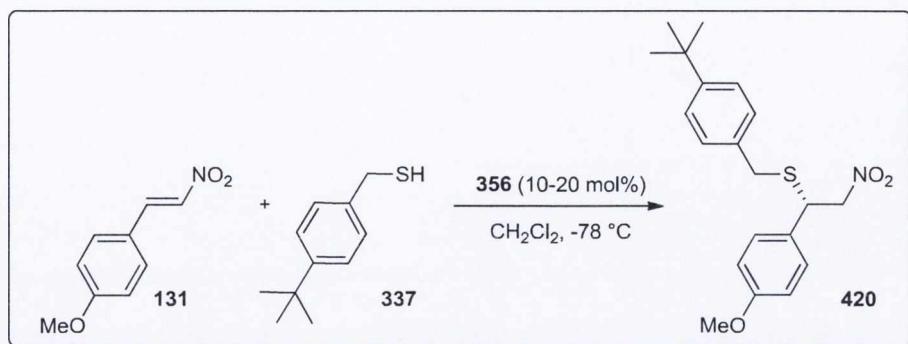


entry	cat. (mol%)	conc. (M)	time (h)	yield (%) ^a	ee (%) ^b
1	10	0.02	20	94	88
2	20	0.01	68	99	89
3	20	0.007	68	93	91

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC.

However, it would not be prudent to conclude that the set of conditions indicated in entry 3 would provide superior results for all the nitroalkenes involved in Table 3.12 and 3.13. The increase in enantioselectivity gained as a result of the dilution of the reaction medium to 0.007 M when using nitroolefin **412** was not observed with **131** (*inter alia*), as outlined in Table 3.15 (entries 1-3).

Therefore, these 3 sets of conditions were considered as alternative methods to use in order to obtain product levels of enantiomeric excess >90% *ee* in as many cases as possible.

Table 3.15 Modifications of catalyst loading/concentration when using substrate **131**

entry	cat. (mol%)	conc. (M)	time (h)	yield (%) ^a	ee (%) ^b
1	10	0.02	20	98	85
2	20	0.01	68	92	90
3	20	0.007	68	86	87

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC.

3.2.5.2 Evaluation of the reaction scope with respect to the alkyl thiols

Aiming at expanding the scope of our sulfa-Michael addition process with respect to the alkyl thiols, the conjugate additions of various mercaptans with nitroolefins **47** and **414** were next investigated. Of particular synthetic utility is the use of alkane thiol derivatives which can serve as synthetic equivalents for H_2S in total synthesis strategies due to their specific cleavage conditions. For instance, the successful orthogonal deprotection of sulfides containing photo-cleavable²²⁰ or acid/ Hg^{2+} -labile²²¹ functionalities have already been discussed in the literature. Sulfides containing such functional groups (*i.e.* products derived from the addition of thiols **427** and **252** respectively, Figure 3.5) may be efficiently prepared using our sulfa-Michael methodology through the selection of the appropriate thiol. In addition, we were also curious to evaluate the compatibility of our optimised organocatalytic method with the non-benzylic thiol **428** and cyclohexylthiol **429**.

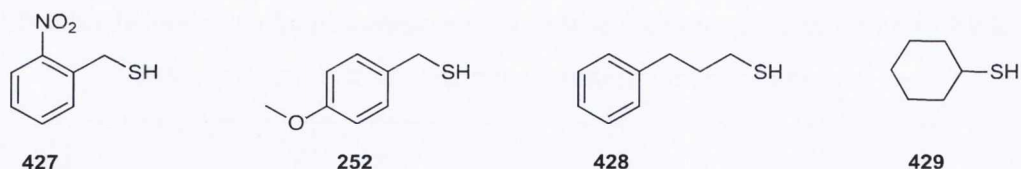
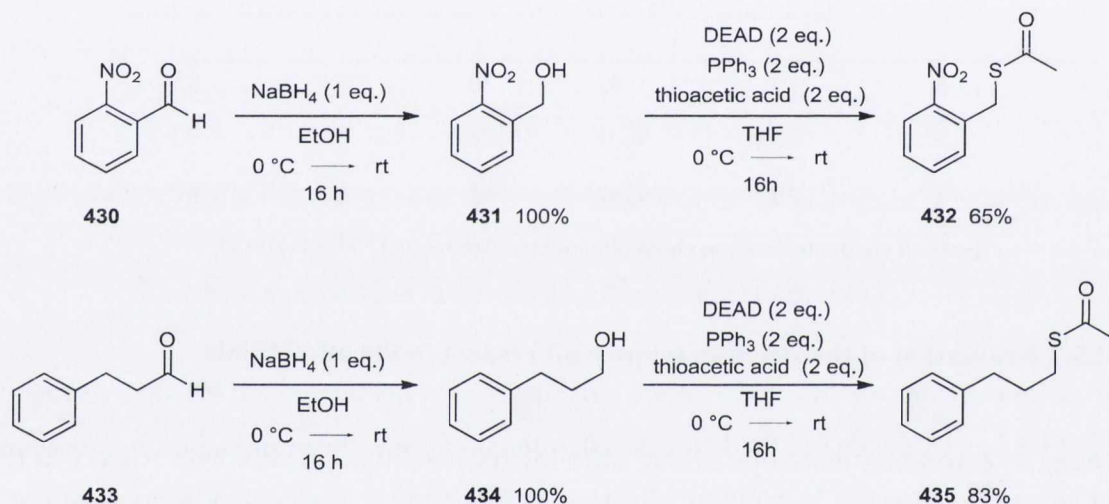


Figure 3.5 Alkyl thiols evaluated in a sulfa-Michael addition process catalysed by **356**

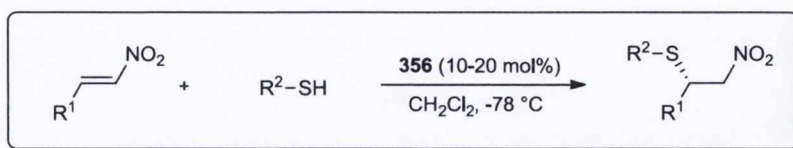
Substrates **252** and **429** were sourced commercially. The other thiols (*i.e.* **427** and **428**) could be readily synthesised by means of a three step synthetic route starting with a straightforward NaBH_4 -mediated reduction of the corresponding aldehydes (*i.e.* **430** and **433**) in ethanol (Scheme 3.5).



Scheme 3.5 Preparation of alkyl thiols *via* Mitsunobu chemistry

After being diluted in water and extracted using CH_2Cl_2 , the crude alcohols (*i.e.* **431** and **434**) were directly involved in a subsequent DEAD- PPh_3 mediated Mitsunobu reaction using thioacetic acid (**268**) as the nucleophile source. Isolation by column chromatography led to the resulting thioesters pure, which could be stored at room temperature. Thioesters **432** and **435** were then subjected to deprotection by treatment with acetyl chloride (1.6 eq.) in carefully degassed methanol. Once the volatiles were removed (under pressure), alkyl thiols **427** and **428** were ready to be directly involved (without further purification) in the organocatalytic sulfa-Michael addition process.

Table 3.16 Sulfa-Michael addition catalysed by **356**: reaction scope



entry	thiol	products	cat. (mol%)	conc. (M)	time (h)	yield (%) ^a	ee (%) ^b
1	 252	 436	10	0.02	20	98	90
			20	0.007	96	95	87
2	 427	 437	10	0.02	20	94	80
			20	0.02	96	92	84
			20	0.01	96	91	88
			20	0.007	96	91	87
3	 427	 438	10	0.02	20	82	93
4	 428	 439	10	0.02	20	82	85
			20	0.01	96	77	89
			20	0.007	96	78	88
5	 428	 440	20	0.01	96	56	94
6 ^c	 429	 441	10	0.02	256	78	25

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC. ^cReaction conducted at -30 °C

Gratifyingly, the corresponding Michael adducts (*i.e.* **436-440**, entries 1-5, Table 3.16) were all generated with high yields and excellent enantioselectivities, except for the very hindered cyclohexyl thiol (*i.e.* **429**, entry 6). 4-Methoxy-derived mercaptan **252** was added with no difficulties to nitroolefin **47**, furnishing the Michael adduct **436** with excellent

yield and enantioselectivity (entry 1). Good asymmetric inductions were also achieved for the 1,4-addition of alkane thiols **427** and **428** to (*E*)- β -nitrostyrene (*i.e.* adducts **437** and **439**, entries 2 and 4, 88-89% *ee*). Interestingly, levels of product *ee* as high as 93-94% *ee* could be obtained with these two mercaptans (**427** and **428**) when electrophile **414** was utilised in the catalytic process (*i.e.* adducts **438** and **440**, entries 3 and 5).

To conclude, synthetically useful adducts **436** and **438** were obtained with excellent yield (90-98%) and enantioselectivities (90-94% *ee*, entries 1 and 3).

3.2.5 Determination of the absolute configurations

Adducts **403** and **421** could be conveniently recrystallised from CH_2Cl_2 , enabling a straightforward determination of their absolute configuration as (*S*)-**403** and (*S*)-**421** *via* X-ray analysis (Figure 3.6, obtained by Thomas McCabe). The subsequent determination of the absolute configuration of the other adducts was conducted by analogy with (*S*)-**403** and (*S*)-**421**.

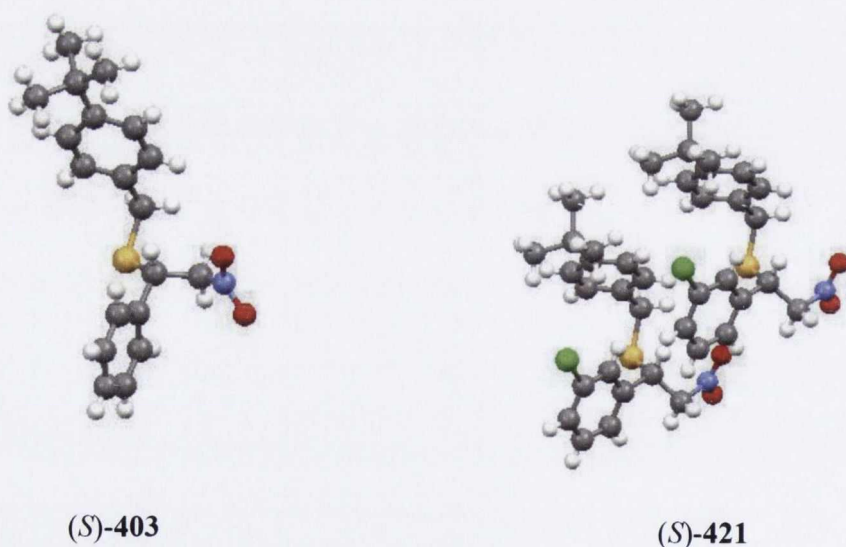


Figure 3.6 X-ray analysis of crystals of (*S*)-**403** and (*S*)-**421**

3.3 Conclusion for Chapter 3

A catalytic system which efficiently promoted the addition of nitroethane to (*E*)- β -nitrostyrene has been developed. In a preliminary study, the smooth preparation of adduct **395** was achieved in moderate yield (65%) and promising enantiocontrol (94% *ee*, 81% *ee*) using promoter **355** (10 mol%). When investigating the use of more hindered substrates (*i.e.* nitroalkane **396**), silyl ether-C-9-modified alkaloid **356** was found to be a superior catalyst to **355** for this particular transformation. The targeted adduct **397** was produced with excellent enantioselectivities (88% *ee* and 90% *ee*), however with a synthetically unsatisfactory yield (46%) and almost no diastereoselectivity (1:1.5). Attributing this low catalyst activity to the significant hindrance and the intrinsic electronic properties of the nitroalkane, we decided to turn our attention towards the use of other types of nucleophiles, in particular alkyl thiols.

Prompted by a curious dependence of enantioselectivity on the acidity of thiol nucleophiles in many organocatalytic conjugate additions, we have developed (to the best of our knowledge) the first general, highly efficient and enantioselective organocatalytic system for the addition of previously problematic alkane thiols to nitrostyrenes. The process is promoted by the readily prepared C-5'-substituted bifunctional cinchona alkaloid catalyst **356** and is of broad scope: a range of alkane thiols (including those containing cleavable benzyl substituents) and a variety of electron deficient, electron rich and heterocyclic nitrostyrenes are compatible (*e.g.* adducts **418-425** and **436-440**).

4.0 The dynamic kinetic resolution of unhindered/hindered racemic azlactones *via* thiolysis

As previously explained in Section 1.9, the Dynamic Kinetic Resolution (DKR) of azlactones is a complex process which is of significant synthetic interest (if conducted with high enantioselectivity). It provides direct access to enantioenriched thioesters potentially invaluable in native chemical ligation (NCL) peptide coupling. Before the research work described herein, only one catalytic system was reported to be capable of the promotion of the DKR of several azlactones using 4-*tert*-butyl benzyl mercaptan (**337**), albeit with enantioselectivities no higher than 73% *ee*.²⁰⁶ Furthermore, only unhindered azlactones could be transformed into their corresponding *N*-protected amino acid derivatives; both activity and selectivity were markedly diminished in the presence of a valine-derived substrate.

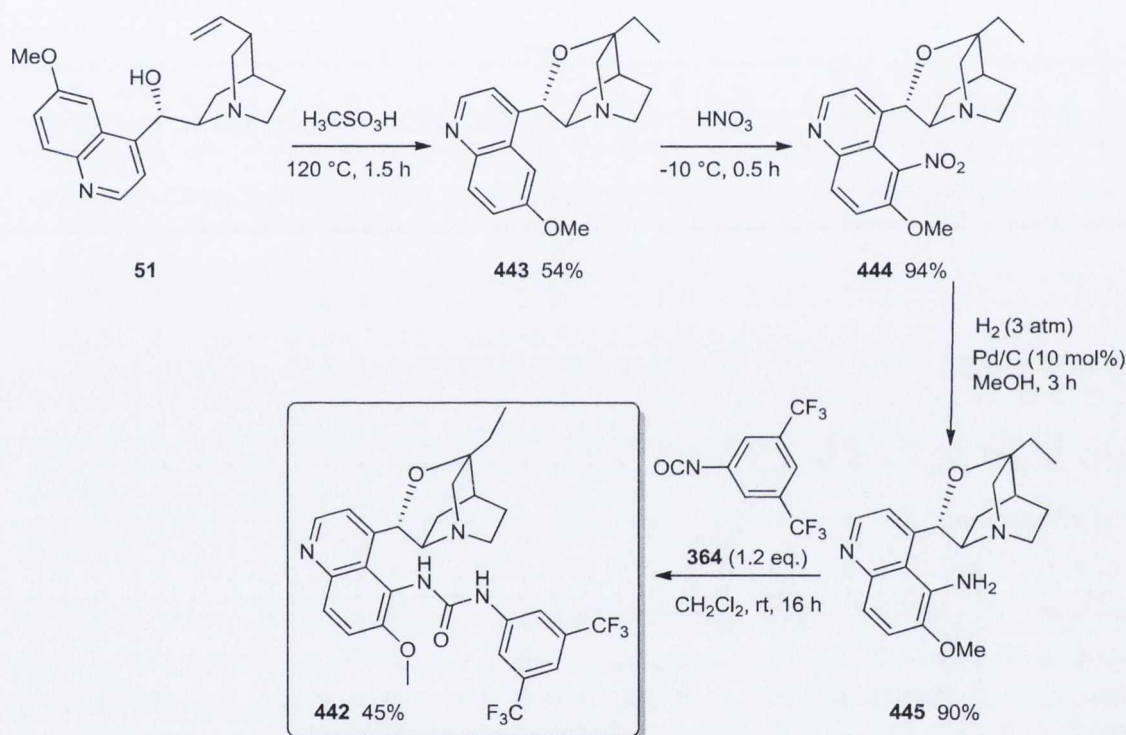
4.1 The preparation of a more rigid C-5'-urea-modified cinchona alkaloid derivative

Considerable scope for improvement remains, in particular from an enantioselectivity standpoint. Given that modification of the C-9 cinchona alkaloid substituent (*i.e.* urea-based **309**, squaramide-based **336** and C-9 arylated literature benchmark **327**, Scheme 1.48) has led to steady yet ultimately unsatisfactory progress (from a synthetic utility perspective), we postulated that the stereoelectronic demands of this particular reaction cannot be satisfied (in an asymmetric catalysis context) by the C-9 substituted catalyst's two bifunctional components (*i.e.* either their proximity to one another or their relative orientation in space - in low energy conformations - is incompatible with efficient catalysis of this transformation). In such a scenario, it is unlikely that either major or minor alterations to the nature of the C-9 substituent will lead to a successful outcome.

Therefore, our search for a catalytic solution to this problem turned towards the C-5'-substituted systems. In Sections 2.0 and 3.0 were described the design and the efficient use of a novel class of dihydroquinine-derived catalysts characterised by the presence of a hydrogen-bond donating urea moiety at C-5'. The goal was to offer the practitioner more variation in the positioning of the catalyst's bifunctional components than is available from the widely employed C-9 and C-6'-substituted analogues (Section 1.5). Of these C-5' substituted systems, alkaloids **355** (Section 2.0) and **356** (Section 3.0) were demonstrated

to outperform C-9-substituted catalysts in highly enantioselective Henry reactions involving trifluoromethylketones and conjugate additions of alkylthiols to nitroolefins (respectively). We were curious as to the potential of these catalysts as promoters of the thiolytic DKR process.

Before commencing the investigation, we also attempted to augment the rigidity of these systems. Inspired by the known catalyst β -ICD (**73**, Section 1.4), we prepared the novel, rigid analogous C-5'-substituted urea-based catalyst **442** as illustrated in Scheme 4.1.

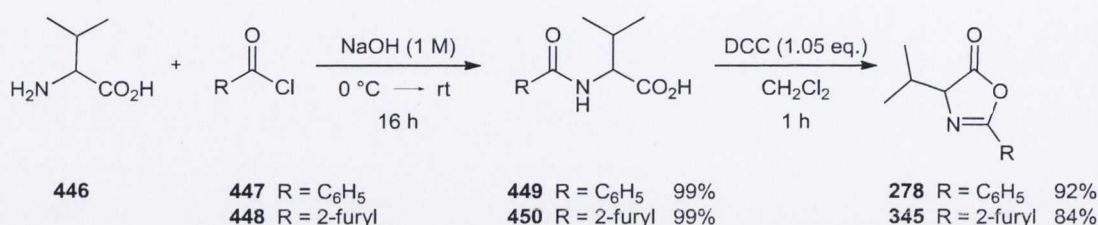


Scheme 4.1 Preparation of the more rigid urea-based β -ICD derivative **442**

The cyclised alkaloid derivative **443** was prepared from quinidine (**51**) according to a procedure developed by Waldmann and Kumar²²² which avoids significant demethylation at C-6' during the acid-mediated etherification reaction. Nitration of this material proceeded regioselectively at C-5' to furnish **444** in excellent yield. Reduction of the nitro group *via* Pd-catalysed hydrogenation afforded the marginally stable **445**, which was reacted with isocyanate **364** to give the required C-5'-substituted urea **442**.

4.2 The DKR of racemic azlactones *via* thiolysis: evaluation of the C-5'-urea-based cinchona alkaloid derivatives

Three different azlactones (**278**, **282** (prepared by Mr. Seán Tallon) and **345**) were selected to evaluate the catalytic performance of the C-5'-urea-based dihydroquinine-derived alkaloids in this reaction. Their synthesis was conducted following a procedure commonly used in our research group (Scheme 4.2).^{53,206}

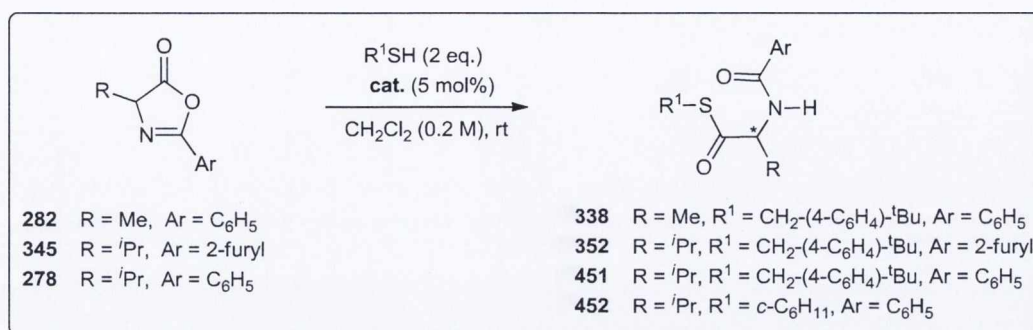


Scheme 4.2 Synthetic route towards the preparation of **278** and **345**

Benzoyl and furoyl *N*-protected valine analogues (*i.e.* **449-450**) were generated in quantitative yields using Schotten-Baumann conditions: racemic valine (**446**) was reacted with the appropriate acyl chloride (*i.e.* **447** or **448**) in an aqueous solution of sodium hydroxide (1 M). Once the protection was complete, the medium was acidified and the *N*-protected acid could be readily isolated by extraction with CH₂Cl₂. The obtained compound was then used in a *N,N'*-dicyclohexylcarbodiimide (DCC)-mediated dehydration reaction. After purification on a short pad of silica, the resulting azlactones (*i.e.* **278** and **345**) were ready to be used in an organocatalysed DKR protocol. Due to their high unstability (hygroscopic), it was necessary to use these substrates immediately following their synthesis.

Thus, **278**, **282** and **345** were subjected to thiolysis by either 4-*tert*-butyl benzyl mercaptan (**337**) or cyclohexane thiol (**429**) in the presence of either quinine (**50**) or one of the C-5'-urea-based catalysts **355**, **356** and **442** (Table 4.1).

Table 4.1 The evaluation of quinine and C-5' urea-substituted cinchona alkaloid catalysts in the thiolitic DKR of azlactones



entry	cat.	azlactone	thiol	product	time (h)	conv. (%) ^a	ee (%) ^b
1	-	282	337	338	96	0	-
2	50	282	337	338	96	100	17
3	355	282	337	338	96	10	2
4	356	282	337	338	96	100	-9
5	442	282	337	338	96	100	6
6	50	345	337	352	44	100	23
7	355	345	337	352	44	100	5
8	356	345	337	352	44	95	0
9	442	345	337	352	44	90	11
10	356	278	337	451	96	100	3
11	442	278	337	451	96	100	26
12	356	278	429	452	96	42	8
13	442	278	429	452	96	25	32

^aDetermined by ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

Beginning with the azlactone derived from *N*-benzoyl alanine (*i.e.* **282**) and the primary thiol **337**, it was found that in the absence of catalyst no reaction occurred after 96 h (entry 1). In the presence of the natural alkaloid quinine (**50**), quantitative thiolysis to afford thioester **338** occurred with modest enantioselectivity (entry 2). The C-5' substituted urea-based catalysts did not fare better than **50** in these processes: the C-9-substituted carbamate **355** proved a relatively inactive catalyst which furnished almost racemic product (entry 3),

and while the corresponding C-9 TBDPS-protected analogue **356** promoted efficient thiolysis, product enantioselectivity was poor (entry 4). It is noteworthy however that the C-9 substituent (which is not postulated to directly participate in catalysis) appeared able to influence not only activity, but also the sense of enantiodiscrimination in these reactions (entries 3 and 4). The rigid analogue **442** also catalysed a clean reaction to give **338** in quantitative conversion, however again with disappointing product *ee* (entry 5). Only marginal improvement was observed on changing the azlactone substrate (but not the thiol nucleophile) to the valine-derived furyl species **345** (entries 6-9), with none of the urea-based catalysts outperforming the parent alkaloid. More interestingly, while the C-9 OTBDPS substituted catalyst promoted the addition of **337** to the analogous phenyl-substituted azlactone **278** with quantitative conversion to furnish **451** as a near racemate (entry 10), use of the novel catalyst **442** resulted in considerably better (yet still modest) enantioselectivity (entry 11). A similar trend characterised the corresponding reactions involving the secondary cyclohexane thiol (*i.e.* **452**, entries 12 and 13), albeit with reduced catalyst activity.

4.3 The DKR of racemic azlactones *via* thiolysis: design of a new catalytic system and preparation of a small library of C-5' hydroxy-modified alkaloids

On analysis of the data outlined in Table 4.1, it is clear that while the alkaloid-derivatives evaluated were highly active at low loadings, the urea substituent at C-5' does nothing to augment the ability of the system to discriminate between the azlactone antipodes in the thiolysis process. Based on an inspection of models and low level (MM2) calculations (*e.g.* a representation of **442** is shown in Figure 4.1), we speculated that this may be due in part to the likely rather crowded nature of the catalyst's active site (as mentioned in Section 3.0). The catalyst conformations likely to facilitate synergistic action of the quinuclidine nitrogen atom and the urea functionality were characterised (by design) by a rather small pocket of space in which bifunctional catalysis must occur. If this were of insufficient volume to accommodate both the large azlactone substrate and the thiol, then less selective monofunctional catalysis would result. It is interesting in this regard that the relatively unhindered quinine alkaloid proved the most able promoter of the enantioselective DKR of **282** and **345** in the study outlined in Table 4.1

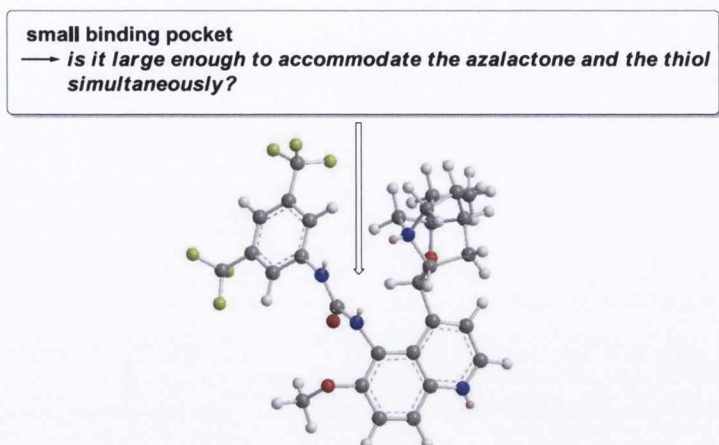


Figure 4.1 An energy minimised (MM2) representation of the likely catalytically active conformation of **442**

Attention therefore turned to C-5' substituted analogues with smaller steric requirements. Given the enormous success of the C-6' demethylated cupreine/cupreidine (*i.e.* **71-72**, Figure 4.2) class of catalysts (Section 1.4) and the burgeoning potential of C-5'-urea-based systems (albeit not in this particular process) we were surprised to learn that no C-5'-hydroxylated analogues (such as **453**, Figure 4.2) had been previously evaluated as bifunctional organocatalysts.

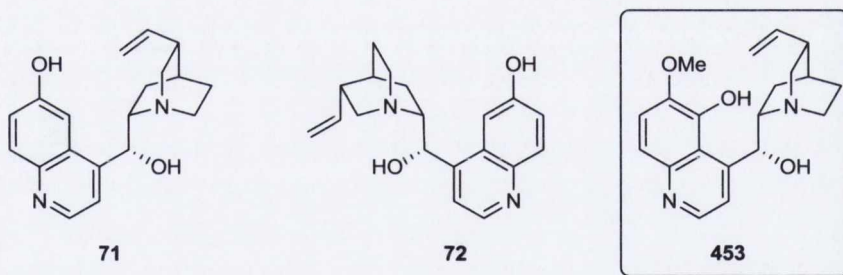


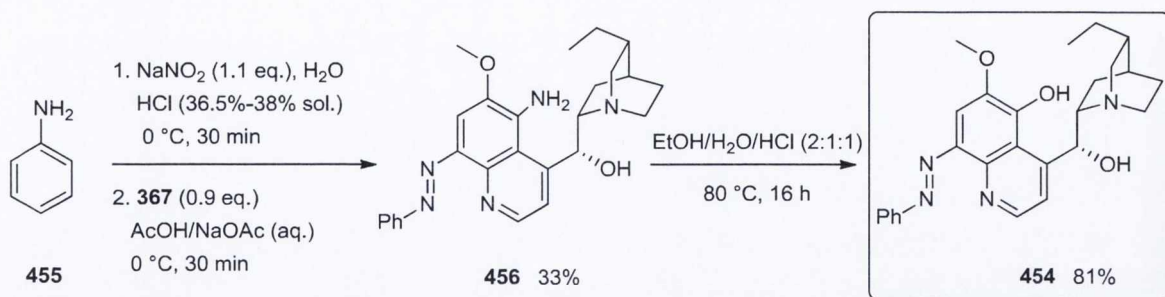
Figure 4.2 Cupreine (**71**), cupreidine (**72**) and the proposed new class of C-5' hydroxylated catalyst **453**

The synthesis of materials of general type **453** proved highly impractical: the key step in the synthesis is the conversion of the C-5'-amino-dihydroquinine to the corresponding phenol. Conversion of the C-5'-amino-dihydroquinine to the corresponding diazonium salt followed by hydrolysis failed to yield to the targeted compound. In 1920, Jacobs and Heidelberg²²³ demonstrated that the introduction of a phenylazo group in the 8' position

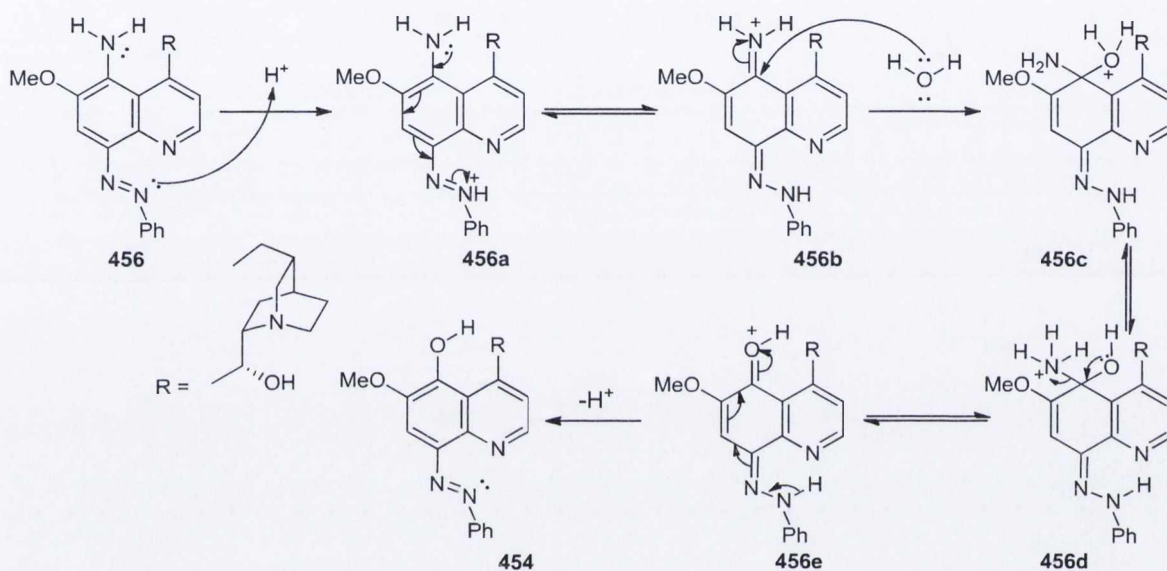
allowed facile hydrolysis of the C-5'-amino group in acidic media – without prior diazotisation. No mechanistic rationale for this has been furnished. We proposed that the conjugation with the azo group might have allowed (acid catalysed) tautomerisation to a structure incorporating an iminium at C-5' and a hydrazone function at C-8' (*i.e.* generation of **456b** from **456a**, Scheme 4.3). Hydrolysis of this imine-like tautomer in the presence of aqueous acid (to form **456c**, **456d** then **456e**), followed by deprotonation of **456e** to afford the corresponding phenol (*i.e.* **454**) may account for the facile incorporation of the hydroxy group in these azo compounds.

Since the C-8'-phenyldiazo appendage is located in a region of the molecule not likely to influence either binding or catalysis in a deleterious fashion, we prepared the C-5'-hydroxy catalyst **454** from C-5'-modified (amino) dihydroquinine analogue **367** as described by Jacobs and Heidelberger. It should be noted that the pK_a of the phenol moiety is of course likely to be influenced by the presence of the C-8'-azo group. However we anticipated that the likely effect would be to increase the acidity of the phenol and hence improve the potential hydrogen-bond donating prowess of the catalyst. To illustrate this theory, it is interesting to compare the pK_a of 4-azophenyl phenol (*i.e.* $pK_a = 8.2$, 25 °C, in H₂O) with the pK_a of phenol (*i.e.* $pK_a = 9.99$, 25 °C, in H₂O).

Aniline (**455**, Scheme 4.3) in concentrated HCl (0.4 M) was treated with an aqueous solution of sodium nitrite (8% in water) at 0 °C. Once the diazonium salt was formed, the obtained mixture was added at 0 °C to an aqueous solution of C-5'-amino dihydroquinine-derived **367** (previously treated with a saturated solution of sodium acetate). After a basic extraction and purification on column chromatography, alkaloid **456** could be separated from the remaining starting material. Unfortunately, it could not be isolated as a pure compound, since **456** underwent some degradation (on silica) when eluted from the column. The impure C-8'-diazo derivative was utilised directly in the next acidic hydrolysis step conducted at 80 °C. After 16 h, the C-5' hydroxy-modified alkaloid **454** was generated in 81% yield after selective precipitation in diethyl ether.

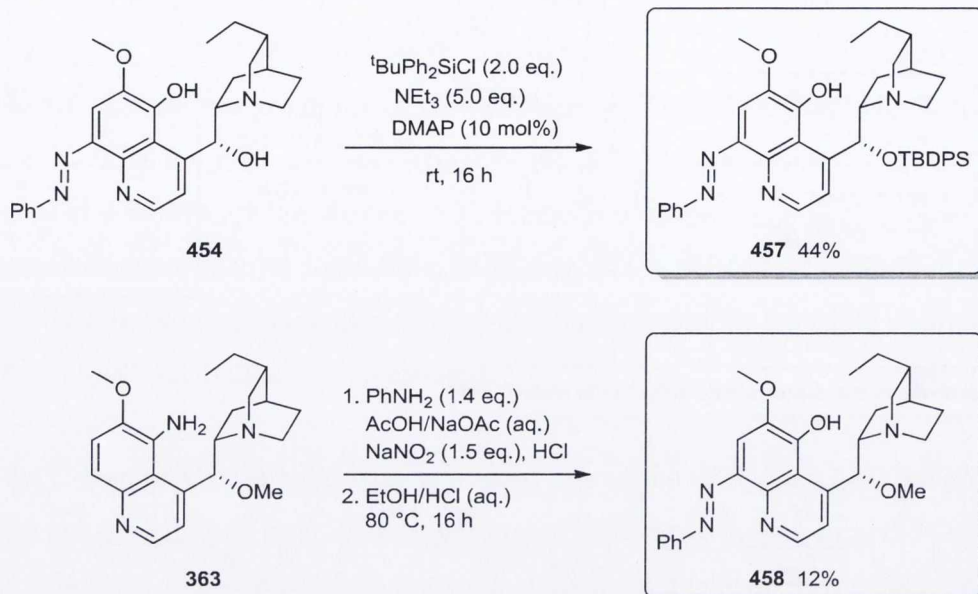


proposed role of the diazo functionality in the hydrolysis



Scheme 4.3 Synthesis of C-5' hydroxy alkaloid **454**

As it has been highlighted in previous sections (Sections 1.4, 1.5, 2.0, 3.0), the bulk of the C-9 substituent can exert significant influence over catalyst performance from both activity and selectivity standpoints. Therefore, in addition to the prototype structure **454**, novel analogues incorporating the large -OTBDPS and the considerably smaller -OMe moiety at C-9 (*i.e.* **457** and **458** respectively) were also prepared as depicted in Scheme 4.4.

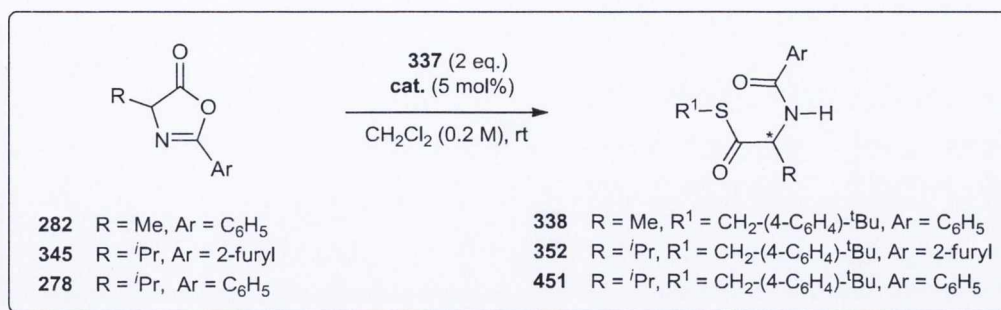


Scheme 4.4 Synthesis of the C-5' hydroxylated catalysts **457** and **458**

Treatment of **454** with 2 equivalents of *tert*-butyldiphenylsilyl chloride in the presence of NEt_3 (5 equivalents) and DMAP (10 mol%) led to the formation of the C-9-protected compound **457** after aqueous workup. The methoxy analogue **458** could not be conveniently accessed from **454** and was instead prepared from the key intermediate **363**: C-5'-amino derivative **363** could be azo-coupled with *in situ* generated benzene diazonium chloride. Heating the crude material in aqueous acidic media led to an hydrolysis reaction which converted the aromatic amine to the corresponding phenol **458** (Scheme 4.4). This alkaloid was obtained in a poor yield (12%) due to a considerable loss of material during the purification by column chromatography. Unfortunately, this ineffective method was required to isolate the compound pure since no selective precipitation methods could be successfully developed to furnish the targeted compound in pure form.

Once prepared, these catalysts were evaluated as promoters in the thiolytic DKR reaction of azlactones **278**, **282** and **345**. (Table 4.2).

Table 4.2 The evaluation of the C-5' hydroxylated cinchona alkaloid catalysts



entry	cat.	azlactone	product	time (h)	conv. (%) ^a	ee (%) ^b
1	454	282	338	96	80	31
2	457	282	338	96	52	14
3	454	345	352	44	75	34
4	457	345	352	44	51	7
5	454	278	451	96	100	40
6	457	278	451	96	60	5

^aDetermined by ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

An immediate improvement in stereocontrol was observed: the relatively unhindered (*i.e.* unsubstituted at C-9) catalyst **454** promoted the thiolysis of the alanine-derived azlactone **282** with considerably higher (albeit still modest) levels of enantioselectivity than was previously possible using either quinine (**50**) or the C-5' urea-based systems **355** and **356** (entry 1 Table 4.2, compare with entries 2-5, Table 4.1). The more bulky analogue **457** participated in less selective catalysis (entry 2, Table 4.2). Gratifyingly, this trend was exaggerated in thiolysis reactions involving azlactones derived from the more hindered *N*-furoyl and *N*-benzoyl valine (*i.e.* **345** and **278** respectively, entries 3-6) where levels of product *ee* using catalyst **454** comfortably exceeded the previous literature benchmark (**352** was obtained in 82% and 23% *ee* with alkaloid **327**, Section 1.9.2).

4.4 The DKR of azlactones *via* thiolysis: optimisation of the reaction conditions

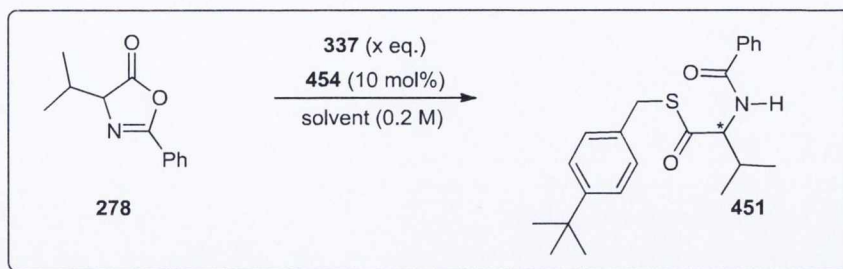
With the optimum catalyst in hand, we next optimised the reaction conditions. We wished first to evaluate the compatibility of the alkaloid derivative **454** with catalytic methods involving low temperatures, different reaction media and increased amount of 4-*tert*-butyl

benzyl mercaptan (Table 4.3). Undertaking the ring opening of azlactone at -30 °C under otherwise identical conditions to those outlined in Table 4.2 (entry 1, Table 4.3) led to a significant increase in enantioselectivity (62% *ee*) without damaging the activity of the catalyst (entry 2, Table 4.3). At -50 °C, thioester **451** was produced with improved enantiocontrol (70% *ee*) and conversion that was maintained at an acceptable level (48%, entry 3). Unfortunately, further lowering of the temperature led to a small improvement in *ee* with a significant drop in reaction rate (entry 4).

Subsequent modification of the reaction medium using CHCl₃, MTBE or toluene did not provide better results (entries 5-7). In fact, chlorinated solvents were found far superior solvents in this transformation to both MTBE and toluene.

In an attempt to increase the rate of the process at -70 °C, the DKR of **278** was undertaken with increased nucleophile loadings. Gratifyingly, treatment of the valine-derived azlactone with 4 equivalents of alkane thiol **337** in the presence of catalyst **454** furnished the thioester **451** with a faster rate and enantiocontrol (44%, 81% *ee*, entry 8). The use of 8 equivalents resulted in a less selective process (entry 9).

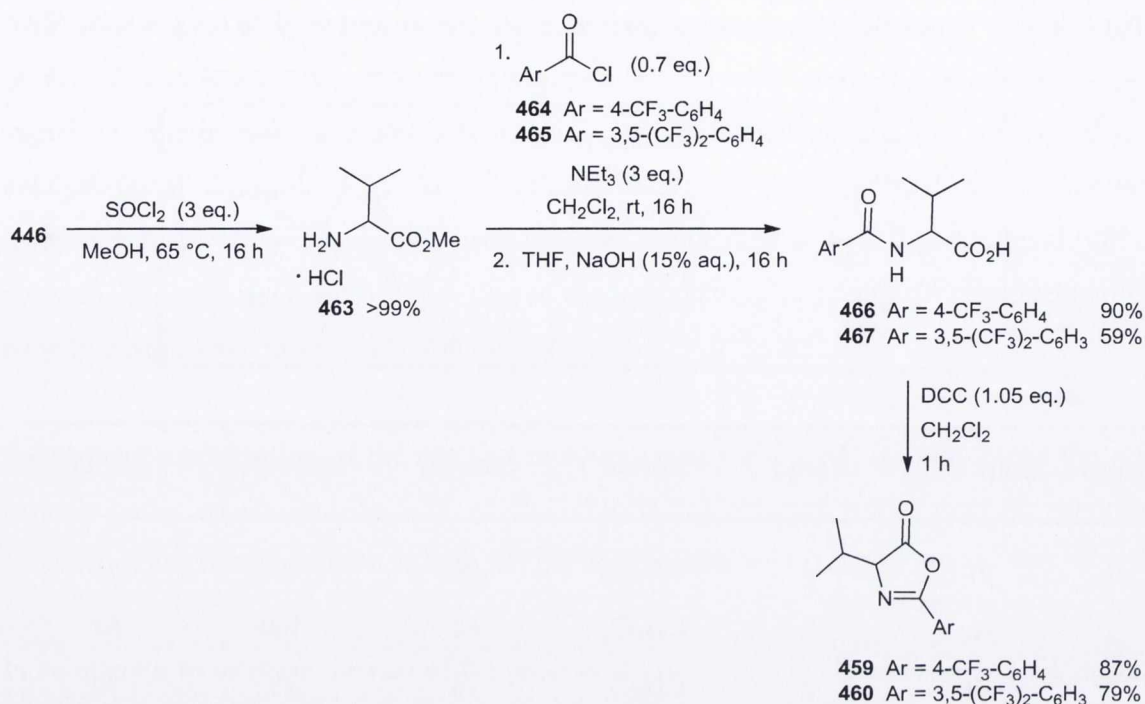
Table 4.3 The effect of reaction temperature and the solvent used on the DKR of **278**



entry	temp. (°C)	x (eq.)	solvent	time (h)	conv. (%) ^a	ee (%) ^b
1	rt	2	CH ₂ Cl ₂	96	100	40
2	-30	2	CH ₂ Cl ₂	68	100	62
3	-50	2	CH ₂ Cl ₂	16	48	70
4	-70	2	CH ₂ Cl ₂	68	32	75
5	-50	2	CHCl ₃	96	66	55
6	-50	2	MTBE	96	34	15
7	-50	2	toluene	96	20	-2
8	-70	4	CH ₂ Cl ₂	68	44	81
9	-70	8	CH ₂ Cl ₂	68	51	66

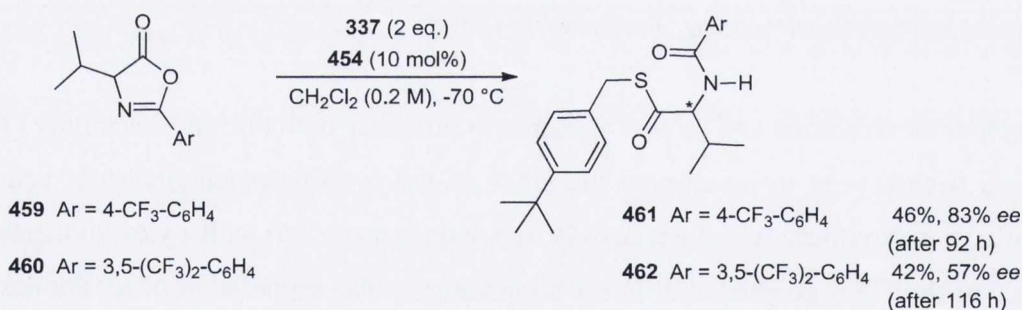
^aDetermined by ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

Noting that the azlactone aryl moiety appeared to influence both rate and selectivity (Table 4.2), we wished next to investigate the DKR of the *p*-trifluoromethylbenzoyl and 3,5-bis(trifluoromethyl)benzoyl azlactones **459** and **460** (Scheme 4.5) with a view to increasing the rate of the DKR conducted at lower temperatures. The preparation of azlactones **459** and **460** required the use of a different synthetic pathway than the Schotten-Baumen conditions (more electrophilic acyl chlorides **464** and **465** hydrolysed first under these conditions). Instead, they could be generated in 3 steps from racemic valine (**446**, Scheme 4.5). Amino acid **446** was first esterified using thionyl chloride (3 eq.) in methanol. The resulting methyl ester protected salt was then reacted with the appropriate acyl chloride (*i.e.* **464** or **465**) in the presence of NEt₃ in CH₂Cl₂. Once the *N*-protected valine derivatives were generated, hydrolysis of the ester groups were carried out under basic conditions. The resulting intermediate **466** and **467** were then ready for DCC-mediated cyclisation to afford azlactones **459** and **460**.



Scheme 4.5 Synthesis of azlactones **459** and **460**

Catalyst **454** promoted the ring-opening of **459** with a significant improvement in both rate and enantioselectivity at $-70\text{ }^\circ\text{C}$ (Scheme 4.6). Considerably lower selectivity was observed during the synthesis of **462**.

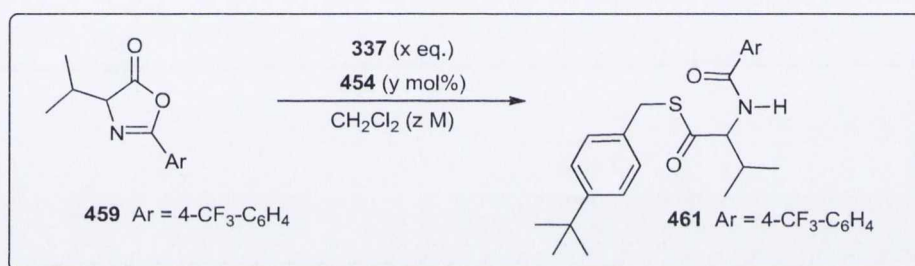


Scheme 4.6 Alkaloid **454** mediated DKR of azlactones **459** and **460**

With the superior substrate (*i.e.* **459**) identified, the influence of the thiol loading on catalysis was examined: treatment of **459** with one equivalent of the thiol **337** (instead of 2 equivalents, entry 1, Table 4.4) in the presence of **454** (5 mol%) in CH_2Cl_2 (0.2 M) led to a small improvement in *ee* with an attendant drop in reaction rate (entry 2, Table 4.4). Attempts to improve selectivity while avoiding a deleterious reduction in rate by increasing catalyst loading to 10 mol% and reducing the reaction temperature to $-50\text{ }^\circ\text{C}$ proved a

qualified success (entry 3): **461** was formed in similar conversion but with improved *ee* (72%). Lowering the concentration did not prove successful (entry 4). As expected, increasing the catalyst loading to 20 mol% and keeping the concentration of the reaction at 0.1 M led to a faster rate without altering the selectivity (entry 5). While a reduction in concentration and reaction temperature led to very good enantioselectivity (entry 6), the obtained conversion under these conditions was unacceptable. Synthetically acceptable conversion and product *ee* from the DKR of **459** with catalyst **454** did not seem attainable when using 1 equivalent of thiol.

Table 4.4 Attempts to optimise the reaction conditions when using 1 equivalent of thiol

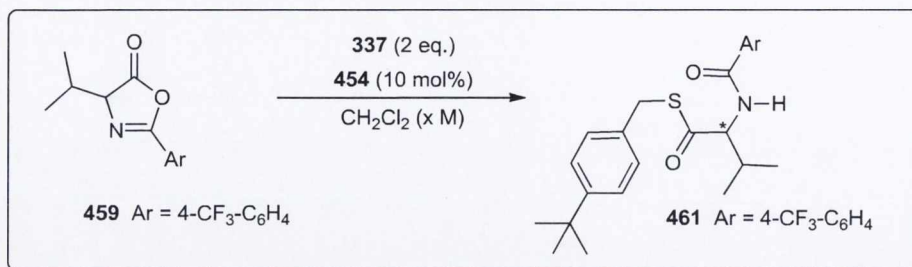


entry	temp. (°C)	x (eq.)	y (mol%)	z (M)	time (h)	conv. (%) ^a	<i>ee</i> (%) ^b
1	rt	2	5	0.2	96	100	40
2	rt	1	5	0.2	68	50	58
3	-50	1	10	0.2	44	52	72
4	-50	1	10	0.1	44	48	72
5	-50	1	20	0.1	44	69	72
6	-85	1	10	0.1	68	15	86

^aDetermined by ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

Returning to conditions involving the use of 2 equivalents of thiol, the next step was to identify the optimum temperature to use to achieve the best compromise between activity and selectivity. The selectivity of the reaction was found to increase when the temperature was lowered from room temperature (entry 1, Table 4.5) to -60 °C and -70 °C (entries 2-4, Table 4.5). However, undertaking the DKR process at -80 °C provided less selectivity and activity (entry 5).

Table 4.5 Effect of the temperature and the solvent used on the DKR of **459**



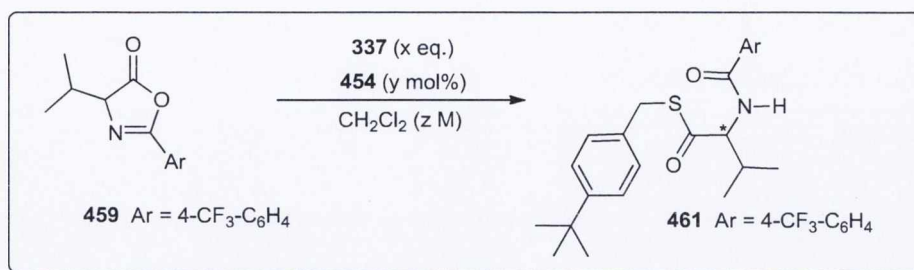
entry	temp. (°C)	x (M)	time (h)	conv. (%) ^a	ee (%) ^b
1	rt	0.2	96	100	40
2	-60	0.2	20	59	78
3	-70	0.2	92	46	83
4	-70	0.1	92	36	86
5	-80	0.1	44	33	78

^aDetermined by ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

Compared to the best results obtained thus far (condition set shown in entry 1 Table 4.6), conducting the reaction at -70 °C and increasing either the thiol loading or the concentration of the reaction medium was a success in terms of activity (entries 2-3, Table 4.6), albeit at the expense of the selectivity. In parallel, the use of higher catalyst loadings (either 15 or 20 mol%) also led to faster rates, but again relatively low selectivity (entries 4-5, Table 4.6).

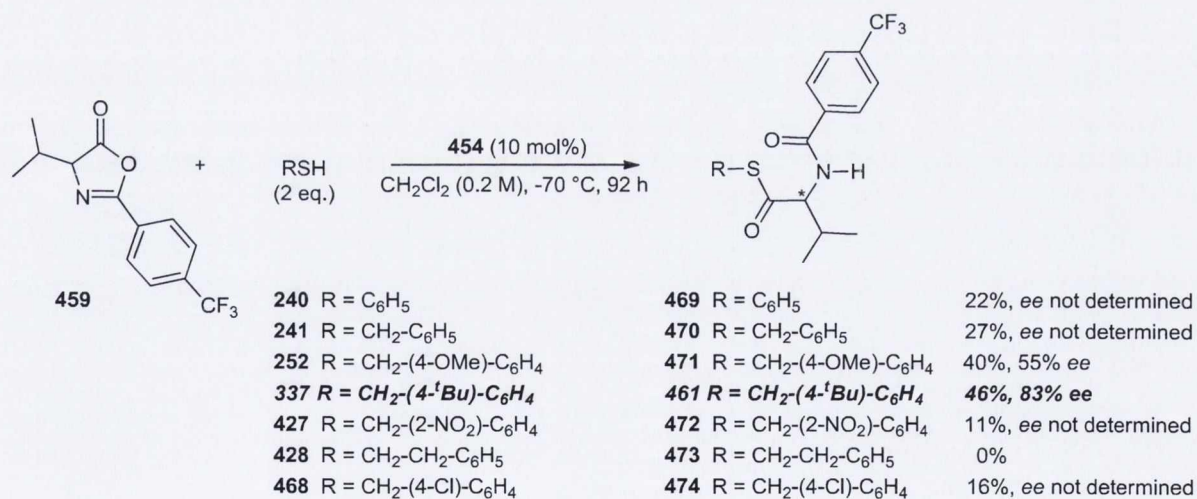
Since we were not able to determine conditions providing a satisfying balance between activity and selectivity, we decided to modify the steric and electronic properties of the nucleophile involved in the reaction (Scheme 4.7). Disappointingly, no thiol proved to be a better nucleophile for this process than **337**. Thus, very low conversions (11-27%, *i.e.* thioesters **469**, **470**, **472** and **474**) were obtained when different mercaptan derivatives (*i.e.* **241**, **427**, **468**) and more acidic thiophenol (**240**) were utilised. It is also worth mentioning that no trace of thioester **473** could be detected after 92 h when non-benzylic phenylethane thiol (**428**) was employed as the nucleophile.

Table 4.6 Increase of the thiol/catalyst loadings and the concentration of the reaction medium



entry	temp. (°C)	x (eq.)	y (mol%)	z (M)	time (h)	conv. (%) ^a	ee (%) ^b
1	-70	2	10	0.2	92	46	83
2	-70	3	10	0.2	92	50	83
3	-70	2	10	0.3	92	44	80
4	-70	2	15	0.2	112	64	75
5	-70	2	20	0.2	92	83	63

^aDetermined by ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.



Scheme 4.7 Use of different thiols in the DKR of **459**

Only *p*-methoxy-substituted mercaptan **252** could be added to azlactone **459** in similar conversion to that observed when 4-*tert*-butyl benzyl mercaptan (**337**) was utilised. However, the enantioselectivity of the reaction was considerably lower.

With these results in hand, it became clear that it would not be possible to improve (at once) both the activity and the selectivity of the process to some synthetically useful level. Since the only efficient catalyst system that had been reported in the literature for the thiolysis of azlactones (*i.e.* alkaloid derivative **327**, Section 1.9.2) afforded excellent conversions but only moderate product *ee*, we decided to focus on developing a catalytic system that would provide high enantiocontrol, despite lower activity.

Employment of a strategy involving careful manipulation of both the concentration and the thiol loading at -70 °C (entries 1-3, Table 4.7) allowed the identification of a set of conditions (entry 3) under which **461** could be formed in 39% conversion and 91% *ee* at a reaction concentration of 0.05 M. It should be highlighted that the same level of conversion was observed after 44 h (39%) and 92 h (40%, entry 3), indicating that the reaction was almost complete after 44 h. Further attempts to improve selectivity through dilution produced only progressively slower reactions (entries 4-6). However, we found that it was possible (at the cost of a small degree of enantioselectivity) to partially mitigate this through increases in either catalyst or thiol loading (entries 7-10).

