Asymmetric Synthesis of Quaternary Centres Using Organocatalysis

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Declaration

This thesis was submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Edinburgh. Unless otherwise stated the work described in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualifications at this, or any other institution.

Aileen Laura Mitchell 2008

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Abstract

Quaternary carbon centres are ubiquitous in nature, typically in natural products. The task of creating an all carbon quaternary centre, bearing an alkyl moiety with differentiated functionalities and substituents is a desired key step in organic synthesis. A variety of endeavours by research groups have lead to the construction of stereogenic quaternary centres, albeit with narrow scope of substrate. Despite the repertoire of transition metals/ligands, chiral auxiliaries and reagents available at hand, efficient enantioselective and organocatalytic methodologies for the construction of all carbon quaternary centres still remains a daunting challenge for synthetic chemists. One of the most popular methods to install a quaternary centre is via a conjugate addition, the addition of a chiral tertiary enolate to an electron deficient alkene or carbonyl compound has led to high levels of synthetic accomplishment over generations. Our strategy to assemble such quaternary centres focused on an organocatalytic tandem Michael-aldol reaction, as an efficient one-pot strategy to install vicinal quaternary centres with good levels of enantioselective induction. Initial 1,4-conjugate addition of the nucleophile with α-acrolein type Michael acceptors generates the enolate, which is now set up to undergo an intramolecular aldol reaction providing the desired molecules. Molecular complexes of this class are also amenable to further catalytic transformations and synthetic elaborations.

This thesis presents our investigations towards organocatalytic enantioselective strategies for the assembly of fully substituted quaternary centres.

Abbreviations

$[\alpha]_D$	observed optical rotation (in degrees)
δ	chemical shift
Å	angstrom(s)
aq	aqueous
atm	atmosphere(s)
bp	boiling point
Br	broad (spectral)
BA*	Brønsted acid
c	conc (g/100 mL)
°C	degree(s) celsius
calcd	calculated
cm^{-1}	wavenumber(s)
COSY	correlation spectroscopy
d	day(s); doublet (spectral)
DEPT	distortionless enhancement by polarization transfer
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
EI	electron impact
equiv	equivalent(s)
ES	electrospray ionisation
EWG	electron withdrawing group
FAB	fast atom bombardment
g	gram(s)
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
h	hour(s)

HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
L	litre(s)
LA	Lewis acid
LB	Lewis base
LUMO	lowest occupied molecular orbital
m	multiplet (spectral)
*m*cpba	meta-chloroperbenzoicacid
mg	milligrams
min	minutes
mL	millilitres
M	molar (moles per litre)
m/z	mass-to-charge ratio
M+	parent molecular ion
MBH	Morita Baylis Hillman
MHz	megahertz
min	minute(s); minimum
mmol	millimole(s)
mol	mole(s)
m.p.	melting point
MS	molecular sieves
Nph	naphthalene
NMR	nuclear magnetic resonance
Nu	nucleophile
ppm	part(s) per million
q	quartet (spectral)
quin	quintet (spectral)

RCM	ring closing metathesis
R_t	retention time
rt	room temperature
s	singlet (spectral); second(s)
sept	septet (spectral)
t	triplet (spectral)
tlc	thin-layer chromatography
μL	micro litre(s)
UV	ultraviolet
w/w	weight per unit weight (weight to weight ratio)
wt	weight
X	halogen

Reagents and solvents

AcOH	acetic acid
BINAP	binapthalene
Bu_4NI	tetrabutylammonium iodide
$CDCl_3$	deuterated chloroform
CSA	10-camphorsulfonic acid
CsOH	caesium hydroxide
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMAP	4-di(methylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EPP	N-ethylpiperidine
HCN	hydrogen cyanide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
$LiBF_4$	lithium tetrafluoroborate
LSB	La-Na-Binol complex
MeCN	acetonitrile
NHC	N-heterocycliccarbene
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
p-TsOH	*para*-toluenesulfonic acid
pybox	pyridinebisoxazoline
t-BuOK	potassium tertbutoxide
TFA	trifluoroacetic acid

THF	tetrahydrofuran
$TiCl_4$	titanium tetrachloride
TPAP	tetrapropylammonium perruthenate
TRAP	2,2-bis[1-(diphenylphosphino)ethyl)-1,1-biferrocene

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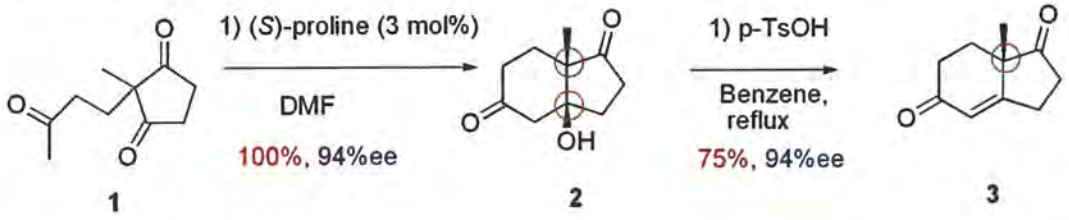
Chapter 1

Asymmetric Conjugate Additions to Construct Quaternary Centres

1 Introduction

1.1 Origin and classification of asymmetric organocatalysis

Organocatalysis is the acceleration of a chemical reaction using a catalytic amount of a small chiral molecule. The term was coined by Macmillan in 2000, who wished to distinguish the new concept of metal free catalysis. However, as the German chemist Wolfgang Langenbeck pointed out, organocatalysis is not an entirely new topic; it comes from the well-known concept of organic catalysis. The first example of asymmetric organocatalysis was reported by Bredig and Friske in 1912,[1(a)] both scientists demonstrated that the addition of HCN to benzaldehyde can be significantly increased in the presence of cinchona alkaloids quinine and quinidine, albeit in optical yield of <10%. Bredig *et al.* underlined the importance of this fundamental concept. However, the majority of work evolved around the Hajos-Parrish-Eder-Sauer-Wiechert [2] reaction, which was discovered several years later, and is now used extensively as a tool in steroid synthesis. Their efforts involved employing (*S*)-proline in the Robinson annulation which enabled them to generate a bicyclic ketol **1** with two quaternary centres, one fully substituted and the other a tertiary alcohol. This annulation step is considered to be an enol-*6*-endo cyclisation, with respect to the enamine C-C bond which is integrated in the bicyclic framework (Scheme 1.1).



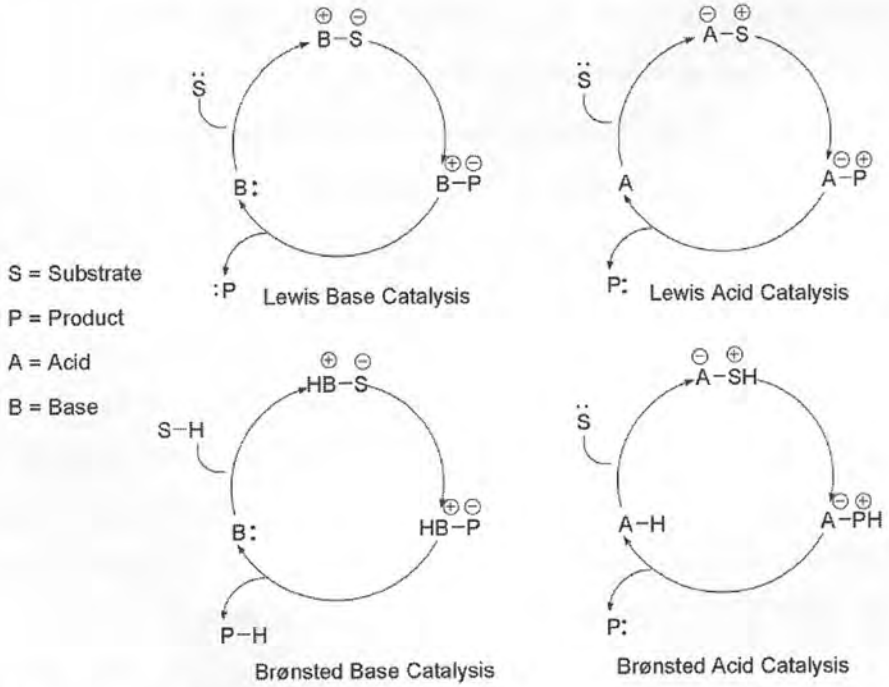
Scheme 1.1 The Hajos-Parrish-Eder-Sauer-Wiechert reaction

Despite the successful preliminary demonstration of using optically active amino acids in C-C bond forming reactions in the 1970`s, proline catalysis remained mostly unexplored for a long time. However, the last decade has seen an explosive growth in

this field. Methodologies, new catalysts, mechanistic studies and the scope of organocatalytic reactions have been unravelled only recently. There is a plethora of C-C bond forming reactions wherein organocatalysis plays a prominent role, for instance Michael, [3] aldol reactions [4] and alkylations. [5] A prominent gap that exists in the literature is the enantioselective organocatalytic construction of quaternary centres, presumably due to the intricate synthesis involved.

In the past, metal and biocatalysis has dominated the field of asymmetric catalysis. However, the issues often associated with metal catalysis, for example, toxic metals, air sensitivity and expensive chiral ligands which are required for asymmetric induction, prompted the renaissance of organocatalysis. Therefore, over the last decade, the application of small organic molecules as catalytically active species (usually consisting of carbon, hydrogen, nitrogen, oxygen, sulfur and phosphorus), has grown rapidly, given their synthetic versatility, operational simplicity and industrial applications.

Organocatalysts can be generally classified as Lewis Bases, Lewis acids, Brønsted bases and Brønsted acids [6] (Scheme 1.2).



Scheme 1.2 Different modes of organocatalysis [6]

Lewis Base (B) catalysts activate the catalytic cycle initially by nucleophilic addition to the substrate (S). The adduct will then undergo a reaction, which will release the desired product and catalyst for further turnover. Lewis Acid catalysts activate the cycle by activating nucleophilic substrates. Brønsted acids and Brønsted bases initiate the catalytic cycle by partial deprotonation or protonation of the substrate. A powerful subset of Brønsted acid catalysis is Hydrogen bond catalysis, [7] which has been introduced as a powerful methodology in asymmetric catalysis. Several groups have explored the broad diversity of this concept. [7]

Over the years, Lewis base organocatalysis has demonstrated remarkable advances in synthetic chemistry. The most commonly used Lewis base organocatalysts are chiral secondary amines, [8] with aldehydes and ketones being the common substrates. Activation of the carbonyl substrate can take place in one of two ways, either by enamine formation (raising the HOMO), or by iminium ion formation (lowering the LUMO). The double activation mode of these organocatalysts is what labels them as suitable candidates for organocascade reactions. The scope of these secondary amine organocatalysts is limited to carbonyl systems; within this class, the use of α-acroleins as suitable substrates represents a highly demanding task. One of the striking features of utilising α-acroleins as starting materials is that products of such reactions are ideal for further elaboration towards complex bioactive molecules.

The enantioselective formation of stereogenic quaternary carbon centres still remains a daunting challenge in organic synthesis. In organic synthesis, there is a growing need to provide efficient methodologies for the construction of these quaternary carbon centres. Quaternary carbon stereogenic centres with four different non hydrogen substituents are found in a wide range of important natural products and pharmaceutical drugs. [9] Fig 1.1 shows some representative examples of natural products and drugs possessing quaternary centres.

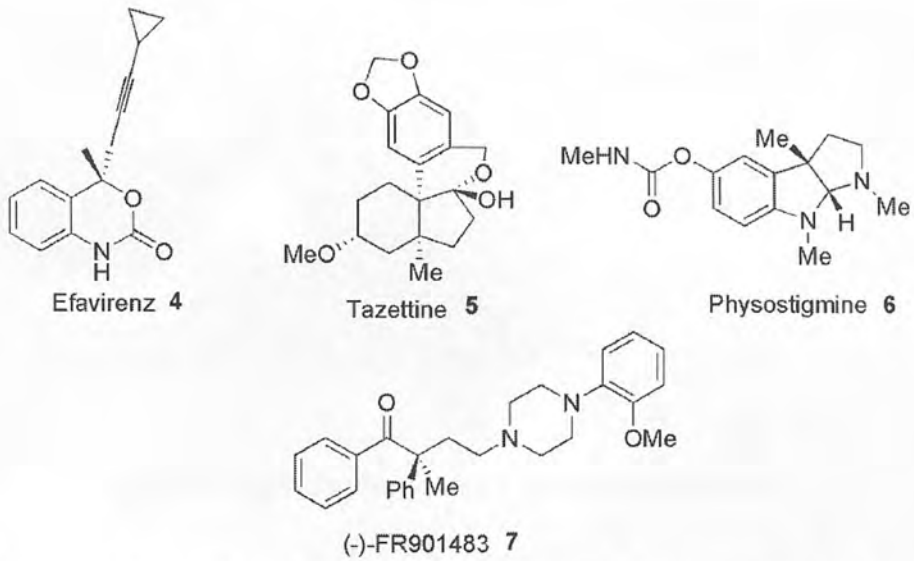
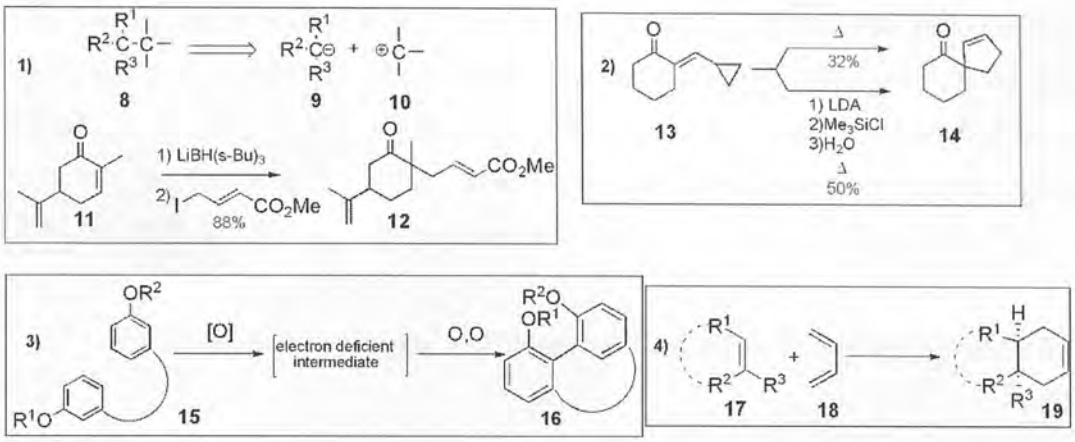


Fig 1.1 Selected examples of natural products and drugs bearing a quaternary centre

Generally, quaternary centres are constructed by employing chiral auxiliaries, ligands, catalysts or by the functional group transformation of *meso* compounds. [10] Despite the requirement of stoichiometric amounts of chiral auxiliaries, they still serve as a valuable source of asymmetric induction. To date, the existing methods to install a fully substituted quaternary centre involve using expensive chiral metal complexes, chiral ligands and chiral auxiliaries. The discovery of environmentally friendly methodologies for the production of fully susbstituted quaternary centres remains a demanding task.

1.2 Existing methodologies for quaternary centre construction

The installation of a quaternary centre remains one of the most constrained methods in organic synthesis. This is possibly due to the restricted access to commercially or synthetically tractable starting materials which possess the requisite tertiary carbon atoms.



Scheme 1.3 Existing strategies for quaternary centre construction

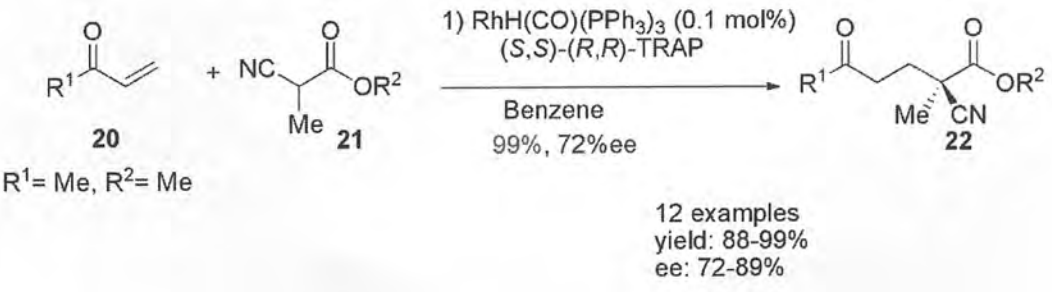
Although vast arrays of synthetic reactions exist for the construction of C-C bonds, there are only four main classes [10a] of C-C bond formation, which lead to the creation of a fully substituted carbon, each of which possess their own limitations and advantages. These comprise of (**1**) the ionic formations, which involve the addition of a tertiary carboanion **9** to a carbocation **10**; rearrangements (**2**), oxidative and reductive couplings (**3**) and cycloaddition reactions (**4**) (Scheme 1.3). Ionic constructions, wherein one new C-C bond is formed offer a considerable degree of flexibility, as a vast range of diverse electrophilic reagents can be employed. Rearrangements, are becoming of importance in organic synthesis, for example, the [1,3] rearrangement of β-cyclopropylenones **13** provide spirobicyclic systems **14** in moderate yield. [10b] However, one of the drawbacks with rearrangements is the tendency for deleterious side reactions to take place. Oxidative and reductive couplings, are rarely synthetically useful, due to numerous side reactions, for example, polymerisation and the steps are often fraught with regio control issues. In contrast, cycloaddition reactions have great importance in synthetic chemistry. Moreover, two new C-C bonds are constructed with high levels of predictable stereocontrol.

Here the primary focus will be on the enantioselective construction of quaternary centres, by means of which the addition of tertiary nucleophiles to electrophiles results

in the construction of quaternary centres. In recent years, 1,4-conjugate additions have been extensively reviewed [11] and, therefore this section will highlight some of the most relevant examples of asymmetric 1,4-conjugate addition methodologies (organocatalytic/metal mediated) to create fully substituted quaternary centres, with a view to demonstrate their general application in tandem Michael-aldol reactions. [12]

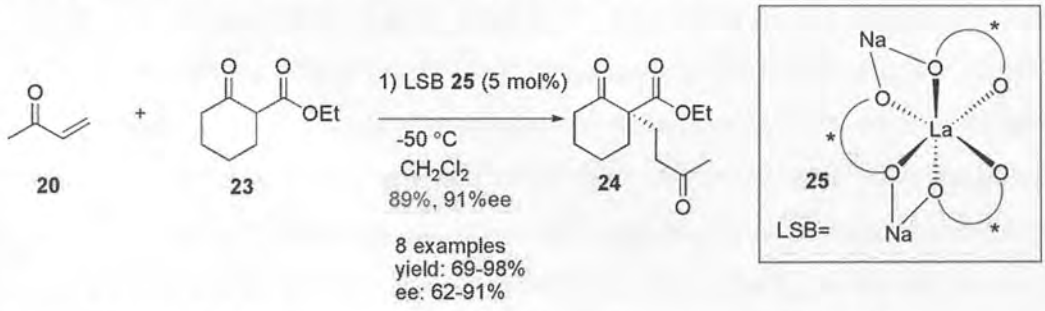
1.3. Asymmetric conjugate additions to afford all carbon quaternary centres

Over the last decade, there have been considerable efforts from a number of research groups in designing new enantioselective conjugate addition methodologies. [3] Conjugate additions (1,4-additions) of carbon nucleophiles to acceptor activated C-C multiple bonds are considered to be one of the most versatile and vital reactions for the installation of an all carbon quaternary centre.[14] Until recently, the most efficient strategy for quaternary centre generation, involved employing catalytic amounts of transition metal catalysts. In 1992, Ito [14] and co-workers demonstrated the prominent role of chiral phosphine ligands which are promoted by transition metal complexes (Scheme 1.4). This rhodium/ligand complex served as an effective catalyst for the first asymmetric enantioselective Michael reaction of chiral transition metals with α–cyano carboxylates **21** and vinyl ketones **20** to give the desired product **22** in good yield and enantioselectivity.



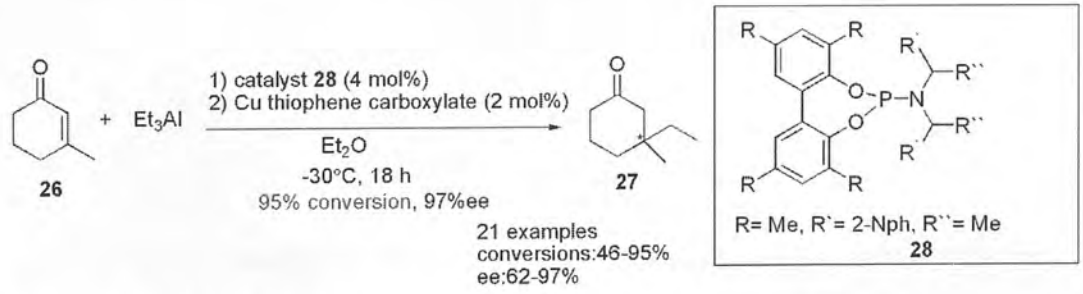
Scheme 1.4 Rhodium catalysed asymmetric Michael addition

The breakthrough in catalytic enantioselective conjugate addition reactions for installing quaternary centres was established by Shibisaki and co-workers. [15] He demonstrated that heterobimetallic catalysts are applicable in Michael reactions with methyl vinyl ketone **20** and cyclic 6-membered rings containing β-ketoesters **23** to give rise to products with fully substituted quaternary centres (Scheme 1.5). The reaction was found to proceed in high yield and enantioselectivity in non polar solvent CH_2Cl_2, it is thought that the Na enolate will remain coordinated to one of the oxygens of LSB **25**, [15] thus allowing slow addition of the Na enolate to the enone, resulting in high enantiomeric excess.



Scheme 1.5. Catalytic Asymmetric Michael reaction promoted by LSB

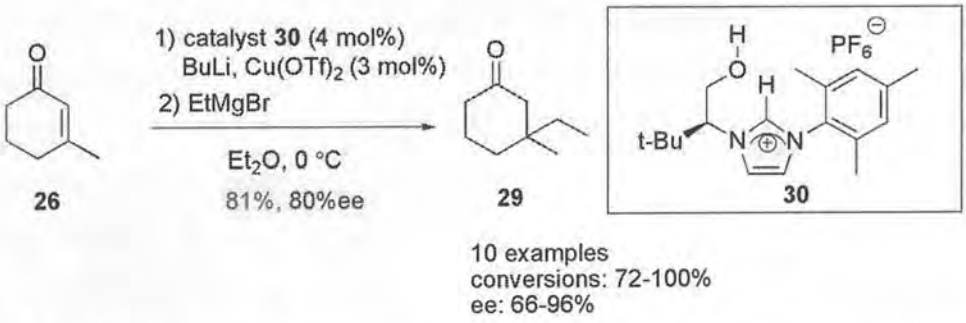
The asymmetric 1,4-conjugate addition reaction is most certainly a versatile tool for the preparation of chiral building blocks, a more recent example of such a reaction is the copper catalysed 1,4-addition to trisubstituted cyclohexenones (Scheme 1.6). [13]



Scheme 1.6 Addition of $AlEt_3$ to various 3-substituted cyclohexenones

Alexakis [16] *et al.* have demonstrated that trialkylaluminium reagents undergo a copper catalysed conjugate addition with trisubstituted enones in the presence of coordinating solvents. Following extensive optimisation; copper thiophene carboxylate in Et_2O with the biphenol-phosphoramidite ligand **28** was found to provide best results, affording the desired product **27** in excellent yield and enantioselectivity. With successful demonstration of this methodology, the group were now in the position to explore further applications of these chiral building blocks.

Alexakis *et al.*[16] reported an additional route for the construction of fully substituted quaternary centres broadly similar in scope to their previous studies. In this instance, a more reactive primary organometallic was employed. Their initial efforts focused on locating chiral ligands which were complementary to copper. A series of N-heterocyclic carbenes were screened, employing trisubstituted enone **26** and ethyl magnesium bromide as a model study. In all cases, the conversion was high; however low enantioselectivities were observed in some cases. In an attempt to tackle this problem, a different class of NHCs were synthesised and, to their delight, NHC **30** exerted high levels of reactivity and enantioselectivity. It is thought that the success of this catalyst is due to the fact that the chiral substituents around the C-N axis are locked in a rigid conformation, discouraging rapid internal rotation of the chiral substituents.



Scheme 1.7 Construction Quaternary centres via a copper-NHC organocatalyst

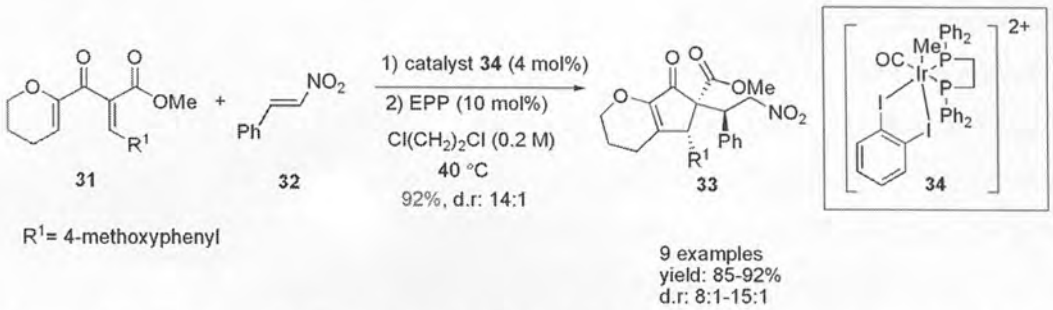
A plethora of variables were explored, primary and secondary Grignard reagents both displayed high levels of enantioselectivity in the presence of **30**. Also, in this

unprecedented asymmetric conjugate addition reaction, various tri-substituted cyclohexenones were suitable candidates.

The above discoveries are all very relevant. However, the limitations of such reactions include the sensitivity of transition metals to air and moisture, the high cost of ligands and their fiddly synthesis, the toxicity of the metals, where there tends to be an expensive recovery procedure for waste treatment. The operational simplicity of organocatalytic reactions makes it an attractive method for the construction of complex molecules; inexpensive bench stable catalysts can be employed in organocatalytic reactions under an aerobic atmosphere in wet solvents. In this regard, there have been considerable efforts to find organocatalytic alternatives to metal catalysis for the construction of fully substituted quaternary centres. Some of the notable examples are reported herein.

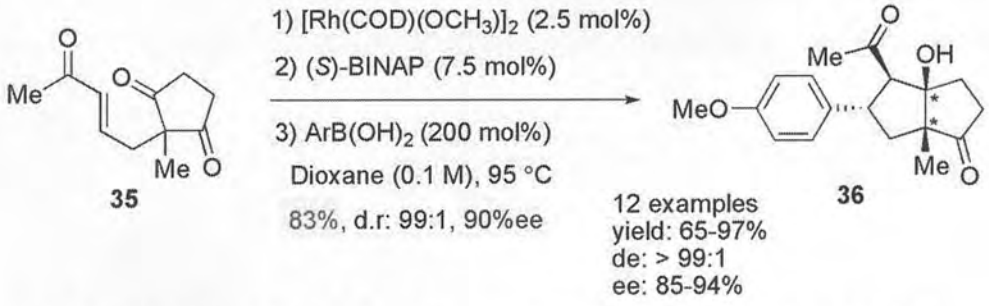
1.3.1 Miscellaneous metal mediated tandem Michael additions to create quaternary centres

Frontier [17] *et al.* have demonstrated the feasibility of a domino-Nazarov-Michael cyclisation using cationic Ir(III) complex **34** which proves to be a highly efficient catalyst in this cyclisation. A broad range of cyclopentenone systems are constructed bearing three contiguous stereocentres, one of which is a quaternary centre in high yield with excellent diastereoselectivities. In order to achieve the best results, a reagent combination of N-ethylpiperidine (EPP) and complex **34** is mandatory. It is thought that Lewis acid activation of nitrostyrene **32** *via* an enolate facilitates a facile intermolecular Michael addition. In an attempt to rationalise the stereochemical outcome of this reaction, Frontier *et al.* have reasoned that the Michael addition takes place on both faces of the nitroalkene from one face of the enolate; simple model studies are the main supporting element of this notion. Its possible application in asymmetric synthesis is an appealing feature of this methodology. By employing chiral organocatalysts, cyclopentenones may be furnished with high levels of enantiocontrol (Scheme 1.8).



Scheme 1.8 Domino Nazarov cyclisation Michael addition catalysed by Ir(III) complex

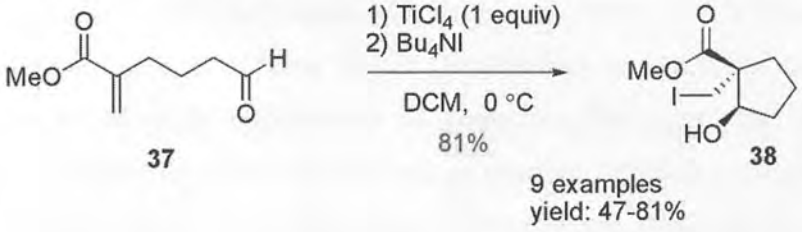
Krische *et al.* reported the enantioselective [18] tandem conjugate addition-aldol cyclisation of enone-diones, in which two covalent C-C bonds are created with control of absolute and relative stereocontrol. This transformation in particular affords five and six membered rings with two fully substituted quaternary centres, albeit one of the quaternary centres is present in the prochiral starting material (Scheme 1.9). Employing $[Rh(COD)(OCH_3)]_2$ as the precatalyst and phenyl boronic acid derivatives as the nucleophile, results in the production of highly diverse products.



Scheme 1.9 Rhodium catalysed tandem-conjugate addition-aldol cyclisation

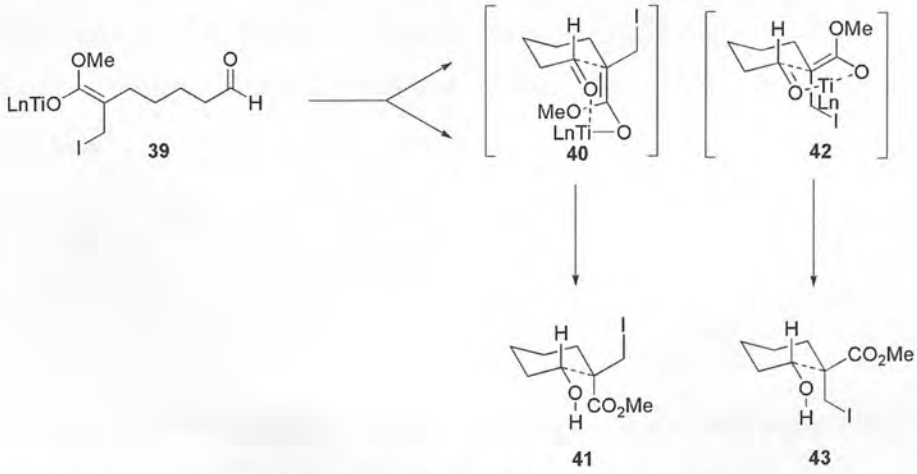
In an analogous fashion to Krische *et al.* the intramolecular tandem Michael-aldol reaction has been explored by Greaney *et al.* [19] However, tetrabutylammonium iodide is employed as the nucleophile and α-substituted enoate aldehydes and ketones were

elected as suitable prochiral starting materials in an attempt to construct fully substituted quaternary centres, which are the most difficult to synthesise. This powerful variant of the tandem Michael-aldol reaction has only been reported by one other group. [20] One of the attractive features of this reaction is the nucleophile is integrated into the product, thus enabling an intramolecular aldol reaction providing single diastereomers of cyclic products with both a fully substituted quaternary centre and vicinal tertiary centre. Treatment of enoate-aldehyde **37** in DCM with a stoichiometric quantity of the Lewis acid $TiCl_4$ and Bu_4NI, gratifyingly gave rise to cyclopentanol **38** with high levels of diastereoselectivity. Naturally, the scope of the reaction was explored and it was found that the reaction was amenable to heterocyclic synthesis.



Scheme 1.10 Lewis acid promoted tandem iodo-aldol cyclisation

The stereochemical outcome of the cyclisation was arrived at by utilising one of the six membered adducts **39** as a model study in order to rationalise the lack of the *cis* product.



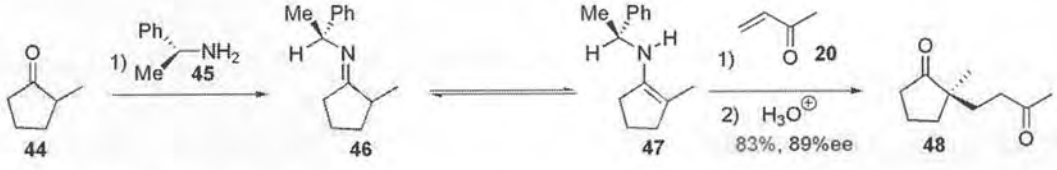
Scheme 1.11 Stereochemical rationalisation for tandem-Michael-aldol cyclisation

The CH_2I group prefers to exist in the least hindered equatorial position, as opposed to occupying the more hindered axial position, thus explaining preferential construction of the *trans* product **41**.

1.4 Chiral auxiliary mediated 1,4 conjugate additions

The application of chiral auxiliaries, in organic synthesis is an attractive strategy to introduce chirality into a compound, by virtue of the fact that simple organic molecules can be employed to generate a temporary stereocentre, usually created by steric hindrance from the auxiliary. Besides their importance in asymmetric synthesis, they often tolerate a wide range of substrates and functional groups, whilst preceding under mild reaction conditions. In addition to this the auxiliary is easily and quantitatively recycled. One of the main applications of chiral auxiliaries is their fundamental contribution in enamine catalysis. The success of enamine catalysis is owed to the fact that they are synthetic equivalents of the parent carbonyl compound and, with enhanced nucleophilicity; enamines can then undergo a conjugate (Michael-type) addition with a broad range of electrophilic acceptors.

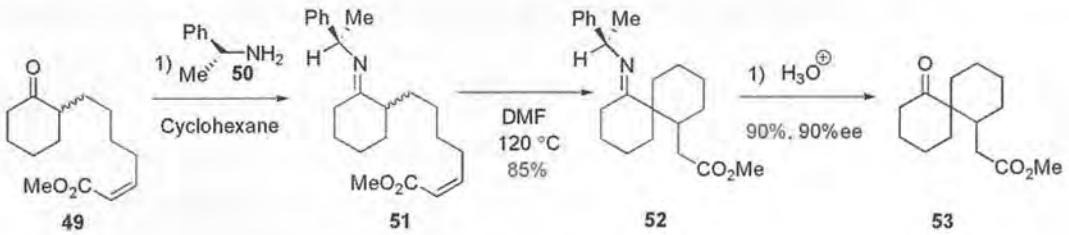
D`Angelo [21] *et al.* reported the intermolecular Michael addition of various cyclanones with a vast range of electrophilic acceptors, utilising (*S*)-(-)-1-phenylethylamine as the chiral auxiliary, which was initially reported by Pfau *et al.* as a universal chiral auxiliary (Scheme 1.12).[22]



Scheme 1.12 Application of (*R*)-1-phenylethylamine in the intermolecular Michael addition

The chiral imine **46** was treated with methyl vinyl ketone **20**, which after hydrolysis leads to diketone **48** with good levels of reactivity and enantioselectivity. Besides controlling the regioselectivity, at the more substituted α-position, the absolute configuration of the newly created stereogenic centre is controlled by employing chiral auxiliary **45**. The intermolecular Michael reaction tolerates both electron withdrawing groups (EWG), positioned in the α–position to the carbonyl group and nitrogen and oxygen atoms incorporated within the cyclanones, albeit with decreased levels of reactivity and enantioselectivity. After exploration of a series of chiral auxiliaries, a significant decrease in enantioselectivity was observed when chiral auxiliaries, not bearing an aromatic group α to the amine moiety, were employed.

D`Angelo [23] *et al.* demonstrated the versatility of this class of auxiliary. In order to achieve the enantioselective formation of a spiro centre (fully substituted quaternary centre), they sought to develop an intramolecular variant of the Michael reaction, giving rise to spiro centres. Keto ester **49** was condensed with (*R*)-1-phenylethylamine **50** at reflux, giving rise to imine **51**. Under high temperature conditions, imine **51** underwent a 6-*exo-trig* cyclisation to afford spiro derivative **52** with high levels of stereocontrol. Hydrolysis of imine **52** led to the formation of ketoester **53** in good yield (Scheme 1.13).

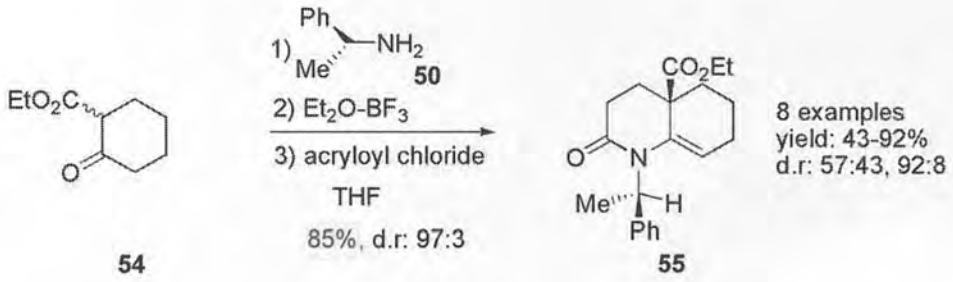


Scheme 1.13. Preparation of spiro [5.5] undecane derivative 53

It is worthy of note that certain crotonates are unreactive to enamines in the intermolecular Michael addition. Nevertheless, in the intramolecular reaction an increase in reactivity and yield is observed with the bifunctional starting material **49**. It is thought that the success of this is due to entropic factors.

In conclusion, D`Angelo [23] *et al.* have demonstrated efficient routes for the installation of fully substituted all carbon quaternary centres, by employing readily available chiral auxiliaries **45** and **50**. Both intramolecular and intermolecular Michael additions are feasible with α-substituted enones, giving rise to complex molecules with high levels of regio- and stereo control. Important features of such processes include the ability of the chiral auxiliary to promote such processes under mild and neutral reaction conditions.

Stille *et al.* have reported [24] that high asymmetric induction can be achieved when tetrasubstituted enamines undergo a Michael addition with acryloyl chloride in the presence of (*R*)-1-phenylethylamine, giving rise to δ-lactam products **55** with high levels of diastereomeric excess (Scheme 1.14).



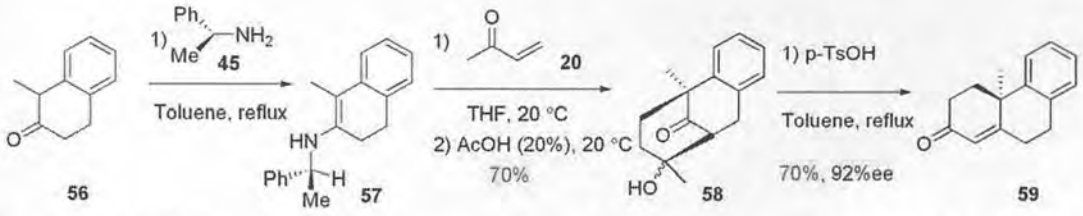
Scheme 1.14 Aza-Annulation of β-enamino esters with acryloyl chloride

Best results were obtained with Et_2O-BF_3 (to promote enamine formation) and (*R*)-1-phenylethylamine **50** in refluxing THF, employing acryloyl chloride as the Michael acceptor. Surprisingly, no Lewis acid catalysts or high pressure [25] was required for the reaction to proceed with high levels of reactivity and stereoselectivity; generally the reactions had gone to completion after 4-6 hours. In order to investigate the outcome different substituents on the chiral framework would have on the stereoselectivity of the reaction, a series of chiral auxiliaries were employed. Any deviation from the use of auxiliary **50** resulted in a dramatic decrease in stereoselectivity. In order to explore the

scope of the reaction, substituted acrylate derivatives were employed to test the feasibility of the simultaneous formation of two stereogenic centres. To their delight, the formation of two vicinal stereogenic centres concomitantly is successful. However, significant loss in yield of the aza-annulation product is observed, which is partially due to impurities arising from side reactions. The aza-annulation serves as a valuable reaction in terms of generating potential precursors for the synthesis of complex bioactive compounds.

1.5 The application of chiral auxiliaries in natural product synthesis

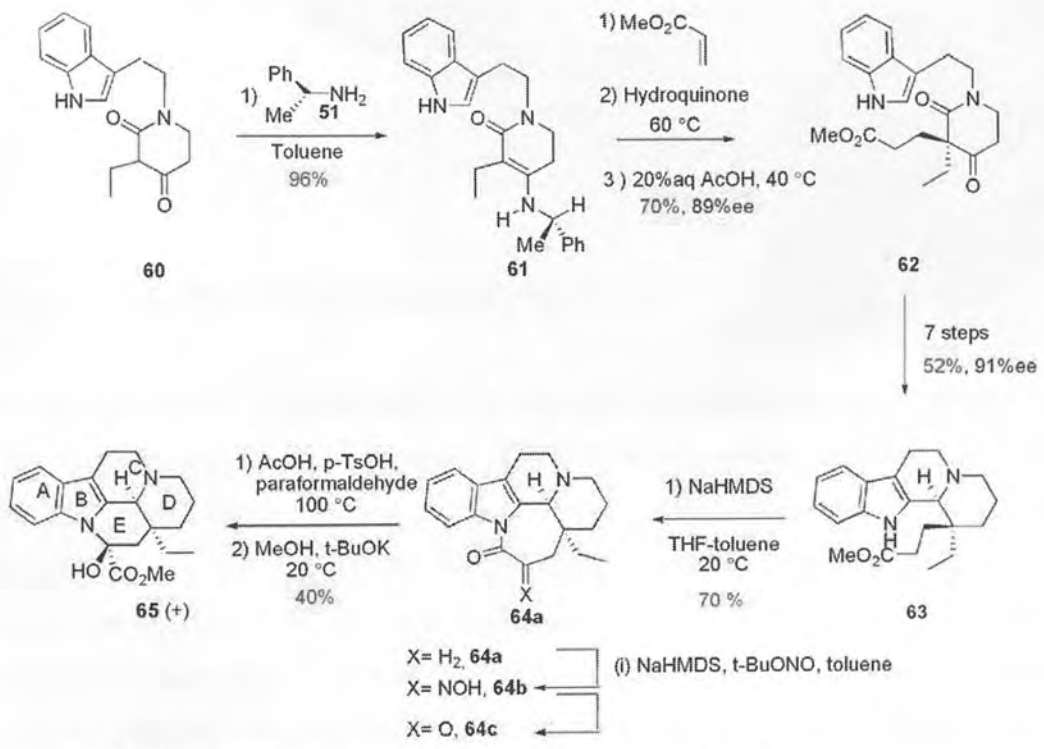
Auxiliary mediated Michael reactions are employed in natural product synthesis [26] to strategically create fully substituted quaternary centres. D'Angelo *et al.* have demonstrated the application of their previously reported methodology, [22] towards the construction of optically active diterpenes and steroids. 1-Methyl-2-tetralone **56** was treated with (*S*)-(-)-1-phenylethylamine **45** in toluene and set to reflux, addition of methyl vinyl ketone gave rise to ketol **59** in good yield. Ketol **58** was subjected to p-TsOH in toluene, after 2 h the desired (*R*)-phenanthrone **59** was generated in moderate yield and excellent enantioselectivity via a retro aldol/aldol cyclisation. The quaternary centre was established via the chiral auxiliary mediated Michael intermolecular step with high levels of asymmetric induction.



Scheme 1.15 Enantioselective synthesis of ring-C aromatic steroids via an asymmetric Michael addition

The major alkaloid encountered in periwinkle, Vincamine was synthesised via a stereocontrolled elaboration of a quaternary centre. The asymmetric Michael conjugate addition was employed as the key step [27] to install the quaternary centre. This, in turn, led to the construction of the [ABD]-type subunit. Early on in the synthesis it became apparent that installation of the quaternary centre was necessary at the beginning of the synthetic route. Chiral auxiliary (*R*)-1-phenylethylamine **50** was treated with **60** to generate enaminolactam **61** in good yield. Formation of enaminolactam **61** set the foundations for the intermolecular Michael addition with

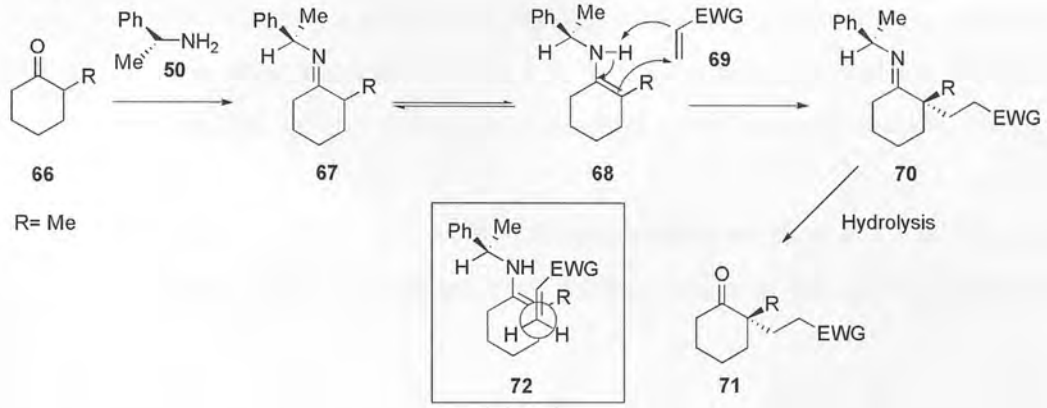
electrophilic partner methyl acrylate. It was suspected that the presence of the keto group (enamine carbonyl) was responsible for the failure of the B-N cyclisation. In spite of this a new synthetic route was devised in order to circumvent the B-N cyclisation issue. Reduction of the keto group with $LiAlH(Ot\text{-}Bu)_3$ in THF led to the formation of the desired secondary alcohol, together with reduction of the ester to the carboxylic acid. After a series of transformations/deprotections, the intramolecular cyclisation was feasible. In the presence of NaHMDS in toluene, cyclisation of **63** afforded enantiomerically pure **64a**, employing Oppolzer's protocol, resulted in a mixture of syn/anti oximes **64b/64c**; further elaboration of **64a** gave rise to (+)-Vincamine **65**.



Scheme 1.16 Enantioselective synthesis of (+)-Vincamine 65

By utilising (*R*)-phenylethylamine **50** as the chiral auxiliary, installation of the crucial quaternary centre was achieved through an asymmetric conjugate Michael addition. The

desired (+)-Vincamine **65** was synthesised, albeit in poor overall yield (1.2 %) in a linear sequence from commercially available tryptamine. The synthesis demonstrates the synthetic utility of chiral auxiliary **50** as an efficient asymmetric inducer in the intermolecular asymmetric Michael reaction, affording new quaternary centres in a stereocontrolled manner. It is thought that the remarkable stereocontrol can be rationalised due to synclinal arrangement of the Michael acceptor with the enamine nucleophile **61**.



Scheme 1.17 Rationale for preference of *endo* product

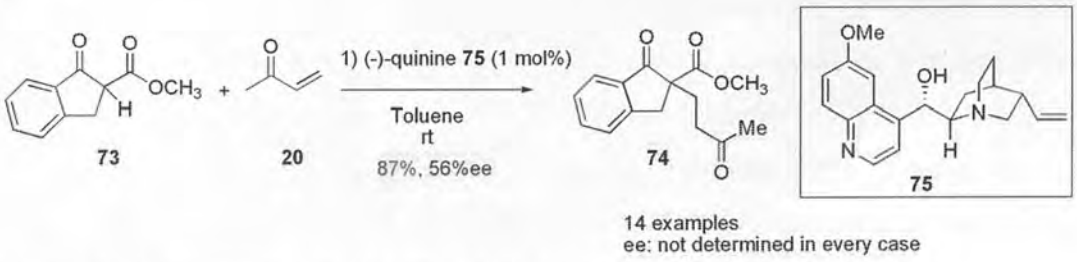
Mechanistic studies [28] strongly suggest that alkylation takes place anti to the phenyl ring of the chiral moiety, thus generating the (*R*) configuration of the quaternary centre. The alkylation predominantly takes place at the more substituted α–side of the enamine functionality, the enamine attacks the electrophile from the *endo* face; this attack strongly prevails over the *exo* face. The *endo* approach is favoured, due to orbital interaction between the nitrogen of the enamine and the electron withdrawing group of the Michael acceptor **69**. However, the *endo*-preference is disfavoured when the Michael acceptor possesses a bulky substituent in the α-position. D`Angelo *et al.* demonstrated [28] that by utilising a variety of α,β-substituted alkenyl acceptors, an additional stereogenic centre could be created adjacent to the all carbon quaternary centre, albeit with the

possibility of trace amounts of the regioisomeric product. Chiral imines have demonstrated impressive synthetic utility in the formation of all carbon quaternary centres, hence the demand to elaborate on existing enantioselective variants.