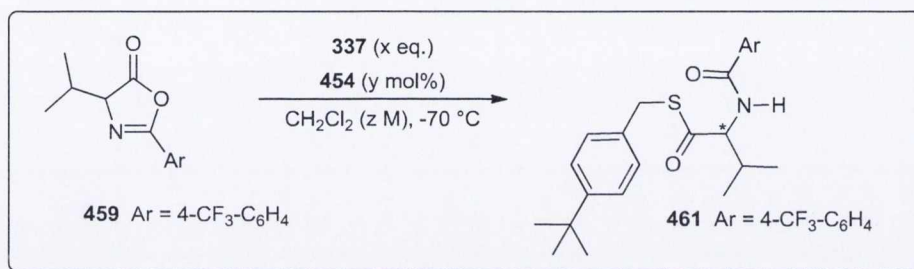
Interestingly, thiol loading (entries 7-9) appeared to be more important than catalyst loading (entry 10). To investigate the possibility of catalyst decomposition being significant in these reactions, we compared a reaction using 20 mol% of catalyst to one involving the same catalyst loading spread between two portion-wise additions of 10 mol% each (the second portion was added after 44 h). To our surprise the portion-wise addition strategy proved inferior (entries 10-11).

Anticipating the unacceptable level of conversions that could be obtained when using branched substrates, another two sets of conditions were devised involving higher thiol and/or catalyst loadings. The conditions used in entries 12 and 13 proved interesting alternatives if higher activities were targeted: under these set of conditions, the valine-derived thioester **461** was produced in 69% conversion and moderate enantiomeric excess.

In summary, this study produced four useful sets of reaction conditions; one which allowed the DKR of an azlactone by thiolysis to occur in >90% *ee* (for the first time) and 39% conversion (condition set A, entry 3, Table 4.7), another involving the use a greater excess of thiol which led to the generation of the product in slightly lower (yet still unprecedented) 87% *ee* and 51% conversion (condition set B, entry 8, Table 4.7). For the

use of difficult branched substrates, another two sets of conditions were optimised which provided faster rates (58-69%) and moderate but still acceptable enantioselectivities (73-82% *ee*, condition sets C and D, entries 12 and 13 respectively, Table 4.7).

Table 4.7 Optimisation of the concentration of the reaction medium in conjunction with the thiol loading

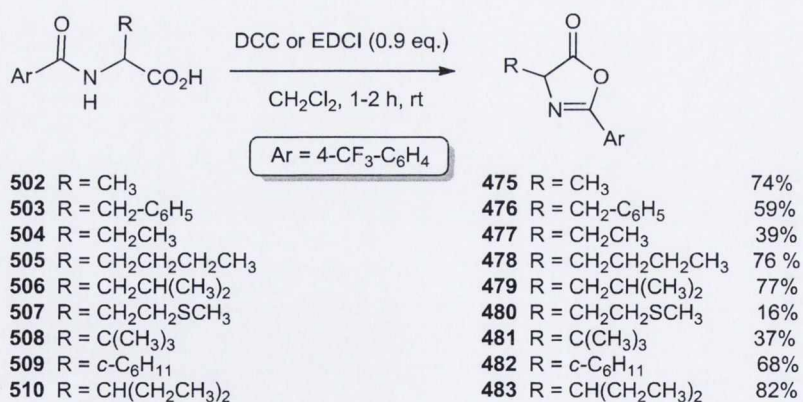
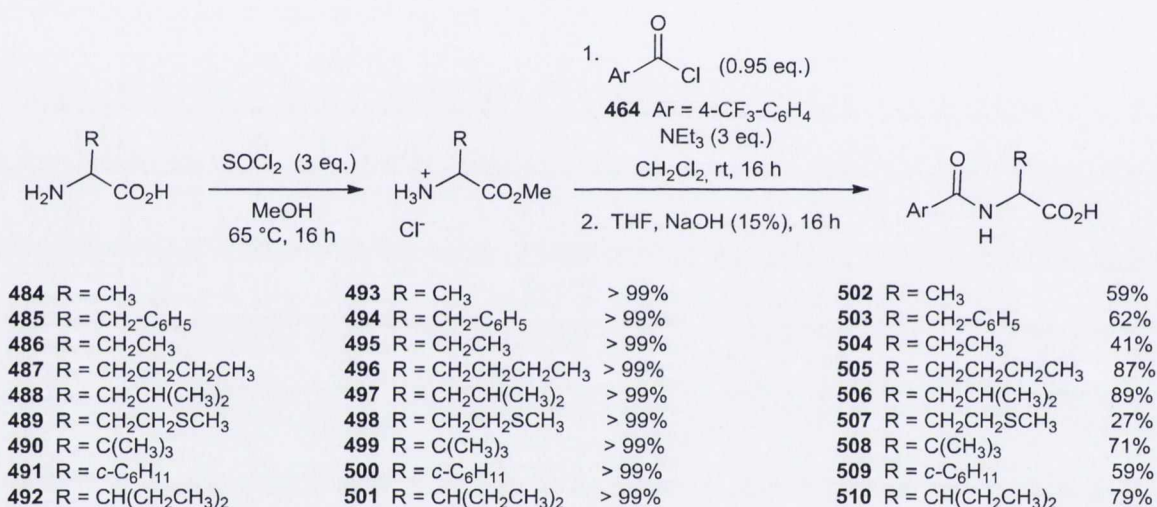


entry	y (mol%)	x (eq.)	z (M)	time (h)	conv. (%) ^a	<i>ee</i> (%) ^b	set
1	10	2	0.1	92	36	86	
2	10	3	0.07	92	36	87	
3	10	2	0.05	44	39(40) ^d	91(90) ^d	A
4	10	2	0.03	92	21	91	
5	10	2	0.01	92	11	88	
6	10	2	0.005	92	4	nd ^c	
7	10	3	0.03	92	35	87	
8	10	4	0.03	92	51	87	B
9	10	6	0.03	92	53	83	
10	20	2	0.03	92	36	85	
11	10+10	2	0.03	92	27	88	
12	10	4	0.05	92	58	82	C
13	20	4	0.05	92	69	73	D

^aDetermined by ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC. ^cNot determined. ^dThe results in parentheses correspond to a 92 h reaction time.

4.5 The DKR of azlactones *via* thiolysis: substrate scope

Attention now focused on the issue of substrate scope. For this purpose, several azlactones (unbranched and branched, *i.e.* **475-483**, Scheme 4.8) were prepared from amino acids **484-492** and according to the synthetic route described in Scheme 4.5: *via* the synthesis of the hydrochloride salts **493-501** (Scheme 4.8) followed by the formation of the corresponding *N*-protected amino acid derivatives (*i.e.* **502-510**). A DCC- or an EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide)-mediated cyclisation was finally undertaken for the preparation of each azlactone.



Scheme 4.8 Synthesis of azlactones **475-483**

Once prepared, azlactones **475-483** were utilised in a DKR process catalysed by the C-5'-hydroxy dihydroquinine derivative **454** (Tables 4.8 and 4.9).

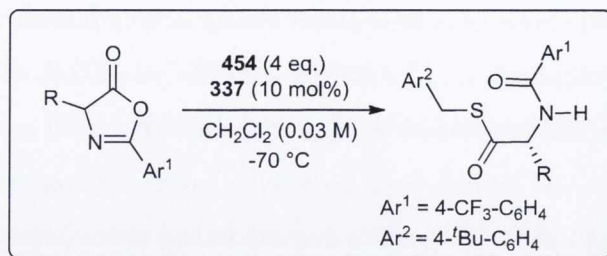
The benchmark catalyst **327** (Section 1.9.2) failed to provide excellent levels of enantiocontrol (*i.e.* >90% *ee*) with any substrate, with the problem particularly exacerbated using azlactones derived from branched chain amino acids such as valine. As such, we were pleased to find that **454** could catalyse the thiolytic DKR of an alanine-derived azlactone **475** with thiol **337** to furnish **511** in 55% yield and 84% *ee* (entry 1, Table 4.8). The enantioselectivity could be improved slightly at lower loadings of the thiol (86% *ee*), at the expense of product yield (35%). The corresponding phenylalanine-derived azlactone **476** behaved in a similar manner; affording thioester **512** in 84% *ee* and 41% yield (entry 2).

Thioesters formally stemming from α -unbranched unnatural amino acid-derived azlactones **477-478** could also be synthesised using this methodology in high *ee* (**513** and **514**, entries 3 and 4). Analogues **515** and **516**, based on the naturally occurring isoleucine and methionine, were also firmly within the orbit of the process and could be formed with excellent *ee* (entry 5 Table 4.8 and entry 1 Table 4.9).

Somewhat gratifyingly, catalyst **454** proved compatible with azlactones prepared from the previously recalcitrant branched chain amino acids. The previously unobtainable *tert*-leucine-derived thioester **517** could be formed in either 90% *ee* (albeit with low isolated yield (26%), entry 2, Table 4.9) or in lower but still satisfying selectivity (77% *ee*) and moderate yield (47%). The unnatural α -cyclohexyl substituted variant **518** was generated with almost identical efficiency and enantioselectivity (entry 3). Thioester **519** is derived from an extraterrestrial amino acid isolated from the carbonaceous Murchison meteorite²²⁴ and was formed in comparatively good yield (56%) and 90% *ee* (entry 4) using conditions D.

To the best of our knowledge this is the first enantioselective synthesis of an NCL-ready thioester variant of this abiotic amino acid. In every case where a comparison was possible, the new methodology outlined above using catalyst **454** provided the thioester products with significantly higher levels of enantiomeric excess than had been previously possible. In addition to providing highly enantioenriched thioesters of potential utility in coupling and NCL methodologies, the scope has been expanded to include azlactones from previously highly problematic branched chain amino acids.

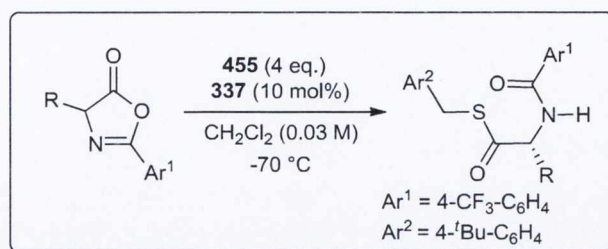
Table 4.8 Evaluation of the substrate scope of our catalytic process

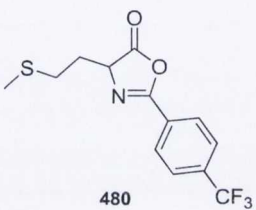
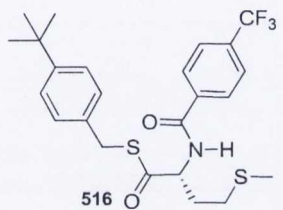
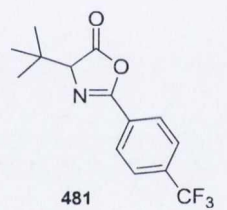
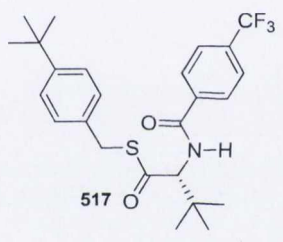
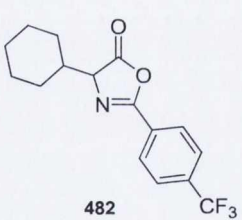
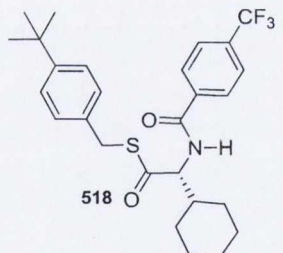
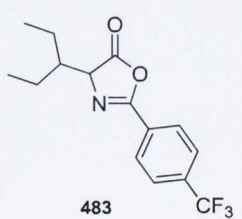
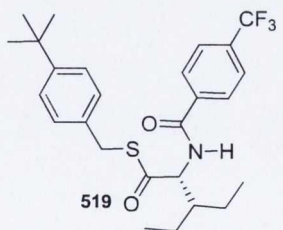


entry	azlactone	products	conditions	time (h)	yield (%) ^a	ee (%) ^b
1			A	68	55	84
			B	68	35	86
2			A	92	41	84
			B	92	46	79
3			A	68	62	81
			B	68	47	85
4			B	68	32	88
5			A	68	60	89
			B	68	48	86

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC.

Table 4.9 Evaluation of the substrate scope of our catalytic process



entry	azlactone	products	conditions	time (h)	yield (%) ^a	ee (%) ^b
1			A	68	24	92
			B	68	32	91
2			A	92	26	90
			B	92	22	89
			C	92	31	87
			D	92	47	77
3			A	68	26	89
			B	68	17	89
			D	68	35	85
4			A	92	16	87
			B	92	<10%	nd ^c
			C	68	46	90
			D	68	56	90

^aIsolated yield after column chromatography. ^bDetermined by CSP-HPLC. ^cNot determined.

4.6 The limitations of the methodology

An obvious limitation associated with this catalytic strategy was lower product yields, which ranged from 24 to 60%. We also observed that, when the progress of these reactions

was followed using ^1H NMR spectroscopy, the reaction rate appeared to diminish rapidly after *ca.* 20-40% conversion (*i.e.* after 68 h). For instance, when monitoring the synthesis of thioester **519** (entry 4, Table 4.9, condition set D), the conversion determined after 6 days (57%) was almost identical to that after only 68 h (56%). It is noteworthy that the ^1H NMR spectrum of the crude reaction after 6 days only indicated the presence of the thioester **519** and the unreacted starting material **483**; *i.e.* no trace of side products could be detected. The same observation could be made for reactions involving each different azlactone evaluated. We speculated that catalyst acylation could be responsible (most likely at C-9, *e.g.* **520**, Figure 4.3). Another explanation would involve the hydrolysis of the azlactone by adventitious water, which would lead to catalyst poisoning *via* protonation by the product *N*-aryl amino acid (*i.e.* **521**, Figure 4.3).

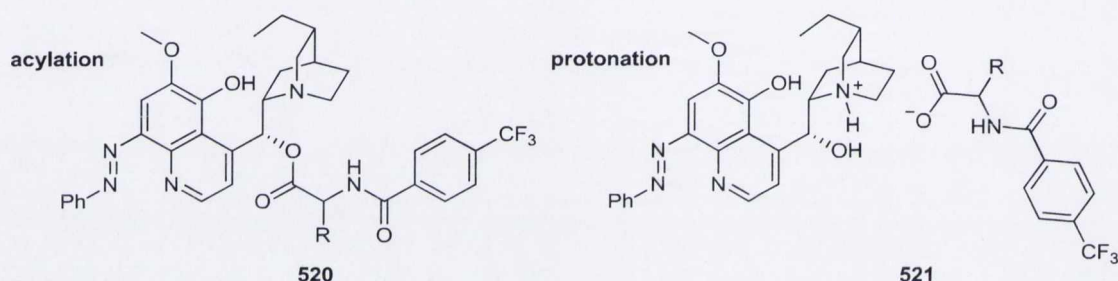
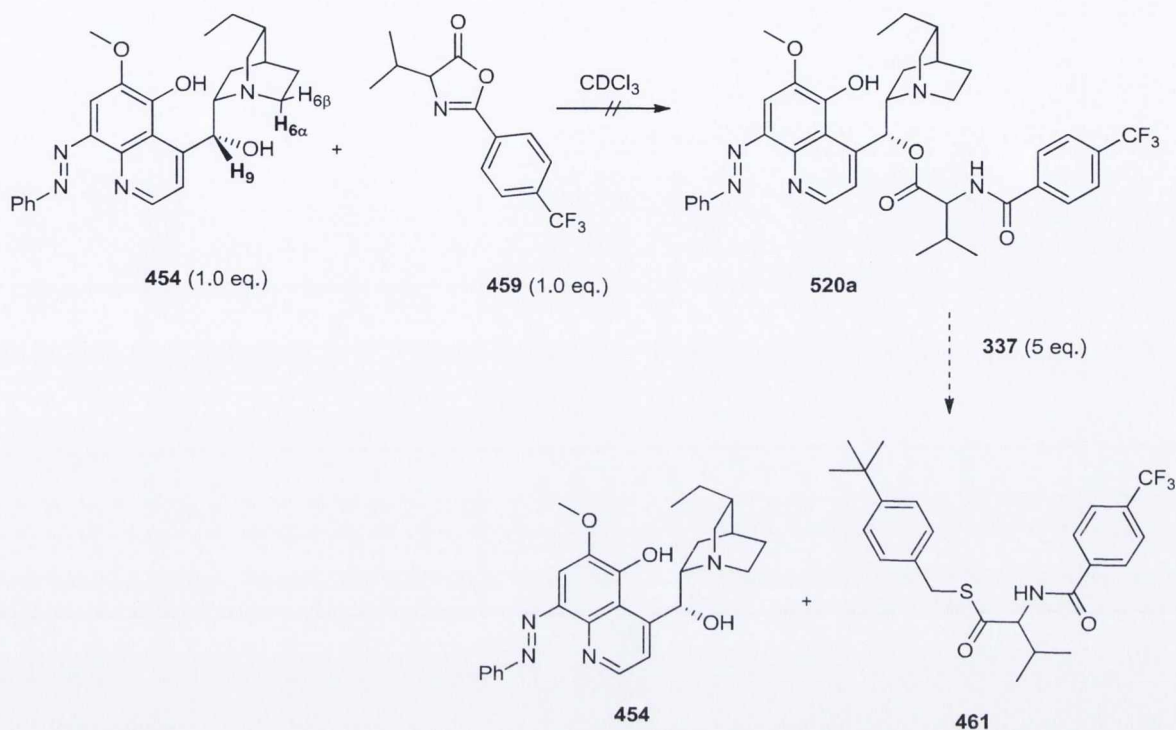


Figure 4.3 Potential catalyst fates leading to inactivity

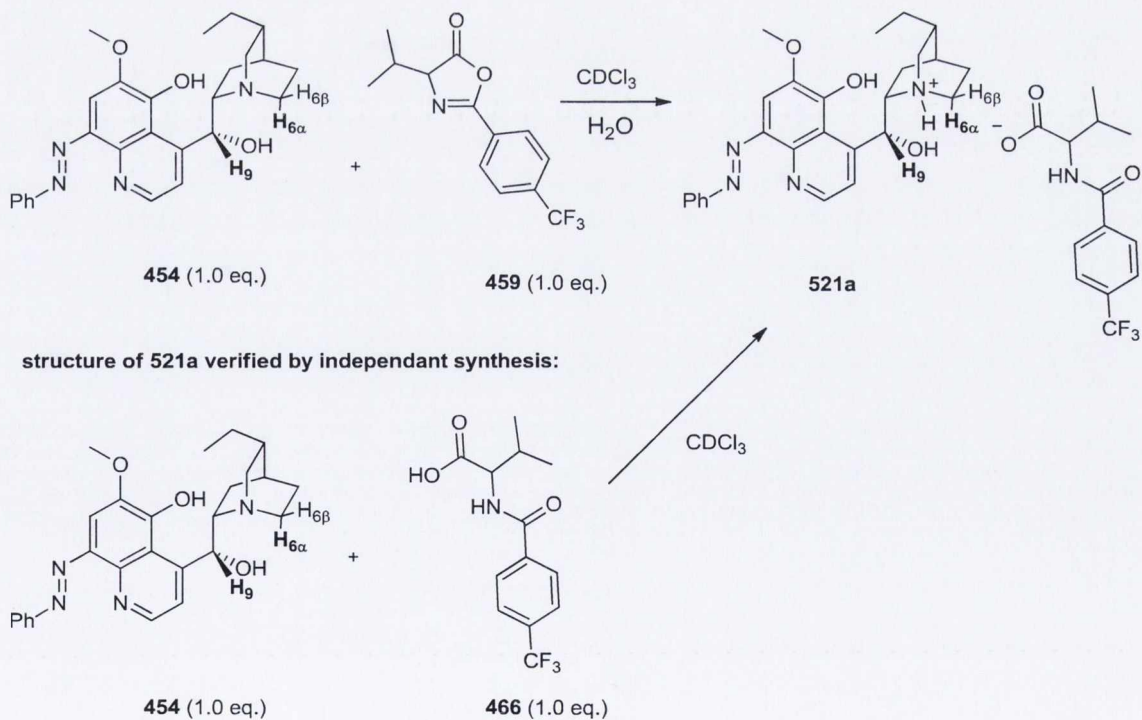
To distinguish between these two possibilities, we reacted azlactone **459** with catalyst **454** (Scheme 4.9) in CDCl_3 (dried over K_2CO_3). Over a period of 4 days, we observed the conversion of **459** and **454** into a new product. The peaks characteristic of **459** completely disappeared (*i.e.* the azlactone was fully consumed) and several key resonances associated with the catalyst (in particular H-9 and H-6 α) shifted downfield during the reaction.

We first postulated that the C-9 acetylated catalyst **520a** was formed by nucleophilic attack on the azlactone **459** by the C-9 hydroxyl group of **454** (Scheme 4.9, first hypothesis). It was theorised that **520a** might preferentially adopt a conformation that would not be propitious for the catalysis of the DKR to occur, explaining the slow rate of the reaction after 68 h. To test the validity of this hypothesis, 4-*tert*-butyl benzyl mercaptan (**337**, 5 eq.) was added to the product of the reaction between catalyst **454** and azlactone **459**.

First hypothesis: catalyst acetylation



Second hypothesis: catalyst poisoning *via* protonation

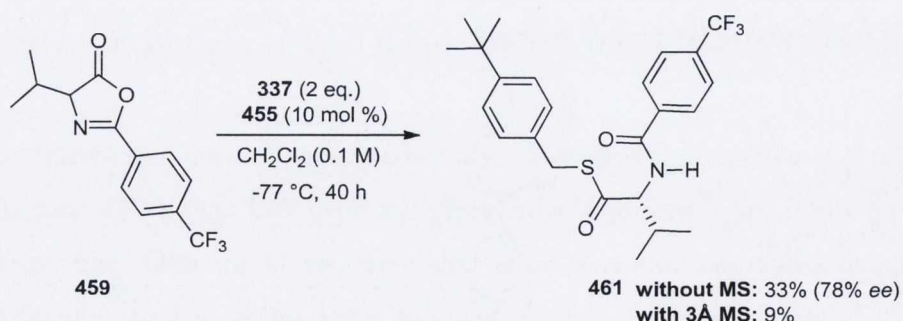


Scheme 4.9 Identification of adventitious water as the source of catalyst deactivation

If **520a** was formed when **459** was reacted with **454**, we expected to observe (using ^1H NMR spectroscopy) the formation of the thioester **461** along with the regeneration of the free catalyst **454**. However, no reaction could be detected after 10 days.

We speculated then that the catalyst might be deactivated *via* the formation of its protonated species **521a** (Scheme 4.9, second hypothesis). This could happen if **454** was somehow in contact with the product of the hydrolysis of azlactone **459** (*i.e.* **466**). Interestingly, when independently mixing catalyst **454** and *N*-*para*-(trifluoromethyl)benzoyl valine **466** (in a 1:1 ratio) in CDCl_3 and when comparing the resultant ^1H NMR spectrum with that those obtained from *in situ* monitoring of the reaction between catalyst **454** and azlactone **459**, the same key resonances associated with the catalyst shifted downfield (H-9 and H-6 α) were observed.

Consequently, we speculated that the same ion pair may be formed during our catalytic DKR of azlactones. In other words, the hydrolysis of the azlactone (*i.e.* water) was postulated to be the source of the sub-optimal yields associated with the methodology. This was quite a surprise, as our group had never encountered hydrolysis (in both related azlactone DKR reactions and other catalytic methodologies involving thioester intermediates/products) as a problem previously when standard precautions to eliminate adventitious water were taken. In an attempt to circumvent this, we carried out the reaction (under unoptimised conditions) in the presence of 3Å molecular sieves (MS). Unfortunately, under these conditions the sieves appeared to actually retard the reaction to a considerable extent (Scheme 4.10).



Scheme 4.10 Attempts to improve yield through the use of molecular sieves

As this thesis was being prepared, we became aware that Hatakeyama had reported that β -ICD (**73**) (when recrystallised from $\text{MeOH}/\text{H}_2\text{O}$) contained a bound water molecule in its

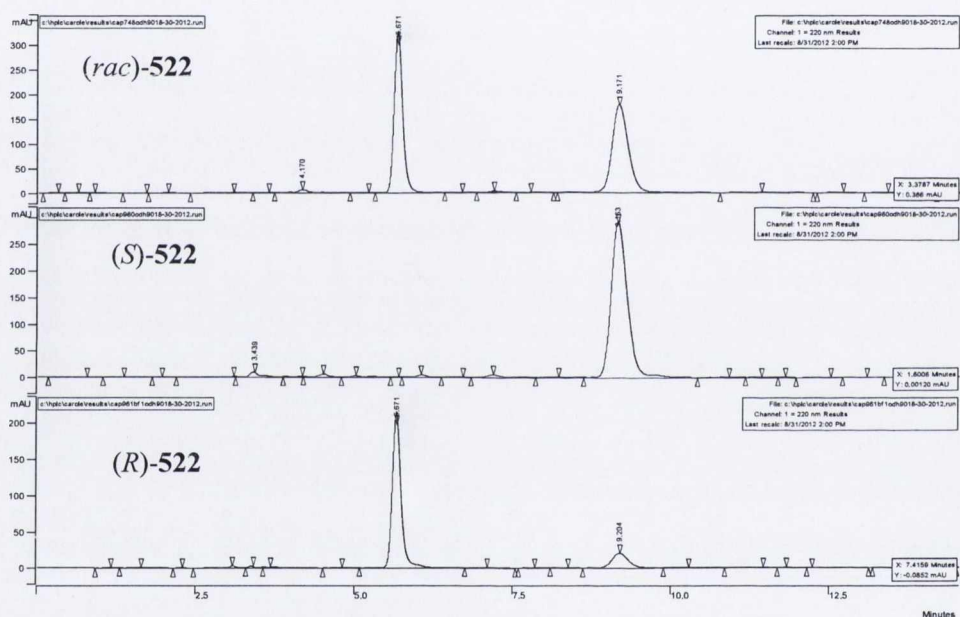
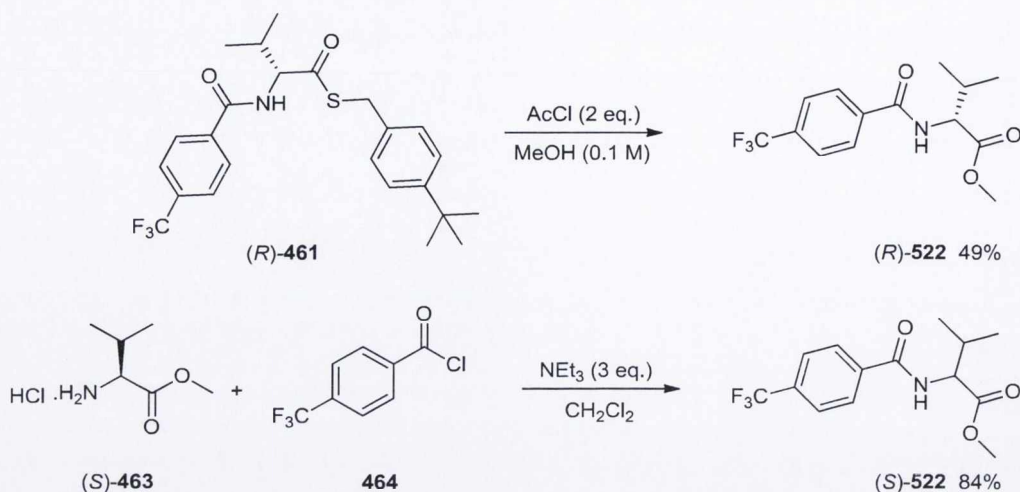
crystalline form.¹⁰⁰ Thus, it is tempting (by analogy) to suggest that **454** (which is also a demethylated cinchona alkaloid) may be particularly hygroscopic, which would explain in part the high propensity for hydrolysis despite considerable precautions to avoid the introduction of moisture into the system.

4.7 Determination of the absolute configuration of the obtained amino acid derivatives

The absolute configuration of (*R*)-**461** (derived from the thiolytic DKR of azlactone **459**) was elucidated by first converting (*R*)-**461** to the corresponding methyl ester (*R*)-**522** (Scheme 4.11) and then comparing the HPLC retention times (CSP-HPLC, Scheme 4.11) with both these associated with a sample of (*S*)-**522** and racemic-**522** (prepared independently from (*S*)-valine methyl ester and the corresponding racemic material respectively (Scheme 4.11)).

We were pleased to find that our catalytic method led to the synthesis of the less readily available, unnatural (*R*)-protected amino acid from racemic azlactones (Scheme 4.11).

To confirm this result, the absolute configuration of thioester (*R*)-**515** (Table 4.8) was also determined following the same method. The absolute configuration of the other thioesters, were then deduced by analogy.



Scheme 4.11 Synthesis of **(R)-522** and **(S)-522** for comparative HPLC analysis and determination of the absolute configuration of **(R)-461**

4.8 Conformational studies

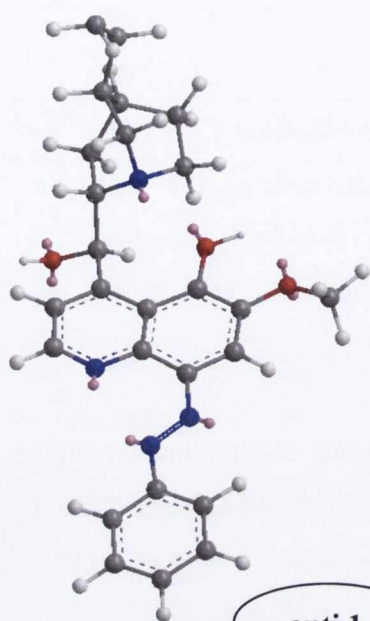
Finally, we were intrigued as to origins of the clear superiority of the C-9 hydroxylated catalyst **454** over its C-9 substituted analogues **457** and **458**. Having ruled out catalyst acylation by the azlactone (*vide supra*), we speculated that conformational issues could be a factor in determining catalyst efficacy. Numerous investigations into the conformation of cinchona alkaloids and derivatives have been reported (Section 1.3.3.1.3), however since C-5' hydroxylated systems have been hitherto neglected in a catalysis context, it is perhaps unsurprising that nothing is known regarding their conformational preferences.

4.8.1 Rationale and analysis

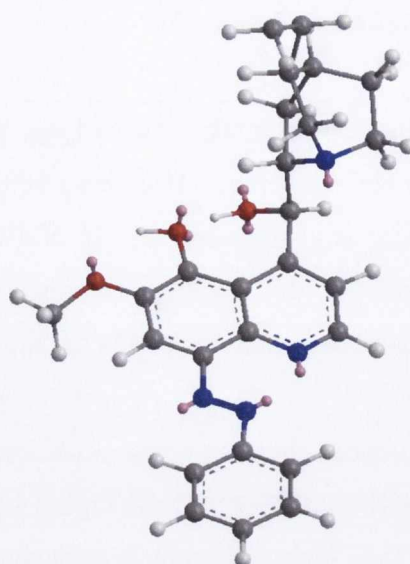
We found the approach taken by Kellogg, Wynberg and Dijkstra (Section 1.3.3.1.3)^{82,84} to be efficient and convenient. Beginning with the C-9 unsubstituted catalyst **454**, we began by unambiguously assigning all ¹H NMR resonances. Four identifiable solution state conformations of the parent alkaloids (*i.e.* quinine and quinidine) are known; the corresponding conformations of **454** are illustrated in Figure 4.4.

We have assigned these as being either *gauche* or *anti* (depending on the dihedral angle between the H-8 and H-9 protons, Figure 4.5). These are further classified as being either 1 (where the C-5' hydroxyl group is orientated towards the quinuclidine nitrogen atom) or 2 (where the hydroxyl group is pointing away).

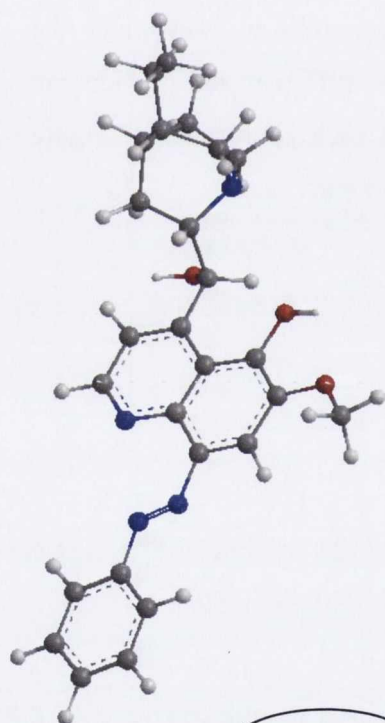
Our study was impeded by the absence of a proton at the C-5' position: NOE contacts between which and the quinuclidine α -protons are usually diagnostic in ascertaining the orientation of the catalyst quinoline heterocycle. Nevertheless, sufficient information can be gleaned from the principal NOE contacts associated with each conformation (Figure 4.5), to be confident of conformational assignment in CD₂Cl₂ in most cases.



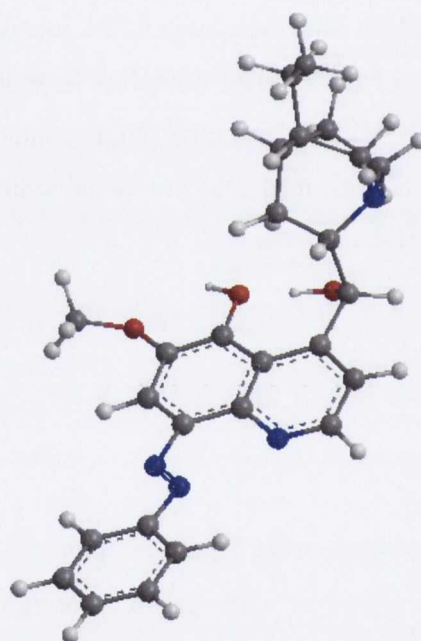
anti 1



anti 2



gauche 1



gauche 2

Figure 4.4 Representations of the four solution state conformations for the C-5'-hydroxy alkaloid **454**

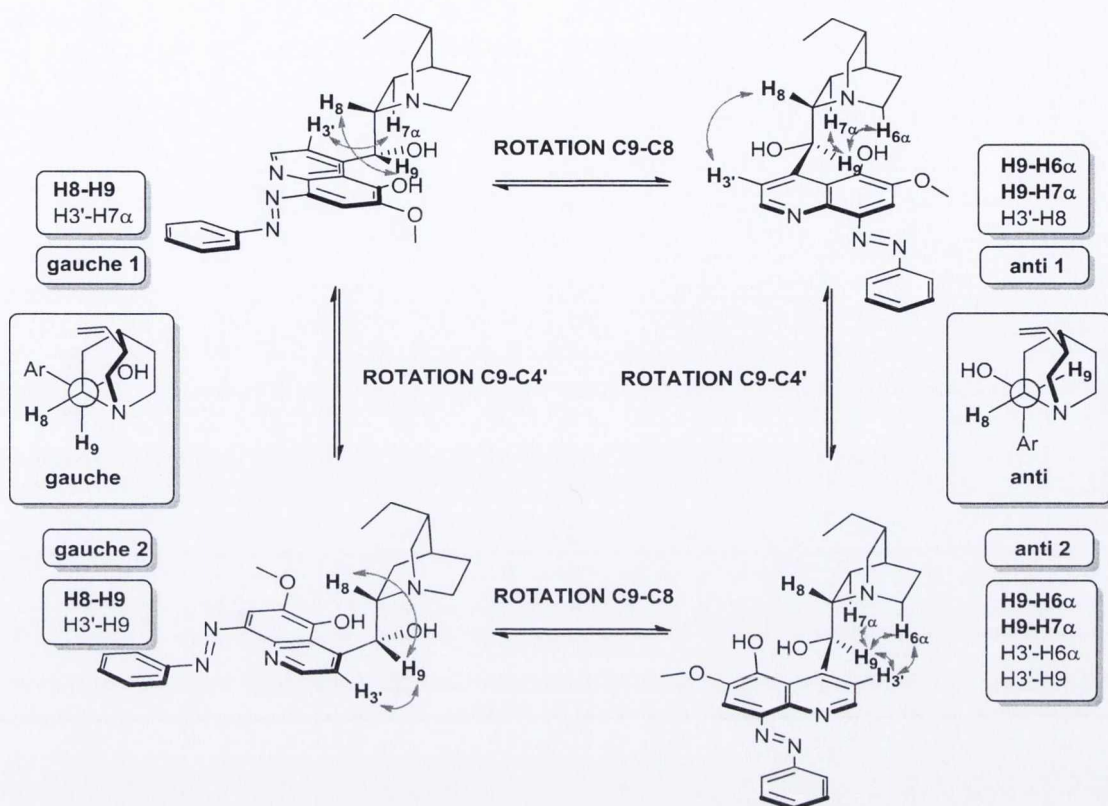


Figure 4.5 The four low energy conformations for C-5'-hydroxy alkaloid **454** and their characteristic NOE contacts

Concerning the issue of the relative populations of the different conformations (Section 1.3.3.1.3),⁸⁴ we maintained an appropriate level of skepticism regarding data obtained from the integration of often incompletely resolved NOE crosspeaks associated with the complex alkaloid spectra, and instead adopted the literature strategy of using low level molecular mechanics (MM2) to aid in assignments: *e.g.* if MM2 models indicate that two protons responsible for an observed NOE enhancement in a particular conformation A are further from each other in space than another pair responsible for an enhancement in conformation B, and the enhancement associated with conformation A is greater than that with conformation B, then one can say with confidence that conformation A is dominant over B. It is important to note that the reverse is not true: *i.e.* if MM2 models indicate that two protons responsible for an observed NOE enhancement in conformation A are closer to each other in space than another pair responsible for an enhancement in conformation B, then a larger enhancement associated with conformation A could simply be due to this greater proximity of the two protons (leading perhaps to greater NOE enhancement), rather

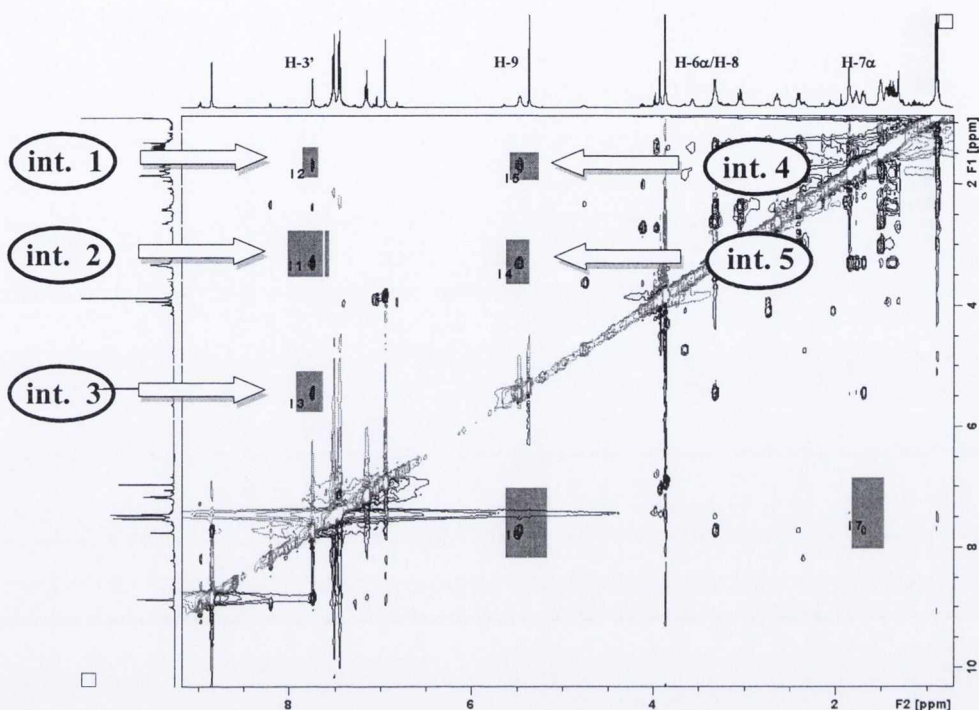
than any dominance of conformation A over B. We have therefore avoided basing assignments on data derived from such scenarios.

4.8.2 Catalyst 454

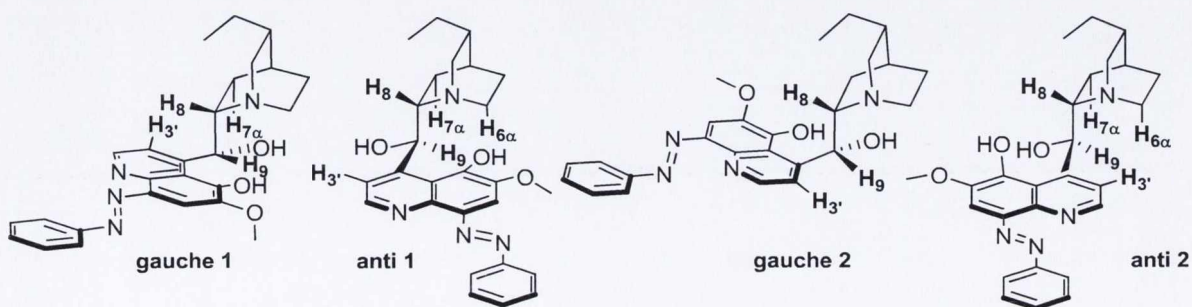
Studies by ^1H NMR spectroscopy (2D-NOESY and selective 1D-NOE) of C-5'-hydroxy-derived **454** indicated that this alkaloid adopted several conformations in CD_2Cl_2 . The presence of an NOE between H-3' and H-7 α (as it appeared in the 2D-spectrum shown in Table 4.10), confirmed that alkaloid **454** adopted the gauche 1 conformation. However significant levels of anti conformations were also present (*i.e.* NOE contacts observed between H-9 and H-7 α , also between H-3' and H-8/H-6 α). Due to an unfortunate coincidence of the resonances associated with H-6 α and H-8, a definitive distinction between anti 1 and anti 2 was difficult. We observed a small NOE between H-3' and H-9 – this could be interpreted as further evidence for the presence of anti 2. However, this could also indicate the presence of gauche 2. Again confirmation of the presence of this conformation was not possible as the corresponding NOE between H-8 and H-9 could not be detected due to the coincidence of H-6 α and H-8 (and, in any event, also its possible presence due to the gauche 1 conformation). It is worth noting that previous literature reports of the conformational studies of dihydroquinine highlighted the fact that the NOE contact characterising the gauche 2 conformation (*i.e.* between H-5' and H-7 α) could not be detected in CD_2Cl_2 .

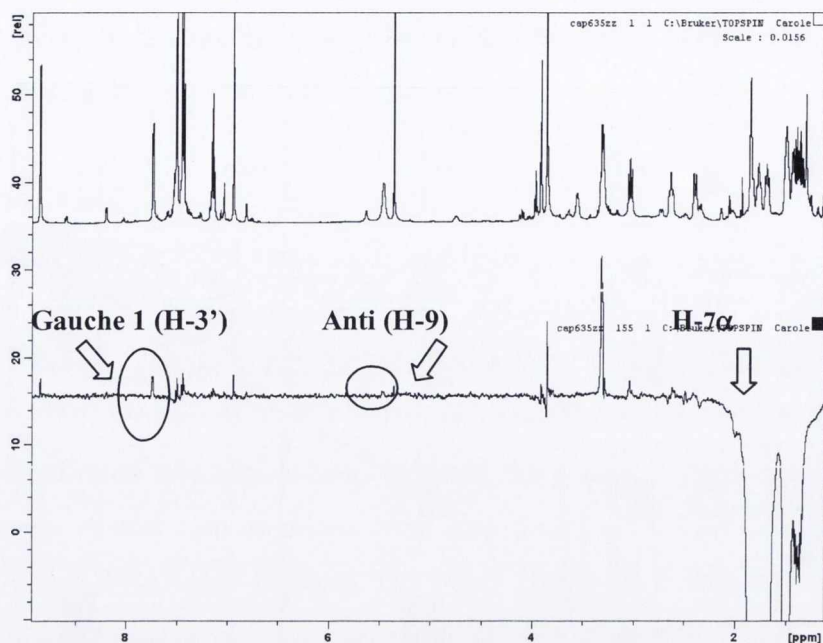
Once we knew that alkaloid **454** adopted the gauche 1 conformation and at least one of the anti-type conformation (anti 1 and/or anti 2), our interest turned towards the determination of the predominant conformation in which this alkaloid was present in CD_2Cl_2 . With this purpose, the 1D-NOE spectrum upon the irradiation of H-7 α was studied (Figure 4.6).

Table 4.10 2D-NOESY NMR spectrum of **454**

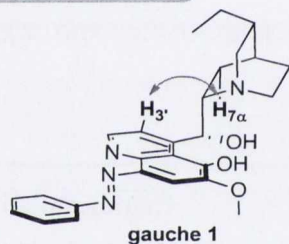


integration	H atoms involved	Conformation
1	H-3'/H-7α	gauche 1
2	H-3'/H-8 or H-6α	anti 1 or anti 2
3	H-3'/H-9	anti 2 or gauche 2
4	H-9/H-7α	anti 1 or anti 2
5	H-9/ H-8 or H-6α	gauche 1 or gauche 2 or anti 1 or anti 2





H-3'/H-7α: 2.643 Å



H-9/H-7α: 2.468 Å

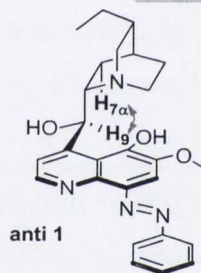


Figure 4.6 1D-NOE NMR spectrum of **454** upon irradiation of H-7α and calculation of atomic distances by computer modeling

Two sets of contacts could be detected: one contact between H-7α and H-3' (characteristic of gauche 1) and another contact between H-7α and H-9 (characteristic of anti). Interestingly, the NOE enhancement corresponding to H-3'/H-7α (gauche 1) was significantly more intense than the NOE enhancement corresponding to H-9/H-7α (anti). However, low level MM2 modeling studies indicated that the protons H-7α and H-3' were positioned further apart from each other in the gauche 1 conformation (the atomic distance H-7α/H-3' was calculated to be 2.643 Å in gauche 1) than were the protons H-7α and H-9 in the anti conformations (the H-7α/H-9 distance in space was calculated to be 2.468 Å in anti, Figure 4.6). We concluded that the gauche 1 conformation was predominantly adopted by **454** in CD₂Cl₂.

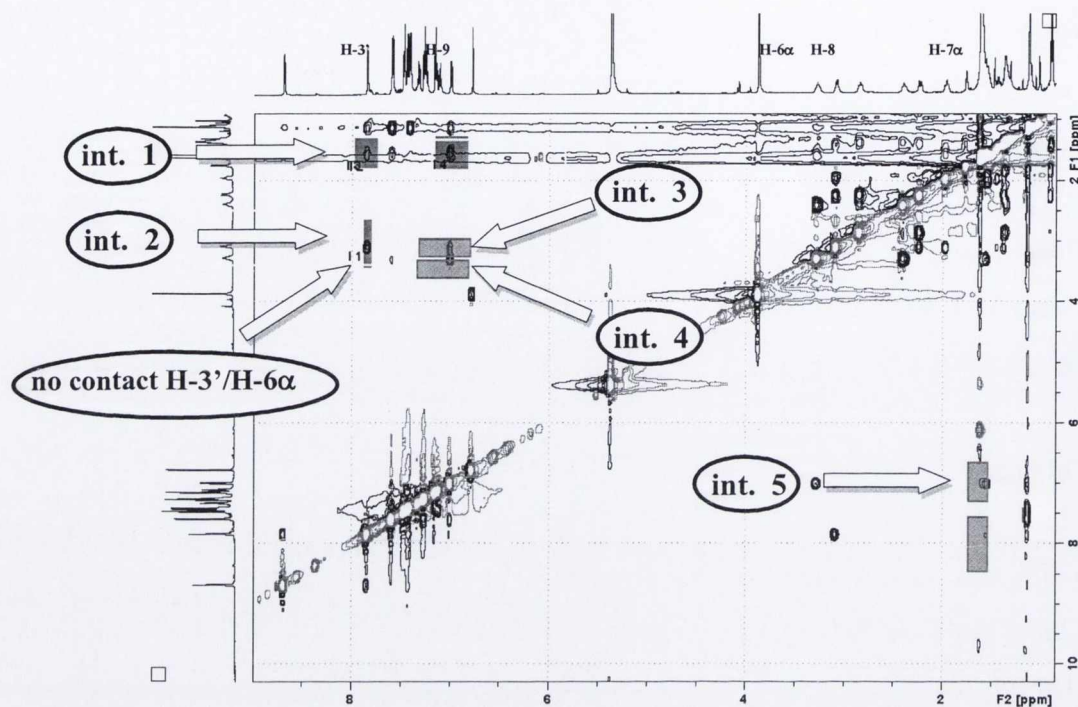
In summary, Kellogg, Wynberg and Dijkstra found that the parent hydroxy alkaloids quinine and quinidine predominantly adopted the gauche 1 conformation in non-coordinating solvents.⁸² We found that, in the case of catalyst **454**, the presence of the C-5' hydroxy moiety did not perturb this conformational equilibrium unduly; gauche 1 was observed as the dominant conformation in CD₂Cl₂. Significant levels of anti conformations were also present (which could be anti 1 and/or anti 2). Finally, NOE contacts characteristic of gauche 2 could also be detectable. However, since the peaks characteristic of H-6 α and H-8 were coincident, we could not confirm that **454** also adopted this conformation (gauche 2).

4.8.3 Catalyst 457

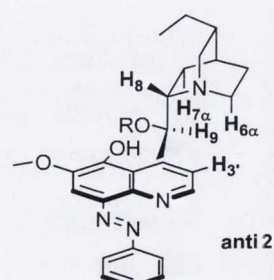
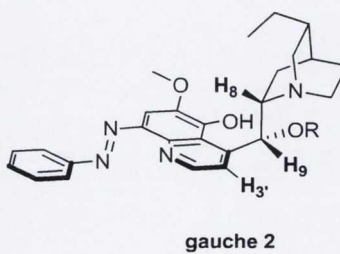
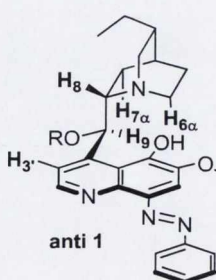
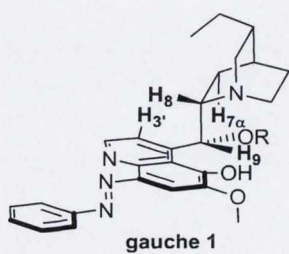
The C-9-silylated catalyst **457** proved less active and promoted less enantioselective thiolysis reactions than **454**, so we (*a priori*) expected to find a distinct conformational profile. The presence of an NOE between H-3' and H-7 α and between H-8 and H-9 confirmed the presence of gauche 1 (Table 4.11). The separation of H-8 and H-6 (in terms of chemical shift) allowed the clear identification of significant levels of the anti 1 conformer *via* an NOE between H-3' and H-8 (together with supporting enhancements between H-9 and both H-6 α and H-7 α). While the non-observance of an NOE is not the strongest evidence possible upon which a particular conformation could be ruled out as being significant, the absence of an NOE enhancement between H-3' and H-6 α protons led us to the conclusion that (on the balance of probability) it was reasonable to tentatively exclude anti 2 on this occasion. With this result, the small NOE interaction observed between H-3' and H-9 (only detectable on the 1D-NOE spectrum upon irradiation of H-9) could only be explained *via* the existence of some (trace) of the material as the gauche 2 conformer.

In this case, the intensity of the NOE enhancements could not be directly compared, since the protons responsible for the largest NOE enhancement (in each 1D-NOE spectrum recorded) were always closer in space than the other pairs responsible for the other enhancements.

Table 4.11 2D-NOESY NMR spectrum of **457**



integration	H atoms involved	Conformation
1	H-3'/H-7α	gauche 1
2	H-3'/H-8	anti 1
3	H-9/H-8	gauche 1
4	H-9/H-6α	anti 1
5	H-9/ H-7α	anti 1



R = TBDPS

However, by comparing the ratio between the 2 NOE contacts H-3'/H-7 α and H-9/H-7 α obtained upon irradiation of H-7 α for alkaloids **454** (Figure 4.6) and **457** (Figure 4.7), it was safe to conclude that alkaloid **457** adopted significantly more frequently the anti-type conformation than **454** (Figure 4.6 should be compared to Figure 4.7).

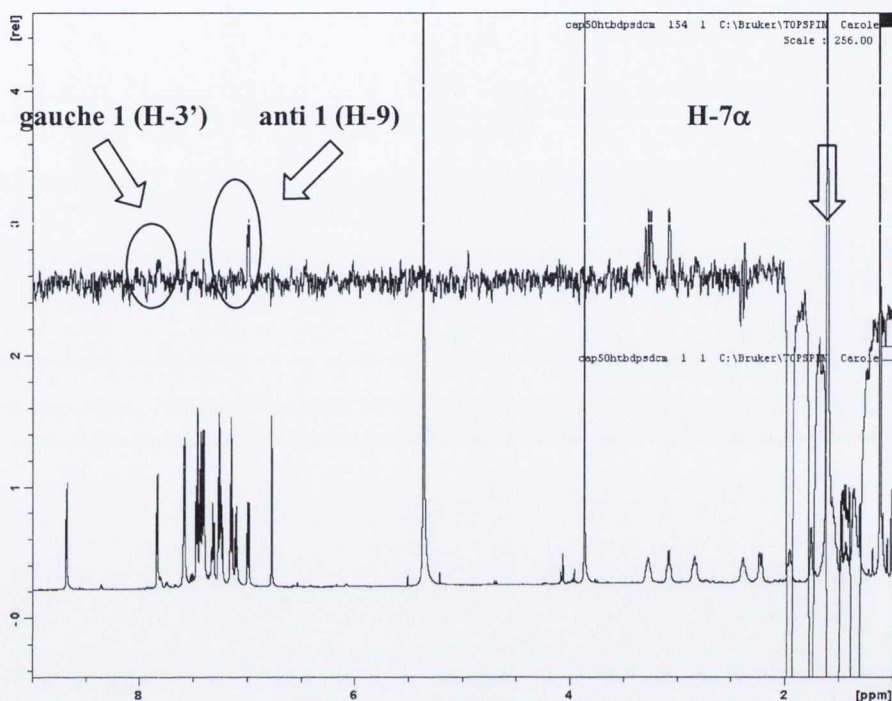


Figure 4.7 1D-NOE NMR spectrum of **457** upon the irradiation of H-7 α

In summary, without being able to conclude whether gauche 1 or anti 1 was the dominant conformation adopted by **457** in CD₂Cl₂, it was clear that significantly more anti 1 conformation (relatively to gauche 1) was detected for alkaloid **457** than for alkaloid **454**. Conformation gauche 2 was also present (in a lower amount), while anti 2 was possibly absent.

4.8.4 Catalyst **458**

The conformation of the methoxy derivatives of the parent alkaloids were studied by Kellogg, Wynberg and Dijkstra (Section 1.3.3.1).⁸² Interestingly, in CDCl₃ gauche 1 was dominant, while anti 1 was also present. In CD₂Cl₂ however, the reverse was true; anti was found to be the main conformation in solution.

We found catalyst **458** more difficult to elucidate the conformational preferences of due to poorly resolved key resonances (in CD₂Cl₂). However we found clear evidence again for the presence of gauche 1 (NOE contacts between H-3' and H-7 α), and also significant levels of anti conformers (as indicated by NOE interactions between H-9 and both H-7 α and H-6 α).

4.8.5 Conclusion on the conformational study

Thus it seemed clear that the conformational preferences of catalysts **454**, **457** and **458** were broadly in line with those which one might predict from an analysis of the literature data associated with the parent cinchona alkaloids. Attempting to directly explain catalytic efficacy through an analysis of conformational preferences alone would be imprudent in a system as complex as thiolytic azlactone DKR. Wynberg *et al.* also found that the conformational preferences of cinchona alkaloids changed in the presence of acids/electrophiles, thus it must be acknowledged that in the reaction medium it is possible that the conformations of the studied C-5'-hydroxy catalysts also change, perhaps with significant implications for catalyst activity and the stereochemical outcome of the process. Nonetheless it is interesting that the catalyst which possessed the superior activity and selectivity profile also exhibited a greater preference for the gauche 1 conformation. This orientation would (from an analysis of models) be expected to be the conformation in which the catalyst's bifunctional units (*i.e.* the quinuclidine ring and the phenolic hydrogen bond donor) are best placed for synergistic cooperation in activating the reaction's nucleophilic and electrophilic components *via* general acid-base catalysis respectively, in an approximately sized 'chiral pocket'.

4.9 Conclusion for Chapter 4

We evaluated the performance of C-5'-substituted cinchona alkaloid catalysts in the dynamic kinetic resolution of azlactones by thiolysis. The C-5' urea-based systems **355** and **356** - which have been demonstrated to serve as effective bifunctional catalysts in other transformations - both performed poorly in this challenging process (from both enantioselectivity and activity standpoints); failing even to catalyse the reaction more effectively than quinine itself. A novel, *ad hoc* designed conformationally restricted urea derivative **442** also performed poorly from an enantioselectivity perspective.

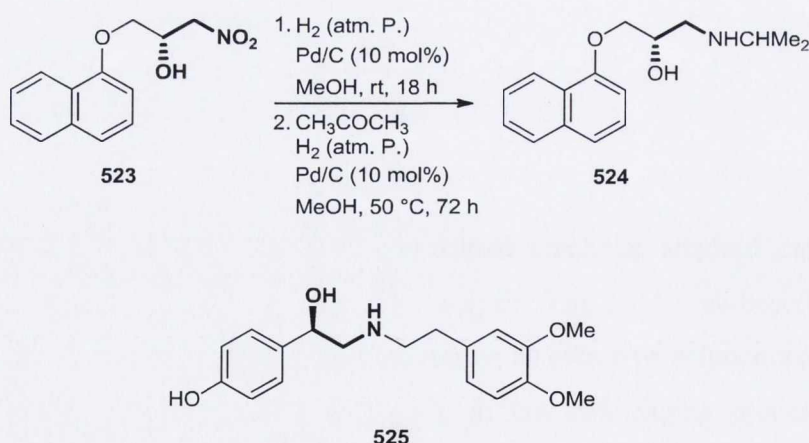
A new class of C-5'-hydroxylated cinchona alkaloid catalysts **454**, **457** and **458** were then developed which were capable of considerably more effective catalysis. Product yields were somewhat moderate: ranging from 26-60%. It was established that this was due to unexpectedly rapid hydrolysis of the azlactone promoted by the catalyst. Attempts to ameliorate this through the use of molecular sieves were not successful. Nevertheless, the most efficient catalyst **454** could promote the thiolytic DKR of azlactones with excellent enantioselectivity (84-92% *ee*) for the first time – surpassing the levels previously possible in the case of all substrates evaluated, including the hitherto recalcitrant azlactones derived from branched chain amino acids. A ¹H NMR spectroscopic study of the three C-5' hydroxylated catalysts indicated that **454**, which promoted the most efficient and enantioselective DKR reactions, also exhibited the strongest predilection towards the gauche 1 conformation, which is assumed to be the orientation best positioned to bring about synergistic cooperation of the catalyst's bifunctional units.

5.0 General conclusion and overview

During the studies described in this thesis, a novel library of bifunctional organocatalysts - based on the dihydroquinine scaffold - has been designed and prepared. The judicious placement of the hydrogen-bond donating group in close proximity to the basic quinuclidine ring, in addition with the possibility of fine-tuning the catalyst properties (*via* either the variation of the C-9 functional group or the modification of the Lewis acidic group at the C-5' position) provided us with efficient promoters for enantioselective transformations. In particular, the use of alkaloids **355**, **356** and **454** allowed us to develop effective catalytic methods for the synthesis of highly enantioenriched adducts from Henry reactions, Michael additions and DKR of azlactones.

These adducts have been reported as valuable building blocks in total synthesis of compounds of pharmaceutical interest. Therefore, developing catalytic methods that allow them to be prepared in an efficacious asymmetric fashion is of utmost importance.

Henry adducts constitute a synthetically useful class of compounds that can be easily derivatised (through oxidations, reductions, eliminations) and provide easy access to β -aminoalcohols.¹⁵⁰ For instance, Saá *et al.* proved it was possible to reduce the nitro functionality of an enantioenriched α -trifluoromethyl tertiary nitroaldol without any loss of stereochemistry.¹⁶¹ Cinchilla and Trost both highlighted the versatility of enantioenriched Henry-adducts in two separate reports (Scheme 5.1).



Scheme 5.1 Preparation of (*R*)-Propanolol (**524**) and (*R*)-Denopamine (**525**)

Propanolol is a β -adrenergic blocker ((*S*)-isomer) and a contraceptive ((*R*)-isomer). Cinchilla and coworkers used adduct **523** to access to (*R*)-Propanolol (**524**) via a short 2-step synthesis (Scheme 5.1).¹⁶² Utilising the same facile hydrogenation of the nitro functionality of Henry-products, Trost *et al.* could prepare (*R*)-Denopamine (**525**) which has been proved to be active for the treatment of congestive cardiomyopathy.¹⁵⁴

Besides, the emergence of molecules such as Efavirenz (anti-HIV drug, **526** Figure 5.1)²⁴¹ on the pharmaceutical market confirmed the need of developing catalytic methods that would render possible the efficient preparation of compounds bearing a α -trifluoromethyl tertiary alcohol on a quaternary asymmetric stereocenter.²⁴² For this matter, one of the methods to use could be the Henry reaction using trifluoromethylketones as substrates.

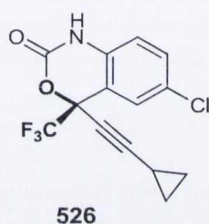


Figure 5.1 The anti-HIV drug Efavirenz (**526**)

The sulfa-Michael addition involving nitroolefins also leads to the preparation of highly versatile potential synthetic building blocks. They incorporate both a sulfur atom and a nitro functionality in a chiral environment; these moieties can be readily transformed into other synthetically useful functionality; such as amines, sulfoxides and disulfides.¹⁶⁷ These are all the more interesting as the 1,2-aminothiol *motif* is common to important biologically active molecules such as (*R*)-penicillamine (**527**, Figure 5.2) and penicillin (**528**).⁷³

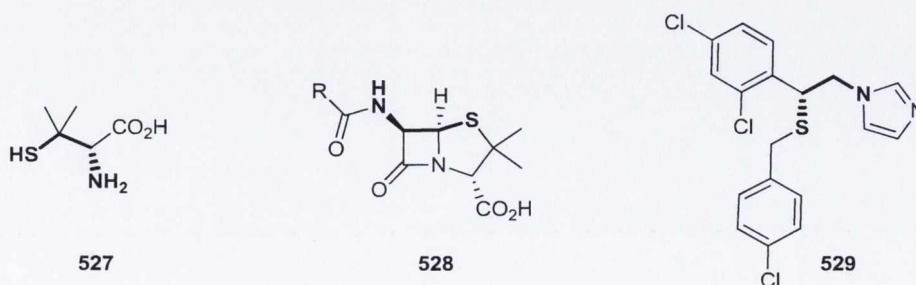
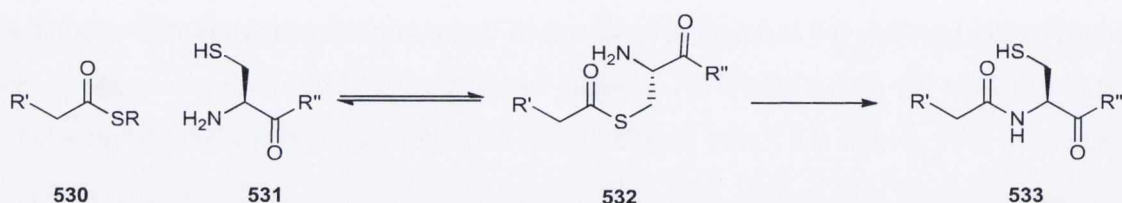


Figure 5.2 (*R*)-Penicillamine (**527**), Penicillin (**528**) and (*R*)-Sulconazole (**529**)

In particular, Ellman and coworkers used Michael-adduct **265** (Scheme 1.37, Section 1.8) for the synthesis of (*R*)-Sulconazole (**529**), an antifungal drug.

Finally, the thioesters products obtained in Section 4 from the DKR of azlactones *via* thiolysis are potentially valuable in NCL peptide coupling. In this process, two unprotected peptides can be coupled (*via* a transthioesterification to obtain intermediate **532**, followed by an acyl transfer generating **533**, scheme 5.2)^{202,203} with no racemisation occurring.



Scheme 5.2 The Native Chemical Ligation (NCL) process

In NCL processes a polypeptide is efficiently obtained without the need for carbonyl-activating agents or protection/deprotection strategies. This strategy leads to the total synthesis of small proteins that can be of pharmaceutical interest. Danishefsky *et al.* reported the use of NCL for the synthesis of Human Parathyroid Hormone (hPTH),²⁴³ which one of its fragments (1-34) is involved in the treatment of osteoporosis. In his review,²⁴⁴ Kent also highlighted that NCL gives to the practitioner the opportunity to modulate the covalent structure of a protein molecule. Coupled to other technologies, such as protein labeling, NCL leads to materials that could also be valuable for biophysical spectroscopic methods, molecular biology or material science.

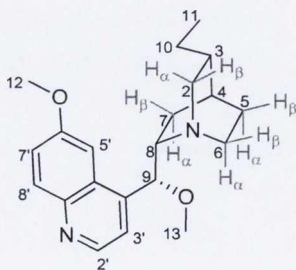
6.0 Experimental section

6.1 General

Proton Nuclear Magnetic Resonance spectra were recorded on a Bruker Avance 400 MHz or 600 MHz spectrometer in CDCl_3 referenced relative to residual CHCl_3 ($\delta = 7.26$ ppm) or DMSO-d_6 referenced relative to residual DMSO-d_6 ($\delta = 2.50$ ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 MHz or 150 MHz) with total proton decoupling. All melting points are uncorrected. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F₂₅₄ slides, and visualised by UV irradiation or KMnO_4 staining. Optical rotation measurements were made on a Rudolph research analytical Autopol IV instrument and are quoted in units of $10^{-1} \text{ deg.cm}^2.\text{g}^{-1}$. Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer. Toluene and methylene chloride were distilled from calcium hydride and stored under argon. Tetrahydrofuran and diethyl ether were distilled over sodium-benzophenone ketyl radical and stored under argon. Analytical CSP-HPLC was performed on Daicel CHIRALPAK AD-H, OD-H or AS (4.6 mm x 25 cm) columns.

6.2 Experimental data for Section 2

6.2.1 C-9-Methoxy-derived dihydroquinine derivative 58b



Potassium hydride (3.96 g, 98.74 mmol) was washed with hexane under a stream of argon and was suspended in anhydrous THF (40.0 mL) in a 250 mL round bottom flask fitted with a septum under an Ar atmosphere. The suspension was cooled to 0 °C. In a second 250 mL round bottom flask fitted with a septum under an Ar atmosphere was dissolved quinine (**50**, 16.00 g, 49.32 mmol) in anhydrous THF (140 mL). This solution was added

via syringe at 0 °C to the stirred potassium hydride suspension. The resulting mixture was stirred at 0 °C for 30 min and at 50 °C for an additional 30 min. It was then cooled to room temperature and methyl iodide (3.2 mL, 51.79 mmol) was added dropwise. After stirring for 16 h, the reaction was cooled to 0 °C. Ice water (50 mL) was added dropwise with caution. The reaction was concentrated *in vacuo* and the residue was dissolved in EtOAc (200.0 mL). The organic layer was washed with water (3 x 200 mL), dried over MgSO₄ and concentrated *in vacuo* to give a colourless oil. A hydrogenation reaction vessel was charged with half of the obtained crude (8.30 g, 24.56 mmol) and methanol (40.0 mL). The reactor was flushed with argon and palladium on charcoal (10%, 2.70 g, 2.54 mmol) was carefully added in small portions. This mixture was reacted under 3 atm of hydrogen for 3 h. After removing the palladium by filtration through a pad of celite, the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatography (100:20 EtOAc/MeOH) to give **58b** (6.20 g, 74%) as a colourless oil. $[\alpha]_D^{22} = -67$ (*c* 0.5, CHCl₃).

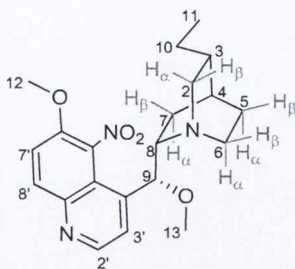
δ_H (400 MHz, CDCl₃): 0.79 (app. t, 3H, CH₃-11), 1.13-1.29 (m, 2H, CH₂-10), 1.30-1.51 (m, 3H, H-3, H-5 β and H-7 β), 1.66-1.82 (m, 3H, H-4, H-5 α and H-7 α), 2.32-2.37 (m, 1H, H-2 α), 2.65-2.73 (m, 1H, H-6 β), 3.00-3.12 (m, 2H, H-2 β and H-8), 3.31 (s, 3H, CH₃-13), 3.49-3.39 (m, 1H, H-6 α), 3.96 (s, 3H, CH₃-12), 5.02 (d, J 2.8, 1H, H-9), 7.33 (d, J 2.4, 1H, H-5'), 7.40 (dd, J 2.4, 9.2, 1H, H-7'), 7.45 (d, J 4.4, 1H, H-3'), 8.06 (d, J 9.2, 1H, H-8'), 8.77 (d, J 4.4, 1H, H-2')

δ_C (100 MHz, CDCl₃): 11.6, 21.1, 25.0, 27.2, 27.9, 37.1, 42.9, 55.4, 56.7, 58.3, 59.3, 82.8, 100.7, 118.2, 121.2 (q), 127.0, 131.3, 144.1 (q), 144.2 (q), 147.1, 157.3 (q)

ν_{max} (neat)/cm⁻¹: 2901, 1623, 1589, 1507, 1449, 1430, 1372, 1227, 1133, 1112, 1086, 1028, 822, 717

HRMS (*m/z* -ES): Found: 341.2234 (M⁺ + H. C₂₁H₂₉N₂O₂ Requires: 341.2229)

6.2.2 C-5'-Nitro-substituted C-9-methoxy-derived dihydroquinine derivative 362



A 250 mL round bottom flask was charged with compound **58b** (5.40 g, 15.89 mmol). Fuming nitric acid (22 mL) was added carefully dropwise at -10 °C while keeping the temperature of the reaction below 5 °C. The resulting solution was stirred at -10 °C for 30 min. Ice water (340 mL) followed by NaOH (25% aqueous solution, 84 mL) were added in a dropwise manner. Finally, a solution of NH₃ (33% aqueous solution, 104 mL) was poured into the obtained mixture. After allowing the reaction to warm to ambient temperature, the expected compound was extracted from the reaction using CH₂Cl₂ (3 x 300 mL). The combined organic extracts were washed with water (3 x 500 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by column chromatography (100:5 EtOAc/MeOH) to give **362** (9.94 g, 86%) as a dark orange solid. M.p. 121-123 °C. $[\alpha]_D^{22} = -162$ (*c* 0.1, CHCl₃).

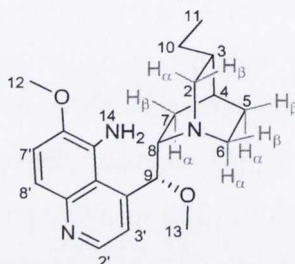
δ_H (400 MHz, CDCl₃): 0.77 (app. t, 3H, CH₃-11), 1.12-1.41 (m, 5H, H-3, H-5 β , H-7 β and CH₂-10), 1.56-1.73 (m, 3H, H-4, H-5 α and H-7 α), 2.39-2.47 (m, 1H, H-2 α), 2.59-2.78 (m, 2H, H-6 β and H-8), 3.04 (dd, *J* 3.2, 10.1, 1H, H-2 β), 3.25-3.41 (m, 4H, H-6 α and CH₃-13), 4.05 (s, 3H, CH₃-12), 4.76 (d, *J* 2.4, 1H, H-9), 7.58 (d, *J* 9.4, 1H, H-7'), 7.76 (d, *J* 4.5, 1H, H-3'), 8.29 (d, *J* 9.4, 1H, H-8'), 8.85 (d, *J* 4.5, 1H, H-2')

δ_C (100 MHz, CDCl₃): 11.7, 20.7, 25.3, 27.3, 28.0, 37.1, 43.1, 56.5, 56.8, 58.2, 60.1, 80.5, 115.0, 118.8, 121.2 (q), 134.3 (q), 134.2, 143.0 (q), 143.5 (q), 148.6, 149.3 (q)

$\nu_{\max}$ (neat)/ cm^{-1} : 2969, 2906, 2862, 1622, 1580, 1526, 1509, 1458, 1443, 1343, 1100, 1085, 942, 903, 795, 787

HRMS (m/z -ES): Found: 386.2087 ($M^+ + H$, $C_{21}H_{28}N_3O_4$ Requires: 386.2080)

6.2.3 C-5'-Amino-substituted C-9-methoxy-derived dihydroquinine derivative **363**



A hydrogenation reaction vessel was charged with **362** (7.05 g, 18.31 mmol) and MeOH (20 mL). The reactor was then flushed with argon and palladium on charcoal (10%, 2.54 g, 2.39 mmol) was carefully added portion-wise. This mixture was reacted under 3 atm of hydrogen for 3 h. After removing the palladium by filtration through celite, the reaction was concentrated *in vacuo*. The crude residue was purified by column chromatography (10:0.2 EtOAc/MeOH) to give **363** (3.40 g, 53%) as a yellow solid. M.p. 56-62 °C. . $[\alpha]_D^{22} = -188$ (c 0.1, CHCl_3).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 0.6:0.1.

Rotamer 1 (major):

δ_{H} (400 MHz, DMSO): 0.72-0.85 (app. t, 3H, CH_3 -11), 1.15-1.44 (m, 5H, H-3, H-5 β , H-7 β and CH_2 -10), 1.56-1.73 (m, 2H, H-4, H-5 α), 1.78-1.96 (m, 2H, H-2 α and H-7 α), 2.24-2.36 (m, 1H, H-6 β), 2.59-2.69 (m, 1H, H-2 β), 2.94-3.12 (m, 1H, H-6 α), 3.29 (s, 3H, CH_3 -13), 3.75 (app. q, 1H, H-8), 3.92 (s, 3H, CH_3 -12), 4.50 (d, J 6.8, 1H, H-9), 5.97 (br. s, 2H, NH_2 -14), 7.25-7.31 (m, 1H, H-3'), 7.34 (d, J 9.1, 1H, H-7'), 7.49 (d, J 9.1, 1H, H-8'), 8.51 (d, J 4.1, 1H, H-2')

δ_C (100 MHz, DMSO): 12.6, 25.4, 26.7, 27.8, 28.7, 37.5, 41.4, 56.4, 57.5, 58.0, 58.5, 89.3, 115.5, 116.9 (q), 117.9, 124.4, 132.7 (q), 143.0 (q), 144.2 (q), 146.0 (q), 147.4

Rotamer 2 (minor):

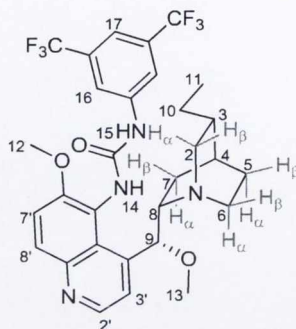
δ_H (400 MHz, DMSO): 0.72-0.85 (app. t, 3H, CH₃-11), 1.15-1.44 (m, 5H, H-3, H-5 β , H-7 β and CH₂-10), 1.56-1.73 (m, 2H, H-4, H-5 α), 1.78-1.96 (m, 1H, H-7 α), 2.24-2.36 (m, 1H, H-2 α), 2.59-2.69 (m, 1H, H-6 β), 2.94-3.12 (m, 3H, H-2 β , H-6 α , H-8), 3.23 (s, 3H, CH₃-13), 3.92 (s, 3H, CH₃-12), 5.40 (br. s, 2H, NH₂-14), 5.55 (d, J 2.0, 1H, H-9), 7.25-7.31 (m, 1H, H-3'), 7.39 (d, J 9.0, 1H, H-7'), 7.47-7.55 (m, 1H, H-8'), 8.60 (d, J 4.3, 1H, H-2')

δ_C (100 MHz, DMSO): 12.4, 19.3, 25.5, 27.2, 28.1, 37.4, 42.6, 55.4, 56.4, 57.3, 60.9, 80.9, 115.9, 116.2, 117.8 (q), 119.0, 132.4 (q), 143.4 (q), 145.6 (q), 147.1 (q), 148.0

$\nu_{\max}$ (neat)/cm⁻¹: 3430, 3318, 2929, 2862, 1621, 1569, 1521, 1457, 1344, 1268, 1206, 1179, 1042, 1039, 810

HRMS (m/z -ES): Found: 356.2338 ($M^+ + H$. C₂₁H₃₀N₃O₂ Requires: 356.2338)

6.2.4 C-5'-(3,5-bis(Trifluoromethyl)phenyl urea)-substituted C-9-methoxy-derived dihydroquinine derivative **353**



Compound **363** (1.00 g, 2.82 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) in a 25 mL round bottom flask fitted with a septum and placed under an atmosphere of Ar. 3,5-(bis-trifluoromethyl)phenyl isocyanate (534. μL , 3.09 mmol) was added dropwise over 5 min at 0 °C. The resulting mixture was stirred for 48 h at room temperature. The reaction was then washed with water (3 x 10 mL). The organic extract was dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (10:0.1 EtOAc/MeOH) to give **353** (420 mg, 24%) as a white solid. M.p. 146-149 °C. $[\alpha]_{\text{D}}^{22} = -111$ (*c* 0.1, CHCl_3).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 0.7:0.3.

Rotamer 1 (major):

δ_{H} (600 MHz, CDCl_3): 0.54 (app. t, 3H, CH_3 -11), 1.20-1.34 (m, 2H, CH_2 -10), 1.64-1.99 (m, 3H, H-3, H-5 β , H-7 β), 2.00-2.20 (m, 2H, H-4, H-5 α), 2.29 (app. t, 1H, H-7 α), 2.55 (app. d, 1H, H-2 α), 2.94-3.05 (m, 1H, H-2 β), 3.17-3.26 (m, 1H, H-6 β), 3.37 (s, 3H, CH_3 -13), 3.77-3.85 (m, 1H, H-8), 4.04 (s, 3H, CH_3 -12), 4.19-4.31 (m, 1H, H-6 α), 6.50 (app. s, 1H, H-9), 7.44-7.53 (m, 2H, H-17, NH-14), 7.58-7.69 (m, 2H, H-3', H-7'), 8.13-8.31 (m, 3H, H-8', H-16), 8.81 (d, *J* 4.4, 1H, H-2'), 10.37 (s, 1H, NH-15)

δ_C (150 MHz, $CDCl_3$): 10.9, 18.4, 24.6, 24.9, 27.1, 35.5, 44.6, 55.7, 56.8, 56.9, 60.2, 77.5, 115.6 ($^3J_{CF}$ 3.6), 116.3, 117.7 (q), 118.0 ($^3J_{CF}$ 3.5), 119.4, 120.1, 123.2 (q, $^1J_{CF}$ 271.2), 126.9 (q), 132.3 (q, $^2J_{CF}$ 32.9), 132.7 (q), 140.5 (q), 141.0 (q), 147.5, 155.7 (q), 156.2 (q)

δ_F (375 MHz, $CDCl_3$): - 63.4 (CF_3)

Rotamer 2 (minor):

δ_H (600 MHz, $CDCl_3$): 0.85 (app. t, 3H, H-11), 1.03-1.44 (m, 2H, CH_2 -10), 1.21-1.35 (m, 1H, H-7 β), 1.64-1.99 (m, 2H, H-3, H-5 β), 2.00-2.20 (m, 3H, H-4, H-5 α , H-7 α), 2.66-2.75 (m, 1H, H-2 α), 2.94-3.05 (m, 1H, H-8), 3.17-3.26 (m, 1H, H-6 β), 3.45 (s, 3H, CH_3 -13), 3.58-3.65 (m, 1H, H-2 β), 3.75-3.87 (m, 1H, H-6 α), 4.03 (s, 3H, CH_3 -12), 6.30 (app. s, 1H, H-9), 7.44-7.53 (m, 1H, H-17), 7.58-7.69 (m, 2H, H-3', H-7'), 7.88 (s, 1H, NH-14), 8.13-8.31 (m, 3H, H-8', H-16), 8.81 (d, J 4.4, 1H, H-2'), 10.57 (s, 1H, NH-15)

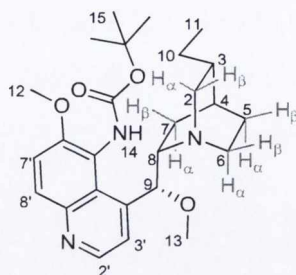
δ_C (150 MHz, $CDCl_3$): 11.3, 17.3, 24.5, 24.6, 26.5, 35.3, 43.7, 56.4, 57.4, 57.5, 60.3, 77.2, 115.2 ($^3J_{CF}$ 3.9), 115.8, 117.9 (q), 118.1 ($^3J_{CF}$ 3.8), 119.4, 123.3 (q, $^1J_{CF}$ 271.2), 125.9 (q), 131.7 (q), 131.7, 131.9 (q, $^2J_{CF}$ 32.9), 141.3 (q), 141.4 (q), 143.5, 155.0 (q), 155.1 (q)

δ_F (375 MHz, $CDCl_3$): - 63.4 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3430, 3318, 2929, 2862, 1621, 1569, 1521, 1457, 1345, 1268, 1206, 1179, 1041, 1039, 977, 943, 916, 882, 857, 810, 795, 737, 716, 693

HRMS (m/z -ES): Found: 611.2448 ($M^+ + H$. $C_{30}H_{33}N_4O_3F_6$ Requires: 611.2457)

6.2.5 C-5'-NHBoc-Substituted C-9-methoxy-derived dihydroquinine derivative 359



Alkaloid **363** (1.00 g, 2.82 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) in a 50 mL round bottom flask fitted with a septum and placed under an Ar atmosphere. NEt_3 (392 μL , 3.10 mmol) was added at ambient temperature. The resulting mixture was stirred for 30 min at room temperature. A solution of Boc_2O (610 mg, 2.82 mmol) and DMAP (34 mg, 0.28 mmol) dissolved in anhydrous CH_2Cl_2 (5 mL) was added dropwise over 5 min. After being stirred at ambient temperature for 40 h, the reaction was washed with water (3 x 15 mL). The organic extract was dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (100:20 EtOAc/MeOH) to give **359** (498 mg, 39%) as a white solid. M.p. 138-141 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{22} = -126$ (*c* 0.1, CHCl_3).

δ_{H} (400 MHz, CDCl_3): 0.78 (app. t, 3H, CH_3 -11), 1.09-1.67 (m, 14H, H-3, H-5 β , H-7 β , CH_2 -10, 3 CH_3 -15), 1.68-1.90 (m, 2H, H-4, H-7 α), 1.93-2.05 (m, 1H, H-5 α), 2.13-2.34 (m, 1H, H-6 β), 2.68-2.91 (m, 2H, H-2 α , H-8), 3.07-3.50 (m, 5H, H-2 β and H-6 α , CH_3 -13), 3.41 (s, 3H, CH_3 -12), 5.59 (app. s, 1H, H-9), 7.41-7.58 (m, 2H, H-3' and H-7'), 8.02 (d, *J* 8.8, 1H, H-8'), 8.66 (app. s, 1H, H-2'), 9.67 (br. s, 1H, NH-14)

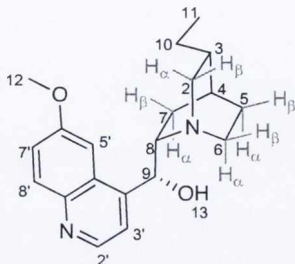
δ_{C} (100 MHz, CDCl_3): 11.5, 17.9, 24.9, 26.8, 27.3, 28.1, 37.0, 42.0, 56.3, 56.6, 57.2, 62.9, 78.8 (q), 79.3, 116.3, 119.4 (q), 124.4 (q), 130.3, 144.7 (q), 147.4 (2C), 147.9 (q), 154.0 (q), 154.3 (q)

ν_{max} (neat)/ cm^{-1} : 3163, 2930, 2871, 1719, 1610, 1582, 1567, 1509, 1454, 1389, 1365, 1303, 1267, 1243, 1180, 1115, 1091, 1062, 1039, 997, 976, 910, 874, 857, 809, 779, 717, 690

HRMS (m/z -ES):

Found: 456.2856 ($M^+ + H$, $C_{26}H_{38}N_3O_4$ Requires: 456.2862)

6.2.6 Dihydroquinine (58a)

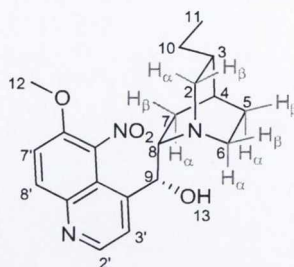


A hydrogenation reaction vessel was charged with quinine (**50**, 9.90 g, 30.82 mmol) and MeOH (50 mL). The reactor was then flushed with argon and palladium on charcoal (10%, 2.70 g, 2.54 mmol) was carefully added portion-wise. This mixture was reacted under 3 atm of hydrogen for 3 h. After removing the palladium by filtration through a pad of celite, the reaction was concentrated *in vacuo*. The crude residue was dissolved in CH_2Cl_2 (100 mL) washed with water (3 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give **58a** (9.52 g, 95%) as a white solid. M.p. 171-172°C, (lit.,²²⁵ 170-171°C). $[\alpha]_D^{22} = -141$ (c 0.2, EtOH), (lit.,²²⁵ $[\alpha]_D^{25} = -144.5$ (c 0.9, EtOH)).

δ_H (400 MHz, $CDCl_3$): 0.73 (app. t, 3H, CH_3 -11), 1.07-1.20 (m, 2H, CH_2 -10), 1.23-1.38 (m, 3H, H-3, H-5 β , H-7 β), 1.65-1.76 (m, 3H, H-4, H-5 α , H-7 α), 2.23-2.32 (m, 1H, H-2 α), 2.47-2.59 (m, 1H, H-6 β), 2.88-3.02 (m, 2H, H-2 β , H-8), 3.45-3.56 (m, 1H, H-6 α), 3.84 (s, 3H, CH_3 -12), 5.51 (d, J 2.5, 1H, H-9), 6.65 (br. s, 1H, OH-13), 7.17 (dd, J 2.3, 9.1, 1H, H-7'), 7.22 (d, J 2.3, 1H, H-5'), 7.43 (d, J 4.4, 1H, H-3'), 7.77 (d, J 9.1, 1H, H-8'), 8.30 (d, J 4.4, 1H, H-2')

The NMR spectrum was consistent with those previously reported in the literature.⁸²

6.2.7 C-5'-Nitro-substituted dihydroquinine derivative 366



A 250 mL round bottom flask was charged with fuming nitric acid (18 mL). The solution was cooled to $-10\text{ }^{\circ}\text{C}$ and dihydroquinine (**58a**, 4.50 g, 13.80 mmol) was added carefully portion-wise while keeping the temperature of the reaction below $5\text{ }^{\circ}\text{C}$. The resulting mixture was stirred at $-10\text{ }^{\circ}\text{C}$ for 30 min. Ice water (320 mL), followed by NaOH (25% aqueous solution, 84 mL) were added in a dropwise manner. Finally, NH_3 (33% aqueous solution, 103 mL) was poured into the obtained mixture. After allowing the reaction to warm to ambient temperature, C-5'-nitro-dihydroquinine **77** was extracted using CH_2Cl_2 (4 x 300 mL). The combined organic extracts were washed with water (3 x 500 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by selective precipitation in a mix of EtOAc/MeOH/*n*-hexane in a ratio 70:10:30 to give **366** (4.88 g, 95%) as a yellow amorphous solid. M.p. $219\text{--}220\text{ }^{\circ}\text{C}$, (lit.,²⁰⁷ $220\text{--}222\text{ }^{\circ}\text{C}$). $[\alpha]_{\text{D}}^{22} = -209$ (*c* 0.7, CHCl_3), (lit.,²²⁶ $[\alpha]_{\text{D}}^{25} = -200$ (*c* 1.4, CHCl_3)).

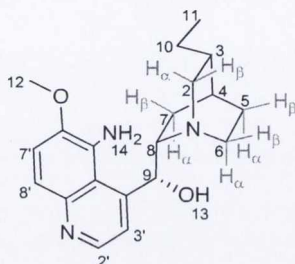
δ_{H} (400 MHz, CDCl_3): 0.87 (app. t, 3H, CH_3 -11), 1.25-1.48 (m, 4H, H-3, H-5 β , CH_2 -10), 1.48-1.57 (m, 1H, H-7 β), 1.59-1.69 (m, 1H, H-7 α), 1.70-1.82 (m, 2H, H-4 and H-5 α), 2.08-2.39 (br. s, 1H, OH-13) 2.40-2.47 (m, 1H, H-2 α), 2.46-2.56 (m, 1H, H-6 β), 2.90-3.00 (m, 1H, H-6 α), 2.99-3.08 (dd, *J* 3.9, 9.4, 1H, H-2 β), 3.08-3.17 (app. q, 1H, H-8), 4.07 (s, 3H, CH_3 -12), 5.07 (d, *J* 6.0, 1H, H-9), 7.57 (d, *J* 9.4, 1H, H-7'), 7.77 (d, *J* 4.6, 1H, H-3'), 8.29 (d, *J* 9.4, 1H, H-8'), 8.87 (d, *J* 4.6, 1H, H-2')

δ_{C} (100 MHz, CDCl_3): 11.7, 23.7, 24.9, 27.2, 27.7, 36.9, 42.1, 58.8, 57.5, 59.0, 69.4, 114.9, 118.7 (q), 122.1, 134.2 (q), 134.4, 143.0 (q), 144.5 (q), 149.0, 149.3 (q)

ν_{max} (neat)/ cm^{-1} : 2925, 2869, 1623, 1571, 1534, 1513, 1461, 1373, 1266, 1117, 1092, 1090, 1017, 995, 939, 910, 875, 849, 821, 785

HRMS (m/z -ES): Found: 372.1927 ($M^+ + H$, $C_{20}H_{26}N_3O_4$ Requires: 372.1923)

6.2.8 C-5'-Amino-substituted dihydroquinine derivative **367**



A hydrogenation reaction vessel was charged with **366** (2.69 g, 7.89 mmol) and MeOH (20 mL). The reactor was then flushed with argon and palladium on charcoal (10%, 0.78 g, 0.73 mmol) was carefully added portion-wise. This mixture was reacted under 3 atm of hydrogen for 3 h. After removing the palladium by filtration through celite, the reaction was concentrated *in vacuo*. The crude residue was purified by selective precipitation in ethyl acetate to give **367** (1.66 g, 67%) as a pale yellow amorphous solid. M.p. 215-217 °C, (lit.,²⁰⁷ 220-221 °C). $[\alpha]_D^{22} = +61$ (c 0.8, CHCl_3), (no data provided in the literature).

δ_H (400 MHz, CDCl_3): 0.89 (app. t, 3H, CH_3 -11), 1.30-1.48 (m, 4H, H-5 β , H-7 β , CH_2 -10), 1.52-1.69 (br m, 2H, H-3, H-7 α) 1.78-1.91 (m, 2H, H-4, H-5 α), 2.39-2.49 (m, 2H, H-2 α , H-6 β), 2.73-2.85 (m, 1H, H-6 α), 2.95-3.03 (dd, J 9.0, 13.1, 1H, H-2 β), 3.39-3.45 (m, 1H, H-8), 3.99 (s, 3H, CH_3 -12), 5.28 (app. br. s, 1H, H-9), 5.92 (br. s, 2H, NH_2 -14), 7.19 (d, J 3.8, 1H, H-3'), 7.38 (d, J 9.0, 1H, H-7'), 7.58 (d, J 9.0, 1H, H-8'), 8.53 (d, J 3.8, 1H, H-2')

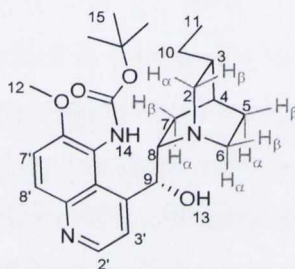
Note: The hydroxyl peak did not appear on the ^1H spectrum when CDCl_3 was used as solvent.

δ_C (100 MHz, $CDCl_3$): 11.8, 23.6, 24.9, 27.2, 27.8, 37.3, 41.9, 56.1, 57.1, 61.3, 75.3, 114.6, 118.9 (q), 119.2, 120.3, 130.2 (q), 144.2 (q), 144.9 (q), 146.6 (q), 147.1

ν_{max} (neat)/ cm^{-1} : 3417, 3272, 2932, 2872, 2863, 1603, 1571, 1519, 1452, 1441, 1400, 1340, 1278, 1263, 1249, 1202, 1182, 1135, 1059, 1045, 1007, 978, 820

HRMS (m/z -ES): Found: 342.2184 ($M^+ + H$, $C_{20}H_{28}N_3O_2$ Requires: 342.2182)

6.2.9 C-5'-NHBoc-substituted dihydroquinine derivative (358)



Compound **367** (3.89 g, 11.40 mmol) was dissolved in freshly distilled CH_2Cl_2 (25 mL) in a 100 mL round bottom flask fitted with a septum and placed under an Ar atmosphere. NEt_3 (1.75 mL, 12.54 mmol) was added at ambient temperature and the resulting mixture was stirred for 30 min. A solution of Boc_2O (2.49 g, 11.40 mmol) and DMAP (139 mg, 1.14 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise over 5 min. The reaction was stirred at room temperature for 5 days after which the obtained solution was washed with water (3 x 40 mL). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (100:2 EtOAc/MeOH) to afford **358** (5.03 g, >99%) as a yellow oil. $[\alpha]_D^{22} = -14$ (c 0.1, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 0.85 (app. t, 3H, CH_3 -11), 1.26-1.37 (m, 3H, H-5 β , CH_2 -10), 1.39-1.50 (m, 10H, H-3, 3 CH_3 -15), 1.54-1.67 (m, 1H, H-7 β), 1.74-1.92 (m, 3H, H-4, H-5 α , H-7 α), 2.12-2.31 (m, 1H, H-2 α), 2.42-2.65 (m, 1H, H-6 β), 2.90-3.05 (m, 1H, H-2 β), 3.10-3.41 (m, 2H, H-6 α , H-8), 4.00 (s, 3H, CH_3 -12), 5.25 (app. d,

1H, NH-13), 7.18 (d, J 5.8, 1H, H-9), 7.37 (d, J 4.4, 1H, H-3'), 7.43 (d, J 9.0, 1H, H-7'), 7.61 (d, J 9.0, 1H, H-8'), 8.70 (d, J 4.4, 1H, H-2')

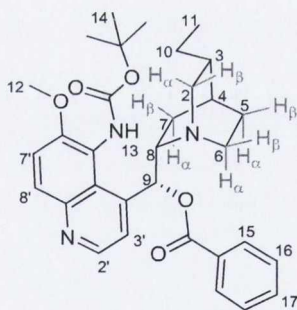
Note: The hydroxyl peak did not appear on the ^1H spectrum when CDCl_3 was used as solvent.

δ_{C} (100 MHz, CDCl_3): 11.6, 23.2, 24.8, 27.0, 27.3, 27.6, 36.8, 41.9, 56.3, 57.2, 61.7, 75.9, 82.6 (q), 115.2, 116.7, 117.9 (q), 120.2, 131.2 (q), 144.2 (q), 144.8 (q), 146.7 (q), 147.3, 152.9 (q)

ν_{max} (neat)/ cm^{-1} : 3418, 3326, 2932, 2864, 1738, 1620, 1582, 1567, 1517, 1459, 1370, 1266, 1254, 1242, 1156, 1087, 1043, 847, 815, 795

HRMS (m/z -ES): Found: 442.2706 ($\text{M}^+ + \text{H}$. $\text{C}_{25}\text{H}_{36}\text{N}_3\text{O}_4$ Requires: 442.2706)

6.2.10 C-5'-NHBoc-substituted C-9-benzoyl-derived dihydroquinine derivative 360



Compound **358** (783 mg, 1.78 mmol) and NEt_3 (260 μL , 1.87 mmol) were dissolved in freshly distilled CH_2Cl_2 (5 mL). Benzoyl chloride (217 μL , 1.87 mmol) was added dropwise over 5 min at ambient temperature and the reaction was stirred at this temperature overnight. The obtained solution was dissolved in CH_2Cl_2 (10 mL) and was washed with water (3 x 15 mL). The organic extract was dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (100:3 EtOAc/MeOH) to give **360** (272 mg, 28%) as a dark yellow solid. $[\alpha]_{\text{D}}^{22} = +7$ (c 0.1, CHCl_3). M.p. 222-225 $^{\circ}\text{C}$.

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 0.52:0.47. Nevertheless, the NMR spectra are not resolved enough to attribute peaks to each rotamer. Only the peaks corresponding to the proton H-2' of the two rotamers are resolved enough on the ^1H spectrum to determine the ratio of the two rotamers.

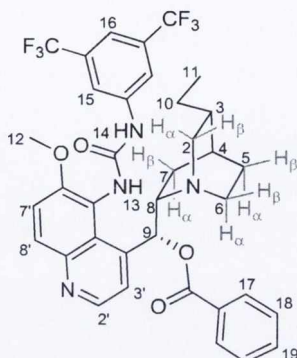
δ_{H} (400 MHz, CDCl_3): 0.82 (app. br. s, 3H, CH_3 -11), 1.12-1.76 (m, 14H, H-3, H-4, H-5 β , CH_2 -10, 3 CH_3 -14), 1.79-1.95 (m, 1H, H-5 α), 2.02-2.14 (m, 1H, H-7 β), 2.14-2.23 (m, 1H, H-6 β), 2.26-2.41 (m, 1H, H-2 α), 2.50-2.62 (m, 1H, H-7 α), 2.72-2.88 (m, 1H, H-6 α), 3.05-3.10 (m, 1H, H-8), 3.07-3.20 (m, 1H, H-2 β), 4.01 (s, 3H, CH_3 -12), 7.09 (app. br. s, 1H, H-9), 7.33-7.68 (m, 5H, H-3', H-7', H-16, H-17), 8.00 (app. s, 1H, H-8'), 8.06-8.26 (m, 2H, H-15), 8.81 (app. s, 1H, H-2'), 9.48 (s, 1H, NH-13)

δ_{C} (100 MHz, CDCl_3): 11.6, 18.2, 24.8, 26.8, 27.2, 29.3, 36.6, 40.6, 56.5, 59.7, 62.1, 73.7 (q), 83.2, 116.4, 119.2 (q), 120.6, 124.7 (q), 127.5, 128.0, 129.4 (q), 130.7, 131.1, 135.4 (q), 144.6 (q), 146.9 (q), 147.2, 151.1 (q), 153.8 (q)

ν_{max} (neat)/ cm^{-1} : 2929, 2857, 1749, 1671, 1603, 1566, 1511, 1462, 1370, 1275, 1257, 1216, 1157, 1097, 1034, 977, 917, 849, 792, 725, 710, 665

HRMS (m/z -ES): Found: 546.2974 ($\text{M}^+ + \text{H}$. $\text{C}_{32}\text{H}_{40}\text{N}_3\text{O}_5$ Requires: 546.2968)

6.2.11 C-5'-(3,5-bis(Trifluoromethyl)phenyl urea)-substituted C-9-benzoyl-derived dihydroquinine derivative **354**



Compound **360** (239 mg, 0.44 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) in a 10 mL round bottom flask fitted with a septum and placed under an Ar atmosphere. Trifluoroacetic acid (TFA) (880 μL , 11.4 mmol) was added dropwise over 5 min at 0 °C. The resulting mixture was stirred for 16 h at ambient temperature. The reaction was then concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (20 mL) and NaHCO_3 was added until the pH of the solution was 8. The resulting organic layer was washed with water (3 x 20 mL). The organic extract was dried over MgSO_4 and concentrated *in vacuo*. The crude residue (122 mg, 0.27 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) in a 10 mL round bottom flask fitted with a septum and placed under an Ar atmosphere. 3,5-(bis-Trifluoromethyl) phenyl isocyanate (**364**, 122 μL , 0.30 mmol) was added dropwise over 5 mins at ambient temperature. The resulting mixture was stirred for 48 h at ambient temperature. The reaction mixture was dissolved in CH_2Cl_2 (10 mL) then washed with water (3 x 10 mL). The organic extract was dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (100:10 EtOAc/MeOH) to give **354** (110 mg, 59%) as a white solid. $[\alpha]_{\text{D}}^{22} = -9$ (c 0.1, CHCl_3). M.p. 215-219 °C.

δ_{H} (400 MHz, CDCl_3): 0.77 (app. t, 3H, CH_3 -11), 1.21-1.43 (m, 5H, CH_2 -5, H-3, CH_2 -10), 1.52 (app. t, 1H, H-7 α) 1.61-1.85 (m, 2H, H-2 α , H-4), 2.12-2.24 (m, 2H, H-6 α , H-7 β), 2.27-2.41 (m, 1H, H-6 β), 2.82-2.88 (dd, J 9.8, 13.4, 1H, H-2 β), 3.01-3.12 (m, 1H, H-8), 4.08 (s, 3H, CH_3 -12), 5.93 (app. s, 1H, H-9), 7.37 (d, J 4.2, 1H, H-3'), 7.47-7.65 (m, 4H, H-16, H-18, H-19), 7.68 (d, J 9.2, 1H, H-7'), 7.87-8.00 (m, 4H, H-15, H-17), 8.17 (br. s,

1H, NH-13), 8.18 (d, J 9.2, 1H, H-8'), 8.76 (d, J 4.2, 1H, H-2'), 8.97 (s, 1H, NH-14)

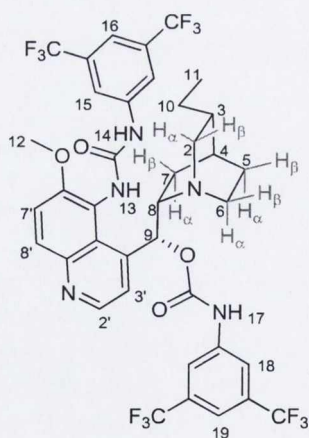
δ_C (100 MHz, $CDCl_3$): 11.9, 25.2, 27.6, 27.9, 29.7, 37.5, 42.2, 57.0, 58.4, 60.9, 81.2, 116.3 (br. s), 116.9, 117.9 (br. s), 118.4 (q), 123.2 (q, $^1J_{CF}$ 275.9), 124.2 (q), 124.7, 128.2 (q), 128.5 (2C), 130.7, 131.7, 132.2 (q, $^2J_{CF}$ 33.4), 136.2 (q), 138.5 (q), 139.9 (q), 147.0, 152.4 (q), 153.5 (q), 171.6 (q)

δ_F (375 MHz, $CDCl_3$): - 63.5 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3230, 3091, 1394, 1702, 1623, 1566, 1514, 1473, 1444, 1385, 1302, 1213, 1171, 1124, 1000, 906, 883, 850, 822, 763, 731, 701, 681

HRMS (m/z -ES): Found: 701.2567 ($M^+ + H$, $C_{36}H_{35}N_4O_4F_6$ Requires: 701.2563)

6.2.12 C-5'-(3,5-bis(Trifluoromethyl)phenyl urea)-substituted C-9-(3,5-bis(trifluoromethyl)phenyl carbamate)-derived dihydroquinine derivative 355



Compound **367** (393 mg, 1.15 mmol) was dissolved in freshly distilled CH_2Cl_2 (3 mL) under an Ar atmosphere. 3,5-bis(Trifluoromethyl)phenyl isocyanate (**364**, 120 μL , 1.15 mmol) was added dropwise over 5 min at ambient temperature and the resulting mixture was stirred for 96 h. The reaction was then diluted in CH_2Cl_2 (10 mL) and washed with

water (3 x 10 mL). The organic extract was dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (100:2 EtOAc/MeOH) to give **355** (196 mg, 21%) as a white solid. M.p. 201-202 °C. $[\alpha]_D^{22} = +63$ (*c* 0.1, CHCl_3).

δ_{H} (600 MHz, Acetone- d_6): 0.60-0.94 (m, 3H, CH_3 -11), 1.06-1.59 (m, 5H, H-3, H-5 β , H-7 α , CH_2 -10), 1.65-1.95 (m, 3H, H-4, H-5 α , H-7 β), 2.30-2.60 (m, 3H, CH_2 -2, H-6 β), 3.16-3.47 (m, 2H, H-8, H-6 α), 4.04 (s, 3H, CH_3 -12), 7.42-7.88 (m, 5H, H-3', H-7', H-9, H-16, H-19), 8.02-8.40 (m, 5H, H-8', H-15, H-18), 8.72 (d, J 4.4, 1H, H-2'), 9.24 (br. s, 2H, NH), 9.76 (s, 1H, NH)

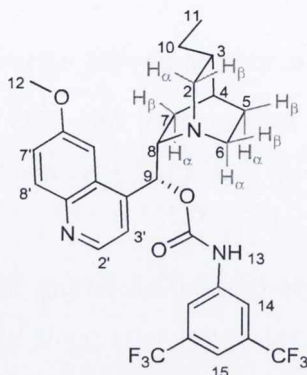
δ_{C} (150 MHz, Acetone- d_6): 11.8, 21.1, 26.8, 27.7, 28.6, 37.8, 43.9, 56.9, 58.3 (2C), 77.1, 113.9 (q), 114.7 (br. s, 2C), 116.2, 117.0, 118.6 (br. s, 2C), 124.0 (q, $^1J_{\text{CF}}$ 270.4), 124.2 (q, $^1J_{\text{CF}}$ 270.3), 126.1 (q), 131.7 (q), 132.1 (q, $^2J_{\text{CF}}$ 33.2, 2C), 132.4, 141.6 (q), 143.3 (q), 145.5 (q), 148.1, 153.2 (q), 155.3 (q), 156.3 (q)

δ_{F} (375 MHz, Acetone- d_6): -64.1 (CF_3), -64.2. (CF_3)

ν_{max} (neat)/ cm^{-1} : 3225, 2934, 2863, 1736, 1624, 1562, 1474, 1386, 1274, 1213, 117, 1125, 1098, 1000, 949, 882, 702, 681

HRMS (m/z -ES): Found: 852.2429 ($\text{M}^+ + \text{H}$. $\text{C}_{38}\text{H}_{34}\text{N}_5\text{O}_4\text{F}_{12}$ Requires: 852.2419).

6.2.13 C-9-(3,5-bis(Trifluoromethyl)phenyl carbamate)-substituted dihydroquinine derivative 370



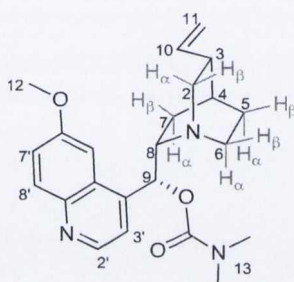
Dihydroquinine (**58a**, 729 mg, 2.24 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) under an Ar atmosphere. 3,5-(bis-trifluoromethyl)phenyl isocyanate (387 μL , 2.24 mmol) was then added dropwise over 5 min at ambient temperature and the reaction was stirred for 3 days at this temperature. After the volatiles were concentrated under vacuum, the obtained residue was charged directly onto a silica column for purification (100:2 EtOAc/MeOH) to give **370** (954 mg, 73%) as a white solid. M.p. 207-209 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{22} = +36$ (c 0.8, CHCl_3).

δ_{H} (400 MHz, CDCl_3): 0.91 (app. t, 3H, CH_3 -11), 1.38-1.42 (m, 2H, CH_2 -10), 1.43-1.60 (m, 3H, H-3, H-5 β , H-7 α), 1.71-1.81 (m, 1H, H-5 α), 1.84-1.97 (m, 2H, H-4, H-7 β), 2.34-2.46 (m, 1H, H-2 α), 2.62-2.69 (m, 1H, H-6 β), 3.09 (m, 2H, H-2 β , H-6 α), 3.38 (app. dd, 1H, H-8), 4.00 (s, 3H, H-12), 6.58 (d, J 8.0, 1H, H-9), 7.25 (d, J 4.8, 1H, H-3'), 7.37 (dd, J 9.2, 2.8, 1H, H-7'), 7.51 (d, J 2.8, 1H, H-5'), 7.54 (s, 1H, H-15), 7.82 (br. s, 1H, NH-13), 7.86 (s, 2H, H-14), 7.98 (d, J 9.2, 1H, H-8'), 8.66 (d, J 4.8, 1H, H-2').

δ_{C} (100 MHz, CDCl_3): 11.7, 24.1, 24.7, 27.3, 27.9, 36.8, 42.1, 55.2, 57.6, 74.1, 58.3, 100.8, 116.3 ($^3J_{\text{CF}}$ 3.7), 117.7 (br. s), 118.4, 121.6, 122.6 (q, $^1J_{\text{CF}}$ 271.2), 126.8 (q), 131.2, 132.0 (q, $^2J_{\text{CF}}$ 33.4), 138.9 (q), 142.7 (q), 144.2 (q), 146.9, 152.0 (q), 157.8 (q)

δ_F (375 MHz, $CDCl_3$):	-63.6 (CF_3)
ν_{max} (neat)/ cm^{-1} :	2974, 1685, 1570, 1473, 1388, 1276, 1165, 1124, 880, 852, 681
HRMS (m/z -ES):	Found: 580.2039 ($M^+ - H$. $C_{29}H_{28}N_3O_3F_6$ Requires: 580.2035).

6.2.14 C-9-Dimethylcarbamate-derived quinine derivative 371



A 100 mL round bottom flask was flushed with Ar and charged with a solution of dimethylcarbamyl chloride (1.67 mL, 18.14 mmol) in CH_2Cl_2 (31 mL) and DMAP (200 mg, 1.64 mmol). The obtained solution was stirred for 45 min. Then, NEt_3 (10.0 mL, 72.00 mmol) was added dropwise *via* syringe and the resulting solution was stirred for another 15 min at ambient temperature. Finally, quinine (**50**, 5 g, 15.43 mmol) was added portion-wise to the reaction. The reaction was stirred at room temperature overnight. The obtained solution was washed with water (3 x 40 mL), the combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and the residue was purified by column chromatography (95:5 EtOAc/MeOH) to afford **371** (3.02 g, 50 %) as a white solid. M.p. 131-132 °C. $[\alpha]_D^{22} = +28$ (c 0.3, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$):	1.52-1.68 (m, 2H, H-5 β , H-7 α), 1.70-1.81 (m, 1H, H-5 α), 1.85-1.99 (m, 2H, H-3, H-7 β), 2.31 (app. s, 1H, H-4), 2.57-2.77 (m, 2H, H-2 α , H-6 β), 2.92 (s, 3H, CH_3 -13), 3.00-3.12 (m, 4H, H-2 β , CH_3 -13), 3.15-3.26 (m, 1H, H-6 α), 3.57 (app. q, 1H, H-8), 3.98 (s, 3H, CH_3 -12), 5.00-5.08 (m, 2H, CH_2 -
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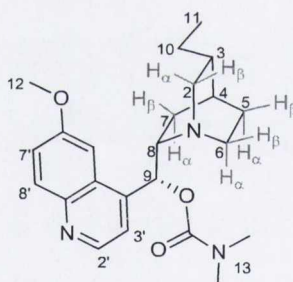
11), 5.87 (ddd, J 7.6, 10.4, 17.6, 1H, H-10), 6.45 (d, J 6.8, 1H, H-9), 7.37 (d, J 4.4, 1H, H-3'), 7.39 (app. d, 1H, H-7'), 7.51 (d, J 2.4, 1H, H-5'), 8.02 (d, J 9.2, 1H, H-8'), 8.76 (d, J 4.4, 1H, H-2')

δ_C (100 MHz, $CDCl_3$): 24.4, 27.6, 27.9, 36.0, 36.7, 39.8, 42.4, 55.7, 56.6, 59.6, 74.8, 101.7, 114.5, 118.8, 121.8, 127.1 (q), 131.8, 141.9, 144.5 (q), 144.9 (q), 147.5, 155.6 (q), 157.8 (q)

ν_{max} (neat)/ cm^{-1} : 2928, 2874, 1706, 1622, 1469, 1382, 1230, 1180, 993, 1021, 911, 854, 825, 771, 685

HRMS (m/z -ES): Found: 396.2290 ($M^+ + H$. $C_{23}H_{30}N_3O_3$ Requires: 396.2287).