1.6 Intermolecular enantioselective organocatalytic conjugate addition reactions

The organocatalytic direct asymmetric conjugate addition reaction is without a doubt, a powerful and versatile method for C-C bond formation. Thus, considerable efforts have been put forward, in order to provide molecules with enantiomerically enriched quaternary centres.

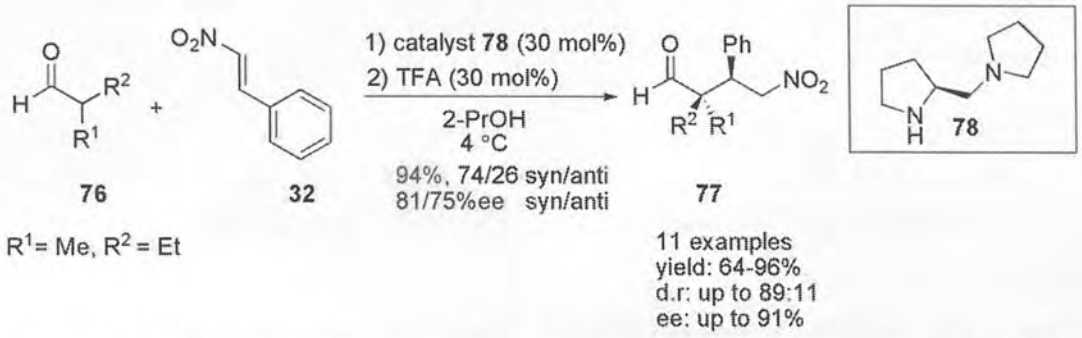
Wynberg and Helder [29] reported the first catalytic enantioselective conjugate addition reaction to construct all carbon quaternary centres, utilising the cinchona alkaloid quinine.



Scheme 1.18 Asymmetric Michael addition utilising quinine

Conducting the reaction in toluene at room temperature in the presence of quinine gave rise to the desired adduct **74** in 87% yield. Chiral shift reagent $Eu(tfc)_3$ was added to product **74** in $CDCl_3$ in small portions resulting in two separate methyl peaks of the ester group being observed in the ^1H NMR, the peaks were integrated to give a 1.3:5 ratio, representing 56% e.e. The scope of the reaction was extensively investigated; a series of Michael donors were compatible with the reaction conditions with methyl vinyl ketones, whilst maintaining a high level of enantioselectivity and chemical yield.

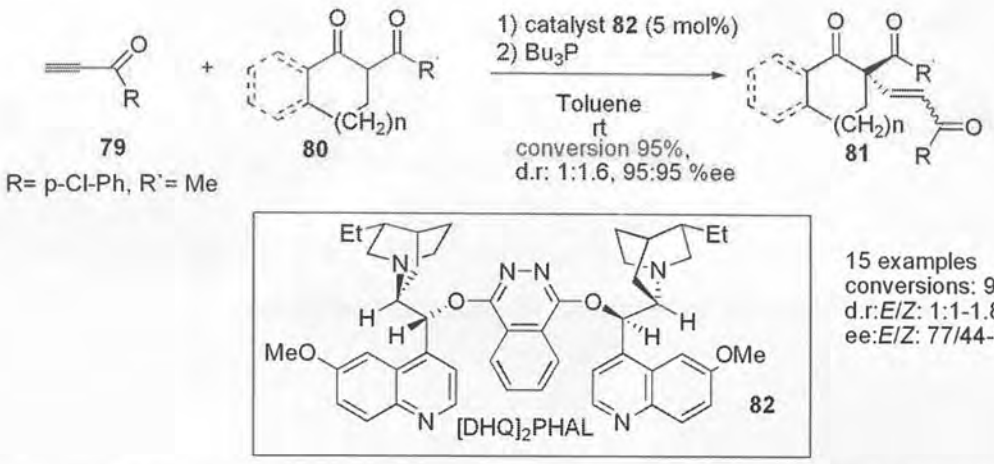
Despite the synthesis of all carbon quaternary centres being intrinsically difficult, Barbas *et al.* [30] have demonstrated the success of the direct Michael reaction of α,α–disubstituted aldehyde donors with (*E*)-β-nitrostyrene Michael acceptors, giving rise to Michael products with all carbon quaternary centres.



Scheme 1.19 Catalytic Michael reaction using chiral-amine bifunctional catalysts

Barbas [30] *et al.* found that when (*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine/TFA was employed as a bifunctional catalyst **78** in the Michael addition between (*E*)-β-nitrostyrene **32** and isobutyraldehyde **76**, the reaction proceeded in excellent yield with good levels of enantioselectivity. Further studies confirmed that a series of α,α-disubstituted aldehydes are tolerated in this class of Michael reaction whilst maintaining high levels of conversion and enantioselectivity.

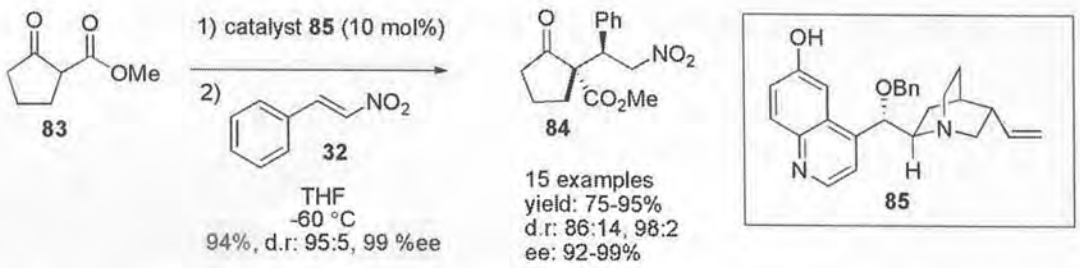
Jørgensen [31] and co-workers, shortly after disclosed a highly enantioselective conjugate addition of β-dicarbonyl compounds with alkynones **79**. Good yields and enantioselectivities were obtained with various β-diketones and aromatic alkynones when the cinchona alkaloid $(DHQ)_2PHAL$ **82** was employed as the organocatalyst (Scheme 1.20).



Scheme 1.20 Intermolecular enantioselective conjugate addition to alkynones

In order to obtain the configurationally stable (*E*)-enone **81**, addition of a catalytic amount of Bu_3P selectively was found to isomerize the *E/Z* mixture in a one-pot procedure without having a detrimental effect on yield or enantioselectivity. One of the attractive features of this methodology is that complex molecules with quaternary centres and C=C double bonds are generated in one pot, which provide a functional handle for further transformations.

In 2005, Deng [32] and co-workers further explored this field of organocatalysis. The asymmetric conjugate addition of cyclic keto esters with nitroalkanes was efficiently mediated by the modified bifunctional cinchona alkaloid quinine **85**. The 1,4 adducts were generated in a 4.5:1 ratio when the reaction was carried out at rt; nevertheless when the reaction was cooled to -60 °C, an impressive increase in diastereoselectivity was observed 18:1. The enantioselectivity is consistent in most cases, regardless of the temperature of the reaction. Based on the kinetic results which are consistent with a bifunctional catalysis mode and the increase in stereoselectivity in aprotic solvents, they are able to propose that the catalyst adopts a gauche-open conformer transition state, which concurrently activates and orientates the Michael acceptor by a series of hydrogen bonds (Scheme 1.21).

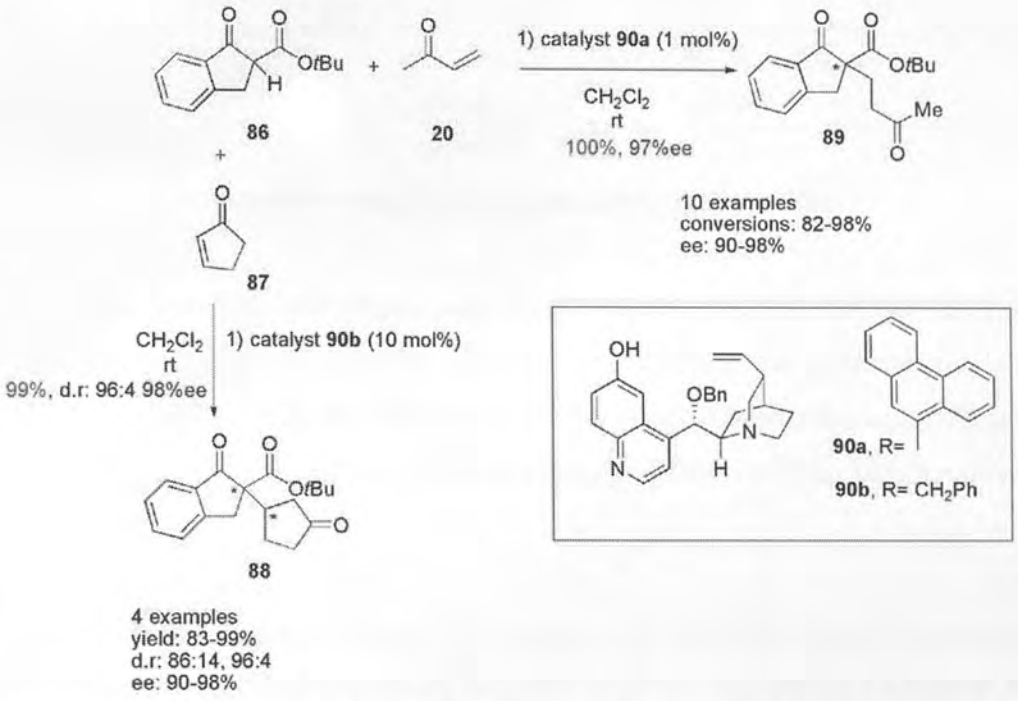


Scheme 1.21 Stereoselective creation of quaternary centres utilising cinchona alkaloid derivatives

Not only does this reaction represent a highly enantioselective and diastereoselective organocatalytic conjugate addition for the stereocontrolled formation of all carbon quaternary centres and tertiary centres, it sets the foundations for the synthesis of highly complex chiral building blocks for future manipulation.

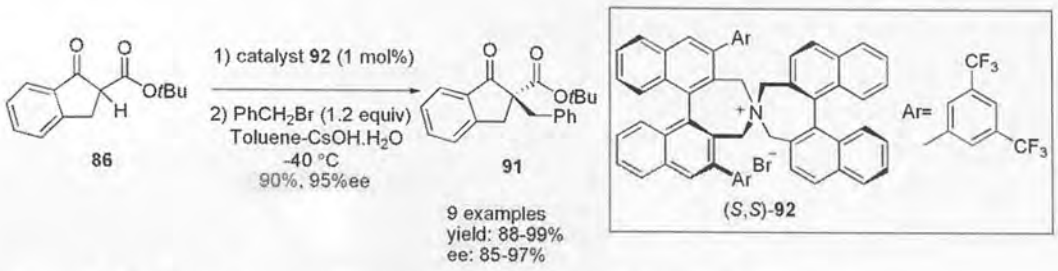
Encouraged by the success of this C-C bond formation, Deng [32] and co-workers further explored conjugate additions. However, in this instance, α,β-unsaturated ketones were employed as the Michael acceptor. [33] When 1 mol% of modified organocatalyst quinine **90a** was employed; the reaction between cyclic *tert*-butyl ketoester **86** and methyl vinyl ketone **20** proceeded smoothly in excellent yield and enantioselectivity. The scope of the reaction was investigated, and, to their delight, they found aromatic cyclic/acyclic β-ketoesters are also good candidates for the Michael addition to methyl, ethyl and aryl vinyl ketones, albeit with an increase in catalyst loading and reaction times. In order to install a fully substituted quaternary centre adjacent to a tertiary centre, β-substituted enones were employed (Scheme 1.12). High enantioselectivities and diastereoselectivities were attained when both five- and six-membered cyclic enones were employed utilising organocatalyst **90b**. The conjugate addition of a tri-substituted carbon to sterically hindered Michael acceptors is a formidable challenge. Here, they

have demonstrated the feasibility of this highly efficient conjugate addition using modified cinchona alkaloids **90a-90b**.



Scheme 1.22 Enantioselective conjugate addition of ketoesters to *α,β*–unsaturated enones

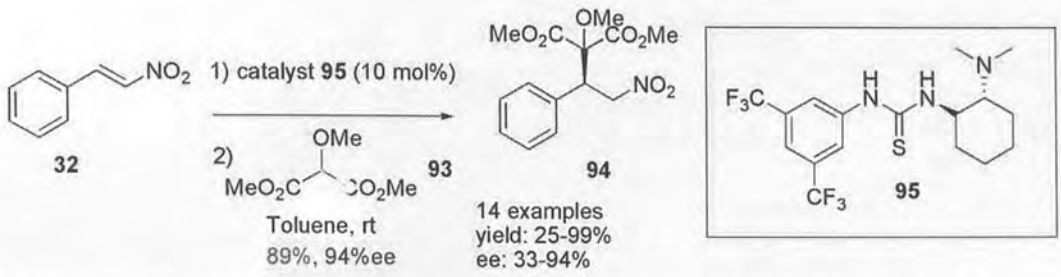
Chiral phase transfer catalysts are an additional class of organocatalysts which have demonstrated excellent asymmetric induction in the construction of all carbon quaternary centres. Maruoka [34] *et al.* discovered that in the presence of chiral quaternary ammonium salt **92**, *β*-ketoester **86** underwent a highly enantioselective phase-transfer alkylation with benzyl bromide. The addition of solid inorganic bases, for example $CsOH.H_2O$ in addition with conducting the reaction at -40 °C increased the reaction rate and the enantioselectivity to 95% e.e. for product **91**. Having successfully demonstrated the feasibility of this conjugate addition and with optimised conditions in hand, the scope of the reaction was explored.



Scheme 1.23 Phase-transfer catalytic asymmetric Michael reaction

Functionalised benzylic side chains and 2-alkoxycarbonylcyclohexanones have also demonstrated high levels of reactivity and enantioselectivity in this particular alkylation. The reaction of β-ketoester **86** with methyl vinyl ketone **20** proceeded smoothly under similar conditions to afford products which comprise of three different functionalities of carbonyl origin.

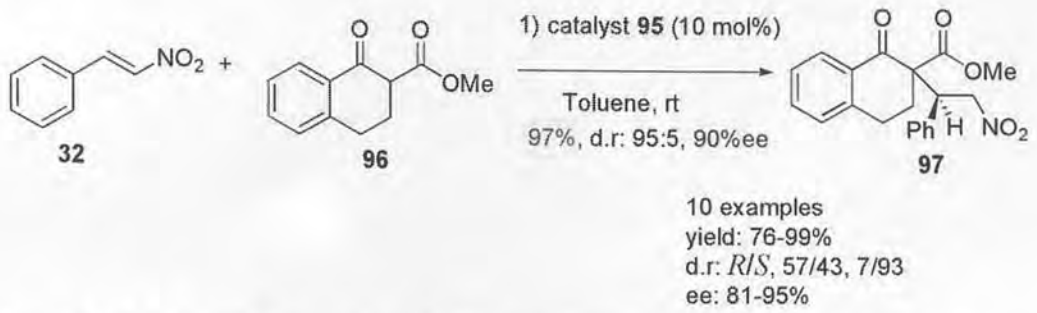
Bifunctional thiourea organocatalysts have proved to be a powerful class of catalysts due to their strong hydrogen bonding ability to a series of functional groups. Previously, urea derivatives have been employed in a wide range of reactions, for example, the Pictet-Spengler, Mannich and Strecker reactions, whilst attaining high levels of enantiomeric excess. Takemoto [7] *et al.* designed a new chiral bifunctional organocatalyst which possesses an amino group and a thiourea moiety embedded in a chiral framework. Thiourea organocatalysts have been generally realised to play a specific role in organocatalysis to achieve high levels of enantioselectivity. The double hydrogen-bonding interaction of the N-H with the nitroolefin and the activation of the nucleophile with the tertiary amine results in high levels of enantioselectivity. Generally, thioureas tend to be only partially soluble in non polar solvents; this is presumably due to strong intermolecular hydrogen bonding interactions. However, the presence of the tertiary amine aids the solubility.



Scheme 1.24 Bifunctional thiourea catalysed intermolecular Michael reaction

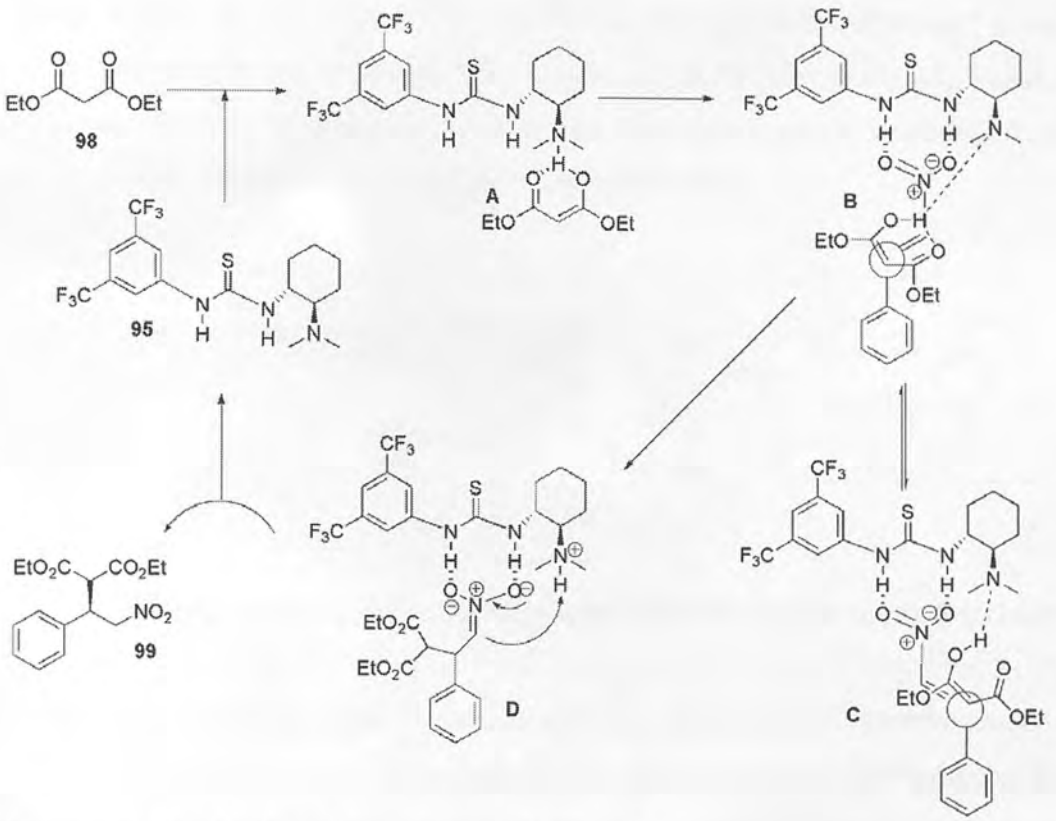
The Michael reaction between β-nitrostyrene **32** and α–substituted malonate **93** in the presence of thiourea catalyst **95**, proceeds efficiently to afford product **94** in 89 % yield. In order to optimise this reaction, first of all a series of thiourea derivatives were screened in an attempt to examine the effect the diamine moiety and the substituents on the aromatic ring have on the reaction stereoselectivity. Thiourea organocatalyst **96** was found to exert the best levels of asymmetric induction. It is thought that catalysts bearing two trifluoromethyl groups display better activity due to the increase in acidity of thiourea N-H groups. The second variable that was investigated was the size of the ester group on the nucleophile. In the case of *tert*-butyl ester the reactivity of the malonate had decreased, leading to trace amounts of the desired product. When malonate **93** was employed the reaction had gone to completion in 24 hours affording the desired product with high levels of enantioselectivity. It appears that in order to achieve high levels of reactivity the acidity of the malonate is crucial.

Thiourea organocatalyst **95** was found to be a suitable organocatalyst with not only symmetrical α–substituted malonates but also with prochiral 1,3-dicarbonyl substrates of type **96**.



Scheme 1.25 Addition of prochiral 1,3-dicarbonyl substrates with nitrolefins

In the above Michael reaction, [7] coupling of *β*-nitrostyrene **32** and 1,3-dicarbonyl **96** gave rise to desired adduct **97** in excellent yield and enantioselectivity. Further investigations into substrate tolerance revealed that when bicyclic *β*-ketoesters are engaged as the reacting partners; it is possible to obtain **97** in high yield and enantioselectivity. A series of nitroolefins were tolerated in the reaction, albeit with longer reaction times; yields and enantioselectivities were not affected. In order to elucidate the reaction mechanism, the reaction of *β*-nitrostyrene **32** and diethyl malonate was carried out utilising thiourea **95**. Conducting the reaction in methanol, for instance, resulted in diminished levels of enantioselectivity, a plausible explanation for this is that MeOH interacts with **95** via hydrogen bonding, disturbing the interaction between thiourea **95** and *β*-nitrostyrene **32** through a network of hydrogen bonding. Solvents such as THF reduced the activity of thiourea organocatalyst **95**, resulting in decreased levels of reactivity. In order to elucidate a reasonable explanation for the stereochemical outcome, the following mechanism was proposed (Scheme 1.26). It is believed that the tertiary amine of thiourea catalyst **95** deprotonates one of the acidic protons of **98**, which leads to complex (**A**). The thiourea moiety then interacts with the nitroolefin **32**. Due to the presence of the cyclohexyl group, approach of the nucleophile by transition state (**C**) is disfavoured. It seems likely that the reaction will proceed via complex (**B**), which in turn will lead to the (**D**). Transition state (**D**) then undergoes hydrolysis to afford the desired product bearing a fully substituted quaternary centre.

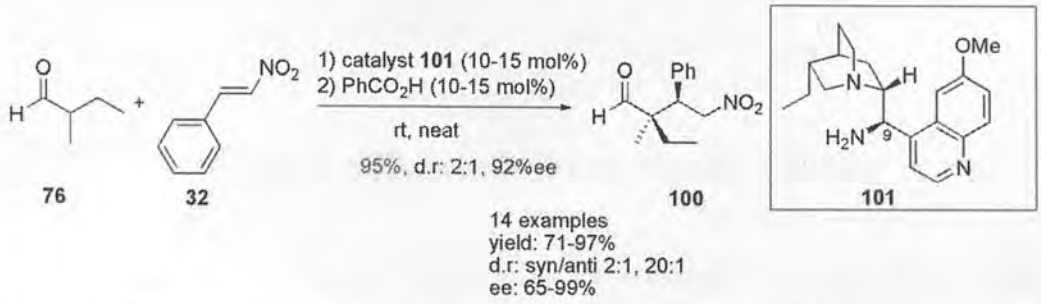


Scheme 1.26 Elucidation of stereochemical outcome

Takemoto [7] et *al.* have synthesised a new class of bifunctional organocatalysts and, in addition, they have demonstrated their use in asymmetric Michael reactions, affording adducts in both high levels of enantioselectivity and diastereoselectivity.

Due to the abundance of highly reactive nitroalkenes, it is understandable that they are elected as suitable Michael acceptors, in the journey to design new organocatalysts. Connon and co-workers [35] have reported that by modifying cinchona alkaloid templates, 1,2-diamine catalysts can be synthesised, which have demonstrated high catalytic activity in the diastereo/enantioselective nitro-Michael addition reaction with α,α-disubstituted aldehydes (Scheme 1.27). Based on developments made by other groups [36, 37] who have demonstrated the advantages associated with fine tuning of the chiral environment of cinchona alkaloids, a series of amine analogue organocatalysts were

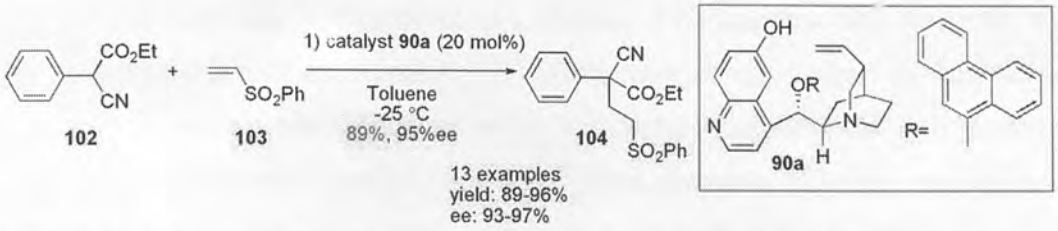
prepared. In their findings the 9-amino derivative of dihyroquinine catalyst **101** proved to be the best catalyst in conjunction with benzoic acid under solvent free conditions at rt. This particular class of organocatalysts have the capacity to catalyse the nitro-Michael addition reaction, whilst tolerating a broad range of substrates.



Scheme 1.27 9-*epi*-amino cinchona alkaloid derivatives as efficient organocatalysts

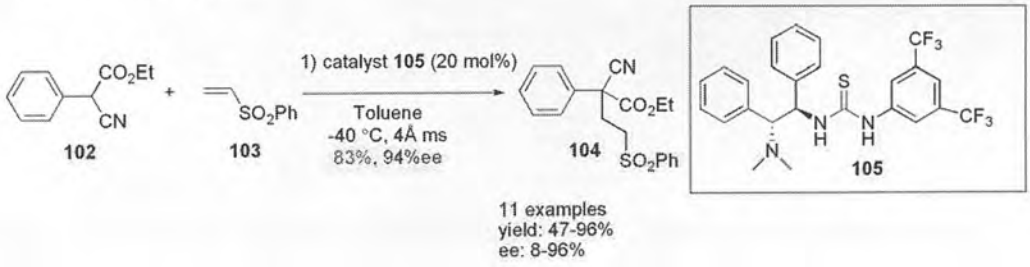
In 2005, Deng and co-workers [38] reported the first highly enantioselective catalytic Michael addition of α,α–disubstituted carbonyl Michael donors with vinyl sulfones. The reaction was successfully carried out in a non air or moisture sensitive environment which was catalysed by cinchona alkaloid derivative **90a** to afford the fully substituted all carbon quaternary centre product **104** (Scheme 1.28). Both Quinine and Quinidine forms of organocatalyst **90a** displayed excellent levels of enantioselective induction. During the organocatalyst screening, it was evident that the presence of an hydroxyl group in the C-6 position and an alkyl or aryl group on the C-9 position displayed the better levels of enantioselective induction, contrary to the use of the natural cinchona alkaloids, which generated the 1,4–adduct as a virtually racemic mixture. In an attempt to explore other parameters, a range of α–cyanoacetates with diverse electronic and steric properties were employed. The nature of the α–cyanoacetate was not detrimental to the enantioselectivity. To their delight, the Michael addition proceeds smoothly with α–alkyl α–cyanoacetate **102** when 3,5-bis (trifluoromethyl) phenyl vinyl sulfones are

employed as the electrophiles. A prominent feature of this asymmetric conjugate addition reaction is its application to the formation of α,α-disubstituted amino acids.



Scheme 1.28 Enantioselective conjugate additions with vinyl sulfones

Following the success of Deng, Chen [39] *et al.* demonstrated that bifunctional thiourea-tertiary amine derivatives of type **105** serve as excellent organocatalysts in the enantioselective asymmetric Michael addition of α–substituted cyanoacetates with vinyl sulfones, which in turn lead to all carbon quaternary centres, one of the attractive outcomes of this addition is the products can smoothly be converted into $\beta^{2,2}$–amino acids (Scheme 1.29).

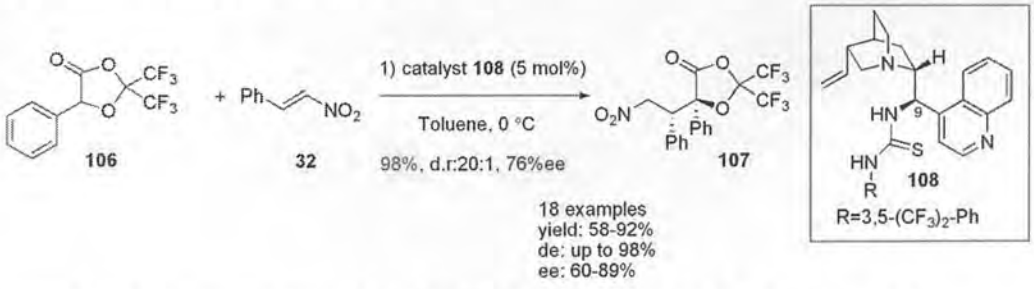


Scheme 1.29 Enantioselective Michael addition of α-cyanoacetates with vinyl sulfones

In order to test the feasibility of the Michael addition utilising α–substituted cyanoacetates with vinyl sulfones, the reaction was conducted in toluene in the presence of a bifunctional thiourea derivative **105**. In all cases, the addition product was isolated in good yield. The catalyst which exhibited highest levels of enantioselectivity was the

acyclic thiourea **105** which was derived from (*R*,*R*)-1,2-diphenyl ethylenediamine. A series of α–aryl substituted ethyl cyanoacetates were also suitable Michael donor candidates, excellent enantioselectivities were achieved in all cases; α–alkyl cyanoacetates were also applicable in this reaction. Vinyl sulfone **103**, however, was replaced with the highly electrophilic 1,1-bis(benzenesulfonyl)ethylene as the Michael acceptor. This reaction serves as an accessible route for the enantioselective formation of products with quaternary centres; moreover these products can then smoothly be converted into $\beta^{2,2}$–amino acids which have significant biological importance.

Dixon and co-workers have recently represented [40] a judicious diastereo- and enantioselective Michael addition reaction utilising 5-aryl-1,3-dioxolan-4-ones **106** as pro-nucleophiles, whereby thiourea derivative **108** catalyses the reaction. Given the general stability, high conformational rigidity and hydrogen bonding proclivities associated with these thiourea derivatives, it is not surprising why they promote this intricate C-C bond formation (Scheme 1.30). [41]

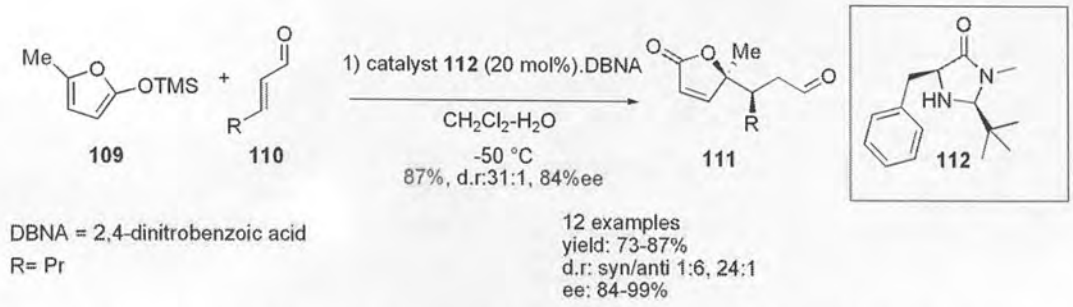


Scheme 1.30 Enantioselective Michael addition of 5-Aryl-1,3-dioxolan-4-ones

Their findings suggest that in order to promote smooth intermolecular addition of 5-phenyl-3-dioxolan-4-ones to β-nitrostyrene **32**, the presence of the two CF_3 groups is necessary. The CF_3 groups sufficiently lower the pKa of the acidic protons, allowing enolisation to take place. With optimised conditions in hand for the reaction between 5-phenyl-3-dioxolan-4-ones **106** and β-nitrostyrene with thiourea **108**, naturally the scope of the Michael addition was surveyed. In the case of *ortho*-substituents on the Michael acceptor, increased enantioselectivities were observed, albeit with an increase in reaction

times. Likewise a series of different aryl groups on the Michael acceptor were tolerated. Simple hydrolysis of this acetal functionality is used to facilitate a wide range of further transformations. One of the remarkable features of this intermolecular Michael addition is the utilisation of α-substituted enones, which successfully installs the fully substituted quaternary carbinol.

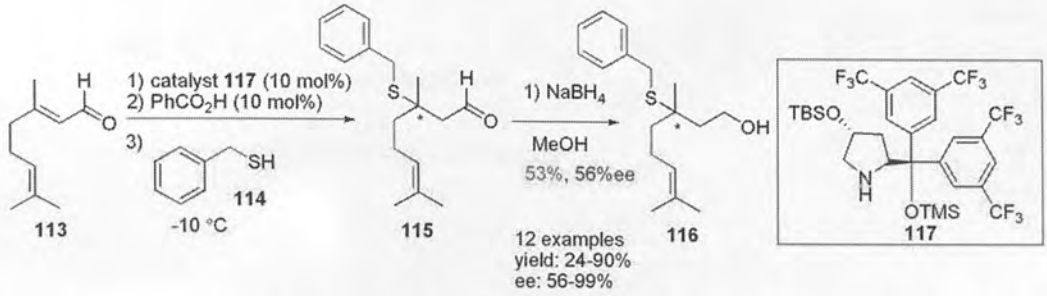
Macmillan and co-workers [42] reported the first organocatalytic Mukaiyama-Michael addition. Iminium ion catalysis provided γ–butenolide adducts in good yields with excellent enantioselectivities. Their anticipation of initial iminium-ion formation of chiral amine **112** with α,β-unsaturated aldehyde derivatives indeed was feasible because it is the higher reactivity of the iminium-ion species in comparison to the carbonyl group which facilitates the addition of the furan **109**. A vast range of furan derivatives are tolerated in the reaction, without having a damaging effect on the enantioselectivity. It also noteworthy, that the nature of the β-olefin has very little influence on the stereochemical outcome of the reaction.



Scheme 1.31 Direct method for the synthesis of enantioenriched γ-butenolide architecture

An application of these compounds is further manipulation of these γ–butenolides **111** can result in the synthesis of spiculisporic acid, which has significant importance in metal decontamination processes and fine polymer production.

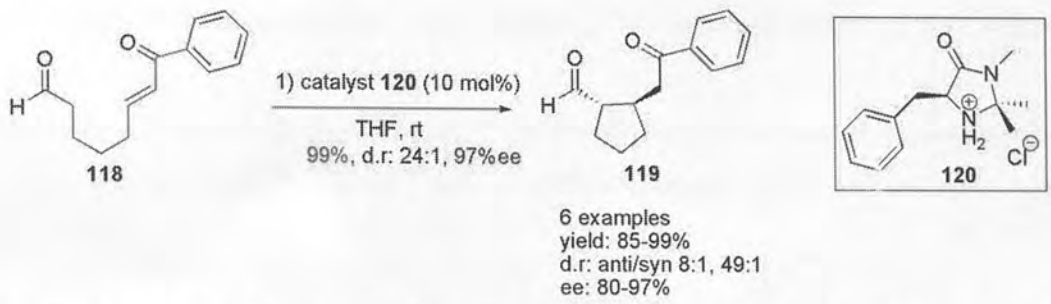
The thiol addition is a well known 1,4-addition reaction which is important in both biochemical processes and in synthesis. It is, therefore, of interest to develop an organocatalytic enantioselective variant of the reaction. Oriyama [43] *et al.* recently reported a solvent free procedure to afford chiral sulfides with fully substituted quaternary centres; this was achieved by employing organocatalyst **117**. This particular reaction (Scheme 1.32), works well with β-substituted α,β–unsaturated aldehydes of type **113**, high enantioselectivities and yields are obtained. Attractive features of this methodology are the significant substrate flexibility, the reaction tolerates both β,β-disubstituted and α,β–unsaturated aldehydes, thus leading to fully substituted carbon centres in the presence of their highly hydrophobic organocatalyst **117**. Reduction of chiral sulfide **115** to the primary alcohol **116**, makes the reaction amenable to further modification.



Scheme 1.32 Intermolecular asymmetric conjugate addition of thiols to α,β–unsaturated aldehydes

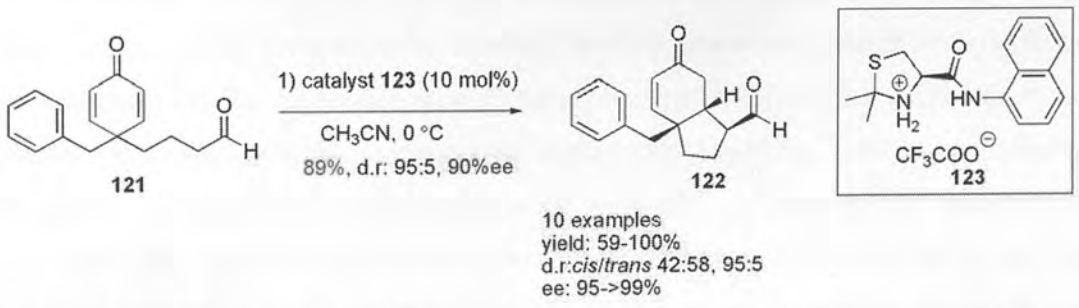
1.7 Enantioselective organocatalytic intramolecular conjugate additions

As previously demonstrated by various groups, there are a number of elegant enantioselective intermolecular Michael additions for the construction of quaternary centres, but there is a lack of enantioselective intramolecular Michael reaction variants. Remarkable progress was reported [44] by List *et al.* whereby cyclic ketoaldehydes were furnished in excellent yields and enantioselectivities. In the presence of Macmillan's first imidazolidinone catalyst **120**, a wide range of formyl enones underwent smooth cyclisation to afford ketoaldehydes **119**. The ketoaldehydes are also applicable in tandem sequences. It is thought that this class of reaction can be further investigated: for instance by introducing an α-substituent on the aldehyde, an entire new field of organocatalysis can be unravelled, with the incentive to construct quaternary centres.



Scheme 1.33 The first reported organocatalytic enantioselective intramolecular Michael reaction

A notable case of an intramolecular Michael addition to create three contiguous stereocentres, whereby one of which is a quaternary centre has been carried out by Hayashi [45] and co-workers. Prochiral substrate **121** was synthesised from 3-ethoxycyclohex-2-en-1-one in a coherent six step sequence. After extensive screening, the trifluoroacetic acid salt of cysteine derived amine **123** was found to provide excellent levels of enantioselectivity and diastereoselectivity of bicycle [4.3.0] nonene products **122** (Scheme 1.34).

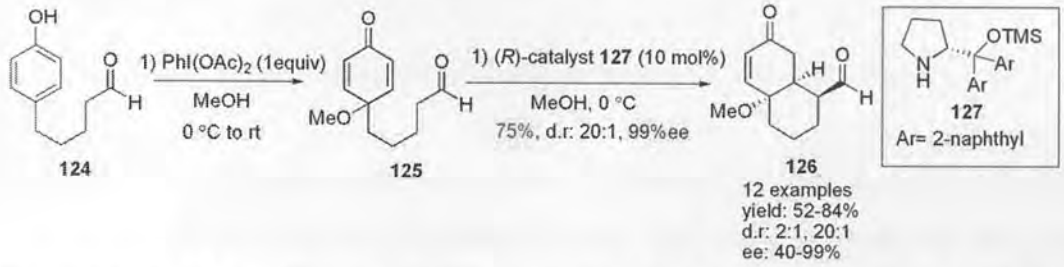


Scheme 1.34 Cysteine-derived organocatalyst promotes intramolecular Michael reaction

One of the attractive features of this methodology is bicycle [4.3.0] nonene carbon skeletons are synthesised in one step via an enamine intermediate, which selectively attacks one of the enantiotopic π–bonds. Carbon skeletons of this type are found in a

wide range of natural products, thus explaining the synthetic utility of this Michael reaction.

Based on the discovery by Hayashi, [45] an organocatalytic oxidative dearomatisation strategy was developed by Gaunt [46] and co-workers (Scheme 1.35).



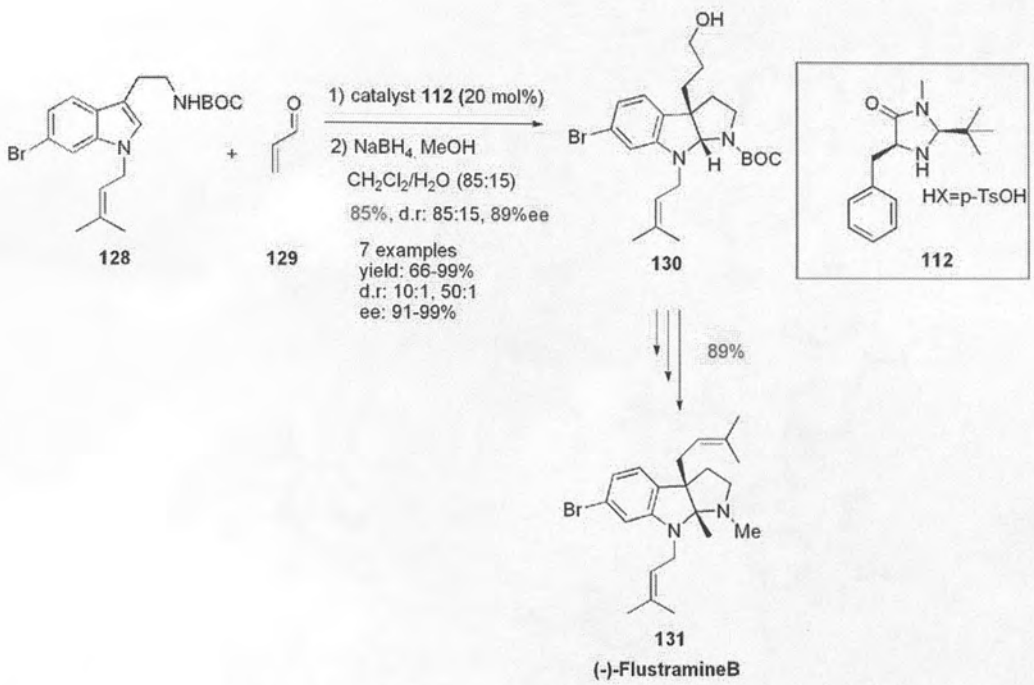
Scheme 1.35 Enantioselective dearomatisation strategy utilising pyrolidine derivatives

Prochiral phenol starting materials **124** are readily oxidised with $PhI(OAc)_2$ to afford *meso*-cyclohexadienones **125** in the presence of protic nucleophiles. Catalyst **127** promotes the intramolecular Michael addition reaction to afford a range of highly functionalised polycyclic molecules **126**. In order to develop optimum conditions for the dearomatisation and intramolecular Michael reaction, *meso*-cyclohexadienone **125** was isolated and used as a model substrate. In the presence of Jørgensen`s organocatalyst, the reaction proceeded in both moderate yield and enantioselectivity. In contrast, replacing the phenyl groups on the chiral framework with two naphthyl groups significantly improved the diastereo/enantioselectivity due to better facial selectivity in the desymmeterisation step. The reaction tolerates a broad range of variables. Biaryl phenols are good candidates for the cyclisation, and non oxygen nucleophiles can also participate in the cyclisation. The incorporation of heteroatoms in the tether also proves to be effective in this reaction, allowing for the construction of highly diverse enantiopure products in high yield. However, substitution on the phenol ring resulted in poor diastereo/enantioselectivity. The stereochemistry is rationalised via a transition state,

which strongly suggests the naphthyl groups shield one face of the enamine, the π–π interaction between the *meso*-cyclohexadienone and the enamine favours an *endo* attack leading to high levels of stereocontrol. This methodology demonstrates the viability of this class of reaction; highly diverse structural architectures possessing quaternary centres are synthesised in a simplistic manner.

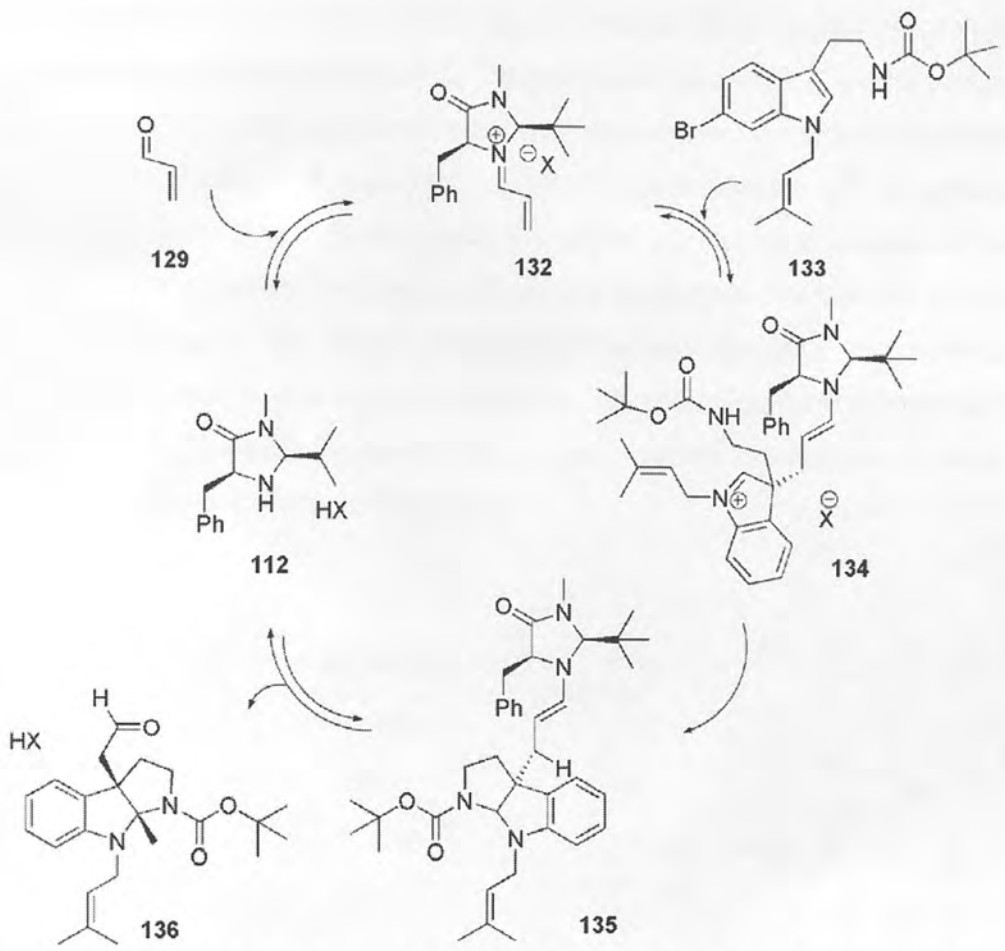
1.8 Asymmetric conjugate additions in natural product synthesis

Aforementioned, conjugate additions are very important C-C bond forming strategies, especially in the installation of quaternary centres for natural product synthesis. The existing methodologies to install quaternary centres via a conjugate addition are reliable and robust, and several groups have demonstrated the utility of these organocatalytic enantioselective methodologies in key steps of natural product synthesis.[47(a)] Macmillan and co-workers have reported the use of their secondary amine [47(b)] organocatalyst **112** in a novel addition cyclisation for the total synthesis of (-)-Flustramine B **131**; the pyrroloindoline motif was constructed in an organocatalytic and enantioselective fashion (Scheme 1.36).