6.2.15 C-9-Dimethylcarbamate-derived dihydroquinine derivative 372



A 50 mL oven-dried round bottom flask was charged the 9-dimethylcarbamate-derived quinine analogue **371** (2.70 g, 6.83 mmol) dissolved in freshly degassed MeOH (25 mL) and palladium on charcoal (10%, 0.74 g, 0.68 mmol). This mixture was reacted under atmospheric pressure of hydrogen for 3 h. After removing the palladium by filtration through a pad of celite, the reaction was concentrated *in vacuo*. The crude residue was purified by column chromatography (95:5 EtOAc/MeOH) to give **372** (832 mg, 31%) as a white solid. M.p. 107-109 °C. $[\alpha]_D^{22} = +32$ (c 0.3, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 0.88 (app. t, 3H, CH_3 -11), 1.24-1.41 (m, 2H, CH_2 -10), 1.44-1.55 (m, 2H, H-3, H-5 β), 1.59-1.68 (m, 1H, H-7 α), 1.70-1.91 (m, 3H, H-4, H-5 α , H-7 β), 2.35 (app. d, 1H, H-2 α), 2.69

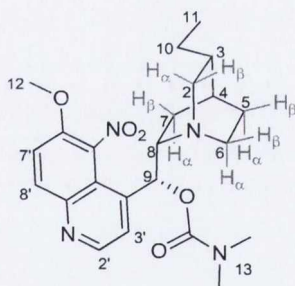
(app. t, 1H, H-6 β), 2.92 (s, 3H, CH₃-13), 3.07 (m, 4H, H-2 β , CH₃-13), 3.14-3.27 (m, 1H, H-6 α), 3.36 (app. dd, 1H, H-8), 3.99 (s, 3H, CH₃-12), 6.47 (br. app. s, 1H, H-9), 7.36-7.37 (m, 2H, H-3', H-7'), 7.51 (d, J 2.0, 1H, H-5'), 8.02 (d, J 9.2, 1H, H-8'), 8.75 (d, J 4.4, 1H, H-2')

δ_C (100 MHz, CDCl₃): 12.1, 24.0, 25.3, 27.7, 28.5, 36.0, 36.7, 37.4, 42.6, 55.7, 58.3, 59.4, 74.8, 101.6, 118.7, 121.9, 127.1 (q), 131.7, 144.6 (q), 144.8 (q), 147.5, 155.5 (q), 157.9 (q)

$\nu_{\max}$ (neat)/cm⁻¹: 2934, 2874, 1709, 1622, 1469, 1367, 1229, 1179, 1074, 1021, 919, 854, 824, 718, 684

HRMS (*m/z* -ES): Found: 398.2434 (M⁺ + H. C₂₃H₃₂N₃O₃ Requires: 398.2444)

6.2.16 C-5'-Nitro-substituted C-9-dimethylcarbamate-derived dihydroquinine derivative 373



A 100 mL round bottom flask was charged with fuming nitric acid (3 mL). The solution was cooled to -10 °C and the C 9-dimethylcarbamate dihydroquinine derivative **372** (732 mg, 1.87 mmol) was added carefully portion-wise while keeping the temperature of the reaction below 5 °C. The resulting mixture was stirred at -10 °C for 30 min. Ice water (150 mL), followed by NaOH (25% aqueous solution, 8 mL) were added in a dropwise manner. Finally, NH₃ (33% aqueous solution, 21 mL) was poured into the obtained mixture. After allowing the reaction to warm to ambient temperature, the expected C-5'-nitro-substitued derivative **373** was extracted using CH₂Cl₂ (3 x 150 mL). The combined organic extracts were washed with water (3 x 500 mL), dried over MgSO₄ and concentrated *in vacuo*. The

crude residue was purified by column chromatography (100:5→100:20 EtOAc/MeOH) to afford **373** (632 mg, 77%) as a brown solid. M.p. 93-97 °C. $[\alpha]_D^{22} = +21$ (c 0.1, CHCl₃).

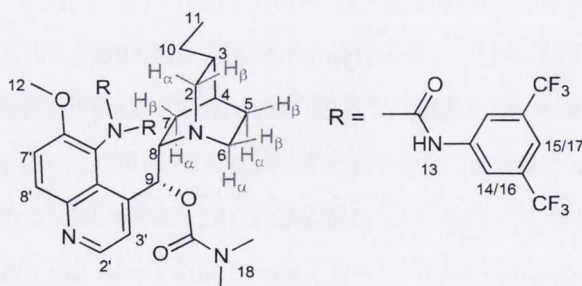
δ_H (400 MHz, CDCl₃): 0.82 (app. t, 3H, CH₃-11), 1.17-1.31 (m, 2H, CH₂-10), 1.38-1.53 (m, 3H, H-3, H-5 β , H-7 α), 1.61-1.87 (m, 3H, H-4, H-5 α , H-7 β), 2.56 (d, J 12.8, 1H, H-2 α), 2.78 (app. t, 1H, H-6 β), 2.91 (s, 3H, CH₃-13), 3.00-3.10 (m, 1H, H-8), 3.10-3.19 (m, 4H, H-2 β , CH₃-13), 3.25 (app. t, 1H, H-6 α), 4.06 (s, 3H, CH₃-12), 6.09 (app. s, 1H, H-9), 7.55 (d, J 4.4, 1H, H-3'), 7.61 (d, J 9.6, 1H, H-7'), 8.29 (d, J 9.6, 1H, H-8'), 8.82 (d, J 4.4, 1H, H-2')

δ_C (100 MHz, CDCl₃): 12.1, 21.6, 25.8, 27.8, 28.5, 36.0, 36.7, 37.3, 43.5, 57.3 58.7, 58.9, 74.8, 115.9, 117.9, 120.8 (q), 134.5, 135.7 (q), 143.5 (q), 148.7, 150.1 (q), 154.7 (q), 158.7 (q)

ν_{max} (neat)/cm⁻¹: 2931, 2875, 1707, 1533, 1509, 1381, 1267, 1177, 1101, 1042, 856, 788, 765, 669

HRMS (m/z -ES): Found: 443.2305 ($M^+ + H$. C₂₃H₃₁N₄O₅ Requires: 443.2294)

6.2.17 C-5'-(bis(3,5-bis(Trifluoromethyl)phenyl urea))-substituted C-9-dimethylcarbamate-derived dihydroquinine derivative **374b**



A hydrogenation reaction vessel was charged with the above nitro-derivatised **373** (482 mg, 1.18 mmol) in MeOH (30 mL). The reactor was then flushed with argon and palladium

on charcoal (10%, 130 mg, 0.12 mmol) was carefully added portion-wise. This mixture was reacted under 1 atm of hydrogen for 1 h. After removing the palladium by filtration through celite, the reaction was concentrated *in vacuo*. The crude residue (404 mg, 0.99 mmol) was then dissolved in anhydrous CH₂Cl₂ (9 mL) in a 25 mL round bottom flask fitted with a septum and placed under an Ar atmosphere. 3,5-(bis-trifluoromethyl)phenyl isocyanate (**364**, 206 μ L, 1.19 mmol) was added dropwise over 5 min at ambient temperature. The resulting mixture was stirred for 18 h. The reaction was then diluted in CH₂Cl₂ (10 mL) and washed with water (3 x 20 mL). The organic extract was dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by column chromatography (95:5 $\rightarrow$ 80:20 EtOAc/MeOH) to give **374** (280 mg, 30%) as a yellow solid. M.p. 122-125 °C. $[\alpha]_D^{22} = -32$ (*c* 0.3, CHCl₃).

δ_H (400 MHz, CDCl₃): 0.61 (app. t, 3H, CH₃-11), 0.98-1.08 (m, 1H, H-10), 1.12-1.19 (m, 2H, H-3, H-10), 1.34-1.39 (m, 1H, H-5 β), 1.59-1.70 (m, 2H, H-5 α , H-7 β), 1.76 (app. br. s, 1H, H-4), 1.92-1.99 (m, 2H, H-2 α , H-7 α), 2.29 (dd, *J* 9.6, 13.6, 1H, H-2 β), 2.52 (m, 1H, H-6 β), 2.82 (s, 3H, CH₃-18), 3.07 (app. t, 1H, H-8), 3.11-3.17 (m, 4H, H-6 α , CH₃-18), 4.08 (s, 3H, CH₃-12), 6.66 (app. s, 1H, H-9), 7.46 (d, *J* 4.8, 1H, H-3'), 7.59 (br. s, 2H, H-15, H-17), 7.67 (d, 1H, *J* 9.2, H-7'), 8.03 (br. s, 2H, H-14 or H-16), 8.14 (br. s, 2H, H-14 or H-16), 8.38 (d, *J* 9.2, 1H, H-8'), 8.84 (d, *J* 4.8, 1H, H-2'), 11.79 (br. s, 2H, 2 NH-13)

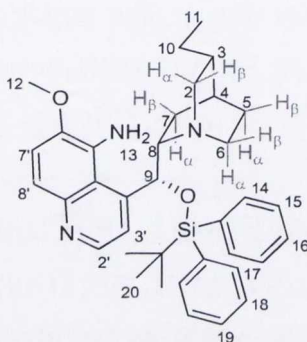
δ_C (100 MHz, CDCl₃): 11.6, 20.6, 26.0, 27.4, 28.6, 35.9, 36.3, 37.1, 43.6, 57.0, 58.0, 58.4, 76.8, 115.7, 116.7 (³*J*_{CF} 3.9), 117.5 (³*J*_{CF} 4.4), 118.2 (q), 119.4, 119.7 (³*J*_{CF} 3.5), 121.5 (³*J*_{CF} 3.5), 123.2 (q, ¹*J*_{CF} 271.2, 2C), 125.7 (q), 132.0 (q, ²*J*_{CF} 33.4, 2C), 135.1, 139.1 (q), 140.0 (q), 144.7 (q), 145.7 (q), 148.4, 152.7 (q), 154.9 (q), 155.6 (q), 156.9 (q)

δ_F (375 MHz, CDCl₃): -62.9 (CF₃)

$\nu_{\max}$ (neat)/ cm^{-1} : 2938, 1701, 1535, 1439, 1383, 1274, 1167, 1125, 884, 758, 682

HRMS (m/z -ES): Found: 923.2811 ($M^+ + H$, $C_{41}H_{39}N_6O_5F_{12}$ Requires: 923.2790)

6.2.18 C-5'-Amino-substituted C-9-(*tert*-butyldiphenylsilyloxy)-derived dihydroquinine derivative **359**



The C-5'-amino derivative **367** (1.50 g, 4.40 mmol) was dissolved in freshly distilled DMF (8 mL). DMAP (55.1 mg, 0.44 mmol) was added and NEt_3 (3.10 mL, 22.20 mmol) was injected *via* syringe. The obtained mixture was cooled to 0 °C and *tert*-butylchlorodiphenylsilane (1.41 mL, 5.28 mmol) was finally added dropwise *via* syringe. The reaction was allowed to warm up to ambient temperature and was stirred overnight. The obtained mixture was then dissolved in 30 mL of ether and was washed with water (4 $\times$ 100 mL). The organic layer was dried over $NaSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (100% EtOAc $\rightarrow$ 80:20 EtOAc/MeOH) to afford the expected silyl protected amino derivative **359** (1.82 g, 71%) as a yellow solid. M.p. 179-180 °C (degradation 131 °C). $[\alpha]_D^{22} = -114$ (c 0.4, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 0.83 (app. t, 3H, CH_3 -11), 1.00 (s, 9H, 3 CH_3 -20), 1.13-1.45 (m, 6H, H-3, CH_2 -5, H-7 α , CH_2 -10), 1.65 (br. s., 1H, H-4), 1.89-2.00 (m, 1H, H-7 β), 2.03-2.11 (m, 1H, H-2 α), 2.31 (app. t, 2H, CH_2 -6), 2.79 (dd, J 4.0, 8.0, 1H, H-2 β), 3.99 (app. q, 1H, H-8), 4.06 (s, 3H, CH_3 -12), 4.69 (d, J 10.1, 1H, H-9), 5.99 (br. s, 2H, NH_2 -13), 6.56 (d, J 4.0, 1H, H-3'), 7.11 (app. t, 2H, H-15 or H-18), 7.25 (d, J 8.0, 2H, H-14 or H-17),

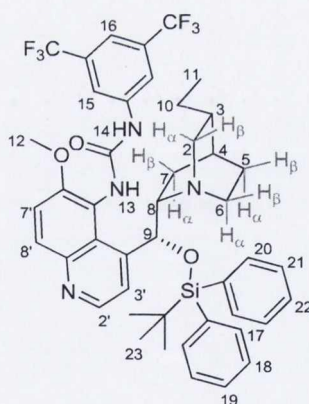
7.30-7.36 (m, 1H, H-16 or H-19), 7.43-7.58 (m, 5H, H-7', H-14 or H-17, H-15 or H-18), 7.79 (app. d, 2H, H-8', H-16 or H-19), 8.41 (d, J 4.0, 1H, H-2')

δ_C (100 MHz, $CDCl_3$): 11.9, 18.9 (q), 24.8, 24.9, 26.7, 27.2, 27.9, 37.2, 40.8, 56.1, 57.1, 59.4, 79.5, 114.4, 116.9 (q), 118.5, 122.0, 126.8 (q), 126.9, 127.5, 129.5, 129.9, 131.4 (q), 131.6 (q), 132.2 (q), 135.7, 135.9, 142.8 (q), 145.7 (q), 147.1

ν_{max} (neat)/ cm^{-1} : 3325, 2933, 1798, 1551, 1454, 1378, 1277, 1182, 1124, 1042, 999, 842, 700

HRMS (m/z -ES): Found: 580.3340 ($M^+ + H$, $C_{36}H_{46}N_3O_2Si$ Requires: 580.3359)

6.2.19 C-5'-(3,5-bis(Trifluoromethyl)phenyl urea)-substituted C-9-(*tert*-butyldiphenylsilyloxy)-derived dihydroquinine derivative **356**



The amino derivative **359** (1.00 g, 1.72 mmol) was dissolved in freshly distilled CH_2Cl_2 (5 mL) under an Ar atmosphere. The obtained solution was cooled to 0 °C and 3,5-bis(trifluoromethyl)phenyl isocyanate (**364**, 350 μ L, 2.00 mmol) was added dropwise over 10 min *via* syringe. The reaction was stirred for 18 h at 0 °C. Finally, the crude mixture was charged directly onto a flash chromatography column for purification (100% EtOAc $\rightarrow$ 100:4 EtOAc/MeOH) to give **356** as a cream coloured solid (848 mg, 59%), M.p. 98-103 °C. $[\alpha]_D^{22} = -55$ (c 0.3, $CHCl_3$).

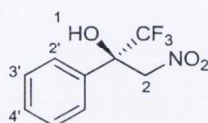
δ_{H} (400 MHz, CDCl_3):	0.46 (app. t, 3H, CH_3 -11), 0.91-1.23 (m, 15H, H-3, CH_2 -5, H-7 α , CH_2 -10, 3 CH_3 -23), 1.58 (app. s, 1H, H-4), 1.93 (app. d, 1H, H-2 α), 2.18 (m, 1H, H-7 β), 2.31 (app. dd, 1H, H-6 β), 2.39-2.48 (m, 1H, H-6 α), 2.71 (dd, J 9.6, 13.2, 1H, H-2 β), 3.48 (app. dd, 1H, H-8), 4.02 (s, 3H, CH_3 -12), 4.85 (d, J 10.2, 1H, H-9), 6.73 (d, J 4.6, 1H, H-3'), 6.88 (br. s, 1H, NH-13), 7.09 (app. t, 2H, H-18 or H-21), 7.15 (d, J 6.6, 2H, H-17 or H-20), 7.30 (t, J 7.2, 1H, H-19 or H-22), 7.50-7.55 (m, 4H, H-16, H-18 or H-21, H-19 or H-22), 7.65 (d, J 9.3, 1H, H-7'), 7.78 (d, J 6.6, 2H, H-17 or H-20), 7.97 (s, 2H, H-15), 8.15 (d, J 9.3, 1H, H-8'), 8.53 (d, 1H, J 4.6, H-2'), 9.31 (br. s, 1H, NH-14)
δ_{C} (100 MHz, CDCl_3):	11.4, 19.2 (q), 25.1, 26.1, 27.0, 27.4, 28.4, 37.5, 41.0, 57.1, 57.9, 60.7, 81.07, 115.8 ($^3J_{\text{CF}}$ 3.5), 117.0, 118.4 (br. s), 118.7 (q), 123.0 (q, $^1J_{\text{CF}}$ 271.2), 124.2 (q), 125.1, 127.3, 127.9, 130.1, 130.4, 131.2, 131.6 (q), 131.9 (q), 132.1 (q, $^2J_{\text{CF}}$ 33.6), 135.8, 136.3, 140.7 (q), 146.0 (q), 147.9, 152.7 (q), 153.1 (q), 171.4 (q)
δ_{F} (375 MHz, CDCl_3):	-63.4 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3264, 2932, 2861, 1686, 1542, 1471, 1429, 1384, 1276, 1175, 1129, 1110, 1026, 863, 701
HRMS (m/z -MALDI):	Found: 835.3334 ($\text{M}^+ + \text{H}$. $\text{C}_{45}\text{H}_{49}\text{F}_6\text{N}_4\text{O}_3\text{Si}$ Requires: 835.3478)

6.2.20 Procedure A: General procedure for the organocatalysed Henry addition of nitromethane to activated ketones at -30 °C

A reduced volume reaction vial containing a stirring bar was flushed with Ar, charged with the dihydroquinine-based cinchona alkaloid **355** (0.1 eq.) and closed with a suitable cap. Anhydrous MTBE (0.38 M) was then injected *via* syringe followed by styrene (1.0 eq.)

and the appropriate 2,2,2-trifluoroacetophenone derivative (1.0 eq.). The vial was introduced in the cooling machine set up at -30 °C and the reaction mixture was stirred for 15 min. Finally, nitromethane (7.0 eq.) was added to the reaction in a dropwise manner *via* syringe. The resulting solution was stirred at -30 °C for 72 h and was then analysed by ¹H-NMR spectroscopy. The product was directly purified by flash chromatography to afford the desired Henry adduct.

6.2.20.1 (*R*)-1,1,1-Trifluoro-3-nitro-2-phenylpropan-2-ol (**216**)



The nitroaldol adduct (*R*)-**216** was prepared according to the general procedure A at -30 °C using 2,2,2-trifluoroacetophenone (**207**, 34 μL, 0.25 mmol), nitromethane (**89**, 97 μL, 1.75 mmol) and the dihydroquinine-based catalyst **355** (21.3 mg, 0.03 mmol) in MTBE (0.5 mL, 0.38 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product (*R*)-**216** was obtained as a pale yellow oil (41.1 mg, 70%). $[\alpha]_{\text{D}}^{22} = -12$ (*c* 0.2, MeOH), (lit., ¹⁶¹ $[\alpha]_{\text{D}}^{25} = +42$ (*c* 1.7, MeOH), (*S*)-**216**, 96% *ee*).

The enantiomeric excess of (*R*)-**216** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_{R} (major) = 34.1 min; t_{R} (minor) = 48.5 min; 90% *ee*. The absolute configuration of (*R*)-**216** was assigned by comparison with literature specific rotation data.¹⁶¹

δ_{H} (400 MHz, CDCl₃): 4.65 (s, 1H, OH-1), 5.05 (d, *J* 13.7, 1H, H-2a), 5.13 (d, *J* 13.7, 1H, H-2b), 7.47-7.49 (m, 3H, H-3', H-4'), 7.61-7.63 (m, 2H, H-2')

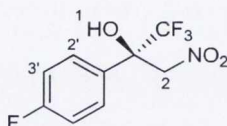
δ_{C} (100 MHz, CDCl₃): 75.9 (q, ²*J*_{CF} 25.9), 77.1, 123.0 (q, ¹*J*_{CF} 283.9), 125.7, 128.5, 129.5, 132.6 (q)

δ_{F} (375 MHz, CDCl₃): -79.2 (CF₃)

The NMR spectra of (*R*)-**216** were consistent with those previously reported in the literature.¹⁶¹

HRMS (*m/z* -ES): Found: 234.0376 ($M^+ - H$, C₉H₇NO₃F₃ Requires: 234.0378)

6.2.20.2 (*R*)-1,1,1-Trifluoro-2-(4-fluorophenyl)-3-nitropropan-2-ol (**220**)



The nitroaldol adduct (*R*)-**220** was prepared according to the general procedure A at -30 °C using 2,2,2,4'-tetrafluoroacetophenone (**211**, 73 μ L, 0.52 mmol), nitromethane (**89**, 197 μ L, 3.64 mmol) and the dihydroquinine-based catalyst **355** (44.3 mg, 0.05 mmol) in MTBE (1.05 mL, 0.38 M). After purification of the crude material by flash chromatography (80:20 *n*-hexane/CH₂Cl₂) the product (*R*)-**220** was obtained as a pale yellow oil (103 mg, 78%). $[\alpha]_D^{22} = -11$ (*c* 0.2, CHCl₃), (lit.,¹⁶¹ $[\alpha]_D^{25} = +15$ (*c* 0.8, CHCl₃), (*S*)-**220**, 97% *ee*).

The enantiomeric excess of (*R*)-**220** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 98:2 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_R (major) = 58.5 min; t_R (minor) = 68.8 min; 90% *ee*. The absolute configuration of (*R*)-**220** was assigned by comparison with literature specific rotation data.¹⁶¹

δ_H (400 MHz, CDCl₃): 4.69 (s, 1H, OH-1), 5.01 (d, *J* 13.6, 1H, H-2a), 5.08 (d, *J* 13.6, 1H, H-2b), 7.15 (m, 2H, H-2'), 7.60 (dd, *J* 5.1, 8.6, 2H, H-3')

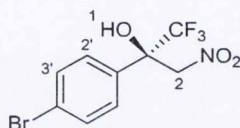
δ_C (100 MHz, CDCl₃): 75.6 (q, ²*J*_{CF} 29.8), 77.0, 115.6 (²*J*_{CF} 21.8), 122.9 (q, ¹*J*_{CF} 284.0), 128.0 (³*J*_{CF} 10.0), 128.3 (q), 163.1 (q, ¹*J*_{CF} 248.7).

δ_F (375 MHz, CDCl₃): -79.5 (CF₃), -111.6 (F).

The NMR spectra of (*R*)-**220** were consistent with those previously reported in the literature.¹⁶¹

HRMS (*m/z* -ES): Found 252.0280 ($M^+ - H$, C₉H₆NO₃F₄ Requires: 252.0284)

6.2.20.3 (*R*)-2-(4-Bromophenyl)-1,1,1-trifluoro-3-nitropropan-2-ol (**376**)



The nitroaldol adduct (*R*)-**376** was prepared according to the general procedure A at -30 °C using 4'-bromo-2,2,2-trifluoroacetophenone (**375**, 60 μ L, 0.40 mmol), nitromethane (**89**, 150 μ L, 2.77 mmol) and the dihydroquinine-based catalyst **355** (33.7 mg, 0.04 mmol) in MTBE (0.8 mL, 0.38 M). After purification of the crude material by flash chromatography (80:20 *n*-hexane/CH₂Cl₂) the product (*R*)-**376** was obtained as a pale yellow oil (96 mg, 77%). $[\alpha]_D^{22} = -9$ (*c* 0.8, CHCl₃), (lit.,¹⁶⁶ $[\alpha]_D^{25} = -2$ (*c* 5.3, CHCl₃), (*R*)-**376**, 90% *ee*).

The enantiomeric excess of (*R*)-**376** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_R (major) = 40.5 min; t_R (minor) = 61.6 min; 85% *ee*. The absolute configuration of (*R*)-**376** was assigned by comparison with literature specific rotation data.¹⁶⁶

δ_H (400 MHz, CDCl₃): 4.68 (s, 1H, OH-1), 5.02 (d, *J* 13.6, 1H, H-2a), 5.09 (d, *J* 13.6, 1H, H-2b), 7.50 (d, *J* 8.6, 2H, H-2'), 7.60-7.65 (m, 2H, H-3')

δ_C (100 MHz, CDCl₃): 76.1 (q, $^2J_{CF}$ 29.9), 77.4, 123.2 (q, $^1J_{CF}$ 284.0), 124.7 (q), 127.9, 132.0 (q), 132.3

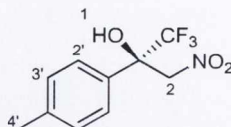
δ_F (375 MHz, CDCl₃): -79.3 (CF₃)

The NMR spectra of (*R*)-**376** were consistent with those previously reported in the literature.¹⁶⁶

HRMS (m/z -ES):

Found: 311.9480 ($M^+ - H$, $C_9H_6NO_3BrF_3$ Requires: 311.9483)

6.2.20.4 (*R*)-1,1,1-Trifluoro-3-nitro-2-*p*-tolylpropan-2-ol (**378**)



The nitroaldol adduct (*R*)-**378** was prepared according to the general procedure A at -25 °C using 4'-methyl-2,2,2-trifluoroacetophenone (**377**, 81 μ L, 0.53 mmol), nitromethane (**89**, 202 μ L, 3.72 mmol) and the dihydroquinine-based catalyst **355** (45.2 mg, 0.05 mmol) in MTBE (1.05 mL, 0.38 M). After purification of the crude material by flash chromatography (80:20 *n*-hexane/ CH_2Cl_2) the product (*R*)-**378** was obtained as a pale yellow oil (92 mg, 69%). $[\alpha]_D^{22} = -2$ (c 0.8, $CHCl_3$).

The enantiomeric excess of (*R*)-**378** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_R (major) = 35.1 min; t_R (minor) = 49.3 min; 83% *ee*. The absolute configuration of (*R*)-**378** was established by analogy with the other compounds synthesised within the study.

δ_H (400 MHz, $CDCl_3$): 2.40 (s, 3H, CH_3 -4'), 4.60 (s, 1H, OH-1), 4.95 (d, J 13.6, 1H, H-2a), 5.11 (d, J 13.6, 1H, H-2b), 7.28 (d, J 7.7, 2H, H-3'), 7.49 (d, J 7.7, 2H, H-2')

δ_C (100 MHz, $CDCl_3$): 20.7, 75.6 (q, $^2J_{CF}$ 29.7), 77.1, 123.0 (q, $^1J_{CF}$ 283.6), 125.6, 129.2, 129.5 (q), 139.7 (q)

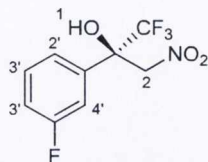
δ_F (375 MHz, $CDCl_3$): -79.4 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3518, 2928, 1560, 1376, 1270, 1185, 1161, 1111, 1051, 965, 813, 718, 674

HRMS (m/z -ES):

Found: 248.0544 ($M^+ - H$, $C_{10}H_9NO_3F_3$ Requires: 248.0535)

6.2.20.5 (*R*)-1, 1, 1-Trifluoro-2-(3-fluorophenyl)-3-nitropropan-2-ol (**380**)



The nitroaldol adduct (*R*)-**380** was prepared according to the general procedure A at -30 °C using 2,2,2,3'-tetrafluoroacetophenone (**379**, 60 μ L, 0.42 mmol), nitromethane (**89**, 161 μ L, 2.94 mmol) and the dihydroquinine-based catalyst **355** (36.4 mg, 0.04 mmol) in MTBE (0.85 mL, 0.38 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product (*R*)-**380** was obtained as a pale yellow oil (78 mg, 73%). $[\alpha]_D^{22} = -16$ (*c* 0.4, CHCl₃).

The enantiomeric excess of (*R*)-**380** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_R (major) = 30.6 min; t_R (minor) = 49.9 min; 85% *ee*. The absolute configuration of (*R*)-**380** was established by analogy with the other compounds synthesised within the study.

δ_H (400 MHz, CDCl₃): 4.75 (s, 1H, OH-1), 5.03 (d, *J* 13.7, 1H, H-2a), 5.09 (d, *J* 13.7, 1H, H-2b), 7.16 (app. td, 1H, H-3'), 7.33-7.57 (m, 3H, H-2', H-4', H-6')

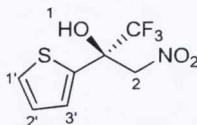
δ_C (100 MHz, CDCl₃): 75.5 (q, $^2J_{CF}$ 30.0), 76.9, 113.6 ($^2J_{CF}$ 24.2), 116.7 ($^2J_{CF}$ 20.9), 121.3, 122.8 (q, $^1J_{CF}$ 284.1), 130.2 ($^3J_{CF}$ 8.2), 135.0 (q, $^3J_{CF}$ 7.2), 161.5 (q, $^1J_{CF}$ 246.3)

δ_F (375 MHz, CDCl₃): -79.1 (CF₃), -111.3 (F)

ν_{max} (neat)/cm⁻¹: 3513, 2800, 1594, 1561, 1447, 1375, 1180, 1139, 1054, 970, 862, 787, 674

HRMS (*m/z* -ES): Found: 252.0279 ($M^+ - H$, C₉H₆NO₃F₄ Requires: 252.0284)

6.2.20.6 (*R*)-1,1,1-Trifluoro-3-nitro-2-(thiophen-2-yl)propan-2-ol (**222**)



The nitroaldol adduct (*R*)-**222** was prepared according to the general procedure A at -25 °C using 2-(trifluoroacetyl)thiophene (**213**, 72 μ L, 0.56 mmol), nitromethane (**89**, 212 μ L, 3.92 mmol) and the dihydroquinine-based catalyst **355** (47.7 mg, 0.06 mmol) in MTBE (1.10 mL, 0.38 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product (*R*)-**222** was obtained as a pale yellow oil (92 mg, 85%). $[\alpha]_D^{22} = -12$ (*c* 0.8, CHCl₃), (lit.,¹⁶¹ $[\alpha]_D^{25} = +5$ (*c* 1.4, CHCl₃), (*S*)-**222**, 76% *ee*).

The enantiomeric excess of (*R*)-**222** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_R (minor) = 34.8 min; t_R (major) = 43.3 min; 82% *ee*. The absolute configuration of (*R*)-**222** was assigned by comparison with literature specific rotation data.¹⁶¹

δ_H (400 MHz, CDCl₃): 5.01 (m, 3H, CH₂-2, OH-1), 7.08 (dd, *J* 3.6, 5.0, 1H, H-2'), 7.18 (dd, *J* 0.8, 3.6, 1H, H-3'), 7.46 (dd, 1H, *J* 0.8, 5.0, H-1')

δ_C (100 MHz, CDCl₃): 75.0 (q, ²*J*_{CF} 31.3), 77.1, 122.5 (q, ¹*J*_{CF} 283.8), 126.2, 127.2, 127.6, 135.9 (q)

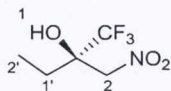
δ_F (375 MHz, CDCl₃): -80.2 (CF₃).

The NMR spectra of (*R*)-**222** were consistent with those previously reported in the literature.¹⁶¹

$\nu_{\max}$ (neat)/cm⁻¹: 3507, 2600, 1560, 1376, 1158, 1054, 958, 707, 679

HRMS (*m/z* -EI): The HRMS analysis (EI and ESI) were not conclusive, even when lower ionisation voltage was utilised

6.2.20.7 (R)-1,1,1-Trifluoro-2-(nitromethyl)butan-2-ol (**224**)



The nitroaldol adduct (*R*)-**224** was prepared according to the general procedure A at -30 °C using 1,1,1-trifluoro-2-butanone (**215**, 107 μ L, 0.79 mmol), nitromethane (**89**, 300 μ L, 5.54 mmol) and the dihydroquinine-based catalyst **355** (67.3 mg, 0.08 mmol) in MTBE (1.60 mL, 0.38 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product (*R*)-**224** was obtained as a pale yellow oil (108 mg, 73%). $[\alpha]_D^{22} = +6$ (c 0.9, CHCl₃), (lit., ¹⁶¹ $[\alpha]_D^{25} = +6$ (c 1.2, CHCl₃), (*R*)-**224**, 93% *ee*).

The enantiomeric excess of (*R*)-**224** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 98:2 *n*-hexane/IPA; 0.6 mL/min; $\lambda = 220$ nm. t_R (major) = 30.2 min; t_R (minor) = 35.1 min; 95% *ee*. The absolute configuration of (*R*)-**224** was established by comparing the optical rotation with the literature data.¹⁶¹

δ_H (400 MHz, CDCl₃): 1.10 (app. t, 3H, CH₃-2'), 1.78-1.90 (m, 1H, H-1'a), 1.92-2.04 (m, 1H, H-1'b), 4.00 (s, 1H, OH-1), 4.60 (d, J 12.9, 1H, H-2a), 4.70 (d, J 12.9, 1H, H-2b)

δ_C (100 MHz, CDCl₃): 6.85, 26.0, 74.8 (q, ²J_{CF} 28.5), 76.05, 124.6 (q, ¹J_{CF} 285.0 Hz)

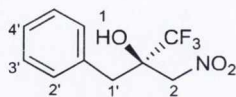
δ_F (375 MHz, CDCl₃): -79.9 (CF₃)

The NMR spectra of (*R*)-**224** were consistent with those previously reported in the literature.¹⁶¹

$\nu_{\max}$ (neat)/cm⁻¹: 3517, 1717, 1601, 1563, 1512, 1376, 1235, 1185, 1159, 1101, 941, 836, 767, 673

HRMS (*m/z* -EI): The HRMS analysis (EI and ESI) were not conclusive, even when lower ionisation voltage was utilised.

6.2.20.8 (*R*)-2-Benzyl-1,1,1-trifluoro-3-nitropropan-2-ol (**223**)



The nitroaldol adduct (*R*)-**223** was prepared according to the general procedure A at -30 °C using 1,1,1-trifluoro-3-phenyl-2-propanone (**214**, 82 μ L, 0.53 mmol), nitromethane (**89**, 201 μ L, 3.71 mmol) and the dihydroquinine-based catalyst **355** (45.2 mg, 0.05 mmol) in MTBE (1.04 mL, 0.38 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product (*R*)-**223** was obtained as a pale yellow oil (98 mg, 78%). $[\alpha]_D^{22} = -3$ (*c* 0.6, CHCl₃).

The enantiomeric excess of (*R*)-**223** was determined by chiral HPLC analysis using a chiralpak AD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_R (major) = 8.9 min; t_R (minor) = 10.3 min; 96% *ee*. The absolute configuration of (*R*)-**223** was established by analogy with the other compounds synthesised within the study.

δ_H (400 MHz, CDCl₃): 2.96 (d, *J* 14.4, 1H, H-1'a), 3.33 (d, *J* 14.4, 1H, H-1'b), 4.27 (d, *J* 13.1, 1H, H-2a), 4.39 (s, 1H, OH-1), 4.68 (d, *J* 13.1, 1H, H-2b), 7.27-7.47 (m, 5H, H-2', H-3', H-4')

δ_C (100 MHz, CDCl₃): 37.9, 74.4 (q, $^2J_{CF}$ 28.4), 75.3, 124.1 (q, $^1J_{CF}$ 285.3), 127.7, 128.4, 130.4, 131.5 (q)

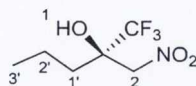
δ_F (375 MHz, CDCl₃): -80.3 (CF₃)

The NMR spectra of (*R*)-**223** were consistent with those previously reported in the literature.¹⁶¹

ν_{max} (neat)/cm⁻¹: 3507, 3109, 1560, 1377, 1289, 1174, 1119, 1037, 911, 743, 703

HRMS (*m/z* -ES): Found: 248.0539 (M⁺ - H. C₁₀H₉NO₃F₃ Requires: 248.0535)

6.2.20.9 (R)-1,1,1-Trifluoro-2-(nitromethyl)pentan-2-ol (384)



The nitroaldol adduct (*R*)-**384** was prepared according to the general procedure A at -30°C using 1,1,1-trifluoro-pentan-2-one (**383**, 90 μL , 0.70 mmol), nitromethane (**89**, 267 μL , 4.90 mmol) and the dihydroquinine-based catalyst **355** (60.0 mg, 0.07 mmol) in MTBE (1.40 mL, 0.38 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product (*R*)-**384** was obtained as a pale yellow oil (98 mg, 70%). $[\alpha]_{\text{D}}^{22} = +5$ (*c* 0.4, CHCl_3).

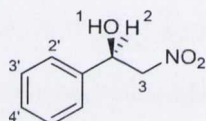
The enantiomeric excess of (*R*)-**384** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 98:2 *n*-hexane/IPA; 0.6 mL/min; $\lambda = 220$ nm. t_{R} (major) = 26.3 min; t_{R} (minor) = 33.4 min; 96% *ee*. The absolute configuration of (*R*)-**384** was established by analogy with the other compounds synthesised within the study.

δ_{H} (400 MHz, CDCl_3) :	1.01 (app. t, 3H, $\text{CH}_3\text{-3'}$), 1.36-1.68 (m, 2H, $\text{CH}_2\text{-2'}$), 1.68-1.79 (td, <i>J</i> 4.0, 12.0, 1H, H-1'a), 1.82-1.92 (td, <i>J</i> 4.0, 12.0, 1H, H-1'b), 4.00 (s, 1H, OH-1), 4.60 (d, <i>J</i> 12.8, 1H, H-2a), 4.70 (d, <i>J</i> 12.8, 1H, H-2b)
δ_{C} (100 MHz, CDCl_3):	13.7, 15.4, 34.5, 74.3 (q, $^2J_{\text{CF}}$ 28.6), 75.9, 124.1 (q, $^1J_{\text{CF}}$ 284.9)
δ_{F} (375 MHz, CDCl_3):	-80.0 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3513, 2974, 1560, 1379, 1286, 1179, 1114, 1038, 919, 743, 683, 667
HRMS (<i>m/z</i> -ES):	Found: 200.0534 ($\text{M}^+ - \text{H}$. $\text{C}_6\text{H}_9\text{NO}_3\text{F}_3$ Requires: 200.0535)

6.2.21 Procedure B: General procedure for the organocatalysed Henry addition of nitroalkane to activated ketones at room temperature

A 5 mL round bottomed flask containing a stirring bar was flushed with Ar, charged with the dihydroquinine-based cinchona alkaloid **355** (0.1 eq.) and fitted with a septum. Anhydrous MTBE (0.36 M) was then injected *via* syringe followed by styrene (1.0 eq.) and the appropriate 2,2,2-trifluoroacetophenone derivative (1.0 eq.). Finally, the appropriate nitroalkane (10.0 eq.) was added to the reaction in a dropwise manner *via* syringe. The resulting solution was allowed to stir at room temperature for 21 h and was then analysed by ^1H -NMR spectroscopy. The product was directly purified by flash chromatography to afford the desired Henry adduct.

6.2.21.1 (*R*)-2-Nitro-1-phenylethanol (**185**)

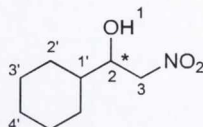


The nitroaldol adduct (*R*)-**185** was prepared according to the general procedure B at ambient temperature, using benzaldehyde (**184**, 67 μL , 0.66 mmol), nitromethane (**89**, 250 μL , 4.62 mmol) and the dihydroquinine-based catalyst **355** (56.2 mg, 0.07 mmol) in MTBE (1.35 mL, 0.38 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product (*R*)-**185** was obtained as a colourless oil (87.9 mg, 80%). $[\alpha]_{\text{D}}^{22} = -31$ (*c* 0.3, CH_2Cl_2), (lit.,²²⁷ $[\alpha]_{\text{D}}^{25} = -53$ (*c* 1.1, CH_2Cl_2 , (*R*)-**185**, 96% *ee*).

The enantiomeric excess of (*R*)-**185** was determined by chiral HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_{R} (major) = 14.6 min; t_{R} (minor) = 21.2 min; 77% *ee*. The absolute configuration of (*R*)-**185** was assigned by comparison with literature HPLC data.²²⁷

δ_{H} (400 MHz, CDCl_3): 2.85 (s, 1H, OH-1), 4.54 (dd, *J* 2.8, 13.4, 1H, H-3a), 4.64 (dd, *J* 9.6, 13.4, 1H, H-3b), 5.50 (app. d, 1H, H-2), 7.35-7.55 (m, 5H, H-2', H-3', H-4')

6.2.21.3 1-Cyclohexyl-2-nitroethanol (**181**)



The nitroaldol adduct (*R*)-**181** was prepared according to the general procedure B at ambient temperature, using cyclohexanecarbaldehyde (**180**, 27 μ L, 0.22 mmol), nitromethane (**89**, 83 μ L, 1.54 mmol) and the dihydroquinine-based catalyst **355** (18.7 mg, 0.02 mmol) in MTBE (0.45 mL, 0.38 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product (*R*)-**181** was obtained as a colourless oil (34.0 mg, 89%).

The enantiomeric excess of (*R*)-**181** was determined by chiral HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 95/5 *n*-hexane/IPA; 0.8 mL/min; λ = 220 nm. t_R (major) = 17.7 min; t_R (minor) = 19.5 min; 9% *ee*.

δ_H (400 MHz, $CDCl_3$): 1.04-1.35 (m, 5H, H-2'a, H-3'a, H-4'a), 1.46-1.90 (m, 6H, H-1', H-2'b, H-3'b, H-4'b), 2.43 (app. br. s, 1H, OH-1), 4.13 (m, 1H, H-2), 4.48 (m, 2H, CH₂-3)

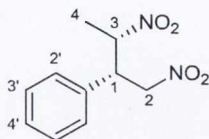
δ_C (100 MHz, $CDCl_3$): 25.7, 25.9, 26.0, 27.9, 28.8, 41.4, 72.8, 79.3

The NMR spectra of (*R*)-**181** were consistent with those previously reported in the literature.²²⁷

HRMS (*m/z* -ES): Found: 172.0976 ($M^+ - H$. C₈H₁₄NO₃ Requires: 172.0974)

6.3 Experimental data for Section 3

6.3.1 (2*S*,3*S*)-1,3-Dinitrobutan-2-yl)benzene (**395**)



An oven-dried 5 mL round-bottomed flask was charged with (*E*)- β -nitrostyrene (**47**, 30.0 mg, 0.20 mmol) and the catalyst **355** (17.0 mg, 0.02 mmol), equipped with a septum and placed under an Ar atmosphere. Anhydrous MTBE (0.4 mL) and nitroethane (**393**, 144 μ L, 2.00 mmol) were added to the reaction *via* syringe. The resulting solution was stirred at -30 °C for four days. The product was then directly purified by flash chromatography (90:10 *n*-hexane/EtOAc) to give the desired Michael adduct as a mixture of two diastereoisomers (d.r. 1:1.5, 28.8 mg (colourless oil), 65%).

The enantiomeric excess of the two diastereoisomers were determined by CSP-HPLC analysis using a Chiralcel AS column (4.6 mm x 25 cm); *n*-hexane/IPA 95/5; 0.8 mL/min; λ = 220 nm. Minor diastereoisomer *anti*: t_R (minor) = 29.05 min; t_R (major) = 32.92 min; 94% *ee*. Major diastereoisomer *syn*: t_R (minor) = 45.91 min; t_R (major) = 51.67 min; 81% *ee*. The relative configuration of the major diastereoisomer was determined by comparison with the HPLC data reported in the literature.²¹²

Major diastereoisomer (*syn*): $[\alpha]_D^{20} = +12$ (*c* 0.1, CHCl₃), (lit.,²¹⁶ $[\alpha]_D^{20} = +7$ (*c* 0.1, CHCl₃, *syn* diastereoisomer, 96% *ee*).

δ_H (400 MHz, CDCl₃): 1.61 (d, *J* 6.7, 3H, CH₃-4), 4.00-4.12 (m, 1H, H-3), 4.82-4.92 (m, 1H, H-1), 4.92-5.04 (m, 2H, CH₂-2), 7.15-7.26 (m, 2H, H-2'), 7.33-7.47 (m, 3H, H-3', H-4')

δ_C (100 MHz, CDCl₃): 16.7, 47.3, 76.1, 84.0, 127.9, 129.1, 129.3, 133.4 (q)

Minor diastereoisomer (*anti*):

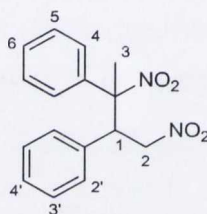
δ_{H} (400 MHz, CDCl_3): 1.45 (d, J 6.7, 3H, CH_3 -4), 4.00-4.12 (m, 1H, H-3), 4.68 (app. dd, 1H, H-1), 4.82-4.92 (m, 2H, CH_2 -2), 7.15-7.26 (m, 2H, H-2'), 7.33-7.47 (m, 3H, H-3', H-4')

δ_{C} (100 MHz, CDCl_3): 17.9, 47.8, 76.8, 84.6, 128.0, 129.1, 129.6, 133.8 (q)

The NMR spectra of **395** were consistent with those previously reported in the literature.²¹²

HRMS (m/z -ES): Found: 224.0804 (M^+ , $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4$ Requires: 224.0797)

6.3.2 (1,3-Dinitrobutane-2,3-diyl)dibenzene (397)



An oven-dried 5 mL round-bottom flask was charged with (*E*)- β -nitrostyrene (**47**, 14.1 mg, 0.09 mmol), the disubstituted nitroalkane **396** (13.9 mg, 0.09 mmol) and the catalyst **356** (15.6 mg, 0.02 mmol), before being equipped with a septum and placed under an Ar atmosphere. Tetrachloroethylene (2.1 mL) was added *via* syringe. The resulting solution was stirred at 30 °C for 112 h and was analysed by ^1H -NMR spectroscopy. The product was then directly purified by flash chromatography (90:10 *n*-hexane/EtOAc) to give the desired Michael adduct as a mixture of two diastereoisomers (dr 1:1.5, 46%). The major diastereoisomer was afforded as a white solid (6.4 mg, 24%). M.p 146-148 °C. $[\alpha]_{\text{D}}^{22} +37$ (c 0.3, CHCl_3). The minor diastereoisomer was obtained as a yellow oil (5.5 mg, 20%). $[\alpha]_{\text{D}}^{22} +50$ (c 0.2, CHCl_3).

The enantiomeric excess of the two diastereoisomers were determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 1 mL/min; λ = 220 nm. Major diastereoisomer: t_{R} (min) = 23.61 min; t_{R} (major) = 26.26 min, 88% *ee*. Minor diastereoisomer: t_{R} (maj) = 57.96 min; t_{R} (min) = 66.14 min, 90% *ee*.

Major diastereoisomer:

δ_{H} (400 MHz, CDCl_3): 1.78 (s, 3H, CH_3 -3), 4.54 (dd, J 2.3, 10.8, 1H, H-1), 4.82 (dd, J 2.3, 14.0, 1H, H-2a), 5.22 (dd, J 10.8, 14.0, 1H, H-2b), 7.16-7.23 (m, 2H, H-2'), 7.25-7.28 (m, 2H, H-4''), 7.32-7.38 (m, 3H, H-3', H-4'), 7.39-7.51 (m, 3H, H-5'', H-6'')

δ_{C} (100 MHz, CDCl_3): 26.3, 52.0, 77.5, 96.8 (q), 124.5, 129.0, 129.1, 129.2 (2C), 129.5, 133.5 (q), 138.6 (q)

ν_{max} (neat)/ cm^{-1} : 2969, 1536, 1446, 1435, 1378, 1262, 1104, 1086, 1071, 1031, 1004, 984, 846, 802, 760, 757, 695

Minor diastereoisomer:

δ_{H} (400 MHz, CDCl_3): 1.98 (s, 3H, CH_3 -3), 4.51 (dd, J 3.6, 13.1, 1H, H-1), 4.68 (app. t, 1H, H-2a), 5.13 (dd, J 3.6, 11.7, 1H, H-2b), 7.16- 7.26 (m, 2H, H-2'), 7.32-7.41 (m, 3H, H-3', H-4'), 7.47-7.54 (m, 3H, H-5'', H-6''), 7.54-7.63 (m, 2H, H-4'')

δ_{C} (100 MHz, CDCl_3): 20.8, 50.8, 76.1, 94.2 (q), 126.5, 128.8, 129.2, 129.8 (2C), 130.1, 133.1 (q), 135.6 (q)

ν_{max} (neat)/ cm^{-1} : 2928, 1546, 1499, 1447, 1376, 1278, 1133, 1033, 1004, 909, 856, 729, 707

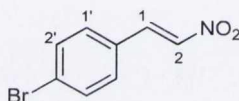
HRMS (m/z -ES): Found: 342.1349 ($[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$. $\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}_4^+$ Requires: 342.1454)

6.3.3 Procedure C: General procedure to prepare nitroalkenes

Potassium *tert*-butoxide (0.54 mmol, 0.1 eq.) was added at 0 °C to a solution of *tert*-butanol (44.40 mmol, 8.2 eq.) and nitromethane (**89**, 8.12 mmol, 1.5 eq.) in THF (7 mL). The appropriate aldehyde (5.40 mmol, 1.0 eq.) was then added to the resulting mixture. The reaction was allowed to warm to ambient temperature and was stirred overnight, before being poured into a saturated solution of NH_4Cl (30 mL) and extracted with EtOAc

(3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL), dried over MgSO₄ and concentrated under vacuum. The crude material was then dissolved in anhydrous CH₂Cl₂. Mesyl chloride (8.10 mmol, 1.5 eq.) was added to the solution *via* syringe in one portion at -10 °C, followed by NEt₃ (16.20 mmol, 3.0 eq.) injected in a dropwise manner. The obtained reaction mixture was stirred for 15 min at -10°C. KHSO₄ (1M sol., 40 mL) was added to the reaction and the mixture was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic layers were washed with water (3 × 40 mL), dried over MgSO₄ and concentrated under vacuum. The product was finally purified by column chromatography.

6.3.3.1 1-Bromo-4-((*E*)-2-nitrovinyl)benzene (**411**)



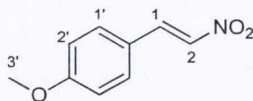
Prepared following procedure C using 4-bromobenzaldehyde (**407**, 1.00 g, 5.40 mmol), potassium *tert*-butoxide (61 mg, 0.54 mmol), *tert*-butanol (4.3 mL) and nitromethane (**89**, 0.44 mL, 8.12 mmol) in THF (7 mL). In the second step, the desired product was obtained using mesyl chloride (0.63 mL, 8.10 mmol) and NEt₃ (2.3 mL, 16.20 mmol) in freshly distilled CH₂Cl₂ (24 mL). After purification of the crude material by flash chromatography (100% *n*-hexane), the nitroalkene **411** was afforded as a yellow solid (856 mg, 71%). M.p. 142-144 °C, (lit.,²³⁰ 147 °C)

δ_H (400 MHz, CDCl₃): 7.71 (d, J 8.0, 2H, H-1'), 7.82 (d, J 8.0, 2H, H-2'), 8.13 (d, J 12.0, 1H, H-1), 8.28 (d, J 12.0, 1H, H-2)

δ_C (100 MHz, CDCl₃): 125.7 (q), 129.7 (q), 131.7, 132.2, 138.1, 138.6

The NMR spectra of **411** were consistent with those previously reported in the literature.²³⁰

6.3.3.2 1-Methoxy-4-((*E*)-2-nitrovinyl)benzene (**131**)



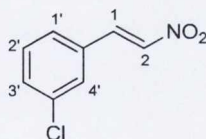
Prepared following procedure C using 4-methoxybenzaldehyde (**197**, 1.00 g, 7.34 mmol), potassium *tert*-butoxide (82 mg, 0.73 mmol), *tert*-butanol (5.77 mL) and nitromethane (**89**, 0.60 mL, 11.07 mmol) in THF (9.5 mL). In the second step, the desired product was obtained using mesyl chloride (0.85 mL, 1.00 mmol) and NEt₃ (3.10 mL, 22.22 mmol) in freshly distilled CH₂Cl₂ (33 mL). After purification of the crude material by flash chromatography (100% *n*-hexane), the nitroalkene **131** was afforded as a yellow solid (971 mg, 55%). M.p. 83-85 °C, (lit.,²³¹ 83-85 °C).

δ_{H} (400 MHz, CDCl₃): 3.90 (s, 3H, CH₃-3'), 6.98 (d, J 8.0, 2H, H-2'), 7.53 (d, J 8.0, 2H, H-1'), 7.56 (d, J 12.0, 1H, H-1), 8.01 (d, J 12.0, 1H, H-2)

δ_{C} (100 MHz, CDCl₃): 55.1, 122.1 (q), 130.7, 134.6, 138.6, 144.5, 162.5 (q)

The NMR spectra of **131** were consistent with those previously reported in the literature.²³¹

6.3.3.3 1-Chloro-3-((*E*)-2-nitrovinyl)benzene (**412**)



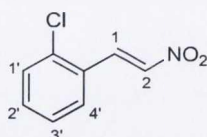
Prepared following procedure C using 3-chlorobenzaldehyde (**408**, 0.80 mL, 7.11 mmol), potassium *tert*-butoxide (80 mg, 0.71 mmol), *tert*-butanol (5.60 mL) and nitromethane (0.60 mL, 11.07 mmol) in THF (9.2 mL). In the second step, the desired product was obtained using mesyl chloride (0.83 mL, 10.67 mmol) and NEt₃ (3.00 mL, 21.50 mmol) in freshly distilled CH₂Cl₂ (30 mL). After purification of the crude material by flash chromatography (100% *n*-hexane → 95:5 *n*-hexane/CH₂Cl₂), the nitroalkene **412** was afforded as a yellow solid (1.02 g, 78%). M.p. 47-48 °C. (lit.,²³² 47°C-48°C).

δ_{H} (400 MHz, CDCl_3): 7.51-7.39 (m, 3H, H-1', H-2', H-3'), 7.55 (app. s, 1H, H-4'), 7.59 (d, J 14.0, 1H, H-1), 7.95 (d, J 14.0, 1H, H-2)

δ_{C} (100 MHz, CDCl_3): 126.8, 128.3, 130.2, 131.4 (q), 131.5, 135.0 (q), 137.0, 137.6

The NMR spectra of **412** were consistent with those previously reported in the literature.

6.3.3.4 (*E*)-1-Chloro-2-(2-nitrovinyl)benzene (**413**)



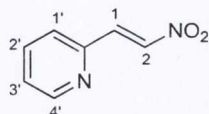
Prepared following procedure C using 2-chlorobenzaldehyde (**409**, 1.00 g, 7.11 mmol), potassium *tert*-butoxide (80 mg, 0.71 mmol), *tert*-butanol (5.88 mL) and nitromethane (**89**, 0.58 mL, 10.70 mmol) in THF (7 mL). In the second step, the desired product was obtained using mesyl chloride (0.83 mL, 10.67 mmol) and NEt_3 (2.98 mL, 21.36 mmol) in freshly distilled CH_2Cl_2 (24 mL). After purification of the crude material by flash chromatography (100% CH_2Cl_2) the nitroalkene **413** was afforded as a brown solid (704 mg, 55%). M.p. 47-49 °C, (lit.,²³³ 45-48°C).

δ_{H} (400 MHz, CDCl_3): 7.37 (td, J 1.3, 7.4, 1H, H-2'), 7.46 (td, J 1.7, 8.06, 1H, H-3'), 7.52 (dd, J 1.3, 8.06, 1H, H-4'), 7.60-7.65 (m, 2H, H-1, H-1'), 8.43 (d, J 13.6, 1H, H-2)

δ_{C} (100 MHz, CDCl_3): 127.5, 128.4 (q), 128.6, 130.7, 132.9, 135.0 (q), 136.0, 138.8

The NMR spectra of **413** were consistent with those previously reported in the literature.²³³

6.3.3.5 3-((*E*)-2-Nitrovinyl)pyridine (**414**)



Prepared following procedure C using 2-pyridine-carbaldehyde (**410**, 1.00 g, 9.34 mmol), potassium *tert*-butoxide (105 mg, 0.93 mmol), *tert*-butanol (7.33 mL) and nitromethane (**89**, 0.76 mL, 14.02 mmol) in THF (12 mL). In the second step, the desired product was obtained using mesyl chloride (1.10 mL, 14.14 mmol) and NEt₃ (3.90 mL, 27.96 mmol) in freshly distilled CH₂Cl₂ (39 mL). After purification of the crude material by flash chromatography (100% CH₂Cl₂) the nitroalkene **414** was afforded as a brown solid (992 mg, 71%). M.p. 57-59 °C, (lit.,²³⁴ 55-58 °C).

δ_{H} (400 MHz, CDCl₃): 7.38-7.41 (m, 1H, H-3'), 7.50 (d, J 7.6, 1H, H-1'), 7.81 (app. t, 1H, H-2'), 7.93 (d, J 13.2, 1H, H-1), 8.03 (d, J 13.2, 1H, H-2), 8.69 (d, J 4.8, 1H, H-4')

δ_{C} (100 MHz, CDCl₃): 125.3, 125.9, 136.7, 136.8, 140.2, 148.9 (q), 150.2

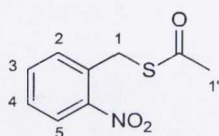
The NMR spectra of were consistent with those previously reported in the literature.²³⁵

6.3.4 Procedure D: General procedure for the preparation of alkane thiols

A 50 mL round-bottomed flask was charged with the appropriate aldehyde (13.23 mmol, 1 eq.), flushed with Ar and fitted with a septum. Ethanol (20.0 mL) was added *via* syringe followed by sodium borohydride (500 mg, 13.23 mmol, 1eq.) portionwise at 0 °C. The resulting mixture was stirred continuously while warming to room temperature. After 12 h, the reaction was concentrated under vacuum, diluted in CH₂Cl₂ (30 mL) and washed with water (3 x 30 mL). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The obtained crude was involved in the second step without further purification. In an oven-dried round-bottomed flask, triphenylphosphine (6.15 g, 26.46 mmol, 2 eq.) was dissolved in freshly distilled THF (40 mL) under an Ar atmosphere. The obtained solution was cooled to 0 °C, diethyl azodicarboxylate (5.25 mL, 26.46 mmol, 2 eq.) was added to it in a dropwise manner and the mixture was stirred at 0 °C for 1 h. A solution of the alcohol

obtained in the first step (13.23 mmol, 1 eq.) and thioacetic acid (1.90 mL, 26.46 mmol, 2 eq.) in THF (15 mL) was then added at 0 °C dropwise *via* syringe. The reaction was allowed to warm to ambient temperature and was stirred overnight. The solvent was evaporated *in vacuo* and the resulting yellow slurry was suspended in *n*-hexane (80 mL) and stirred vigorously for 2 h. After removal of the precipitate by filtration, the filtrate was concentrated under vacuum and was charged onto a silica flash chromatography column for purification.

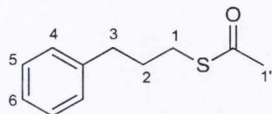
6.3.4.1 *S*-2-Nitrophenyl ethanethioate (432)



Prepared following general procedure D, using 2-nitrobenzaldehyde (**430**, 2.00 g, 13.23 mmol). The resulting thioester was obtained after purification by column chromatography on silica gel (100 % *n*-hexane → 90:10 *n*-hexane/EtOAc) as a colourless oil (1.80 g, 65 %).

δ_{H} (400 MHz, CDCl_3):	2.35 (s, 3H, $\text{CH}_3\text{-1}'$), 4.45 (s, 2H, $\text{CH}_2\text{-1}$), 7.45 (td, J 1.1, 8.4, 1H, H-4), 7.59 (td, J 1.1, 6.8, 1H, H-3), 7.66 (d, J 6.8, 1H, H-2), 8.06 (d, J 8.4, 1H, H-5)
δ_{C} (100 MHz, CDCl_3):	29.6, 30.5, 124.6, 128.1, 132.2, 133.2, 147.5 (q), 168.1 (q), 194.5 (q)
ν_{max} (neat)/ cm^{-1} :	2986, 1749, 1688, 1522, 1342, 1261, 1132, 1098, 956, 787, 710
HRMS (m/z -ES):	Found : 234.0212 ($\text{M}^+ + \text{Na}$. $\text{C}_9\text{H}_9\text{NO}_3\text{NaS}$ Requires: 234.0201)

6.3.4.2 *S*-3-Phenylpropyl ethanethioate (**435**)



Prepared following general procedure D, using hydrocinnamaldehyde (**433**, 1.74 mL, 13.23 mmol). The resulting thioester was obtained after purification by column chromatography on silica gel (100 % *n*-hexane → 95:5 *n*-hexane/EtOAc) as a colourless oil (2.13 g, 83 %).

δ_{H} (400 MHz, CDCl₃): 1.93 (m, 2H, CH₂-2), 2.36 (s, 3H, CH₃-1'), 2.72 (t, 2H, J 7.4, CH₂-3), 2.91 (t, 2H, J 7.6, CH₂-1), 7.21 (app. t, 3H, H-4, H-6), 7.31 (app. t, 2H, H-5)

δ_{C} (100 MHz, CDCl₃): 28.5, 30.0, 33.8, 37.7, 125.6, 128.0, 128.1, 140.6 (q), 194.5 (q)

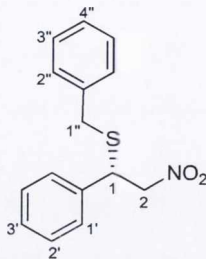
ν_{max} (neat)/cm⁻¹: 3027, 2922, 1732, 1688, 1496, 1453, 1352, 1132, 1107, 949, 743, 698

HRMS (*m/z* -ES): Found: 194.0759 (M⁺. C₁₁H₁₄OS Requires: 194.0765)

6.3.5 Procedure E: Organocatalysed Michael addition at room temperature

An oven-dried 5 mL round-bottomed flask was charged with (*E*)- β -nitrostyrene (**47**, 0.20 mmol, 1.00 eq.) and the cinchona alkaloid catalyst **355** (0.01 mmol, 0.05 eq.), equipped with a septum and placed under an Ar atmosphere. A solution of the appropriate nucleophile (0.20 mmol, 1.00 eq.) in MTBE (0.40 mL, 0.5 M) was added to the reaction *via* syringe. The resulting solution was stirred at ambient temperature for 40 h and was then analysed by ¹H-NMR spectroscopy. The product was directly purified by flash chromatography to furnish the desired Michael adduct.

6.3.5.1 (*S*)-Benzyl(2-nitro-1-phenylethyl)sulfane (**404**)



Compound (*S*)-**404** was prepared according to general procedure E at RT using (*E*)- β -nitrostyrene (**47**, 30.0 mg, 0.20 mmol), benzylmercaptan (**241**, 24 μ l, 0.20 mmol) and catalyst **355** (8.5 mg, 0.01 mmol) in MTBE (0.40 mL). The product was directly purified by flash chromatography (90:10 *n*-hexane/EtOAc) to give the Michael adduct (*S*)-**404** as a white solid (54.6 mg, >99%). M.p. 38-40 °C (lit,¹⁷³ 37.5-38.5 °C). $[\alpha]_D^{22} = +7$ (*c* 0.4, CHCl₃), (no literature data available)

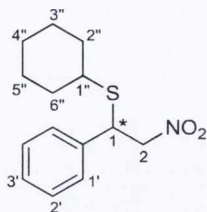
The enantiomeric excess of (*S*)-**404** was determined by CSP-HPLC analysis using a Chiralcel AS column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_R (major) = 8.49 min; t_R (minor) = 13.03 min; 25% *ee*. The absolute configuration of (*S*)-**404** was established by analogy with (*S*)-**403**.

δ_H (400 MHz, CDCl₃): 3.62 (d, *J* 13.6, 1H, H-1''a), 3.71 (d, *J* 13.6, 1H, H-1''b), 4.44 (dd, *J* 6.8, 9.0, 1H, H-1), 4.70 (m, 2H, CH₂-2), 7.26-7.42 (m, 10H, H-1', H-2', H-3', H-2'', H-3'', H-4'')

δ_C (100 MHz, CDCl₃): 36.0, 45.9, 79.1, 127.5, 127.8, 128.5, 128.7, 128.9, 129.0, 136.9 (q), 139.0 (q)

The NMR spectra of (*S*)-**404** were consistent with those previously reported in the literature.²³⁶

6.3.5.2 Cyclohexyl(2-nitro-1-phenylethyl)sulfane (**405**)



Compound **405** was prepared according to general procedure E at RT using (*E*)- β -nitrostyrene (**47**, 30.0 mg, 0.20 mmol), cyclohexanethiol (**402**, 25 μ l, 0.20 mmol) and catalyst **355** (8.5 mg, 0.01 mmol) in MTBE (0.40 mL). The product was directly purified by flash chromatography (90:10 *n*-hexane/EtOAc) to give the Michael adduct **405** as a colourless oil (53.1 mg, >99%).

The enantiomeric excess of **405** was determined by CSP-HPLC analysis using a Chiralcel AS column (4.6 mm x 25 cm); 98:2 *n*-hexane/IPA; 0.8 mL/min; λ = 220 nm. t_R (major) = 8.97 min; t_R (minor) = 9.83 min; 4% *ee*.

δ_H (400 MHz, $CDCl_3$): 1.18-1.41 (m, 5H, H-2''a, H-3''a, H-4''a, H-5''a, H-6''a), 1.51-1.57 (m, 1H, H-4''b), 1.69-1.81 (m, 2H, H-3''b, H-5''b), 1.85-1.91 (m, 1H, H-6''b), 1.93-2.03 (m, 1H, H-2''b), 2.53-2.68 (m, 1H, H-1''), 4.62-4.67 (m, 1H, H-1), 4.74-4.80 (m, 2H, CH_2 -2), 7.28-7.42 (m, 5H, H-1', H-2', H-3')

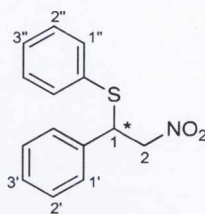
δ_C (100 MHz, $CDCl_3$): 25.6, 25.7, 25.8, 33.4, 33.4, 43.9, 45.1, 79.8, 127.5, 128.3, 129.0, 138.1 (q)

The NMR spectra of **405** were consistent with those previously reported in the literature.²³⁶

ν_{max} (neat)/ cm^{-1} : 2929, 2853, 1551, 1449, 1374, 1263, 1179, 1079, 999, 888, 818, 742, 697

HRMS (*m/z* -EI): α -clivage of the C-S bond. Fragments found:
Found: 150.0542 (M^+ . $C_8H_8NO_2$ Requires: 150.0550)
Found: 115.0580 (M^- . $C_6H_{11}S$ Requires: 115.0581)

6.3.5.3 2-Nitro-1-phenylethyl(phenyl)sulfane (**406**)



Compound **406** was prepared according to general procedure E at RT using (*E*)- β -nitrostyrene (**47**, 30.0 mg, 0.20 mmol), thiophenol (**240**, 21 μ l, 0.20 mmol) and catalyst **355** (8.5 mg, 0.01 mmol) in MTBE (0.40 mL). The product was directly purified by flash chromatography (90:10 *n*-hexane/EtOAc) to give the Michael adduct **406** as a white solid (51.9 mg, >99%). M.p. 73–75 °C (lit,²³⁶ 73–74 °C).

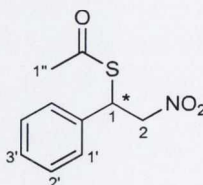
The enantiomeric excess of **406** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); *n*-hexane/IPA 99/1; 1.0 mL/min; λ = 220 nm. t_R (major) = 11.78 min; t_R (minor) = 13.99 min; 3% *ee*.

δ_H (400 MHz, CDCl₃): 4.74 (dd, *J* 4.8, 11.6, 1H, H-1), 4.83–4.95 (m, 2H, CH₂-2), 7.32–7.48 (m, 10H, H-1', H-2', H-3', H-1'', H-2'', H-3'')

δ_C (100 MHz, CDCl₃): 49.8, 78.5, 127.6, 128.6, 128.8, 129.0, 129.3, 131.9 (q), 133.7, 136.3 (q)

The NMR spectra of **406** were consistent with those previously reported in the literature.²³⁶

6.3.5.4 2-Nitro-1-phenylethyl ethanethioate (**269**)



Compound **269** was prepared according to general procedure E at RT using (*E*)- β -nitrostyrene (**47**, 30.0 mg, 0.20 mmol), thioacetic acid (**268**, 23 μ l, 0.20 mmol) and catalyst

355 (8.5 mg, 0.01 mmol) in MTBE (0.40 mL). The product was directly purified by flash chromatography (90:10 *n*-hexane/EtOAc) to give the Michael adduct **269** as a white solid (39.2 mg, 87%). M.p. 127-129 °C, (lit.,²³⁷ 126-127 °C).

The enantiomeric excess of **269** was determined by CSP-HPLC analysis using a Chiralcel AS column (4.6 mm x 25 cm); 98:2 *n*-hexane/IPA; 0.8 mL/min; λ = 220 nm. t_R (major) = 11.46 min; t_R (minor) = 12.97 min; 0% *ee*.

δ_H (400 MHz, CDCl₃): 2.39 (s, 3H, CH₃-1''), 4.87 (app. d, 2H, CH₂-2), 5.32 (app. t, 1H, H-1), 7.31-7.42 (m, 5H, H-1', H-2', H-3')

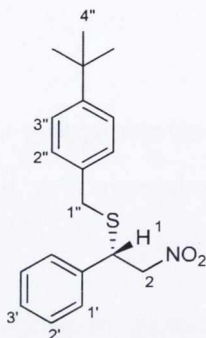
δ_C (100 MHz, CDCl₃): 30.3, 44.5, 78.0, 127.7, 128.8, 129.2, 135.6 (q), 193.3 (q)

The NMR spectra of **269** were consistent with those previously reported in the literature.²³⁷

6.3.6 Procedure F: organocatalysed Michael addition at -78 °C

A reaction vessel containing a stirring bar was flushed with Ar, charged with the appropriate (*E*)- β -nitrostyrene derivative (0.20 mmol, 1.0 eq.) and the dihydroquinine-based catalyst **356** (0.02-0.04 mmol, 0.1-0.2 eq.), before being closed with a suitable cap. Freshly distilled CH₂Cl₂ (10-30 mL, 0.020-0.007 M) was injected *via* syringe. The vial was then introduced in the cooling machine set up at -78 °C and the reaction mixture was stirred for 10 min. The appropriate alkane thiol (0.20 mmol, 1.0 eq.) was added dropwise to the reaction media *via* syringe. The resulting solution was stirred at -78 °C for 20 h. The obtained solution was analysed by ¹H-NMR spectroscopy. The product was then directly purified by flash chromatography.

6.3.6.1 (S)-(4-*tert*-Butylbenzyl)(2-nitro-1-phenylethyl)sulfane (403)



The Michael adduct (*S*)-**403** was prepared according to general procedure F using (*E*)- β -nitrostyrene (**47**, 30.0 mg, 0.20 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 37 μ L, 0.20 mmol) and the dihydroquinine-based catalyst **356** (16.7 mg, 0.02 mmol) in CH_2Cl_2 (10.0 mL, 0.02 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc) the product was obtained as a white solid (63.2 mg, 96%). M.p. 42–45 °C. $[\alpha]_{\text{D}}^{22} = +135$ (*c* 0.2, CHCl_3).

The enantiomeric excess of (*S*)-**403** was determined by CSP-HPLC analysis using a Chiralcel AS column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (major) = 7.85 min; t_{R} (minor) = 10.85 min; 92% *ee*. The absolute configuration of (*S*)-**403** was established by X-ray crystal structure analysis (see crystal structure data in appendix 1).

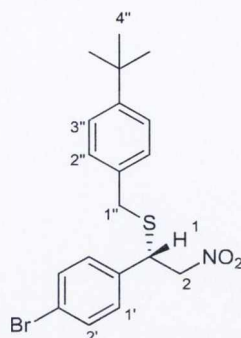
δ_{H} (400 MHz, CDCl_3): 1.36 (s, 9H, 3 CH_3 -4''), 3.61 (d, *J* 13.6, 1H, H-1'' α), 3.70 (d, *J* 13.6, 1H, H-1'' β), 4.47 (dd, *J* 9.2, 6.8, 1H, H-1), 4.77–4.66 (m, 2H, CH_2 -2), 7.21 (d, *J* 8.4, 2H, H-2''), 7.44–7.27 (m, 7H, H-3'', H-1', H-2', H-3')

δ_{C} (100 MHz, CDCl_3): 31.3, 34.6 (q), 35.7, 46.0, 79.1, 125.7, 127.8, 128.5, 128.6, 129.0, 133.8 (q), 137.1 (q), 150.2 (q)

ν_{max} (neat)/ cm^{-1} : 2965, 1551, 1426, 1374, 1266, 1190, 905, 836, 751, 697

HRMS (*m/z* -ES): Found: 329.1442 (M^+ . $\text{C}_{19}\text{H}_{23}\text{NO}_2\text{S}$ Requires: 329.1450)

6.3.6.2 (S)-(4-*tert*-Butylbenzyl)(1-(4-bromophenyl)-2-nitroethyl)sulfane (418)



The Michael adduct (*S*)-**418** was prepared according to general procedure F using nitroalkene **411** (34.2 mg, 0.15 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 28 μ L, 0.15 mmol) and the dihydroquinine-based **356** (12.5 mg, 0.02 mmol) in CH_2Cl_2 (7.5 mL, 0.02 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/ CH_2Cl_2), the product was obtained as a yellow oil (58.3 mg, 96%). $[\alpha]_{\text{D}}^{22} = +152$ (*c* 0.4, CHCl_3).

The enantiomeric excess of (*S*)-**418** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (minor) = 7.36 min; t_{R} (major) = 8.49 min; 90% *ee*. The absolute configuration of (*S*)-**418** was established by analogy with (*S*)-**403**.

δ_{H} (400 MHz, CDCl_3): 1.32 (s, 9H, 3 CH_3 -4''), 3.57 (d, *J* 13.6, 1H, H-1''a), 3.67 (d, *J* 13.6, 1H, H-1''b), 4.38 (app. t, 1H, H-1), 4.64 (app. d, 2H, CH_2 -2), 7.20-7.10 (m, 4H, H-2'', H-1'), 7.33 (d, *J* 8.2, 2H, H-3''), 7.46 (d, *J* 8.4, 2H, H-2')

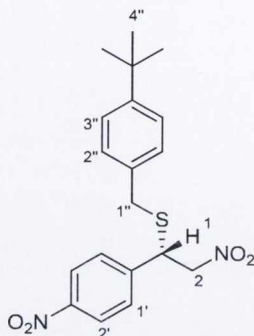
δ_{C} (100 MHz, CDCl_3): 31.3, 34.6 (q), 35.8, 45.4, 78.8, 122.4 (q), 125.7, 128.6, 129.5, 132.2, 133.5 (q), 136.4 (q), 150.7 (q)

ν_{max} (neat)/ cm^{-1} : 2961, 1552, 1488, 1373, 1268, 1107, 1073, 1010, 825, 713

HRMS (*m/z* -EI): α -clivage of the C-S bond. Fragments found:
Found: 179.0807 (*M* $^+$. $\text{C}_{11}\text{H}_{15}\text{S}^+$ Requires: 179.0894)

Found: 226.9556 (M^+ . $C_8H_6NO_2Br$ Requires: 226.9582)

6.3.6.3 (S)-(4-*tert*-Butylbenzyl)(2-nitro-1-(4-nitrophenyl)ethyl)sulfane (419)



The Michael adduct (*S*)-**419** was prepared according to general procedure F using nitroalkene **415** (12.5 mg, 0.06 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 12 μ L, 0.06 mmol) and the dihydroquinine-based catalyst **356** (12.5 mg, 0.02 mmol) in CH_2Cl_2 (6.4 mL, 0.01 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/ CH_2Cl_2), the product was obtained as a yellow oil (23.6 mg, 98%). $[\alpha]_D^{22} = +175$ (*c* 0.3, $CHCl_3$).

The enantiomeric excess of (*S*)-**419** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_R (minor) = 13.12 min; t_R (minor) = 16.73 min; 85% *ee*. The absolute configuration of (*S*)-**419** was established by analogy with (*S*)-**403**.

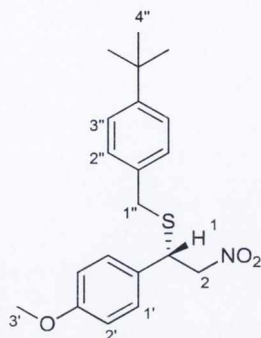
δ_H (400 MHz, $CDCl_3$): 1.35 (s, 9H, 3 CH_3 -4''), 3.65 (d, *J* 13.6, 1H, H-1''a), 3.75 (d, *J* 13.6, 1H, H-1''b), 4.52 (app. t, 1H, H-1), 4.73 (app. d, 2H, CH_2 -2), 7.18 (d, *J* 8.0, 2H, H-2''), 7.36 (d, *J* 8.0, 2H, H-3''), 7.44 (d, *J* 8.4, 2H, H-1'), 8.20 (d, *J* 8.4, 2H, H-2')

δ_C (100 MHz, $CDCl_3$): 30.9, 34.1 (q), 35.6, 44.7, 77.9, 123.7, 125.3, 128.1, 128.4, 132.6 (q), 144.4 (q), 147.3 (q), 150.5 (q)

ν_{max} (neat)/ cm^{-1} : 2962, 2867, 1553, 1519, 1344, 1268, 1108, 857, 832, 696

HRMS (*m/z* -ES): Found: 373.1222 ($M^+ - H$ $C_{19}H_{21}N_2O_4S$ Requires: 373.1223.
224

6.3.6.4 (S)-(4-*tert*-Butylbenzyl)(1-(4-methoxyphenyl)-2-nitroethyl)sulfane (**420**)



The Michael adduct (*S*)-**420** was prepared according to general procedure F using nitroalkene **131** (26.9 mg, 0.15 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 28 μ L, 0.15 mmol) and the dihydroquinine-based catalyst **356** (25.1 mg, 0.03 mmol) in CH_2Cl_2 (15.0 mL, 0.01 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/ CH_2Cl_2), the product was obtained as a yellow oil (52.1 mg, 97%). $[\alpha]_{\text{D}}^{22} = +187$ (*c* 0.2, CHCl_3).

The enantiomeric excess of (*S*)-**420** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_{R} (minor) = 26.72 min; t_{R} (major) = 31.32 min; 90% *ee*. The absolute configuration of (*S*)-**420** was established by analogy with (*S*)-**403**.

δ_{H} (400 MHz, CDCl_3): 1.35 (s, 9H, 3 CH_3 -4''), 3.67 (d, *J* 13.6, 1H, H-1''a), 3.59 (d, *J* 13.6, 1H, H-1''b), 3.83 (s, 3H, CH_3 -3'), 4.43 (dd, *J* 6.8, 8.8, 1H, H-1), 4.74-4.61 (m, 2H, CH_2 -2), 6.89 (d, *J* 8.8, 2H, H-2'), 7.27-7.17 (m, 4H, H-1', H-2''), 7.36 (d, *J* 8.2, 2H, H-3'')

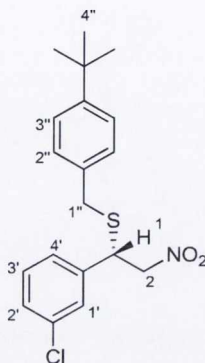
δ_{C} (100 MHz, CDCl_3): 30.9, 34.1 (q), 35.1, 45.2, 54.8, 78.8, 113.9, 125.2, 128.1, 128.5, 133.4 (q), 140.0 (q), 150.0 (q), 159.1 (q)

ν_{max} (neat)/ cm^{-1} : 2960, 1610, 1552, 1511, 1374, 1249, 1177, 1111, 1032, 832, 675

HRMS (*m/z* -EI): α -clivage of the C-S bond. Fragment found.

Found: 180.0972 (M^+ , $C_9H_{10}NO_3^+$ Requires: 180.0655)

6.3.6.5 **(*S*)-(4-*tert*-Butylbenzyl)(1-(3-chlorophenyl)-nitroethyl)sulfane (421)**



The Michael adduct (*S*)-**421** was prepared according to general procedure F using nitroalkene **412** (27.5 mg, 0.15 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 28 μ L, 0.15 mmol) and the dihydroquinine-based catalyst **356** (25.1 mg, 0.03 mmol) in CH_2Cl_2 (22.5 mL, 0.007 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/ CH_2Cl_2), the product was obtained as a white solid (45.7 mg, 84%). M.p. 62-64 $^{\circ}C$. $[\alpha]_D^{22} = +158$ (c 0.4, $CHCl_3$).

The enantiomeric excess of (*S*)-**421** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_R (minor) = 10.08 min; t_R (major) = 15.43 min; 91% *ee*. The absolute configuration of (*S*)-**421** was established by X-ray crystal structure analysis (see crystal structure data in appendix 2).

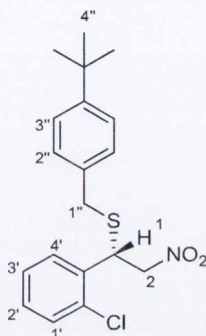
δ_H (400 MHz, $CDCl_3$): 1.36 (s, 9H, 3 CH_3 -4''), 3.62 (d, J 13.6, 1H, H-1''a), 3.71 (d, J 13.6, 1H, H-1''b), 4.41 (dd, J 6.8, 8.8, 1H, H-1), 4.68 (m, 2H, CH_2 -2), 7.23-7.15 (m, 3H, H-2'', H-3'), 7.33-7.26 (m, 3H, H-1', H-4', H-2'), 7.37 (d, J 8.0, 2H, H-3'')

δ_C (100 MHz, $CDCl_3$): 30.9, 34.1 (q), 35.4, 44.9, 78.3, 125.3, 125.5, 127.6, 128.1, 128.2, 129.9, 133.0 (q), 134.4 (q), 138.9 (q), 150.2 (q)

ν_{max} (neat)/ cm^{-1} : 2965, 2911, 1556, 1474, 1429, 1376, 1235, 1194, 1083, 831, 786, 693

HRMS (m/z -ES): Found: 363.1069 (M^+ . $\text{C}_{19}\text{H}_{22}\text{NO}_2\text{SCl}$ Requires: 363.1060)

6.3.6.6 (*S*)-(4-*tert*-Butylbenzyl)(1-(2-chlorophenyl)-2-nitroethyl)sulfane (**422**)



The Michael adduct (*S*)-**422** was prepared according to general procedure F using nitroalkene **413** (27.5 mg, 0.15 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 28 μL , 0.15 mmol) and the dihydroquinine-based **356** (25.1 mg, 0.03 mmol) in CH_2Cl_2 (15 mL, 0.01 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/ CH_2Cl_2), the product was obtained as a white solid (51.1 mg, 94%). M.p. 52-53 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{22} = +36$ (c 0.2, CHCl_3).

The enantiomeric excess of (*S*)-**422** was determined by CSP-HPLC analysis using a Chiralcel AS column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 0.5 mL/min; $\lambda = 220$ nm. t_{R} (minor) = 13.04 min; t_{R} (major) = 16.58 min; 34% *ee*. The absolute configuration of (*S*)-**422** was established by analogy with (*S*)-**403** and (*S*)-**421**.

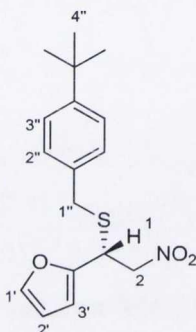
δ_{H} (400 MHz, CDCl_3): 1.36 (s, 9H, 3 CH_3 -4''), 3.78 (app. s, 2H, CH_2 -1''), 4.64 (dd, J 7.2, 13.2, 1H, H-1), 4.81 (dd, J 8.2, 13.2, 1H, H-2a), 5.04 (app. t, 1H, H-2b), 7.23 (d, J 8.2, 2H, H-2''), 7.25-7.44 (m, 2H, H-2', H-3'), 7.37 (d, J 8.2, 2H, H-3''), 7.39-7.48 (m, 2H, H-1', H-4')

δ_{C} (100 MHz, CDCl_3): 30.9, 34.1 (q), 36.2, 42.4, 77.5, 125.2, 127.0, 128.2, 128.2, 129.0, 129.7, 133.2 (q), 133.3, (q), 134.4 (q), 150.1 (q)

ν_{max} (neat)/ cm^{-1} : 2960, 2918, 2850, 1547, 1438, 1376, 1055, 836, 826, 751, 686, 674

HRMS (m/z -EI): Found: 363.1067 (M^+ , $\text{C}_{19}\text{H}_{22}\text{NO}_2\text{SCl}$ Requires: 363.1060)

6.3.6.7 (R)-2-(1-(4-*tert*-Butylbenzylthio)-2-nitroethyl)furan (423)



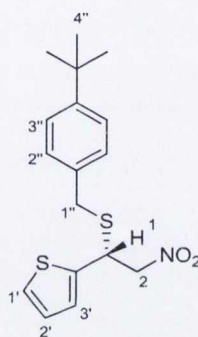
The Michael adduct (*S*)-**423** was prepared according to general procedure F using nitroalkene **416** (20.9 mg, 0.15 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 28 μL , 0.15 mmol) and the dihydroquinine-based catalyst **356** (25.1 mg, 0.03 mmol) in CH_2Cl_2 (15.0 mL, 0.01 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/ CH_2Cl_2), the product was obtained as a clear yellow solid (47.6 mg, 99%). M.p. 64–66 °C. $[\alpha]_{\text{D}}^{22} = +139$ (c 0.4, CHCl_3).

The enantiomeric excess of (*S*)-**423** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (minor) = 15.15 min; t_{R} (major) = 17.33 min; 90% *ee*. The absolute configuration of (*S*)-**423** was established by analogy with (*S*)-**403** and (*S*)-**421**.

δ_{H} (400 MHz, CDCl_3): 1.35 (s, 9H, 3 CH_3 -4''), 3.72 (d, J 13.6, 1H, H-1''a), 3.78 (d, J 13.6, 1H, H-1''b), 4.68–4.58 (m, 2H, CH_2 -2), 4.82 (dd, J 11.2, 15.2, 1H, H-1), 6.28 (d, J 3.2, 1H, H-3'), 7.25 (d, J 8.4, 2H, H-2''), 6.36 (dd, J 1.8, 3.2, 1H, H-2'), 7.38 (d, J 8.4, 2H, H-3''), 7.43 (d, J 1.8, 1H, H-1')

δ_{C} (100 MHz, CDCl_3):	30.9, 34.1 (q), 35.1, 38.8, 76.2, 108.1, 110.2, 125.3, 128.1, 133.2, 142.6 (q), 149.1 (q), 150.2 (q)
ν_{max} (neat)/ cm^{-1} :	2966, 1552, 1427, 1373, 1185, 1150, 1015, 965, 838, 808, 751, 695
HRMS (m/z -EI):	Found: 319.1202 (M^+ . $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{S}$ Requires: 363.1242)

6.3.6.8 (*R*)-2-(1-(4-*tert*-Butylbenzylthio)-2-nitroethyl)thiophene (**424**)



The Michael adduct(*S*)-**424** was prepared according to general procedure F using nitroalkene **417** (23.3 mg, 0.15 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 28 μL , 0.15 mmol) and the dihydroquinine-based catalyst **356** (12.5 mg, 0.015 mmol) in CH_2Cl_2 (7.5 mL, 0.02 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/ CH_2Cl_2), the product was obtained as a yellow solid (46.8 mg, 93%). M.p. 60-62 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{22} = +164$ (c 0.4, CHCl_3).

The enantiomeric excess of (*S*)-**424** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (min) = 14.89 min; t_{R} (major) = 16.55 min; 92% *ee*. The absolute configuration of (*S*)-**424** was established by analogy with (*S*)-**403** and (*S*)-**421**.

δ_{H} (400 MHz, CDCl_3):	1.34 (s, 9H, 3 CH_3 -4''), 3.69 (d, J 13.4, 1H, H-1''a), 3.76 (d, J 13.4, 1H, H-1''b), 4.84-4.64 (m, 3H, H-1, CH_2 -2), 6.97 (m,
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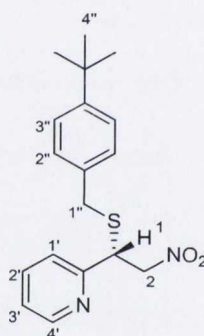
2H, H-3', H-2'), 7.21 (d, J 8.2, 2H, H-2''), 7.32 (dd, J 1.2, 4.2, 1H, H-1'), 7.37 (d, J 8.2, 2H, H-3'')

δ_C (100 MHz, $CDCl_3$): 30.9, 34.1 (q), 35.2, 40.8, 79.2, 125.2, 125.7, 126.3, 126.5, 128.2, 133.1 (q), 140.6 (q), 150.2 (q)

ν_{max} (neat)/ cm^{-1} : 2965, 1551, 1425, 1374, 1268, 1107, 1044, 838, 712, 663

HRMS (m/z -EI): The HRMS analysis (EI and ESI) were not conclusive, even when lower ionisation voltage was utilised.

6.3.6.9 (*R*)-3-(1-(4-*tert*-Butylbenzylthio)-2-nitroethyl)pyridine (**425**)



The Michael adduct (*S*)-**425** was prepared according to general procedure F, using nitroalkene **414** (22.5 mg, 0.15 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 28 μ L, 0.15 mmol) and the dihydroquinine-based catalyst **356** (12.5 mg, 0.015 mmol) in CH_2Cl_2 (7.5 mL, 0.02 M). After purification of the crude material by flash chromatography (80:20 $\rightarrow$ 50:50 *n*-hexane: CH_2Cl_2), the product was obtained as a dark yellow oil (45.0 mg, 91%). $[\alpha]_D^{22} = -15$ (c 0.2, $CHCl_3$).

The enantiomeric excess of (*S*)-**425** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_R (major) = 29.97 min; t_R (minor) = 39.81 min; 96% *ee*. The absolute configuration of (*S*)-**425** was established by analogy with (*S*)-**403** and (*S*)-**421**.

δ_H (400 MHz, $CDCl_3$): 1.34 (s, 9H, 3 CH_3 -4''), 3.68 (d, J 13.2, 1H, H-1''a), 3.78 (d, J 13.2, 1H, H-1''b), 4.59 (dd, J 5.6, 9.2, 1H, H-1), 4.75 (dd, J

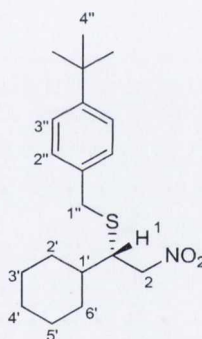
5.6, 13.6, 1H, H-2a), 5.28 (dd, J 9.2, 13.6, 1H, H-2b), 7.17-7.27 (m, 4H, H-2'', H-1', H-3'), 7.36 (d, J 8.2, 2H, H-3''), 7.65 (td, J 1.6, 7.6, 1H, H-2'), 8.54 (d, J 4.4, 1H, H-4')

δ_C (100 MHz, $CDCl_3$): 30.9, 34.1 (q), 34.8, 45.6, 76.2, 122.3, 123.0, 125.2, 128.2, 133.5 (q), 136.5, 148.8, 150.1 (q), 156.5 (q)

ν_{max} (neat)/ cm^{-1} : 2959, 1686, 1553, 1470, 1386, 1277, 1176, 1132, 1110, 1027, 864, 731, 702, 681

HRMS (m/z -ES): Found: 331.1481 ($M^+ + H$, $C_{18}H_{23}N_2O_2S$ Requires: 331.1480)

6.3.6.10 (*S*)-(4-*tert*-Butylbenzyl)(1-cyclohexyl-2-nitroethyl)sulfane (**426**)

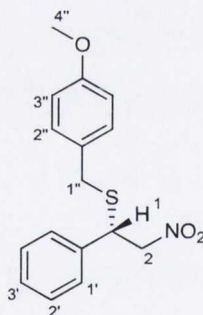


The Michael adduct (*S*)-**426** was prepared according to the general procedure F at $-30\text{ }^{\circ}\text{C}$, using nitroalkene **141** (21.1 mg, 0.14 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 26 μL , 0.14 mmol) and the dihydroquinine-based catalyst **356** (11.7 mg, 0.014 mmol) in CH_2Cl_2 (7.0 mL, 0.02 M). After purification of the crude material by flash chromatography (100% CH_2Cl_2) the product was obtained as a colourless oil (45.97 mg, 98%). $[\alpha]_D^{22} = -26$ (c 0.1, $CHCl_3$).

The enantiomeric excess of (*S*)-**426** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220\text{ nm}$. t_R (minor) = 9.16 min; t_R (major) = 9.73 min; 32% *ee*. The absolute configuration of (*S*)-**426** was established by analogy with (*S*)-**403** and (*S*)-**421**.

δ_{H} (400 MHz, CDCl_3):	0.94-1.35 (m, 14H, H-2'a, H-3'a, H-4'a, H-5'a, H-6'a, 3 CH ₃ -4''), 1.38-1.77 (m, 6H, H-1' H-2'b, H-3'b, H-4'b, H-5'b, H-6'a), 3.16 (td, 1H, J 3.9, 7.5, H-1), 3.69 (d, 1H, J 13.1, H-1''a), 3.73 (d, 1H, J 13.1, H-1''b), 4.35 (dd, J 7.5, 12.6, 1H, H-2a), 4.54 (dd, J 7.5, 12.6, 1H, H-2b), 7.23 (d, J 8.3, 2H, H-2''), 7.33 (d, J 8.3, 2H, H-3'')
δ_{C} (100 MHz, CDCl_3):	26.0, 26.0, 26.1, 28.3, 30.2, 31.3, 34.5 (q), 36.9, 40.1, 48.8, 78.0, 125.5, 128.7, 134.4 (q). 15.0.4 (q)
ν_{max} (neat)/ cm^{-1} :	2926, 2854, 1551, 1449, 1375, 1268, 1107, 1019, 891, 835, 701
HRMS (m/z -EI):	Found: 335.1906 (M^+ . $\text{C}_{19}\text{H}_{29}\text{NO}_2\text{S}$ Requires: 335.1919)

6.3.6.11 (*S*)-(4-Methoxybenzyl)(2-nitro-1-phenylethyl)sulfane (**436**)

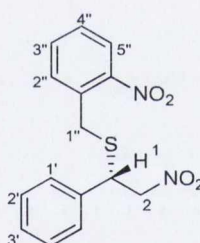


The Michael adduct (*S*)-**436** was prepared according to the general procedure F, using (*E*)- β -nitrostyrene (**47**, 30.0 mg, 0.2 mmol), thiol **252** (28 μL , 0.2 mmol) and the dihydroquinine-based catalyst **356** (16.7 mg, 0.02 mmol) in CH_2Cl_2 (10.0 mL, 0.02 M). After purification of the crude material by flash chromatography (CH_2Cl_2), the product was obtained as a yellow oil (59.5 mg, 98%). $[\alpha]_{\text{D}}^{22} = +55$ (c 0.4, CHCl_3).

The enantiomeric excess of (*S*)-**436** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 0.8 mL/min; $\lambda = 220$ nm. t_{R} (minor) = 28.65 min; t_{R} (minor) = 31.50 min; 90% ee. The absolute configuration of (*S*)-**436** was established by analogy with (*S*)-**403** and (*S*)-**421**.

δ_{H} (400 MHz, CDCl_3):	3.58 (d, J 13.6, 1H, H-1''a), 3.67 (d, J 13.6, 1H, H-1''b), 3.84 (s, 3H, CH_3 -4''), 4.43 (dd, J 7.2, 8.8, 1H, H-1), 4.79-4.63 (m, 2H, CH_2 -2), 6.88 (d, J 8.4, 2H, H-3''), 7.19 (d, J 8.4, 2H, H-2''), 7.43-7.23 (m, 5H, H-1', H-2', H-3')
δ_{C} (100 MHz, CDCl_3):	35.0, 45.4, 54.9, 78.7, 113.6, 127.3, 128.0, 128.3 (q), 128.6, 129.6, 136.7 (q), 158.5 (q)
ν_{max} (neat)/ cm^{-1} :	2914, 2836, 1609, 1551, 1510, 1374, 1243, 1174, 1030, 830, 747, 698
HRMS (m/z -ES):	Found: 303.0944 (M^+ . $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{S}$ Requires: 303.0929)

6.3.6.12 (2-Nitrobenzyl)((*S*)-2-nitro-1-phenylethyl)sulfane (**437**)



2-Nitrobenzyl ethanethiolate (**432**, 144 mg, 0.68 mmol) was dissolved in freshly degassed MeOH (3.0 mL). Acetyl chloride (153 μL , 2.15 mmol) was added *via* syringe under an Ar atmosphere and the obtained solution was allowed to stir at room temperature for 18 h. The solvent was then evaporated *in vacuo* and the resulting thiol **427** was used in the next step without the need of further purification. The adduct (*S*)-**437** was prepared according to the general procedure F, using (*E*)- β -nitrostyrene (22.5 mg, 0.15 mmol), thiol **427** (25.4 mg, 0.15 mmol) and the dihydroquinine-based catalyst **356** (25.2 mg, 0.03 mmol) in CH_2Cl_2 (15.0 mL, 0.01 M). After purification of the crude material by flash chromatography (CH_2Cl_2) the product was obtained as a clear yellow oil (43.3 mg, 91%). $[\alpha]_{\text{D}}^{22} = +24$ (*c* 0.2, CHCl_3).

The enantiomeric excess of (*S*)-**437** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; λ = 220 nm. t_R (minor) = 16.71 min; t_R (major) = 17.89 min; 88% ee. The absolute configuration of (*S*)-**437** was established by analogy with (*S*)-**403** and (*S*)-**421**.

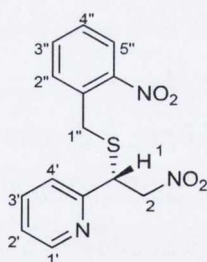
δ_H (400 MHz, $CDCl_3$): 3.95 (d, *J* 13.6, 1H, H-1''a), 4.13 (d, *J* 13.6, 1H, H-1''b), 4.52 (app. t, 1H, H-1), 4.73 (app. d, 2H, CH_2 -2), 7.25-7.41 (m, 6H, H-2'', H-1', H-2', H-3'), 7.46 (app. t, 1H, H-3''), 7.56 (app. t, 1H, H-4''), 8.01 (d, *J* 8.0, 1H, H-5'')

δ_C (100 MHz, $CDCl_3$): 33.3, 46.8, 79.0, 125.6, 127.7, 128.6, 128.7, 129.1, 131.9, 132.9 (q), 133.2, 136.6 (q), 148.5 (q)

ν_{max} (neat)/ cm^{-1} : 2920, 1552, 1520, 1425, 1375, 1342, 1079, 860, 786, 750, 698

HRMS (*m/z* -ES): Found: 317.0589 (M^+ - H $C_{15}H_{13}N_2O_4S$ Requires: 317.0596)

6.3.6.13 (*R*)-2-(2-Nitro-1-(2-nitrobenzylthio)ethyl)pyridine (**438**)



2-Nitrobenzyl ethanethiolate (**432**, 144 mg, 0.68 mmol) was dissolved in freshly degassed MeOH (3.0 ml). Acetyl chloride (153 μ l, 2.15 mmol) was added *via* syringe under an Ar atmosphere and the obtained solution was allowed to stir at ambient temperature for 18 h. The solvent was then evaporated *in vacuo* and the resulting thiol **427** was used in the organocatalysed Michael-type addition without the need of further purification. The adduct (*S*)-**438** was prepared according to the general procedure F, using nitroalkene **414** (21.3 mg, 0.14 mmol), thiol **427** (24.1 mg, 0.14 mmol) and the dihydroquinine-based cinchona catalyst **356** (11.9 mg, 0.01 mmol) in CH_2Cl_2 (7.0 mL, 0.02 M). After purification of the

crude material by flash chromatography (80:20 *n*-hexane/CH₂Cl₂) the product was obtained as a clear yellow oil (36.4 mg, 82%). [α]_D²² = +24 (*c* 0.2, CHCl₃).

The enantiomeric excess of (*S*)-**438** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 1.0 mL/min; λ = 220 nm. *t*_R (minor) = 46.52 min; *t*_R (major) = 49.35 min; 93% ee. The absolute configuration of (*S*)-**438** was established by analogy with (*S*)-**403** and (*S*)-**421**.

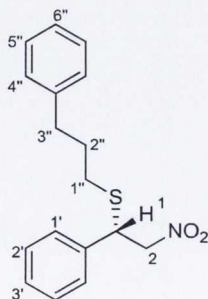
δ_{H} (400 MHz, CDCl₃): 4.04 (d, *J* 13.6, 1H, H-1''a), 4.12 (d, *J* 13.6, 1H, H-1''b), 4.66 (dd, *J* 6.0, 8.8, 1H, H-1), 4.79 (dd, *J* 6.0, 13.8, 1H, H-2a), 5.28 (dd, *J* 8.8, 13.8, 1H, H-2b), 7.22 (dd, *J* 4.7, 6.8, 1H, H-2'), 7.32 (d, *J* 7.4, 1H, H-2''), 7.39 (d, *J* 7.6, 1H, H-4'), 7.45 (app t, 1H, H-4''), 7.56 (td, *J* 0.8, 7.4, 1H, H-3''), 7.67 (td, *J* 1.6, 7.6, 1H, H-3'), 8.00 (dd, *J* 0.8, 8.0, 1H, H-5''), 8.52 (d, *J* 4.7, 1H, H-1')

δ_{C} (100 MHz, CDCl₃): 31.7, 46.0, 76.1, 122.6, 123.1, 125.1, 128.2, 131.5, 132.7 (q), 132.9, 136.8, 148.1 (q), 148.7, 155.9 (q)

ν_{max} (neat)/cm⁻¹: 2930, 1731, 1553, 1522, 1342, 1242, 1173, 1044, 858, 786, 751, 696

HRMS (*m/z* -ES): Found: 320.0709 (M⁺ + H. C₁₄H₁₄N₃O₄S Requires: 320.0705)

6.3.6.14 (*S*)-2-Nitro-1-phenylethyl(3-phenylpropyl)sulfane (**439**)



3-Phenylpropyl ethanethiolate (**435**, 300 mg, 1.54 mmol) was dissolved in freshly degassed MeOH (3.0 ml). Acetyl chloride (175 μ l, 2.46 mmol) was added *via* syringe under an Ar

atmosphere and the obtained solution was allowed to stir at room temperature for 18 h. The solvent was then evaporated *in vacuo* and the resulting thiol **428** was used in the next step without the need of further purification. The adduct (*S*)-**439** was prepared according to the general procedure F, using (*E*)- β -nitrostyrene (**47**, 30.0 mg, 0.20 mmol), thiol **428** (30 μ L, 0.20 mmol) and the dihydroquinine-based catalyst **356** (33.4 mg, 0.04 mmol) in CH₂Cl₂ (20.0 mL, 0.01 M). After purification of the crude material by flash chromatography (80:20 *n*-hexane/CH₂Cl₂) the product was obtained as a yellow oil (46.3 mg, 77%). $[\alpha]_D^{22} = +71$ (*c* 0.2, CHCl₃).

The enantiomeric excess of (*S*)-**439** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 99:1 *n*-hexane/IPA; 1 mL/min; $\lambda = 220$ nm. t_R (minor) = 15.11 min; t_R (major) = 16.57 min; 89% ee. The absolute configuration of (*S*)-**439** was established by analogy with (*S*)-**403** and (*S*)-**421**.

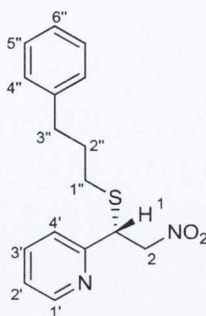
δ_H (400 MHz, CDCl₃): 1.81-1.91 (m, 2H, CH₂-2''), 2.47 (t, *J* 7.2, 2H, CH₂-1''), 2.64-2.69 (m, 2H, CH₂-3''), 4.56 (app. t, 1H, H-1), 4.76 (app. d, 2H, CH₂-2), 6.90-7.63 (m, 10H, H-1', H-2', H-3', H-4'', H-5'', H-6'')

δ_C (100 MHz, CDCl₃): 30.7, 30.9, 34.5, 46.5, 79.3, 126.1, 127.6, 128.4, 128.4, 128.5, 129.1, 137.4 (q), 141.0 (q)

ν_{max} (neat)/cm⁻¹: 2921, 1634, 1552, 1495, 1452, 1342, 1260, 1200, 1078, 966, 745, 697

HRMS (*m/z* -ES): Found: 302.1212 (M⁺ + H. C₁₇H₂₀NO₂S Requires: 302.1215)

6.3.6.15 (R)-2-(2-Nitro-1-(3-phenylpropylthio)ethyl)pyridine (440)



3-Phenylpropyl ethanethiolate (**435**, 300 mg, 1.54 mmol) was dissolved in freshly degassed MeOH (3.0 ml). Acetyl chloride (175 μ l, 2.46 mmol) was added *via* syringe under an argon atmosphere and the obtained solution was allowed to stir at room temperature for 18 h. The solvent was then evaporated *in vacuo* and the resulting thiol **428** was used in the next step without the need of further purification. The adduct (*S*)-**440** was prepared according to the general procedure F, using nitroalkene **414** (23.2 mg, 0.16 mmol), thiol **428** (23 μ L, 0.16 mmol) and the dihydroquinine-based catalyst **356** (25.8 mg, 0.03 mmol) in CH₂Cl₂ (15.5 mL, 0.01 M). After purification of the crude material by flash chromatography (CH₂Cl₂) the product was obtained as a clear yellow oil (26.3 mg, 56%). $[\alpha]_D^{22} = +34$ (*c* 0.2, CHCl₃).

The enantiomeric excess of (*S*)-**440** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_R (minor) = 16.09 min; t_R (major) = 17.27 min; 94% ee. The absolute configuration of (*S*)-**440** was established by analogy with (*S*)-**403** and (*S*)-**421**.

δ_H (400 MHz, (CD₃)₂CO): 1.76-1.90 (m, 2H, CH₂-2''), 2.50-2.59 (m, 1H, H-1''a), 2.62-2.75 (m, 3H, H-1''b, CH₂-4'), 4.80 (dd, *J* 6.0, 9.2, 1H, H-1), 5.07 (dd, *J* 6.0, 14.0, 1H, H-2a), 5.39 (dd, *J* 9.2, 14.0, 1H, H-2b), 7.14-7.33 (m, 6H, H-4'', H-5'', H-6'', H-2'), 7.58 (d, *J* 7.6, 1H, H-4'), 7.82 (td, *J* 1.6, 7.6, 1H, H-3'), 8.48 (d, *J* 4.4, 1H, H-1')

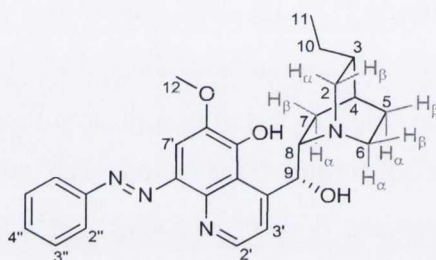
δ_C (100 MHz, (CD₃)₂CO): 29.0, 30.9, 33.9, 45.3, 75.9, 122.3, 123.1, 125.4, 127.8, 127.9, 136.7, 141.0 (q), 148.3, 157.2 (q)

ν_{max} (neat)/ cm^{-1} : 2923, 1702, 1589, 1550, 1471, 1434, 1375, 1294, 1076, 949, 744, 699

HRMS (m/z -ES): Found: 303.1174 ($M^+ + H$. $C_{16}H_{19}N_2O_2S$ Requires: 303.1167)

6.4 Experimental data for Section 4

6.4.1 C-5'-Hydroxy C-8'-(*E*)-(2-phenyldiazenyl)-substituted dihydroquinine derivative 454



Hydrochloric acid (aq. 36.5-38%, 54 mL) was added to an open round bottom flask along with freshly distilled aniline (1.8 mL, 19.86 mmol). The obtained mixture was allowed to cool to 0 °C and a solution of NaNO_2 (1.50 g, 21.6 mmol) in water (18 mL) was added to it dropwise. The mixture was stirred at 0 °C for 30 min. Meanwhile, the cinchona derivative C-5'-amino-dihydroquinine **367** (6.00 g, 17.40 mmol) was dissolved in a solution of glacial acetic acid (36 mL) in water (360 mL). The obtained solution was treated with a saturated solution of sodium acetate (36 mL) and cooled to 0 °C. Then, the diazotizing mixture was added to the solution containing **367**, in a dropwise manner, insuring that the reaction temperature remained below 0 °C. The resulting reaction was stirred at 0 °C for 30 min. Finally, ammonia solution (300 mL) was added to the reaction mixture, and the product extracted with CH_2Cl_2 (3 x 250 mL). The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The resulting crude material was purified by column chromatography (90:10:4 EtOAc/MeOH/ $\text{NEt}_3 \rightarrow 100:30$ EtOAc/MeOH). The impure (degradates on silica) amino intermediate **456** was obtained as a deep red solid and was used directly in the next step without further purification. Compound **456** (2.10 g, 4.80 mmol) was then dissolved in ethanol (12 mL) and a mixture of $\text{H}_2\text{O}/\text{HCl}$ 1:1 (12 mL) was added. The resulting solution was heated under reflux overnight before being allowed to cool and diluted with H_2O (20 mL). A saturated solution

of NaHCO₃ was added until the pH of the solution reached 8 and the product was extracted using CH₂Cl₂ (3 x 40 mL). The combined organic extracts were dried over MgSO₄ and concentrated under vacuum. Finally, the compound was purified by selective precipitation using diethyl ether to afford alkaloid **454** as a deep red solid (1.70 g, 24%). M.p. >300 °C (lit.²²³ m.p. 145-148 °C); [α]_D²² = -91 (c 0.6, CHCl₃).

δ_H (400 MHz, CDCl₃): 0.89 (app. t, 3H, CH₃-11), 1.19-1.37 (m, 2H, CH₂-10), 1.40-1.49 (m, 2H, H-3, H-5 β), 1.56-1.73 (m, 2H, H-5 α , H-7 α), 1.83 (app. s, 1H, H-4), 2.02-2.10 (m, 1H, H-7 β), 2.34 (app. d, 1H, H-2 α), 2.55 (app. t, 1H, H-6 β), 2.95-3.10 (m, 2H, H-2 β , H-6 α), 3.43 (app. dd, 1H, H-8), 3.96 (s, 3H, CH₃-12), 5.14 (app. br. s, 1H, H-9), 7.03 (s, 1H, H-7'), 7.14 (t, J 7.2, 1H, H-4''), 7.43 (app. t, 2H, H-3''), 7.49 (d, J 7.8, 2H, H-2''), 7.61 (d, J 4.8, 1H, H-3'), 8.80 (d, J 4.8, 1H, H-2'), 15.75 (1H, s, OH)

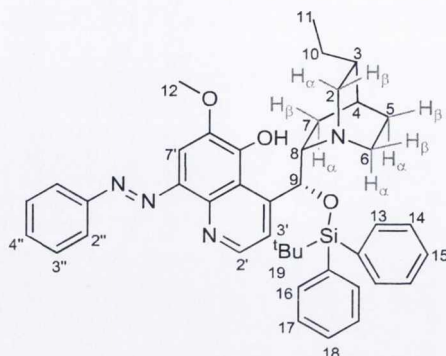
Note: The hydroxyl functionality at the C-9 position doesn't appear on the spectrum

δ_C (100 MHz, CDCl₃): 12.0, 25.3, 27.6, 28.1, 29.6, 37.6, 42.4, 55.8, 57.7, 58.8, 77.1, 115.4, 117.2, 123.5, 124.0 (q), 124.1, 128.7 (q), 129.5, 142.8 (q), 149.0 (q), 149.8, 150.9 (q), 155.5 (q), 179.0 (q)

ν_{max} (neat)/cm⁻¹: 3239, 1619, 1519, 1475, 1340, 1232, 1069, 983

HRMS (*m/z* -ES): Found: 447.2394 (M⁺ + H. C₂₆H₃₁N₄O₃ Requires: 447.2396)

6.4.2 C-5'-Hydroxy C-8'-(*E*)-(2-phenyldiazenyl)-substituted C-9-(*tert*-butyldiphenylsilyloxy)-derived dihydroquinine derivative **457**



Catalyst **454** (1.00 g, 2.24 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL). DMAP (27 mg, 0.22 mmol) and NEt_3 (1.60 mL, 11.20 mmol) were added. The solution was cooled to 0 °C and *tert*-butylchlorodiphenylsilane (1.30 mL, 4.87 mmol) was added dropwise *via* syringe. The reaction was then allowed to warm to ambient temperature and stirred overnight. The resulting solution was concentrated *in vacuo* and the crude residue purified directly by column chromatography (100% EtOAc $\rightarrow$ 70:30:5 EtOAc/MeOH/ NEt_3) to give the expected silyl protected derivative **457** as a red solid (670 mg, 44%). M.p. 79-81 °C. $[\alpha]_{\text{D}}^{22} = -176$ (*c* 0.1, CHCl_3).