Scheme 1.36 Total synthesis of (-)-Flustramine B

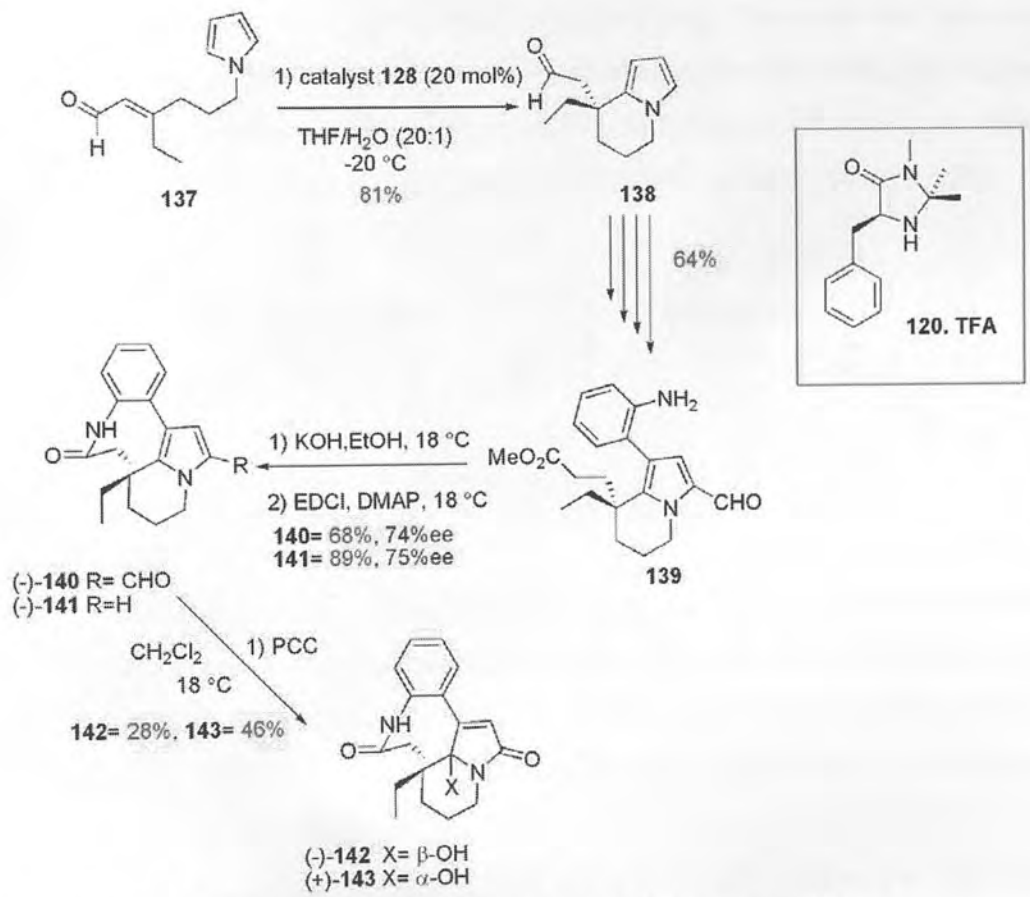
Pyrroloindolines **128** are a subclass of alkaloid motifs which have been isolated from a diverse range of natural sources. They have shown to demonstrate remarkable biological activity, hence the desire to develop new enantioselective methods for the construction of these complex molecules.



Scheme 1.37 Pyrroloindoline synthesis via a cascade addition-cyclisation strategy

This conjugate addition of indoles to α,β-unsaturated aldehydes is achieved with high levels of of enantiocontrol when the tosic acid salt of chiral catalyst **112** is employed. Addition of the indole **128** to iminium ion **132**, gives rise to the desired fully substituted quaternary centre. The pending amine group then undergoes a 5-*exo*-heterocyclisation to the indolium ion **134**, giving rise to tricyclic structure **135**, whilst regenerating imidazolidinone catalyst **112**. This class of conjugate addition tolerates both diverse α,β–unsaturated aldehydes and modified indole rings with no erosion on reaction or selectivity.

Given the success of the intermolecular conjugate addition of indoles to α,β-unsaturated aldehydes reported by Macmillan *et al.* [47, 48] Banwell and co-workers [49] employed this strategy to install the fully substituted quaternary centre. The central issue involved in the synthesis of these novel anti-cancer agents, is the installation of the quaternary centre. With a view to install the quaternary centre via an intramolecular Michael reaction in an enantioselective manner, Macmillan's imidazolidinone **120** was employed as the organocatalyst to ensure smooth cyclisation affording enantioenriched tetrahydroindolizine **138**. Due to the instability of **138**, reduction to the primary alcohol was carried out to determine the enantiomeric purity. With the stable alcohol in hand the complete synthesis of **139** was accomplished.

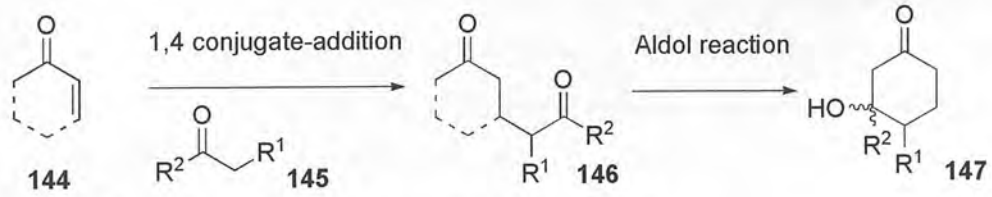


Scheme 1.38 Total synthesis of (-)-leuconolam and (+)-*epi*-leuconolam

Treatment of **140-141** with PCC in the presence of 4 Å molecular sieves, generated a separate mixture of (-)-leuconolam **142** and (+)-*epi*-leuconolam **143**. Here, the success of the intramolecular Michael reaction provides an efficient enantioselective assembly of fully substituted quaternary centres.

1.9 Enantioselective tandem Michael-aldol reactions

Tandem reactions are those which involve a combination of two or more reactions, which take place in a consecutive manner. [50] Asymmetric tandem transformations are an attractive strategy for the construction of complex molecules with one or more contiguous stereocentres. The advantages of this class of reaction are the reaction takes place in one pot using a single catalyst, while producing less waste and minimising excessive handling. Tandem organic reactions are often initiated by conjugate additions. The secondary reaction can then occur in an intermolecular or intramolecular manner leading to the desired adduct, without isolation of the intermediates (Scheme 1.39).

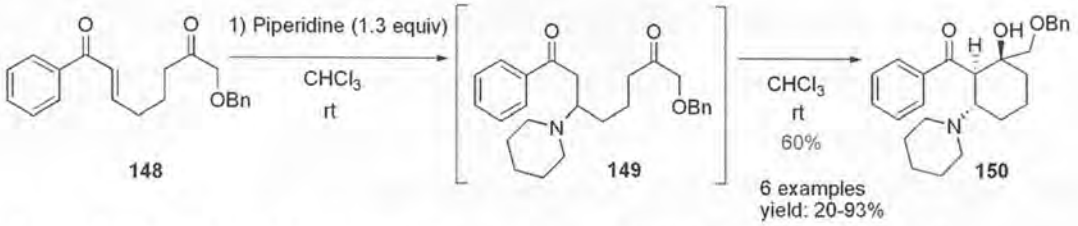


Scheme 1.39 Typical tandem-Michael aldol cyclisation

Due to the high demand for efficient methods to access these complex molecules by both academia and industry, considerable efforts have been put forward, in order to find new methodologies for catalytic asymmetric enantioselective tandem transformations, as to date there is a lack of tandem Michael-aldol reactions, which result in the formation of quaternary centres.

One of the first notable examples of a tandem Michael-aldol reaction was reported by Murphy [51] *et al.* this reaction was mediated by secondary amines, thiols and phosphines.

Treatment of ketone **148** in chloroform with an excess of piperidine afforded **150** in 60% yield. In each and every case, one single diastereomer was produced. This observation led them to believe that the reaction takes place through initial conjugate addition of the amine, subsequently generating the enol which can then undergo an intramolecular aldol cyclisation.



Scheme 1.40 Tandem Michael aldol reaction mediated by secondary amines

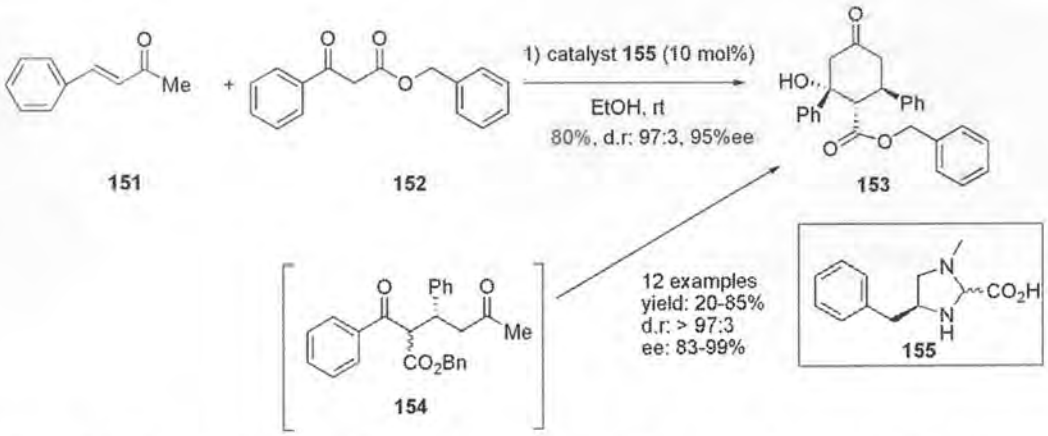
Cyclic adduct **150** was found to be stable for <6 days, without any sign of the elimination Baylis-Hillman product. Murphy *et al.* rely on the union of prochiral starting material **148** and nucleophile piperidine, for the installation of quaternary centres.

It is worth emphasising that the above tandem Michael-aldol reaction proceeds in the presence of an achiral secondary amine (Scheme 1.40). Therefore, it appears that by introducing a secondary chiral amine into this reaction may indeed result in some enantioselective induction in Michael additions. Chiral amines can serve either to attack the Michael acceptor in the β-position, or activate the Michael acceptor by forming an iminium species or an enamine intermediate. In regard to enantioselective tandem reactions triggered by conjugate additions, there have been considerable efforts put forth by many research groups. [12,52] However, the installation of an all carbon quaternary centre via an organocatalytic enantioselective tandem Michael-aldol reaction still is in its infancy.

With a view to create C-C bonds in a consecutive manner, and given the lack of enantioselective organocatalytic strategies in the literature Jørgensen [53] *et al* disclosed

the first highly enantioselective and diastereoselective organocatalytic tandem Michael-aldol reaction. Inspired by Macmillan's imidazolidinone organocatalyst, they developed an imidazoline which was synthesised from readily available phenylalanine.

Catalyst **155** exhibited high levels of enantioselective induction in previous studies for the enantioselective conjugate addition of nitroalkanes, [54] *β*-ketoesters [55] and 1,3-dicarbonyl substrates [56] to *α,β*-unsaturated enones. To their delight the reaction preceded in various solvents but, on closer inspection, the use of protic solvents increased yields significantly. Ethanol was elected as the solvent for further reactions. In the presence of catalyst **155** in ethanol, cyclohexanone **153** is generated via a tandem Michael-aldol transformation.

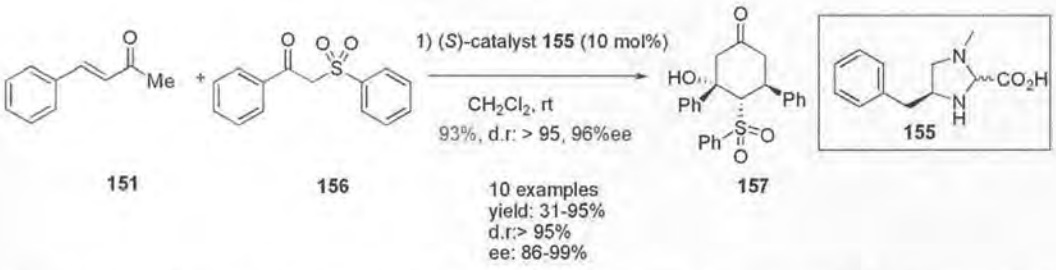


Scheme 1.41 Tandem Michael-aldol reaction of acyclic *β*-ketoesters with *α,β*-unsaturated ketones

It is thought that chiral catalyst **155** catalyses the intermolecular Michael reaction by initial iminium ion formation with Michael acceptor **151**, which then lowers the LUMO of the acceptor, rendering it more electrophilic. In addition to forming the iminium ion, organocatalyst **155** acts as a base by deprotonating the *β*-ketoester **152**, which readily attacks the Michael acceptor. The Michael adduct exists as a mixture of *syn/anti*

isomers. Nevertheless, the intramolecular aldol reaction takes place via in a six membered chair transition state which sets the large groups in an equatorial position leading to high levels of diastereoselctivity. In order to determine the scope of the tandem Michael-aldol reaction, various aromatic and heteroaromatic β-substituted unsaturated ketones were treated with β-ketoester **152** to afford cyclohexanones with high levels of reactivity and enantioselectivity.

Further developments of this class of reaction were explored. [57] The reaction scope can be extended to β-diketones and β-ketosulfones as Michael donors with α,β-unsaturated enones in the presence of catalyst **155** (Scheme 1.42).

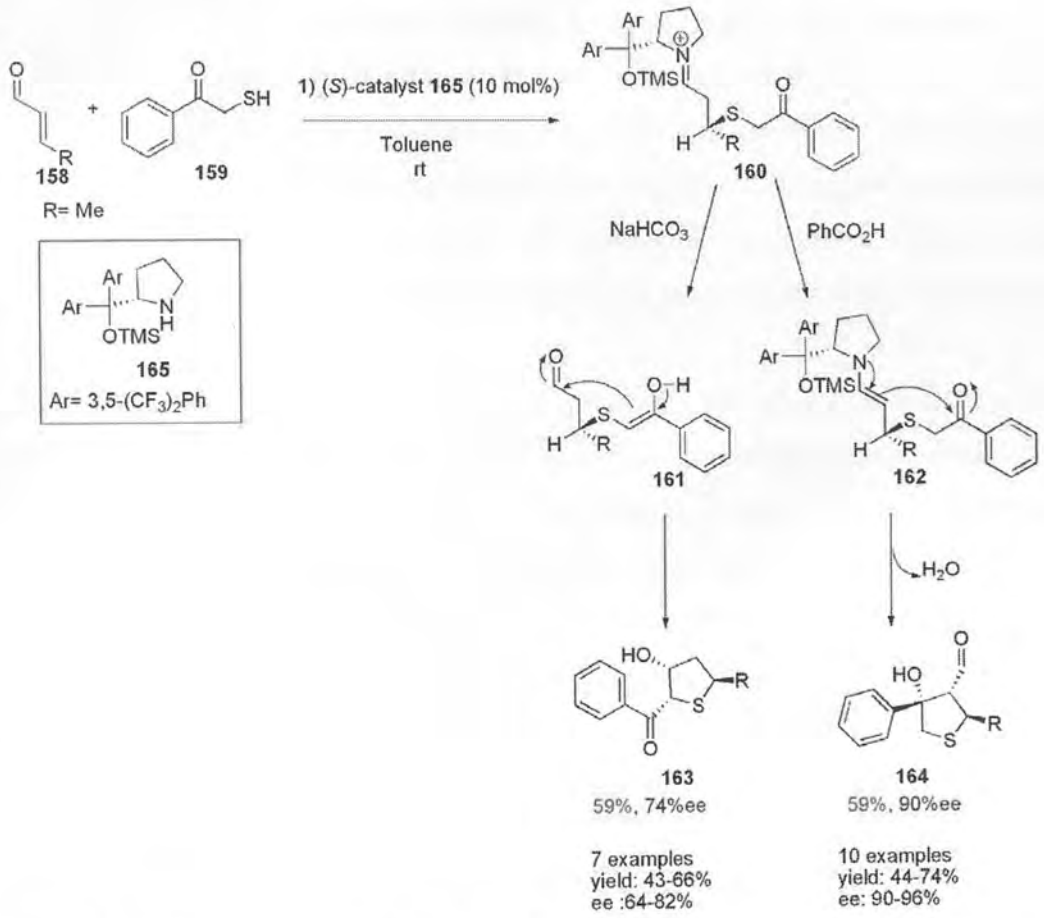


Scheme 1.42 Enantioselective Tandem Michael-aldol reaction of β-diketones with α,β-unsaturated ketones

One of the advantages of this approach is optically active cyclohexanones are synthesised in a one pot procedure, bearing ketone and sulfone functionalities. The reactions proceeded well using various electron donating and electron withdrawing group's substituted on the α,β-unsaturated ketones. Various α,β-unsaturated ketones reacted with 2-phenylsulfonylacetophenone **156** to form cyclohexanones in a diastereoselective and enantioselective fashion. Cyclohexanones possessing these functional groups are then attractive substrates for facile transformations.

Given the success of the tandem Michael-aldol reaction previously reported by Jørgensen, [53] curiosities prompted the research group to further investigate other possibilities of this class of reaction. [58] Given the biological activity associated with

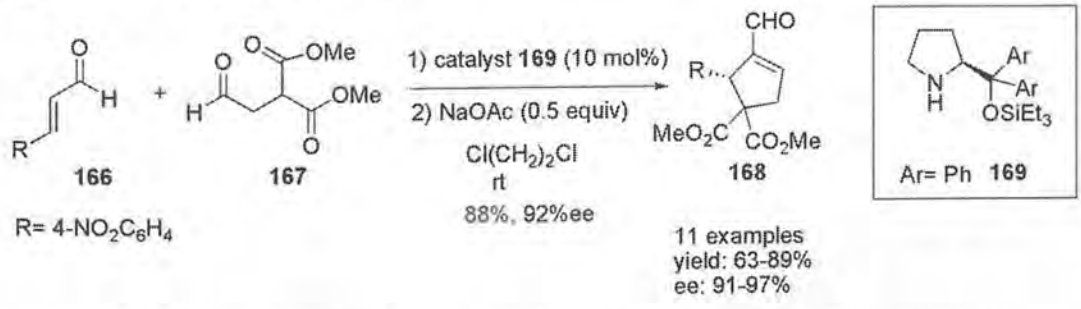
sulfur containing compounds, [59] employing thiols as the nucleophilic source was an attractive route to explore. One of the notable observations in this account is that acidic conditions promote the formation of the quaternary centre tetrahydrothiophene carbaldehyde **164**. However, in the presence of base, a different pathway is taken which results in the formation of tetrahydrothiophene **163**. The outcome of the reaction therefore depends on the variations in the intramolecular aldol step [60] (Scheme 1.43).



Scheme 1.43 Enantioselective tandem Michael-aldol reaction of thiols to α,β-unsaturated enones

In both cases, acidic or basic, the reaction proceeded well in toluene yielding the tetrahydrothiophene derivatives. When thiol **159** was treated with α,β-unsaturated aldehyde **158** in the presence of benzoic acid and organocatalyst **165**, the asymmetric tandem reaction favoured the formation of **164**. Based on the product generated in the presence of the acid, it is thought that following the Michael reaction, the catalyst accelerates the intramolecular aldol reaction, whereas in the presence of the base, simple enolisation of **160** followed by a diastereospecific aldol reaction lead to the formation of **163**. The higher levels of enantioselectivity observed with tetrahydrothiophene **164** reflect this argument. This mechanistic study provides strong evidence that the enantiodiscriminating step is in the Michael addition and no further enantioselective induction takes place in the second catalytic step. Tetrahydrothiophene carbaldehydes **164** undergo smooth reduction to afford the corresponding alcohols. This functional group transformation can be used to mediate a wide range of reactions to form stable aromatic thiophenes.

Cyclopentenes are found in a vast range of bioactive molecules, thus there has been considerable interest by organic chemists to develop efficient asymmetric methods for their construction. However, in the past the general methods are transition metal mediated. Wang and co-workers [61] have efficiently assembled functionalised chiral cyclopentenes, by means of an organocatalysed cascade Michael-aldol reaction. Besides the installation of a quaternary centre, two new C-C bonds are generated in one pot with high yields and enantioselectivities.

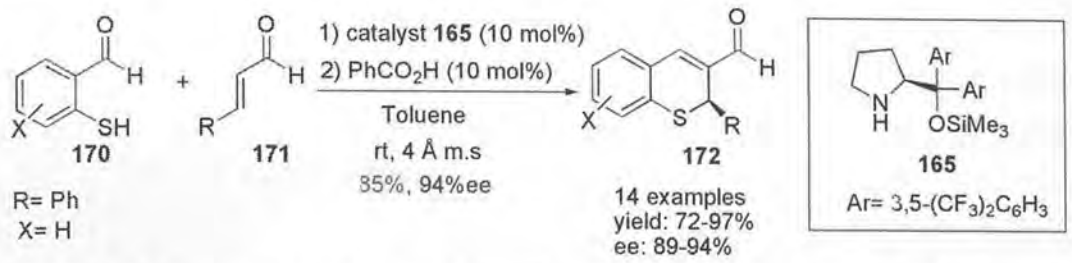


Scheme 1.44 Enantioselective assembly of functionalised chiral cyclopentenes

They decided to use dimethyl 2-oxoethylmalonate **167**, as a suitable substrate, not only is it a stable electron rich nucleophile, but also has an electrophilic aldehyde, which serves as an efficient electrophile for the subsequent intramolecular aldol step. It is also thought that malonate **167**, as a nucleophile will prevent undesirable side reactions, this is presumably due to the ease in which it is enolised together with the steric hindrance. It has been demonstrated that α,β-unsaturated aldehyde **166** with dimethyl 2-oxoethylmalonate **167** in the presence of 10 mol% of catalyst **169** is most efficient in terms of yield and enantioselectivity.

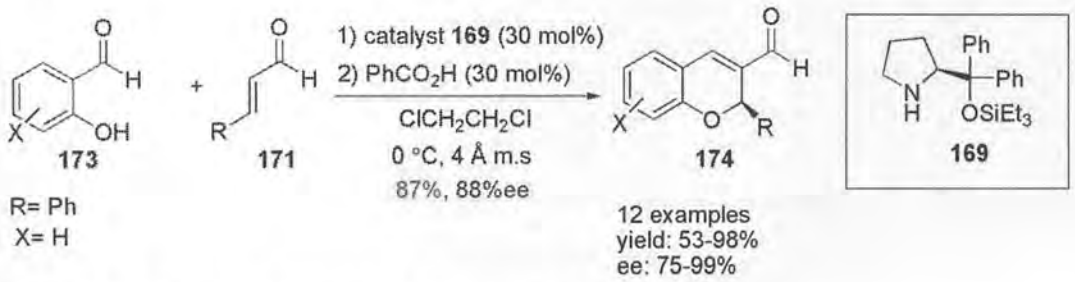
1.10 Wang's thiol mediated tandem Michael-aldol reactions

In 2006, Wang *et al.* disclosed [58] a new enantioselective organocatalysed tandem Michael-aldol reaction which furnished thiochromenes in high yields and enantioselectivities (Scheme 1.45). Simple activation of aldehyde **171** with chiral pyrolidine **165** and benzoic acid as an additive, led to formation of the iminium ion; nucleophilic conjugate addition of thiol **170** to the iminium ion then triggers the cascade Michael-aldol process, which subsequently undergoes dehydration to afford the desired thiochromene **172**. Following extensive screening, the reaction was found to be applicable with a variety of α,β-unsaturated aldehydes and 2-mercaptobenzaldehyde derivatives. At first glance, it may seem straightforward to install a quaternary centre within this class of molecule; one may simply employ α-substituted aldehydes, which subsequently would inhibit the dehydration step. However, iminium ion activation with chiral secondary amine organocatalysts tends to be problematic with α-alkyl-substituted enals.



Scheme 1.45 Cascade Michael-aldol reaction using 2-mercaptobenzaldehydes

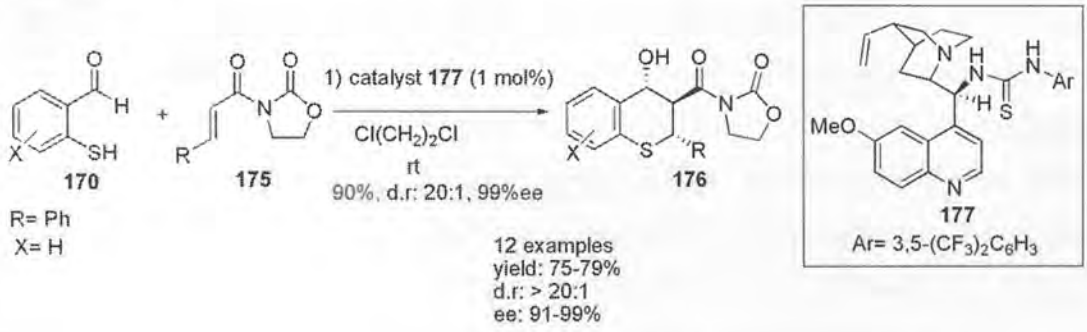
Given the broad utility of the thiol promoted Michael-aldol reaction (*vide supra*), Wang and co-workers [62] embarked upon an oxygen variant of this class of reaction. This challenge was tackled, simply by replacing the thiol moiety of the nucleophile with a phenol.



Scheme 1.46 One-pot approach to chiral chromenes

However, to their surprise no reaction occurred when the same reaction conditions for the thio-Michael aldol reaction were employed. In an attempt to ascertain the reason behind this, a series of different organocatalysts were surveyed, which closely resembled **169**. To their delight, the reaction between *trans*-cinnamaldehyde **154** and salicylaldehyde **173** with 30 mol% (*S*)-diphenylpyrrolinol triethylsilyl ether **169** proceeded smoothly affording chromene **174** in high yield and enantioselectivity, albeit with considerably longer reaction times. The oxa-Michael-aldol reaction was tolerant to a diverse range of substrates, but reaction efficiency and enantioselectivity varied depending on the electronic and steric nature of the α,β-unsaturated aldehyde.

Given that tandem reactions serve as a powerful tool for the construction of complex structures in both academic and industrial laboratories, Wang [63] *et al.* further investigated this class of reaction. In this instance, benzothiopyrans were generated in a concise fashion, again using the tandem Michael-aldol process (Scheme 1.47). Three contiguous centres are generated with high enantio and diastereoselectivity. Wang and co-workers envisioned that by changing the aldehyde to a carboxylic acid derivative the undesirable dehydration process may be avoided, therefore creating two further stereocentres.



Scheme 1.47 Thiourea promoted Michael-aldol reaction of 2-mercapto-benzaldehydes with α,β-unsaturated oxazolidinones

They anticipated that the conjugate addition step may be accelerated by changing the nature of the Michael acceptor from an aldehyde to an oxazolidinone. This hypothesis was based upon the capacity of bifunctional thiourea catalysts to form multiple hydrogen bonding interactions with the Michael acceptor. In the presence of thiourea **177**, the tandem thio-Michael aldol reaction proceeds smoothly in just 1 hour, affording benzothiopyrans **176** in high chemical yield (Scheme 1.47). The overall reaction efficiency is not influenced by the electronic and steric nature of the Michael acceptor, however, the enantioselectivities varied significantly depending on the thiourea

organocatalyst. From these results they concluded that in order to achieve high levels of enantiocontrol, the basic and acidic functional group on the catalyst's framework must be correctly orientated towards the Michael acceptor, together with a network of hydrogen bonds.

1.11 Conclusions

An extensive survey of existing methodologies, which lead to the construction of all carbon quaternary centres, has been reported. The construction of complex organic molecules bearing quaternary centres represents one of the most important synthetic challenges. This, in some measure, is due to the abundance of quaternary carbon centres found in a wide range of naturally occurring compounds, and the high level of stereo- and regiocontrol which can be achieved by employing an organocatalyst. In this respect, both the enantioselective inter- and intramolecular variants of the conjugate addition have proven to be a prominent strategic theme in natural product synthesis.

The stereoselective synthesis of natural products relies on asymmetric conjugate additions to install quaternary centres. These complex molecules can then undergo further manipulations. Quaternary centres are found in a vast array of natural products. There are endless examples, Napalilactone, [64] Vincamine, (+)-Quebrachamine, [65] (-)-Aspidospermidine, (-)-Eburnamomine, physostigmine and podocarpic acid, all of which depend on an asymmetric conjugate addition to install the all carbon quaternary centre. The enormous versatility associated with the asymmetric conjugate addition makes it a highly desirable method to construct complex building blocks, which would be difficult to obtain by other means.

Several groups have elegantly utilised both inter- and intramolecular asymmetric conjugate additions, as an efficient way to install quaternary centres. All modes of organocatalysis are applicable in this class of reaction, Lewis acid, Lewis base, Brønsted acid and Brønsted Base. Without a doubt, Lewis Base organocatalysis is the most abundant in organocatalysis, hence the extensive review herein. However, the use of

chiral H-bond donors (Brønsted acids) is becoming an attractive emerging field in organocatalysis. It is worthy to note that the majority of asymmetric conjugate additions are intermolecular and involve acyclic starting materials. This may be due to several factors, first of all the abundance of readily available acyclic starting materials, and secondly often a lengthy synthetic sequence of the starting material is required for the intramolecular variant.

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Chapter 2

The α-effect in Organocatalysis

2.1 Asymmetric Cyclopentannulation

Given the importance of oxygenated five membered rings in medicinal and natural-product chemistry, [1,2] our principal aim was to devise a novel organocatalytic enantioselective methodology, for the assembly of five membered carbocycles. Fig 2.1 shows representative examples of cyclopentanoids embedded within natural products.

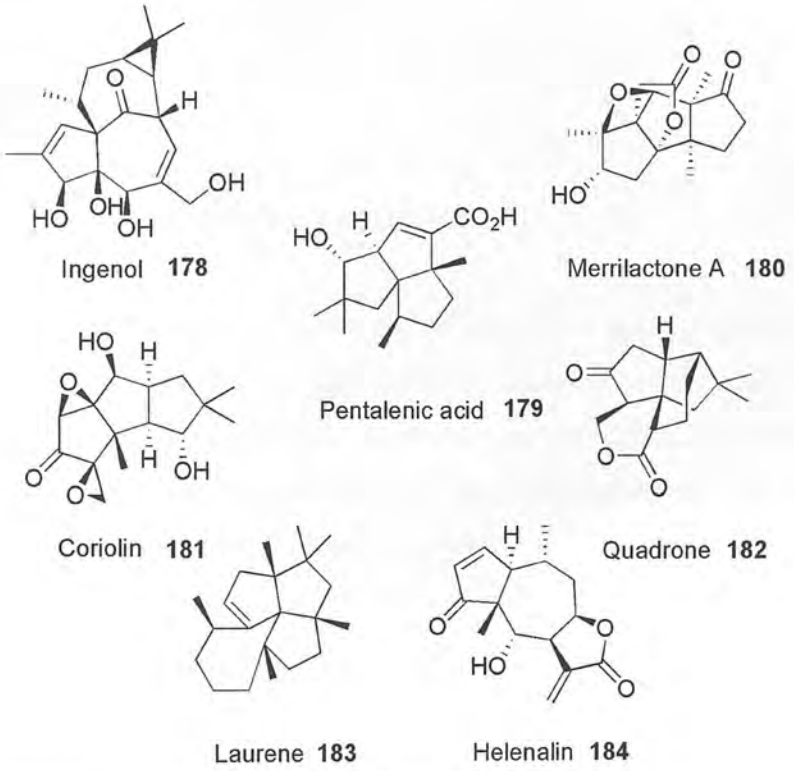


Fig 2.1 Representative cyclopentanoid natural products

The construction of six-membered rings plays a dominant role in synthetic organic chemistry. However, with regard to the assembly of five-membered rings; there is no particular cyclopentannulation strategy. The isolation of various terpene natural products, instigated investigations by several research groups for the construction of new cyclopentannulation strategies (Fig 2.1). Prominent methodologies are the Pauson

Khand reaction, [3+2] cycloaddition of olefins, ring closing metathesis and the Nazarov cyclisation (Fig 2.2).

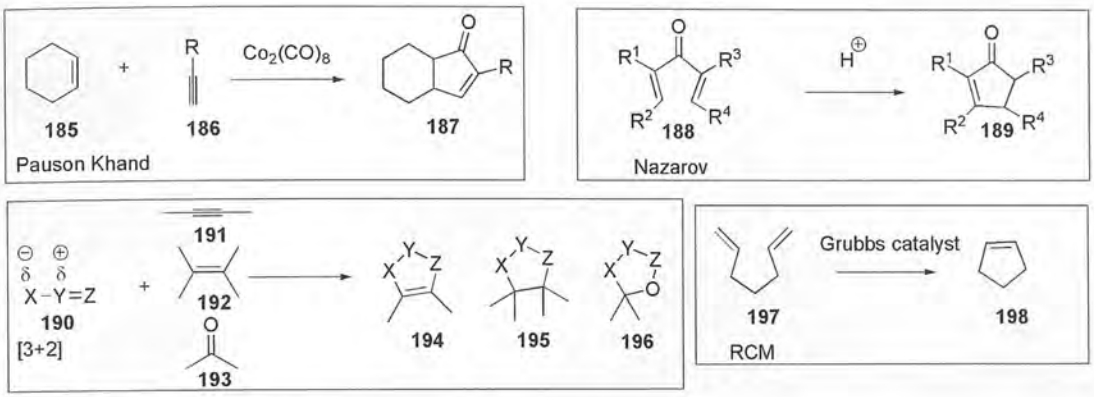
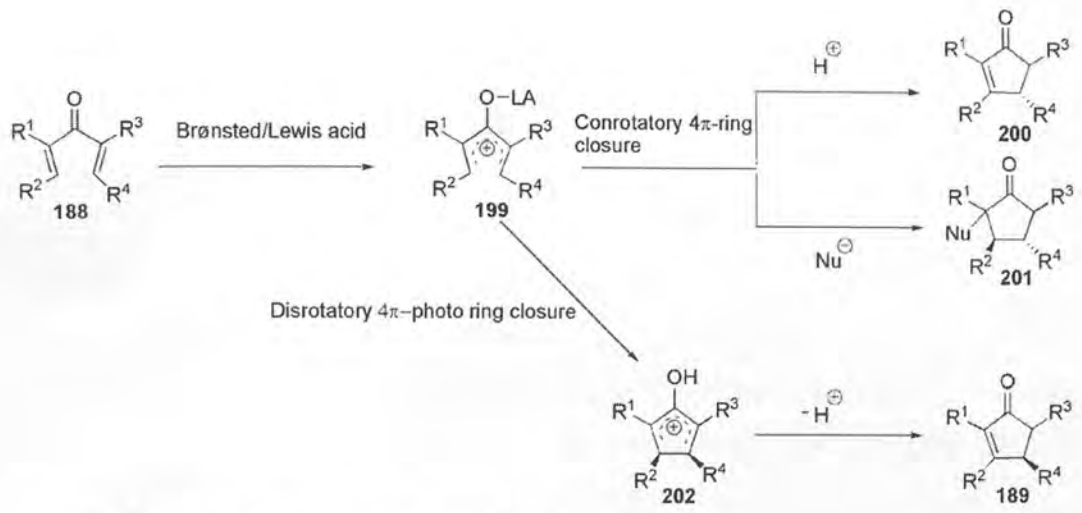


Fig 2.2 Existing cyclopentannulation strategies

However, given that the existing routes are confined to a narrow substrate class, we embarked upon developing a new organocatalytic enantioselective cyclopentannulation methodology for the synthesis of highly functionalised enantiopure cyclopentanoids. We reasoned that iminium ion catalysis in the Nazarov cyclisation could be employed as an elegant asymmetric catalytic route for their synthesis.

2.2 Nazarov Cyclisation

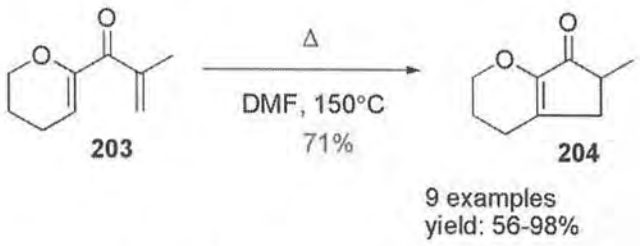
The Nazarov electrocylclisation was discovered in 1949, by Ivan Nikolaevich Nazarov. This class of reaction [3] generally involves the use of cross–conjugated enones, which upon treatment with a Lewis acid or Brønsted acid induces the formation of a pentadienyl cation **199**. The cation then undergoes a thermally allowed 4π–electrocyclisation; resulting in migration of the proton, followed by tautomerisation of the enol to afford the cyclopentenone **200**. The double bond will usually reside in the most thermodynamically stable position, *i.e.*, that with the highest degree of substitution.



Scheme 2.1 Nazarov electrocyclisation mechanism

Over the years, there has been considerable interest in the Nazarov cyclisation. [4-6] Besides, the simplicity in generating the dienone precursors, the reaction proceeds under mild reaction conditions with fast reaction times.

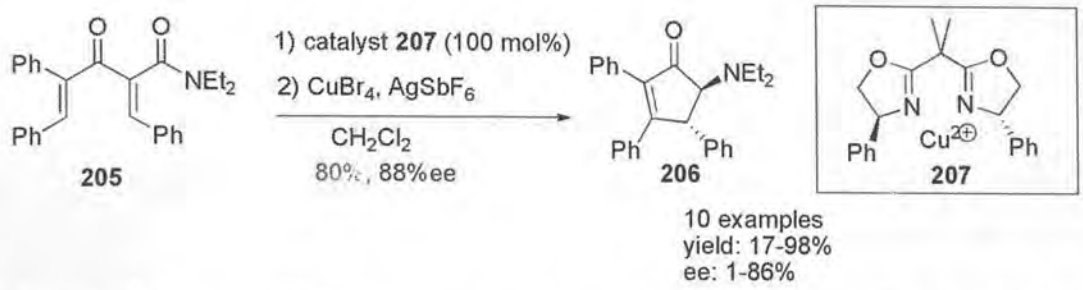
Work carried out within the Greaney group, illustrates the success of the Nazarov cyclisation under mild reagent free conditions, [7] *i.e.* in the absence of a strong Lewis acid promoter. Divinyl ketones of type **203** in the absence of any harsh acid promoter undergo cyclopentannulation in the presence of heat, producing a reagent-free transformation. The success of this transformation was compatible with both α,α^1–dialkyl and oxyallyl dienone substrates, which indicates that the reaction is tolerant to a broad range of functional groups. The most prominent feature of this methodology is the development of these neutral conditions may be applicable with acid sensitive substrates, which were inaccessible previously.



Scheme 2.2 Reagent free Nazarov cyclisations

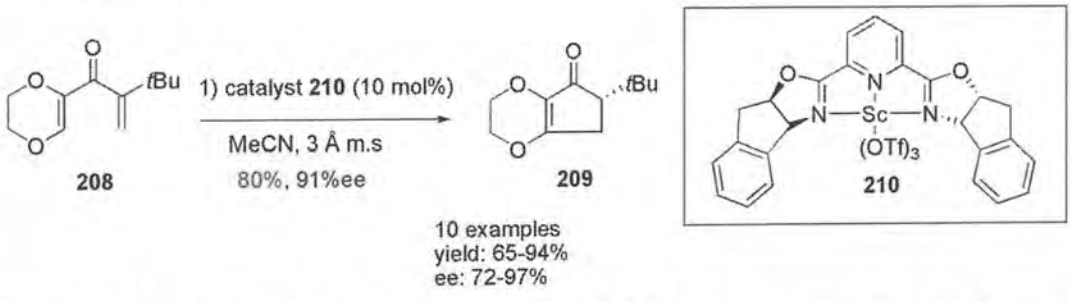
The Nazarov reaction is one of the few electrocyclisations which are subject to catalysis. However, despite the synthetic utility of this cyclisation, it was not until 2003 that asymmetric variants began to surface in the literature.

Aggarwal [5] and Trauner, [6] reported the first asymmetric Nazarov cyclisation, utilising chiral Lewis acids in 2003. They envisioned that asymmetric induction can be achieved if the direction of conrotation can be controlled. Divinyl ketones bearing an ester moiety in the α–position, together with copper box complexes were employed as suitable substrates in order to test the effect these substrates would have on the conformation of the Lewis Acid substrate complex. The levels of reactivity and stereoselectivity were capricious; nevertheless substituting the ester moiety with an amine resulted in higher levels of reactivity and stereoselectivity. This is most probably due to the decrease in electron withdrawing ability of the amine. In the presence of a stoichiometric amount of copper bisoxazoline **207**, $CuBr_4$ and $AgSbF_6$, divinyl ketone **205** undergoes smooth cyclisation to afford the desired cyclopentenone **206** with good levels of enantioselectivity.



Scheme 2.3 Asymmetric Nazarov cyclisations using chiral bisoxazoline Lewis acids

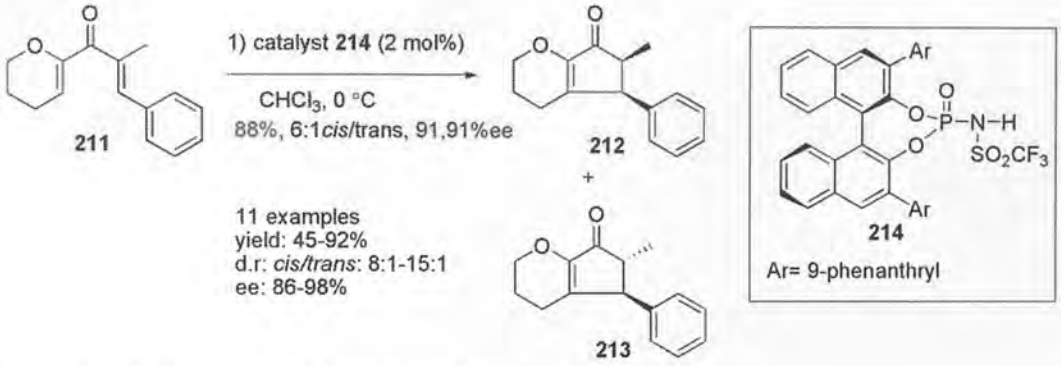
In an effort to address the issues often associated with Nazarov cyclisations, for example, catalyst turnover and strong acidic solvents. Trauner [6] *et al.* have disclosed a truly catalytic enantioselective Nazarov reaction, involving an asymmetric protonation as the key step which is promoted by chiral Lewis acid **210** (Scheme 2.4). Employing 2-alkoxy-1,4-pentadien-3-ones as substrates together with scandium pybox complex **210**, gave rise to cyclopentenone **209** in good yield. It is thought that substrates of type **208** (not bearing a substituent at the β-position), are responsible for the higher levels of enantioselectivity. This is most probably due to strong coordination of the chiral ligand to the Lewis acid and not the termini of the divinyl ketone **208**. A catalytic amount of scandium pybox complex **210** provides cyclopentenones in relatively high e.e., whilst addressing the regio-and stereoselectivity issues often associated with this class of electrocyclisation.



Scheme 2.4 Enantioselective Nazarov cyclisation via an asymmetric proton transfer

Frontier, [4] Trauner [6] and co-workers have demonstrated that the Nazarov cylclisation can proceed in the presence of a catalytic amount of Lewis acid.

However, the outstanding development with regard to the Nazarov cyclisation, is the invention of an organocatalytic asymmetric variant. Rueping [8] *et al.* in 2007 reported the first enantioselective organocatalytic Nazarov reaction, by means of employing chiral Brønsted acids (Scheme 2.5).

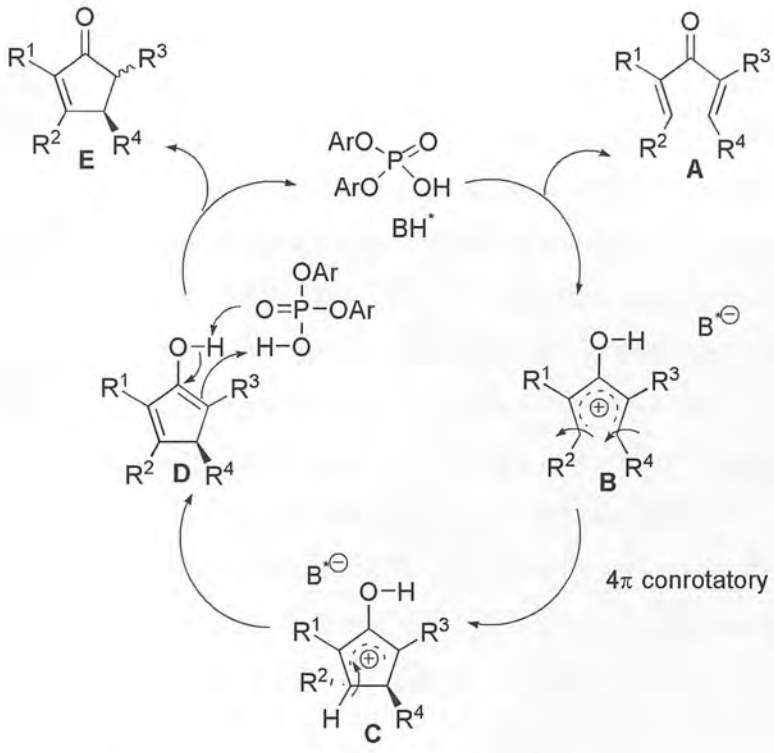


Scheme 2.5 Brønsted acid catalysed Nazarov cyclisation

Over the years, the application of Brønsted acid catalysis has been introduced as a powerful methodology [8] in asymmetric catalysis. However, despite the demonstrated success of catalysis through hydrogen bonding; [9] its application in electrocyclisations has not been extensively researched.

Based on the central function performed by Brønsted acids, Rueping *et al.* envisioned that catalytic protonation of a divinyl ketone would be feasible by employing chiral binol phosphates (BH^*). Activation of the electrophile by catalytic protonation would result in the formation of the intermediary chiral ion pair (pentadienyl cation and the phosphate anion) **B** adduct, subsequent anticlockwise conrotatory 4π electrocyclisation gives rise to oxyallyl cation **C**, which following regioselective elimination of a proton gives rise to **D**. The enol is then reprotonated by the phosphonate, which results in the

formation of the desired cyclopentenone, together with regeneration of the Brønsted acid catalyst.



Scheme 2.6 Brønsted acid catalysed Nazarov cyclisation

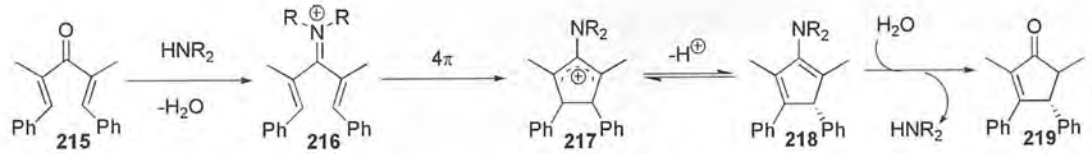
Excellent levels of enantioselectivity were achieved utilising chiral binol phosphates. However, by employing catalyst of type **214**, not only was there an increase in reactivity but additionally there was a significant increase in diastereoselectivity and enantioselectivity. This may be due to the increase in acidity of the Brønsted acid in comparison to the binol phosphate, as the presence of the N-trifyl group [10] increases the stability of the counteranion and lowers the pK_a of the acidic proton, thus increasing the reactivity. With the optimised conditions in hand, a variety of diverse divinyl ketones underwent smooth cyclisation to afford cyclopentenones with excellent yields and enantioselectivities.

2.3 Results and Discussion I

At the beginning of our study, no organocatalytic enantioselective variant of the Nazarov cyclisation had surfaced in the literature. It still remains a daunting challenge in organocatalysis. The challenges often associated with the Nazarov reaction involve controlling the regio and stereoselectivity in the proto/deprotonation steps, in addition to possible racemisation of the cyclopentenone if cyclisation takes place slowly.

Due to the scarcity of asymmetric variants in the literature, we embarked on a novel asymmetric Lewis base organocatalysed cyclopentannulation strategy, which could in principle generate any cyclopentanoid structure as a single enantiomer.

We envisaged that if a simple chiral amine was added to a divinyl ketone **215**, a chiral divinyl iminium ion **216** could be generated, subsequently this increase in electrophilicity of the carbonyl functionality will promote torqueselective cyclisation, giving rise to aminallyl cation **217**, followed by hydrolysis *in situ* to regenerate the chiral amine catalyst together with the desired cyclopentenone **219**.



Scheme 2.7 Organocatalytic iminium ion mediated cyclisation

However, on close inspection, there are a number of factors which have to be considered in order to achieve our goal. One of the most prominent being initial iminium ion formation between the divinyl ketone and the amine. Divinyl ketones tend to be deactivated towards nucleophilic attack at the carbonyl group, in addition with the steric hindrance accompanied with a number of Nazarov substrates. In this instance, it is therefore essential that the catalyst has the ability to undergo initial iminium ion formation with the divinyl ketones.