δ_{H} (600 MHz, CDCl_3): 0.91 (app. t, 3H, CH_3 -11), 1.11 (s, 9H, 3 CH_3 -19), 1.25-1.51 (m, 4H, H-3, H-5 β , CH_2 -10), 1.55-1.63 (m, 2H, H-5 α , H-7 α), 1.77 (app. s, 1H, H-4), 2.07 (app. t, 1H, H-7 β), 2.24 (app. d, 1H, H-2 α), 2.41 (app. t, 1H, H-6 β), 2.89 (dd, *J* 9.6, 13.2, 1H, H-2 β), 3.15 (app. dd, 1H, H-8), 3.38 (m, 1H, H-6 α), 3.88 (s, 3H, CH_3 -12), 6.72 (s, 1H, H-7'), 7.00 (d, *J* 9.0, 1H, H-9), 7.09 (t, *J* 6.9, 1H, H-4''), 7.16-7.18 (m, 4H, H-14, H-17), 7.22-7.26 (m, 2H, H-15, H-18), 7.39-7.45 (m, 6H, H-2'', H-3'', H-13 or H-16), 7.50 (d, *J* 7.2, 2H, H-13 or H-16), 7.82 (d, *J* 4.8, 1H, H-3'), 8.64 (d, *J* 4.8, 1H, H-2'), 15.45 (s, 1H, OH)

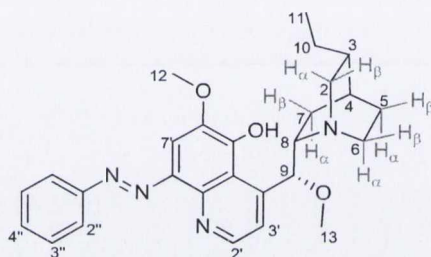
δ_{C} (150 MHz, CDCl_3): 12.2, 19.6 (q), 25.4, 26.8, 27.2, 27.9, 28.7, 37.8, 43.0, 55.6, 58.2, 65.1, 71.5, 114.7, 115.1, 122.4, 123.0, 123.5 (q), 127.1, 127.1, 128.7 (q), 129.3, 129.4, 129.4, 133.1 (q), 133.9 (q),

135.6, 135.9, 143.1 (q), 148.2 (q), 148.7, 150.6 (q), 158.7 (q), 178.5 (q)

$\nu_{\max}$ (neat)/ cm^{-1} : 2928, 2858, 1631, 1517, 1475, 1336, 1228, 1199, 1151, 1105, 1045, 861, 700

HRMS (m/z -ES): Found: 685.3566 ($M^+ + H$. $C_{42}H_{49}N_4O_3Si$ Requires: 685.3574)

6.4.3 C-5'-hydroxy C-8'-(*E*)-(2-phenyldiazenyl)-substituted C-9-methoxy-derived dihydroquinine derivative 458



A 50 mL open round bottom flask was charged with hydrochloric acid (aq. sol. 36.5-38%, 8.5 mL) and freshly distilled aniline (0.26 mL, 2.87 mmol) was added. The obtained mixture was allowed to cool to 0 °C and a solution of NaNO_2 (220 mg, 3.17 mmol) in water (2.6 mL) was added dropwise. This was stirred at 0 °C for 30 min. Meanwhile, **363** (750 mg, 2.11 mmol) was dissolved in a solution of glacial acetic acid (5.1 mL) in water (51 mL). The obtained solution was treated with a saturated solution of sodium acetate (5.1 mL) and cooled to 0 °C. The diazotizing mixture was then added to the solution of the substrate dropwise, keeping the reaction temperature at 0 °C. The reaction was then stirred at 0 °C for 30 min. Ammonia solution (aq., 70 mL) was added and the product was extracted using CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over NaSO_4 and concentrated under vacuum. The resulting crude was purified by column chromatography (100% $\text{CH}_2\text{Cl}_2 \rightarrow 100:5:5 \text{ CH}_2\text{Cl}_2/\text{MeOH}/\text{NEt}_3$). The impure (degrades on silica) amino derivative was obtained as a deep red solid and was used in the second step without further purification. It was dissolved in ethanol (6 mL) and a mixture of $\text{H}_2\text{O}/\text{HCl}$ 1:1 (12 mL) was added. The reaction was heated at reflux temperature overnight. The resulting solution was diluted in water (20 mL) and a saturated solution of NaHCO_3 was

added until the pH of the solution reached 8. The product was then extracted using CH₂Cl₂ (3 x 40 mL), the combined organic extracts were dried over MgSO₄ and condensed under vacuum. Finally, the resulting crude material was purified by column chromatography (100:2 EtOAc/NEt₃ -> 100:6 EtOAc/ NEt₃) to give the desired compound **458** as a deep red solid (112 mg, 12%). M.p 80-82 °C. $[\alpha]_D^{22} = -11$ (c 0.1, CHCl₃).

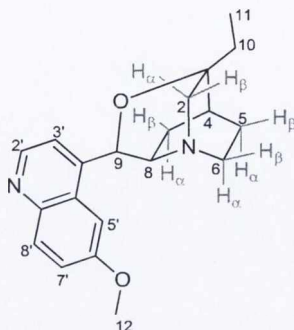
δ_H (600 MHz, CDCl₃): 0.86 (app. t, 3H, CH₃-11), 1.35-1.44 (m, 2H, CH₂-10), 1.60 (app. t, 1H, H-7 α), 1.67-1.81 (m, 2H, H-3, H-5 β), 1.90-2.05 (m, 3H, H-4, H-5 α , H-7 β), 2.86 (app. d, 1H, H-2 α), 3.15 (m, 1H, H-6 β), 3.37 (s, 3H, CH₃-13), 3.43 (app. t, 1H, H-2 β), 3.61 (m, 1H, H-8), 3.82-3.96 (m, 4H, H-6 α , CH₃-12), 6.36 (d, J 3.6, 1H, H-9), 6.98 (s, 1H, H-7'), 7.13 (t, J 7.5, 1H, H-4''), 7.42 (app. t, 2H, H-3''), 7.48 (d, J 7.5, 2H, H-2''), 7.81 (d, J 4.8, 1H, H-3'), 8.92 (d, J 4.8, 1H, H-2'), 15.49 (s, 1H, OH)

δ_C (150 MHz, CDCl₃): 11.7, 24.7, 26.0, 27.2, 36.1, 44.0, 53.3, 55.6, 56.8, 57.3, 59.8, 78.6, 115.1, 116.3, 120.7, 123.8, 123.9 (q), 128.2 (q), 129.4, 142.6 (q), 148.7 (q), 149.8, 150.7 (q), 152.2 (q), 178.2 (q)

ν_{max} (neat)/cm⁻¹: 2956, 2916, 2849, 1620, 1518, 1473, 1463, 1366, 1221, 1230, 1158, 1103, 803, 730, 719

HRMS (*m/z* -ES): Found: 459.2570 (M⁺ - H. C₂₇H₃₁N₄O₃ Requires: 459.2556)

6.4.4 β -Isoquinidine (**443**)



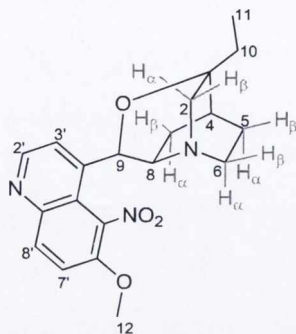
Quinidine (**51**, 5.00 g, 15.5 mmol) was dissolved in methanesulfonic acid (50 mL) and the obtained solution was heated at 120 °C for 1.5 h. The reaction was allowed to cool to ambient temperature, before being added dropwise to a solution of potassium hydroxide (20% aqueous solution, 100 mL) at 0 °C. The product formed was extracted with CH₂Cl₂ (3 x 100 mL), the combined organic layers were dried over MgSO₄ and the solvent was removed under vacuum. Once obtained, the crude was purified by column chromatography (95:5 → 80:20 EtOAc/MeOH) to give **443** as a white solid (2.70 g, 54%). M.p. 119-120 °C, (lit.,²²² 144 °C). $[\alpha]_D^{22} = +8.3$ (*c* 0.8, CHCl₃).

δ_H (400 MHz, CDCl₃): 1.03 (app. t, 3H, CH₃-11), 1.25 (m, 1H, H-7 β), 1.47-1.51 (m, 1H, H-5 β), 1.61-1.70 (m, 3H, H-5 α , CH₂-10), 1.72-1.80 (app. dd, 1H, H-7 α), 2.13 (app. s, 1H, H-4), 2.67 (d, J 13.6, 1H, H-2 β), 3.00 (m, 2H, CH₂-6), 3.47 (app. d, 1H, H-8), 3.54 (d, J 13.6, 1H, H-2 α), 3.94 (s, 3H, CH₃-12), 5.92 (app. s, 1H, H-9), 7.15 (d, J 2.8, 1H, H-5'), 7.33 (dd, J 2.8, 9.2, 1H, H-7'), 7.71 (d, J 4.0, 1H, H-3'), 8.01 (d, J 9.2, 1H, H-8'), 8.77 (d, J 4.0, 1H, H-2')

δ_C (100 MHz, CDCl₃): 7.3, 23.6, 24.3, 27.4, 32.9, 46.7, 54.8, 55.9, 56.2, 73.1, 77.2 (q), 100.6, 119.4, 121.5, 126.5 (q), 131.8, 143.1 (q), 144.0 (q), 147.6, 157.9 (q)

The spectroscopic data were consistent with the data reported in the literature.²²²

6.4.5 C-5'-Nitro-substituted β -isoquinidine derivative 444



A 100 mL round bottom flask was charged with fuming nitric acid (7 mL) and the solution was cooled to $-10\text{ }^{\circ}\text{C}$. β -Isoquinidine (**443**, 1.62 g, 4.99 mmol) was added carefully portion-wise while keeping the temperature of the reaction below $5\text{ }^{\circ}\text{C}$. The resulting mixture was stirred at $-10\text{ }^{\circ}\text{C}$ for 30 min. Ice water (200 mL), followed by NaOH (25% aqueous solution, 21 mL) were added in a dropwise manner. Finally, NH_3 (33% aqueous solution, 56 mL) was poured into the resulting mixture. After allowing the reaction to warm to ambient temperature, the desired compound was extracted using CH_2Cl_2 (3 x 300 mL). The combined organic extracts were washed with water (3 x 400 mL), dried over MgSO_4 and concentrated *in vacuo*. The desired compound was obtained as a green solid (1.75 g, 94 %) pure enough to be used in the next step without further purification. M.p. $157\text{--}159\text{ }^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{22} = +170$ (c 1.3, CHCl_3).

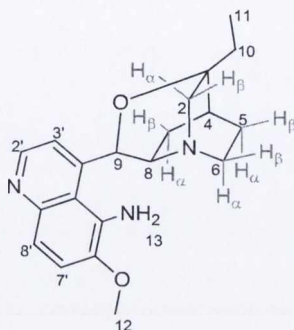
δ_{H} (400 MHz, CDCl_3): 1.01 (app. t, 3H, CH_3 -11), 1.15 (app. q, 1H, H-7 β), 1.42-1.48 (m, 1H, H-5 β), 1.55-1.69 (m, 4H, H-5 α , H-7 α , CH_2 -10), 2.07 (app. t, 1H, H-4), 2.64 (d, J 13.6, 1H, H-2 β), 2.89-2.97 (m, 1H, H-6 α), 3.05 (app. dd, 1H, H-6 β), 3.15 (app. d, 1H, H-8), 3.42 (d, J 13.6, 1H, H-2 α), 4.06 (s, 3H, CH_3 -12), 5.74 (br. app. s, 1H, H-9), 7.59 (d, J 9.6, 1H, H-7'), 8.06 (d, J 4.6, 1H, H-3'), 8.31 (d, J 9.6, 1H, H-8'), 8.89 (d, J 4.6, 1H, H-2')

δ_{C} (100 MHz, CDCl_3): 7.4, 23.6, 23.8, 27.4, 32.8, 46.8, 54.7, 57.3, 57.6, 72.0, 77.8 (q), 115.4, 118.5 (q), 122.6, 134.8, 134.9 (q), 142.3 (q), 143.2 (q), 149.0, 150.2 (q)

$\nu_{\max}$ (neat)/ cm^{-1} : 2939, 2882, 1619, 1530, 1509, 1350, 1267, 1100, 1089, 1012, 917, 795, 702

HRMS (m/z -ES): Found: 370.1761 ($M^+ + H$, $C_{20}H_{24}N_3O_4$ Requires: 370.1767)

6.4.6 C-5'-Amino-substituted β -isoquinidine-derivative **445**



A hydrogenation reaction vessel was charged with **444** (0.90 g, 2.51 mmol) and MeOH (20 mL). The reactor was flushed with argon and palladium on charcoal (10%, 0.15 g, 0.25 mmol) was added carefully portion-wise. This mixture was reacted under 3 atm of hydrogen for 3 h. After removing the palladium by filtration through celite, the reaction was concentrated *in vacuo* to give **445** as a deep yellow solid (0.77 g, 90%). M.p. 63-66 °C. $[\alpha]_D^{22} = +54$ (c 0.4, CHCl_3).

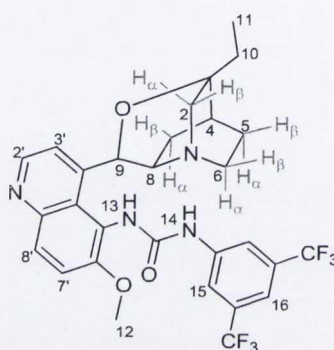
δ_H (600 MHz, CDCl_3): 1.03 (app. t, 3H, CH_3 -11), 1.40 (app. q, 1H, H-7 β), 1.54-1.61 (m, 1H, H-5 β), 1.63-1.83 (m, 3H, H-5 α , CH_2 -10), 2.00-2.06 (app. dd, 1H, H-7 α), 2.07-2.11 (m, 1H, H-4), 2.68 (d, J 13.5, 1H, H-2 β), 3.00-3.08 (m, 2H, CH_2 -6), 3.57 (d, J 13.5, 1H, H-2 α), 3.66 (app. d, 1H, H-8), 3.99 (s, 3H, CH_3 -12), 5.04 (br. s, 2H, NH_2 -13), 6.32 (app. s, 1H, H-9), 7.42-7.44 (m, 2H, H-3', H-7'), 7.63 (d, J 9.0, 1H, H-8'), 8.69 (d, J 4.2, 1H, H-2')

δ_C (150 MHz, CDCl_3): 7.3, 23.5, 23.7, 27.5, 32.5, 46.6, 54.3, 56.3, 56.6, 73.8, 78.5 (q), 115.1, 118.1, 118.3 (q), 120.2, 131.3 (q), 143.6 (q), 143.9 (q), 145.2 (q), 147.6

ν_{max} (neat)/ cm^{-1} : 3307, 2934, 1733, 1616, 1573, 1456, 1253, 1140, 997, 911, 817

HRMS (m/z -ES): Found: 340.2021 ($M^+ + H$. $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_2$ Requires: 340.2025)

6.4.7 C-5'-(3,5-bis(trifluoromethyl)phenyl urea)-substituted β -isoquinidine derivative **442**



The amino derivative **445** (700 mg, 2.07 mmol) was dissolved in freshly distilled CH_2Cl_2 (5 mL) under an Ar atmosphere. The obtained solution was cooled to 0 °C and 3,5-bis(trifluoromethyl)phenyl isocyanate (430 μL , 2.45 mmol) was added dropwise over 10 min *via* syringe. The reaction was allowed to warm to ambient temperature and stirred overnight. Finally, the crude mixture was charged directly onto a flash chromatography column for purification (90:10 EtOAc/MeOH) to give **442** as a cream solid (535 mg, 45%). M.p. 132-138 °C. $[\alpha]_{\text{D}}^{22} = -53$ (c 0.6, CHCl_3).

δ_{H} (400 MHz, CDCl_3): 1.07 (app. t, 3H, CH_3 -11), 1.27-1.37 (m, 1H, H-7 β), 1.72-1.66-1.85 (m, 5H, H-7 α , CH_2 -5, CH_2 -10), 2.33-2.40 (m, 1H, H-4), 2.96 (d, J 12.8, 1H, H-2 β), 3.23-3.42 (m, 2H, CH_2 -6), 3.85 (m, 2H, H-2 α , H-8), 4.00 (s, 3H, CH_3 -12), 6.43 (app. s, 1H, H-9), 7.47-7.56 (m, 2H, H-16, NH-13), 7.59 (d, J 9.4, 1H, H-7'), 7.88 (d, J 4.4, 1H, H-3'), 8.15 (s, 2H, H-15), 8.22 (d, J 9.4, 1H, H-8'), 8.82 (d, J 4.4, 1H, H-2'), 10.52 (br. s, 1H, NH-14)

δ_{C} (100 MHz, CDCl_3):	7.2, 21.3, 21.6, 27.1, 32.1, 46.2, 53.4, 56.5, 58.7, 72.0, 76.1 (q), 115.3, 115.5 ($^3J_{\text{CF}}$ 3.7), 117.6 (q), 118.1 (br. s), 120.6, 123.4 (q, $^1J_{\text{CF}}$ 271.4), 125.3 (q), 131.9 (q), 132.0 (q, $^2J_{\text{CF}}$ 33.1), 132.2, 141.2 (q), 144.2 (q), 147.8, 155.0 (q), 156.0 (q)
δ_{F} (375 MHz, CDCl_3):	-62.9 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3222, 2971, 2536, 1702, 1572, 1473, 1386, 1274, 1172, 1127, 1098, 909, 881, 727, 681
HRMS (m/z -ES):	Found: 595.2147 ($\text{M}^+ + \text{H}$, $\text{C}_{29}\text{H}_{29}\text{F}_6\text{N}_4\text{O}_3$ Requires: 595.2144)

6.4.8 General procedures for the preparation of racemic *N*-protected amino acids

6.4.8.1 Procedure G: using the Schotten-Baumann conditions

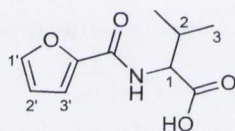
A 100 mL round-bottom flask was charged with the appropriate amino acid (8.50 mmol, 1.0 eq.) and a solution of NaOH (1 M sol., 43 mL) was added to it. The reaction was cooled to 0 °C and the appropriate acyl chloride (8.50 mmol, 1.0 eq.) was injected into the reaction *via* syringe in a dropwise manner. The reaction was allowed to warm to ambient temperature and was stirred overnight. A solution of HCl (37%, 20 mL) was added to the reaction mixture to set the pH to 1. The product was then extracted using CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The resulting protected amino acid was utilised without further purification.

6.4.8.2 Procedure H: *via* the protection of the carboxylic acid functionality

A 250 mL round bottom flask was charged with MeOH (50 mL), fitted with a septum under an argon atmosphere and cooled to 0°C. Thionyl chloride (10 mL, 3.0 eq.) was slowly added to it *via* syringe over 10 min. The obtained solution was stirred for 10 min and the appropriate amino acid (0.40 mol, 1.0 eq.) was added to it. The mixture was allowed to reach ambient temperature, stirred for an hour and before being heated under reflux overnight. The MeOH and the unreacted thionyl chloride were then distilled under vacuum and the resulting methyl ester hydrochloric salt was obtained. This solid (5.05

mmol, 1.5 eq.) was, without further purification, dissolved in freshly distilled CH_2Cl_2 (7 mL) under an Ar atmosphere. The obtained solution was cooled to 0°C and NEt_3 (10.11 mmol, 3.0 eq.) was slowly injected into the reaction mixture followed by the appropriate acyl chloride (3.37 mmol, 1.0 eq.). The reaction was allowed to warm to room temperature and was stirred overnight. The resulting solution was washed with a HCl solution (2 M, 2 x 10 mL) and then a NaOH solution (15 %, 2 x 10 mL). The organic layer was dried over MgSO_4 and was concentrated *in vacuo*. Finally the obtained product (3.0 mmol) was dissolved in THF (10 mL) and a solution of NaOH (15 %, 10 mL) was added to it. The biphasic reaction was strongly stirred at ambient temperature overnight. The resulting mixture was made acidic by addition of HCl (2 M, 20 mL) and the product extracted using CH_2Cl_2 . The organic extracts were dried over MgSO_4 and concentrated under vacuum. The desired *N*-protected amino acid was obtained as a solid.

6.4.8.3 *N*-Furoyl-valine (**450**)



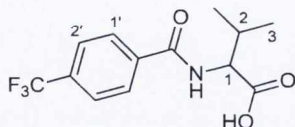
The described general procedure G was followed using D,L-valine (**446**, 1.00 g, 8.50 mmol) and furoyl chloride (**448**, 0.9 mL, 8.50 mmol) in NaOH (1 M, 43 mL). Compound **450** was obtained as a white solid (1.78 g, 99% yield). M.p. 111-113 $^\circ\text{C}$ (lit,²⁰⁶ 113-114 $^\circ\text{C}$)

δ_{H} (400 MHz, DMSO-d_6): 0.93 (d, J 6.4, 3H, CH_3 -3), 1.04 (d, J 6.4, 3H, CH_3 -3), 2.17 (m, 1H, H-2), 4.25 (app. t, 1H, H-1), 6.65 (m, 1H, H-3'), 7.24 (dd, J 2.8, 20.8, 1H, H-2'), 7.89 (d, J 20.8, 1H, H-1'), 8.18 (d, J 8.0, 1H, NH), 12.80 (br. s, 1H, COOH)

δ_{C} (100 MHz, DMSO-d_6): 23.7, 24.4, 34.7, 62.6, 117.0, 119.1, 150.4, 152.4 (q), 163.1 (q), 178.1 (q)

The NMR spectra of **278** were consistent with those previously reported in the literature.²⁰⁶

6.4.8.4 *N*-4-Trifluoromethylbenzoyl valine (**466**)



The described general procedure H was followed using D,L-valine (**446**, 5.00 g, 85.40 mmol) and thionyl chloride (9.4 mL, 0.13 mol) in MeOH (40 mL). The hydrochloric salt (1.50 g, 9.76 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.83 mmol) and NEt₃ (4.1 mL, 29.27 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (30 mL). Compound **466** was obtained as a white solid (1.48 g, 76%). M.p. 188-189 °C.

δ_{H} (400 MHz, DMSO-*d*₆): 0.95 (app. t, 6H, 2 CH₃-3), 2.18 (m, 1H, H-2), 4.26 (app. t, 1H, H-1), 7.83 (d, *J* 7.8, 2H, H-2'), 8.01 (d, *J* 7.8, 2H, H-1'), 8.72 (d, *J* 8.0, 1H, NH), 12.68 (br. s, 1H, COOH)

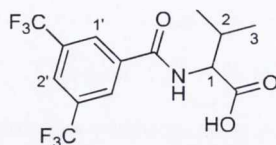
δ_{C} (100 MHz, DMSO-*d*₆): 19.1, 19.7, 29.9, 59.1, 123.0 (q, ¹*J*_{CF} 270.0), 125.7 (³*J*_{CF} 3.7), 128.9, 131.7 (q, ²*J*_{CF} 32.2), 138.3 (q), 166.8 (q), 173.4 (q)

δ_{F} (375 MHz, DMSO-*d*₆): -61.8 (CF₃)

ν_{max} (neat)/cm⁻¹: 3298, 2932, 1626, 1551, 1322, 1167, 1122, 1066, 1016, 857, 776

HRMS (*m/z* -ES): Found: 312.0835 (M⁺ + Na. C₁₃H₁₄NO₃F₃Na Requires: 312.0823

6.4.8.5 *N*-(3,5-bis-Trifluoromethyl)benzoyl valine (**467**)



The described general procedure H was followed using D,L-valine (**446**, 5.00 g, 85.40 mmol) and thionyl chloride (9.4 mL, 0.13 mol) in MeOH (40 mL). The hydrochloric salt (2.00 g, 11.93 mmol) was then directly used with 3,5-bis(trifluoromethyl)benzoyl chloride (**465**, 1.4 mL, 7.96 mmol) and NEt₃ (5.4 mL, 39.02 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (40 mL). Compound **467** was obtained as a white solid (1.64 g, 59%). M.p. 136-139 °C

δ_{H} (400 MHz, DMSO-*d*₆): 1.00 (app t, 6H, 2 CH₃-3), 2.22 (m, 1H, H-2), 4.36 (app. t, 1H, H-1), 8.36 (s, 1H, H-2'), 8.56 (s, 2H, H-1'), 9.01 (d, J 8.2, NH), 12.61 (br. s, 1H, COOH)

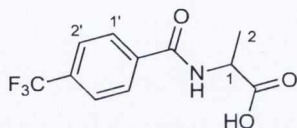
δ_{C} (100 MHz, DMSO-*d*₆): 19.0, 19.5, 30.0, 59.0, 123.5 (q, ¹J_{CF} 271.5), 125.2 (br. s), 128.8 (³J_{CF} 3.2), 130.8 (q, ²J_{CF} 33.1), 136.5 (q), 164.5 (q), 173.1 (q)

δ_{F} (375 MHz, DMSO-*d*₆): -61.3 (CF₃)

ν_{max} (neat)/cm⁻¹: 3311, 1706, 1653, 1542, 1271, 1181, 1129, 1109, 907, 700, 651

HRMS (*m/z* -ES): Found: 380.0699 (M⁺ + Na. C₁₄H₁₃NO₃F₆Na Requires: 380.0697)

6.4.8.6 *N*-4-Trifluoromethylbenzoyl alanine (**502**)



The described general procedure H was followed using D,L-alanine (**484**, 4.00 g, 44.90 mmol) and thionyl chloride (10 mL, 2.72 mol) in MeOH (50 mL). The hydrochloric salt (1.50 g, 10.74 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.74 mmol) and NEt₃ (4.5 mL, 32.23 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (40 mL). Compound **502** was obtained as a white solid (1.03 g, 59%). M.p. 147-148 °C, (lit,²³⁸ 146-147 °C).

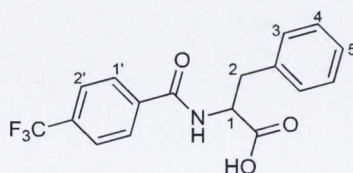
δ_{H} (400 MHz, DMSO-*d*₆): 1.42 (d, *J* 7.2, 3H, CH₃-2), 4.45 (m, 1H, H-1), 7.87 (d, *J* 8.0, 2H, H-2'), 8.09 (d, *J* 8.0, 2H, H-1'), 8.95 (d, *J* 7.2, 1H, NH), 12.62 (br. s, 1H, COOH)

δ_{C} (100 MHz, DMSO-*d*₆): 17.2, 48.8, 124.4 (q, ¹*J*_{CF} 270.7), 125.7 (³*J*_{CF} 3.6), 128.8, 131.7 (q, ²*J*_{CF} 31.6), 138.1 (q), 165.5 (q), 174.5 (q)

δ_{F} (375 MHz, DMSO-*d*₆): -61.9 (CF₃)

The NMR spectra of **502** were consistent with those previously reported in the literature.²³⁸

6.4.8.7 *N*-4-Trifluoromethylbenzoyl phenylalanine (**503**)



The described general procedure H was followed using D,L-phenyl alanine (**485**, 5.00 g, 30.30 mmol) and thionyl chloride (6.7 mL, 92.59 mmol) in MeOH (30 mL). The hydrochloric salt (2.29 g, 10.11 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.83 mmol) and NEt₃ (4.1 mL, 29.27

mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (30 mL). Compound **503** was obtained as a white solid (1.41 g, 62%). M.p. 132-135°C, (lit,²³⁸ 133-135 °C).

δ_H (400 MHz, DMSO- d_6): 3.04 (dd, J 10.9, 13.5, 1H, H-2a), 3.21 (dd, J 4.2, 13.5, 1H, H-2b), 4.63 (m, 1H, H-1), 7.11-7.37 (m, 5H, H-3, H-4, H-5), 7.81 (d, J 8.2, 2H, H-2'), 7.94 (d, J 8.2, 2H, H-1'), 8.99 (d, J 8.0, 1H, NH), 12.67 (br. s, 1H, COOH)

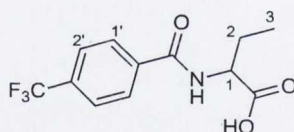
δ_C (100 MHz, DMSO- d_6): 41.4, 59.5, 129.1 (q, $^1J_{CF}$ 271.2), 130.5 ($^3J_{CF}$ 3.8), 131.6, 133.4, 133.4, 134.2, 136.4 (q, $^2J_{CF}$ 31.7), 142.8 (q), 143.2 (q), 170.4 (q), 178.1 (q)

δ_F (375 MHz, DMSO- d_6): -61.9 (CF₃)

The NMR spectra of **503** were consistent with those previously reported in the literature.²³⁸

HRMS (m/z -ES): Found: 360.0825 ($M^+ + Na$. C₁₇H₁₄NO₃F₃Na Requires: 360.0823)

6.4.8.8 *N*-4-Trifluoromethylbenzoyl butiric acid (**504**)



The described general procedure H was followed using D,L-aminobutyric acid (**486**, 5.00 g, 48.49 mmol) and thionyl chloride (11.0 mL, 0.15 mol) in MeOH (40 mL). The hydrochloric salt (1.55 g, 10.11 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.74 mmol) and NEt₃ (4.10 mL, 30.33 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (30 mL). Compound **504** was obtained as a white solid (1.12 g, 41%). M.p. 145-147 °C.

δ_{H} (400 MHz, DMSO- d_6): 2.03 (s, 3H, CH₃-3), 2.49-2.63 (m, 2H, CH₂-2), 4.51 (ddd, J 5.4, 8.2, 13.8, 1H, H-1), 7.84 (d, J 8.3, 2H, H-2'), 8.04 (d, J 8.3, 2H, H-1'), 8.87 (d, J 8.2, 1H, NH), 12.68 (br. s, 1H, COOH)

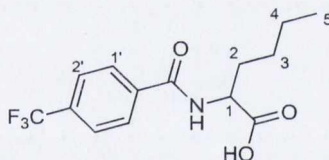
δ_{C} (100 MHz, DMSO- d_6): 11.2, 24.3, 54.7, 124.4 (q, $^1J_{\text{CF}}$ 272.1), 125.7 ($^3J_{\text{CF}}$ 3.8), 128.8, 131.8 (q, $^2J_{\text{CF}}$ 31.7), 138.2 (q), 165.9 (q), 173.8 (q)

δ_{F} (375 MHz, DMSO- d_6): -61.9 (CF₃)

ν_{max} (neat)/cm⁻¹: 3316, 2919, 1702, 1644, 1551, 1322, 1164, 1054, 1017, 944, 859, 773, 687

HRMS (m/z -ES): Found: 274.0691 (M⁺ - H. C₁₂H₁₁NO₃F₃ Requires: 274.0692)

6.4.8.9 *N*-4-Trifluoromethylbenzoyl norleucine (**505**)



The described general procedure H was followed using D,L-norleucine (**487**, 5.00 g, 38.12 mmol) and thionyl chloride (8.4 mL, 0.12 mol) in MeOH (60 mL). The hydrochloric salt (1.85 g, 10.11 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.74 mmol) and NEt₃ (4.1 mL, 30.33 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (30 mL). Compound **505** was obtained as a white solid (1.78 g, 87%). M.p. 147-150 °C.

δ_{H} (400 MHz, DMSO- d_6): 0.88 (t, J 6.7, 3H, CH₃-5), 1.20-1.48 (m, 4H, CH₂-3, CH₂-4), 1.67-1.93 (m, 2H, CH₂-2), 4.38 (app. q, 1H, H-1), 7.88 (d, J 8.0, 2H, H-2'), 8.09 (d, J 8.0, 2H, H-1'), 8.86 (d, J 7.6, 1H, NH), 12.69 (br. s, 1H, COOH)

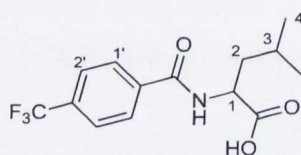
δ_C (100 MHz, DMSO- d_6): 14.3, 22.2, 28.4, 30.7, 53.2, 124.5 (q, $^1J_{CF}$ 272.1), 125.7 (br. s), 128.8, 131.8 (q, $^2J_{CF}$ 30.6), 138.2 (q), 166.0 (q), 174.1 (q)

δ_F (375 MHz, DMSO- d_6): -61.8 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3312, 2962, 1715, 1640, 1547, 1322, 1163, 1127, 1064, 1016, 857, 773

HRMS (m/z -ES): Found: 326.0973 ($M^+ + Na$. Requires: $C_{14}H_{16}NO_3F_3Na$ 326.0980)

6.4.8.10 *N*-4-Trifluoromethylbenzoyl leucine (**506**)



The described general procedure H was followed using D,L-leucine (**488**, 5.00 g, 38.12 mmol) and thionyl chloride (8.4 mL, 0.12 mol) in MeOH (60 mL). The hydrochloric salt (1.85 g, 10.11 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.74 mmol) and NEt_3 (4.1 mL, 30.33 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/ $NaOH$ (15%) (30 mL). Compound **506** was obtained as a white solid (1.82 g, 89%). M.p. 130-132 °C, (lit,²³⁸ 82 °C)

δ_H (400 MHz, DMSO- d_6): 0.88 (d, J 6.3, 3H, CH_3 -4), 0.94 (d, J 6.3, 3H, CH_3 -4), 1.57-1.82 (m, 3H, H-3, CH_2 -2), 4.44-4.50 (m, 1H, H-1), 7.87 (d, J 8.0, 2H, H-2'), 8.09 (d, J 8.0, 2H, H-1'), 8.88 (d, J 7.8, 1H, NH), 12.68 (br. s, 1H, COOH)

δ_C (100 MHz, DMSO- d_6): 21.1 (2C), 22.9, 24.5, 51.0, 124.0 (q, $^1J_{CF}$ 271.0), 125.3 ($^3J_{CF}$ 3.6), 128.4, 131.3 (q, $^2J_{CF}$ 31.6), 137.7 (q), 165.4 (q), 174.0 (q)

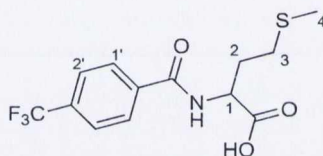
δ_F (375 MHz, DMSO- d_6): -61.9 (CF_3)

The NMR spectra of **506** were consistent with those previously reported in the literature.²³⁸

ν_{max} (neat)/ cm^{-1} : 3291, 2962, 1710, 1638, 1545, 1325, 1164, 1133, 1065, 1017, 860, 778

HRMS (m/z -ES): Found: 326.0973 ($M^+ + Na$. $C_{14}H_{16}NO_3F_3Na$ Requires: 326.0980)

6.4.8.11 *N*-4-Trifluoromethylbenzoyl methionine (**507**)



The described general procedure H was followed using D,L-Methionine (**489**, 5.00 g, 33.51 mmol) and thionyl chloride (7.4 mL, 0.10 mol) in MeOH (50 mL). The hydrochloric salt (1.65 g, 10.11 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.74 mmol) and NEt_3 (4.1 mL, 30.33 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/ $NaOH$ (15%) (20 mL). Compound **507** was obtained as a white solid (519 mg, 27%). M.p. 128-130 °C.

δ_H (400 MHz, DMSO- d_6): 1.99-2.13 (m, 5H, CH_2 -2, CH_3 -4), 2.57 (m, 2H, CH_2 -3), 4.55 (app. dd, 1H, H-1), 7.88 (d, J 8.0, 2H, H-2'), 8.09 (d, J 8.0, 2H, H-1'), 8.92 (d, J 7.6, 1H, NH), 12.91 (br. s, 1H, OH)

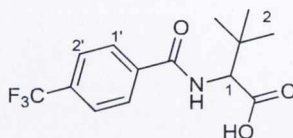
δ_C (100 MHz, DMSO- d_6): 14.5, 30.0, 30.1, 51.7, 123.9 (q, $^1J_{CF}$ 273.0), 125.3 ($^3J_{CF}$ 3.6), 128.4, 131.3 (q, $^2J_{CF}$ 31.5), 137.7 (q), 165.5 (q), 173.2 (q)

δ_F (375 MHz, DMSO- d_6): -61.8 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3301, 2976, 1721, 1626, 1546, 1324, 1223, 1167, 1118, 1068, 1016, 855, 774, 674

HRMS (m/z -ES): Found: 320.0572 ($M^+ - H$, $C_{13}H_{13}NO_3F_3S$ Requires: 320.0568)

6.4.8.12 *N*-4-Trifluoromethylbenzoyl *tert*-leucine (**508**)



The described general procedure H was followed using *L*-*tert*-leucine (**490**, 1.20 g, 9.22 mmol) and thionyl chloride (1.7 mL, 23.22 mmol) in MeOH (10 mL). The hydrochloric salt (1.50 g, 8.20 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.83 mmol) and NEt_3 (3.4 mL, 24.60 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (24 mL). Compound **508** was obtained as a white solid (1.41 g, 71%). M.p. 134-135 °C.

δ_H (400 MHz, DMSO- d_6): 1.09 (s, 9H, 2 CH_3 -2), 4.39 (d, J 8.8, 1H, H-1), 7.83 (d, J 8.1, 2H, H-2'), 8.05 (d, J 8.1, 2H, H-1'), 8.52 (d, J 8.8, 1H, NH), 12.76 (br. s, 1H, COOH)

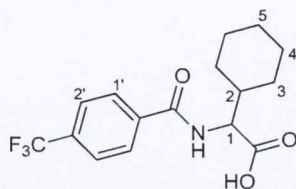
δ_C (100 MHz, DMSO- d_6): 26.9, 33.6 (q), 61.1, 124.0 (q, $^1J_{CF}$ 273.3), 125.1 ($^3J_{CF}$ 3.2), 128.7, 131.0 (q, $^2J_{CF}$ 31.5), 138.2 (q), 166.2 (q), 172.3 (q)

δ_F (375 MHz, DMSO- d_6): -61.9 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3311, 2967, 1717, 1630, 1548, 1321, 1215, 1169, 1132, 1063, 1016, 852, 697

HRMS (m/z -ES): Found: 326.0971 ($M^+ + Na$, $C_{14}H_{16}NO_3F_3Na$ Requires: 326.0980)

6.4.8.13 *N*-4-Trifluoromethylbenzoyl 2-cyclohexyl glycine (**509**)



The described general procedure H was followed using L- 2-amino-2-cyclohexylacetic acid (**491**, 5.00 g, 31.80 mmol) and thionyl chloride (6.9 mL, 95.07 mmol) in MeOH (60 mL). The hydrochloric salt (2.10 g, 10.11 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 1.0 mL, 6.74 mmol) and NEt₃ (4.2 mL, 30.33 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (30 mL). Compound **509** was obtained as a white solid (1.30 g, 59%). M.p. 147-148 °C

δ_{H} (400 MHz, DMSO-*d*₆): 0.94-1.24 (m, 5H, H-3a, H-4a, H-5a), 1.60-1.76 (m, 5H, H-3b, H-4b, H-5b), 1.82-1.84 (m, 1H, H-2), 4.28 (app. t, 1H, H-1), 7.79 (d, *J* 8.2, 2H, H-2'), 8.04 (d, *J* 8.2, 2H, H-1'), 8.66 (d, *J* 8.0, 1H, NH), 12.48 (br. s, 1H, COOH)

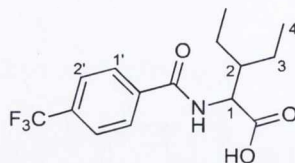
δ_{C} (100 MHz, DMSO-*d*₆): 26.1, 26.7, 29.7, 30.3, 39.8, 59.0, 68.0, 124.9 (q, ¹*J*_{CF} 270.9), 126.1 (³*J*_{CF} 3.8), 129.5, 132.2 (q, ²*J*_{CF} 31.7), 138.9 (q), 166.8 (q), 173.9 (q)

δ_{F} (375 MHz, DMSO-*d*₆): -61.5 (CF₃)

ν_{max} (neat)/cm⁻¹: 3302, 2971, 1715, 1625, 1549, 1321, 1236, 1167, 1126, 1063, 1016, 855, 688

HRMS (*m/z* -ES): Found: 328.1161 (M⁺ - H. C₁₆H₁₇NO₃F₃ Requires: 328.1153)

6.4.8.14 *N*-4-Trifluoromethylbenzoyl 2-amino-3-ethylpentanoic acid (**510**)



The described general procedure H was followed using D,L-2-amino-3-ethylpentanoic acid (**492**, 850 mg, 5.85 mmol) and thionyl chloride (1.3 mL, 17.55 mmol) in MeOH (50 mL). The hydrochloric salt (917 mg, 4.69 mmol) was then directly used with 4-(trifluoromethyl)benzoyl chloride (**464**, 0.6 mL, 4.26 mmol) and NEt₃ (2.6 mL, 14.07 mmol). Finally, the resulting crude residue was dissolved in a 1:1 mixture of THF/NaOH (15%) (30 mL). Compound **510** was obtained as a white solid (1.06 g, 79%). M.p. 138-140 °C

δ_{H} (400 MHz, DMSO-*d*₆): 0.82-0.94 (m, 6H, 2 CH₃-4), 1.29-1.49 (m, 4H, 2CH₂-3), 1.82 (m, 1H, H-2), 4.61 (dd, *J* 6.2, 8.3, 1H, H-1), 7.85 (d, *J* 8.1, 2H, H-2'), 8.06 (d, *J* 8.1, 2H, H-1'), 8.64 (d, *J* 8.3, 1H, NH), 12.98 (br. s, 1H, COOH)

δ_{C} (100 MHz, DMSO-*d*₆): 11.1, 11.2, 21.8, 21.9, 42.3, 54.4, 123.9 (q, ¹*J*_{CF} 270.7), 125.2 (³*J*_{CF} 3.7), 128.6, 131.2 (q, ²*J*_{CF} 31.9), 138.0 (q), 166.0 (q), 173.4 (q)

δ_{F} (375 MHz, DMSO-*d*₆): -61.9 (CF₃)

ν_{max} (neat)/cm⁻¹: 3302, 2971, 1715, 1625, 1549, 1321, 1236, 1167, 1126, 1063, 1016, 855, 688

HRMS (*m/z* -ES): Found: 316.1156 (M⁺ - H. C₁₅H₁₇NO₃F₃ Requires: 316.1161)

6.4.9 General procedure for the synthesis of racemic azlactones

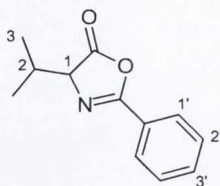
6.4.9.1 Procedure I: using DCC as a coupling agent

In a 50 mL round bottom flask flushed with argon, fitted with a septum and a magnetic stirring bar, was charged the appropriate *N*-protected amino acid (1.32 mmol, 1.00 eq.). Freshly distilled CH_2Cl_2 (5 mL) was added *via* syringe, followed by a solution of 1,3-dicyclohexylcarbodiimide (1.26 mmol, 0.95 eq.) in freshly distilled CH_2Cl_2 (5.0 mL). The reaction was stirred at room temperature for 1-2 h. The resulting mixture was filtered and the filtrate was concentrated *in vacuo*. The remaining DCC by-product was precipitated using EtOAc and filtered. The obtained filtrate was concentrated under vacuum and was directly charged onto a short pad of silica gel for purification. The desired azlactone was obtained pure as an oil that solidified after drying under high vacuum (hygroscopic). This was used immediately.

6.4.9.2 Procedure J: using EDCI as a coupling agent

A 50 mL round bottom flask flushed with argon, fitted with a septum and a magnetic stirring bar, was charged with the appropriate *N*-protected amino acid (1.08 mmol, 1.00 eq.). Freshly distilled CH_2Cl_2 (10 mL) was added *via* syringe, followed by a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.19 mmol, 1.10 eq.) in freshly distilled CH_2Cl_2 (5 mL). The reaction was stirred at room temperature for 1 h. The resulting mixture was washed twice with a saturated solution of NaHCO_3 at 0 °C (2 x 10 mL). The resulting organic layer was dried over MgSO_4 , concentrated under vacuum and was directly charged onto a short pad of silica gel for purification. The desired azlactone was obtained pure as an oil that solidified after drying under high vacuum (hygroscopic). This was used immediately.

6.4.9.3 *N*-Benzoyl valine azlactone (**278**)

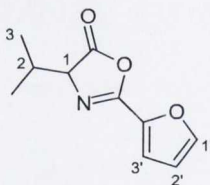


Prepared according to the general procedure I, using *N*-protected amino acid **449** (1.00 g, 4.52 mmol) and DCC (780 mg, 3.78 mmol) in freshly distilled CH₂Cl₂ (10 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane/EtOAc), azlactone **278** was obtained as a white solid (843 mg, 92%). M.p. 49-50 °C, (lit.,²³⁹ 48-51 °C).

δ_{H} (400 MHz, CDCl₃): 1.05 (d, *J* 6.6, 3H, CH₃-3), 1.18 (d, *J* 6.6, 3H, CH₃-3), 2.42 (m, 1H, H-2), 4.32 (d, *J* 4.4, 1H, H-1), 7.52 (app. t, 2H, H-2'), 7.61 (t, *J* 7.0, 1H, H-3'), 8.05 (d, *J* 8.0, 2H, H-1')

The NMR spectra of **278** were consistent with those previously reported in the literature.¹⁹⁵

6.4.9.4 *N*-Furoyl-Valine azlactone (**345**)

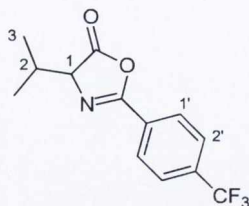


Prepared according to the general procedure I, using *N*-protected amino acid **450** (525 mg, 2.49 mmol) and DCC (780 mg, 3.78 mmol) in freshly distilled CH₂Cl₂ (10 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane/EtOAc), azlactone **345** was obtained as a white solid (843 mg, 84%). M.p. 114-115 °C, (lit.,²⁰⁶ 113-114 °C).

δ_{H} (400 MHz, CDCl₃): 1.04 (d, *J* 6.6, 3H, CH₃-3), 1.18 (d, *J* 6.6, 3H, CH₃-3), 2.42 (m, 1H, H-2), 4.30 (d, *J* 4.4, 1H, H-1), 6.61 (m, 1H, H-2'), 7.13 (d, *J* 3.6, 1H, H-3'), 7.69 (app. s, 1H, H-1')

The NMR spectra of **345** were consistent with those previously reported in the literature.²⁰⁶

6.4.9.5 *N*-4-Trifluoromethylbenzoyl valine azlactone (**459**)



Prepared according to the general procedure I, using *N*-protected amino acid **466** (500 mg, 1.73 mmol) and DCC (371 mg, 1.80 mmol) in freshly distilled CH₂Cl₂ (10 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane/EtOAc), azlactone **459** was obtained as a white solid (406 mg, 87%). M.p. 40-42 °C.

δ_{H} (400 MHz, CDCl₃): 1.05 (d, *J* 6.8, 3H, CH₃-3), 1.19 (d, *J* 6.8, 3H, CH₃-3), 2.44 (m, 1H, H-2), 4.35 (d, *J* 4.4, 1H, H-1), 7.78 (d, *J* 8.4, 2H, H-2'), 8.17 (d, *J* 8.4, 2H, H-1')

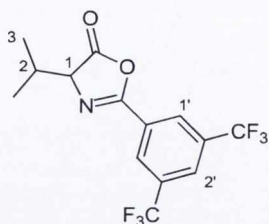
δ_{C} (100 MHz, CDCl₃): 17.1, 18.3, 30.8, 70.4, 123.2 (q, ¹*J*_{CF} 271.0), 125.4 (³*J*_{CF} 3.7), 127.9, 128.8 (q), 133.7 (q, ²*J*_{CF} 32.0), 160.1 (q), 176.7 (q)

δ_{F} (375 MHz, CDCl₃): -63.6 (CF₃)

ν_{max} (neat)/cm⁻¹: 2976, 2939, 1823, 1649, 1412, 1322, 1164, 1119, 1109, 1036, 1005, 889, 840, 753, 699

HRMS (*m/z* -ES): Found: 270.0748 (M⁺ - H. C₁₃H₁₁NO₂F₃ Requires: 270.0742)

6.4.9.6 *N*-(3,5-bis-Trifluoromethyl)benzoyl valine azlactone (**460**)



Prepared according to the general procedure I, using *N*-protected amino acid **467** (500 mg, 1.41 mmol) and DCC (305 mg, 1.48 mmol) in freshly distilled CH₂Cl₂ (10 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane/EtOAc), azlactone **460** was obtained as a white solid (378 mg, 79%). M.p. 47-48 °C.

δ_{H} (400 MHz, CDCl₃): 1.06 (d, *J* 6.5, 3H, CH₃-3), 1.20 (d, *J* 6.5, 3H, CH₃-3), 2.45 (m, 1H, H-2), 4.38 (d, *J* 4.5, 1H, H-1), 8.10 (s, 1H, H-2'), 8.50 (s, 2H, H-1')

δ_{C} (100 MHz, CDCl₃): 17.1, 18.3, 30.9, 70.5, 122.3 (q, ¹*J*_{CF} 271.3), 125.5 (³*J*_{CF} 3.5), 127.5 (br. s), 127.7 (q), 132.1 (q, ²*J*_{CF} 34.1), 159.0 (q), 175.9 (q)

δ_{F} (375 MHz, CDCl₃): -63.5 (CF₃)

ν_{max} (neat)/cm⁻¹: 2971, 1837, 1728, 1659, 1276, 1132, 985, 897, 845, 696, 681

HRMS (*m/z* -ES): Found: 338.0612 (M⁺ - H. C₁₄H₁₀NO₂F₆ Requires: 338.0616)

6.4.9.7 *N*-4-Trifluoromethylbenzoyl alanine azlactone (475)



Prepared according to the general procedure I, using *N*-protected amino acid **502** (400 mg, 1.53 mmol) and DCC (272 mg, 1.32 mmol) in freshly distilled CH₂Cl₂ (10 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane/EtOAc), azlactone **475** was obtained as a white solid (276 mg, 74%). M.p. 38-39 °C.

δ_{H} (400 MHz, CDCl₃): 1.65 (d, *J* 7.2, 3H, CH₃-2), 4.52 (q, *J* 7.6, 1H, H-1), 7.79 (d, *J* 8.4, 2H, H-2'), 8.15 (d, *J* 8.4, 2H, H-1')

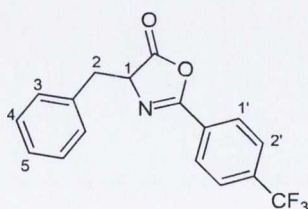
δ_{C} (100 MHz, CDCl₃): 53.0, 60.7, 123.3 (q, ¹*J*_{CF} 271.2), 125.3 (³*J*_{CF} 3.7), 127.8, 128.7 (q), 133.8 (q, ²*J*_{CF} 32.7), 160.1 (q), 177.8 (q)

δ_{F} (375 MHz, CDCl₃): -63.6 (CF₃)

ν_{max} (neat)/cm⁻¹: 2920, 1830, 1650, 1413, 1317, 1171, 1126, 1104, 1065, 850, 684

HRMS (*m/z* -ES): Found: 242.0440 (M⁺ - H. C₁₁H₇NO₂F₃ Requires: 242.0429)

6.4.9.8 *N*-4-Trifluoromethylbenzoyl phenylalanine azlactone (476)



Prepared according to the general procedure I, using *N*-protected amino acid **503** (400 mg, 1.19 mmol) and DCC (257 mg, 1.25 mmol) in freshly distilled CH₂Cl₂ (10 mL). After

purification onto a short pad of silica gel (95:5 *n*-hexane/EtOAc), azlactone **476** was obtained as a white solid (223 mg, 59%). M.p. 81-82 °C, (lit,²⁴⁰ 84 °C).

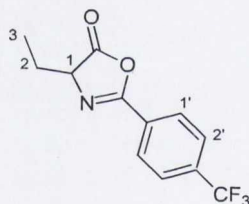
δ_{H} (400 MHz, CDCl_3): 3.35 (d, *J* 6.0, 2H, CH_2 -2), 4.77 (app. s, 1H, H-1), 7.06-7.54 (m, 5H, H-3, H-4, H-5), 7.75 (app. s, 2H, H-2'), 8.07 (app. s, 2H, H-1')

δ_{C} (100 MHz, CDCl_3): 36.6, 66.2, 123.0 (q, $^1J_{\text{CF}}$ 271.1), 125.3 ($^3J_{\text{CF}}$ 3.7), 126.9, 127.8, 128.0, 128.6 (q), 129.1, 133.8 (q, $^2J_{\text{CF}}$ 32.6), 134.5 (q), 160.2 (q), 176.5 (q)

δ_{F} (375 MHz, CDCl_3): -63.7 (CF_3)

The NMR spectra of **476** were consistent with those previously reported in the literature.²⁴⁰

6.4.9.9 *N*-4-Trifluoromethylbenzoyl butiric acid azlactone (**477**)



Prepared according to the general procedure J, using *N*-protected amino acid **504** (406 mg, 1.48 mmol) and EDCI (367 mg, 1.92 mmol) in freshly distilled CH_2Cl_2 (7 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane/EtOAc), azlactone **477** was obtained as a white solid (148 mg, 39%). M.p. 24-26 °C.

δ_{H} (400 MHz, CDCl_3): 1.06 (app. t, 3H, CH_3 -3), 1.94-2.01 (m, 1H, H-2a), 2.05-2.14 (m, 1H, H-2b), 4.42 (app. t, 1H, H-1), 7.76 (d, *J* 8.1, 2H, H-2'), 8.13 (d, *J* 8.1, 2H, H-1')

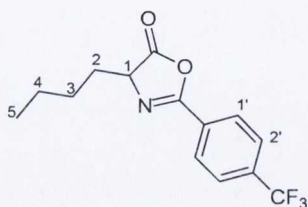
δ_{C} (100 MHz, CDCl_3): 9.5, 24.9, 66.6, 123.5 (q, $^1J_{\text{CF}}$ 271.4), 125.8 ($^3J_{\text{CF}}$ 3.7), 128.3, 129.2 (q), 134.3 (q, $^2J_{\text{CF}}$ 31.7), 160.6 (q), 177.7 (q)

δ_{F} (375 MHz, CDCl_3): -63.2 (CF_3)

ν_{max} (neat)/ cm^{-1} : 2975, 2942, 1827, 1654, 1413, 1317, 1127, 1066, 1013, 880, 853, 692

HRMS (m/z -ES): Found: 256.0589 ($M^+ - H$, $C_{12}H_9NO_2F_3$ Requires: 256.0585)

6.4.9.10 *N*-4-Trifluoromethylbenzoyl norleucine azlactone (**478**)



Prepared according to the general procedure J, using *N*-protected amino acid **505** (328 mg, 1.08 mmol) and EDCI (228 mg, 1.19 mmol) in freshly distilled CH_2Cl_2 (10 mL). After purification onto a short pad of silica gel (95:5 *n*-hexane/EtOAc), azlactone **478** was obtained as a white solid (234 mg, 76%). M.p. 42-44 °C.

δ_H (400 MHz, $CDCl_3$): 0.93 (t, J 7.2, 3H, CH_3 -5), 1.34-1.55 (m, 4H, CH_2 -3, CH_2 -4), 1.81-1.94 (m, 1H, H-2a), 1.98-2.1 (m, 1H, H-2b), 4.44 (dd, J 5.8, 7.0, 1H, H-1), 7.76 (d, J 8.3, 2H, H-2'), 8.13 (d, J 8.3, 2H, H-1')

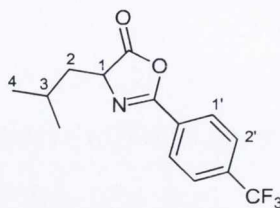
δ_C (100 MHz, $CDCl_3$): 13.7, 22.2, 27.3, 31.2, 65.5, 123.7 (q, $^1J_{CF}$ 271.1), 125.7 ($^3J_{CF}$ 3.9), 128.2, 129.2 (q), 134.2 (q, $^2J_{CF}$ 32.7), 160.5 (q), 177.8 (q)

δ_F (375 MHz, $CDCl_3$): -63.3 (CF_3)

ν_{max} (neat)/ cm^{-1} : 2959, 2864, 1818, 1655, 1412, 1320, 1167, 1126, 1107, 1068, 879, 852, 689

HRMS (m/z -ES): Found: 284.0892 ($M^+ - H$, $C_{14}H_{13}NO_2F_3$ Requires: 284.0898)

6.4.9.11 *N*-4-Trifluoromethylbenzoyl leucine azlactone (**479**)



Prepared according to the general procedure I, using *N*-protected amino acid **506** (400 mg, 1.32 mmol), DCC (259 mg, 1.25 mmol) in freshly distilled CH₂Cl₂ (10 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane/EtOAc), azlactone **479** was obtained as a white solid (291 mg, 77%). M.p. 25-27 °C.

δ_{H} (400 MHz, CDCl₃): 1.02 (d, *J* 6.7, 3H, CH₃-4), 1.04 (d, *J* 6.7, 3H, CH₃-4), 1.69 (m, 1H, H-2a), 1.86 (m, 1H, H-2b), 2.02-2.12 (m, 1H, H-3), 4.44 (dd, *J* 5.6, 9.0, 1H, H-1), 7.75 (d, *J* 8.3, 2H, H-2'), 8.12 (d, *J* 8.3, 2H, H-1')

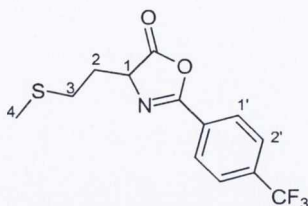
δ_{C} (100 MHz, CDCl₃): 22.0, 22.7, 25.3, 40.7, 64.1, 123.5 (q, ¹*J*_{CF} 271.2), 125.8 (³*J*_{CF} 3.8), 128.3, 129.4 (q), 134.2 (q, ²*J*_{CF} 33.2), 160.3 (q), 178.3 (q)

δ_{F} (375 MHz, CDCl₃): -63.2 (CF₃)

ν_{max} (neat)/cm⁻¹: 2962, 2874 1829, 1655, 1414, 1320, 1171, 1132, 1066, 1042, 1017, 882, 854, 694

HRMS (*m/z* -ES): Found: 284.0890 (M⁺ - H. C₁₄H₁₃NO₂F₃ Requires: 284.0898)

6.4.9.12 *N*-4-Trifluoromethylbenzoyl methionine azlactone (**480**)



Prepared according to the general procedure J, using *N*-protected amino acid **507** (350 mg, 1.09 mmol) and EDCI (271 mg, 1.42 mmol) in freshly distilled CH₂Cl₂ (10 mL). After purification onto a short pad of silica gel (95:5 *n*-hexane/EtOAc), azlactone **480** was obtained as a white solid (54 mg, 16%). M.p. 47-48 °C

δ_{H} (400 MHz, CDCl₃): 2.11-2.22 (m, 4H, H-2a, CH₃-4), 2.29-2.39 (m, 1H, H-2b), 2.74 (app. t, 2H, CH₂-3), 4.65 (app. t, 1H, H-1), 7.76 (d, J 8.2, 2H, H-2'), 8.13 (d, J 8.2, 2H, H-1')

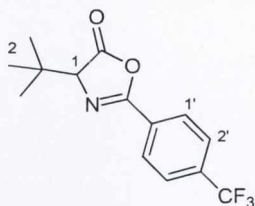
δ_{C} (100 MHz, CDCl₃): 15.1, 30.1, 30.3, 63.8, 123.5 (q, ¹J_{CF} 271.1), 125.8 (³J_{CF} 3.7), 128.3, 129.2 (q), 134.3 (q, ²J_{CF} 32.7), 161.0 (q), 177.8 (q)

δ_{F} (375 MHz, CDCl₃): -63.2 (CF₃)

ν_{max} (neat)/cm⁻¹: 2921, 1827, 1652, 1413, 1317, 1126, 1063, 1013, 880, 852, 693

HRMS (*m/z* -ES): Found: 302.0464 (M⁺ - H. C₁₃H₁₁NO₂F₃S Requires: 302.0463)

6.4.9.13 *N*-4-Trifluoromethylbenzoyl *tert*-leucine azlactone (**481**)



Prepared according to the general procedure I, using *N*-protected amino acid **508** (400 mg, 1.32 mmol) and DCC (259 mg, 1.26 mmol) in freshly distilled CH₂Cl₂ (10 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane/EtOAc), azlactone **481** was obtained as a white solid (138 mg, 37%). M.p. 51-53 °C.

δ_{H} (400 MHz, CDCl₃): 1.15 (s, 9H, 3 CH₃-2), 4.11 (s, 1H, H-1), 7.75 (d, *J* 8.2, 2H, H-2'), 8.14 (d, *J* 8.2, 2H, H-1')

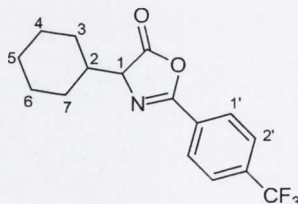
δ_{C} (100 MHz, CDCl₃): 26.1, 36.0 (q), 74.2, 123.6 (q, ¹*J*_{CF} 271.1), 125.7 (³*J*_{CF} 3.8), 128.3, 129.3 (q), 134.1 (q, ²*J*_{CF} 32.9), 160.2 (q), 176.3 (q)

δ_{F} (375 MHz, CDCl₃): -63.2 (CF₃)

ν_{max} (neat)/cm⁻¹: 2928, 1830, 1650, 1413, 1317, 1171, 1104, 1065, 993, 877, 850, 682

HRMS (*m/z* -ES): Found: 284.0894 (M⁺ - H. C₁₄H₁₃NO₂F₃ Requires: 284.0898)

6.4.9.14 *N*-4-Trifluoromethylbenzoyl 2-cyclohexyl glycine azlactone (**482**)



Prepared according to the general procedure J, using *N*-protected amino acid **509** (500 mg, 1.52 mmol) and EDCI (319 mg, 1.67 mmol) in freshly distilled CH₂Cl₂ (10.0 mL). After

purification onto a short pad of silica gel (95:5 *n*-hexane/EtOAc), azlactone **482** was obtained as a cream solid (322 mg, 68%). M.p. 39-40 °C.

δ_{H} (400 MHz, CDCl_3): 1.11-1.49 (m, 5H, H-3a, H-4a, H-5a, H-6a, H-7a), 1.63-1.96 (m, 5H, H-3b, H-4b, H-5b, H-6b, H-7b), 2.10 (m, 1H, H-2), 4.33 (d, *J* 4.4, 1H, H-1), 7.78 (d, *J* 8.1, 2H, H-2'), 8.16 (d, *J* 8.1, 2H, H-1')

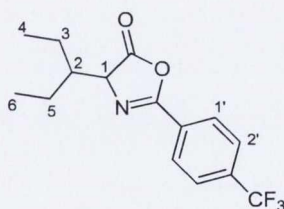
δ_{C} (100 MHz, CDCl_3): 25.3, 25.4, 25.5, 27.3, 28.7, 40.2, 70.0, 123.1 (q, $^1J_{\text{CF}}$ 271.2), 125.3 ($^3J_{\text{CF}}$ 3.6), 127.8, 128.8 (q), 133.5 (q, $^2J_{\text{CF}}$ 32.6), 160.0 (q), 176.7 (q)

δ_{F} (375 MHz, CDCl_3): -63.7 (CF_3)

ν_{max} (neat)/ cm^{-1} : 2934, 2859, 1820, 1651, 1454, 1412, 1320, 1297, 1166, 1110, 1064, 1013, 928, 879, 859, 843, 688, 685

HRMS (*m/z* -ES): Found: 310.1052 ($\text{M}^+ - \text{H}$. $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{F}_3$ Requires: 310.1055)

6.4.9.15 *N*-4-Trifluoromethylbenzoyl 2-amino-3-ethylpentanoic acid azlactone (**483**)



Prepared according to the general procedure J, using using *N*-protected amino acid **510** (400 mg, 1.26 mmol) and EDCI (266 mg, 1.39 mmol) in freshly distilled CH_2Cl_2 (7.0 mL). After purification onto a short pad of silica gel (90:10 *n*-hexane /EtOAc), azlactone **483** was obtained as a cream solid (307 mg, 82%). M.p. 23-25 °C.

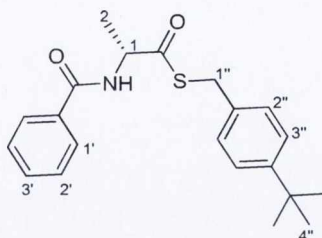
δ_{H} (400 MHz, CDCl_3): 0.93 (app. t, 3H, CH_3 -4), 1.02 (app. t, 3H, CH_3 -6), 1.37 (m, 2H, H-3a, H-5a), 1.55 (m, 2H, H-3b, H-5b), 1.89-2.01 (m,

	1H, H-2), 4.52 (d, J 3.9, 1H, H-1), 7.75 (d, J 8.2, 2H, H-2'), 8.13 (d, J 8.2, 2H, H-1')
δ_C (100 MHz, $CDCl_3$):	11.6 (2C), 22.5, 23.1, 44.4, 67.6, 123.6 (q, $^1J_{CF}$ 271.2), 125.7 ($^3J_{CF}$ 3.8), 128.2, 129.3 (q), 134.1 (q, $^2J_{CF}$ 32.7), 160.4 (q), 178.0 (q)
δ_F (375 MHz, $CDCl_3$):	-62.8 (CF_3)
ν_{max} (neat)/ cm^{-1} :	2940, 2877, 1823, 1651, 1412, 1317, 1124, 1067, 941, 882, 847, 695
HRMS (m/z -ES):	Found: 298.1046 (M^+ - H. $C_{15}H_{15}NO_2F_3$ Requires: 298.1055)

6.4.10 Procedure K: general procedures for the organocatalysed dynamic kinetic resolution of azlactones using 4-*tert*-butyl benzyl mercaptan at -70 °C

A reaction vessel containing a stirring bar was flushed with argon, charged with the dihydroquinine-based catalyst **454** (0.01 eq. or 0.02 eq. as appropriate) and the azlactone (1.00 eq.), before being closed with a suitable cap. Freshly distilled CH_2Cl_2 (0.05 M or 0.03M as appropriate) was injected *via* syringe. The vial was then introduced in the cooling machine set up at -70 °C and the reaction mixture was let stir for 10 min in order to reach this temperature. Finally, 4-*tert*-butyl benzyl mercaptan (**337**, 2.00 eq. or 4.00 eq. as appropriate) was added dropwise to the reaction media *via* syringe. The resulting solution was stirred at -70 °C for 3-4 d. The resulting product was then directly purified by flash chromatography.

6.4.10.1 (*R*)- 4-*tert*-Butylbenzyl 2-benzamidopropanethioate (**338**)



Prepared as per general procedure K at ambient temperature, using the alanine-derived azlactone **282** (24.1 mg, 0.14 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 47 μ L, 0.28 mmol) and the dihydroquinine-based cinchona alkaloid catalyst **454** (3.2 mg, 0.007 mmol) in freshly distilled CH_2Cl_2 (0.70 mL, 0.2 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc), the thioester (*R*)-**338** was obtained as a white solid (39.8 mg, 80 %). M.p. 103-105 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{22} = +5.8$ (*c* 0.12, CHCl_3).

The enantiomeric excess of (*R*)-**338** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 80:20 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (major) = 6.87 min; t_{R} (minor) = 12.95 min; 31% *ee*. The absolute configuration of (*R*)-**338** was established by analogy with (*R*)-**461**.

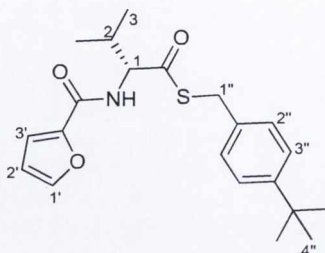
δ_{H} (400 MHz, CDCl_3): 1.32 (s, 9H, 3 CH_3 -4''), 1.55 (d, *J* 7.2, 3H, CH_3 -2), 4.15 (app. s, 2H, CH_2 -1''), 4.99 (m, 1H, H-1), 6.78 (d, *J* 7.6, 1H, NH), 7.24 (d, *J* 8.4, 2H, H-2''), 7.34 (d, *J* 8.4, 2H, H-3''), 7.45 (app. t, 1H, H-2'), 7.54 (t, *J* 7.2, 2H, H-3'), 7.84 (d, *J* 7.6, 2H, H-1')

δ_{C} (100 MHz, CDCl_3): 18.6, 30.9, 32.5, 34.1 (q), 54.9, 125.2, 126.7, 128.1, 128.2, 131.5, 133.2 (q), 133.3 (q), 150.0 (q), 166.6 (q), 200.2 (q)

ν_{max} (neat)/ cm^{-1} : 3304, 2967, 1693, 1646, 1517, 1287, 1267, 1095, 974, 835, 694

HRMS (*m/z* -ES): Found: 378.1509 ($\text{M}^+ + \text{Na}$. $\text{C}_{21}\text{H}_{25}\text{NO}_2\text{NaS}$ Requires: 378.1504)

6.4.10.2 (R)-4-tert-Butylbenzyl-2-(furan-2-carboxamido)-3-methylbutane-thioate (352)



Prepared as per general procedure K using the valine-derived azlactone **345** (20.8 mg, 0.10 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 40 μ L, 0.21 mmol) and the dihydroquinine-based cinchona alkaloid catalyst **454** (2.4 mg, 0.005 mmol) in freshly distilled CH_2Cl_2 (0.55 mL, 0.2 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc), the thioester (*R*)-**352** was obtained as a colourless oil (28.1 mg, 75 %). $[\alpha]_{\text{D}}^{22} = +55$ (*c* 0.4, CHCl_3), (lit.²⁰⁶ $[\alpha]_{\text{D}}^{22} = -2.5$ (*c* 0.3, CHCl_3)).

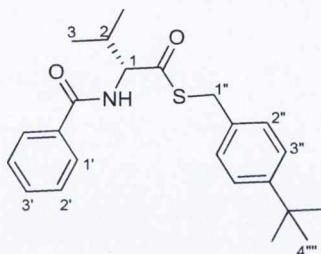
The enantiomeric excess of (*R*)-**352** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (major) = 6.81 min; t_{R} (minor) = 8.27 min; 34% *ee*. The absolute configuration of (*R*)-**352** was established by analogy with (*R*)-**461** and compared to literature specific rotation data.²⁰⁶

δ_{H} (400 MHz, CDCl_3): 0.97 (d, *J* 6.8, 3H, CH_3 -3), 1.04 (d, *J* 6.8, 3H, CH_3 -3), 1.31 (s, 9H, 3 CH_3 -4''), 2.43 (m, 1H, H-2), 4.15 (app. s, 2H, CH_2 -1''), 4.88 (dd, *J* 3.4, 9.2, 1H, H-1), 6.54 (app. t, 1H, H-2'), 6.80 (d, *J* 9.2, 1H, NH), 7.18 (d, 1H, *J* 2.4, H-3'), 7.23 (d, *J* 7.2, 2H, H-2''), 7.36 (d, *J* 7.2, 2H, H-3''), 7.50 (app. s, 1H, H-1')

The NMR spectra of (*R*)-**352** were consistent with those previously reported in the literature.²⁰⁶

HRMS (*m/z* -ES): Found: 396.1621 ($\text{M}^+ + \text{Na}$. $\text{C}_{21}\text{H}_{27}\text{NO}_3\text{NaS}$ Requires: 396.1609)

6.4.10.3 (R) -4-*tert*-Butylbenzyl 2-benzamido-3-methylbutanethioate (451)



Prepared as per general procedure K using the valine-derived azlactone **278** (17.5 mg, 0.09 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 65 μ L, 0.036 mmol) and the dihydroquinine-based cinchona alkaloid catalyst **454** (3.9 mg, 0.009 mmol) in freshly distilled CH_2Cl_2 (0.44 mL, 0.2 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc), the thioester (*R*)-**451** was obtained as a colourless oil (15.2 mg, 44%). $[\alpha]_{\text{D}}^{22} = +10.9$ (*c* 0.1, CHCl_3).

The enantiomeric excess of (*R*)-**451** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (major) = 7.36 min; t_{R} (minor) = 9.03 min; 81% *ee*. The absolute configuration of (*R*)-**451** was established by analogy with compound (*R*)-**461**.

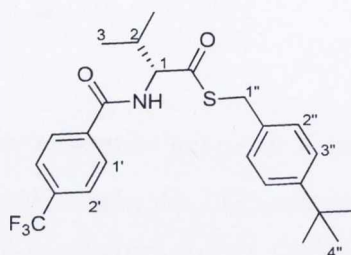
δ_{H} (400 MHz, CDCl_3): 0.97 (d, *J* 6.8, 3H, CH_3 -3), 1.07 (d, *J* 6.8, 3H, CH_3 -3), 1.32 (s, 9H, 3 CH_3 -4''), 2.44 (m, 1H, H-2), 4.17 (app. s, 2H, CH_2 -1''), 4.96 (dd, *J* 4.8, 9.2, 1H, H-1), 6.60 (d, *J* 9.2, 1H, NH), 7.24 (d, *J* 8.4, 2H, H-2''), 7.34 (d, *J* 8.4, 2H, H-3''), 7.49 (app. t, 1H, H-2'), 7.57 (t, *J* 7.4, 2H, H-3'), 7.85 (d, *J* 7.0, 2H, H-1')

δ_{C} (100 MHz, CDCl_3): 17.1, 19.5, 31.3, 31.7, 33.0, 34.5 (q), 63.9, 125.6, 127.1, 128.6, 128.7, 131.9, 133.7 (q), 134.0 (q), 150.4 (q), 167.4 (q), 199.7 (q)

ν_{max} (neat)/ cm^{-1} : 3294, 2963, 1648, 1509, 1363, 1267, 1231, 1076, 1027, 908, 830, 729

HRMS (m/z -ES): Found: 406.1811 ($M^+ + Na$. $C_{23}H_{29}NO_2NaS$ Requires: 406.1817)

6.4.10.4 (R)-4-tert-Butylbenzyl-3-methyl-2-(4-(trifluoromethyl)benzamido) butanethioate (461)



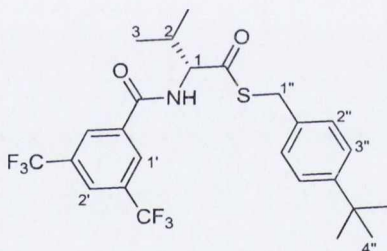
Prepared as per the general procedure K using the valine-derived azlactone **459** (21.0 mg, 0.08 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 29 μ L, 0.016 mmol) and the dihydroquinine-based catalyst **454** (3.5 mg, 0.008 mmol) in freshly distilled CH_2Cl_2 (1.60 mL, 0.05 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc), the thioester (*R*)-**461** was obtained as a colourless oil (13.9 mg, 39%). $[\alpha]_D^{22} = -22.7$ (c 0.2, $CHCl_3$).

The enantiomeric excess of (*R*)-**461** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_R (major) = 6.40 min; t_R (minor) = 7.53 min; 91% *ee*. The absolute configuration of (*R*)-**461** was established by first converting (*R*)-**461** to the corresponding methyl ester (*R*)-**522** (see 5.4.11) and then comparing the HPLC retention times (CSP-HPLC) with both these associated with a sample of (*S*)-**522** and of racemic-**522**.

δ_H (400 MHz, $CDCl_3$): 0.97 (d, J 6.9, 3H, CH_3 -3), 1.07 (d, J 6.9, 3H, CH_3 -3), 1.32 (s, 9H, 3 CH_3 -4''), 2.36-2.59 (m, 1H, H-2), 4.18 (app. s, 2H, CH_2 -1''), 4.95 (dd, J 4.8, 9.2, 1H, H-1), 6.64 (d, J 9.2, 1H, NH), 7.24 (d, J 8.4, 2H, H-2''), 7.34 (d, J 8.4, 2H, H-3''), 7.75 (d, J 8.0, 2H, H-2'), 7.95 (d, J 8.0, 2H, H-1')

δ_{C} (100 MHz, CDCl_3):	16.9, 19.4, 31.1, 31.7, 32.9, 34.4 (q), 63.8, 123.3 (q, $^1J_{\text{CF}}$ 270.8), 125.5, 125.6 ($^3J_{\text{CF}}$ 3.7), 127.5, 128.4, 133.4 (q), 133.5 (q, $^2J_{\text{CF}}$ 32.6), 137.1 (q), 150.4 (q), 166.0 (q), 199.2 (q)
δ_{F} (375 MHz, CDCl_3):	-63.5 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3313, 2967, 1742, 1647, 1535, 1323, 1161, 1126, 1065, 1017, 858, 733
HRMS (m/z -ES):	Found: 474.1698 ($\text{M}^+ + \text{Na}$. $\text{C}_{24}\text{H}_{28}\text{NO}_2\text{F}_3\text{NaS}$ Requires: 474.1691)

6.4.10.5 (R)-4-tert-Butylbenzyl-2-(3,5-bis(trifluoromethyl)benzamido)-3-methylbutanethioate (462)

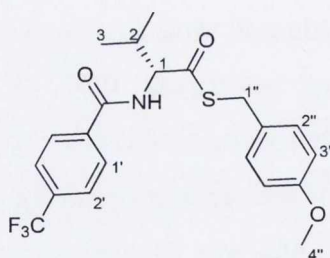


Prepared as per the general procedure K using the valine-derived azlactone **460** (22.3 mg, 0.07 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 25 μL , 0.013 mmol) and the dihydroquinine-based catalyst **454** (2.9 mg, 0.007 mmol) in freshly distilled CH_2Cl_2 (0.33 mL, 0.2 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc), the thioester (*R*)-**462** was obtained as a colourless oil (14.8 mg, 31%). $[\alpha]_{\text{D}}^{22}$ -38.3 (*c* 0.1, CHCl_3).

The enantiomeric excess of (*R*)-**462** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm); 98:2 *n*-hexane/IPA; 0.5 mL/min; λ = 220 nm. t_{R} (minor) = 10.27 min; t_{R} (major) = 12.41 min; 57% *ee*. The absolute configuration of (*R*)-**462** was established by analogy with (*R*)-**461**.

δ_{H} (400 MHz, CDCl_3):	0.95 (d, J 6.8, 3H, CH_3 -3), 1.04 (d, J 6.8, 3H, CH_3 -3), 1.28 (s, 9H, 3 CH_3 -4''), 2.39 (m, 1H, H-2), 4.14 (d, J 13.8, 1H, H-1''a), 4.18 (d, J 13.8, 1H, H-1''b), 4.93 (dd, J 4.9, 8.8, 1H, H-1), 6.67 (d, J 8.8, 1H, NH), 7.16 (d, J 8.2, 2H, H-2''), 7.33 (d, J 8.2, 2H, H-3''), 8.03 (s, 1H, H-2'), 8.22 (s, 2H, H-1')
δ_{C} (100 MHz, CDCl_3):	17.2, 19.5, 31.3, 32.0, 33.1, 34.5 (q), 64.2, 122.8 (q, $^1J_{\text{CF}}$ 271.8), 125.4 (br. s), 125.6, 128.5, 129.07 (br. s), 132.4 (q, $^2J_{\text{CF}}$ 33.8), 133.4 (q), 136.0 (q), 150.5 (q), 164.5 (q), 198.9 (q)
δ_{F} (375 MHz, CDCl_3):	-62.9 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3329, 2964, 1649, 1535, 1325, 1278, 1135, 1067, 1017, 907, 731, 681
HRMS (m/z -ES):	Found: 542.1555 ($\text{M}^+ + \text{Na}$. $\text{C}_{25}\text{H}_{27}\text{NO}_2\text{NaF}_6\text{S}$ Requires: 542.1564)

6.4.10.6 (R)-4-Methoxybenzyl-3-methyl-2-(4-(trifluoromethyl)benzamido)butanethioate (471)



Prepared as per the general procedure K using the valine-derived azlactone **459** (15.3 mg, 0.06 mmol), *para*-methoxy-substituted mercaptan **252** (16 μL , 0.012 mmol) and the dihydroquinine-based catalyst **454** (2.5 mg, 0.006 mmol) in freshly distilled CH_2Cl_2 (0.3 mL, 0.2 M). After purification of the crude material by flash chromatography (90:10 *n*-hexane/EtOAc), the thioester (*R*)-**471** was obtained as a yellow oil (10.2 mg, 40%). $[\alpha]_{\text{D}}^{22} = +2.9$ (*c* 0.1, CHCl_3).

The enantiomeric excess of (*R*)-**471** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; λ = 220 nm. t_R (major) = 11.23 min; t_R (minor) = 15.33 min; 55% *ee*. The absolute configuration of (*R*)-**471** was established by analogy with (*R*)-**461**.

δ_H (400 MHz, $CDCl_3$): 0.92 (d, *J* 6.8, 3H, CH_3 -3), 1.02 (d, *J* 6.8, 3H, CH_3 -3), 1.54 (s, 3H, H-4''), 2.38 (m, 1H, H-2), 4.12 (app. t, 2H, CH_2 -1''), 4.90 (dd, *J* 4.7, 9.1, 1H, H-1), 6.55 (d, *J* 9.1, 1H, NH), 6.81 (d, *J* 8.6, 2H, H-3''), 7.19 (d, *J* 8.6, 2H, H-2''), 7.71 (d, *J* 8.2, 2H, H-2'), 7.90 (d, *J* 8.2, 2H, H-1')

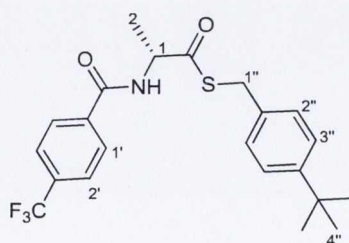
δ_C (100 MHz, $CDCl_3$): 17.1, 19.5, 31.8, 32.9, 55.2, 63.9, 114.1, 123.3 (q, $^1J_{CF}$ 273.2), 125.7 ($^3J_{CF}$ 3.8), 127.5, 128.7 (q), 130.0, 130.5 (q), 133.5 (q, $^2J_{CF}$ 33.0), 158.9 (q), 168.6 (q), 187.5 (q)

δ_F (375 MHz, $CDCl_3$): -63.0 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3305, 2970, 1648, 1513, 1326, 1251, 1169, 1067, 1017, 857, 735

HRMS (*m/z* -ES): Found: 448.1159 ($M^+ + Na$. $C_{21}H_{22}NO_3F_3NaS$ Requires: 448.1170)

6.4.10.7 (*R*)-4-*tert*-Butylbenzyl-2-(4-(trifluoromethyl)benzamido)propanethioate (**511**)



Prepared as per the general procedure K using the alanine-derived azlactone **475** (18.3 mg, 0.08 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 28 μ L, 0.016 mmol) and the

dihydroquinine-based catalyst **454** (3.4 mg, 0.008 mmol) in freshly distilled CH₂Cl₂ (1.5 mL, 0.05 M). After purification of the crude material by flash chromatography (95:5 *n*-hexane/EtOAc), the thioester (*R*)-**511** was obtained as a white solid (11.2 mg, 35%). M.p. 103-105 °C [α]_D²² = -2.9 (*c* 0.1, CHCl₃).

The enantiomeric excess of (*R*)-**511** was determined by CSP-HPLC analysis using a Chiralcel AS column (4.6 mm x 25 cm), 90:10 *n*-hexane/IPA, 1.0 mL/min, λ = 220 nm. *t*_R (major) = 8.00 min, *t*_R (minor) = 10.64 min. 86% *ee*. The absolute configuration of (*R*)-**511** was established by analogy with (*R*)-**461**.

δ_H (400 MHz, CDCl₃): 1.32 (s, 9H, 3 CH₃-4''), 1.57 (d, *J* 7.1, 3H, CH₃-2), 4.18 (app. t, 2H, CH₂-1''), 4.97-5.04 (m, 1H, H-1), 6.75 (d, *J* 7.5, 1H, NH), 7.24 (d, *J* 8.2, 2H, H-2''), 7.35 (d, *J* 8.2, 2H, H-3''), 7.74 (d, *J* 8.1, 2H, H-2'), 7.94 (d, *J* 8.1, 2H, H-1')

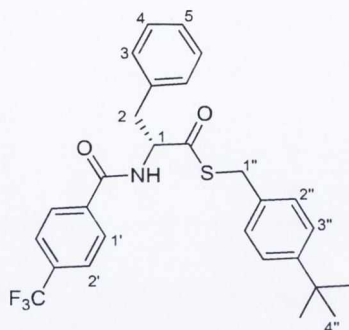
δ_C (100 MHz, CDCl₃): 19.2, 31.3, 33.0, 34.5 (q), 55.4, 123.4 (q, ¹*J*_{CF} 271.0), 125.7, 125.8 (³*J*_{CF} 3.7), 127.6, 128.6, 133.4 (q, ²*J*_{CF} 32.7), 133.8 (q), 137.0 (q), 150.6 (q), 165.6 (q), 200.1 (q)

δ_F (375 MHz, CDCl₃): -63.0 (CF₃)

$\nu_{\max}$ (neat)/cm⁻¹: 3312, 2959, 1684, 1645, 1534, 1505, 1323, 1167, 1110, 1064, 1017, 862, 840, 774, 694

HRMS (*m/z* -ES): Found: 446.1378 (M⁺ + Na. C₂₂H₂₄NO₂F₃NaS Requires: 446.1385)

6.4.10.8 (R)-4-*tert*-Butylbenzyl-3-phenyl-2-(4-(trifluoromethyl)benzamido)propanethioate (512)



Prepared as per the general procedure K using the phenylalanine-derived azlactone **476** (24.1 mg, 0.076 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 56 μ L, 0.30 mmol) and the dihydroquinine-based catalyst **454** (3.4 mg, 0.008 mmol) in freshly distilled CH_2Cl_2 (2.5 mL, 0.03 M). After purification of the crude material by flash chromatography (95:5 $\rightarrow$ 85:15 *n*-hexane/EtOAc), the thioester (*R*)-**512** was obtained as a white solid (15.1 mg, 40%). M.p. 34-36 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{22} +24.9$ (*c* 0.1, CHCl_3).

The enantiomeric excess of (*R*)-**512** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm), 90:10 *n*-hexane/IPA, 1.0 mL/min, $\lambda = 220$ nm. t_{R} (major) = 15.91 min, t_{R} (minor) = 18.96 min. 84% *ee*. The absolute configuration of (*R*)-**512** was established by analogy with (*R*)-**461**.

δ_{H} (400 MHz, CDCl_3): 1.34 (s, 9H, 3 CH_3 -4''), 3.30 (d, *J* 5.6, 2H, CH_2 -2), 4.16 (app. s, 2H, CH_2 -1''), 5.25 (app. dd, 1H, H-1), 6.64 (d, *J* 8.4, 1H, NH), 7.10 (d, *J* 3.6, 2H, H-3), 7.20-7.31 (m, 5H, H-4, H-5, H-2''), 7.36 (d, *J* 8.2, 2H, H-3''), 7.70 (d, *J* 7.6, 2H, H-2'), 7.80 (d, *J* 7.6, 2H, H-1')

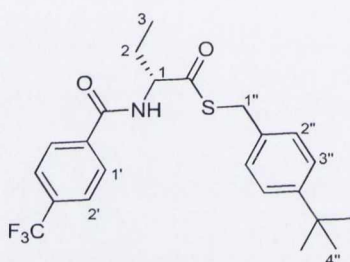
δ_{C} (100 MHz, CDCl_3): 30.9, 32.6, 34.1 (q), 37.9, 59.2, 123.1 (q, $^1J_{\text{CF}}$ 270.9), 125.2, 125.3 ($^3J_{\text{CF}}$ 3.7), 127.0, 127.0, 128.2, 128.3, 129.0, 133.1 (q), 133.2 (q, $^2J_{\text{CF}}$ 33.1), 134.6 (q), 136.5 (q), 150.1 (q), 165.2 (q), 198.5 (q)

δ_F (375 MHz, $CDCl_3$): -63.1 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3291, 2963, 1647, 1536, 1324, 1169, 1129, 1066, 1017, 909, 836, 731, 698

HRMS (m/z -ES): Found: 522.1684 ($M^+ + Na$. $C_{28}H_{28}NO_2F_3NaS$ Requires: 522.1691)

6.4.10.9 (R)-4-tert-Butylbenzyl-2-(4(trifluoromethyl)benzamido)butanethioate (513)



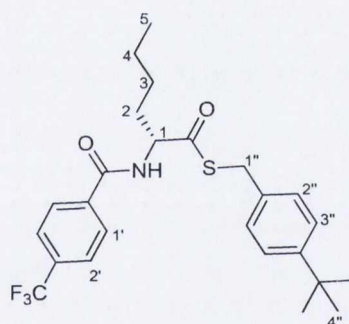
Prepared as per general procedure K using the aminobutiric acid-derived azlactone **477** (32.4 mg, 0.13 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 48 μ L, 0.26 mmol) and the dihydroquinine-based catalyst **454** (5.8 mg, 0.01 mmol) in freshly distilled CH_2Cl_2 (2.6 mL, 0.05 M). After purification of the crude material by flash chromatography (95:5 *n*-hexane/EtOAc), the thioester (*R*)-**513** was obtained as a colourless oil (18.30 mg, 47%). $[\alpha]_D^{22} = +11.3$ (c 0.2, $CHCl_3$).

The enantiomeric excess of (*R*)-**513** was determined by CSP-HPLC analysis using a Chiralcel OD-H column (4.6 mm x 25 cm), 90:10 *n*-hexane/IPA, 1.0 mL/min, $\lambda = 220$ nm. t_R (major) = 7.92 min, t_R (minor) = 10.30 min. 85% *ee*. The absolute configuration of (*R*)-**513** was established by analogy with (*R*)-**461**.

δ_H (400 MHz, $CDCl_3$): 0.97 (app. t, 3H, CH_3 -3), 1.28 (s, 9H, 3 CH_3 -4''), 1.76-1.87 (m, 1H, H-2a), 2.03-2.14 (m, 1H, H-2b), 4.14 (app. s, 2H, CH_2 -1''), 4.91 (ddd, J 5.1, 7.9, 12.8, 1H, H-1), 6.62 (d, J 7.9, 1H, NH), 7.19 (d, J 8.3, 2H, H-2''), 7.30 (d, J 8.3, 2H, H-3''), 7.70 (d, J 8.2, 2H, H-2'), 7.90 (d, J 8.2, 2H, H-1')

δ_{C} (100 MHz, CDCl_3):	9.5, 26.4, 31.3, 33.0, 34.5 (q), 60.5, 123.5 (q, $^1J_{\text{CF}}$ 271.2), 125.6, 125.7 ($^3J_{\text{CF}}$ 3.8), 127.6, 128.5, 133.5 (q), 133.6 (q, $^2J_{\text{CF}}$ 32.7), 137.1 (q), 150.5 (q), 165.8 (q), 199.4 (q)
δ_{F} (375 MHz, CDCl_3):	-63.0 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3326, 2960, 1676, 1650, 1525, 1506, 1327, 1170, 1123, 1065, 1018, 855, 777, 706, 687
HRMS (m/z -ES):	Found: 460.1554 ($\text{M}^+ + \text{Na}$. $\text{C}_{23}\text{H}_{26}\text{NO}_2\text{F}_3\text{NaS}$ Requires: 460.1534)

6.4.10.10 (*R*)-4-*tert*-Butylbenzyl-2-(4-(trifluoromethyl)benzamido)hexanethioate (514)

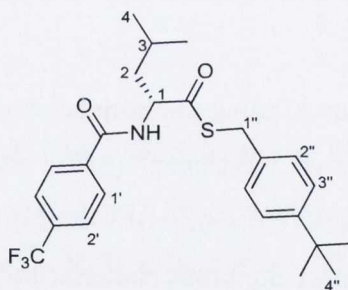


Prepared as per general procedure K using the norleucine-derived azlactone **478** (38.2 mg, 0.13 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 100 μL , 0.52 mmol) and the dihydroquinine-based catalyst **454** (6.0 mg, 0.013 mmol) in freshly distilled CH_2Cl_2 (4.5 mL, 0.03 M). After purification of the crude material by flash chromatography (95:5 *n*-hexane/EtOAc), the thioester (*R*)-**514** was obtained as a colourless oil (18.0 mg, 32%). $[\alpha]_{\text{D}}^{22} = -8.0$ (*c* 0.2, CHCl_3).

The enantiomeric excess of (*R*)-**514** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm), 90:10 *n*-hexane/IPA, 1.0 mL/min, $\lambda = 220$ nm. t_{R} (major) = 15.74 min, t_{R} (minor) = 16.89 min. 88% *ee*. The absolute configuration of (*R*)-**514** was established by analogy with (*R*)-**461**.

δ_{H} (400 MHz, CDCl_3):	0.88 (t, J 6.9, 3H, CH_3 -5), 1.17-1.42 (m, 13H, H-3, H-4, 3 CH_3 -4''), 1.64-1.81 (m, 1H, H-2a), 1.94-2.11 (m, 1H, H-2b), 4.13 (app. s, 2H, CH_2 -1''), 4.94 (ddd, J 5.0, 8.2, 13.1, 1H, H-1), 6.63 (d, J 8.2, 1H, NH), 7.19 (d, J 8.3, 2H, H-2''), 7.30 (d, J 8.3, 2H, H-3''), 7.69 (d, J 8.1, 2H, H-2'), 7.89 (d, J 8.1, 2H, H-1')
δ_{C} (100 MHz, CDCl_3):	13.8, 22.3, 27.3, 31.2, 32.9, 33.0, 34.5 (q), 59.5, 123.6 (q, $^1J_{\text{CF}}$ 271.2), 125.6, 125.7 ($^3J_{\text{CF}}$ 3.7), 127.6, 128.5, 133.5 (q), 133.6 (q, $^2J_{\text{CF}}$ 32.6), 137.1 (q), 150.5 (q), 165.8 (q), 199.7 (q)
δ_{F} (375 MHz, CDCl_3):	-63.0 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3284, 2961, 1646, 1535, 1324, 1167, 1129, 1086, 1017, 909, 857, 732
HRMS (m/z -ES):	Found: 488.1834 ($\text{M}^+ + \text{Na}$. $\text{C}_{25}\text{H}_{30}\text{NO}_2\text{F}_3\text{NaS}$ Requires: 488.1847)

6.4.10.11 (*R*)-4-*tert*-Butylbenzyl-4-methyl-2-(4-(trifluoromethyl)benzamido)pentanethioate (515)



Prepared as per the general procedure K using the leucine-derived azlactone **479** (20.5 mg, 0.072 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 54 μL , 0.29 mmol) and the dihydroquinine-based catalyst **454** (3.2 mg, 0.007 mmol) in freshly distilled CH_2Cl_2 (2.4 mL, 0.03 M). After purification of the crude material by flash chromatography (95:5 *n*-

hexane/EtOAc), the thioester (*R*)-**515** was obtained as a colourless oil (19.3 mg, 60%).
 $[\alpha]_D^{22} = +15.1$ (*c* 0.1, CHCl₃).

The enantiomeric excess of (*R*)-**515** was determined by CSP-HPLC analysis using a Chiralcel AD-H column (4.6 mm x 25 cm), 90:10 *n*-hexane/IPA, 1.0 mL/min, $\lambda = 220$ nm. t_R (major) = 6.61 min, t_R (minor) = 8.40 min. 89% *ee*. The absolute configuration of (*R*)-**515** was established by analogy with (*R*)-**461**.

δ_H (400 MHz, CDCl₃): 0.98 (t, *J* 6.2, 6H, 2 CH₃-4), 1.29 (s, 9H, 3 CH₃-4''), 1.59-1.80 (m, 2H, H-3, H-2a), 1.81-1.90 (m, 1H, H-2b), 4.13 (app. s, 2H, CH₂-1''), 5.25 (ddd, *J* 4.6, 9.1, 13.6, 1H, H-1), 6.47 (d, *J* 9.1, 1H, NH), 7.20 (d, *J* 8.3, 2H, H-2''), 7.31 (d, *J* 8.3, 2H, H-3''), 7.71 (d, *J* 8.1, 2H, H-2'), 7.80 (d, *J* 8.1, 2H, H-1')

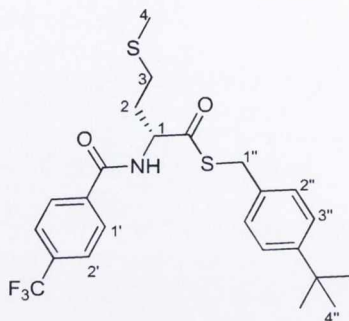
δ_C (100 MHz, CDCl₃): 21.7, 23.6, 25.0, 31.3, 33.0, 34.5 (q), 42.1, 58.1, 123.6 (q, $^1J_{CF}$ 271.1), 125.6, 125.7 ($^3J_{CF}$ 3.7), 127.6, 128.5, 133.4 (q), 133.6 (q, $^2J_{CF}$ 30.4), 137.1 (q), 150.5 (q), 165.9 (q), 200.1 (q)

δ_F (375 MHz, CDCl₃): -63.0 (CF₃)

ν_{max} (neat)/cm⁻¹: 3312, 2962, 1646, 1535, 1325, 1262, 1169, 1131, 1066, 1017, 907. 802, 730

HRMS (*m/z* -ES): Found: 488.1870 ($M^+ + Na$. C₂₅H₃₀NO₂F₃NaS Requires: 488.1847)

6.4.10.12 (R)-4-*tert*-Butylbenzyl 4-(methylthio)-2-(4-(trifluoromethyl)benzamido)butanethioate (516)



Prepared as per the general procedure K, using the methionine-derived azlactone **480** (26.3 mg, 0.085 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 32 μ L, 0.17 mmol) and the dihydroquinine-based cinchona alkaloid catalyst **454** (3.9 mg, 0.009 mmol) in freshly distilled CH_2Cl_2 (1.7 mL, 0.05 M). After purification of the crude material by flash chromatography (98:2 $\rightarrow$ 95:5 *n*-hexane/EtOAc), the thioester (*R*)-**516** was obtained as a colourless oil (10.1 mg, 24%). $[\alpha]_{\text{D}}^{22} = +19$ (*c* 0.1, CHCl_3).

The enantiomeric excess of (*R*)-**516** was determined by CSP-HPLC analysis using a Chiralcel AS column (4.6 mm x 25 cm); 95:5 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (major) = 16.22 min; t_{R} (minor) = 21.82 min; 92% *ee*. The absolute configuration of (*R*)-**516** was established by analogy with (*R*)-**461**.

δ_{H} (400 MHz, CDCl_3): 1.28 (s, 9H, 3 CH_3 -4''), 2.02-2.21 (m, 4H, H-2a, CH_3 -4), 2.24-2.35 (m, 1H, H-2b), 2.53-2.63 (m, 2H, CH_2 -3), 4.14 (app. s, 2H, CH_2 -1''), 5.09 (ddd, *J* 4.6, 7.7, 12.4, 1H, H-1), 7.16-7.24 (m, 3H, H-2'', NH), 7.31 (d, *J* 8.3, 2H, H-3''), 7.72 (d, *J* 8.2, 2H, H-2'), 7.93 (d, *J* 8.2, 2H, H-1')

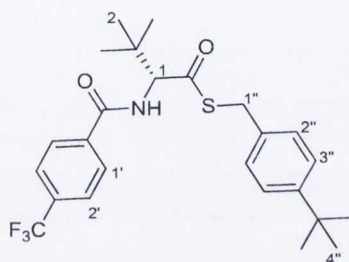
δ_{C} (100 MHz, CDCl_3): 15.5, 30.1, 31.2, 31.4, 33.1, 34.5 (q), 59.1, 123.6 (q, $^1J_{\text{CF}}$ 271.1), 125.6, 125.7 ($^3J_{\text{CF}}$ 3.7), 127.7, 128.5, 133.4 (q), 133.7 (q, $^2J_{\text{CF}}$ 32.6), 136.8 (q), 150.6 (q), 165.9 (q), 199.3 (q)

δ_{F} (375 MHz, CDCl_3): -63.1 (CF_3)

$\nu_{\max}$ (neat)/ cm^{-1} : 3271, 2922, 1682, 1537, 1327, 1261, 1170, 1130, 1071, 1018, 854, 799, 705

HRMS (m/z -ES): Found: 506.1419 ($M^+ + \text{Na}$. $\text{C}_{24}\text{H}_{28}\text{NO}_2\text{F}_3\text{NaS}_2$ Requires: 506.1411)

6.4.10.13 (*R*)-4-*tert*-Butylbenzyl 3,3-dimethyl-2-(4(trifluoromethyl)benzamido)butanethioate (**517**)



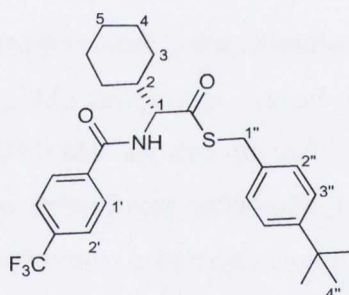
Prepared as per the general procedure K, using the *tert*-leucine-derived azlactone **481** (35.6 mg, 0.125 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 93 μL , 0.50 mmol) and the dihydroquinine-based cinchona alkaloid catalyst **454** (5.6 mg, 0.012 mmol) in freshly distilled CH_2Cl_2 (4.2 mL, 0.03 M). After purification of the crude material by flash chromatography (98:2 $\rightarrow$ 95:5 *n*-hexane/EtOAc), the thioester (*R*)-**517** was obtained as a colourless oil (15.30 mg, 26%). $[\alpha]_{\text{D}}^{22} = +8.6$ (c 0.1, CHCl_3).

The enantiomeric excess of (*R*)-**517** was determined by CSP-HPLC analysis using a Chiralcel ADH column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (major) = 7.91 min; t_{R} (minor) = 8.73 min; 90% *ee*. The absolute configuration of (*R*)-**517** was established by analogy with (*R*)-**461**.

δ_{H} (400 MHz, CDCl_3): 1.08 (s, 9H, 3 CH_3 -2), 1.29 (s, 9H, 3 CH_3 -4''), 4.11 (d, J 13.7, 1H, H-1''a), 4.19 (d, J 13.7, 1H, H-1''b), 4.79 (d, J 9.4, 1H, H-1), 6.66 (d, J 9.4, 1H, NH), 7.20 (d, J 8.2, 2H, H-2''), 7.31 (d, J 8.2, 2H, H-3''), 7.72 (d, J 8.2, 2H, H-2'), 7.90 (d, J 8.2, 2H, H-1')

δ_{C} (100 MHz, CDCl_3):	24.3, 28.7, 30.8, 31.9 (q), 32.7 (q), 63.8, 121.1 (q, $^1J_{\text{CF}}$ 271.2), 123.0, 123.2 ($^3J_{\text{CF}}$ 3.8), 125.0, 125.9, 130.8 (q), 130.9 (q), 130.7 (q, $^2J_{\text{CF}}$ 32.0), 147.9 (q), 163.1 (q), 195.8 (q)
δ_{F} (375 MHz, CDCl_3):	-63.0 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3301, 2965, 1647, 1527, 1500, 1323, 1168, 1129, 1066, 1017, 909, 856, 732
HRMS (m/z -ES):	Found: 488.1852 ($\text{M}^+ + \text{Na}$. $\text{C}_{25}\text{H}_{30}\text{NO}_2\text{F}_3\text{NaS}$ Requires: 488.1847)

6.4.10.14 (R)-4-tert-Butylbenzyl 2-cyclohexyl-2-(4-(trifluoromethyl)benzamido)ethanethioate (518)

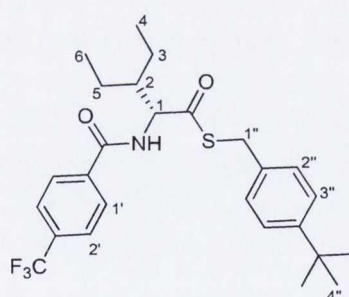


Prepared as per the general procedure K, using the 2-cyclohexylglycine-derived azlactone **482** (34.7 mg, 0.11 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 83 μL , 0.44 mmol) and the dihydroquinine-based cinchona alkaloid catalyst **454** (5.0 mg, 0.011 mmol) in freshly distilled CH_2Cl_2 (3.7 mL, 0.03 M). After purification of the crude material by flash chromatography (95:5 *n*-hexane/EtOAc), the thioester (*R*)-**518** was obtained as a white solid (14.3 mg, 26%). M.p. 113-114 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{22} = -20.0$ (c 0.1, CHCl_3).

The enantiomeric excess of (*R*)-**518** was determined by CSP-HPLC analysis using a Chiralcel ODH column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220$ nm. t_{R} (major) = 5.31 min; t_{R} (minor) = 6.59 min; 89% *ee*. The absolute configuration of (*R*)-**518** was established by analogy with (*R*)-**461**.

δ_{H} (400 MHz, CDCl_3):	1.03-1.24 (m, 5H, H-3a, H-4a, H-5a), 1.28 (s, 9H, 3 CH_3 -4''), 1.58-1.80 (m, 5H, H-3b, H-4b, H-5b), 1.97-2.08 (m, 1H, H-2) 4.13 (app. s, 2H, CH_2 -1''), 4.88 (dd, J 5.1, 9.1, 1H, H-1), 6.59 (d, J 9.1, 1H, NH), 7.19 (d, J 8.4, 2H, H-2''), 7.30 (d, J 8.4, 2H, H-3''), 7.70 (d, J 8.2, 2H, H-2'), 7.90 (d, J 8.2, 2H, H-1')
δ_{C} (100 MHz, CDCl_3):	25.9, 25.9, 25.9, 27.7, 29.9, 31.3, 33.1, 34.5 (q), 41.5, 63.7, 123.6 (q, $^1J_{\text{CF}}$ 271.2), 125.6, 125.7 ($^3J_{\text{CF}}$ 3.8), 127.6, 128.5, 133.4 (q), 133.5 (q, $^2J_{\text{CF}}$ 32.6), 137.2 (q), 150.5 (q), 165.9 (q), 199.2 (q)
δ_{F} (375 MHz, CDCl_3):	-63.0 (CF_3)
ν_{max} (neat)/ cm^{-1} :	3400, 2931, 1672, 1655, 1521, 1485, 1323, 1269, 1164, 1128, 1066, 1017, 856, 772, 700
HRMS (m/z -ES):	Found: 514.1995 ($\text{M}^+ + \text{Na}$. $\text{C}_{27}\text{H}_{32}\text{NO}_2\text{F}_3\text{NaS}$ Requires: 514.2004)

6.4.10.15 (R)-4-tert-Butylbenzyl 3-ethyl-2-(4-(trifluoromethyl)benzamido) pentanethioate (519)



Prepared as per the general procedure K, using the 3-pentylglycine-derived azlactone **483** (33.1 mg, 0.11 mmol), 4-*tert*-butyl benzyl mercaptan (**337**, 83 μL , 0.44 mmol) and the dihydroquinine-based cinchona alkaloid catalyst **454** (9.9 mg, 0.022 mmol) in freshly distilled CH_2Cl_2 (2.2 mL, 0.05M). After purification of the crude material by flash chromatography (95:5 *n*-hexane/EtOAc), the thioester (*R*)-**519** was obtained as a white solid (27.7 mg, 51%). M.p. 60-62 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{22} = -6.11$ (*c* 0.2, CHCl_3).

The enantiomeric excess of (*R*)-**519** was determined by CSP-HPLC analysis using a Chiralcel ADH column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; λ = 220 nm. t_R (major) = 7.49 min; t_R (minor) = 9.37 min; 90% *ee*. The absolute configuration of (*R*)-**519** was established by analogy with (*R*)-**461**.

δ_H (400 MHz, $CDCl_3$): 0.92 (app. t, 3H, CH_3 -4), 1.00 (app. t, 3H, CH_3 -6), 1.18-1.32 (m, 11H, H-3a, H-5a, 3 CH_3 -4''), 1.37-1.55 (m, 2H, H-3b, H-5b) 1.91-2.03 (m, 1H, H-2), 4.13 (app. s, 2H, CH_2 -1''), 5.12 (dd, J 3.8, 9.4, 1H, H-1), 6.49 (d, J 9.4, 1H, NH), 7.19 (d, J 8.3, 2H, H-2''), 7.30 (d, J 8.3, 2H, H-3''), 7.71 (d, J 8.2, 2H, H-2'), 7.90 (d, J 8.2, 2H, H-1')

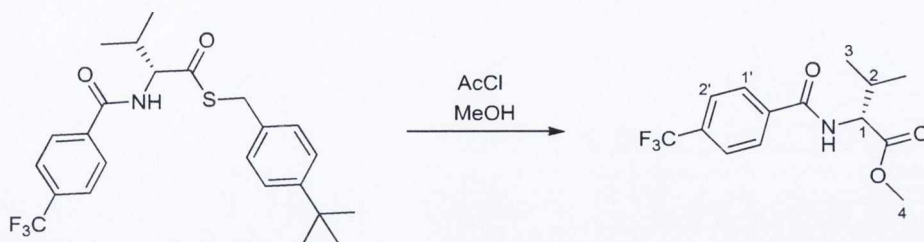
δ_C (100 MHz, $CDCl_3$): 11.8, 11.9, 22.4, 23.0, 31.3, 33.1, 34.5 (q), 45.0, 61.0, 123.6 (q, $^1J_{CF}$ 271.9), 125.6, 125.8 ($^3J_{CF}$ 3.7), 127.6, 128.5, 133.5 (q), 133.6 (q, $^2J_{CF}$ 34.0), 137.3 (q), 150.5 (q), 166.1 (q), 200.1 (q)

δ_F (375 MHz, $CDCl_3$): -63.0 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3284, 2965, 1676, 1641, 1535, 1322, 1166, 1130, 1066, 1017, 857, 839, 770, 697

HRMS (m/z -ES): Found: 502.1999 ($M^+ + Na$. $C_{26}H_{32}NO_2F_3NaS$ Requires: 11502.2004)

6.4.10.16 (*R*)-Methyl-2-(4-(trifluoromethyl)benzamido)-3-methylbutanoate (**522**)



A reaction vessel containing a stirring bar was flushed with Ar, charged with the dihydroquinine-based catalyst **454** (8.7 mg, 0.019 mmol) and valine-derived azlactone **459** (52.4 mg, 0.19 mmol), before being closed with a suitable cap. Freshly distilled CH_2Cl_2 (1.0 mL, 0.2 M) was injected *via* syringe. The vial was then introduced in the cooling machine set up at $-30\text{ }^\circ\text{C}$ and the reaction mixture was allowed to reach this temperature. Finally, *tert*-butylbenzylmercaptan (**337**, 72 μL , 0.012 mmol) was added dropwise *via* syringe. The resulting solution was stirred at $-30\text{ }^\circ\text{C}$ for 3 d and the crude material was directly purified by flash chromatography (90:10 *n*-hexane/EtOAc) to afford (*R*)-**461** as a colourless oil (73 mg, 84%, 70% *ee*). The obtained product was dissolved in anhydrous MeOH (2.0 mL) and acetyl chloride (22 μL , 0.32 mmol) was added to it at room temperature. The reaction mixture was stirred for 8 d and was then concentrated *in vacuo*. The obtained crude material was purified by column chromatography (95:5 $\rightarrow$ 85:15 *n*-hexane/EtOAc). The *N*-protected compound (*R*)-**522** was obtained as a white solid (18 mg, 49%). M. p. $61\text{--}64\text{ }^\circ\text{C}$.

The enantiomeric excess of (*R*)-**522** was determined by CSP-HPLC analysis using a Chiralcel ODH column (4.6 mm x 25 cm); 90:10 *n*-hexane/IPA; 1.0 mL/min; $\lambda = 220\text{ nm}$. t_{R} (major) = 5.67 min; t_{R} (minor) = 8.58 min; 70% *ee*. The absolute configuration of (*R*)-**522** was established by analogy with the HPLC data of (*S*)-**522** and racemic-**522**.

δ_{H} (400 MHz, CDCl_3): 1.00 (d, *J* 7.0, 3H, CH_3 -3), 1.02 (d, *J* 7.0, 3H, CH_3 -3), 2.30 (m, 1H, H-2), 3.79 (s, 3H, CH_3 -4), 4.78 (dd, *J* 4.8, 8.4, 1H, H-1), 6.67 (d, *J* 8.4, 1H, NH), 7.72 (d, *J* 8.2, 2H, H-2'), 7.92 (d, *J* 8.2, 2H, H-1')

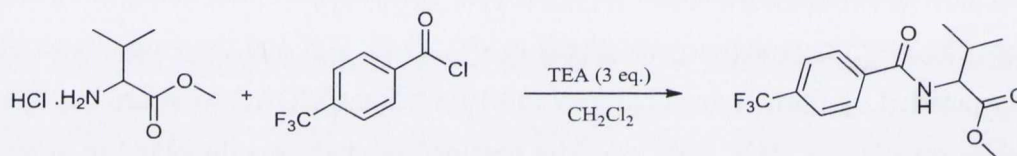
δ_C (150 MHz, $CDCl_3$): 18.0, 19.0, 31.7, 52.4, 57.6, 123.7 (q, $^1J_{CF}$ 271.1), 125.7 ($^3J_{CF}$ 3.8), 127.6, 133.5 (q, $^2J_{CF}$ 32.6), 137.4 (q), 166.0 (q), 172.5 (q)

δ_F (375 MHz, $CDCl_3$): -63.0 (CF_3)

ν_{max} (neat)/ cm^{-1} : 3255, 2970, 1745, 1634, 1547, 1323, 1156, 1133, 1119, 1080, 1014, 860, 781, 746, 673

HRMS (m/z -ES): Found: 302.1010 ($M^+ - H$, $C_{14}H_{15}NO_3F_3$ Requires: 302.1004)

6.4.10.17 (S)- and racemic-methyl-2-(4-(trifluoromethyl)benzamido)-3-methylbutanoate (**522**)



A 50 mL round bottom flask was charged with MeOH (15.0 mL), fitted with a septum under an Ar atmosphere and cooled to 0 °C. Thionyl chloride (1.9 mL, 25.62 mmol, 3.0 eq.) was slowly added *via* syringe over 5 min. The obtained solution was stirred for 10 min and L- (or D,L-)valine (1.00 g, 8.54 mmol, 1.0 eq.) was added (for the synthesis of (S)-(**522**) or racemic-(**522**) respectively). The mixture was allowed to reach ambient temperature, stirred for 1 h and was then heated at reflux temperature overnight. The crude material was purified by distillation and the resulting C-protected hydrochloride salt amino acid was obtained quantitatively as a solid. This salt (576 mg, 3.44 mmol, 1.5 eq.) was, without further purification, added to a 50 mL round bottom flask filled with an argon atmosphere and fitted with a septum. Freshly distilled CH_2Cl_2 (7.0 mL) was added *via* syringe and the obtained solution was cooled to 0 °C. NEt_3 (1.4 mL, 10.32 mmol, 3.0 eq.) was then slowly injected into the reaction followed by 4-(trifluoromethyl)benzoyl chloride (0.34 mL, 2.29 mmol, 1.0 eq.). The reaction was allowed to warm to room temperature and was stirred overnight. The obtained solution was washed with a solution of HCl (2 M, 2 x 10.0 mL) and then NaOH (15% aqueous solution, 2 x 10.0 mL). The organic layer was dried over $MgSO_4$ and was concentrated *in vacuo*. The desired N-protected compound (S)-**522** (or racemic **522**) was obtained as a white solid (2.20 g, 84%).