Our aim was to develop a catalyst which had the capacity to mediate a wide range of enantioselective organocatalytic reactions; above all focussing on organocatalysts for application in the Nazarov reaction.

We sought to develop a novel catalyst which would undergo facile iminium ion formation; would be hydrolytically labile to permit catalyst turnover and last of all must exert excellent asymmetric induction. The pioneering work demonstrated by Macmillan [11] *et al.* whereby chiral imidazolidinones exhibit high levels of asymmetric induction in the enantioselective Diels-Alder reaction, prompted us to consider chiral hydrazines and hydroxylamines as a potential class of organocatalysts which would be fit for application in the Nazarov electrocyclisation. These two classes of compound are excellent nucleophiles, due to the neighbouring heteroatom (the α-effect). [12, 13]

Tomkinson *et al.* have extensively explored the α-effect [12] concept in iminium ion catalysis. A series of experiments were carried out in order to establish whether the incorporation of a heteroatom adjacent to the nucleophile increased the rate of iminium ion formation, which is believed to be the rate determining step in this class of reaction. By utilising the Diels-Alder reaction as a model study, their endeavours did suggest that the incorporation of an adjacent heteroatom does indeed accelerate the rate of reaction significantly.

An additional feature when considering nucleophilicity is the nitrogen cone angle. As demonstrated by Tomkinson [12] *et al.* acyclic nucleophiles bearing a heteroatom adjacent to the nitrogen atom are reactive catalysts in the Diels-Alder reaction. However, cyclic derivatives lead to an increase in reaction rate and yield of isolated products. It is thought that the underlying explanation [13] for this is due to the conformational restriction produced by the cyclic ring, as the ease of which hybridisation can take place in cyclic derivatives is considerably more difficult than acyclic. For this reason, together with an increase in equilibrium constant (due to stabilisation of the iminium ion), explains why

secondary amines embedded within a five membered ring are far more efficient as organocatalysts than primary amines.

In an attempt to develop novel catalysts which have the capacity to provide an effective platform for iminium ion catalysis with deactivated divinyl ketones, we focussed on synthesising chiral secondary amines embedded within a chiral framework which would have the ability to impart facial selectivity (Fig 2.3).

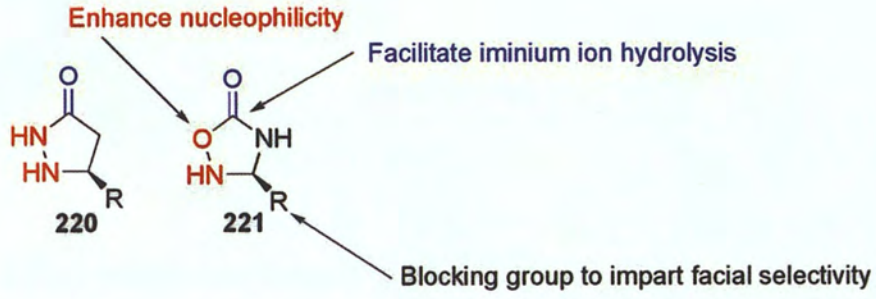
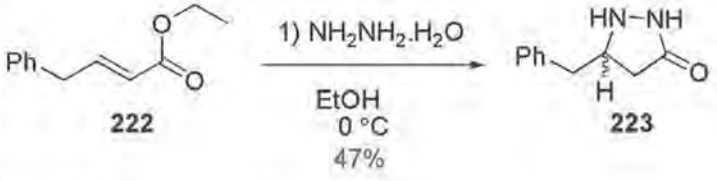


Fig 2.3 Pyrazolidinones and oxadiazolidinones as potential organocatalysts

2.3.1 Enantioselective synthesis of 1,2,4-Oxadiazolidinone 230

Taking into consideration all of the above features, we embarked upon the synthesis of a novel enantiomerically pure secondary amine organocatalyst. Initial studies involved the racemic synthesis of pyrrazolidinones, but since kinetic resolution was required in order to obtain one enantiomer of the desired product, we decided to abandon this approach, due to poor isolated yield of the racemic pyrrazolidinone. Synthesis of pyrrazolidinone **223** is depicted in (Scheme 2.8).

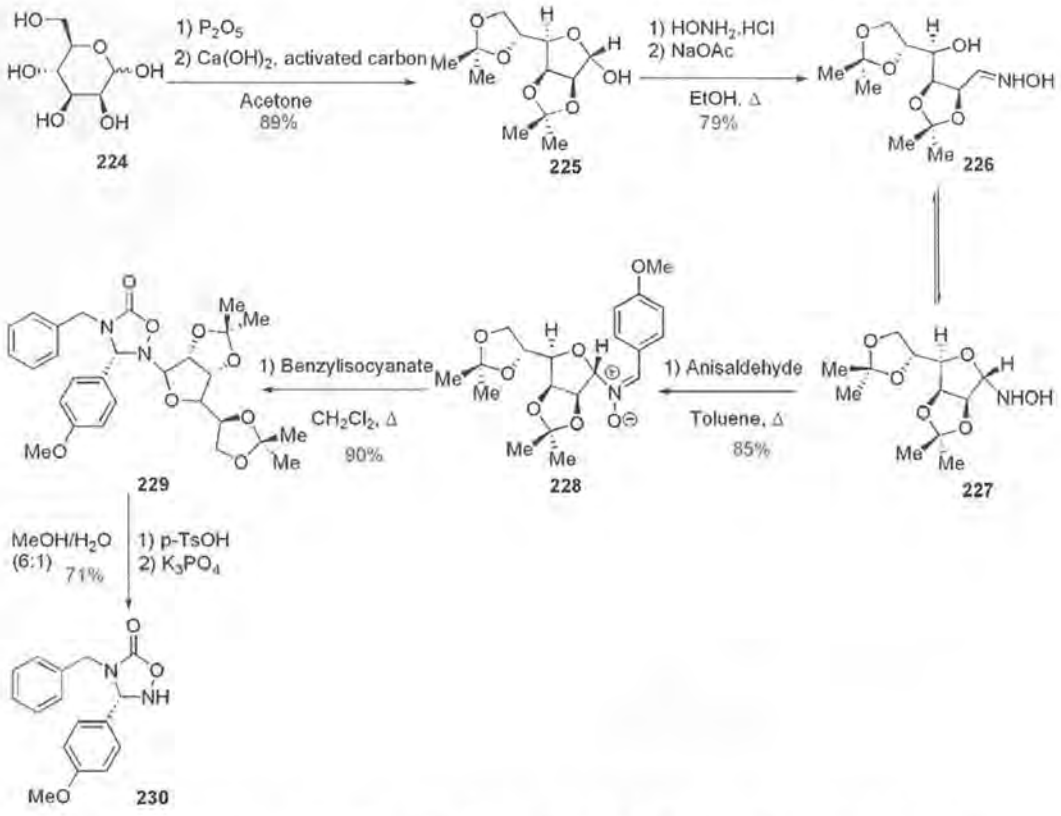


Scheme 2.8 Pyrrazolidinone racemic synthesis

We envisaged a more direct approach, which did not involve resolution. Captivated by the work carried out by Carreira *et al.* which involved the synthesis of 1,2,4-Oxadiazolidinones [14] as configurationally stable chiral building blocks, we decided to adopt this route as an efficient way to gain access to five-membered rings which possess the desired features necessary in order to ascertain their potential as versatile organocatalysts. At first glance, this route seems to be an elegant way to incorporate highly diverse functional groups within the catalysts framework. In addition to the carbonyl group present on the α-heteroatom which will facilitate the iminium-ion hydrolysis.

The origin of enantioselectivity is created by employing a mannosyl derived chiral auxiliary [15] (Scheme 2.9). D-Mannose **224** is converted to acetonide **225**, upon treatment of **225** with N-hydroxylamine hydrochloride in ethanol, giving rise to high levels of mannose oxime **227**, the oxime is in equilibrium with the hydroxylamine tautomer **226**,

this is evidenced by exposure of **226/227** to anisaldehyde in toluene at high temperature resulting in the formation of nitrone **228**.

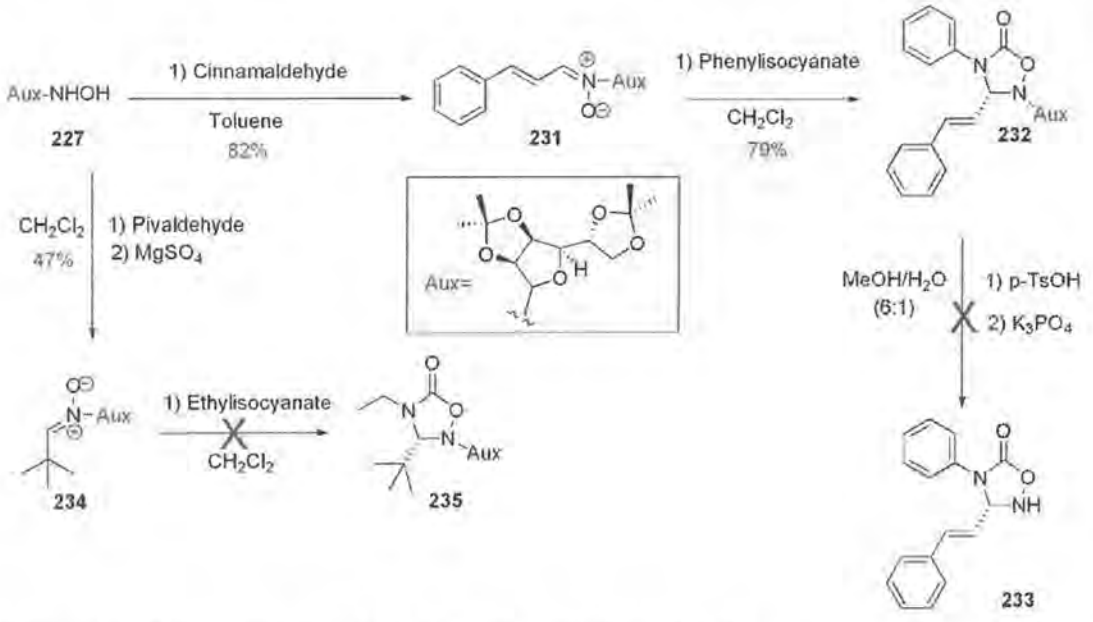


Scheme 2.9 Chiral auxiliary mediated synthesis of oxadiazolidinone 230

Nitrone **228** is treated with benzyl isocyanate. This concerted 1,3-dipolar [16] cycloaddition leads to the construction of 1,2,4-oxadiazolidinone **229** with extremely high levels of diastereoselectivity. After filtration, the cycloadduct **229** is triturated with methanol, leaving behind a white solid. The next step is removal of the sugar derived auxiliary. Exposure of cycloadduct **229** to acidic media in $MeOH/H_2O$, eliminates the isopropylidene groups to give the tetrol, this is demonstrated by tlc, the reaction is left standing until complete hydrolysis, whereby the 1,2,4-oxadiazolidinone **230** is released together with the water soluble carbohydrate remnant.

In conjunction with the synthesis of cycloadduct **230**, other derivatives were synthesised in order to have an array of 1,2,4-oxadiazolidinones at hand. It is necessary to incorporate blocking groups which have the ability to impart facial selectivity. Pivaldehyde was selected as a suitable candidate, given its steric hindrance implications. Treatment of nitrone **234** with ethylisocyanate, proved to be disappointing, tlc analysis displayed unreacted starting material, which after prolonged reaction times lead to decomposition.

Cycloadduct **232** was synthesised in an analogous manner to **230**, though hydrolysis of the auxiliary proved to be troublesome. Employing the stated conditions resulted in degradation of cycloadduct **232** (Scheme 2.10).



Scheme 2.10 Modification of 1,2,4-oxadiazolidinone 230

In an effort to overcome the limitations associated with auxiliary hydrolysis, we carried out a series of experiments. First of all, several variations in reaction conditions were attempted, for example, different acids, reduction in reaction temperature, and a

decreased number of acid equivalents were employed in order to circumvent the hydrolysis issues. However, all attempts failed to yield the desired hydrolysed oxadiazolidinone **233** (Scheme 2.10).

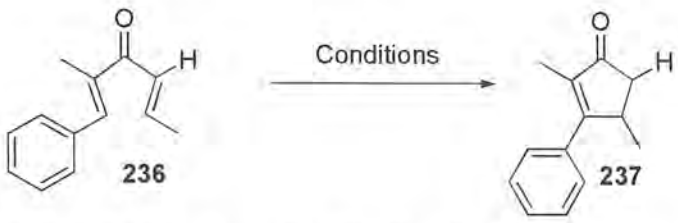
It is thought that the oxadiazolidinone **232** degrades in the presence of acid, due to the presence of the labile N-O bond.

2.3.2 Lewis base Nazarov cyclisation

Table (2-1) Attempts to hydrolyse the sugar derived auxiliary

Entry	Acid	Conditions	Product **233**
1	p-TsOH(10eq)	MeOH/H_2O(6:1) 50 °C	decomposition
2	(-)CSA(10eq)	MeOH/H_2O(6:1) 50 °C	decomposition
3	p-TsOH(10eq)	MeOH/H_2O(6:1) 0 °C	decomposition
4	p-TsOH(5eq)	MeOH/H_2O(6:1) 0 °C	decomposition
5	p-TsOH(5eq)	DCM, rt	decomposition

To examine the feasibility of a novel Lewis Base Nazarov cyclisation, we envisaged employing oxadiazolidinone **230** as the free amine in the Nazarov cyclisation directly, together with an acid co-catalyst. Simple divinyl ketone substrates (Scheme 2.11) were synthesised as suitable models, to explore this concept. Following literature [17] precedents, divinyl ketones of type **236** were synthesised in a simple manner. Straightforward Grignard addition to the appropriate aldehyde gave rise to the desired diol, subsequent oxidation with PCC, gave rise to the desired substrates.



Scheme 2.11 Model divinyl ketones for the Lewis base organocatalysed Nazarov cyclisation

Table (2-2) Optimisation of Lewis base organocatalysed Nazarov cyclisation

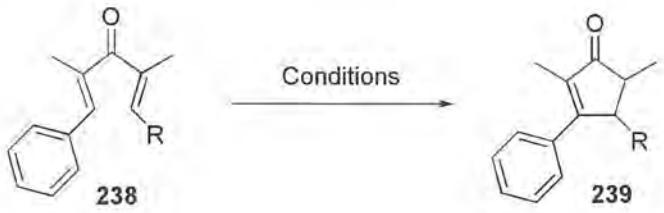
Entry	Substrate	Acid/Catalyst (mol %)	Conditions	Yield (%)
1	**236**	TFA(10)	DMF, rt, 18h	66
2	**236**	TFA/**230**(10)	MeOH/H_2O(19:1), rt, 24h	73
3	**236**	TFA/**230**(10)	MeOH/H_2O(19:1),70 °C, 16h	58
4	**236**	TFA/**230**(20)	MeOH/H_2O(19:1),70 °C, 16h	61
5	**236**	TFA/**230**(100)	MeOH/H_2O(19:1), rt,10-12h	76
6	**236**	TFA/**230**(10)	MeOH/H_2O(19:1),-78°C, 32h	59

Initial investigations involved exploring the feasibility of this cyclopentannulation strategy utilising substrate **236**. First of all, a catalytic amount of TFA was added to **236** in DMF, this served as the control experiment. To our delight, after 18h at rt, cyclopentenone **237** was isolated in good yield. Following this result, we repeated the reaction, in this instance oxadiazolidinone organocatalyst **230** was introduced with a view to imply asymmetric induction. Due to the insolubility of oxadiazolidinone **230** in DMF, we opted to replace DMF with a MeOH/H_2O mixture. After 24 h at rt, **237** was isolated in slightly higher yield (Table 2-2, entry 1 *vs* 2), albeit with prolonged reaction times. This was an encouraging result, as it suggested the background reaction was not

performing a prominent role, therefore iminium ion catalysis indeed could be taking place. In an attempt to reduce the reaction time, the reaction was repeated and left to reflux at 70 °C, we were pleased to isolate the clean product after 16 h, albeit in slightly attenuated yield. In an attempt to keep reaction time to a minimum, together with good yield of the cyclopentenone, the catalyst loading was increased to 20 mol%. However, the reaction rate was consistent, regardless of a slight increase in catalyst loading (entry 3 *vs* 4). In the presence of a stoichiometric amount of organocatalyst **230**, both yield and reaction rate increased. However, in order to avoid employing one equivalent of oxadiazolidinone **230**, we envisaged that with optimisation, similar results could be obtained with a catalytic quantity of **230**. When the mixture was kept at lower temperatures (< -78 °C), cyclisation was slower, however, in spite of this the chemical yield of divinyl ketone **237** was reasonable. (Table 2-2)

With an assay in hand of cyclopentenone **237**, we were enthusiastic to determine if iminium ion catalysis/Brønsted acid catalysis was taking place when oxadiazolidinone **230** was introduced in the reaction, moreover, if **230** provided an asymmetric environment for the cyclisation. Analysis by chiral HPLC was used as a suitable method to determine the enantiomeric excess. Initially, separation by means of a chiralpak OD-H column proved to be problematic. However, after optimisation, a clean trace of racemic cyclopentenone **237** was obtained. With optimised conditions in hand, sample **237** (Table 2-2, entry 2) was analysed. However, despite cyclopentenone **237** having being exposed to an asymmetric environment, we did not observe any enantioselectivity by chiral HPLC. In an attempt to determine whether epimerisation had taken place upon storage (0 °C), the reaction was repeated. As before, identical results were obtained. All samples (Table 2-2) which were analysed by chiral HPLC displayed no enantioselectivity. The rationale behind this may lie with the fact that oxadiazolidinone **230** does not display the correct blocking group which is essential for enantiofacial discrimination. Further efforts were carried out in order to establish the fundamental

obstruction responsible for lack of enantioselectivity. Given that, both position and nature of substituents on the divinyl ketone are important factors which influence the reactivity of these substrates. We decided to introduce derivatised divinyl ketones **238a-238b**. (Table 2-3)



238

238a R= Ph
238b R= H

239

239a R= Ph
239b R= H

Scheme 2.12 Nazarov cyclisation using derivatised divinyl ketones

Table (2-3) Limitations and scope of the Lewis base organocatalysed Nazarov cyclisation.

Entry	Substrate	Acid/ Catalyst (mol %)	Conditions	Yield (%)
1	**238a**	TFA(10)	MeOH/H_2O(19:1), rt, 18h	58
2	**238a**	TFA/**230**(10)	MeOH/H_2O(19:1), rt, 8h	73
3	**238b**	TFA(10)	MeOH/H_2O(19:1), rt, 16h	67
4	**238b**	TFA/**230**(10)	MeOH/H_2O(19:1), rt, 6h	55
5	**238b**	TFA/**230**(20)	MeOH/H_2O(19:1), rt, 5h	49

We next turned our attention to exploring the scope of this methodology, by employing alternative substrates. Divinyl ketones **238a-238b** were synthesised [17] in a similar manner as before. When symmetrical substrates of type **238a** were added to a

MeOH/H_2O mixture in the presence of TFA, smooth cyclisation took place affording cyclopentenone **239a** in good yield. The next step involved subjecting **238a** to the optimised conditions (Table 2-3 entry 2). To our delight **239a** was generated in higher yield, together with a decrease in reaction time. However, despite smooth cyclisation of **238a**, analysis by chiral HPLC again displayed no enantioselectivity. In a similar manner to **238a**, divinylketone **238b** underwent smooth cyclisation in the presence of TFA (10 mol%) affording **239b** in moderate yield. When **230** is introduced together with TFA, the cyclisation of **238b** takes place at a considerably faster rate (Table 2-3, entry 3 *vs* 4), however, cyclopentenone **239b** is obtained in a slightly attenuated 55% yield. In all cases, regardless of the nature of the divinyl ketone, no enantioselectivity was observed. (Table 2-3, entries 3, 4 and 5). Table 2-3 outlines the different conditions which were employed in order to optimise the reaction.

Given these results, this led us to judge that oxadiazolidinone **230** serves as an organocatalyst. However, it does not provide any asymmetric induction in this system. This is evidenced by the fact that the reaction proceeds at a faster rate when **230** is present. (Table 2-3, entry 1 *vs* 2).

We next turned our attention to employing different strengths of co-acid, in an effort to achieve superior levels of reactivity and enantioselectivity. It is thought that acids facilitate the formation of activated iminium ion species, consequently promoting the reaction. Activation of the carbonyl moiety originates by virtue of acid protonation, subsequently this encourages nucleophilic addition of oxadiazolidinone **230** to the highly electrophilic carbonyl functional group. As a result of this the iminium ion is generated. It is therefore necessary to delve into the nature of the additive, as the strength of the acid may affect the level of enantioselectivity. (Table 2-4)

Table (2-4) Screening of co-acids

Entry	Substrate	Acid/ Catalyst (mol %)	Conditions	Yield (%)
1	**238b**	CF_3SO_3H/**230**(10)	MeOH/H_2O(19:1), rt, 8h	57
2	**238b**	p-TsOH/**230**(10)	MeOH/H_2O(19:1), rt, 12h	63
3	**238b**	$C_6H_5CO_2H$/**230**(10)	MeOH/H_2O(19:1), rt, 30h	55

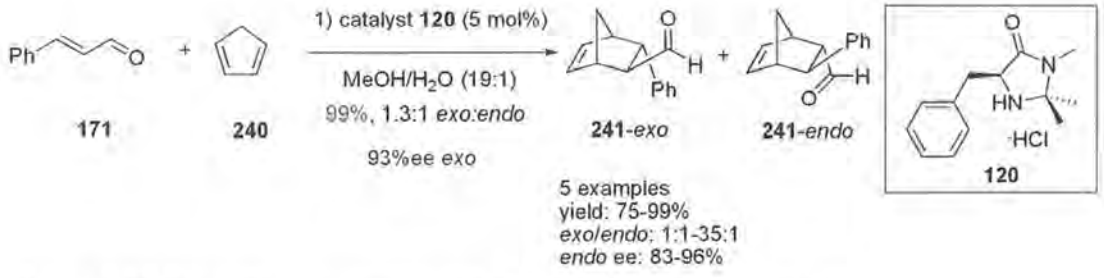
When **238b** was treated with oxadiazolidinone **230** and triflic acid as the co-acid, as expected the reaction was significantly faster, albeit with diminished yield. Given that triflic acid is considered as a very strong acid, we opted to employ an acid which was weaker than triflic acid, but stronger than TFA. In this respect p-TsOH seemed fit for this purpose, given that it exists in solid form and can therefore be conveniently weighed out. Yet again, the reaction was significantly faster. However, in both cases chiral HPLC displayed no enantioselectivity. Concerned by this observation we considered that the strength of the acid may lead to erosion in enantioselectivity upon workup. We next turned our attention to employing a considerably weaker acid, benzoic acid was chosen. In this instance, the cyclisation was slower together with a decrease in yield. It is with these observations, which led us to conclude that formation of the iminium ion is rate determining, due to the rate enhancement in the presence of a stronger acid. (Table 2.4 entry 1 *vs* 3). Disappointingly no enantioselective discrimination took place.

In conclusion oxadiazolidinone **230** serves as an organocatalyst; but it does not possess the correct chiral architecture necessary for enantioselective induction. As a result of this we decided to employ our oxadiazolidinone **230** in a different class of organocatalytic reaction, in an attempt to decipher the fundamental cause of this observation and to test the true power and elegant application of oxadiazolidinone **230** in asymmetric synthesis.

2.3.3 Enantioselective Diels-Alder cyclisation

The Diels-Alder cycloaddition which involves a conjugated diene engaging with a dienophile was first documented [18] by Otto Diels and Kurt Alder in 1928. Since then, considerable interest has arisen in developing an asymmetric variant of this cycloaddition.

Macmillan *et al.* reported [11] the first enantioselective organocatalytic Diels-Alder cyclisation. Their efforts to explore this strategy involved using (*E*)-cinnamaldehyde **171** with a broad range of chiral secondary amine salts, this results in formation of the iminium ion (Scheme 2.13). It is this LUMO-lowering activation which is responsible for engaging the diene partner in the reaction. Following extensive screening of a broad range of secondary amines, Macmillan *et al.* discovered that imidazolidinone **120** was by far the superior catalyst in terms of enantiocontrol.



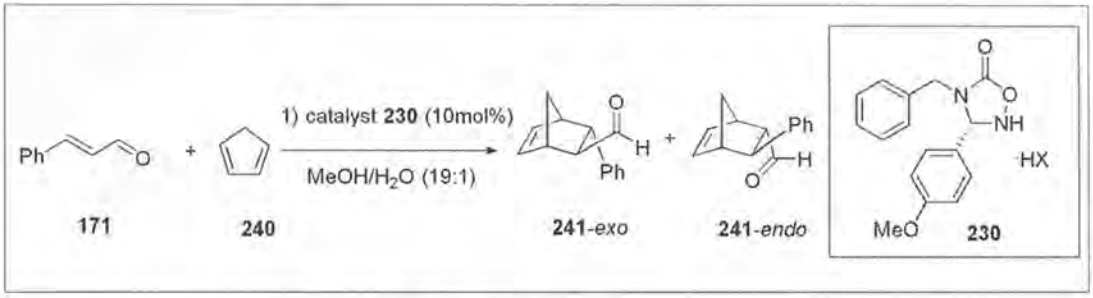
Scheme 2.13 Macmillan`s organocatalysed Diels-Alder reaction

Borrowing from Macmillan`s [11] methodology, wherein chiral secondary amines of type **120** have the capacity to catalyse the asymmetric Diels-Alder [18] reaction. We decided to employ oxadiazolidinone **230** in this class of reaction.

When considering iminium ion catalysis, there are three main issues which have to be addressed, first of all iminium ion formation is crucial, secondly efficient cycloaddition and last of all simple hydrolysis to release the desired product with regeneration of the

catalyst is necessary. We envisaged that by employing oxadiazolidinone **230** in this reaction as a novel molecular scaffold, it could serve as an effective enantioselective organocatalyst. We rationalised that the rate of the reaction could be accelerated by exploiting the α-effect.

Initial studies involved using (*E*)-cinnamaldehyde **171** and cyclopentadiene **240** as a benchmark reaction in order to establish the optimal conditions for this cyclisation.



Scheme 2.14 Model reaction for Diels-Alder cyclisation

Given the simplicity of Macmillan's strategy, we adopted these conditions as a standard platform for optimal screening. Our initial efforts, focussed on the strength of the co-acid, as previously mentioned the nature of the co-acid influences both the overall reaction rate and level of enantioselectivity.

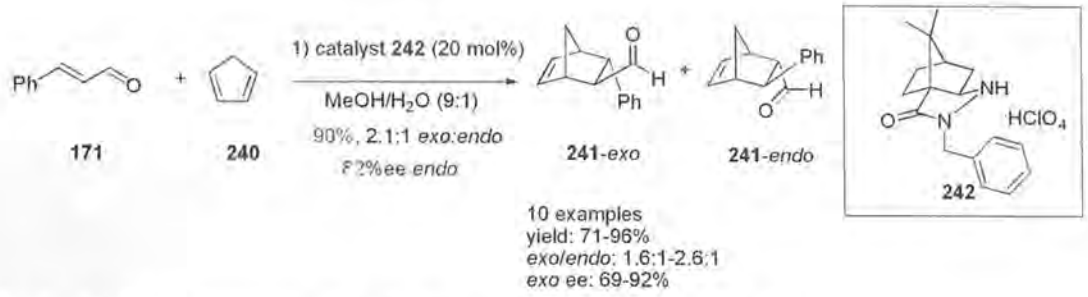
Table (2-5) Optimisation of Diels-Alder cyclisation

Entry	Acid/ Catalyst (mol %)	Conditions	Yield (%)	*endo*/*exo*
1	CF_3SO_3H/**230**(10)	MeOH/H_2O(19:1), rt, 10h	62	1:1.5
2	$HClO_4$/**230**(10)	MeOH/H_2O(19:1), rt	-	-
3	HCl/**230**(10)	MeOH/H_2O(19:1), rt, 12h	59	1:1.6
4	CF_3CO_2H/**230**(10)	MeOH/H_2O(19:1), rt, 12h	88	1:1.8
5	p-TsOH/**230**(10)	MeOH/H_2O(19:1), rt, 14-16h	73	1.4:1

Oxadiazolidinone **230** in MeOH/H_2O (1 M solution) was added to freshly distilled (*E*)-cinnamaldehyde, shortly after the co-acid was added via syringe or directly added by a spatula; this solution was left to stir for 1-2 minutes before addition of cyclopentadiene. When stronger acids are employed in this reaction (Table 2-5, entries 1-3), the cycloaddition takes place at a faster rate compared to when weaker acids

are used (Table 2-5, entry 1 *vs* 5), albeit in moderate yield. In all cases, the cycloaddition is facile in the presence of **230**, favouring formation of the *exo* isomer, it is thought that in polar solvents the *endo* selectivity is enhanced, together with acceleration in reaction rate. [19] This is presumably due to enforced hydrophobic interactions between the diene and dienophile, allowing the reagents to be in close proximity, which results in rate acceleration. Upon addition of perchloric acid to the catalyst-aldehyde mixture, the reaction turns a black/green colour, when cyclopentadiene is added. It is thought this is due to polymerisation of the cyclopentadiene or degradation of other reagents caused by the strength of the acid. Attempts to circumvent this issue involved decreasing the MeOH/H_2O ratio; we envisaged that if the amount of H_2O in the reaction media is increased, then the possibility of degradation or polymerisation would be diminished. However, with regard to perchloric acid, a greenish black slurry was obtained in all cases.

In parallel with our studies, Ogilvie [20] *et al.* in 2005 developed an asymmetric variant of the Diels-Alder cyclisation by means of exploiting the α-effect. In this instance, the chirality is derived from a hydrazide, which is embedded within a dense camphor scaffold. Initial screening involved using hydrazide catalyst **242** possessing a phenyl side chain, to their delight this strategy promoted the cycloaddition, albeit in modest enantioselectivity and yield (Scheme 2.15).

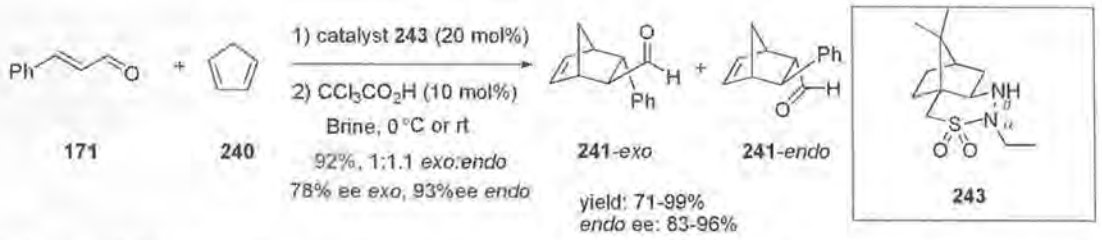


Scheme 2.15 Aqueous enantioselective Diels-Alder reactions

Further studies, revealed that when the sidechain is modified from a phenyl to a benzyl then there is a significant increase in yield and enantioselectivity. Upon closer inspection, a prominent correlation was apparent between the strength of the co-acid and reaction efficiency. Their findings demonstrated that as the acid strength increases both enantioselectivity, yield and rate of the reaction increase with prevalence of the *exo* isomer in each case. Preliminary mechanistic studies disclose that iminium formation is far more facile with hydrazide **242** and (*E*)-cinnamaldehyde compared with Macmillan's imidazolidinone organocatalyst **120**. This reaction tolerates a broad range of both dienophiles and dienes, whilst maintaining high levels of enantioselectivity.

Ogilvie *et al.* have inspired other groups to investigate this class of organocatalytic Diels-Alder cycloaddition. Lee and co-workers [21] have recently demonstrated that the asymmetric Diels-Alder cyclisation can be catalysed by cyclic sulfonyl hydrazines. A series of chiral cyclic sulfonyl hydrazines have been synthesised from camphor sulfonic acid. In their findings, best results were achieved using sulfonyl hydrazine **242** alongside trichloroacetic acid as the co-acid. In terms of catalyst structure, alkylating at the N^{α} position led to superior levels of enantiomeric excess, in comparison to alkylation at the N^{β} position. Virtually all N^{α} alkylated catalysts performed well. However, benzyl and ethyl groups in the N^{α} position proved to provide the best chemical yields and enantioselectivities. Naturally, in order to further explore the scope and limitations of this methodology, a series of varied dienophiles were introduced. Equally, both aliphatic

and aromatic aldehydes were tolerated in the reaction; but aromatic aldehydes gave better enantioselectivities, whilst aliphatic dienophiles had faster reaction rates.

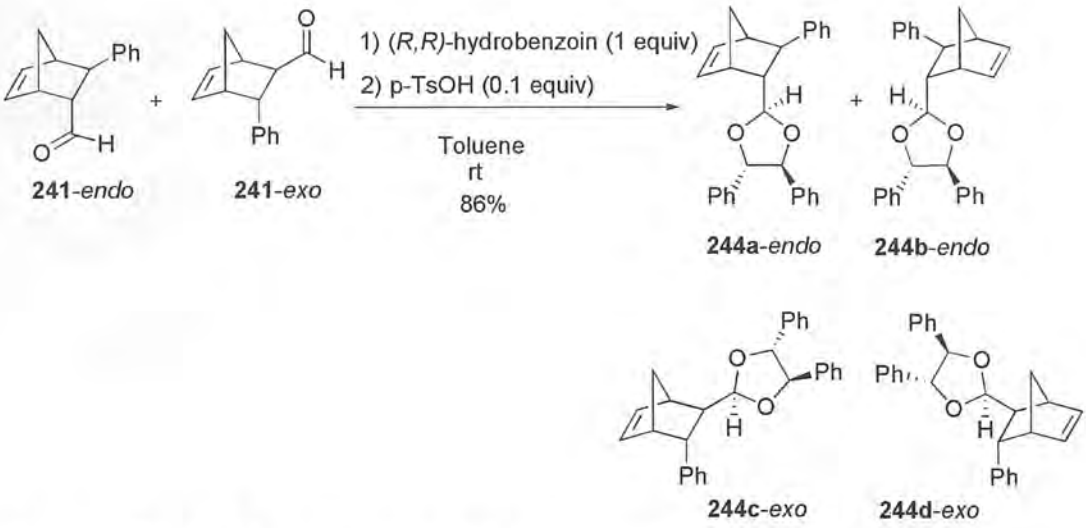


Scheme 2.16 Camphor sulfonyl hydrazines as organocatalysts in the Diels-Alder reaction

Conducting the reaction in brine, not only affords the products in better chemical yield and e.e., but is considerably faster. It is thought that in the presence of some salts; the cyclisation can be promoted; this can be owed to the hydrophobic effect. [23] It is thought, that certain salts enhance hydrophobic packing of the diene and the dienophile in the transition state.

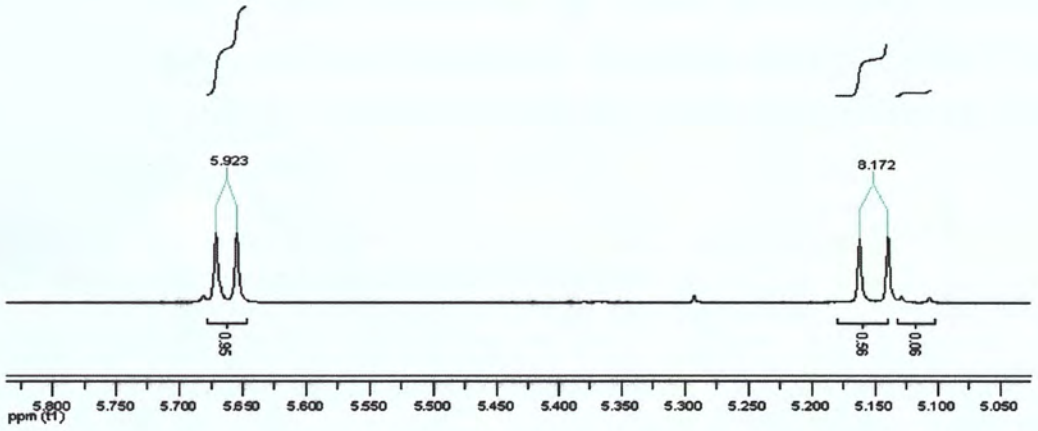
At this stage, our efforts focused on determining the enantioselectivity of our organocatalysed Diels-Alder reaction. Access to a chiral GLC was not possible; so we decided to expose our substrates to chiral HPLC. Numerous attempts to obtain a clean trace of both *exo* and *endo* isomers were carried out, although all attempts met with failure. Separation by means of chiral HPLC was intrinsically difficult, despite the strong chromophore inherent within the product. In an attempt to resolve this problem, further efforts focussed on establishing a simplistic, yet accurate method to determine the enantioselectivity. In our findings, it became apparent that Fujioka [22] *et al.* had established an efficient route to combat this issue. As a result of employing (+)-(*R,R*)-hydrobenzoin, an acetalisation takes place giving rise to a diastereomeric mixture,

furthermore by using ^{1}H NMR, the ratio of diastereomers would indicate the enantiomeric excess (Scheme 2.17).

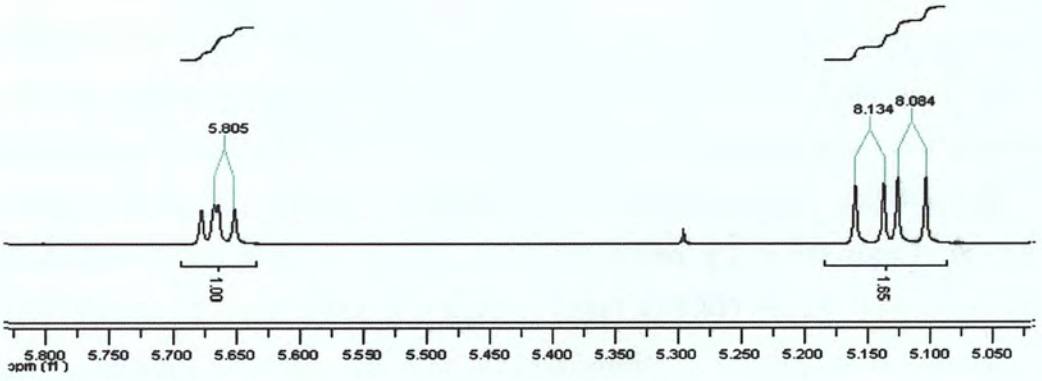


Scheme 2.17 (+)-(*R,R*)-auxiliary to determine enantiomeric excess

Optical resolution [21] of Diels-Alder norbornene aldehyde derivatives (Table 2.6 entry 1 and 4), was carried out using (+)-(*R,R*)-hydrobenzoin as a chiral auxiliary in the presence of a catalytic amount of p-TsOH. The acetilisation of **241** proceeded in good yield furnishing a diastereomeric mixture **244** which was isolated by column chromatography.



(a)



(b)

Fig 2.4(a) Enantiomeric excess in the presence of Macmillan`s (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one monohydrochloride and (b) (*R*)-4-benzyl-3-(4-methoxy phenyl)-[1,2,4]-oxadiazolidin-5-one

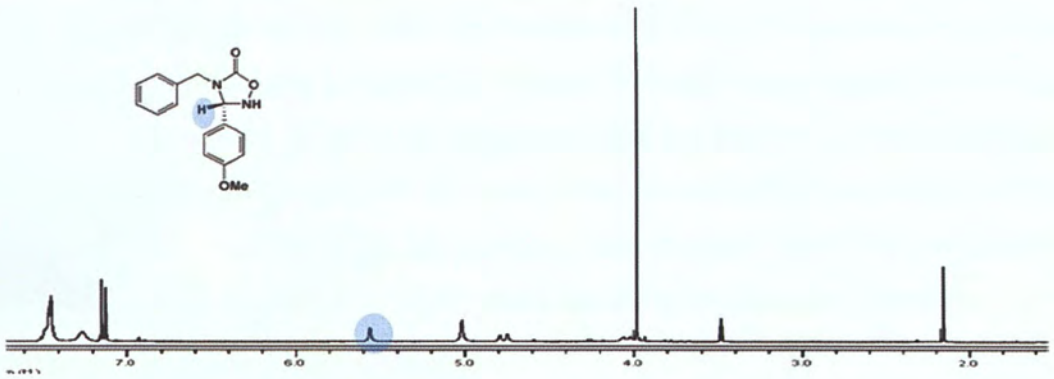
Amplification of the acetal proton signal of cycloadducts **244** by ^{1}H NMR, illustrated a 10% enantiomeric excess of the *exo* isomer (Fig 2.4(b)). In order to determine if this was an accurate method to measure enantioselectivity, a control experiment was carried out **(Fig 2.4(a)). In the presence of Macmillan's organocatalyst 120**, as expected ^{1}H NMR analysis illustrated a 93% enantiomeric excess of the *exo* isomer. Despite

observing low levels of enantiocontrol with **230** in some respect it was a gratifying result, as it suggested iminium ion catalysis was taking place. However, further exploration was required in order to promote high levels of enantiocontrol whilst maintaining reaction efficiency.

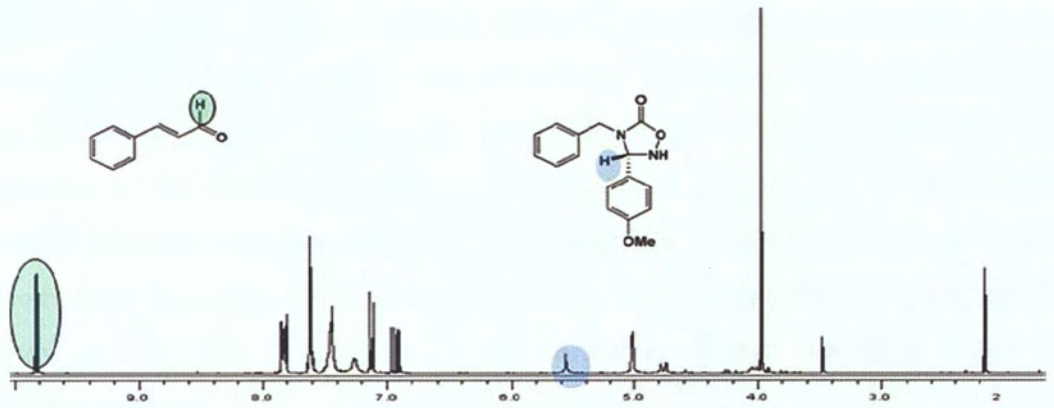
2.3.4 NMR studies of iminium ion formation

To better understand the overall process, we decided to study the catalytic cycle by means of ^{1}H NMR, given that our catalyst performed well in a MeOH/H_2O combination we opted for this solvent mixture for our NMR studies.

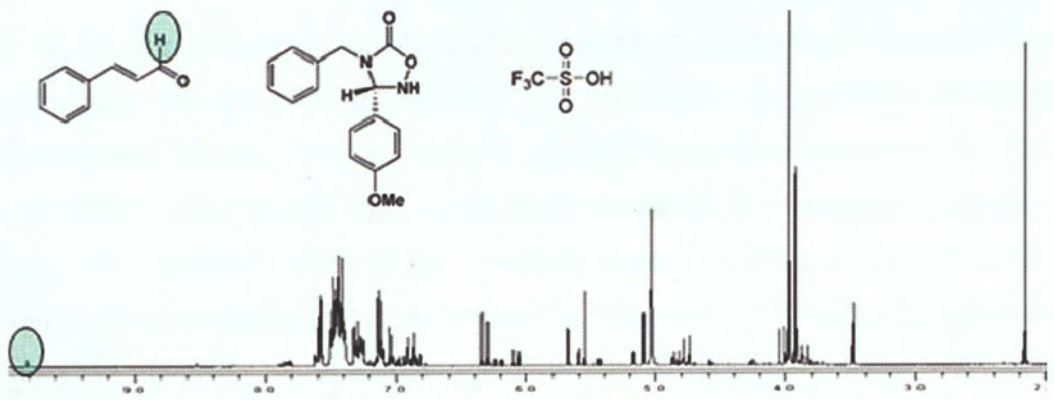
It is thought that the presence of the H_2O enhances the rate of iminium ion formation due to the increased proton transfer between the carbonyl compound and the organocatalyst. Iminium ion formation was studied by employing equimolar quantities of freshly distilled (*E*)-cinnamaldehyde (0.04 g, 0.303 mmol), (*R*)-4-benzyl-3-(4-methoxyphenyl)-[1,2,4]-oxadiazolidin-5-one **230** (0.086 g , 0.303 mmol) in a 19:1 CD_3OD:D_2O (1 mL), and triflic acid (27 μL, 0.045 g, 0.303 mmol). The reaction was maintained at rt by ^{1}H NMR, which involved acquiring spectra at five minute intervals. First of all, a ^{1}H NMR was taken of catalyst **230** in CD_3OD:D_2O, (*E*)-cinnamaldehyde was added to the mixture, upon addition of triflic acid, the (*E*)-cinnamaldehyde proton peak in the NMR declines instantaneously (Fig 2.5(c)). After fifteen minutes no change was apparent in the spectrum. In an attempt to elucidate in detail the mechanistics involved, the reaction was repeated in the absence of the catalyst, one equivalent of triflic acid was added to (*E*)-cinnamaldehyde. In this instance the aldehyde peak in the NMR did not diminish.



(a)



(b)



(c)

Fig 2.5(a) ^{1}H NMR of (*R*)-4-benzyl-3-(4-methoxyphenyl)-[1,2,4]-oxadiazolidin-5-one in CD_3OD. (b) ^{1}H NMR of (*R*)-4-benzyl-3-(4-methoxyphenyl)-[1,2,4]-oxadiazolidin-5-one together with (*E*)-cinnamaldehyde in CD_3OD. (c) ^{1}H NMR following addition of triflic acid

In order to gain insight into the effect the counteranion has on the process, we repeated the reaction using different strengths of co-acid. In most cases, similar results were obtained in the presence of p-TsOH, suggesting that the strength of the acid did not correlate with the catalyst efficiency. However, when weaker acids bromoacetic acid and chloroacetic acid were used in the reaction, the aldehyde peak did not decline, suggesting no proton transfer was taking place, inhibiting iminium ion formation.

Our mechanistic studies provided us with strong evidence that iminium formation was taking place rapidly. Despite depleted levels of enantiomeric excess, this was an encouraging result as it suggested oxadiazolidinone **230** was promoting iminium form ation. However, it was the nature of the sidechain at the chiral centre which was deleterious to the enantiomeric excess. We envisaged that changes to the indicated sidechain were essential in order to observe appropriate levels of enantiocontrol. Given that our route for organocatalyst construction is highly adaptable, [13] we choose this strategy as a suitable method to incorporate highly diverse sidechains within the catalysts framework.

First of all, we wished to rationalise the success of Macmillan's imidazolidinone organocatalyst with regard to the Diels-Alder cycloaddition, in an attempt to decipher the fundamental obstacle involved with our strategy. Upon closer inspection, the puzzle was unravelled. The success with regard to stereocontrol in Macmillan's approach is based on two elements. First of all, complete control of iminium ion geometry is achieved, the (*E*)-iminium isomer is favoured in order to avoid nonbonding interactions between the aldehyde olefin and the geminal methyl substituent, hence locking the structure in a fixed geometry, secondly the presence of the benzyl group successfully blocks the dienophile from approaching the *re* face, which therefore promotes attack of the dienophile from the *si* face, thus achieving high levels of enantiocontrol of both *endo-exo* products (Fig 2.6). In most cases, the *exo* product predominates with extended

reaction times; it is believed this is because the *exo* product is thermodynamically favoured.