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Appendix

Appendix 1: X-ray crystal structure data for compound 403 (obtained by Thomas McCabe)

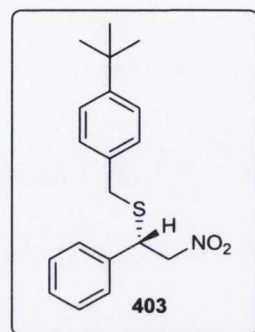
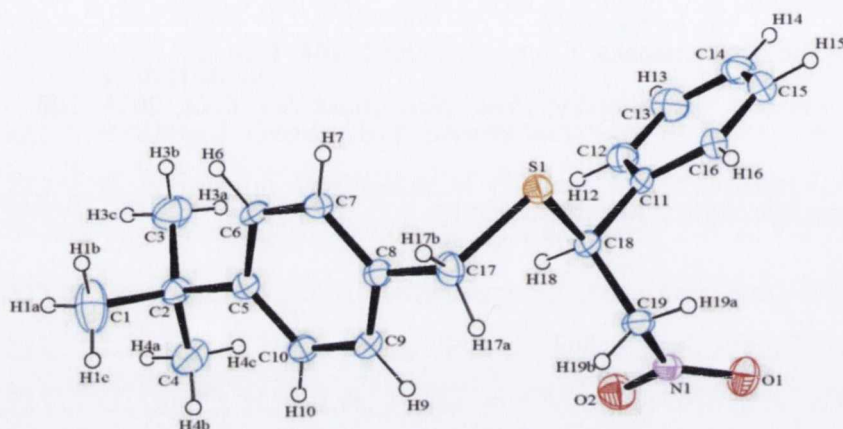


Table 1. Crystal data and structure refinement for compound 403 (cap500)

Identification code	cap500	
Empirical formula	C ₁₉ H ₂₃ N O ₂ S	
Formula weight	329.44	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.4220(17) Å	α = 90°.
	b = 10.230(2) Å	β = 90°.
	c = 20.787(4) Å	γ = 90°.
Volume	1790.9(6) Å ³	
Z	4	
Density (calculated)	1.222 Mg/m ³	
Absorption coefficient	0.190 mm ⁻¹	
F(000)	704	
Crystal size	0.4 x 0.4 x 0.2 mm ³	
Theta range for data collection	2.61 to 24.99°.	
Index ranges	-10 ≤ h ≤ 9, -8 ≤ k ≤ 12, -17 ≤ l ≤ 24	
Reflections collected	8407	
Independent reflections	3084 [R(int) = 0.0718]	

Completeness to theta = 24.99°	98.4 %
Absorption correction	Sadabs
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3084 / 0 / 211
Goodness-of-fit on F ²	1.156
Final R indices [I>2sigma(I)]	R1 = 0.0639, wR2 = 0.1937
R indices (all data)	R1 = 0.0855, wR2 = 0.2624
Absolute structure parameter	-0.22(19)
Largest diff. peak and hole	0.660 and -0.654 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound 403. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

S(1)	3633(2)	3310(1)	2069(1)	38(1)
N(1)	1999(6)	-374(4)	1684(2)	39(1)
C(19)	2647(6)	756(5)	2062(3)	39(1)
C(18)	3035(6)	1881(4)	1599(2)	33(1)
C(17)	1751(6)	3798(5)	2428(2)	39(1)
C(2)	-3037(7)	6218(5)	738(2)	38(1)
C(6)	-328(6)	6183(5)	1322(2)	35(1)
C(11)	4379(6)	1551(4)	1157(2)	32(1)
C(7)	796(6)	5629(5)	1707(2)	36(1)
C(8)	562(6)	4378(4)	1966(2)	32(1)
C(12)	4167(7)	1612(5)	486(3)	43(1)
O(2)	791(5)	-213(5)	1380(2)	59(1)
O(1)	2718(6)	-1423(4)	1707(2)	62(1)
C(9)	-832(7)	3719(5)	1800(2)	37(1)
C(16)	5870(6)	1174(5)	1391(3)	43(1)
C(10)	-1971(6)	4294(5)	1411(2)	36(1)
C(5)	-1763(6)	5538(5)	1164(2)	36(1)
C(15)	7102(7)	873(6)	978(3)	54(2)
C(14)	6846(8)	916(6)	321(3)	55(2)
C(4)	-4285(8)	5267(7)	496(3)	60(2)
C(1)	-3836(10)	7286(8)	1156(4)	77(2)
C(3)	-2241(9)	6834(8)	152(3)	66(2)
C(13)	5382(9)	1287(6)	76(3)	56(2)

Table 3. Bond lengths [Å] and angles [°] for compound 403

S(1)-C(17)	1.822(5)
S(1)-C(18)	1.829(5)
N(1)-O(2)	1.209(6)
N(1)-O(1)	1.234(6)
N(1)-C(19)	1.499(7)
C(19)-C(18)	1.535(7)
C(18)-C(11)	1.497(7)
C(17)-C(8)	1.510(7)
C(2)-C(4)	1.518(8)
C(2)-C(3)	1.528(8)
C(2)-C(1)	1.550(9)
C(2)-C(5)	1.556(7)
C(6)-C(7)	1.363(7)
C(6)-C(5)	1.416(7)
C(11)-C(16)	1.401(7)
C(11)-C(12)	1.407(7)
C(7)-C(8)	1.402(7)
C(8)-C(9)	1.397(7)
C(12)-C(13)	1.372(8)
C(9)-C(10)	1.386(7)
C(16)-C(15)	1.381(8)
C(10)-C(5)	1.383(7)
C(15)-C(14)	1.384(10)
C(14)-C(13)	1.386(10)
C(17)-S(1)-C(18)	101.4(2)
O(2)-N(1)-O(1)	123.5(5)
O(2)-N(1)-C(19)	118.4(5)
O(1)-N(1)-C(19)	118.1(5)
N(1)-C(19)-C(18)	109.1(4)
C(11)-C(18)-C(19)	112.1(4)
C(11)-C(18)-S(1)	107.5(3)
C(19)-C(18)-S(1)	108.9(3)
C(8)-C(17)-S(1)	115.1(3)
C(4)-C(2)-C(3)	107.7(5)
C(4)-C(2)-C(1)	109.7(6)
C(3)-C(2)-C(1)	110.3(6)
C(4)-C(2)-C(5)	112.3(4)

C(3)-C(2)-C(5)	109.6(5)
C(1)-C(2)-C(5)	107.2(4)
C(7)-C(6)-C(5)	122.3(4)
C(16)-C(11)-C(12)	118.0(5)
C(16)-C(11)-C(18)	121.9(5)
C(12)-C(11)-C(18)	120.2(4)
C(6)-C(7)-C(8)	120.5(5)
C(9)-C(8)-C(7)	117.6(5)
C(9)-C(8)-C(17)	121.7(4)
C(7)-C(8)-C(17)	120.6(5)
C(13)-C(12)-C(11)	120.7(5)
C(10)-C(9)-C(8)	121.4(5)
C(15)-C(16)-C(11)	121.3(5)
C(5)-C(10)-C(9)	121.3(5)
C(10)-C(5)-C(6)	116.8(5)
C(10)-C(5)-C(2)	122.4(5)
C(6)-C(5)-C(2)	120.8(4)
C(16)-C(15)-C(14)	119.3(6)
C(15)-C(14)-C(13)	120.6(5)
C(12)-C(13)-C(14)	120.1(6)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound 403. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
S(1)	30(1)	30(1)	54(1)	-4(1)	0(1)	-3(1)
N(1)	37(2)	33(2)	47(2)	1(2)	11(2)	-3(2)
C(19)	40(3)	34(2)	42(2)	1(2)	12(2)	-7(2)
C(18)	30(2)	25(2)	45(2)	2(2)	-2(2)	-2(2)
C(17)	40(3)	35(2)	41(2)	-7(2)	4(2)	5(2)
C(2)	37(3)	34(2)	42(2)	2(2)	-5(2)	-6(2)
C(6)	37(3)	21(2)	47(2)	5(2)	1(2)	-8(2)
C(11)	30(2)	19(2)	47(3)	2(2)	0(2)	0(2)
C(7)	31(3)	30(2)	46(3)	-1(2)	6(2)	-6(2)
C(8)	37(3)	26(2)	31(2)	-5(2)	6(2)	-2(2)
C(12)	44(3)	39(3)	45(3)	-2(2)	0(2)	-5(2)
O(2)	44(2)	58(3)	76(3)	-9(2)	-11(2)	-11(2)
O(1)	71(3)	34(2)	79(3)	-8(2)	9(3)	8(2)
C(9)	41(3)	25(2)	46(2)	2(2)	2(2)	-3(2)
C(16)	33(3)	38(3)	58(3)	9(2)	3(2)	6(2)
C(10)	35(3)	30(2)	41(2)	-3(2)	-1(2)	-5(2)
C(5)	34(3)	31(2)	44(2)	2(2)	0(2)	-2(2)
C(15)	34(3)	41(3)	86(4)	8(3)	6(3)	4(2)
C(14)	50(3)	41(3)	75(4)	-5(3)	29(3)	-3(3)
C(4)	58(4)	49(3)	72(4)	11(3)	-24(3)	-9(3)
C(1)	76(5)	73(5)	82(5)	-19(4)	-32(4)	32(4)
C(3)	63(4)	64(4)	71(4)	29(3)	-11(3)	-7(4)
C(13)	60(4)	54(4)	54(3)	-15(3)	10(3)	-9(3)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound 403.

	x	y	z	U(eq)
H(19A)	3600	489	2289	46
H(19B)	1871	1041	2376	46
H(18)	2090	2096	1345	40
H(17A)	1276	3038	2631	46
H(17B)	1964	4433	2764	46
H(6)	-145	7015	1157	42
H(7)	1724	6084	1799	43
H(12)	3195	1876	319	51
H(9)	-998	2876	1954	45
H(16)	6034	1125	1833	52
H(10)	-2894	3835	1314	43
H(15)	8093	644	1140	64
H(14)	7663	694	41	66
H(4A)	-5059	5731	245	90
H(4B)	-4798	4857	856	90
H(4C)	-3787	4612	234	90
H(1A)	-4572	7774	898	115
H(1B)	-3039	7864	1323	115
H(1C)	-4394	6881	1506	115
H(3A)	-1818	6158	-119	99
H(3B)	-1396	7397	290	99
H(3C)	-3008	7334	-85	99
H(13)	5223	1315	-366	68

Table 6. Torsion angles [°] for compound 403

O(2)-N(1)-C(19)-C(18)	-60.7(6)
O(1)-N(1)-C(19)-C(18)	120.1(5)
N(1)-C(19)-C(18)-C(11)	-66.9(6)
N(1)-C(19)-C(18)-S(1)	174.3(3)
C(17)-S(1)-C(18)-C(11)	167.3(3)
C(17)-S(1)-C(18)-C(19)	-71.1(4)
C(18)-S(1)-C(17)-C(8)	-70.7(4)
C(19)-C(18)-C(11)-C(16)	-56.8(6)
S(1)-C(18)-C(11)-C(16)	62.8(5)
C(19)-C(18)-C(11)-C(12)	123.2(5)
S(1)-C(18)-C(11)-C(12)	-117.3(4)
C(5)-C(6)-C(7)-C(8)	-0.1(7)
C(6)-C(7)-C(8)-C(9)	1.7(7)
C(6)-C(7)-C(8)-C(17)	-175.8(4)
S(1)-C(17)-C(8)-C(9)	110.9(5)
S(1)-C(17)-C(8)-C(7)	-71.7(5)
C(16)-C(11)-C(12)-C(13)	1.2(8)
C(18)-C(11)-C(12)-C(13)	-178.7(5)
C(7)-C(8)-C(9)-C(10)	-2.1(7)
C(17)-C(8)-C(9)-C(10)	175.4(4)
C(12)-C(11)-C(16)-C(15)	0.1(8)
C(18)-C(11)-C(16)-C(15)	-179.9(5)
C(8)-C(9)-C(10)-C(5)	0.9(8)
C(9)-C(10)-C(5)-C(6)	0.7(7)
C(9)-C(10)-C(5)-C(2)	-178.7(4)
C(7)-C(6)-C(5)-C(10)	-1.1(7)
C(7)-C(6)-C(5)-C(2)	178.3(4)
C(4)-C(2)-C(5)-C(10)	-14.2(7)
C(3)-C(2)-C(5)-C(10)	-133.9(6)
C(1)-C(2)-C(5)-C(10)	106.3(6)
C(4)-C(2)-C(5)-C(6)	166.4(5)
C(3)-C(2)-C(5)-C(6)	46.7(7)
C(1)-C(2)-C(5)-C(6)	-73.0(7)
C(11)-C(16)-C(15)-C(14)	-1.5(9)
C(16)-C(15)-C(14)-C(13)	1.5(9)
C(11)-C(12)-C(13)-C(14)	-1.2(9)
C(15)-C(14)-C(13)-C(12)	-0.2(9)

Table 7. Hydrogen bonds for compound 403 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
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Appendix 2: X-ray crystal structure data for compound 421 (obtained by Thomas McCabe)

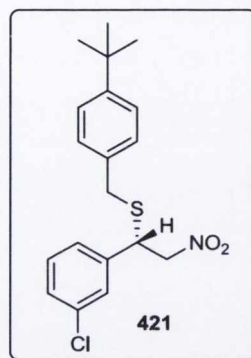
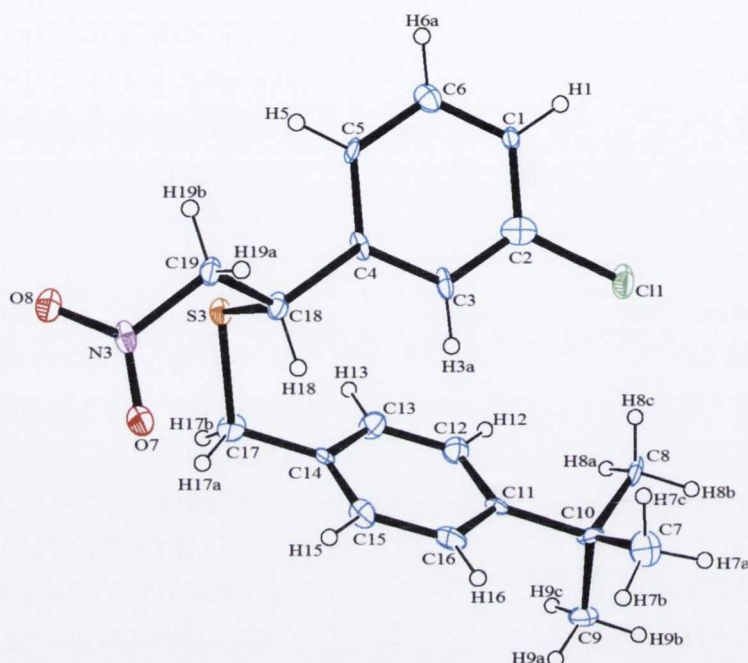


Table 1. Crystal data and structure refinement for compound 421 (cap565)

Identification code	cap565	
Empirical formula	C ₁₉ H ₂₂ Cl N O ₂ S	
Formula weight	363.89	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 11.758(2) Å	α = 90.00(3)°.
	b = 7.5790(15) Å	β = 97.24(3)°.
	c = 20.521(4) Å	γ = 90.00(3)°.
Volume	1814.2(6) Å ³	
Z	4	
Density (calculated)	1.332 Mg/m ³	
Absorption coefficient	0.337 mm ⁻¹	
F(000)	768	
Crystal size	0.70 x 0.35 x 0.15 mm ³	
Theta range for data collection	1.00 to 24.99°.	

Index ranges	-13 < = h < = 10, -9 < = k < = 9, -
24 < = l < = 24	
Reflections collected	13869
Independent reflections	9663 [R(int) = 0.0574]
Completeness to theta = 24.99°	94.5 %
Absorption correction	Sadabs
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9663 / 3 / 877
Goodness-of-fit on F ²	1.095
Final R indices [I > 2sigma(I)]	R1 = 0.0705, wR2 = 0.2288
R indices (all data)	R1 = 0.1001, wR2 = 0.2915
Absolute structure parameter	0.04(10)
Largest diff. peak and hole	0.624 and -0.726 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound 421. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S(1)	4013(1)	943(2)	3053(1)	21(1)
S(3)	-990(2)	947(2)	3053(1)	23(1)
S(4)	3127(1)	5943(2)	11083(1)	22(1)
S(2)	8123(1)	5946(2)	11086(1)	21(1)
Cl(4)	2503(2)	2250(2)	8402(1)	33(1)
Cl(3)	7501(2)	2252(2)	8402(1)	36(1)
Cl(2)	4628(2)	-2745(2)	5733(1)	32(1)
Cl(1)	-361(2)	-2752(2)	5740(1)	36(1)
C(57)	9197(7)	1403(10)	9358(4)	29(2)
C(37)	1947(7)	7485(9)	10825(3)	24(2)
C(49)	3026(6)	-2892(9)	3597(4)	22(2)
C(24)	804(7)	7098(11)	8751(4)	37(2)
C(52)	4720(6)	-1181(8)	3286(3)	15(1)
C(2)	-965(7)	-2799(11)	4933(4)	34(2)
C(30)	3037(6)	2908(8)	10353(4)	21(1)
C(65)	7429(6)	3837(9)	10868(3)	23(2)
C(39)	4890(6)	2889(9)	4503(3)	21(2)
C(31)	4091(6)	2073(9)	10516(4)	22(2)
C(36)	2397(7)	2706(9)	11473(3)	26(2)

C(38)	5619(7)	2319(9)	4051(4)	27(2)
C(46)	4006(7)	-2778(8)	4914(3)	19(2)
C(26)	329(5)	6829(8)	7988(3)	5(1)
C(12)	301(7)	2747(10)	5182(3)	30(2)
C(17)	185(7)	2455(9)	3328(4)	29(2)
C(21)	1559(6)	7356(8)	10092(3)	14(1)
C(54)	8014(6)	2900(8)	10351(3)	18(1)
C(50)	4115(6)	-2114(8)	3770(3)	21(1)
N(2)	1806(5)	3719(7)	11967(3)	23(1)
O(6)	806(5)	4154(8)	11795(3)	40(2)
C(41)	6340(6)	2023(9)	5411(4)	23(2)
C(10)	1742(6)	1998(10)	6154(3)	23(2)
C(60)	6544(7)	7354(11)	10091(4)	34(2)
C(4)	-890(6)	-2082(8)	3802(3)	17(1)
N(4)	5336(6)	-1272(7)	2177(3)	26(1)
C(35)	2438(6)	3825(8)	10869(3)	18(1)
C(45)	7463(7)	3628(12)	6335(4)	37(2)
O(4)	4778(5)	-906(7)	1639(2)	29(1)
C(53)	4717(7)	-2310(9)	2652(3)	24(2)
C(15)	1661(7)	1676(10)	4266(3)	28(2)
C(11)	1315(5)	2041(9)	5415(3)	17(1)
C(23)	1889(6)	7731(9)	8974(3)	19(2)
C(64)	5106(6)	6490(10)	9185(3)	22(2)
O(3)	6329(5)	-844(8)	2341(3)	34(1)
C(58)	8144(6)	2217(9)	9220(4)	22(2)
C(59)	7563(6)	2949(8)	9701(3)	21(2)
C(34)	3148(6)	2216(10)	9213(3)	23(2)
C(20)	489(6)	6660(11)	9880(4)	33(2)
O(5)	2325(5)	4089(7)	12497(2)	33(1)
C(27)	-328(7)	8596(12)	7807(3)	33(2)
N(1)	6800(5)	3720(7)	11973(3)	21(1)
C(28)	1382(7)	6987(12)	7573(4)	36(2)
O(8)	-212(5)	-900(7)	1644(2)	32(1)
C(61)	7245(7)	7902(10)	9622(4)	30(2)
C(56)	9662(7)	1361(9)	10025(4)	26(2)
N(3)	358(6)	-1296(7)	2176(3)	24(1)
C(62)	6852(7)	7755(10)	8959(4)	32(2)
O(1)	7329(5)	4099(7)	12499(2)	33(1)
C(29)	2585(7)	2935(9)	9696(3)	25(2)
C(47)	2938(7)	-3569(10)	4745(4)	33(2)

C(3)	-406(7)	-2054(9)	4445(3)	23(2)
C(51)	4570(7)	-2052(9)	4430(4)	28(2)
C(1)	-2058(6)	-3568(9)	4773(3)	17(1)
C(16)	2004(7)	1511(11)	4941(4)	33(2)
C(7)	2443(8)	307(11)	6315(5)	41(2)
C(22)	2258(8)	7910(10)	9645(3)	32(2)
C(8)	728(7)	1961(12)	6556(3)	32(2)
C(40)	5264(7)	2778(9)	5161(4)	29(2)
C(43)	6725(7)	1964(10)	6142(4)	26(2)
O(7)	1325(5)	-849(8)	2338(3)	38(1)
C(70)	5194(8)	2431(11)	3313(3)	33(2)
C(19)	-270(6)	-2309(10)	2655(3)	24(2)
C(48)	2454(6)	-3616(9)	4099(4)	24(2)
C(32)	4686(6)	1379(10)	10015(4)	29(2)
C(68)	4691(7)	5332(11)	7818(5)	41(2)
C(63)	5816(6)	7041(8)	8717(3)	13(1)
C(55)	9098(7)	2078(10)	10508(4)	25(2)
C(9)	2461(7)	3625(11)	6318(4)	34(2)
C(42)	7017(6)	1502(10)	4942(4)	26(2)
C(6)	-2553(7)	-3640(10)	4110(4)	28(2)
O(2)	5818(5)	4147(8)	11797(3)	38(1)
C(18)	-261(7)	-1206(9)	3277(3)	24(2)
C(44)	5734(6)	1959(13)	6566(4)	38(2)
C(5)	-1956(6)	-2925(9)	3648(3)	23(2)
C(13)	-125(7)	2897(11)	4492(4)	32(2)
C(67)	7423(7)	2709(9)	11482(3)	25(2)
C(33)	4198(6)	1444(9)	9380(3)	22(2)
C(14)	605(6)	2348(10)	4039(3)	24(2)
C(69)	5448(6)	7212(9)	7975(4)	28(2)
C(66)	6961(9)	7425(12)	10808(5)	48(2)
C(25)	122(6)	6518(11)	9195(4)	34(2)
C(78)	4677(6)	8616(11)	7806(4)	29(2)
C(80)	6661(7)	1633(10)	4290(4)	36(2)
C(77)	6409(6)	6963(12)	7584(3)	31(2)
C(76)	5483(7)	6661(10)	9858(4)	32(2)
C(79)	7450(8)	311(12)	6332(5)	43(2)
C(85)	-332(7)	5320(12)	7812(4)	40(2)

Table 3. Bond lengths [Å] and angles [°] for compound 421

S(1)-C(70)	1.817(8)
S(1)-C(52)	1.847(6)
S(3)-C(17)	1.826(8)
S(3)-C(18)	1.873(7)
S(4)-C(35)	1.826(7)
S(4)-C(37)	1.839(7)
S(2)-C(66)	1.803(10)
S(2)-C(65)	1.824(7)
Cl(4)-C(34)	1.741(7)
Cl(3)-C(58)	1.752(7)
Cl(2)-C(46)	1.747(6)
Cl(1)-C(2)	1.717(9)
C(57)-C(58)	1.380(11)
C(57)-C(56)	1.409(11)
C(37)-C(21)	1.519(9)
C(49)-C(50)	1.414(10)
C(49)-C(48)	1.411(10)
C(24)-C(25)	1.360(12)
C(24)-C(23)	1.386(11)
C(24)-C(26)	1.607(10)
C(52)-C(50)	1.473(9)
C(52)-C(53)	1.558(8)
C(2)-C(3)	1.386(11)
C(2)-C(1)	1.412(11)
C(30)-C(29)	1.386(10)
C(30)-C(31)	1.394(10)
C(30)-C(35)	1.512(9)
C(65)-C(54)	1.513(9)
C(65)-C(67)	1.522(9)
C(39)-C(40)	1.369(10)
C(39)-C(38)	1.408(9)
C(31)-C(32)	1.415(10)
C(36)-N(2)	1.509(8)
C(36)-C(35)	1.508(9)
C(38)-C(80)	1.365(12)
C(38)-C(70)	1.536(10)
C(46)-C(51)	1.376(10)
C(46)-C(47)	1.396(11)

C(26)-C(85)	1.404(10)
C(26)-C(27)	1.567(10)
C(26)-C(28)	1.595(9)
C(12)-C(11)	1.338(11)
C(12)-C(13)	1.445(11)
C(17)-C(14)	1.483(10)
C(21)-C(22)	1.373(10)
C(21)-C(20)	1.383(11)
C(54)-C(59)	1.373(9)
C(54)-C(55)	1.418(10)
C(50)-C(51)	1.393(10)
N(2)-O(5)	1.212(8)
N(2)-O(6)	1.229(8)
C(41)-C(42)	1.382(9)
C(41)-C(40)	1.424(10)
C(41)-C(43)	1.511(10)
C(10)-C(9)	1.509(10)
C(10)-C(8)	1.533(10)
C(10)-C(11)	1.537(9)
C(10)-C(7)	1.537(11)
C(60)-C(76)	1.382(12)
C(60)-C(61)	1.405(11)
C(60)-C(66)	1.493(12)
C(4)-C(3)	1.370(9)
C(4)-C(5)	1.407(10)
C(4)-C(18)	1.533(9)
N(4)-O(3)	1.219(8)
N(4)-O(4)	1.241(8)
N(4)-C(53)	1.509(9)
C(45)-C(43)	1.554(10)
C(15)-C(14)	1.368(11)
C(15)-C(16)	1.399(11)
C(11)-C(16)	1.401(9)
C(23)-C(22)	1.396(9)
C(64)-C(76)	1.401(11)
C(64)-C(63)	1.413(9)
C(58)-C(59)	1.385(9)
C(34)-C(33)	1.370(11)
C(34)-C(29)	1.371(9)
C(20)-C(25)	1.422(12)

N(1)-O(1)	1.209(7)
N(1)-O(2)	1.209(8)
N(1)-C(67)	1.526(8)
O(8)-N(3)	1.243(8)
C(61)-C(62)	1.386(11)
C(56)-C(55)	1.373(10)
N(3)-O(7)	1.192(8)
N(3)-C(19)	1.512(9)
C(62)-C(63)	1.368(10)
C(47)-C(48)	1.375(11)
C(1)-C(6)	1.412(10)
C(43)-C(44)	1.540(10)
C(43)-C(79)	1.538(11)
C(19)-C(18)	1.525(9)
C(32)-C(33)	1.356(11)
C(68)-C(69)	1.689(11)
C(63)-C(69)	1.535(10)
C(42)-C(80)	1.354(12)
C(6)-C(5)	1.360(10)
C(13)-C(14)	1.406(10)
C(69)-C(78)	1.413(10)
C(69)-C(77)	1.478(10)

C(70)-S(1)-C(52)	99.3(4)
C(17)-S(3)-C(18)	99.5(3)
C(35)-S(4)-C(37)	101.2(3)
C(66)-S(2)-C(65)	99.8(4)
C(58)-C(57)-C(56)	116.0(6)
C(21)-C(37)-S(4)	111.4(4)
C(50)-C(49)-C(48)	118.6(7)
C(25)-C(24)-C(23)	119.1(8)
C(25)-C(24)-C(26)	116.7(7)
C(23)-C(24)-C(26)	124.0(7)
C(50)-C(52)-C(53)	110.5(5)
C(50)-C(52)-S(1)	110.7(4)
C(53)-C(52)-S(1)	108.0(4)
C(3)-C(2)-C(1)	120.1(8)
C(3)-C(2)-Cl(1)	120.8(6)
C(1)-C(2)-Cl(1)	119.1(6)
C(29)-C(30)-C(31)	117.3(6)

C(29)-C(30)-C(35)	121.3(6)
C(31)-C(30)-C(35)	121.3(6)
C(54)-C(65)-C(67)	111.5(6)
C(54)-C(65)-S(2)	110.7(5)
C(67)-C(65)-S(2)	109.8(5)
C(40)-C(39)-C(38)	119.0(6)
C(30)-C(31)-C(32)	120.0(7)
N(2)-C(36)-C(35)	109.4(5)
C(80)-C(38)-C(39)	118.2(7)
C(80)-C(38)-C(70)	122.8(7)
C(39)-C(38)-C(70)	119.0(7)
C(51)-C(46)-C(47)	119.6(7)
C(51)-C(46)-Cl(2)	120.5(6)
C(47)-C(46)-Cl(2)	120.0(6)
C(85)-C(26)-C(27)	113.3(7)
C(85)-C(26)-C(28)	111.4(6)
C(27)-C(26)-C(28)	101.6(6)
C(85)-C(26)-C(24)	117.9(6)
C(27)-C(26)-C(24)	102.9(5)
C(28)-C(26)-C(24)	108.2(6)
C(11)-C(12)-C(13)	124.4(6)
C(14)-C(17)-S(3)	114.5(5)
C(22)-C(21)-C(20)	120.2(7)
C(22)-C(21)-C(37)	120.8(7)
C(20)-C(21)-C(37)	119.0(6)
C(59)-C(54)-C(55)	117.3(6)
C(59)-C(54)-C(65)	121.0(6)
C(55)-C(54)-C(65)	121.4(6)
C(51)-C(50)-C(49)	118.9(7)
C(51)-C(50)-C(52)	118.7(6)
C(49)-C(50)-C(52)	122.0(6)
O(5)-N(2)-O(6)	123.4(6)
O(5)-N(2)-C(36)	120.0(6)
O(6)-N(2)-C(36)	116.7(6)
C(42)-C(41)-C(40)	115.3(7)
C(42)-C(41)-C(43)	123.7(7)
C(40)-C(41)-C(43)	120.8(6)
C(9)-C(10)-C(8)	110.3(6)
C(9)-C(10)-C(11)	107.9(6)
C(8)-C(10)-C(11)	110.6(5)

C(9)-C(10)-C(7)	111.3(7)
C(8)-C(10)-C(7)	107.5(7)
C(11)-C(10)-C(7)	109.2(6)
C(76)-C(60)-C(61)	117.2(8)
C(76)-C(60)-C(66)	121.6(8)
C(61)-C(60)-C(66)	121.0(8)
C(3)-C(4)-C(5)	118.2(6)
C(3)-C(4)-C(18)	119.5(6)
C(5)-C(4)-C(18)	122.4(6)
O(3)-N(4)-O(4)	124.5(6)
O(3)-N(4)-C(53)	118.9(6)
O(4)-N(4)-C(53)	116.6(6)
C(36)-C(35)-C(30)	112.5(5)
C(36)-C(35)-S(4)	110.9(5)
C(30)-C(35)-S(4)	110.0(5)
N(4)-C(53)-C(52)	107.7(5)
C(14)-C(15)-C(16)	120.4(6)
C(12)-C(11)-C(16)	115.7(7)
C(12)-C(11)-C(10)	121.8(5)
C(16)-C(11)-C(10)	122.2(6)
C(24)-C(23)-C(22)	121.2(7)
C(76)-C(64)-C(63)	120.2(7)
C(57)-C(58)-C(59)	122.9(7)
C(57)-C(58)-Cl(3)	118.1(5)
C(59)-C(58)-Cl(3)	119.0(5)
C(54)-C(59)-C(58)	121.1(6)
C(33)-C(34)-C(29)	119.4(6)
C(33)-C(34)-Cl(4)	121.1(5)
C(29)-C(34)-Cl(4)	119.5(6)
C(21)-C(20)-C(25)	119.4(6)
O(1)-N(1)-O(2)	124.6(6)
O(1)-N(1)-C(67)	118.2(6)
O(2)-N(1)-C(67)	117.1(6)
C(62)-C(61)-C(60)	119.8(8)
C(55)-C(56)-C(57)	121.9(7)
O(7)-N(3)-O(8)	124.5(6)
O(7)-N(3)-C(19)	119.3(6)
O(8)-N(3)-C(19)	116.0(6)
C(63)-C(62)-C(61)	124.1(7)
C(34)-C(29)-C(30)	122.4(7)

C(48)-C(47)-C(46)	120.0(7)
C(4)-C(3)-C(2)	120.9(7)
C(46)-C(51)-C(50)	121.8(7)
C(6)-C(1)-C(2)	119.5(7)
C(15)-C(16)-C(11)	122.8(7)
C(21)-C(22)-C(23)	119.4(7)
C(39)-C(40)-C(41)	122.7(6)
C(41)-C(43)-C(44)	114.0(6)
C(41)-C(43)-C(79)	111.3(6)
C(44)-C(43)-C(79)	106.8(6)
C(41)-C(43)-C(45)	108.5(6)
C(44)-C(43)-C(45)	107.2(6)
C(79)-C(43)-C(45)	108.8(7)
C(38)-C(70)-S(1)	113.4(5)
N(3)-C(19)-C(18)	108.2(6)
C(47)-C(48)-C(49)	121.1(7)
C(33)-C(32)-C(31)	119.7(6)
C(62)-C(63)-C(64)	116.4(6)
C(62)-C(63)-C(69)	117.0(6)
C(64)-C(63)-C(69)	125.7(6)
C(56)-C(55)-C(54)	120.8(7)
C(80)-C(42)-C(41)	122.3(7)
C(5)-C(6)-C(1)	118.0(7)
C(19)-C(18)-C(4)	113.4(6)
C(19)-C(18)-S(3)	108.5(5)
C(4)-C(18)-S(3)	107.6(5)
C(6)-C(5)-C(4)	123.3(6)
C(14)-C(13)-C(12)	117.3(7)
C(65)-C(67)-N(1)	108.5(5)
C(34)-C(33)-C(32)	120.9(6)
C(15)-C(14)-C(13)	119.3(7)
C(15)-C(14)-C(17)	122.1(6)
C(13)-C(14)-C(17)	118.6(7)
C(78)-C(69)-C(77)	118.3(7)
C(78)-C(69)-C(63)	113.5(6)
C(77)-C(69)-C(63)	112.9(6)
C(78)-C(69)-C(68)	106.4(7)
C(77)-C(69)-C(68)	102.1(6)
C(63)-C(69)-C(68)	101.1(6)
C(60)-C(66)-S(2)	115.5(6)

C(24)-C(25)-C(20)	120.5(7)
C(38)-C(80)-C(42)	122.4(7)
C(60)-C(76)-C(64)	122.3(7)

Table 4. Anisotropic displacement parameters (Å²x 10³) for compound 421. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
S(1)	34(1)	16(1)	15(1)	1(1)	6(1)	3(1)
S(3)	35(1)	16(1)	19(1)	0(1)	4(1)	0(1)
S(4)	34(1)	16(1)	15(1)	-3(1)	6(1)	-4(1)
S(2)	34(1)	14(1)	16(1)	2(1)	3(1)	-3(1)
Cl(4)	59(1)	30(1)	11(1)	-3(1)	7(1)	-1(1)
Cl(3)	55(1)	33(1)	19(1)	-2(1)	6(1)	2(1)
Cl(2)	55(1)	28(1)	14(1)	2(1)	10(1)	-3(1)
Cl(1)	57(1)	33(1)	16(1)	2(1)	1(1)	-4(1)
C(57)	51(5)	16(4)	21(4)	-4(3)	15(3)	-2(3)
C(37)	51(5)	7(3)	15(3)	11(2)	9(3)	15(3)
C(49)	28(4)	16(3)	23(4)	-5(3)	3(3)	-1(3)
C(24)	34(5)	26(4)	48(5)	6(4)	-10(4)	-8(3)
C(52)	26(4)	12(3)	6(3)	-1(2)	-2(2)	8(2)
C(2)	29(4)	25(4)	48(5)	-6(4)	6(4)	3(3)
C(30)	21(4)	9(3)	32(4)	6(3)	-4(3)	-5(3)
C(65)	30(4)	27(4)	13(3)	-5(3)	8(3)	-6(3)
C(39)	13(4)	24(4)	26(4)	-4(3)	0(3)	14(3)
C(31)	29(4)	15(3)	20(3)	-3(3)	0(3)	1(3)
C(36)	49(5)	17(3)	14(3)	-4(3)	10(3)	-3(3)
C(38)	52(5)	12(3)	20(4)	-11(3)	16(3)	-13(3)
C(46)	49(5)	9(3)	0(3)	-3(2)	6(3)	-4(3)
C(26)	10(3)	0(3)	1(2)	0(2)	-11(2)	-3(2)
C(12)	42(5)	31(4)	21(4)	-21(3)	19(3)	-2(3)
C(17)	45(5)	11(4)	30(4)	-9(3)	-1(3)	-8(3)
C(21)	17(4)	7(3)	20(3)	4(2)	12(3)	13(2)
C(54)	29(4)	16(3)	7(3)	0(2)	-4(3)	1(3)
C(50)	29(4)	10(3)	21(3)	3(3)	-8(3)	-1(3)
N(2)	34(4)	18(3)	19(3)	6(2)	4(3)	-2(2)

O(6)	42(4)	52(4)	28(3)	-5(3)	9(3)	7(3)
C(41)	23(4)	17(4)	28(4)	-5(3)	4(3)	-6(3)
C(10)	16(4)	30(4)	22(3)	-8(3)	-1(3)	-7(3)
C(60)	37(5)	27(4)	36(4)	0(3)	0(4)	6(3)
C(4)	29(4)	12(3)	13(3)	-2(2)	15(3)	7(3)
N(4)	45(4)	16(3)	20(3)	-3(2)	12(3)	5(3)
C(35)	22(4)	18(3)	13(3)	6(3)	6(3)	1(3)
C(45)	41(5)	42(5)	26(4)	0(3)	-1(3)	-13(4)
O(4)	42(3)	28(3)	15(2)	10(2)	-3(2)	11(2)
C(53)	42(5)	18(3)	13(3)	3(3)	6(3)	1(3)
C(15)	43(5)	26(4)	19(3)	-13(3)	13(3)	-9(3)
C(11)	14(4)	17(3)	21(3)	-4(3)	10(3)	-4(3)
C(23)	24(4)	28(4)	8(3)	1(3)	12(3)	-5(3)
C(64)	16(4)	32(4)	18(3)	5(3)	6(3)	10(3)
O(3)	24(3)	49(4)	30(3)	3(3)	4(2)	-2(2)
C(58)	22(4)	14(3)	29(4)	-1(3)	0(3)	2(3)
C(59)	37(4)	9(3)	18(3)	0(3)	4(3)	7(3)
C(34)	35(4)	28(4)	7(3)	1(3)	8(3)	-9(3)
C(20)	25(4)	45(5)	35(4)	26(4)	23(3)	12(3)
O(5)	58(4)	27(3)	15(3)	-2(2)	7(2)	-6(2)
C(27)	36(5)	51(5)	9(3)	11(3)	-4(3)	8(4)
N(1)	29(4)	18(3)	14(3)	1(2)	-2(2)	2(2)
C(28)	34(5)	55(5)	20(4)	-1(4)	5(3)	7(4)
O(8)	39(3)	32(3)	22(3)	1(2)	1(2)	2(2)
C(61)	35(4)	23(4)	34(4)	-8(3)	15(3)	-7(3)
C(56)	29(4)	18(4)	31(4)	6(3)	5(3)	3(3)
N(3)	44(4)	14(3)	15(3)	-5(2)	12(3)	1(3)
C(62)	23(4)	32(4)	36(4)	11(3)	-13(3)	-9(3)
O(1)	51(4)	28(3)	19(3)	-8(2)	9(2)	-7(2)
C(29)	47(5)	14(3)	17(3)	0(3)	10(3)	-6(3)
C(47)	24(4)	19(4)	53(5)	19(3)	-5(4)	13(3)
C(3)	44(5)	15(3)	11(3)	1(2)	10(3)	1(3)
C(51)	44(5)	10(3)	29(4)	-9(3)	3(3)	-2(3)
C(1)	17(4)	19(3)	15(3)	5(3)	2(3)	1(3)
C(16)	22(4)	38(4)	40(4)	-1(4)	15(3)	-5(3)
C(7)	49(6)	32(5)	43(5)	2(4)	7(4)	8(4)
C(22)	61(6)	19(4)	12(3)	8(3)	-8(3)	-5(3)
C(8)	36(5)	46(5)	11(3)	7(3)	-8(3)	2(4)
C(40)	37(5)	15(4)	34(4)	1(3)	4(3)	9(3)
C(43)	39(5)	21(4)	21(4)	2(3)	12(3)	-12(3)

O(7)	31(3)	55(4)	27(3)	10(3)	5(2)	-6(3)
C(70)	56(5)	38(5)	8(3)	5(3)	12(3)	-17(4)
C(19)	30(4)	26(4)	15(3)	1(3)	0(3)	0(3)
C(48)	5(4)	29(4)	37(4)	5(3)	4(3)	1(3)
C(32)	5(4)	28(4)	52(5)	-7(4)	-10(3)	7(3)
C(68)	27(5)	36(5)	58(6)	-8(4)	1(4)	-1(3)
C(63)	27(4)	11(3)	0(2)	3(2)	3(2)	17(3)
C(55)	34(4)	23(4)	18(3)	5(3)	-4(3)	-3(3)
C(9)	28(4)	40(5)	34(4)	-4(4)	0(3)	-15(3)
C(42)	16(4)	26(4)	39(4)	-14(3)	10(3)	0(3)
C(6)	34(5)	21(4)	29(4)	-1(3)	10(3)	-1(3)
O(2)	45(4)	43(4)	26(3)	-5(3)	3(3)	1(3)
C(18)	36(4)	16(3)	18(3)	1(3)	-2(3)	-2(3)
C(44)	16(4)	60(6)	38(5)	12(4)	1(3)	-3(4)
C(5)	35(4)	23(4)	8(3)	0(3)	-6(3)	-7(3)
C(13)	31(5)	36(5)	29(4)	-4(3)	0(3)	0(3)
C(67)	46(5)	10(3)	22(3)	0(3)	13(3)	3(3)
C(33)	24(4)	16(3)	29(4)	-4(3)	11(3)	2(3)
C(14)	25(4)	29(4)	19(3)	4(3)	4(3)	-18(3)
C(69)	20(4)	6(3)	60(5)	-8(3)	11(3)	-26(3)
C(66)	77(7)	29(5)	43(5)	-11(4)	26(5)	-2(4)
C(25)	5(4)	44(5)	53(5)	11(4)	-2(3)	-2(3)
C(78)	20(4)	39(4)	27(4)	0(3)	-2(3)	18(3)
C(80)	40(5)	21(4)	53(5)	-7(4)	26(4)	-4(3)
C(77)	13(4)	61(5)	21(4)	-6(4)	7(3)	5(3)
C(76)	46(5)	26(4)	29(4)	6(3)	24(4)	10(3)
C(79)	46(6)	39(5)	43(5)	15(4)	3(4)	8(4)
C(85)	29(5)	45(5)	41(5)	-8(4)	-13(4)	-25(4)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound 421

	x	y	z	U(eq)
H(57)	9576	911	9031	34
H(37A)	1306	7224	11064	29
H(37B)	2198	8680	10933	29
H(49)	2693	-2925	3161	27
H(52)	5514	-960	3477	18
H(65)	6632	4068	10686	27
H(39)	4166	3334	4357	26
H(31)	4403	1972	10954	26
H(36A)	1982	1622	11355	31
H(36B)	3169	2399	11662	31
H(12)	-160	3169	5484	36
H(17A)	819	2209	3082	35
H(17B)	-68	3653	3226	35
H(35)	1647	4061	10677	21
H(45A)	7018	4668	6219	55
H(45B)	8126	3623	6105	55
H(45C)	7702	3622	6800	55
H(53A)	5103	-3425	2755	29
H(53B)	3936	-2551	2460	29
H(15)	2153	1326	3969	34
H(23)	2381	8042	8672	23
H(64)	4388	6013	9047	26
H(59)	6855	3484	9581	25
H(20)	13	6289	10182	40
H(27A)	-989	8664	8037	49
H(27B)	-567	8631	7342	49
H(27C)	170	9577	7930	49
H(28A)	1107	6921	7113	54
H(28B)	1911	6039	7689	54
H(28C)	1764	8095	7666	54
H(61)	7970	8362	9757	36
H(56)	10373	833	10142	31
H(62)	7322	8167	8660	38

H(29)	1874	3460	9577	30
H(47)	2553	-4064	5069	40
H(3A)	307	-1528	4555	27
H(51)	5274	-1505	4547	33
H(1)	-2449	-4023	5102	20
H(16)	2721	1029	5081	39
H(7A)	2626	197	6782	62
H(7B)	3138	364	6116	62
H(7C)	2002	-697	6147	62
H(22)	2971	8401	9787	38
H(8A)	276	3009	6468	48
H(8B)	1010	1907	7015	48
H(8C)	263	942	6436	48
H(40)	4796	3214	5457	35
H(70A)	5827	2160	3068	40
H(70B)	4952	3631	3206	40
H(19A)	104	-3433	2758	29
H(19B)	-1053	-2534	2463	29
H(48)	1738	-4133	3992	28
H(32)	5408	881	10121	35
H(68A)	4465	5225	7354	61
H(68B)	4020	5364	8041	61
H(68C)	5157	4340	7971	61
H(55)	9429	2023	10944	31
H(9A)	3023	3725	6019	51
H(9B)	2840	3535	6760	51
H(9C)	1977	4649	6281	51
H(42)	7742	1046	5079	31
H(6A)	-3265	-4161	3992	33
H(18)	536	-978	3461	28
H(44A)	5193	1057	6412	57
H(44B)	5360	3087	6535	57
H(44C)	6032	1729	7015	57
H(5)	-2268	-2998	3210	27
H(13)	-854	3338	4353	39
H(67A)	8203	2455	11672	30
H(67B)	7036	1600	11370	30
H(33)	4582	957	9054	27
H(66A)	6322	7162	11049	57
H(66B)	7207	8622	10919	57

H(25)	-588	6024	9049	41
H(78A)	4392	8547	7347	44
H(78B)	5066	9720	7894	44
H(78C)	4048	8536	8060	44
H(80)	7145	1242	3995	44
H(77A)	6855	8026	7595	47
H(77B)	6112	6693	7138	47
H(77C)	6885	6009	7765	47
H(76)	5002	6295	10158	38
H(79A)	8146	364	6134	64
H(79B)	7025	-723	6180	64
H(79C)	7632	259	6801	64
H(85A)	72	4290	7987	60
H(85B)	-470	5232	7342	60
H(85C)	-1051	5405	7986	60

Table 6. Torsion angles [°] for compound 421.

C(35)-S(4)-C(37)-C(21)	-61.6(6)
C(70)-S(1)-C(52)-C(50)	119.8(5)
C(70)-S(1)-C(52)-C(53)	-119.2(5)
C(66)-S(2)-C(65)-C(54)	116.0(5)
C(66)-S(2)-C(65)-C(67)	-120.5(5)
C(29)-C(30)-C(31)-C(32)	3.4(10)
C(35)-C(30)-C(31)-C(32)	-173.7(7)
C(40)-C(39)-C(38)-C(80)	1.7(10)
C(40)-C(39)-C(38)-C(70)	179.5(7)
C(25)-C(24)-C(26)-C(85)	-34.0(10)
C(23)-C(24)-C(26)-C(85)	140.1(8)
C(25)-C(24)-C(26)-C(27)	91.4(8)
C(23)-C(24)-C(26)-C(27)	-94.5(8)
C(25)-C(24)-C(26)-C(28)	-161.6(7)
C(23)-C(24)-C(26)-C(28)	12.5(10)
C(18)-S(3)-C(17)-C(14)	-60.5(6)
S(4)-C(37)-C(21)-C(22)	-68.5(7)
S(4)-C(37)-C(21)-C(20)	111.2(6)
C(67)-C(65)-C(54)-C(59)	137.6(7)
S(2)-C(65)-C(54)-C(59)	-99.9(7)
C(67)-C(65)-C(54)-C(55)	-48.3(9)
S(2)-C(65)-C(54)-C(55)	74.3(8)
C(48)-C(49)-C(50)-C(51)	-1.6(9)
C(48)-C(49)-C(50)-C(52)	-174.1(6)
C(53)-C(52)-C(50)-C(51)	139.4(6)
S(1)-C(52)-C(50)-C(51)	-101.1(6)
C(53)-C(52)-C(50)-C(49)	-48.1(8)
S(1)-C(52)-C(50)-C(49)	71.4(7)
C(35)-C(36)-N(2)-O(5)	-117.5(7)
C(35)-C(36)-N(2)-O(6)	61.2(8)
N(2)-C(36)-C(35)-C(30)	179.1(6)
N(2)-C(36)-C(35)-S(4)	55.5(7)
C(29)-C(30)-C(35)-C(36)	135.3(7)
C(31)-C(30)-C(35)-C(36)	-47.7(9)
C(29)-C(30)-C(35)-S(4)	-100.6(7)
C(31)-C(30)-C(35)-S(4)	76.4(7)
C(37)-S(4)-C(35)-C(36)	-117.5(5)
C(37)-S(4)-C(35)-C(30)	117.4(5)

O(3)-N(4)-C(53)-C(52)	59.4(7)
O(4)-N(4)-C(53)-C(52)	-120.2(6)
C(50)-C(52)-C(53)-N(4)	179.4(5)
S(1)-C(52)-C(53)-N(4)	58.2(6)
C(13)-C(12)-C(11)-C(16)	3.3(11)
C(13)-C(12)-C(11)-C(10)	177.2(7)
C(9)-C(10)-C(11)-C(12)	-92.8(8)
C(8)-C(10)-C(11)-C(12)	27.9(10)
C(7)-C(10)-C(11)-C(12)	146.0(8)
C(9)-C(10)-C(11)-C(16)	80.6(8)
C(8)-C(10)-C(11)-C(16)	-158.7(7)
C(7)-C(10)-C(11)-C(16)	-40.5(9)
C(25)-C(24)-C(23)-C(22)	-5.0(12)
C(26)-C(24)-C(23)-C(22)	-179.0(7)
C(56)-C(57)-C(58)-C(59)	-0.3(11)
C(56)-C(57)-C(58)-Cl(3)	-178.1(5)
C(55)-C(54)-C(59)-C(58)	0.3(10)
C(65)-C(54)-C(59)-C(58)	174.7(7)
C(57)-C(58)-C(59)-C(54)	0.0(11)
Cl(3)-C(58)-C(59)-C(54)	177.7(5)
C(22)-C(21)-C(20)-C(25)	0.3(10)
C(37)-C(21)-C(20)-C(25)	-179.4(6)
C(76)-C(60)-C(61)-C(62)	0.8(11)
C(66)-C(60)-C(61)-C(62)	177.4(7)
C(58)-C(57)-C(56)-C(55)	0.5(11)
C(60)-C(61)-C(62)-C(63)	-2.3(12)
C(33)-C(34)-C(29)-C(30)	-0.3(11)
Cl(4)-C(34)-C(29)-C(30)	178.2(5)
C(31)-C(30)-C(29)-C(34)	-1.5(10)
C(35)-C(30)-C(29)-C(34)	175.5(7)
C(51)-C(46)-C(47)-C(48)	-0.2(10)
Cl(2)-C(46)-C(47)-C(48)	-179.2(5)
C(5)-C(4)-C(3)-C(2)	-1.5(10)
C(18)-C(4)-C(3)-C(2)	178.5(6)
C(1)-C(2)-C(3)-C(4)	-1.3(11)
Cl(1)-C(2)-C(3)-C(4)	-179.6(5)
C(47)-C(46)-C(51)-C(50)	-1.3(10)
Cl(2)-C(46)-C(51)-C(50)	177.7(5)
C(49)-C(50)-C(51)-C(46)	2.2(10)
C(52)-C(50)-C(51)-C(46)	175.0(6)

C(3)-C(2)-C(1)-C(6)	2.8(11)
Cl(1)-C(2)-C(1)-C(6)	-178.9(5)
C(14)-C(15)-C(16)-C(11)	-1.2(12)
C(12)-C(11)-C(16)-C(15)	-0.9(11)
C(10)-C(11)-C(16)-C(15)	-174.7(7)
C(20)-C(21)-C(22)-C(23)	-1.4(10)
C(37)-C(21)-C(22)-C(23)	178.3(6)
C(24)-C(23)-C(22)-C(21)	3.8(11)
C(38)-C(39)-C(40)-C(41)	-3.4(11)
C(42)-C(41)-C(40)-C(39)	3.8(11)
C(43)-C(41)-C(40)-C(39)	178.8(7)
C(42)-C(41)-C(43)-C(44)	-159.3(8)
C(40)-C(41)-C(43)-C(44)	26.2(10)
C(42)-C(41)-C(43)-C(79)	-38.4(10)
C(40)-C(41)-C(43)-C(79)	147.1(7)
C(42)-C(41)-C(43)-C(45)	81.3(9)
C(40)-C(41)-C(43)-C(45)	-93.2(8)
C(80)-C(38)-C(70)-S(1)	110.7(7)
C(39)-C(38)-C(70)-S(1)	-67.0(8)
C(52)-S(1)-C(70)-C(38)	-60.4(6)
O(7)-N(3)-C(19)-C(18)	57.2(8)
O(8)-N(3)-C(19)-C(18)	-118.8(6)
C(46)-C(47)-C(48)-C(49)	0.7(10)
C(50)-C(49)-C(48)-C(47)	0.1(10)
C(30)-C(31)-C(32)-C(33)	-3.6(11)
C(61)-C(62)-C(63)-C(64)	2.3(11)
C(61)-C(62)-C(63)-C(69)	171.9(7)
C(76)-C(64)-C(63)-C(62)	-1.0(9)
C(76)-C(64)-C(63)-C(69)	-169.5(6)
C(57)-C(56)-C(55)-C(54)	-0.2(11)
C(59)-C(54)-C(55)-C(56)	-0.1(11)
C(65)-C(54)-C(55)-C(56)	-174.5(7)
C(40)-C(41)-C(42)-C(80)	-2.7(11)
C(43)-C(41)-C(42)-C(80)	-177.5(7)
C(2)-C(1)-C(6)-C(5)	-1.3(10)
N(3)-C(19)-C(18)-C(4)	179.2(6)
N(3)-C(19)-C(18)-S(3)	59.7(7)
C(3)-C(4)-C(18)-C(19)	136.3(6)
C(5)-C(4)-C(18)-C(19)	-43.6(9)
C(3)-C(4)-C(18)-S(3)	-103.6(6)

C(5)-C(4)-C(18)-S(3)	76.5(7)
C(17)-S(3)-C(18)-C(19)	-120.5(5)
C(17)-S(3)-C(18)-C(4)	116.4(5)
C(1)-C(6)-C(5)-C(4)	-1.7(10)
C(3)-C(4)-C(5)-C(6)	3.1(10)
C(18)-C(4)-C(5)-C(6)	-176.9(7)
C(11)-C(12)-C(13)-C(14)	-3.6(12)
C(54)-C(65)-C(67)-N(1)	-178.8(6)
S(2)-C(65)-C(67)-N(1)	58.1(7)
O(1)-N(1)-C(67)-C(65)	-118.4(7)
O(2)-N(1)-C(67)-C(65)	58.7(8)
C(29)-C(34)-C(33)-C(32)	0.1(11)
Cl(4)-C(34)-C(33)-C(32)	-178.3(6)
C(31)-C(32)-C(33)-C(34)	1.8(11)
C(16)-C(15)-C(14)-C(13)	0.9(11)
C(16)-C(15)-C(14)-C(17)	-176.6(7)
C(12)-C(13)-C(14)-C(15)	1.3(11)
C(12)-C(13)-C(14)-C(17)	178.9(7)
S(3)-C(17)-C(14)-C(15)	110.5(7)
S(3)-C(17)-C(14)-C(13)	-67.1(8)
C(62)-C(63)-C(69)-C(78)	-98.8(8)
C(64)-C(63)-C(69)-C(78)	69.7(9)
C(62)-C(63)-C(69)-C(77)	39.3(8)
C(64)-C(63)-C(69)-C(77)	-152.2(7)
C(62)-C(63)-C(69)-C(68)	147.7(6)
C(64)-C(63)-C(69)-C(68)	-43.9(8)
C(76)-C(60)-C(66)-S(2)	109.9(8)
C(61)-C(60)-C(66)-S(2)	-66.5(10)
C(65)-S(2)-C(66)-C(60)	-61.3(7)
C(23)-C(24)-C(25)-C(20)	3.9(12)
C(26)-C(24)-C(25)-C(20)	178.3(7)
C(21)-C(20)-C(25)-C(24)	-1.6(11)
C(39)-C(38)-C(80)-C(42)	-0.7(11)
C(70)-C(38)-C(80)-C(42)	-178.4(7)
C(41)-C(42)-C(80)-C(38)	1.3(12)
C(61)-C(60)-C(76)-C(64)	0.4(11)
C(66)-C(60)-C(76)-C(64)	-176.2(7)
C(63)-C(64)-C(76)-C(60)	-0.3(10)

Table 7. Hydrogen bonds for compound 421 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	< (DHA)
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