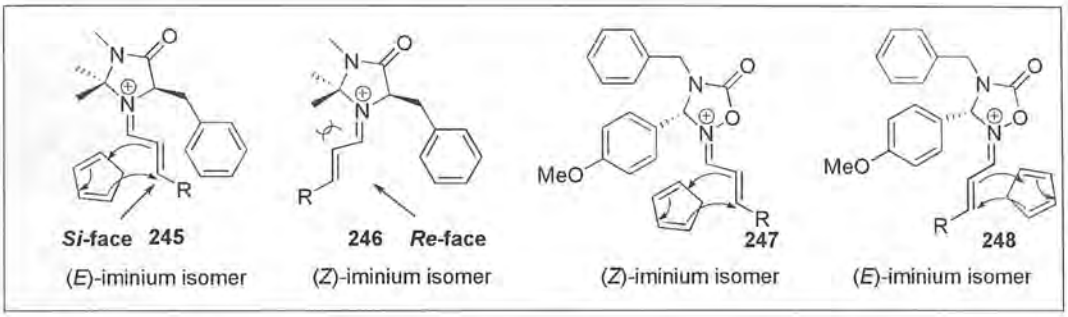
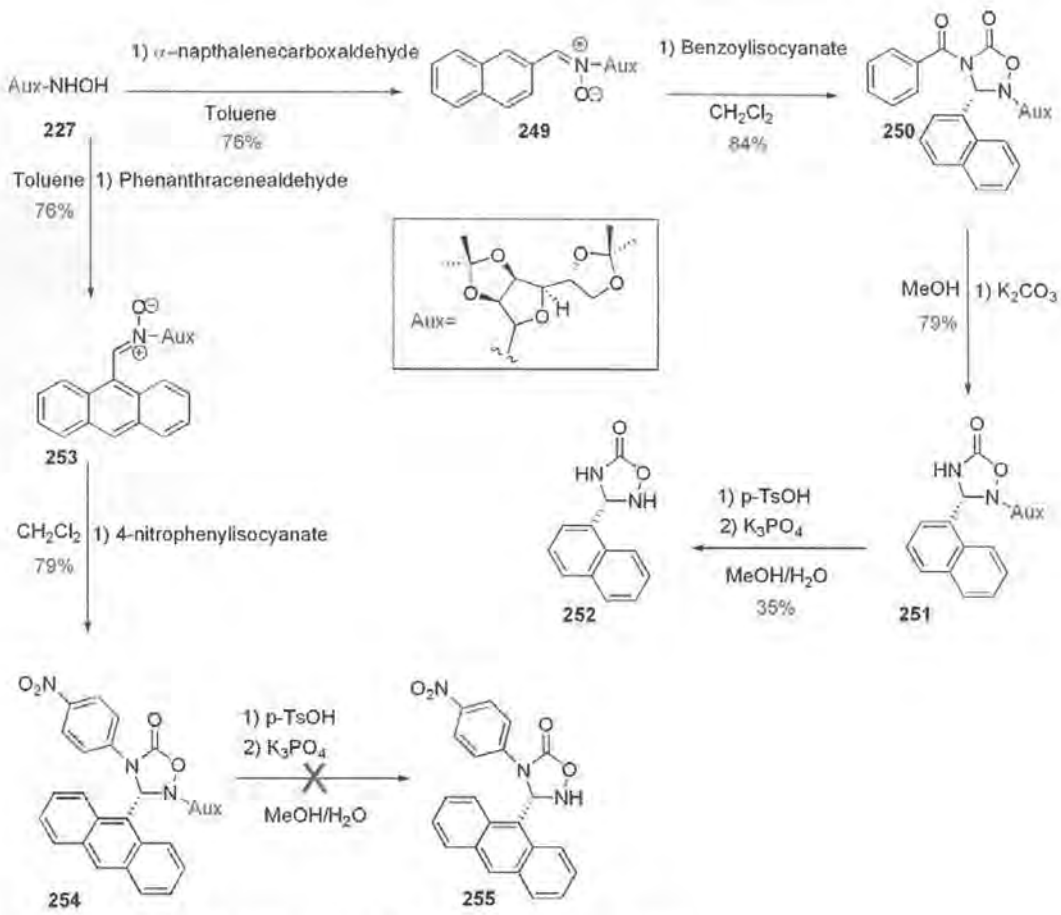


Fig 2.6 Control of iminium ion geometry

With respect to oxadiazolidinone **230**, all attempts to deliver significant levels of enantiocontrol failed. We believe this is due to lack of control of the iminium ion geometry, it is thought that in the absence of geminal dimethyl groups both geometries are likely to exist, and as a result of this both the *Re* and *Si* face are exposed to cycloaddition which explain the lack of enantiocontrol. To further investigate this rationale, we decided to synthesise a novel oxadiazolidinone organocatalyst, which would have the capacity to block one face regardless of the iminium ion geometry adopted by the substrate. We focussed on inserting a sidechain which was large enough to hinder attack from both faces. In terms of catalyst modification, we adopted the strategy of employing a naphthalene group (Scheme 2.18).



Scheme 2.18 Derivitisation of 1,2,4-oxadiazolidinones

In a similar manner to oxadiazolidinone **230**, nitrone **249** was synthesised in good yield, nitrone **249** was then exposed to benzoylisocyanate which after one hour gave rise to cycloadduct **250** in excellent yield, and simple trituration provided us with a white precipitate. The presence of the benzoyl group within the catalysts framework is not essential in order to achieve good enantiocontrol, although it is necessary to remove the benzoyl portion prior to auxiliary cleavage in order to avoid complex mixtures soon after. Aforementioned, auxiliary hydrolysis tends to be capricious, following smooth deprotection of the benzoyl group cycloadduct **251** successfully underwent auxiliary hydrolysis, albeit in low yield to afford cycloadduct **252**. A misfortune which

accompanied cycloadduct **252** was its insolubility in a wide range of solvents. Cycloadduct **252** failed to dissolve in a MeOH/H_2O mixture, H_2O and a range of organic solvents. Failure of **252** to dissolve inhibited our exploration of the potential of **252** as an organocatalyst. In conjunction with the synthesis of **252**, we developed nitrone **253** which is derived form oxime **227** and anthracenealdehyde. In order to address the solubility issue associated with cycloadduct **252**, we treated nitrone **253** with 4-nitrophenylisocyanate, we believed that the presence of the nitrophenyl group would aid solubility, whilst displaying blocking group potential. To our delight cycloadduct **254** proved to be a stable complex molecule, subsequently this prompted us to expose **254** to acidic media. In spite of this **255** was not isolated as a free base, yet again numerous spots appeared on tlc which signified destruction in the presence of acid.

2.4 Conclusions

Initially, our first objective was to develop a novel enantioselective methodology for the construction of highly functionalised cyclopentanoids. Our initial strategy for this invention was to develop a unique organocatalyst which would embrace chiral iminium ion catalysis, predominantly focusing on the Nazarov cyclisation. The scarcity of reports in the literature of this type of reaction was the driving force behind this innovative application. However the most prominent and single model of an enantioselective organocatalytic Nazarov reaction is the Brønsted acid catalysed reaction reported by Rueping [8] *et al.* In this instance chiral binol phosphates were used to activate the carbonyl moiety, this was a sufficient method to promote the electrocyclisation.

Based on our results we concluded that our oxadiazolidinone **230** was an efficient organocatalyst however it was not a viable source of chirality in the Nazarov reaction, despite exploring numerous reaction conditions. This unfortunate but relevant result led us to devise an alternative application of **230** which was based on the Diels-Alder reaction as a model system. Whilst **230** was an efficient organocatalyst in the Diels-

Alder cycloaddition, due to lack of control of iminium ion geometry, poor levels of enantiocontrol were observed as a consequence of this.

Having successfully identified a suitable scaffold which can serve as an organocatalyst, we next turned our attention to tackle the iminium ion geometry matter; we envisioned that this issue would be addressed if alterations to the catalysts framework were carried out. However, despite successfully synthesising diverse oxadiazolidinones, hydrolysis of the auxiliary proved not to be a trivial feat.

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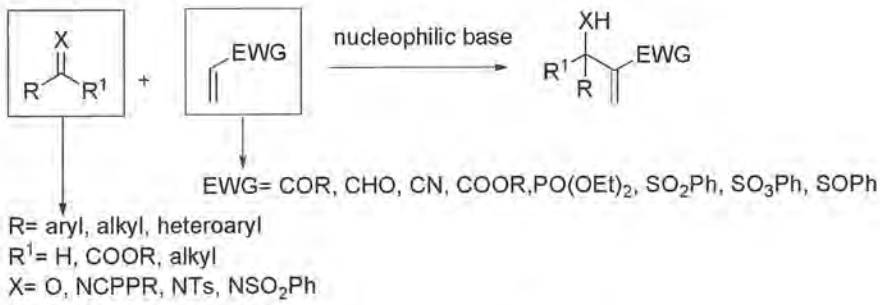
Chapter 3

Chiral Brønsted acid Organocatalysis in the Thio-Aldol Cyclisation

3.1 Introduction The Morita-Baylis-Hillman reaction

The development of an efficient method to access intricate molecular architectures remains one of the most significant challenges in organic synthesis. Asymmetric tandem transformations are an attractive approach. An increase in molecular complexity is attained, *i.e.*, products with two or more contiguous stereocentres, simply by employing readily available starting materials and a catalyst.[1,2]

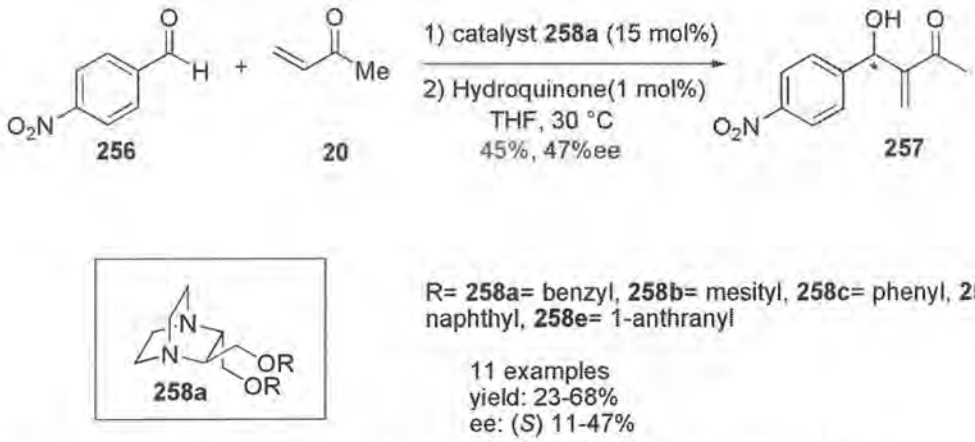
An important and useful carbon-carbon bond forming reaction is the Morita-Baylis-Hillman (MBH) reaction, [3] which belongs to the family of tandem conjugate addition aldol processes. The (MBH) is an attractive reaction, it is atom economic, simple prochiral starting materials can be employed to afford complex molecules without generating waste or byproducts, [4] and last of all it can be selective. The (MBH) reaction was reported by Morita in 1968, where tertiary phosphines were employed to catalyze the reaction of acrylic compounds with aldehydes. [5] Shortly after, a German patent was then filed by Baylis and Hillman in 1972. [6] The three component reaction involves the coupling of the α–position of the activated alkene with a carbon electrophile containing an electron deficient sp^2 carbon which is catalyzed by a tertiary amine, to generate multifunctional molecules [3] (Scheme 3.1).



Scheme 3.1 Classic Morita-Baylis-Hillman reaction

3.1.1 Asymmetric Morita Baylis Hillman reactions

The Morita-Baylis-Hillman reaction results in the formation of a chiral centre, which opens up the possibility of asymmetric induction. The chiral induction can be delivered from any one of the four components, *i.e.*, the activated alkene, tertiary amine, and electrophile or solvent. Discovering new catalytic systems for the (MBH) reaction has attracted considerable attention; however, few successful chiral catalysts have been demonstrated. In 1995, Hirama *et al.* reported the asymmetric Baylis-Hillman reaction using C_2-symmetric 2,3-disubstituted DABCOs [7] (Scheme 3.2).

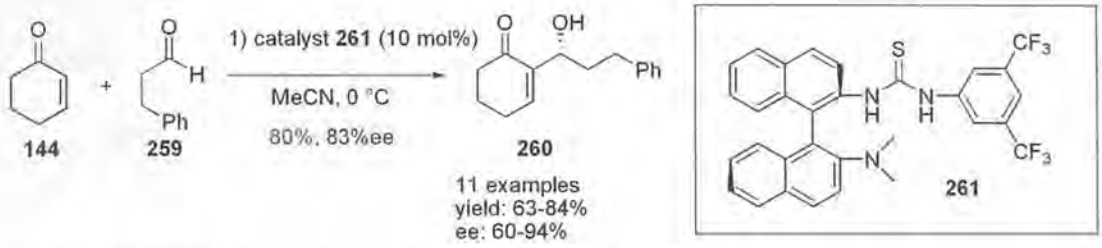


Scheme 3.2 Asymmetric Morita Baylis Hillman using chiral DABCO

Hirama[7] and co-workers found that when catalyst **258a** was employed in the above reaction under atmospheric pressure the reaction proceeded very slowly. However, when the reaction was subjected to high pressure conditions (5 kbar), a dramatic increase in reaction rate and enantioselectivity was observed.

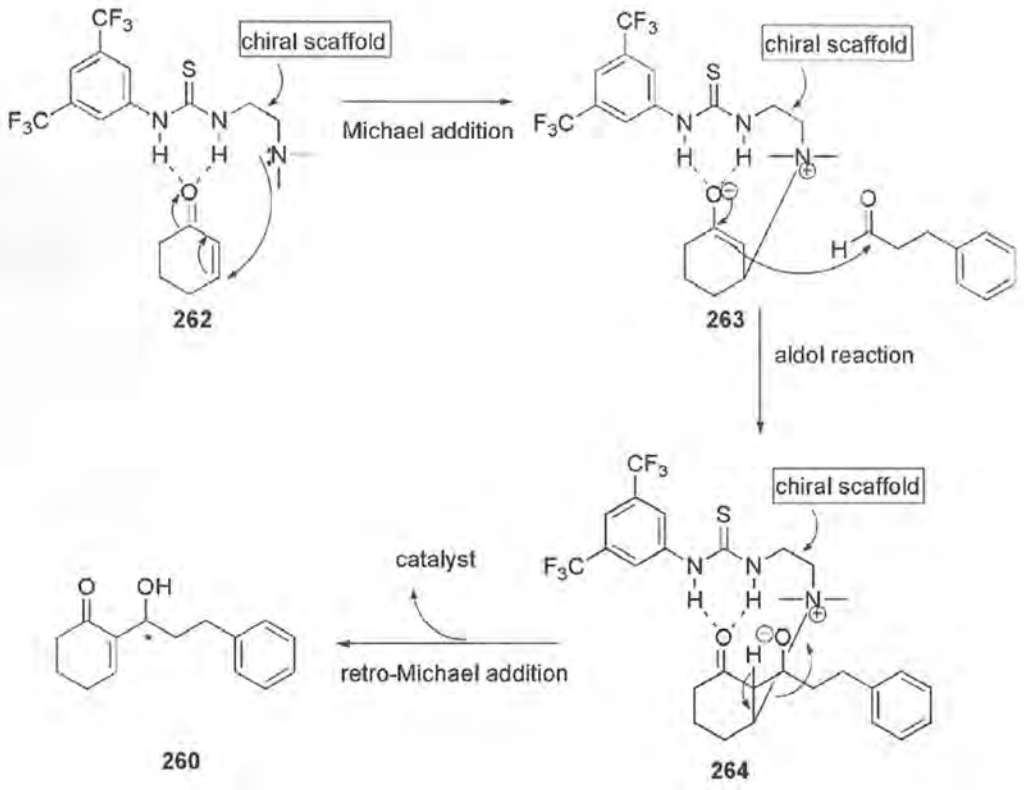
In 2005, Wang [8] *et al.* reported the use of a new type of bifunctional organocatalyst which has been developed to promote the enantioselective (MBH) reaction. The reaction rate proceeded smoothly with cyclohexanone and various aldehydes, whilst attaining

high levels of chemical yield. The thiourea group has hydrogen bond acidity which activates the carbonyl group of α,β-unsaturated substrates, this activation facilitates the Michael addition of the tertiary amine to the Michael acceptor (Scheme 3.4).



Scheme 3.3 Morita Baylis Hillman promoted by bifunctional thiourea organocatalysts

The reaction of 2-cyclohexen-1-one with 3-phenylpropionaldehyde to afford allylic alcohols was used as a model reaction, [7] in order to test the catalytic ability of the bifunctional organocatalysts. After extensive screening of reaction conditions, it was found that the best levels of enantioselectivity (94% e.e.) were achieved when the reaction was conducted in acetonitrile at 0 °C with 10 mol% of bifunctional amine-thiourea catalyst **261**. Thiourea catalyst **261** proved to be superior in this transformation (Scheme 3.3), this is due to the stronger H-bonding interaction with the carbonyl group, which was brought about by the 3,5-bis(trifluoromethyl)phenyl group. A plausible mechanism for the asymmetric (MBH) reaction is outlined below (Scheme 3.4).

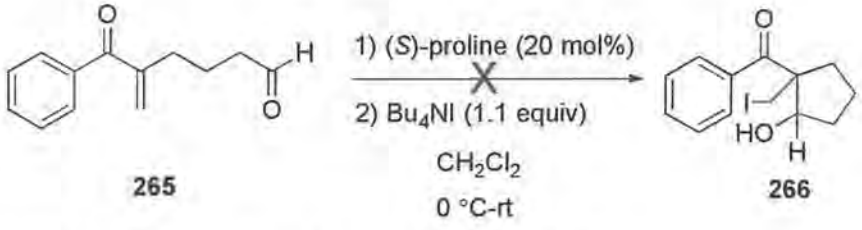


Scheme 3.4 Mechanism of bifunctional thiourea organocatalyst

The vast majority of tandem aldol reactions reported in the literature are intermolecular and use mono or 1,2-substituted Michael acceptors. However, in order to successfully install a quaternary centre, α-substituted Michael acceptors are required. The development of stereoselective methodologies for the formation of quaternary centres remains a huge challenge for synthetic chemists. Given the importance of quaternary stereogenic centres in biologically active molecules, this provided us with the incentive to develop new selective methodologies for the construction of quaternary centres. [9]

3.2 Results and Discussion II

Given the value of the iodo-aldol cyclisation, [10] we were curious to examine the scope of this process, with a view to introduce chirality into the system. Initial efforts to develop an asymmetric variant of this process involved employing enone-aldehyde prochiral substrates of nature **265**, (*S*)-proline as the organocatalyst and Bu_4NI as the nucleophile. However, disappointingly all attempts of an enol-5-*exo* ring closure met with failure. It is thought that the reagent combination $TiCl_4/Bu_4NI$ is exceptionally effective at generating the *β*–iodo carbonyl compounds. However, when Bu_4NI is paired with a catalytic amount of the Lewis base organocatalyst (*S*)-proline, no 1,4-addition or cyclisation takes place. Similarly, when (*S*)-proline is replaced by Macmillan's organocatalyst **120** and oxadiazolidinone **230**, yet again no reaction takes place which results in recovered starting material. These observations suggest that in the absence of a strong Lewis acid resembling $TiCl_4$, Bu_4NI proves to be an ineffective nucleophile.

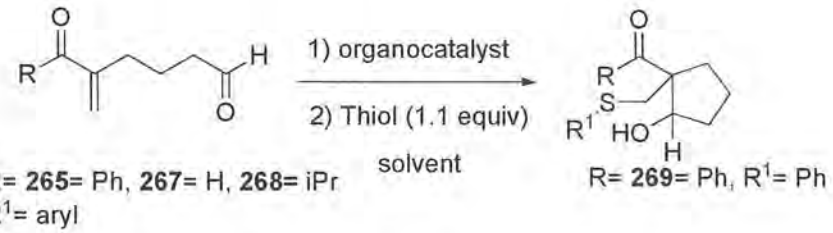


265 **266**

Scheme 3.5 Iodo-aldol reaction of enone-aldehyde 265

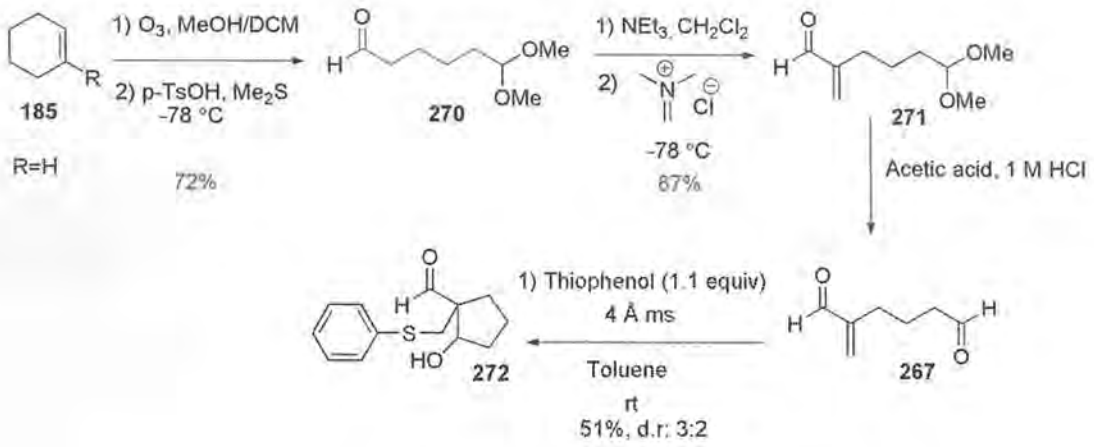
In order to synthesise hindered *γ*–thioalcohols, allowing for the formation of full carbon quaternary stereogenic centres. We decided to explore the scope of the enantioselective thio-aldol reaction. To the best of our knowledge, the utilisation of *α*–acroleins in enantioselective synthesis is still in its infancy, [11] this is presumably due to the difficulty involved in activating *α*–acroleins with organocatalysts. In order to introduce chirality into our system, we relied on the chiral information stored within the organocatalyst.

3.2.1 Thiol mediated Michael-aldol cyclisation



Scheme 3.6 Proposed thio-aldol cyclisation

Our initial idea was to employ enal-aldehyde substrate **267** as a model substrate for the thio-aldol cyclisation. Simple ozonolysis of cyclohexene gave rise to hexanal in high yield, which upon methenylation afforded the aldehyde acetal substrate **270**. 6,6-dimethoxy-2-methylenehexanal **271** underwent straightforward hydrolysis using acidic conditions to afford the desired 2-methylenehexanal **267**. Due to the unstability of **267** with silica and high volatility, determination of the yield was not feasible. When 2-methylenehexanal **267** was treated with thiophenol in toluene, the reaction had gone to completion in less than one hour. However, the reaction was repeated and monitored by ^{1}H NMR and taking aliquots. After fifteen minutes, ^{1}H NMR analysis displayed no starting material or side products. Due to the rate at which this cyclisation takes place, it seemed that the background reaction would dominate, thus inhibiting organocatalysis to take place. The reaction was repeated and carried out at lower temperatures; however, the reaction took place at a similar rate.



Scheme 3.7 Synthesis of enal-aldehyde substrate 267

We next turned our attention to developing an alternative dialdehyde substrate. Greaney *et al.*[10] reported the use of α–substituted enoate aldehydes in the iodo-aldol cyclisation. Based on this work, we envisioned that if reduction of the ester functional group to the enal was feasible, then this class of substrate may be an interesting starting material in the thio-aldol cyclisation. Ester-acetal substrate **273** was subjected to DIBAL-H in toluene at -78 °C, after 3 hours there was traces of the alcohol, together with the desired aldehyde. Purification by column chromatography gave rise to enal-acetal **274**. In order to gain access to more starting material, the alcohol-acetal was oxidised with PCC in dichloromethane, which afforded enal-acetal **274**. The initial strategy to hydrolyse the acetal functionality of **274**, was to treat enal-acetal **274** with acetic acid in HCl (1 M). Unfortunately, the deprotection of the acetal functionality under these conditions met with failure. Further endeavours to hydrolyse the acetal, involved employing DDQ, however, yet again all attempts to smoothly hydrolyse **274**, were unsuccessful.

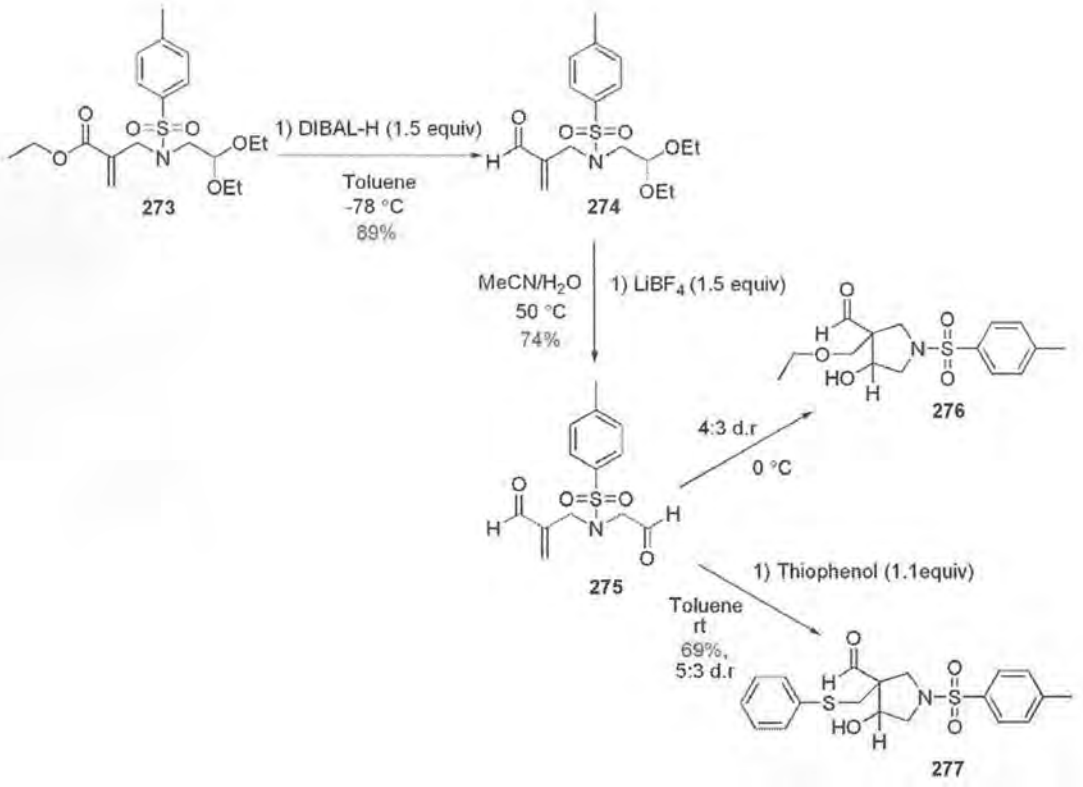
Finally enal-acetal **274** underwent deprotection using PPTS in aqueous acetonitrile, albeit in 52% yield (Scheme 3.8). Nevertheless, an optimum yield of 74% was achieved, by replacing PPTS with lithium tetrafluoroborate (1.2 equiv), a surprising result, when considering that unsubstituted 1,3-dioxolanes as protecting groups, usually proceed at a

slow rate with low to moderate yields in the presence of this mild Lewis acid. [12] However, enal-aldehyde **275** proved to be unstable to silica. Crude ^{1}H NMR analysis revealed **275** to be of suitable purity, without the need for purification by column chromatography.

Enal-aldehyde **275** was treated with thiophenol (1.1 equiv) in toluene, rendering **277** as a (5:3) mixture of diastereomers, in 69% yield; both of which were stable to silica; allowing for successful purification, by means of column chromatography.

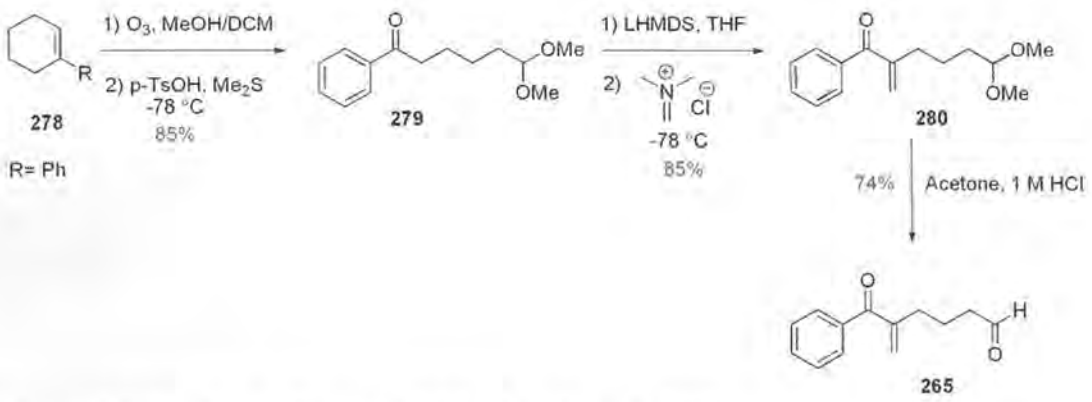
After successful introduction of thiophenol to enal-aldehyde **275**, by means of a Michael-aldol tandem process, we turned our attention to generate more starting material **275**, in an attempt to further explore this reaction. However, on close inspection the hydrolysis of enal-acetal **274** is troublesome when repeated on large scale. Significant depletion in the chemical yield was observed, together with formation of an unexpected carbocycle **276**. It is thought that this serendipitous discovery occurs during hydrolysis of the acetal, the ethoxy groups attack the highly reactive enal, subsequently giving rise to carbocycle **276** as a 4:3 mixture of diastereomers.

Despite enal substrate **275** undergoing smooth ring closure to afford **277**, given the lack of material, the uncertainty of the purity and the intricate synthesis involved in the preparation of the prochiral starting material, we decided not to embark on an asymmetric version of this reaction, whilst utilising enal substrate **275**.



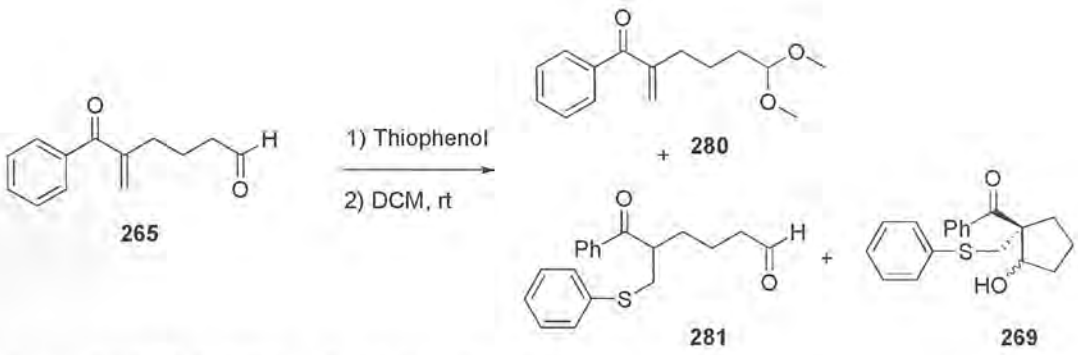
Scheme 3.8 Synthesis of enal-aldehyde substrate 275

In our search for electing suitable substrates, enone-aldehydes were chosen as appropriate carbocyclization substrates. We envisioned that by employing less reactive substrates in this reaction, the background reaction would be minimised, allowing for organocatalysis to play a role. These can be synthesised as shown in [13] (Scheme 3.9).



Scheme 3.9 Synthesis of enone-aldehyde substrate 265

1-Phenylcycloxexene **278** underwent ozonolysis [13] in the presence of MeOH/DCM to produce a chain with an acetal group at the termini. The presence of the acetal group is essential, in order to allow insertion of the exo-methylene group adjacent to the ketone. LiHMDS was used as the base to generate the enolate, which then reacted with Böhme's or Eschenmoser's salt, allowing installation of the enal functionality in one single step. The enal-acetal substrate was then deprotected in acetone with a catalytic amount of 1M HCl to afford the desired enone-aldehyde substrate. To explore the possibility of the tandem thio-aldol reaction, a model reaction between **265** and thiophenol (1.1 equiv) was performed in DCM under an atmosphere of N_2 at rt, in the absence of any organocatalyst. To our delight, after 4 h at rt, tlc monitoring showed total consumption of the starting material, and after purification by column chromatography, the desired cyclopentenol was isolated in 56% yield, together with the 1,4-addition product **282** in 18% yield (Scheme 3.10). ^{1}H NMR analysis of the crude mixture indicated a 3:2 mixture of diastereomers; this was indicated by the proton at the tertiary centre.



Scheme 3.10 Thio Michael-aldol cyclisation

The above reaction was repeated and heated to 50 °C and left to stir for 2 h. In this instance we did observe the cyclopentenol as the sole product in 69% yield (5:4 *trans:cis*), without any of the 1,4-addition product **281**. In order to investigate the effect a polar solvent would have on the yield and rate of the reaction, we replaced DCM with MeOH as a solvent. The desired cyclopentenol **269** was isolated in 34% yield, but the major product was the dimethyl acetal product **280** in 47% yield (Table 3-1). Screening of different solvents was carried out; which demonstrated toluene to be the most effective solvent, providing the desired product in the best yield.

With the model reaction proceeding smoothly in the absence of any organocatalyst, our next goal was to introduce chirality into this system. In order to achieve high levels of asymmetric induction in the 1,4 addition reaction of thiols to α,β-unsaturated compounds, several factors have to be considered, *i.e.,* structure of catalyst, donors, acceptors, solvent, concentration and temperature of reaction media.

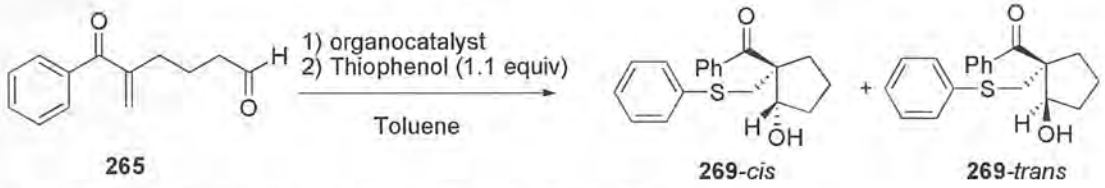
Table (3-1) Solvent screening of racemic tandem thio-aldol reaction

Entry	Solvent	Thiophenol (eq)	Temperature (°C)	Time (h)	Yield (%)	d.r *trans:cis*
1	DCM	1.1	rt	4	56	3:2
2	MeOH	1.1	rt	6	34	3:2
3	DCM	1.1	50	2	69	5:4
4	Toluene	1.1	rt	4	89	3:2

Since the 1960`s, cinchona alkaloids have been considered to be useful tools for highly enantioselective reactions. [14] In an attempt to carry out the above reaction in an asymmetric manner, we employed 5 mol% (-) cinchonine as the organocatalyst. A solution of the enone-aldehyde substrate **265** in toluene was added to a stirred solution of 5 mol% (-) cinchonidine in dry toluene under an atmosphere of N_2. The mixture was left to stir for 20 min at rt and then cooled to -20 °C. A solution of thiophenol in dry toluene was then added dropwise to the solution. When the reaction had reached completion, the reaction was washed with H_2O, and extracted with diethyl ether. ^1H NMR analysis of the crude reaction mixture indicated a 3:2 mixture of diastereomers (determined from the integration of the two tertiary proton peaks at δ_{min}= 4.62 ppm (t, 1H, J = 6.4 Hz) *vs trans* δ_{maj} = 4.56 ppm (m, 1H) in the ^1H NMR), which could be separated by chromatography. Chiral HPLC analysis was employed to determine the enantiomeric excess, the best separation was found with chiralpak AD-H column (Table 3-2, entry 1, 24:0 e.e.). In an effort to improve the enantioselectivity and diastereoselectivity, we increased the catalyst loading to 10 mol% and cooled the reaction to -78 °C, before addition of the thiophenol in toluene. The reaction was complete after 6 h compared with (Table 3-2, entry 1); at -20 °C for 4 h. However, there was no significant change in yield; it was observed that the enantiomeric excess had decreased when the catalyst loading was increased. The decrease in enantioselectivity is

presumably due to the lower reaction temperature, suggesting that racemisation takes place at lower temperatures.

3.2.2 Organocatalyst screening of the thio-aldol cyclisation



265 **269-*cis*** **269-*trans***

Scheme 3.11 Brønsted acid catalysed thio-aldol cyclisation

Table (3-2) Optimisation studies of the Brønsted acid catalysed thio-aldol cyclisation

Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)	d.r. *trans*:*cis*	e.e. (%) *cis*:*trans*
1	Cinchonidine 5	-20	4	85	3:2	24:0
2	Cinchonidine 10	-78	6	87	2:1	2:15
3	Quinine 10	-20	2	81	3:2	49:23
4	Cinchonine 10	-20	4	89	2:3	35:33
5	Cinchonine 10(5equiv H_2O)	-20	10	64	4:5	2:6
6	Quinidine 10	-20	4	88	2:3	40:37
7	Quinine 10	-40	5	75	3:2	51:32

When (-) cinchonidine was replaced with (-) quinine, the reaction rate and e.e. had increased significantly. Quinine appears to be a superior catalyst in comparison to (-) cinchonidine in the addition of thiophenol to enone-aldehyde **265**. There have been breakthrough contributions put forth by several groups, reporting the success of the enantioselective aldol reactions in aqueous media. [15,16] In view of this precedent, the thio-aldol reaction was carried out, in the presence of H_2O (5 equiv). The reaction proceeded at a slower rate than the others (Table 3-2, entry 5); however, there was significant erosion in the enantioselectivity. It is thought that the hydrogen bond accepting solvents like H_2O are responsible for weakening the ionic interaction between the anion and the cation in the transition state (*vide* Fig 3.0). It is the hydroxyl group of the catalyst which forms the hydrogen bond with the carbonyl group leading to a structured transition state, therefore a possible explanation for the decrease in e.e. could be that the coordinating solvents block the hydroxyl group, therefore activation of the electrophiles is inhibited, which consequently leads to a destabilisation of the transition state, resulting in low levels of enantioselectivity.

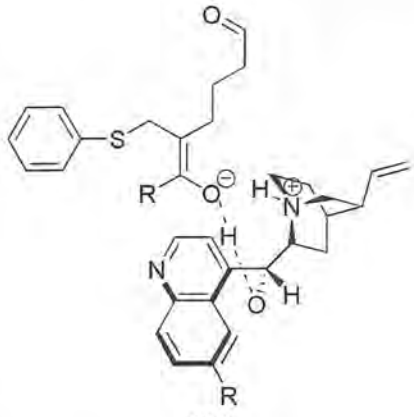


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Fig 3.0 Cinchona alkaloid catalyst transition state

When (+)-cinchonine was used in the reaction, an increase in yield was observed, together with increased levels of enantiocontrol. (Table 3-2, entry 1 *vs* 4). By employing

(+)-quininidine to the reaction mixture, moderate levels of enantiocontrol were achieved. At lower reaction temperatures (Table 3-2, entry 3 *vs* 7), increased levels of enantiocontrol are observed for both diastereomers when (-)-quinine is employed.

Wynberg *et al.* reported [17] that cinchona alkaloids and β-amino alcohols catalyze the reaction of thiols to α,β-unsaturated compounds. However, desirable enantioselectivities were not attained. They proposed that the chinchona alkaloids catalyse the reaction via a tight transition state complex. There are three stabilizing interactions responsible for catalysing the reaction, first of all there must be an electrostatic interaction between the thiolate anion and the ammonium cation of the cinchona alkaloid, secondly there must be a hydrogen bond interaction between the hydroxyl group on the catalyst and the enone of the carbonyl group, and last of all there must be a dispersion interaction between the aromatic ring system of the catalyst and the thiol anion. These findings coincide with ours, in the way that when we employ (-) quinine as the organocatalyst we observe increased levels of enantioselectivity of both diastereomers. The above experiments indicate that the presence of the free hydroxyl group is essential in order to achieve high conversion and enantioselectivity. The presence of the methoxy group illustrates an increase in e.e, this suggests that the dispersion reaction between the aromatic ring system and the thiol anion plays an important role in the transition state of the reaction, as its absence results in lower enantioselectivities. Gratifyingly, the natural cinchona alkaloids can be employed in the tandem thio-aldol reaction, albeit with modest enantioselectivity.

3.2.3 Derivitisation of cinchona alkaloids

In an attempt to improve the enantioselctivity of these reactions, we were interested in modifying existing cinchona alkaloids. Deng and co-workers [18] have developed a new class of chiral bifunctional organic catalysts which are derived from cinchona alkaloids. These organocatalysts are easily accessible from (-)-quinine and (+)-quinidine, and have

been shown to be effective in asymmetric conjugate additions. Given their straightforward assembly and high efficiency in the conjugate addition of malonate to nitroalkanes,[19] this encouraged us to synthesise these derivatives.

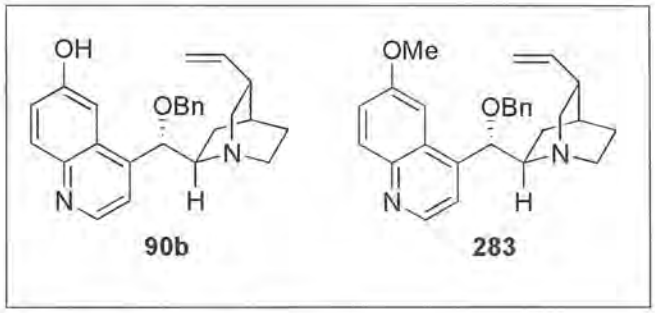
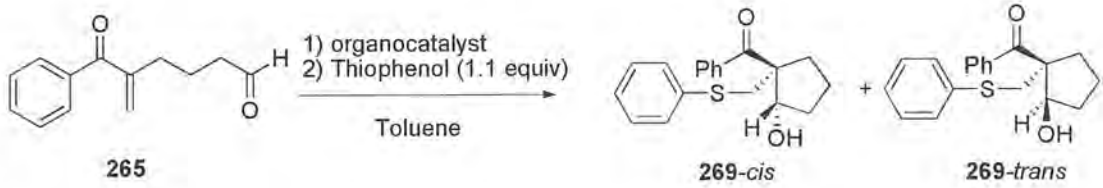


Fig 3.1 Modification of cinchona alkaloids

Catalyst **90b** was prepared in one-step by adding NaH to a solution of (+)-quinidine in DMF, the reaction was left to stir at rt for 2 h, Benzyl chloride was added dropwise via a syringe. Purification by flash chromatography gave yellowish oil. Having synthesised catalyst **283**, we turned our efforts to investigate its applicability in the thio-aldol reaction. Our findings illustrated that when the C-9 hydroxyl group is substituted with an OR group, a significant drop in enantioselectivity is observed, this observation suggests that the presence of the hydroxyl group is necessary in order to achieve moderate enantioselectivity. This strongly indicates that the hydroxyl group stabilises the anion intermediate through hydrogen bonding, which accelerates the aldol addition reaction.



265 **269**-*cis* **269**-*trans*

Scheme 3.12 Brønsted acid catalysed thio-aldol cyclisation

Table (3-3) Further optimisation of the thio-aldol cyclisation

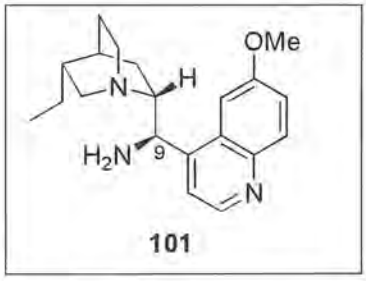
Entry	Catalyst (10 mol%)	Temp (°C)	Time (h)	Yield (%)	d.r. *trans*:*cis*	e.e. (%) *cis*:*trans*
1	**283**	-20	6	78	1:2	12:27
2	**90b**	-20	5	83	1:1	28:28
3	Hydroquinine	-20	3	85	5:4	22:29
4	Hydroquinidine	-20	3	79	4:5	47:43
5	**101**	-20	2	91	3:2	40:61
6	**284**	-20	4	79	5:4	14:5
7	Ephedrine **286**	-20	1	86	3:2	0:19
8	Ephedrine **287**	-20	1	89	2:1	0:15
9	**230**	-20	24	74	3:2	0:46
10	**230**	-40	36	68	3:2	0:42
11	**323***	-20	6	59	5:4	32:37

* See experimental for catalyst structure

In order to rationalise the key role played by the hydroxyl group, we synthesised [18] catalyst **90b**. Catalyst **283** is suspended in DMF with NaSEt; this gave rise to the desired demethylated catalyst **90b**. Deng and co-workers reported that cinchona alkaloids bearing a hydroxyl group in the 6` position instead of a methoxy group improve the enantioselectivity of the 1,4-addition reaction with malonates to nitroalkanes. In spite of this report, catalyst **90b** is less efficient in the thio-aldol reaction (Table 3-2 entry 6 *vs* Table 3-3 entry 2), in terms of enantioselectivity when C-9= OBn. The position of the hydroxyl group is highly influential in our reaction, these results are consistent with the

notion that the hydroxyl group at C-9 is conformationally mobile and utilises both the C-9 hydroxyl and quinuclidine functionalities to stabilise the transition state, allowing enantioselective 1,4 addition.

When hydroquinine and hydroquinidine were employed as bifunctional organocatalysts the reaction rates were faster, and the enantioselectivity in the case of hydroquinidine was moderate. When the C-9 hydroxyl is replaced by NH_2, the conversion is greater in favour of the minor diastereomer (Table 3-3, entry 5). Catalyst **101** afforded promising catalytic capacity in terms of enantioselectivity, this is presumably due to stronger hydrogen bonding interaction between the α,β-carbonyl substrate **265** and the NH_2 of catalyst **101**. Encouraged by these results, we began to investigate the use of thiourea organocatalysts, these bifunctional thiourea derivatives [7] of cinchona alkaloids have a dual hydrogen bonding [19] Lewis acid activation interaction with the carbonyl substrates. The amine function activates the nucleophile and the thiourea moiety hydrogen bonds with the carbonyl substrate, allowing facile addition of the nucleophile.



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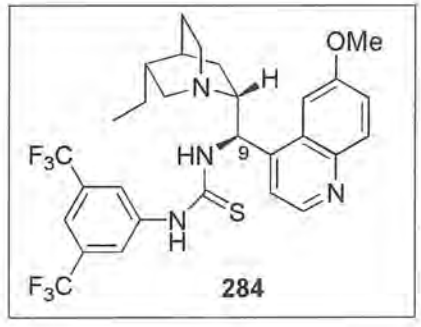

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Fig 3.2 Thiourea Organocatalysts

The N-H groups of the thiourea provide a binding site for the electrophile; they are also responsible for stabilising the catalyst-enolate ion pair by hydrogen bonds. The ion pairs **285a-285b** (*vide* Fig 3.3), could exist in both forms, prior to addition of the thiophenol.

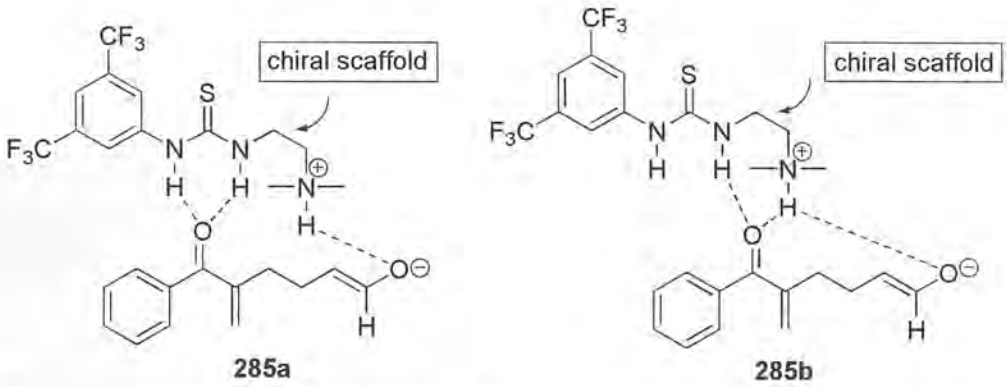
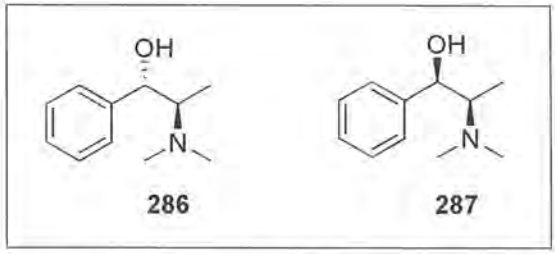


Fig 3.3 Thiourea Transition State Models

In the case of thioureas, two reaction pathways can be envisioned (*vide* Fig 3.3), it is reasonable to assume that ion pair **285b** exists before addition of the thiophenol. In order to organise and gain access to the available asymmetric binding pockets for the reacting substrates, ion pair **285a** is adopted, allowing addition of the nucleophile. We employed thiourea **284** in our model reaction with enone-aldehyde **265**. To our surprise the enantioselectivity of the reaction was significantly lower when thiourea **284** (Table 3-3, entry 6), was employed in our reaction.

Ephedra and erythro alkaloids are frequently used in asymmetric synthesis as the source of chirality. Not only have these β-hydroxy amines been reported to considerably accelerate the rate of reactions and levels of enantioselectivity; they can be easily modified, allowing straightforward investigations of the scope and utility of this class of catalyst. Given that this type of bifunctional catalyst is commercially available and performs well in a wide range of reactions, we decided to employ them in our thio-aldol cyclisation (Table 3-3, entries 7 and 8). However, to our surprise, we observed a significant depletion in enantioselectivity, despite having an increase in rate acceleration. Both, (-)-N-methylephedrine **286** and (+)-N-methylephedrine **287** were poor asymmetric inducers in the thio-aldol cyclisation (*vide* Fig 3.4).



286 **287**

Fig 3.4 (-)-N-methylephedrine and (+)-N-methylephedrine

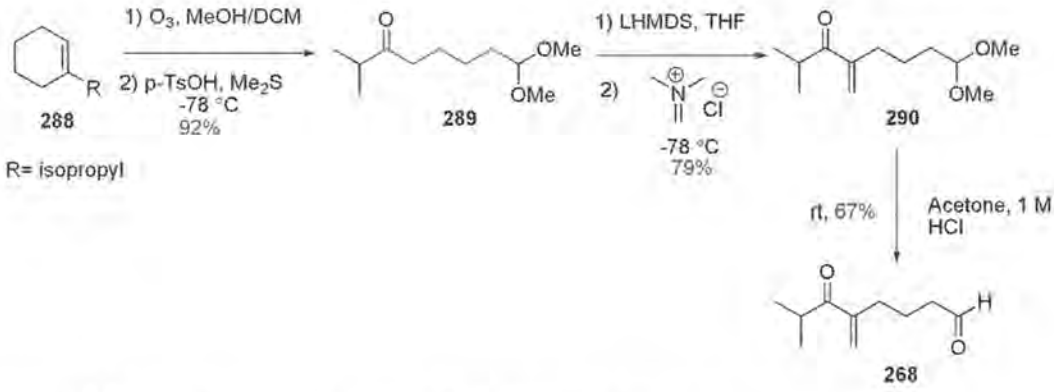
There is a scarcity in the literature of chiral secondary amines reacting with α-alkyl-substituted enals. This is attributed to unsuccessful iminium ion formation due to steric hindrance around the catalyst framework. The organocatalysts which are successful in the Diels-Alder reaction, prove not to be effective with α-acrolein type Michael acceptors. Oxadiazolidinone **230** did not perform well in the Diels-Alder reaction; however, we decided to employ it in reactions utilising α-acroleins, to find out if iminium ion formation was feasible. Using the same conditions to the other thio-aldol reactions, 10 mol% of **230** was added (Table 3-3, entry 9). The reaction was set up at -20 °C and left overnight, allowing it to warm to rt. Following, workup and purification the sample was analysed by chiral HPLC. To our delight, we did observe some stereofacial control. The *cis* diastereomer was obtained with an impressive 46% e.e., albeit with the *trans* diastereomer being racemic.

In order to gain insight into this reaction, utilising **230** in the absence of any co-acid, the reaction was repeated at -40 °C. Yet again, the *trans* diastereomer was racemic, and the *cis* diastereomer was obtained with an enantiomeric excess of 42%. Oxadiazolidinone **230**, may catalyse the reaction, in one of two ways. It might undergo iminium ion formation with enone-aldehyde **265**, lowering the LUMO, or by Brønsted acid catalysis, which would activate the electrophilic enone by catalytic protonation. Commercially available (*S*)-proline and Macmillan's organocatalyst **120** were employed in this reaction, in order to explore different natured chiral secondary amines. After 6 hours the

reaction had gone to completion. Purification by column chromatography, followed by chiral HPLC analysis proved the sample to be racemic in both cases.

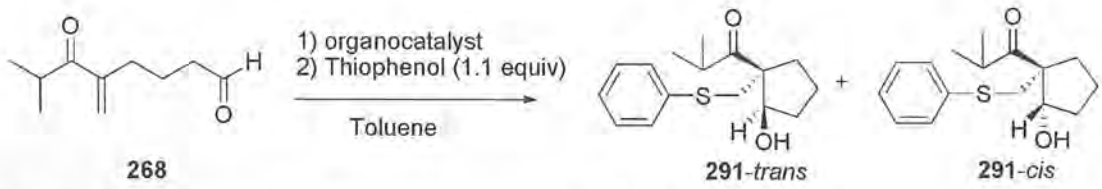
However, when oxadiazolidinone **230** was employed as the chiral source with enone-aldehyde **268**, no reaction took place. This could be due to steric hindrance imparted by the isopropyl group, discouraging iminium ion formation of substrate **268** with oxadiazolidinone **230**.

In an attempt to increase the diastereoselectivity and enantioselectivity of the thio-aldol reaction, we next turned our attention to altering the nature of the R group on the enone-aldehyde substrate Substrate enone-aldehyde **268** was synthesised in an analogous route to the synthesis of enone-aldehyde **265**. (Scheme 3.13)



Scheme 3.13 Synthesis of thio-aldol isopropyl substrate

A solution of substrate **268** in toluene was added to a solution of quinine in toluene and left to stir for 20 minutes. The reaction was cooled to -20 °C and the thiophenol/toluene solution was added dropwise to the reaction mixture (Scheme 3.14).



Scheme 3.14 Brønsted acid catalysed thio-aldol cyclisation

When quinine was employed as the catalyst (Table 3-4, entry 1), the reaction was slower compared with enone-aldehyde **265** with quinine (Table 3-2, entry 3). The 1,4 addition of the thiophenol to **268** was facile. However, the 1,4-addition product was visible by tlc, and after 20 minutes an aliquot was taken. The crude ^{1}H NMR indicated the sole product as the 1,4-addition products. Nevertheless, the aldolisation proceeded, and after 8 h the reaction had gone to completion. The thio-aldol product **291** was isolated in an impressive 89% yield as a 3:1 mixture of inseparable diastereomers. The enantioselectivity was moderate in this instance (Table 3-4, entry 1).We were pleased to observe smooth cyclisation in 8 h to afford the hindered γ–thioalcohol **291**.

However, there is substantial room for improvement in terms of enantioselectivity. Quinidine the quasienantiomer of quinine was utilised in the reaction, and as expected quinidine gave the opposite enantiomer with higher enantioselectivity of the major diastereomer. Cinchonidine which differs from quinine only by the absence of a methoxy group at C-6` provided the desired γ–thioalcohol **291** smoothly in good yield, albeit with an erosion in enantioselectivity. Cinchonidine illustrated the most promising catalytic capacity in terms of diastereoselectivity and enantioselectivity (Table 3-4, entry 4). The major *cis* diastereomer exhibited higher levels of enantioselectivity. In all cases the diastereoselectivity was consistent, in favour of the major *cis* diastereomer **291**. When enone-aldehyde **268** was added to toluene in the absence of an organocatalyst, hindered γ–thioalcohol **291** was not formed; instead a complex mixture was isolated. This indicates that the aldolisation is mediated by the presence of a cinchona alkaloid

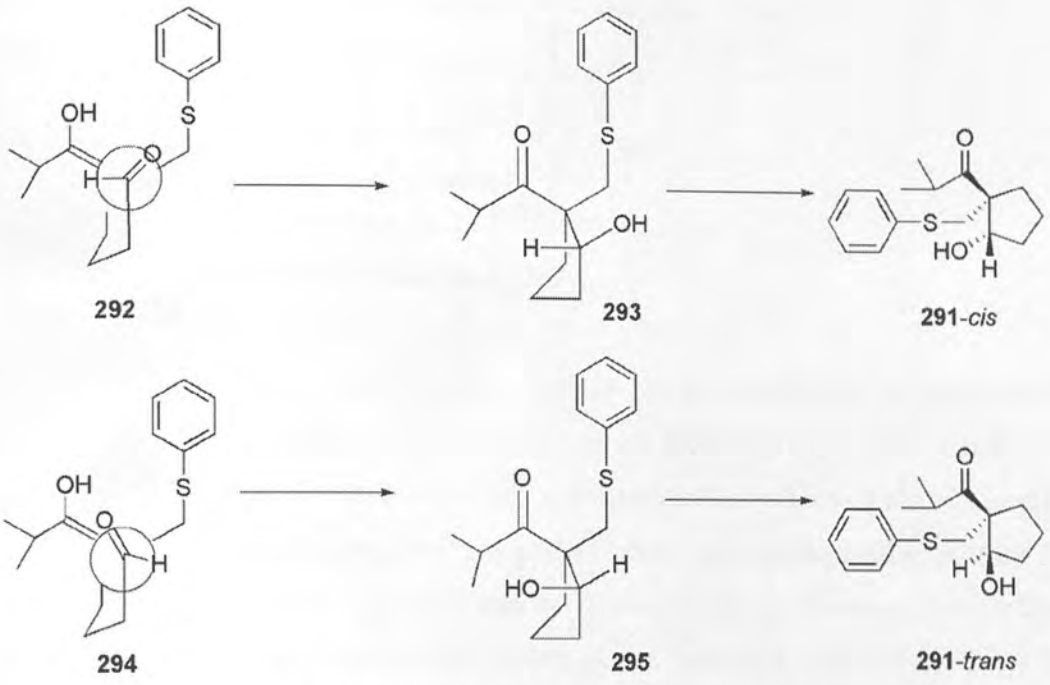
with respect to **268**; therefore a non-enantioselective variant was not easily recognised. The enantioselectivity was determined by chiral HPLC, by elucidating the ratio of diastereomers and calculating the enantioselectivity respectively.

Table (3-4) Investigations of substrate scope for the thio-aldol cyclisation

Entry	Catalyst (10 mol %)	Temp (°C)	Time (h)	Yield (%)	d.r *trans:cis*	e.e. (%)
1	Quinine	-20	8	89	1:3	32:17
2	Quinidine	-20	6	85	1:4	3:34
3	Cinchonine	-20	7	90	1:2	11:11
4	Cinchonidine	-20	7	93	1:7	32:70

3.2.4 Stereochemical rationale for thio-aldol product 291

The diastereoselectivity remains, however, low in most cases for carbocycle **269**. Nevertheless, when substrate **268** is employed, there is an increase in the diastereoselectivity. A possible explanation for this increase is illustrated (*vide infra* 3.15), using the model shown for substrate **268**.



Scheme 3.15 Stereochemical model for thio-aldol cyclisation for substrate 268

The increase in diastereoselectivity is thought to arise from the steric hindrance imparted by the isopropyl group. The initial conjugate addition of the thiophenol generates the *cis* enolate which undergoes subsequent intramolecular aldol cyclisation *via* a five-membered transition state. The presence of the isopropyl group promotes the hydroxyl group and the thiomethyl group to exist in a *cis* relationship. Discrimination between the two conformations maybe attributed to the orientation of the hydroxyl group, which is placed in the less hindered position, *i.e.*, *cis* to the thiomethyl protons, with the tertiary proton occupying the axial position. The *trans* structure which has the hydroxyl group occupying the more hindered axial position, illustrates why the *cis* product is favoured in this instance.

With respect to **269**, the phenyl group imparts less steric hindrance, therefore both *cis* and *trans* transition states are of equal energy, accounting for the lower levels of stereocontrol in the aldol cyclisation step.

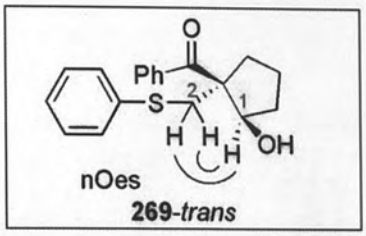


Fig 3.5 Stereochemical conformation of 269

Two dimensional NMR studies revealed that the major diastereomer of 2-hydroxy-1-(phenylthiomethyl) cyclopentyl (phenyl) methanone **269** had a *trans* relationship. This assumption was based upon NOESY experimentation, which showed medium enhancements between the proton at the tertiary centre and the thiomethyl protons (2), this indicated that the hydroxyl groups and the thiomethyl groups were on opposite faces of the carbocycle. The diastereomer which is the minor in most cases has a *cis* relationship, a triplet peak for the tertiary proton (1) appeared at δ_{min}= 4.62 ppm (t, 1H, J= 6.4Hz) *vs trans* δ_{maj} = 4.56 ppm (m, 1H) in the ^{1}H NMR.

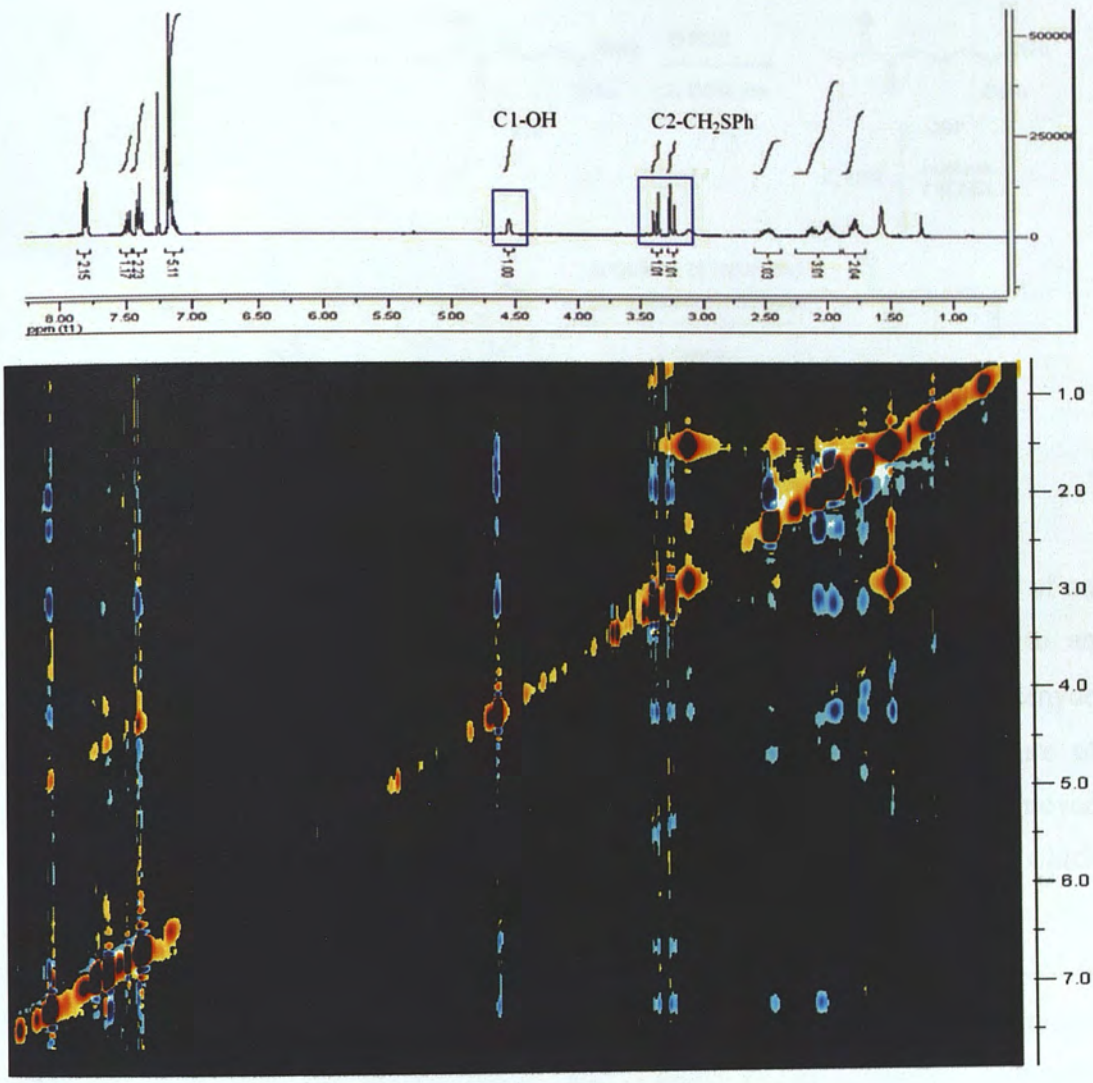
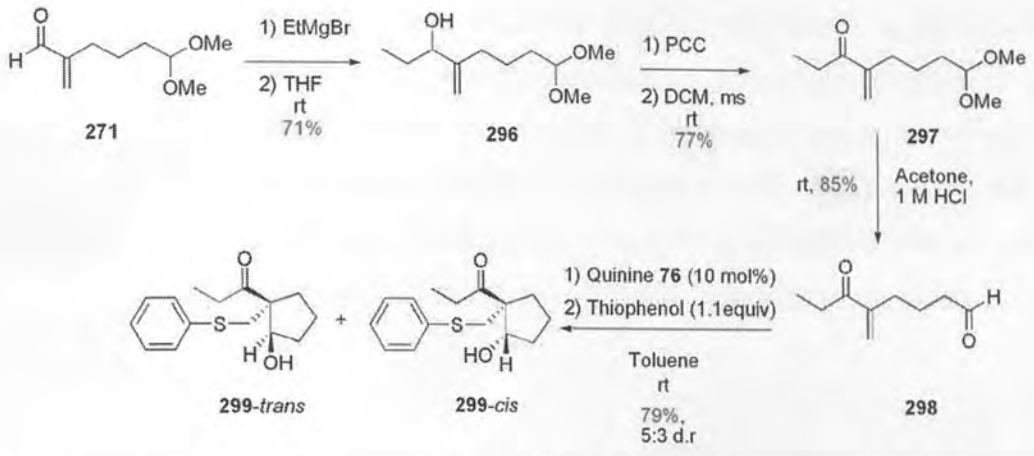


Fig 3.6 NOESY spectra illustrating *trans* assignment of 269

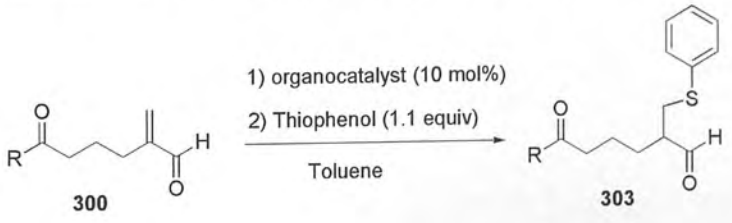
In order to investigate the substrate scope of the thio-aldol reaction, enone-aldehyde **301** was synthesised. Enal-acetal **271** was synthesised from cyclohexene. [13] Ethyl magnesium bromide was added dropwise to **271**, to afford the secondary alcohol **296** (71%), which was then oxidised with PCC to afford the desired enone-acetal **297** (77%). HCl (1 M) was added dropwise to a solution of enone-acetal **297** to give rise to enone-aldehyde **298** (Scheme 3.16).



Scheme 3.16 Derivitisation of enone-aldehyde substrate 265

Ethylenone-aldehyde **298** was treated with thiophenol in toluene in the absence of an organocatalyst. The reaction was complete after 10 hours, which gave rise to an inseparable diastereomeric mixture (4:3) of γ–thioalcohol **299**. Ethylenone-aldehyde **298** was then treated with quinine, which gave rise to **299** as a 5:3 mixture of diastereomers. Due to the inseparable mixture of diastereomers, HPLC analysis proved to be complex in terms of e.e. determination. Four peaks were observed, two of which are diastereomers, and the enantiomer of each diastereomer. (Appendix 2)

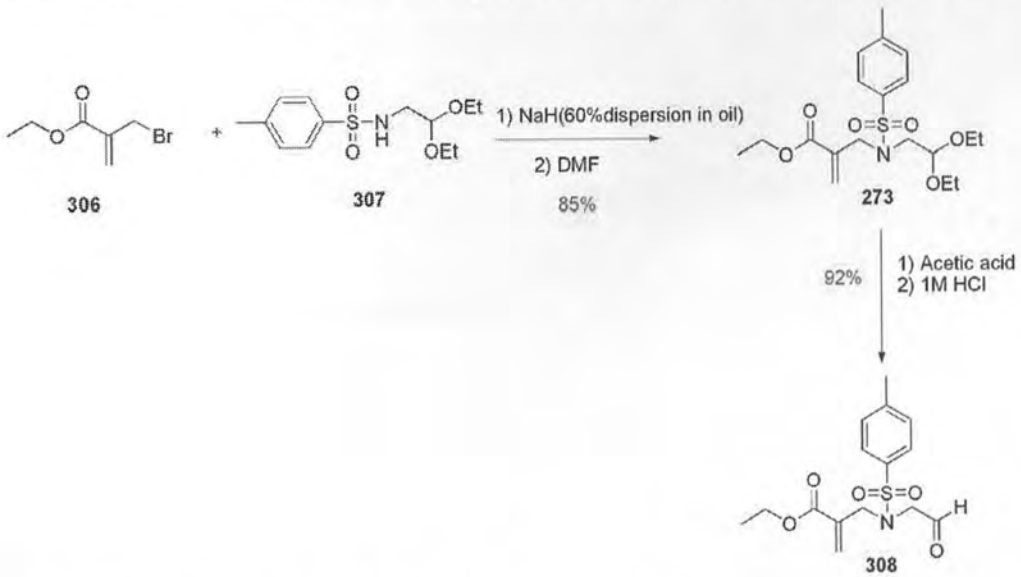
With quinine and cinchonidine as promising catalyst systems at hand, we decided to explore the scope and limitations of this methodology. It was of interest to prepare substrates with different functionalities, for example enoate-aldehydes, aldehyde-aldehyde substrates and enal-enone substrates. (Scheme 3.17)



Scheme 3.17 1,4-conjugate addition reaction with enal-enone substrates

In the presence of a catalytic amount of cinchona alkaloid, substrates **300**, **301** and **302** failed to afford the desired cyclopentenols. Successsful 1,4 addition took place in fast reaction times both in the presence and absence of an organocatalyst, however, the intramolecular aldol reaction did not occur. It is thought that this result may be due to the lower levels of reactivity associated with the enone acceptor, together with the steric hindrance imparted by the nature of the R group are plausible factors responsible for the unsuccessful cyclisation.

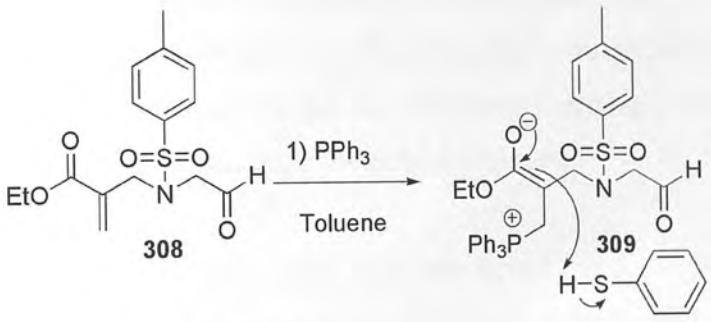
The iodo-aldol cyclisation reported by the Greaney group, [10] demonstrated the smooth cyclisation of enoate-aldehyde **308** with $TiCl_4$ to give rise to the γ–iodoalcohol product with high levels of diastereoselectivity. With the synthetic sequence of substrate **273** established, we synthesised enoate-aldehyde **308** to utilise in our thio-aldol reaction.



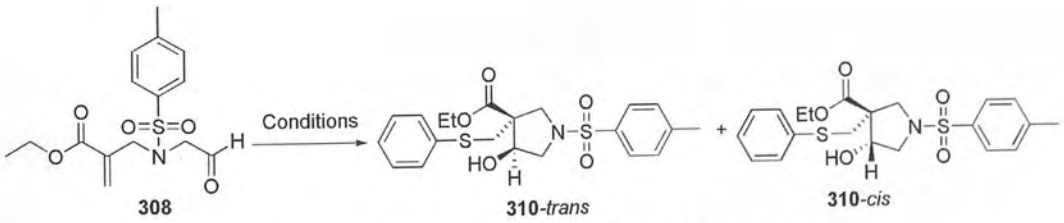
Scheme 3.18 Synthesis of ester-aldehyde substrate 308

In this instance the enantioselective variant was not so easily recognised, due to the lower reactivity of enoates, thus the addition of thiophenol would proceed at a slow rate, if at all. However, slow addition of thiophenol to enoate-aldehyde **308** may circumvent

the moderate enantioselectivity levels displayed by enone-aldehyde **269**, as the background reaction maybe too facile, causing a decrease in enantioselectivity. When thiophenol is added to enoate-aldehyde **308** (Table 3-5, entry 1), in the absence of any catalyst at -20 °C, no reaction took place despite the reaction warming to rt. This observation had promising potential in terms of inducing high levels of asymmetric induction. The non enantioselective variant (Scheme 3.19) of this reaction was found to proceed in the presence of a catalytic amount of triphenylphosphine, it is thought that the triphenylphosphine performs as a nucleophilic catalyst; first of all it undergoes 1,4-addition to the enoate-aldehyde, this in turn will generate the enolate **309**, the enolate will deprotonate the thiol, promoting addition of the thiol anion to the Michael acceptor.



Scheme 3.19 Role of triphenylphosphine



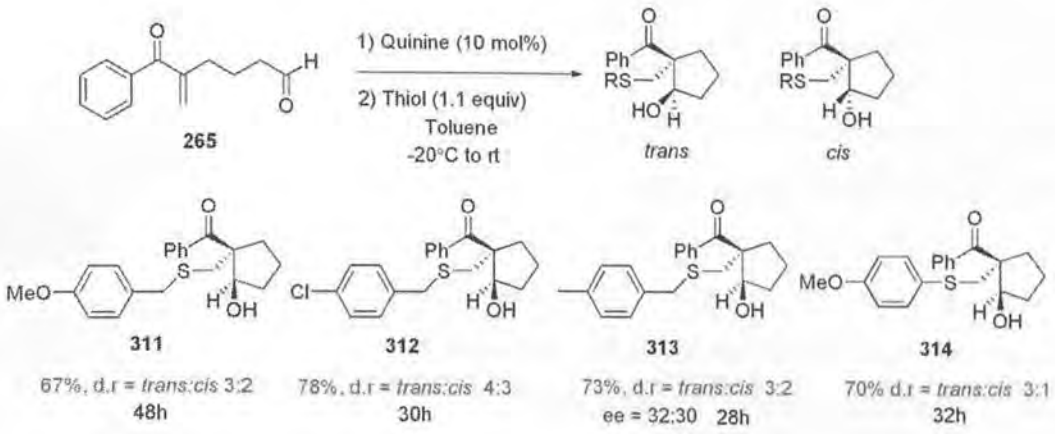
Scheme 3.20 Reaction screening of enoate-aldehyde 308

Table (3-5) Investigations of substrate scope for the thio-aldol cyclisation

Entry	Catalyst (10 mol%)	Temp (°C)	Time (h)	Yield (%)	d.r	e.e. (%)
1	–	-20	–	–	–	–
2	PPh_3	-20	12	59	2:1	–
3	Cinchonine	-20	8	73	1:2	5:19
4	Quinine	-20	6	68	3:2	25:14

When catalytic amounts of cinchonine and quinine were employed in the reaction (Table 3-5, entries 3 and 4), the reaction proceeded smoothly to afford the desired functionally diverse hetero γ–thioalcohol **310** as a mixture of diastereomers, albeit with low levels of enantioselctivity. This result suggests that the background reaction is not deleterious to the enantioselectivity in the enone-aldehyde carbocyclisation.

In an attempt to improve the enantioselectivity, we turned our attention of altering the structure of the thiol. We anticipated that the rate of the conjugate addition step may be influenced by changing the nature of the thiol. We found that when we employed 4-methoxytoluenethiol the reaction rate had decreased significantly, this effect maybe due to the presence of the CH_2 which increases the pKa of the thiol, thiophenol is more acidic SH pKa~6.5 than 4-methoxytoluenethiol SH pKa~ 9.43, therefore the rate of reaction with thiophenol is significantly faster.



Scheme 3.21 Scope of Brønsted acid catalysed thio-aldol cyclisation

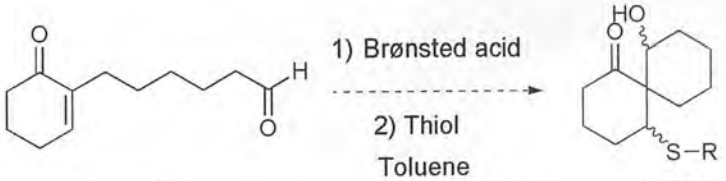
We were pleased to find that when 4-methoxytoluenethiol was utilised in the reaction, after 48 hours the reaction had gone to completion, giving rise to product **311** as an inseparable 3:2 diastereomeric mixture. We found that when benzylic thiols are employed the reaction rate was slower; this again can be attributed to the higher pKa of the SH. When 4-methoxybenzenethiol was used, the reaction was faster (32h). However, when compared to the reaction when thiophenol is used (2h) this is a considerably slower reaction.

In all cases the diastereoselectivity is moderate and in some cases the diastereomers were inseparable by column chromatography or recrystallisation. Therefore, determining the enantiomeric excess was somewhat difficult. The minor and major diastereomers of the γ–thioalcohol **313** were isolated, with modest enantioselectivity. We were optimistic by the compatibility of the thio-aldol reaction with a range of diverse thiols. These results illustrate that the moderate enantioselectivities are not caused by the facile addition of thiophenol in our earlier studies. When 4-methylbenzylmercaptan is employed the enantioselectivities are comparable with thiophenol (Table 3-2, entry 4). In the absence of a catalyst, the non-enantioselective variant was not feasible when benzylic thiols were utilised. Due to lack of material, PPh_3 was not employed to test the feasibility of the racemic variant.

3.3 Conclusions

Finally, a suitable asymmetric methodology for the construction of five-membered carbocycles has been developed. The tandem intramolecular Michael-aldol cyclisation tolerates a broad range of enone-aldehyde substrates. Furthermore, a series of carbocycles are constructed which possess *vicinal* quaternary and secondary/tertiary stereocentres in high yield with moderate enantioselectivities. The sequence is efficiently catalysed by cinchona alkaloids and occurs in impressive high yields, whilst creating two new sterically congested stereocentres.

Further efforts should focus on enhancing levels of enantiomeric excess in addition with exploring the use of different nucleophiles and substrates. Future work should concentrate on demonstrating the versatility of this methodology, allowing for an efficient asymmetric synthesis of spirocyclic compounds of type **316**, which were previously accessible by alkylations [20] using transition metals (Scheme 3.22).



315 **316**

Scheme 3.22 Futurework should focus on investigating the versatility of the thio-aldol cyclisation

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4.0 Conclusions and Future Work

The overall aim of the PhD was to develop innovative and robust asymmetric cyclopentannulation methodologies for the synthesis of highly functionalised cyclopentanoids given that five-membered rings are a ubiquitous feature in a plethora of bio-active compounds.

Our initial studies focussed on developing new reactions and novel organocatalysts, whereby both concepts could be applied resulting in the construction of biologically important motifs. Primitive studies focussed on developing enantioselective organocatalysts for application in the Nazarov electrocyclisation. Successful synthesis of the oxadiaxolidinone **230**, allowed us to test the feasibility of an iminium ion catalysed Nazarov cyclisation. After extensive studies of different reaction conditions, disappointingly considerable levels of enantiocontrol were not observed. At this stage we decided to employ oxadiazolidinone **230** in an existing enantioselective reaction, the Diels-Alder reaction was an attractive cyclisation to explore despite its distant association with the construction of five-membered rings. The enantioselective Diels-Alder reaction is well documented and would allow us to gain insight into the underlying mechanism of **230**, in addition to analysis of the asymmetric material. Unfortunately only low levels of enantiofacial discrimination were observed in the Diels-Alder reaction, this is presumably due to lack of iminium ion geometry control. In spite of these negative results, it allowed us to investigate new methods for the construction of five-membered rings.

We next turned our attention to developing an alternative asymmetric route towards the synthesis of five- membered rings bearing vicinal quaternary centres. Given the lack of reports in the literature, we decided to embark upon an efficient strategy for the synthesis of these complex molecules. This challenge was accomplished via a novel Brønsted acid catalysed promoted thio-Michael aldol cyclisation of enone-aldehyde prochiral starting materials. Our findings indicated that the steric hindrance imparted by

the isopropyl group enhanced the stereoselectivity and enantioselctivity, chiral HPLC illustrated that in the addition reaction levels of 70% e.e. were reached, despite the difficulties often associated with sterically hindered aldol cyclisations. The use of a variety of thiol nucleophiles proved to be very successful, resulting in the assembly of diverse five-membered rings with two stereogenic centres.

One of the striking features of this methodology is that this one-pot procedure results in the assembly of complex five-membered rings which can be further elaborated for the synthesis of complex bio-active compounds.

Immediate future work should focus on further optimisation to enhance both diastereoselectivity and enantiomeric excess, in addition with further elaboration of these five-membered rings to mediate the synthesis of complex natural products, further highlighting the applications of this powerful methodology.

Chapter 5

Experimental Procedures

5.1 General Procedures

^{1}H nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on either a Bruker AC250 (250 MHz) or a Bruker DPX360 (360 MHz) Fourier transform instrument. The data is presented as follows: chemical shift (in ppm on the δ scale), integration, multiplicity, coupling constant (J in Hz) and the assignment. ^{13}C NMR spectra were recorded at ambient probe temperatures on either a Bruker AC250 (63 MHz) or a Bruker DPX360 (91 MHz) instrument and are reported in ppm on the δ scale. Distortion Enhancement Polarisation Transfer (DEPT) spectra were recorded to assign the carbon signals as methyl (CH_3), methylene (CH_2), methine (CH) or quaternarycarbons (C). Infra Red spectra were recorded on a JASCO FT/IR-460 plus instrument using 4mm sodium chloride plates. The wavelengths of the maximum absorbance (ν_{max}) are quoted in cm^{-1}. Samples were sent to the EPSRC National Mass Spectrometry Service Centre, Swansea for MS analysis. Accurate mass measurements were obtained on a Finnigan MAT 900 XLT double focusing mass spectrometer. The data is recorded as the ionisation method followed by the calculated and measured masses. Optical rotations were measured on an AA-1000 polarimeter with a pathlength of 0.5 dm at the sodium D line (589 nm) and reported as follows: $[\alpha]_D$ concentration (c in g/100 mL) and solvent. Melting points were determined on a Gallenkamp Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck 60F254 silica plates and visualised by UV light and/or anisaldehyde[i] or potassium permanganate [ii] stains. Compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70A) silica under a positive pressureand the eluent compositions are quoted as a percentage. Chiral HPLC was performed using a Waters instrument with an AD-H column equipped with a UV detector. A standard flow rate of 1 mL/min of a propan-2-ol/hexanes mixture as the eluent was used. Anhydrous toluene, dichloromethane, tetrahydrofuran, diethyl ether, methanol and acetonitrile were obtained from an innovative technologies solvent

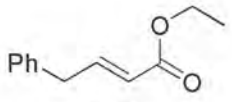
purification system unless otherwise stated. All other chemicals were used as supplied except where otherwise stated in the text. All experiments were performed under an inert atmosphere of nitrogen under anhydrous conditions using oven dried apparatus cooled in a dessicator prior to use. Standard techniques for handling air-sensitive materials were employed.

[i]Anisaldehyde stain was prepared as follows: Concentrated sulfuric acid (10 mL) was added carefully to a cooled solution of ethanol (200 mL) and p-methoxybenzaldehyde (10 mL).

[ii]Potassium Permanganate stain was prepared as follows:Potassium Permanganate(6 g) and potassium carbonate (40 g) were dissolved in 5 % sodium hydroxide (10 mL) and water (600 mL).

5.2 Experimental Procedures For Chapter 2

(E)-Ethyl-4-phenylbut-2-enoate, 222 [1]

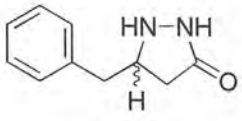


222

To a stirred solution of freshly distilled phenylacetaldehyde (2.00 g, 16.66 mmol, 1 equiv) in dry DCM (28 mL), was added carboethoxymethylene triphenylphosphorane (6.95 g, 19.9 mmol, 1.2 equiv) in one portion at room temperature. The solution was left to stir for 16 h. After stirring the solution was concentrated *in vacuo*, redissolved in (10:1) Petroleum ether: Et_2O filtered and concentrated. This procedure was repeated twice. Purification by column chromatography (SiO_2, 96 % Petroleum ether, Et_2O) afforded the (*Z*)-isomer (132 mg, 5 %) as a colorless oil, followed by the (*E*)-isomer (1.50 g, 47 %) as a colorless oil; (*Z*)-isomer **IR** (neat)/ cm^{-1}): υ_{max} 3020 (Ar), 1726 (C=O), 1660. **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.45-7.19 (m, 5H, **ArH**), 6.41 (dt, 1H, J= 7.5, and 11.4 Hz, **CH**=CH), 5.90 (dt, 1H, J= 1.6 and 11.4 Hz, CH=**CH**), 4.25 (q, 2H, J= 7.1 Hz, **OCH_2CH_3**), 4.06 (dd, 2H, J= 1.6 and 7.5 Hz, **CH_2Ar**), 1.37 (t, 3H, J= 7.1 Hz, **OCH_2CH_3**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 169.8 (C=O), 146.5 (CH=CH), 138.1 (*ipso*), 130.2 (ArH), 128.6 (CH=CH), 127.2 (ArH), 122.3 (ArH), 61.0 (OCH_2CH_3), 39.2 (CH_2Ar), 14.2 (OCH_2CH_3). (*E*)-isomer **IR** (neat)/ cm^{-1}): υ_{max} 3022 (Ar), 1724 (C=O), 1659. **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.43-7.21 (m, 5H, **ArH**), 7.16 (dt, 1H, J= 6.8, and 15.6 Hz, **CH**=CH), 5.86 (dt, 1H, J= 1.5 and 15.5 Hz, CH=**CH**), 4.23 (q, 2H, J= 7.2 Hz, **OCH_2CH_3**), 3.55 (dd, 2H, J= 1.5 and 6.8 Hz, **CH_2Ar**), 1.35 (t, 3H, J= 7.2 Hz, **OCH_2CH_3**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 166.8 (C=O), 147.8 (CH=CH), 138.2 (*ipso*), 129.3 (ArH), 129.1 (CH=CH), 127.2 (ArH), 122.8 (ArH), 60.5 (OCH_2CH_3), 38.7 (CH_2Ar), 14.7 (OCH_2CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature [1]

5-benzylpyrazolidin-3-one, 223

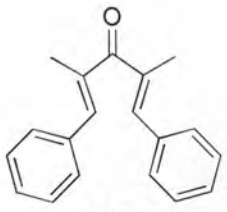


223

To a solution of ethanol (5 mL), (E)-ethyl-4-phenylbut-2-enoate **222** (200 mg, 1.05 mmol, 1 equiv) was added. The solution was cooled to 0 °C. Hydrazine monohydrate (58 mg, 1.16 mmol, 1.1 equiv) was added to ethanol (5 mL) and added dropwise to the three necked-flask. After 24 h the reaction was refluxed at 70 °C for a further 48 h. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2, 98 % DCM, methanol) afforded the title compound (85 mg, 46 %) as a colorless oil; **IR** (neat) cm^{-1}): υ_{max} 3209 (Ar), 1685 (C=O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ:7.93-7.16 (m, 5H, ArH), 3.77 (m, 1H, **CH**), 2.84 (dd, 1H, J= 6.8 and 12.1 Hz, **CH**C=O), 2.69 (dd, 1H, J= 7.2 AND 13.8 Hz, **CH**C=O), 2.39 (dd, 1H, J= 7.3 and 16.3 Hz, **CH**Ar), 2.17 (dd, 1H, J= 7.6 and 16.3 Hz, **CH**Ar). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 176.7 (C=O), 137.1 (ipso), 128.9 (ArH), 128.1 (ArH), 126.6 (ArH), 59.4 (CH), 37.8 (CH_2Ar), 37.1 (CH_2).

The synthesis of divinyl ketones, **236**, **238a** and **238b** were synthesised according to literature precedents. [2,3]

2, 4-Dimethyl-1,5-diphenylpenta-1,4-dien-3-one, 238a

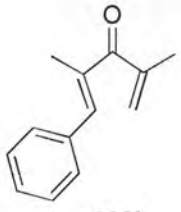


238a

White solid; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.45-7.25 (m, 10H, **ArH**), 7.25-7.15 (m, 2H, 2 x **CH**), 2.20 (s, 6H, 2 x **CH_3**).

^{1}H NMR data was in agreement with the literature [2]

2, 4-Dimethyl-1-phenylpenta-1,4-dien-3-one, 238b

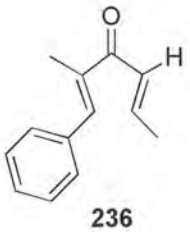


238b

Colorless oil; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.42-7.25 (m, 6H, **ArH**, 1 x **CH**), 5.68 (dq, 1H, J= 1.5, 1.5 Hz, 1 x **CH**), 5.56 (dq, 1H, J= 1.0, 1.5 Hz, 1 x **CH**), 2.10 (d, 3H, J= 1.4 Hz, **CH_3**), 2.02 (dd, 3H, J= 0.9, 1.5 Hz, **CH_3**).

^{1}H NMR data was in agreement with the literature. [3]

2, 5-Dimethyl-1-phenylpenta-1,4-dien-3-one, 236



236

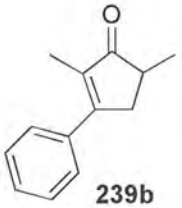
Colorless oil; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.47 (q, 1H, J= 1.3 Hz, 1 x **CH**), 7.42-7.38 (m, 4H, **ArH**), 7.33-7.29 (m, 1H, **ArH**), 6.59 (dq, 1H, J= 1.7, 11.5 Hz, 1 x **CH**), 6.25 (dq, 1H, J= 7.0, 11.6 Hz, 1 x **CH**), 2.10 (d, 3H, J= 1.5 Hz, 1 x **CH_3**), 2.02 (dd, 3H, J= 1.8, 7.2 Hz, **CH_3**).

^{1}H NMR data was in agreement with the literature. [3b]

General Procedure for Amine-Catalysed Nazarov Cyclisation

To a solution of (*R*)-4-benzyl-3-(4-methoxyphenyl)-[1,2,4]-oxadiazolidin-5-one in MeOH/H_2O (95/5, v/v, 1.0 M) was added the divinyl ketone. The solution was left to stir for 1-2 minutes before addition of the co-acid. After completion of the reaction the mixture was diluted with Et_2O and washed successively with H_2O and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 10 % Et_2O, hexanes) afforded the title compound.

2,5-dimethyl-3-phenylcyclopent-2-enone, 239b



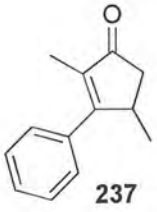
239b

Colorless oil; [iii] **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.55-7.39 (m, 5H, **ArH**), 3.15 (ddq, 1H, J= 18.1, 7.0 and 2.0 Hz, **CH_2** *trans* to CH_3), 2.55 (m, 1H, **CH**), 2.32 (m, 1H, **CH**), 1.92 (m, 3H, **CH_3**CH), 1.26 (d, 3H, J= 7.1 Hz, **CH_3**).

^{1}H NMR data was in agreement with the literature. [4]

[iii] See Appendix for HPLC data of compound **239b**.

2,4-dimethyl-3-phenylcyclopent-2-enone, 237

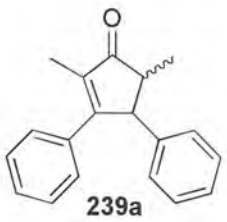


237

Colorless oil; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.41-7.22 (m, 5H, **ArH**), 3.39-3.31 (m, 1H, **CH**CH_3), 2.80 (dd, 1H, J= 6.4, 18.8 Hz, **CHCO**), 2.13 (dd, 1H, J= 2.1, 18.8 Hz, **CHCO**), 1.84 (d, 3H, J= 1.6 Hz, **CH_3**), 1.05 (d, 3H, J= 7.1 Hz, **CH_3**).

^{1}H NMR data was in agreement with the literature. [5]

2,5-dimethyl-3,4-diphenylcyclopent-2-enone, 239a



239a

trans/cis 4:1

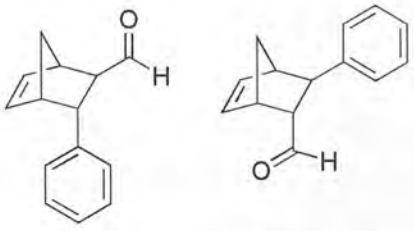
Colorless oil; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.37-7.06 (m, 10H, **ArH**), 3.98 (m, 1H, **CH**CH_3), 2.41 (m, 1H, **CH**), 2.01 (d, 3H, J= 2.0 Hz, **CH_3**), 1.35 (d, 3H, J= 7.3 Hz, **CH_3**).

^{1}H NMR data was in agreement with the literature. [5]

General Procedure for Amine-Catalysed Diels-Alder Cyclisation [6a]

To a solution of (*R*)-4-benzyl-3-(4-methoxyphenyl)-[1,2,4]-oxadiazolidin-5-one in MeOH/H_2O (95/5, v/v, 1.0 M) was added the α,β-unsaturated aldehyde, followed by addition of the co-acid. The solution was left to stir for 1-2 minutes before addition of the freshly cracked cyclopentadiene. Upon consumption of the limiting reagent, the reaction mixture was diluted with Et_2O and washed successively with H_2O and brine (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated by rotary evaporation. Hydrolysis of the diemthylacetal was achieved by stirring the crude product mixture in TFA:H_2O:$CHCl_3$ (1:1:2) for 2h at room temperature, followed by neutralisation with saturated aq. $NaHCO_3$ and extraction with Et_2O. Purification by column chromatography (SiO_2, 10 % Et_2O, hexanes) afforded the title compound as a colorless oil.

(1*R*,2*R*,3*R*,4*S*)-3-phenylbicyclo [2.2.1] hept-5-ene-2-carbaldehyde and (1*S*,2*S*,3*S*, 4*R*)-3-phenylbicyclo [2.2.1] hept-5-ene-2-carbaldehyde (Table 2.6 entry 1) 241



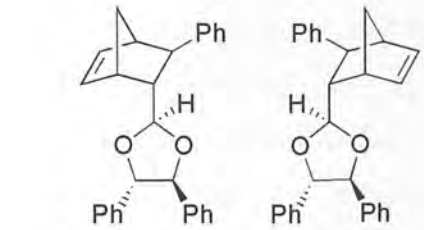
241-*exo* **241**-*endo*

Prepared according to the general procedure with (*E*)-cinnamaldehyde (144 μL, 1.14 mmol, 1 equiv), cyclopentadiene (278 μL, 3.41 mmol, 3 equiv) and (*R*)-4-benzyl-3-(4-methoxyphenyl)-[1,2,4]-oxadiazolidin-5-one (0.033 g, 0.114 mmol, 0.1 equiv) affording the title compound as a colourless oil. (140 mg, 62%). *exo:endo* (1:1.5). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.89 (d, 1H, J= 2.0 Hz, **CHO**, *endo*), 9.57 (d, 1H, J= 2.2 Hz, **CHO**, *exo*), 7.31-7.09 (m, 10H, **ArH**), 6.39 (dd, 1H, J= 3.2, 5.6 Hz, **CH**=CH), 6.31 (dd, 1H, J= 3.7, 5.7 Hz, **CH**=CH), 6.15 (dd, 1H, J= 2.7, 5.7 Hz, **CH**=CH), 6.05 (dd, 1H, J= 3.3, 5.7 Hz, **CH**=CH), 3.70 (m, 1H, **CH**), 3.31 (br, 1H, **CH**), 3.22-3.17 (m, 2H, **CH**), 3.12-3.04 (m, 2H, **CH**), 2.95 (ddd, 1H, J= 2.2, 3.5, 4.9 Hz, **CH**), 2.57 (dt, 1H, J= 1.8, 3.5 Hz, **CH**), 1.80 (m, 1H, **CH**), 1.76 (m, 1H, **CH**), 1.63-1.53 (m, 2H, 2 x **CH**).

^{1}H NMR and data was in agreement with the literature. [6a, 6b]

General Procedure for Optical Resolution of Norbornene Aldehyde Derivatives [7]

A catalytic amount of p-TsOH (0.1 equiv) was added to a solution of 3-phenylbicyclo [2.2.1] hept-5-ene-2-carbaldehyde, (+)-(*R,R)*-hydrobenzoin (1 equiv) was added in toluene under an atmosphere of N_2 and the resulting mixture was stirred for 12 h at rt. After completion of the reaction, the solution was quenched with $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 10 % EtOAc, hexanes) afforded the acetal product as a diastereomeric mixture of **244a** and **244c**.

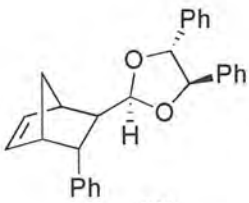


endo

244a

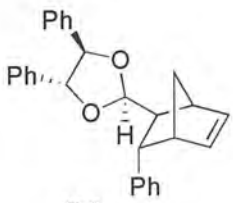
endo

244b



exo

244c



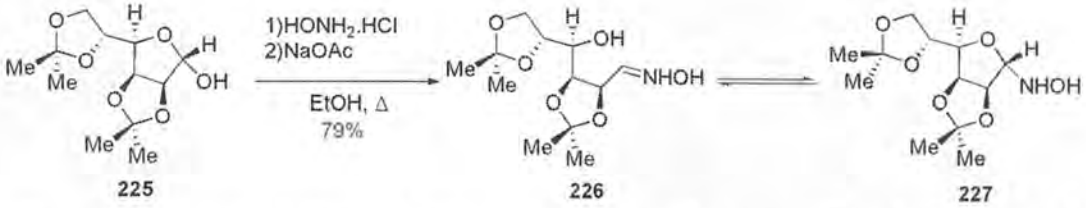
exo

244d

Prepared according to the general procedure with p-TsOH (0.0033 g, 0.0192 mmol, 0.1 equiv) 3-phenylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (0.036 g, 0.192 mmol, 1 equiv) and (+)-(*R,R*)-hydrobenzoin (0.036 g, 0.192 mmol, 1 equiv) afforded the title compound (65 mg, 86 %) as a colorless oil. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 5.67 (d, 1H, J= 4.7 Hz,

CHO_2, *exo*), 5.66 (d, 1H, J= 5.9 Hz, **CHO_2**, *exo*), 5.15 (d, 1H, J= 8.1 Hz, **CHO_2**, *endo*), 5.12 (d, 1H, J= 8.1 Hz, **CHO_2**, *endo*). [7]

2,3:5,6-Di-O-isopropylidene-D-mannose Oxime 227

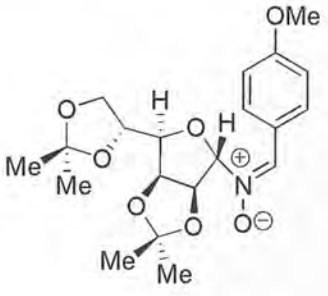


A three-necked round bottomed flask was charged with acetone (50 mL, HPLC grade) and D-mannose (5.00 g, 27.75 mmol, 1 equiv) P_2O_5 (32.69 g, 115.16 mmol, 4.15 equiv) is added in portions and the mixture is stirred overnight for 25 hours. $Ca(OH)_2$ (3.70 g, 49.95 mmol, 1.8 equiv) and activated carbon (1.42 g) are added and the mixture is stirred for ca.20 min before it is filtered through celite, rinsing thoroughly with acetone. This afforded a light yellow filtrate, which was evaporated to dryness *in vacuo* leaving **225** (6.46 g, 89 %) as a light yellow solid. The crude lactol (6.46 g, 27.75 mmol) is dissolved in absolute ethanol (100 mL), $NH_2OH.HCl$ (2.41 g, 34.69 mmol, 1.25 equiv) and $NaOAc.3H_2O$ (4.72 g, 34.69 mmol, 1.25 equiv) are added and the mixture is warmed to 65-70 °C for 1 h. After cooling to room temperature, the bulk of the ethanol is removed *in vacuo* and the residue is partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic layer is washed with saturated $NaHCO_3$ solution. The combined aqueous portions are extracted with EtOAc (2 x 250 mL) and the combined organic extracts are a washed with brine (2 x 150 mL), and dried over magnesium sulphate to afford the title (6.03 g, 79 %) compound as a yellow solid; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.69 (br, 1H, **NH**), 7.11 (d, 1H, J= 3.5 Hz, **CH**C=N), 5.25 (dd, 1H, J= 3.5, 7.6 Hz, **CH**), 4.56 (d, 1H, J= 7.5 Hz, **CH**), 4.52 (d, 1H, J= 6.8 Hz, **CH**), 4.16 (m, 1H, **CH**), 4.11-4.0 (m, 2H, 2 x **CH**), 3.68 (d, 1H, J= 6.7 Hz, **CH**), 1.52 (s, 3H, **CH_3**), 1.42 (s, 3H, **CH_3**), 1.40 (s, 3H, **CH_3**), 1.34 (s, 3H, **CH_3**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ:

152.8 (CNH), 110.2 ($C(CH_3)_2$), 86.0 (CH), 78.5 (CH), 78.0 (CH) 73.5 (CH), 68.3 (CH_2), 65.7 (CH), 26.7 (CH_3), 26.6 (CH_3), 25.3 (CH_3) and 25.2 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [8]

[(3a*S*,4*S*,6*R*,6a*S*)-6-(*R*)-2,2-Dimethyl-1[1,3]dioxol-4-yl]-[1-4(-methoxy-phenyl)-meth-(*E*)-ylidene]-amine N-oxide 228



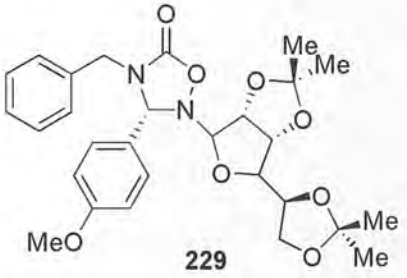
228

To 4-methoxybenzaldehyde (1.19 g, 1.06 mL, 8.72 mmol, 1.2 equiv) and 2,3:5,6-O-isopropylidene-D-Mannose oxime **227** (2 g, 7.264 mmol, 1 equiv) is added toluene (10 mL). Upon heating to reflux, all solids dissolve and the resulting solution is kept at reflux for 16 h. Water is continuously removed from the reaction mixture using a Dean-Stark trap. The stirred solution is cooled and the crystals formed are filtered off, washed with hexane, and dried *in vacuo* to afford the target compound (2.45 g, 85 %) as a colorless crystals; lit. [9] **m.p.** 154 °C (toluene); **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 8.22 (d, 2H, J= 7.0 Hz, **ArH**), 7.48 (s, 1H, **ArH**), 6.95 (m, 2H, **ArH**), 5.44 (s, 1H, **CH**NO), 5.35 (d, 1H, J= 6.0 Hz, **CH**), 5.00 (dd, 1H, J= 4.0, 6.0 Hz, **CH**), 4.69 (dd, 1H, J= 3.9, 7.3 Hz **CH**), 4.40 (m, 1H, **CH**), 4.10 (d, 2H, J= 9.5 Hz, **CH_2**), 3.86 (s, 3H, O**CH_3**), 1.53 (s, 3H, **CH_3**), 1.46 (s, 3H, **CH_3**), 1.38 (s, 3H, **CH_3**), 1.37 (s, 3H, **CH_3**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 162.3 (OMe *ipso*), 133.8 (ArH), 131.8 (ArH), 123.1 (*ipso*), 114.7 (CH=NO),

113.9 (C $(CH_3)_2$), 110.0 (C $(CH_3)_2$), 103.8 (CH), 86.3 (CH), 85.2 (CH), 81.1 (CH), 73.9 (CH), 67.2 (CH_2), 56.1 (OCH_3), 27.5 (CH_3), 26.7 (CH_3), 25.9 (CH_3) and 25.1 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [9]

(*R*)-4-Benzyl-2-[(3a*S*,4*S*,6*R*,6a*S*)-6-(*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl]-3-(4-methoxy-phenyl)-[1,2,4]oxadiazolidin-5-one 229



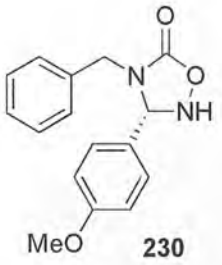
229

To nitrone **228** (2.45 g, 6.21 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at 23 °C is added benzyl isocyanate (0.827 g, 6.21 mmol, 1 equiv). The solution is heated to reflux and kept at this temperature for 40 h. After cooling, the suspension is concentrated in vacuo to afford an off-white solid. The solid is recrystallised from isopropanol and the crystals are dried *in vacuo* to afford the target compound (2.94 g, 90 %) as colourless crystals; lit. [9] **m.p.** 190 °C (methanol); **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.38-7.32 (m, 3H, **ArH**), 7.19-7.12 (m, 4H, **ArH**), 6.96-6.91 (m, 2H, **ArH**), 5.20 (s, 1H, **CH**NO), 4.93 (d, 1H, J= 6.0 Hz, **CH**), 4.84-4.71 (m, 2H, 2 x **CH**), 4.59 (s, 1H, **CH**), 4.23 (m,1H, **CH**), 3.90 (dd, 1H, J= 6.4, 8.7 Hz, **CH**), 3.83 (s, 3H, O**CH_3**), 3.71-3.64 (m, 2H, 2 x **CH**), 3.49 (dd, 1H , J= 4.8, 8.7 Hz, **CH**), 1.44 (s, 3H, **CH_3**), 1.30 (s, 3H, **CH_3**), 1.29 (s, 3H, **CH_3**), 1.25 (s, 3H, **CH_3**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 161.0 (OMe *ipso*), 156.6 (C=O), 135.4 (*ipso*), 129.8 (*ipso*), 129.6 (ArH), 129.1 (ArH), 127.9 (ArH), 114.9 (ArH), 113.6 ((C $(CH_3)_2$), 110.0 ((C $(CH_3)_2$), 99.0 (CH), 84.4 (CH), 83.4 (CH), 83.4 (CH), 80.6 (CH), 79.2 (CHN),

73.5 (CH), 67.4 (CH_2), 56.3 (OCH_3), 46.7 (CH_2), 27.6 (CH_3), 26.8 (CH_3), 26.1 (CH_3) and 25.3 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [9]

(*R*)-4-benzyl-3-(4-methoxyphenyl)-[1,2,4]-oxadiazolidin-5-one 230

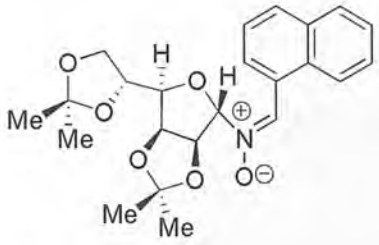


230

To oxadiazolidinone **229** (10.02 g, 19.0 mmol, 1 equiv) in methanol/water (6:1) (250 mL) at 23 °C is added 4-toluenesulfonic acid hydrate (36.14 g, 190.0 mmol, 10 equiv). The solution is heated at reflux and kept at this temperature for 2 h. After cooling, K_3PO_4 (24.20 g, 114.0 mmol, 6 equiv) is added and the suspension is concentrated in vacuo to a quarter of the original volume. To this suspension is added EtOAc and water. The phases are separated and the aqueous phase is extracted with EtOAc. The combined organic phases are washed with brine (3 x 100 mL), dried $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40 % EtOAc, hexanes) afforded the title compound (3.85 g, 71 %). as a colorless oil; $[\alpha]_D^{25}$= +158° (c 0.30, $CHCl_3$); lit.[9] $[\alpha]_D^{35}$= +170° (c 0.95, $CHCl_3$); **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.32-7.25 (m, 5H, **ArH**), 7.12-7.07 (m, 2H, **ArH**), 6.99-6.94 (m, 2H, **ArH**), 5.35 (s, 1H, **CH**NH), 4.77 (d, 1H, J= 14.8 Hz, **CH_2**Ar), 3.85 (s, 3H, O**CH_3**), 3.78 (d, 1H, J= 14.8 Hz **CH_2**Ar). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 162.1 (OMe *ipso*), 160.2 (C=O), 135.1 (*ipso*), 129.9 (*ipso*), 129.5 (ArH), 129.4 (ArH), 128.9 (ArH), 128.8 (ArH), 115.5 (ArH), 77.1 (CHN), 56.0 (OCH_3) and 46.9 (CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [9]

[(3a*S*,4*S*,6*R*,6a*S*)-6-((*R*)2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-[1-naphthalen-1-yl–meth-(*E*)-ylidene]-amineN-oxide 249

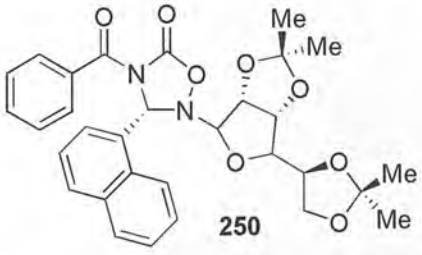


249

To *α*-naphthylcarboxaldehyde (6.78 g, 43.4 mmol, 1 equiv) and 2,3:5,6-*O*-isopropylidene-D-mannose **227** (11.95 g, 43.4 mmol, 1 equiv) is added toluene (90 mL). Upon heating to reflux, all solids dissolve and the resulting solution is kept at reflux for 30 h. Water is continuously removed from the reaction using a Dean Stark trap. The stirred solution is cooled and the crystals formed are filtered off, washed with hexane, and dried *in vacuo* to afford the target compound (13.6 g, 76 %) as colourless crystals; lit. [9] **m.p.** 153 °C (toluene); **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.52 (d, 1H, J= 8.6 Hz, **ArH**), 8.44 (s, 1H, **CH**NO), 8.03 (d, 1H, J= 8.2 Hz, **ArH**), 7.97-7.89 (m, 2H **ArH**), 7.63-7.52 (m, 3H, **ArH**), 5.63 (s, 1H, **CH**), 5.44 (d, 1H, J= 6.0 Hz, **CH**), 5.03 (dd, 1H, J= 3.9, 5.9 Hz, **CH**),4.75 (dd, 1H, J= 3.9, 7.0 Hz **CH**), 4.49 (m, 1H, **CH**), 4.21-4.17 (m, 2H, **CH_2**),1.57 (s, 3H, **CH_3**), 1.49 (s, 3H, **CH_3**), 1.41 (s, 3H, **CH_3**), 1.40 (s, 3H, **CH_3**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 134.1 (CHNO), 132.4 (ArH), 131.4 (*ipso*), 130.0 (*ipso*), 129.4 (ArH), 128.1 (ArH), 127.9 (*ipso*), 126.7 (ArH), 126.2 (ArH), 125.1 (ArH), 122.1 (ArH), 114.0 ($C(CH_3)_2$), 110.1 ($C(CH_3)_2$), 104.6 (CH), 86.2 (CH), 85.3 (CH), 80.9 (CH), 73.9 (CH), 67.2 (CH_2), 27.5 (CH_3), 26.7 (CH_3), 25.8 (CH_3) and 25.1 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [9]

(3*R*)-4-benzoyl-2-(6-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3, 4-d][1,3]dioxol-4-yl)-3-(naphthalene-1-yl)-1,2,4-oxadiazolidin-5-one 250

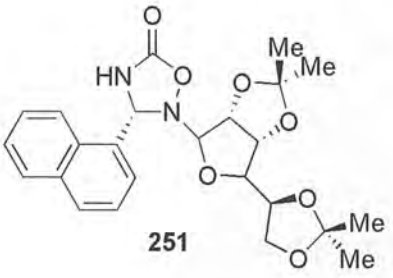


250

To Nitrone **249** (7.11 g, 17.2 mmol, 1 equiv) in CH_2Cl_2 (18 mL) at 23 °C is added Benzoyl isocyanate (2.53 g, 17.2 mmol, 1 equiv). The solution is left to stir for 18 h, and then the suspension is concentrated *in vacuo* to afford an off-white solid. The solid is recrystallised from isopropanol and the crystals are dried *in vacuo* to afford the target compound (8.08 g, 84 %) as colourless crystals; lit. [8] **m.p.** 168 °C (methanol); **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 8.25 (d, 1H, J= 8.5 Hz, **ArH**), 7.92-7.89 (m, 2H, **ArH**), 7.76-7.71 (m, 3H, **ArH**), 7.63-7.47 (m, 6H, **ArH**), 7.29 (s, 1H, **CHN**), 5.87 (s, 1H, **CH**),5.03 (bs, 1H, **CH**), 4.96 (d, 1H, J= 6.0 Hz, **CH**), 4.76 (dd, 1H, J= 3.8, 5.8 Hz, **CH**), 4.49-4.37 (m, 2H, **CH_2**), 4.09 (d, 1H, J= 5.8 Hz, **CH**), 1.51 (s, 3H, **CH_3**), 1.47 (s, 3H, **CH_3**), 1.41 (s, 3H, **CH_3**), 1.32 (s, 3H, **CH_3**).

^{1}H NMR data was in agreement with the literature. [9]

(*R*)-2-((3a*R*,6a*R*)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-(naphthalene-1-yl)-1,2,4-oxadiazolidin-5-one 251

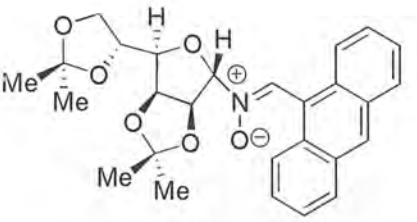


251

To oxadiazolidinone **250** (5.5 g, 9.81 mmol, 1 equiv) in methanol (50 mL) at 23 °C is added K_2CO_3 (0.136 g, 0.981 mmol, 0.1 equiv). The solution is stirred for 1 h, and then diluted with aqueous NH_4Cl, H_2O and EtOAc. The phases are separated and the aqueous phase is extracted with EtOAc. The combined organic phases are washed with brine, dried $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 60 % EtOAc, hexanes) afforded the title compound (3.54 g, 79 %) as a colorless solid; lit. [9] **m.p.** 197 °C (toluene); **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 8.16 (d, 1H, J= 8.5 Hz, **ArH**), 7.9 (d, 2H, J= 8.1 Hz, **ArH**), 7.73-7.45 (m, 4H, **ArH**), 6.59 (s, 1H, **CH**N), 5.92 (s, 1H, **CH**), 5.06 (s, 1H, **CH**), 4.97 (d, 1H, J= 6.1 Hz, **CH**), 4.76 (dd, 1H, J= 3.8, 6.1 Hz, **CH**), 4.45 (m, 1H, **CH**), 4.33 (dd, 1H, J= 3.9, 5.1 Hz, **CH**), 4.08 (d, 1H, J= 6.0 Hz, **CH**), 1.51 (s, 3H ,**CH_3**), 1.45 (s, 3H, **CH_3**), 1.41 (s, 3H, **CH_3**), 1.32 (s, 3H, **CH_3**).

^{1}H NMR data was in agreement with the literature. [9]

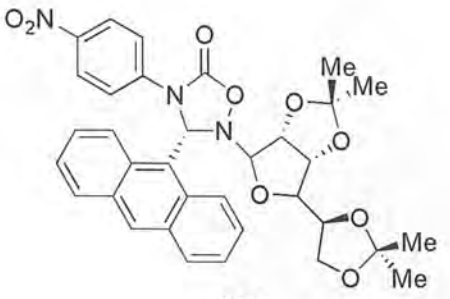
Nitrone 253



253

To anthracenealdehyde (6.11 g, 29.6 mmol, 1 equiv) and 2,3:5,6-*O*-isopropylidene-D-mannose (8.15 g, 29.6 mmol, 1 equiv) is added toluene (60 mL). Upon heating to reflux, all solids dissolve and the resulting solution is kept at reflux for 22 h. Water is continuously removed from the reaction using a Dean Stark trap. The stirred solution is cooled and the crystals formed are filtered off, washed with hexane, and dried *in vacuo* to afford the target compound (10.74 g, 76 %) as yellowish crystals; $[\alpha]_D^{25}$= -49° (c 0.38, $CHCl_3$); **m.p.** 223-225 °C (EtOAc in hexanes); **IR** (neat)cm^{-1}): υ_{max} 2941(C-H), 1118(C-O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 8.56 (d, 2H, J= 7.7 Hz, **ArH**), 8.02 (d, 2H, J= 8.1 Hz, **ArH**), 7.82 (d, 2H, J= 8.9 Hz, **ArH**), 7.56-7.48 (m, 4H **ArH**), 5.85 (s, 1H, **CH**NO), 5.28 (d, 1H, J= 6.0 Hz, **CH**), 5.07 (dd, 1H, J= 3.8, 6.0 Hz, **CH**), 4.81 (dd, 1H, J= 3.9, 7.4 Hz, **CH**), 4.50-4.45 (m, 2H, **CH_2**), 4.18 (d, 1H, J= 5.3 Hz ,**CH**), 1.59 (s, 3H, **CH_3**), 1.47 (s, 3H, **CH_3**), 1.43 (s, 3H, **CH_3**), 1.40 (s, 3H, **CH_3**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 131.8 (*ipso*), 130.3 (*ipso*), 129.8 (CHNO), 127.6 (ArH), 126.1 (ArH), 125.5 (ArH), 114.1 ($C(CH_3)_2$), 110.2 ($C(CH_3)_2$), 104.2 (CH), 86.7 (CH), 85.3 (CH), 81.2 (CH), 73.9 (CH), 67.4 (CH_2), 27.5 (CH_3), 26.8 (CH_3), 25.9 (CH_3) and 25.3 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{27}H_{30}NO_6$ $[M+H]^+$ 464.2068, found 464.2070.

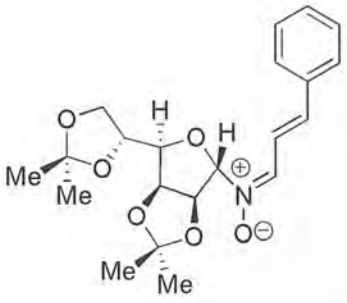
(*R*)-3-(anthracen-10-yl)-2-((3a*R*,6a*R*)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-tetrahydofuro[3,4-*d*][1,3]dioxol-4-yl)-4-(4-nitrophenyl)-[1,2,4]-oxadiazolidin-5-one 254



254

To Nitrone **253** (1.7 g, 3.55 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at 23 °C is added 4-nitrophenylisocyanate (0.58 g, 3.55 mmol, 1 equiv). The solution is left at rt to stir for 48 h. The suspension is concentrated *in vacuo* to afford a yellow solid. Purification by column chromatography (SiO_2, 30% Et_2O, hexanes) afforded the title compound (1.77 g, 79 %) as yellow crystals; $[\alpha]_D^{25}$= -88° (c 0.25, CH_2Cl_2); **m.p.** 167-169°C (EtOAc in hexanes); **IR** (neat) cm^{-1}): υ_{max} 2986 (ArCH), 1770 (C=O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 8.60-8.55 (m, 4H, **ArH**), 8.05-8.03 (m, 2H, **ArH**), 7.84-7.78 (m, 2H, **ArH**), 7.58-7.41 (m, 2H, **ArH**), 7.27-7.23 (m, 3H, **ArH**), 5.19 (s, 1H, **CH**N), 5.09 (d, 1H, J= 6.0 Hz, **CH**), 4.64 (dd, 1H, J= 3.7, 6.0 Hz, **CH**), 3.90-3.86 (m, 1H, **CH**), 3.49 (s, 1H, **CH**), 3.07 (dd, 1H, J= 6.1, 8.8 Hz, **CH**), 2.89 (dd, 1H, J= 3.5, 8.7 Hz, **CH**), 1.58 (dd, 1H, J= 5.0, 8.9 Hz, **CH**), 1.46 (s, 3H, **CH_3**), 1.33 (s, 3H, **CH_3**), 1.08 (s, 3H, **CH_3**), 0.72 (s, 3H, **CH_3**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 153.3 (C=O), 145.1 (*ipso*), 141.2 (*ipso*), 133.1 (ArH), 130.9 (*ipso*), 125.9 (ArH), 124.9 (ArH), 122.1 (ArH), 121.6 (*ipso*), 113.7 ((C $(CH_3)_2$), 109.6 ((C $(CH_3)_2$), 101.2 (CHN), 84.2 (CH), 83.8 (CH), 80.4 (CH), 79.0 (CH), 72.5 (CH), 66.5 (CH_2), 26.8 (CH_3), 26.6 (CH_3), 25.9 (CH_3) and 25.1 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{34}H_{33}N_3O_9$ $[M+Na]^+$ 650.2109, found 650.2119.

[(3a*S*,4*S*,6*R*,6a*S*)-6-((*R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-[(*E*)-3-phenyl-prop-2-en-(*E*)-ylidene]-amine-N-oxide, 231

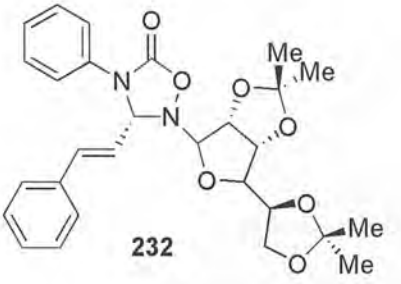


231

To (*E*)-cinnamaldehyde (0.59 g, 562 µL, 4.45 mmol, 1.24 equiv) and 2,3:5,6-*O*-isopropylidene-D-mannose (0.99 g, 3.59 mmol, 1 equiv) is added toluene (10 mL). Upon heating to reflux, all solids dissolve and the resulting solution is kept at reflux for 14 h. Water is continuously removed from the reaction using a Dean Stark trap. The stirred solution is cooled and the crystals formed are filtered off, washed with hexane, and dried *in vacuo* to afford the target compound (1.14 g, 82 %) as an off white solid; lit. [9] **m.p.** 176 °C (toluene); **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.54-7.30 (m, 7H, ArH, 2 x **CH**=CH), 7.04 (d, 1H, J= 14.7 Hz, **CH**=CH), 5.37 (s, 1H, **CH**), 5.24 (d, 1H, J= 6.0 Hz, **CH**), 4.97 (dd, 1H, J= 3.9, 5.9 Hz, **CH**), 4.57 (dd, 1H, J= 3.9, 7.2 Hz, **CH**), 4.42 (m, 1H, **CH**), 4.13-4.09 (m, 2H, **CH_2**), 1.52 (s, 3H, **CH_3**), 1.47 (s, 3H, **CH_3**), 1.32 (s, 3H, **CH_3**), 1.30 (s, 3H, **CH_3**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 141.0 (CHNH), 136.5 (CH), 136.2 (*ipso*), 130.3 (ArH), 129.6 (ArH), 128.2 (ArH), 117.8 (CH), 113.9 (C $(CH_3)_2$), 110.1 (C $(CH_3)_2$), 102.7 (CH), 86.0 (CH), 85.1 (CH), 80.9 (CH), 73.9 (CH), 67.2 (CH_2), 27.5 (CH_3), 26.7 (CH_3), 25.9 (CH_3) and 25.1 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [9]

(*R*)-2-[(3a*S*,4*S*,6*R*,6a*S*)-6-((*R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-4-phenyl)-3-((*E*)-styryl)-[1,2,4] oxadiazolidin-5-one, 232

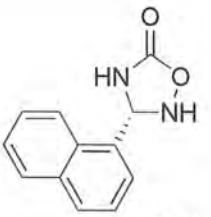


232

To nitrone **231** (0.50 g, 1.29 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at 23 °C is added phenyl isocyanate (0.154 g, 1.29 mmol, 1 equiv). The solution is left stirring at rt for 16 h. The suspension is concentrated *in vacuo* to afford an off-white solid. The solid is recrystallised from isopropanol and the crystals are dried *in vacuo* to afford the target compound (520 mg, 79 %) as colourless crystals; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.41-7.09 (m, 10H, **ArH**), 6.64 (d, 1H, J= 15.8 Hz, **CH**=CH), 6.16 (dd, 1H, J= 6.8, 15.9 Hz, 1H, **CH**=CH), 5.75 (d, 1H, J= 6.7 Hz, **CH**N), 4.91 (d, 1H, J= 6.0 Hz, **CH**), 4.79 (dd, 1H, J= 3.6, 6.0 Hz, **CH**), 4.68 (s, 1H, **CH**), 4.32 (m, 1H, **CH**), 4.12-3.91 (m, 3H, 1 x **CH**, 1 x **CH_2**), 1.38 (s, 3H, **CH_3**), 1.34 (s, 3H, **CH_3**), 1.28 (s, 3H, **CH_3**), 1.25 (s, 3H, **CH_3**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 154.6 (C=OO), 136.4 (CHN), 135.5 (*ipso*), 130.0 (ArH), 129.7 (ArH), 129.6 (ArH), 129.4 (ArH), 127.7 (ArH), 126.2 (ArH), 124.1 (*ipso*), 121.0 (CH), 113.7 (C $(CH_3)_2$), 109.9 (C $(CH_3)_2$), 97.4 (CH), 84.3 (CH), 83.9 (CH), 80.6 (CH), 78.2 (CH), 73.7 (CH), 67.3 (CH_2), 27.5 (CH_3), 26.5 (CH_3), 25.8 (CH_3) and 25.0 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [9]

(*R*)-3-Naphthalene-1-yl-[1,2,4]-oxadiazolidin-5-one 252



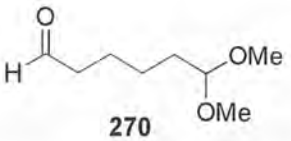
252

To oxadiazolidinone **251** (3 g, 6.57 mmol, 1 equiv) in methanol/water (6:1) (170 mL) at 23 °C is added 4-toluenesulfonic acid hydrate (12.49 g, 65.7 mmol, 10 equiv). The solution is heated at reflux and kept at this temperature for 2 h. After cooling, K_3PO_4 (8.37 g, 39.4 mmol, 6 equiv) is added and the suspension is concentrated *in vacuo* to a quarter of the original volume. To this suspension is added EtOAc and water. The phases are separated and the aqueous phase is extracted with EtOAc. The combined organic phases are washed with brine (3 x 100 mL), dried $MgSO_4$ and concentrated *in vacuo* to afford the target compound (490 mg, 35 %) as colourless crystals. lit. [8] **m.p.** 136 °C (toluene); $[\alpha]_D^{25}$= +11° (c 0.2, CH_2Cl_2); lit.[8] $[\alpha]_D^{35.6}$= +180° (c 0.40, CH_2Cl_2); **^{1}H NMR** (250 MHz, CD_3OD) δ: 9.17 (s, 1H, **CH**N), 8.60 (m, 1H, **ArH**), 8.10-7.91 (m, 3H, **ArH**), 7.67-7.52 (m, 3H, **ArH**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 156.0 (C=O), 136.1 (CHN), 134.1 (*ipso*), 130.8 (ArH), 130.7 (*ipso*), 129.6 (ArH), 128.4 (ArH), 127.2 (*ipso*), 126.1 (ArH) and 125.0 (ArH).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [9]

5.3 Experimental Procedures For Chapter 3

6,6-dimethoxyhexenal 270

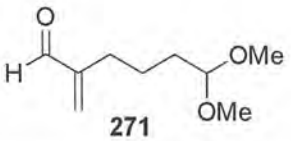


270

A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a glass stopper and a magnetic stirring bar and is charged with cyclohexene (10.02 g, 122 mmol, 1 equiv), 250 mL dichloromethane, and 50 mL of methanol. The flask is cooled to -78 °C and ozone is bubbled through the solution when stirring. Reaction completion is judged by tlc, nitrogen is then passed through the solution and then the cold bath is removed. The ozone inlet is replaced with a glass stopper; p-TsOH is added (2.025 g, 12.2 mmol, 0.1 equiv). The solution is allowed to warm to room temperature as it stirs under an atmosphere of nitrogen for 90 min. Anhydrous sodium bicarbonate (3.56 g, 30.5 mmol, 0.4 equiv) is added to the flask and the mixture is stirred for 15 min, and then 18 mL of dimethylsulfide is added. After being stirred for 12 h, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Dichloromethane is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of dichloromethane, and the combined organic layers are washed with water. After extracting the aqueous layer with dichloromethane, the organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 30% Et_2O, hexanes) afforded the title compound (14.1 g, 72 %) as a colorless oil. **^{1}H NMR** (250 MHz ,$CDCl_3$) δ: 10.0 (t, 1H, J= 1.7 Hz, **CHO**), 4.57 (t, 1H, J= 5.6 Hz , **CH**$(OCH_3)_2$), 3.54 (s, 6H, **$(OCH_3)_2$**), 2.73 (t, 2H, J= 7.3 Hz, **CH_2**CHO), 1.72-1.46 (m, 6H, 3 x **CH_2**). **^{13}C NMR** (63 MHz ,$CDCl_3$) δ: 202.8 (CHO), 104.6 (CH(OCH_3), 53.2 (CH_3), 44.2 (CH_2), 32.6 (CH_2), 24.5 (CH_2) and 22.5 (CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [10]

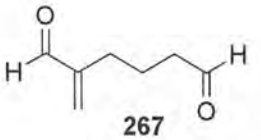
6,6-dimethoxy-2-methylenehexanal 271



271

To a solution of 6,6-dimethoxyhexenal (1.02 g, 6.37 mmol, 1 equiv) in dichloromethane (99.5 mL) and triethylamine (3.09 g, 4.26 mL, 30.56 mmol, 4.8 equiv) was added Eschenmoser's salt (5.65 g, 30.56 mmol, 4.8 equiv). After stirring for 18 h the reaction was quenched with saturated $NaHCO_3$ and extracted three times with dichloromethane. The combined organic layers were washed with brine (3 x 50 mL), dried $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30% Et_2O, hexanes) afforded the title compound (954 mg, 87 %) as a colorless oil; **^{1}H NMR** (250 MHz,$CDCl_3$) δ: 9.64 (s, 1H, **CHO**), 6.37 (d, 1H, J= 0.7 Hz, **CH_2=**), 6.11 (d, 1H, J= 0.7 Hz, **CH_2=**), 4.47 (t, 1H, J= 5.9 Hz , **CH**$(OCH_3)_2$), 3.41 (6H, s, **$(OCH_3)_2$**), 2.37 (t, 2H, J= 7.3 Hz, **CH_2**$CHOCH_3$), 1.85-1.64 (m, 2H, 1 x **CH_2**), 0.93 (m, 2H, 1 x **CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 195.0 (CHO), 150.3 (quat), 134.6 (CH_2=), 104.7 ($CH(OCH_3)$, 53.2 (CH_3), 32.5 (CH_2), 27.9 (CH_2) and 23.1 (CH_2).

2-methylenehexanal 267

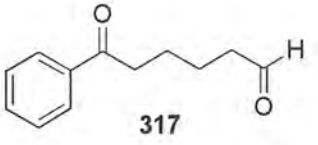


267

6,6-Dimethoxy-2-methylenehexanal (100 mg, 0.58 mmol, 1 equiv) was dissolved in acetic acid (0.7 mL) and the solution was cooled to 0-5 °C in an ice bath. As soon as the solution started to freeze, HCl solution (1 M, 0.2 mL) was added at once and the solution was left to stir for 2 h in the same bath. The mixture was diluted with DCM (30 mL) and the solution washed successively with water (4 mL), saturated $NaHCO_3$ solution (until the aqueous layer was basic), water (4 mL) and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30 % Et_2O, hexanes) afforded the title compound (59 mg, yield not determined) as a colorless oil. **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.82 (t, 1H, J= 1.5 Hz, **CHO**CH_2), 9.6 7(s, 1H, **CHO**), 6.35 (d, 1H, J= 0.5 Hz, **CH_2**=), 6.12 (d, 1H, J= 0.5 Hz, CH_2=), 2.53 (t, 2H, J= 7.3 Hz, **CH_2**CHO), 2.37 (t, 2H, J= 6.8 Hz, **CH_2CH_2**=), 1.92-1.79 (m, 2H, 1 x **CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 202.2 (CHO), 194.7 (CHO), 149.9 (quat), 134.9 (CH_2=), 35.0 (CH_2), 31.9 (CH_2) and 25.6 (CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [11]

6-oxo-6-phenylhexanal 317



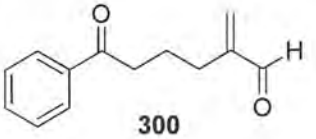
317

A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a glass stopper and a magnetic stirring bar and is charged with phenyl-1-cyclohexene

(6.06 g, 38.3 mmol, 1 equiv), dichloromethane (250 mL) and methanol (50 mL). The flask is cooled to -78 °C and ozone is bubbled through the solution when stirring. Reaction completion is judged by tlc, nitrogen is then passed through the solution and then the cold bath is removed. The solution is allowed to warm to room temperature as it stirs under an atmosphere of nitrogen then triphenylphosphine (11.95 g, 45.58 mmol, 1.19 equiv) was added. After being stirred for 12 h, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Purification by column chromatography (SiO_2, 20 % Et_2O, hexanes) afforded the title compound (6.69 g, 92 %) as a white solid; **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.8 (t, 1H, J= 1.6Hz, **CHO**), 7.97-7.94 (m, 2H, **ArH**), 7.57-7.43 (m, 3H, **ArH**), 3.01 (t, 2H, J= 6.8 Hz, **CH_2C=O**), 2.51 (dt, 2H, J= 1.6, 7.0 Hz, **CH_2CHO**), 1.83-1.69 (m, 4H, 2 x **CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 202.2 (C=O), 199.7 (CHO), 136.9 (*ipso*), 133.0 (ArH), 128.6 (ArH), 128.0 (ArH), 43.8 (CH_2), 38.1 (CH_2), 23.6 (CH_2), and 21.7 (CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [12]

2-methylene-6-oxo-6-phenylhexanal 300

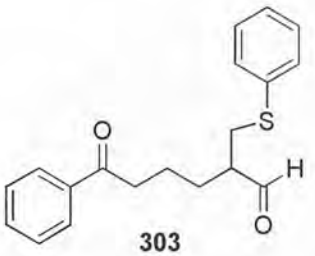


300

To a solution of 6-oxo-6-phenylhexanal **317** (0.150 g, 0.789 mmol, 1 equiv) in DCM (20 mL) and NEt_3 (0.398 g, 549 μL, 3.94 mmol, 5 equiv) was added Böhme's salt (0.221 g, 2.36 mmol, 3 equiv). The reaction was left to stir for 18 h, and then quenched with $NaHCO_3$ and extracted three times with DCM. After completion the solvent was evaporated and the crude product was purified by column chromatography (25 % Et_2O, hexanes) afforded the title compound (135 mg, 85 %) as a colorless oil. **IR** (neat)/cm^{-1}): υ_{max} 3061 (CHAr), 2936 (CH_2), 1690 (C=O), 1687 (C=O). **^{1}H NMR** (360 MHz, $CDCl_3$)

δ: 9.56 (s, 1H, **CHO**), 7.96-7.94 (m, 2H, **ArH**), 7.57-7.26 (m, 3H, **ArH**), 6.33 (s, 1H, **CH_2**=), 6.05 (s, 1H, **CH_2**=), 3.00 (t, 2H, J= 7.4 Hz, **CH_2**C=O), 2.36 (t, 2H, J= 7.2 Hz, **CH_2CH_2**=), 1.97-1.89 (m, 2H, 1 x **CH_2**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 199.7 (C=O), 194.6 (CHO), 149.6 (quat), 136.9 (*ipso*), 134.5 (CH_2=), 133.0 (ArH), 128.6 (ArH), 128.0 (ArH), 37.8 (CH_2), 27.2 (CH_2) and 22.2 (CH_2). **HRMS** (ES+) *m/z* calculated for $C_{13}H_{15}O_2$ $[M+H]^+$ 203.1067, found 203.1070.

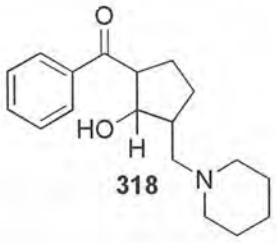
6-oxo-6-phenyl-2-(phenylthiomethylhexanal 303



303

To a solution of 2-methylene-6-oxo-6-phenylhexanal **300** (0.1 g, 0.495 mmol, 1 equiv) in toluene (1 mL), thiophenol was added (0.082 g, 76 μL, 0.742 mmol, 1.5 equiv) and the resulting solution was stirred for 3 h at rt. After completion the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, 10 % Et_2O, hexanes) afforded the title compound (127 mg, 82 %) as a colorless oil; **IR** (neat)/cm^{-1}): υ_{max} 1724 (C=O), 1684 (C=O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.60 (d, 1H, J= 2.0 Hz, **CHO**), 7.86-7.81 (m, 2H, **ArH),** 7.47-7.11 (m, 8H, **ArH**), 3.18 (ABX, 1H, J_{AB}= 13.4 Hz, J_{AX}= 5.9Hz, J_{BX}= 7.5 Hz, **CH_2**SPh), 2.97 (ABX, 1H, J_{AB}= 13.3 Hz, J_{AX}= 5.9 Hz, J_{BX}= 7.3 Hz, **CH_2**SPh), 2.90 (t, 2H, J= 6.6 Hz, **CH_2**C=O), 2.50 (m, 1H, **CH**CH_2SPh), 1.78-1.57 (m, 4H, 2 x **CH_2**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 202.7 (C=O), 199.3 (C=O), 136.7 (*ipso*), 135.2 (*ipso*), 133.1 (ArH), 130.2 (ArH), 129.1 (ArH), 128.6 (ArH), 127.9 (ArH), 126.7 (ArH), 50.9 (CH), 38.0 (CH_2), 32.9 (CH_2), 27.8 (CH_2) and 21.0 (CH_2). **HRMS** (EI) *m/z* calculated for $C_{19}H_{20}O_2S$ [M] 312.1179, found 312.1184.

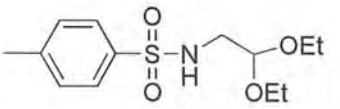
2-Hydroxy-4-(piperidin-1-ylmethylcyclopentyl) phenylmethanone 318



318

To a solution of 2-methylene-6-oxo-6-phenylhexanal **300** (0.1 g, 0.495 mmol, 1 equiv) in toluene (1 mL), piperidine was added (0.055 g, 64 μL, 0.643 mmol, 1.3 equiv) and the resulting solution was stirred for 8 h at rt. After completion the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, 10% Et_2O, hexanes) affording the title compound (121 mg, 85 %) as a colorless oil. **IR** (neat) cm^{-1}): υ_{max} 3346 (OH), 2933 (CH_2), 1676 (C=O), 1125 (C-O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 8.05-8.00 (m, 2H, **ArH**), 7.53 (m, 1H, **ArH**), 7.48-7.42 (m, 2H, **ArH**), 4.07 (t, 1H, J= 8.9 Hz, **CH**OH), 3.77 (m, 1H, **CH**COPh), 2.60 (d, 1H, J=3.7, **CH**), 2.57 (d, 1H, J= 3.7 Hz, **CH**), 2.41-1.47 (m, 15H, 7 x **CH_2**, 1 x **CH**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 202.3 (C=O), 137.3 (*ipso*), 132.9 (ArH), 128.7 (ArH), 128.4 (ArH), 82.7 (CHOH), 63.8 (CH_2), 55.3 (CH_2), 52.5 (CH), 43.2 (CH), 26.5 (CH_2), 26.1 (CH_2), 26.0 (CH_2) and 24.1 (CH_2). **HRMS** (EI) *m/z* calculated for $C_{18}H_{25}O_2N$ [M] 287.1880, found 287.1878.

N-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide 307

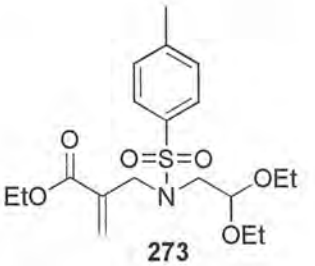


307

To a solution of 2,2-diethoxy-ethylamine (4 g, 30.03 mmol, 1 equiv) in dry DCM (80 mL), triethylamine was added (9.11 g, 90.09 mmol, 3 equiv), the reaction was cooled to 0 °C and p-toluenesulfonylchloride was added to the solution. After 24 h, the reaction mixture was quenched with water and extracted with DCM (3 x 100 mL). The combined organic layers were dried $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallised from dichloromethane/hexane to give the title compound (7.5 g, 87 %) as a crystalline solid; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.73 (d, J= 6.6 Hz, 2H, **ArH**), 7.33 (d, J= 6.6 Hz, 2H, **ArH**), 4.46 (t, 1H, J= 5.6Hz, **CH**$(OEt)_2$), 3.67-3.43 (m, 4H, (**CH_2**$CH_3)_2$), 3.02 (d, 2H, J= 6.5 Hz, **CH_2**$CH(OEt)_2$), 2.42 (s, 3H, **CH_3**ArH), 1.17 (t, 6H, J= 7.0 Hz, **CH_3**$CH_2)_2$). **^{13}C NMR** (63 MHz, $CDCl_3$); 143.5 (*ipso*), 136.8 (*ipso*), 129.7 (ArH), 127.1 (ArH), 100.7 ($CH(OCH_2CH_3)$, 63.2 (CH_2), 45.4 (CH_2), 21.5 (CH_3) and 15.2 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [13]

Ethyl 2-((N-(2,2-diethoxyethyl)-4-methylphenylsulfonamide)methylacrylate, 273

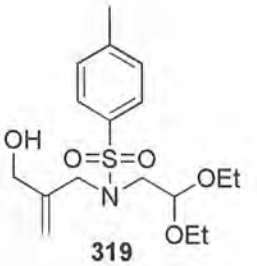


273

To a solution of N-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide (1.98 g, 6.89 mmol, 1 equiv) in dry DMF (50 mL) at 0 °C, NaH (60 % dispersion, 0.301 g, 8.96 mmol, 1.3 equiv) was added, the suspension was stirred for 30 min at rt before adding the methyl 2-(bromoethyl) acrylate (2.86 g, 14.81 mmol, 2.15 equiv) dropwise. After 24 h, the reaction mixture was quenched with water and extracted with diethylether (3 x 150 mL).The combined organic layers were dried $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (SiO_2, 10 % Et_2O/hexanes) to give the title compound (2.35 g, 85 %) as a colourless oil; **IR** (neat)/ cm^{-1}): υ_{max} 2976 (CH_2), 1719 (C=O), 1159 (C-O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.38 (d, 2H, J= 8.2 Hz, **ArH**), 7.27 (d, 2H, J= 8.2 Hz, **ArH**), 6.29 (s, 1H, **CH_2**=), 5.74 (s, 1H, **CH_2**=), 4.57 (t, 1H, J= 5.4 Hz, **CH**$(OEt)_2$), 4.16 (q, 2H, J= 7.1 Hz, O**CH_2**CH_3), 3.68-3.59 (m, 2H, (O**CH_2**$CH_3)_2$), 3.50-3.38 (m, 2H, (O**CH_2**$CH_3)_2$), 3.28 (d, 2H, J= 5.5 Hz, **CH_2**$CH(OCH_2CH_3)_2$), 2.41 (s, 3H, **CH_3**ArH), 1.58 (s, 2H, (**CH_2**CH_2=), 1.26 (t, 3H, J= 7.1 Hz, O**CH_3**CH_2), 1.15 (t, 6H, J= 7.0 Hz, O**CH_3**$CH_2)_2$). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 165.9 (COOEt), 143.3 (quat), 137.2 (ArH), 135.7 (*ipso*), 129.6 (CH_2=), 127.2 (ArH), 126.8 (ArH), 102.1 ($CHOCH_3$), 63.2 (CH_2), 60.8 (CH_2), 50.9 (CH_2), 49.7 (CH_2), 21.5 (CH_3), 15.2 (CH_3) and 14.1 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [14]

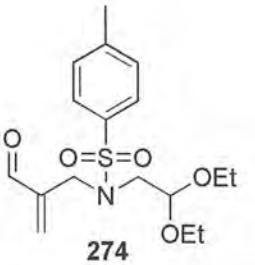
N-(2,2-diethoxyethyl)-N-(2-(hydroxymethyl) allyl-4-methylbenzenesulfonamide 319



319

To Ethyl-2-((N-(2,2-diethoxyethyl)-4methylphenylsulfonamide) methylacrylate **273** (1.85 g, 4.63 mmol, 1 equiv) in dry DCM (50 mL) and toluene (10 mL) at -78 °C, was added DIBAL-H dropwise (1M solution in hexane, 5.09 mL, 5.09 mmol, 1.1 equiv), the suspension was stirred for 12 h. To the reaction mixture was added potassium sodium tartrate solution; the mixture was vigorously stirred for 30 min and extracted with DCM (3 x 100 mL). The combined organic layers were dried $MgSO_4$, filtered and concentrated *in vacuo*. After completion, the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, 40 % Et_2O, hexanes) to afford the title compound (1.49 g, 90 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3452 (OH), 3062 (CHAr), 2970 (CH_2), 1148 (C-O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ:7.70 (d, 2H, J= 8.3 Hz, **ArH**), 7.33 (d, 2H, J= 8.0 Hz, **ArH**), 5.20 (s, 1H, **CH_2**=), 5.00 (s, 1H, **CH_2**=), 4.62 (t, 1H, J= 5.5 Hz, **CH**$(OEt)_2$), 4.12 (br, d, 2H, J= 4.4 Hz, **CH_2**OH), 3.89 (s, 2H, **CH_2**CH_2=), 3.68-3.62 (m, 2H, O**CH_2**$CH_3)_2$), 3.49-3.39 (m, 2H, O**CH_2**$CH_3)_2$), 3.24 (d, 2H, J= 5.5 Hz, **CH_2**$CH(OCH_2CH_3)_2$,), 2.43 (s, 3H, **CH_3**ArH), 1.15 (t, 6H, J= 7.0 Hz, O**CH_3**$CH_2)_2$). **^{13}C NMR** (63 MHz, $CDCl_3$) δ:143.6 (quat), 143.4 (quat), 136.4 (quat), 129.5 (ArH), 127.1 (ArH), 115.1 (CH_2=), 101.3 (CHOEt), 63.2 (CH_2), 62.8 (CH_2), 51.5 (CH_2), 49.4 (CH_2), 21.3 (CH_3) and 15.0 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{17}H_{31}O_5N_2S$ $[M+NH_4]^+$ 375.1954, found 375.1957.

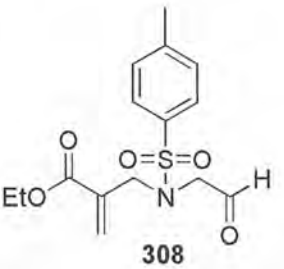
N-(2,2-diethoxyethyl)-N-(2-(formylallyl)-4-methylbenzenesulfonamide, 274



274

N-(2,2-Diethoxyethyl)-N-(2-(hydroxymethyl)allyl-4-methylbenzenesulfonamide (0.490 g, 1.37 mmol, 1 equiv) in DCM was added sequentially celite (equal amount by mass PCC), molecular sieves and PCC (0.366 g, 1.70 mmol, 1.24 equiv). After stirring at rt for 3 h, the solution was filtered through a plug of silica (DCM) and the solvent was evaporated to afford the title compound (431 mg, 89 %) as a white solid; **IR** (neat) / cm^{-1}): υ_{max} 1691 (CHO), 1427 (S=O), 1154 (C-O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.55 (s, 1H, **CHO**), 7.70 (d, 2H, J= 8.3 Hz, **ArH)**, 7.30 (d, 2H, J= 8.0 Hz, ArH), 6.49 (s, 1H, **CH_2**=) 6.17 (s, 1H, **CH_2**=), 4.53 (t, 1H, J= 5.4 Hz, **CH**$(OEt)_2$), 4.11 (s, 2H, **CH_2**N), 3.70-3.57 (m, 2H, O**CH_2**CH_3), 3.47-3.36 (m, 2H, O**CH_2**CH_3), 3.23 (d, 2H, J= 5.4 Hz, **CH_2**CH), 2.42 (s, 3H, **CH_3**ArH), 1.14 (t, 6H, J= 7.0 Hz, (**$CH_3CH_2)_2$**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 193.4 (CHO), 145.2 (quat), 143.6 (quat), 136.5 (quat), 135.5 (CH_2=), 129.7 (ArH), 127.2 (ArH), 101.8 (CHOEt), 63.0 (CH_2), 51.2 (CH_2), 47.2 (CH_2), 21.5 (CH_3Ar), and 15.2 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{17}H_{26}O_5NS$ $[M+H]^+$ 356.1532, found 356.1534.

Ethyl-2-((4-methyl-N-(2-oxoethyl) phenylsulfonamide) methylacrylate, 308

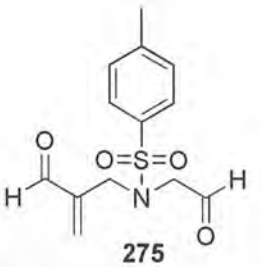


308

Ethyl-2-((N-(2,2-diethoxyethyl)-4-methylphenylsulfonamide) methylacrylate (1.0 g, 2.50 mmol, 1 equiv) was dissolved in acetic acid (2.5 mL) and the solution was cooled to 0-5 ˚C in an ice bath. As soon as the solution started to freeze, HCl solution (1M, 700 µL) was added at once and the solution was stirred overnight in the same bath. The mixture was diluted with DCM and the solution was washed successively with water (100 mL) and saturated $NaHCO_3$ (100 mL). The combined organic layers were dried $MgSO_4$, filtered and concentrated *in vacuo*. After completion the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, 40 % Et_2O, hexanes) to afford the title compound (910 mg, 92 %) as a colorless oil; **IR** (neat) cm^{-1}): υ_{max} 2809 (CHCHO), 1718 (C=O), 1705 (C=O), 1431 (S=O), 1122 (C-O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.72 (s, 1H, **CHO**) 7.75-7.55 (d, 2H, J= 8.2 Hz, **ArH**), 7.27 (d, 2H, J= 8.2 Hz, **ArH**), 6.28 (d, 1H, J= 1.0 Hz, **CH_2**=), 5.75 (d, 1H, J= 1.0 Hz, **CH_2**=), 4.32 (s, 2H, **CH_2CH_2**=), 4.25(q, 2H, J= 7.3 Hz, O**CH_2CH_3**), 3.25 (s, 2H, **CH_2**CHO), 2.40 (s, 3H, **CH_3**ArH), 1.35(t, 3H, J= 7.2 Hz, O**CH_3CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 198.2 (CHO), 166.2 (C=O), 144.3 (quat), 135.7 (CH_2=), 135.3 (quat), 130.0 (ArH), 129.1 (ArH), 127.6 (quat), 61.6 (CH_3), 57.7 (CH_2CHO), 52.3 (CH_2CH_3), 50.1 (CH_2) and 21.7 (CH_3).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature [14]

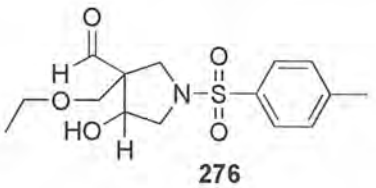
N-(2-formylallyl)-4-methyl-N-(2-oxoethyl)benzenesulfonamide 275



275

To N-(2,2-diethoxyethyl)-N-(2-(formylallyl)-4-methylbenzenesulfonamide (0.400 g, 1.13 mmol, 1 equiv) in MeCN (3 mL) and H_2O (100 μL), $LiBF_4$ (0.127 g, 1.35 mmol, 1.2 equiv) was added in a flask MeCN (3 mL) and H_2O (100 μL) and heated to reflux at 50 °C for 3 h. After stirring for 3 h, the reaction mixture was quenched with $NaHCO_3$ and extracted with Et_2O (2 x 100 mL). The combined organic layers were dried $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound (235 mg, 74 %) as an amorphous white solid; **m.p.**= 67-69 °C (Et_2O/ hexanes); **IR** (neat) cm^{-1}): υ_{max} 1682 (C=O), 1422 (S=O), 1154 (C-O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.56 (s, 1H, **CHO**) 9.53 (t, 1H, J= 1.2 Hz, **CHO**), 7.76 (d, 2H, J= 8.2 Hz, **ArH**), 7.34 (d, 2H, J= 8.2 Hz, **ArH**), 6.65 (s, 1H, **CH_2**=), 6.28 (s, 1H, **CH_2**=), 4.01 (s, 2H, **CH_2**), 3.91 (s, 2H, **CH_2**CHO), 2.44 (s, 3H, **CH_3ArH**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 197.1 (CHO), 193.3 (CHO), 144.5 (quat), 144.3 (quat), 137.3 (CH_2=), 135.3 (quat), 129.9 (ArH), 127.4 (ArH), 57.9 (CH_2), 46.8 (CH_2), and 21.5 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{13}H_{19}O_4N_2S$ $[M+NH_4]^+$ 299.1060, found 299.1062.

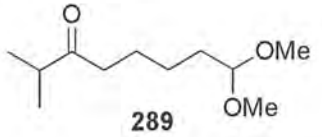
3-(Ethoxymethyl)-4-hydroxy-1-tosylpyrrolidine-3-carbaldehyde 276



276

Purification by column chromatography (SiO_2, 15 % Et_2O, hexanes) afforded the title compound (4:3 d.r.) as a colorless oil/solid; **IR** (neat)/ cm^{-1}): υ_{max} 3469 (OH), 1694 (CHO), 1085 (C-O). Inseparable mixture of diastereomers. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.65 (s, 1H, **CHO**), 7.75-7.68 (m, 4H, **ArH**), 7.36-7.31 (m, 4H, **ArH**), 4.43 (m, 1H, **CHOH**), 3.74-3.36 (m, 12H, 6 x **CH_2**), 3.31-3.15 (m, 4H, 2 x **CH_2CH_3**), 2.44 (s, 6H, **CH_3**Ar), 1.13 (t, 3H, J= 7.0 Hz, **CH_3CH_2**). Minor diastereomer diagnostic peaks: **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.51 (s, 1H, **CHO**), 4.50 (m, 1H, **CHOH**). 1.12 (t, 3H, J= 7.0 Hz, **CH_3CH_2**) **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 201.2 (CHO), 200.1 (CHO), 143.7 (*ipso*), 132.8 (*ipso*), 129.6 (ArH), 127.5 (ArH), 77.1 (CHOH), 73.7 (CHOH), 71.5 (CH_2), 70.6 (CH_2), 68.3 (CH_2), 67.1 (CH_2), 61.0 (quat), 60.4 (quat), 54.6 (CH_2), 54.1 (CH_2), 48.9 (CH_2), 48.6 (CH_2), 21.4 (CH_3Ar), and 14.5 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{15}H_{22}O_5SN$ $[M+H]^+$ 328.1213, found 328.1213.

8,8-dimethoxy-2-methyloctan-3-one 289

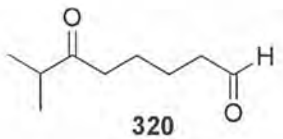


289

A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a glass stopper and a magnetic stirring bar and is charged with isopropyl-1-cyclohexene (5 g, 40.2 mmol, 1 equiv) and dichloromethane (250 mL) with methanol (50 mL). The flask is cooled to -78 °C and ozone is bubbled through the solution when stirring. Reaction completion is judged by tlc, nitrogen is then passed through the solution and

then the cold bath is removed. The solution is allowed to warm to room temperature as it stirs under an atmosphere of nitrogen triphenylphosphine (12.7 g, 48.3 mmol, 1.2 equiv) was added. After being stirred for 12 h, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Dichloromethane (250 mL) is added and the mixture is washed with water (3 x 50 mL). The aqueous layer is extracted with two more portions of dichloromethane, and the combined organic layers are washed with water. After extracting the aqueous layer with dichloromethane, the organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 20 % Et_2O, hexanes) afforded the title compound (7.48 g, 92 %) as a white solid. **m.p.** = 81-83 °C (Et_2O/ hexanes); **IR** (neat)/ cm^{-1}): υ_{max} 2918 (CH_2), 1709 (C=O), 1080 (C-O). **^{1}H NMR**(360 MHz, $CDCl_3$) δ: 4.36 (t, IH, J= 5.7 Hz, **CH**$(OCH_3)_2$), 3.30 (s, 6H, **$(OCH_3)_2$**), 2.57 (sept, 1H, J= 6.9 Hz, **CH**$(CH_3)_2$), 2.45 (t, 2H, J= 7.3 Hz, **CH_2**CHO), 1.64-1.53 (m, 4H, 2 x **CH_2**), 1.38-1.23 (m, 2H, 1 x **CH_2**), 1.08 (d, 6H, J= 6.9 Hz, **$(CH_3)_2$**CH). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 214.8 (C=0), 104.3 ($CHOCH_3$), 52.7 (CH_3OCH), 40.8 ($CHCH_3$), 40.1 (CH_2), 32.3 (CH_2), 24.3 (CH_2), 23.5 (CH_2) and 18.2 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{11}H_{26}O_3N$ $[M+NH_4]^+$ 220.1912, found 220.1914.

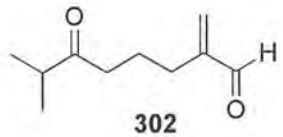
7-methyl-6-oxooctanal 320



320

8,8-Dimethoxy-2-methyloctan-3-one (4.00 g, 19.8 mmol, 1 equiv) was dissolved in acetic acid (10 mL) and the solution was cooled to 0-5 °C in an ice bath. As soon as the solution started to freeze, HCl solution (1 M, 1.5 mL) was added at once and the solution was stirred overnight in the same bath. The mixture was diluted with DCM and the solution was washed successively with water and saturated $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20 % Et_2O, hexanes) afforded the title compound (3.09 g, 84 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 2918 (CH_2), 1709 (C=O), 1687 (CHO). **^{1}H NMR** (360 MHz, $CDCl_3$)δ: 9.76 (t, 1H, J= 1.6 Hz, **CHO)**, 2.57 (sept, 1H, J= 6.9 Hz, **CH**$(CH_3)_2$), 2.51-2.42 (m, 4H, 2 x **CH_2**), 1.66-1.57 (m, 4H, 2 x **CH_2**), 1.09 (d, 6H, J= 6.9 Hz, **$(CH_3)_2$**CH). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 214.3 (C=0), 194.5 (CHO), 40.6 (CH), 39.3 (CH_2), 31.5 (CH_2), 26.9 (CH_2), 21.6 (CH_2) and 18.0 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_9H_{20}O_2N$ $[M+NH_4]^+$ 174.1489, found 174.1490.

7-methyl-2-methylene-6-oxoctanal 302

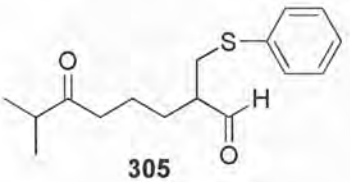


302

To a solution of 7-methyl-6-oxoctanone (4.0 g, 25.6 mmol, 1 equiv) in DCM (200 mL) and NEt_3 (12.9 g, 18 mL, 128 mmol, 5 equiv) was added Böhme's salt (7.2 g, 76.9 mmol, 3 equiv). The reaction was left to stir for 18 h, and then quenched with $NaHCO_3$ and extracted three times with DCM (3 x 150 mL). Purification by column

chromatography (SiO_2, 25 % Et_2O, hexanes) afforded the title compound (3.79 g, 88 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3082 (CH_2=), 2963 (CH_2), 1736 (C=O), 1693 (C=O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.47 (s, 1H, **CHO**), 6.23 (s, 1H, **CH_2**=), 5.97 (s, 1H, **CH_2**=), 2.75 (sept, 1H, J= 6.9 Hz, **CH**(CH_3)$_2$), 2.66 (t, 2H, J= 7.3Hz, **CH_2**C=O), 2.45-2.39 (m, 2H, 2 x **CH_2**), 1.98-1.86 (m, 2H, 2 x **CH_2**), 1.26 (d, 6H, J= 6.9 Hz, (**CH_3**)$_2$CH). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 214.0 (C=O), 194.4 (CHO), 149.6 (quat), 134.2 (CH_2=), 40.7 (CH (CH_3)$_2$), 39.4 (CH_2), 27.0 (CH_2), 21.6 (CH_2) and 18.1 (CH_3). **HRMS** (EI) *m/z* calculated for $C_{10}H_{16}O_2$ [M] 168.1145, found 168.1143.

7-Methyl-6-oxo-2-(phenylthiomethyl)octanal 305

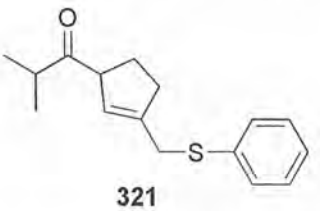


305

To a solution of 7-methyl-2-methylene-6-oxoctanal (0.05 g, 0.297 mmol, 1 equiv) in DCM (1 mL) with molecular sieves, thiophenol was added (0.036 g, 34 µl, 0.327 mmol, 1.1 equiv) and the resulting solution was stirred for 6 h at rt. After completion the solvent was evaporated. The mixture was diluted with DCM and the solution was washed successively with water and saturated $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 25 % Et_2O, hexanes) afforded the title compound (60 mg, 73 %) as a colorless oil. **IR** (neat) cm^{-1}): υ_{max} 3062 (CHAr), 2817 (HC=O), 1737 (C=O), 1696 (C=O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.60 (d, 1H, J= 2.0 Hz, **CHO**), 7.37-7.23 (m, 5H, **ArH**), 3.20 (dd, 1H, J= 7.5, 13.4 Hz, **CH_2**SPh), 3.05 (dd, 1H, J= 6.0, 13.3 Hz, **CH_2**SPh), 2.54 (sept, 1H, J= 6.9 Hz, **CH**(CH_3)$_2$), 2.43 (t, 2H, J= 7.0 Hz, **CH_2**C =O), 1.63-1.57 (m, 5H, 2 x **CH_2**, 1 x **CH**), 1.06 (d, 6H, J= 6.9 Hz, (**CH_3**)$_2$CH). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 213.9 (CHO), 202.7 (C=O), 136.7 (*ipso*), 130.2 (ArH), 129.1 (ArH), 126.7 (ArH), 50.9 (CHCHO), 40.8 (CH(CH_3)$_2$), 39.7 (CH_2), 32.9 (CH_2), 27.9 (CH_2),

20.6 (CH_2) and 18.2 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{16}H_{26}O_2NS$ $[M+NH_4]^+$ 296.1679, found 296.1678. **HPLC** (Chiralcel AD-H), hexane/isopropanol= 98/2, 1.0 mL/min, λ = 254 nm, retention time: enantiomers (20.1, 21.6 mins).

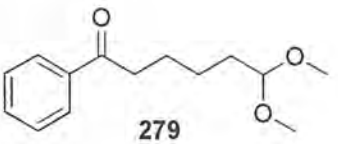
2-Methyl-1-(3-(phenylthiomethyl) cyclopent-2-enyl) prop-1-one 321



321

To a solution of 7-methyl-2-methylene-6-oxoctanal (0.05 g, 0.298 mmol, 1 equiv) in MeCN (2.5 mL) and H_20 (107 µl, 5.96 mmol, 20 equiv) was added thiophenol (0.036 g, 34 µl, 0.328 mmol, 1.1 equiv) and t-BuOK (0.200 g, 1.78 mmol, 6 equiv). The reaction was left to stir for 18 h. After completion the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, 20 % Et_2O, hexanes) affording the title compound (47 mg, 61 %). as a colorless oil. **IR** (neat)/ cm^{-1}): υ_{max} 1716 (C=O), 1274 (CH); **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.44-7.40 (m, 2H, **ArH**), 7.33-7.27 (m, 2H, **ArH**), 7.22 (m, 1H, **ArH**), 6.37 (t, 1H, J= 1.9 Hz, **CH**=), 3.29 (d, 2H, J= 1.5 Hz, **CH_2**), 2.98 (sept, 1H, J= 6.9 Hz, **CH**(CH_3)$_2$), 2.74-2.64 (m, 2H, 1 x **CH_2**), 2.50 (m, 1H, **CH**), 2.18 (m, 1H, **CH**), 2.04 (m, 1H, **CH**), 1.07 (d, 3H, J= 6.9 Hz, (**CH_3**)CH), 1.00 (d, 3H, J= 6.9 Hz, (**CH_3**)CH). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 203.8 (C=O), 144.8 (quat), 142.6 (CH=), 130.0 (quat), 129.2 (ArH), 126.8 (ArH), 85.7 (CH=O), 45.3 (CH_2), 37.1 (CH_2), 36.5 ($CH(CH_3)_2$), 29.3 (CH_2) and 19.1 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{16}H_{24}ONS$ $[M+NH_4]^+$ 278.1577, found 278.1579.

6,6-Dimethoxy-1-phenylhexan-1-one 279

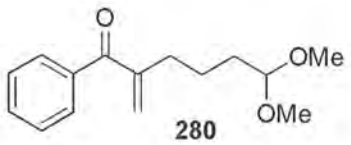


279

A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a glass stopper and a magnetic stirring bar and is charged with 1-phenylcyclohexene (2.05 g, 12.9 mmol, 1 equiv), dichloromethane (100 mL) and methanol (25 mL). The flask is cooled to -78 °C and ozone is bubbled through the solution when stirring. Reaction completion is judged by tlc, nitrogen is then passed through the solution and then the cold bath is removed. The solution is allowed tom warm to room temperature as it stirs under an atmosphere of nitrogen triphenylphosphine (3.46 g, 13.2 mmol, 1.02 equiv) was added. After being stirred for 6 h, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Dichloromethane (150 mL) is added and the mixture is washed with water (75 mL). The aqueous layer is extracted with two more portions of dichloromethane, and the combined organic layers are washed with water. After extracting the aqueous layer with dichloromethane, the organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 20 % Et_2O, hexanes) afforded the title compound (2.59 g, 85 %) as a colorless oil. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.97-7.94 (m, 2H, **ArH**), 7.58-7.43 (m, 3H, **ArH**), 4.38 (t, 1H, J= 5.7 Hz, **CH**$(OCH_3)_2$), 3.32 (s, 6H, **OCH$_3$**)$_2$), 2.98 (t, 2H, J= 7.0 Hz, **CH$_2$**C=O), 1.81-1.63 (m, 4H, 2 x **CH$_2$**), 1.49-1.40 (m, 2H, 2 x **CH$_2$**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 200.4 (C=O), 137.1 (*ipso*), 133.1 (ArH), 128.7 (ArH), 128.2 (ArH),104.5 (CH(OMe_2), 52.9 (CH_3), 38.6 (CH_2), 32.5 (CH_2), 24.5 (CH_2) and 24.2 (CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature.[16]

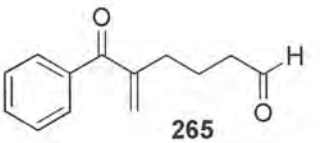
6,6-Dimethoxy-2-methylene-1-phenylhexan-1-one 280



280

A solution of LHMDS (635 μL, 0.635 mmol, 1.5 equiv), in THF was cooled to -78 °C before dropwise addition of phenyl acetal **279** (0.100 g, 0.423 mmol, 1 equiv) in THF (4 mL). The mixture was stirred for 1 h, then canulated into a stirred suspension of Böhme`s salt (0.119 g, 1.27 mmol, 3 equiv) in THF (5 mL) at -78 °C for 10 minutes. The contents of the flask were then transferred to a separatory funnel containing ether and $NaHCO_3$. The aqueous layer is extracted with two more portions of dichloromethane, and the combined organic layers are washed with water. After extracting the aqueous layer with dichloromethane (100 mL), the organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. The oil was then dissolved in DCM (15 mL), $NaHCO_3$ (10 mL), mcpba (0.146 g, 0.846 mmol, 2 equiv) was added in one portion and left to stir for 20 minutes. The contents were then transferred to a separatory funnel, the aqueous layer is extracted with two more portions of dichloromethane, and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 20 % Et_2O, hexanes) afforded the title compound (89 mg, 85 %) as a colorless oil; **IR** (neat) cm^{-1}): υ_{max} 3077 (CH_2=), 1710 (C=O), 1085 (C-O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.75-7.70 (m, 2H, **ArH**), 7.54-7.48 (m, 1H, **ArH**), 7.44-7.38 (m, 2H, **ArH**), 5.84 (s, 1H, **CH_2**=), 5.59 (s, 1H, **CH_2**=), 4.38 (t, 1H, J= 5.5 Hz, **CH**(OCH_3)$_2$), 3.30 (s, 6H, **OCH_3**)$_2$), 2.52 (t, 2H, J= 6.8 Hz, **CH_2CH_2**=), 1.70-1.51 (m, 4H, 2 x **CH_2**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 198.3 (C=O), 147.9 (quat), 137.8 (quat), 132.2 (ArH), 129.5 (ArH), 128.2 (ArH), 125.7 (CH_2=), 104.3 ($CHOCH_3$), 52.8 (OCH_3), 32.2 (CH_2), 32.0 (CH_2) and 23.1 (CH_2). **HRMS** (ES+) *m/z* calculated for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1490, found 249.1489.

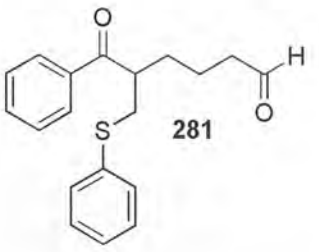
5-Benzoylhex-5-enol, 265



265

6,6-Dimethoxy-2-methylene-1-phenylhexan-1-one (2.0 g, 8.05 mmol, 1 equiv) was dissolved in acetic acid (10 mL) and the solution was cooled to 0-5 °C in an ice bath. As soon as the solution started to freeze, HCl solution (1 M, 2.5 mL) was added at once and the solution was stirred for 5h in the same bath. The mixture was diluted with Et_2O and the solution was washed successively with water and saturated $NaHCO_3$. The combined organic layers were dried $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 15 % Et_2O, hexanes) afforded the title compound (1.48 g, 74 %) as a colourless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3082 (CH_2=), 3063 (CHAr), 2932 (CH_2), 1692 (C=O), 1686 (CHO). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.79 (t, 1H, J= 1.5 Hz, **CHO**), 7.76-7.72 (m, 2H, ArH), 7.55 (m, 1H, ArH), 7.47-7.40 (m, 2H, ArH), 5.89 (s, 1H, **CH_2**=), 5.66 (s, 1H, **CH_2**=), 2.55 (m, 4H, 2 x **CH_2**), 1.92 (quin, 2H, J= 7.6 Hz, **CH_2**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 202.1 (CHO), 198.0 (C=O), 147.2 (quat), 137.6 (quat), 132.3 (ArH), 129.5 (ArH), 128.2 (ArH), 126.5 (CH_2=), 43.3 (CH_2), 31.5 (CH_2) and 20.7 (CH_2). **HRMS** (ES+) *m/z* calculated for $C_{13}H_{15}O_2$ $[M+H]^+$ 203.1067, found 203.1070.

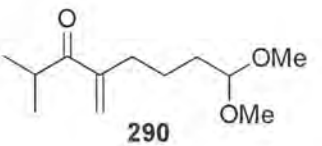
6-oxo-6-phenyl-5-(phenylthiomethyl) hexanal 281



281

To a solution of 5-benzoylhex-5-enol (0.08 g, 0.396 mmol, 1 equiv) in DCM (1 mL) with molecular sieves, thiophenol was added (0.048 g, 45 µl, 0.436 mmol, 1.1 equiv) and the resulting solution was stirred for 4 h at rt. After completion the solvent was evaporated. Purification by column chromatography (SiO_2, 20 % Et_2O, hexanes) afforded the title compound (108 mg, 88 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 1721 (C=O), 1678 (C=O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.69 (t, 1H, J = 1.5 Hz, **CHO**), 7.83-7.79 (m, 2H, **ArH**), 7.57 (m, 1H, **ArH**), 7.45-7.40 (m, 2H, **ArH**), 7.35-7.20 (m, 5H, **ArH**), 3.73-3.63 (m, 1H, **CHC=O**), 3.34 (ABX, 1H, J_{AB}= 13.2 Hz, J_{AX}= 5.9 Hz, J_{BX}= 7.2 Hz, **CH_2**SPh), 3.06 (ABX, 1H, J_{AB}= 13.2 Hz, J_{AX}= 6.5 Hz, J_{BX}= 6.7Hz, **CH_2**SPh) 2.39 (dt, 2H, J= 1.5, 7.2 Hz, **CH_2**CH). 1.93-1.56 (m, 2 x **CH_2**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 202.0 (C=O), 201.7 (C=O), 136.8 (*ipso*), 135.6 (*ipso*), 133.4 (ArH), 130.3 (ArH), 129.0 (ArH), 128.7 (ArH), 128.3 (ArH), 126.7 (ArH), 45.4 (CHCOPh), 43.7 (CH_2), 36.1 (CH_2), 31.4 (CH_2) and 19.6 (CH_2). **HRMS** (ES+) *m/z* calculated for $C_{19}H_{21}O_2S$ $[M+H]^+$ 313.1257, found 313.1256.

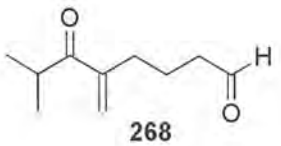
8,8- dimethoxy-2-methyl-4-methleneoctan-3-one 290



290

A solution of LHMDS (11.2 mL, 11.2 mmol, 1.5 equiv), in THF was cooled to -78 °C before dropwise addition of isopropylacetal **289** (1.5 g, 7.43 mmol, 1 equiv) in THF (40 mL). The mixture was stirred for 1 h, then canulated into a stirred suspension of Böhme`s salt (2.08 g, 22.3 mmol, 3 equiv) in THF (50 mL) at -78 °C for 10 minutes. The contents of the flask were then transferred to a separatory funnel containing ether and $NaHCO_3$. The aqueous layer is extracted with two more portions of dichloromethane, and the combined organic layers are washed with water. After extracting the aqueous layer with dichloromethane (2 x 100 mL), the organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. The oil was then dissolved in DCM (15 mL), $NaHCO_3$ (10 mL), mcpba (2.56 g, 14.9 mmol, 2 equiv) was added in one portion and left to stir for 20 minutes. The contents were then transferred to a separatory funnel, the aqueous layer is extracted with two more portions of dichloromethane, and the combined organic layers are dried over $MgSO_4$, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 10% Et_2O, hexanes) afforded the title compound (1.26 g, 79 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3084 (CH_2=), 2958 (CH_2) 1735 (C=O), 1097 (C-O). **^{1}H NMR** (360 MHz, $CDCl_3$)δ: 5.96 (s, 1H, **CH_2**=), 5.72 (s, 1H, **CH_2**=), 4.35 (t, 1H, J= 5.7 Hz, **CH**(OCH_3)$_2$), 3.30 (s, 6H, (**OCH_3**)$_2$), 3.29 (sept, 1H, J= 6.6 Hz, **CH**(CH_3)$_2$), 2.26 (t, 2H, J= 7.7 Hz, **CH_2**CH_2=), 1.64-1.55 (m, 2H, 1 x **CH_2**), 1.49-1.39 (m, 2H, 1 x **CH_2**) 1.07 (d, 6H, J= 6.9 Hz, (**CH_3**)$_2$CH).**^{13}C NMR** (63 MHz, $CDCl_3$) δ: 206.2 (C=O), 147.6 (quat), 123.2 (CH_2=), 104.4 ($CHOCH_3$), 52.8 (OCH_3), 34.5 ($CH(CH_3)_2$, 32.8 (CH_2), 31.0 (CH_2), 23.4 (CH_2) and 19.3 (CH_3). **HRMS** (EI) *m/z* calculated for $C_{12}H_{22}O_3$ [M] 214.1569, found 214.1567.

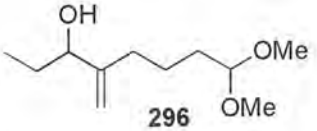
7-methyl-5-methylene-6-oxooctanol 268



268

8,8-dimethoxy-2-methyl-4-methleneoctan-3-one (0.9 g, 4.2 mmol, 1 equiv) was dissolved in acetic acid (5 mL) and the solution was cooled to 0-5 °C in an ice bath. As soon as the solution started to freeze, HCl solution (1 M, 1 mL) was added at once and the solution was stirred for 5 h in the same bath. The mixture was diluted with Et_2O and the solution was washed successively with water and saturated $NaHCO_3$. The combined organic layers were dried $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20 % Et_2O hexanes) afforded the title compound (473 mg, 67 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3086 (CH_2=), 2968 (CH_2) 1737 (C=O), 1693 (C=O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.75 (1H, t, J= 1.6 Hz, **CHO**), 6.00 (s, 1H, **CH_2**=), 5.77 (s, 1H, **CH_2**=), 3.29 (sept, 1H, J= 6.6 Hz, **CH(CH_3)$_2$**,), 2.44 (dt, 2H, J= 1.6, 7.3 Hz, **CH_2CH_2**=), 2.30 (dt, 2H, J= 1.0, 7.9 Hz **CH_2**CHO), 1.77-1.68 (m, 2H, 1 x **CH_2**), 1.09 (d, 6H, J= 6.9 Hz, **(CH_3)$_2$**CH). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 205.9 (C=O), 202.2 (CHO), 146.9 (quat), 123.9 (CH_2=), 43.4 (CH_2), 34.5 ($CH(CH_3)_2$), 30.7 (CH_2), 21.0 (CH_2) and 19.3 (CH_3). **HRMS** (EI) *m/z* calculated for $C_{10}H_{16}O_2$ [M] 168.1145, found 168.1143.

8,8- dimethoxy-4-methyleneoctan-3-ol 296

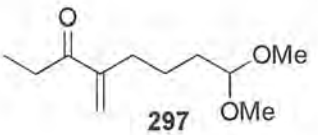


296

To a solution of ethylmagnesium bromide (1M THF, 8.7 mmol, 8.7 mL,1.5 equiv) at -78 °C, was added dropwise a solution of 6,6-dimethoxy-2-methylenehexanal (1 g, 5.8

mmol, 1 equiv) in THF (25 mL).The reaction was left to stir at -78 °C for 30 mins then warmed to 0 °C and left to stir for 5 h. After being stirred for 5 h, NH_4Cl is added. The aqueous layer is extracted with Et_2O (3 x 100 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 60 % Et_2O, hexanes) afforded the title compound (833 mg, 71 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3438 (OH), 3080 (CH_2=), 2937 (CH_2), 1127 ($COCH_3$). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 5.02 (s, 1H, **CH_2**=), 4.86 (s, 1H, **CH_2**=), 4.36 (t, 1H, J= 5.7 Hz, **CH**(OCH_3)$_2$), 3.99 (t, 1H, J= 6.2 Hz, **CHOH**), 3.31 (s, 6H, (**OCH_3**)$_2$), 2.07-2.01 (m, 2H, 1 x **CH_2**CH_3), 1.70-1.45 (m, 6H, 3 x **CH_2**), 0.88 (t, 3H, J= 7.4 Hz, **CH_3**CH_2). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 151.2 (quat), 109.8 (CH_2=), 104.4 ($CHOCH_3$), 76.7 (CHOH), 52.7 (OCH_3), 32.3 (CH_2), 31.0 (CH_2), 28.2 (CH_2), 22.9 (CH_2) and 9.9 (CH_3CH_2). **HRMS** (ES+) *m/z* calculated for $C_{11}H_{26}O_3N$ $[M+NH_4]^+$ 220.1907, found 220.1905.

8,8- dimethoxy-4-methyleneoctan-3-one 297

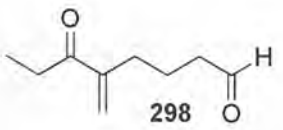


297

To a solution of 8,8-dimethoxy-4-methyleneoctan-3-ol (0.400 g, 1.98 mmol, 1 equiv) in DCM was added sequentially celite (equal mass to 8,8-dimethoxy-4-methyleneoctan-3-ol), molecular sieves and PCC (0.853 g, 3.96 mmol, 2 equiv), the solution was filtered through a plug of silica. Purification by column chromatography (SiO_2, 40 % Et_2O,hexanes) afforded the title compound (305 mg, 77 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3079 (CH_2=), 2933 (CH_2), 1721 (C=O), 1120 (C-OMe). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 6.02 (s, 1H, **CH_2**=), 5.75 (t, 1H, J= 1.3 Hz, **CH_2**=), 4.37 (1H, t, J= 5.5 Hz, **CH**(OCH_3)$_2$), 3.32 (s, 6H, (**OCH_3**)$_2$), 2.69 (q, 2H, J= 7.3 Hz, **CH_2**CH_3), 2.36-2.26 (m, 4H, 2 x **CH_2**), 1.79-1.67 (m, 2H, 1 x **CH_2**), 1.1 (t, 3H, J= 7.3 Hz, **CH_3**CH_2). **^{13}C**

NMR (91 MHz, $CDCl_3$) δ: 202.3 (C=O), 147.6 (quat), 124.1 (CH_2=), 104.3 ($CHOCH_3$), 51.5 (OCH_3), 33.5 (CH_2), 30.8 (CH_2), 30.2 (CH_2), 23.6 (CH_2) and 8.4 (CH_3CH_2). **HRMS** (ES+) *m/z* calculated for $C_{11}H_{24}O_3N$ $[M+NH_4]^+$ 218.1756, found 218.1755.

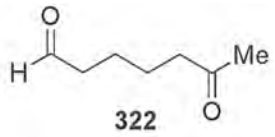
5-methylene-6-oxooctanal 298



298

8,8-dimethoxy-4-methyleneoctan-3-one (0.200 g, 1 mmol, 1 equiv) was dissolved in acetic acid (2 mL) and the solution was cooled to 0-5 °C in an ice bath. As soon as the solution started to freeze, HCl solution (1 M, 1 mL) was added at once and the solution was stirred for 2h in the same bath. The mixture was diluted with Et_2O and the solution was washed successively with water and saturated $NaHCO_3$. The combined organic layers were dried $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20 % Et_2O hexanes) afforded the title compound (131 mg, 85 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3081 (CH_2=), 2957 (CH_2) 1728 (C=O), 1695 (C=O). **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.75 (t, 1H, J= 1.6 Hz, **CHO**), 6.25 (s, 1H, **CH_2**=), 5.97 (s, 1H,**CH_2**=), 2.92 (q, 2H, J= 7.3 Hz, **CH_2CH_3**), 2.66 (dt, 2H, J= 1.6, 7.3 Hz, **CH_2**CHO), 2.31-2.23 (m, 2H, 1 x **CH_2**), 1.79-1.64 (m, 2H, 1 x **CH_2**), 1.08 (t, 3H, J= 7.3 Hz, **CH_3**CH_2). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 206.9 (C=O), 202.2 (CHO), 147.7 (quat), 124.2 (CH_2=), 43.3 (CH_2), 30.9 (CH_2), 30.8 (CH_2), 21.0 (CH_2) and 8.4 (CH_3).

6-oxoheptanal 322

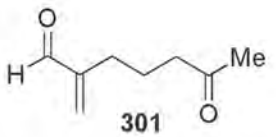


322

A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a glass stopper and a magnetic stirring bar and is charged with 1-methylcyclohexene (8.1 g, 84.2 mmol, 1 equiv), and dichloromethane (500 mL). The flask is cooled to -78 °C and ozone is bubbled through the solution when stirring. Reaction completion is judged by tlc, nitrogen is then passed through the solution and then the cold bath is removed. The solution is allowed tom warm to room temperature as it stirs under an atmosphere of nitrogen triphenylphosphine (26.5 g, 101 mmol, 1.2 equiv was added. After being stirred for 12 h, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Dichloromethane is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of dichloromethane, and the combined organic layers are washed with water. After extracting the aqueous layer with dichloromethane, the organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 20 % Et_2O, hexanes) afforded the title compound (7.99 g, 74 %) as a colorless oil .**^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.73 (1H, t, J= 1.5 Hz, **CHO**), 2.43-2.37 (m, 4H, 2 x **CH_2**), 2.07 (s, 3H, **CH_3**), 1.57-1.49 (m, 4H, 2 x **CH_2**).

^{1}H NMR data was in agreement with the literature [17]

2-methylene-6-oxoheptanal 301

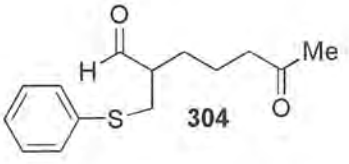


301

To a solution of 6-oxoheptanal (0.700 g, 5.47 mmol, 1 equiv) in DCM (30 mL) and NEt_3 (2.76 g, 27.35 mmol, 5 equiv) was added Böhme's salt (1.54 g, 16.41 mmol, 3 equiv). The reaction was left to stir for 18 h, and then quenched with $NaHCO_3$ and extracted three times with DCM. After completion the solvent was evaporated. Purification by column chromatography (SiO_2, 25 % Et_2O, hexanes) afforded the title compound (498 mg, 65 %) as a colorless oil; **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 9.59 (s, 1H, **CHO**), 6.43 (d, 1H, J= 0.6 Hz, **CH_2**=), 6.17 (d, 1H, J= 0.6 Hz, **CH_2**=), 2.59 (t, 2H, J= 7.3 Hz, **CH_2**C=O), 2.38 (t, 2H, J= 7.5 Hz, **CH_2CH_2**=), 2.28 (s, 3H, **CH_3**), 1.91-1.66 (m, 2H, 1 x **CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 208.3 (C=O), 194.5 (CHO), 149.6 (quat), 134.4 (CH_2=), 42.9 (CH_2), 29.9 (CH_3), 27.1 (CH_2) and 21.8 (CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature [14]

6-oxo-2-(phenylthiomethyl) heptanal 304

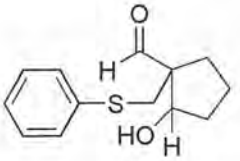


304

A solution of 2-methylene-6-oxoheptanal (0.080 g, 0.606 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) quinine (0.019 g, 0.0571 mmol, 0.1 equiv) in dry toluene (0.5 mL). The mixture was srirred for 15 min. Then a solution of thiophenol (0.074 g, 68 μL, 0.667 mmol, 1.1 equiv) was added in dry toluene (0.5 mL) was added dropwise to the solution at rt. After being stirred for 4 h, Et_2O is added and the mixture

is washed with water (50 mL). The aqueous layer is extracted with two more portions of Et_2O, and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 10 % Et_2O,hexanes) afforded the title compound (128 mg, 84 %) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3055 (CHAr), 2918 (CH_2), 1716 (C=O), 1651 (C=O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.67 (d, 1H, J= 1.9 Hz, **CHO**), 7.40-7.19 (m, 5H, **ArH**), 3.25 (ABX, 1H, J_{AB}= 13.4 Hz, J_{AX}= 6.0 Hz, J_{BX}= 7.4 Hz, **CH_2**SPh), 3.03 (ABX, 1H, J_{AB} = 13.4 Hz, J_{AX}= 6.2 Hz, J_{BX}= 7.2 Hz, **CH_2**SPh), 2.55 (m, 1H, 1 x **CH_2**), 2.42 (t, 2H, J= 6.5 Hz, **CH_2**C=O), 2.12 (s, 3H, **CH_3**), 1.79-1.48 (m, 4H, 2 x **CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 208.0 (C=O), 202.7 (C=O), 135.3 (*ipso*), 130.3 (ArH), 129.1 (ArH), 126.8 (ArH), 50.9 (CHCHO), 43.2 (CH_2), 33.0 (CH_2), 31.0 (CH_3), 27.7 (CH_2) and 20.6 (CH_2). **HRMS** (EI) *m/z* calculated for $C_{14}H_{18}O_2S$ [M] 250.1022, found 250.1017.

2-hydroxy-1-(phenylthiomethyl) cyclopentanecarbaldehyde 272

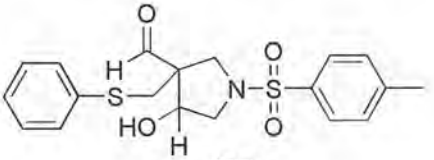


272

To a solution of 2-methylenehexanal (0.300 g, 2.4 mmol, 1 equiv) in the presence of 4 Å molecular sieves (0.05 g) in toluene (1 mL) was added thiophenol (0.290 g, 270 µl, 2.64 mmol, 1.1 equiv) and the resulting solution was stirred for 2 h at rt. Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O (2 x 100 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 10 % Et_2O, hexanes) afforded the title compound (289 mg, 51 %, 3:2 d.r.) as a colorless oil; **IR** (neat)/cm^{-1}): υ_{max} 3419 (OH), 1651 (C=O), 1088 (C-O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.76 (s, 1H, **CHO**), 9.58 (s, 1H, **CHO**), 7.41-7.20 (m,

10H, **ArH**), 4.46 (m, 1H, **CHOH**), 4.34 (m, 1H, **CHOH**), 3.43 (d, 1H, J= 12.5 Hz, **CH_2SPh**), 3.30 (d, 1H, J= 12.5 Hz, **CH_2SPh**), 3.27 (d, 2H, J= 1.5 Hz, **CH_2SPh**), 2.30-1.62 (m, 12H, 6 x **CH_2**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 204.7 (CHO), 202.9 (CHO), 136.6 (*ipso*), 136.5 (*ipso*), 130.1 (ArH), 129.9 (ArH), 129.1 (ArH), 128.9 (ArH), 126.8 (ArH), 126.7 (ArH), 80.0 (CHOH), 74.4 (CHOH), 62.5 (quat), 60.5 (quat), 39.0 (CH_2), 36.0 (CH_2), 34.0 (CH_2), 31.1 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 21.2 (CH_2) and 20.8 (CH_2). **HRMS** (EI) *m/z* calculated for $C_{13}H_{15}O_2S$ [M] 236.0866, found 236.0865

4-hydroxy-3-(phenylthiomethyl)-1-tosylpyrrolidine-3-carbaldehyde 277

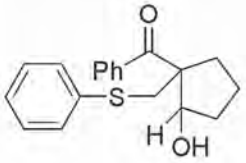


277

To a solution of N-(2-formylallyl)-4-methyl-N-(2-oxoethyl) benzenesulfonamide (0.05 g, 0.178 mmol, 1 equiv) in DCM (2.5 mL) was added thiophenol (0.022 g, 21 µl, 0.195 mmol, 1.1 equiv). The reaction was left to stir for 2 h. After completion the solvent was evaporated diethylether is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O, and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 40 % Et_2O, hexanes) afforded the title compound (48 mg, 69 %, 5:3 d.r) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3484 (OH), 2925 (CH_2), 1726 (C=O), 1090 (C-O). Major diastereomer. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.41 (s, 1H, **CHO**), 7.68 (d, 2H, J= 8.3 Hz, **ArH**), 7.36-7.24 (m, 7H, **ArH**), 4.43 (m, 1H, **CHOH**), 3.71 (d, 1H, J= 10.6 Hz, **CH**CHO), 3.49 (ABX, 1H, J_{AB} = 11.1 Hz, J_{AX}= 4.9 Hz, J_{BX}= 6.2 Hz, **CH**CHOH), 3.35 (d, 1H, J= 13.1 Hz, **CH_2SPh**), 3.3-3.24 (m, 2H, **CH_2**), 3.19 (d, 1H, J= 13.1 Hz, **CH_2SPh**), 2.43 (s, 3H, **CH_3Ar**). **^{13}C NMR** (63 MHz,$CDCl_3$) δ: 199.6 (CHO), 143.7 (*ipso*), 134.8 (*ipso*), 133.1 (*ipso*), 130.8 (ArH),

129.8 (ArH), 129.3 (ArH), 127.6 (ArH), 127.5 (ArH), 71.6 (CHOH), 62.2 (quat), 54.9 (CH_2), 50.7 (CH_2), 29.7 (CH_2) and 21.6 (CH_3). Minor diastereomer **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 9.55 (s, 1H, **CHO**), 7.70 (d, J= 8.3 Hz, 2H, **ArH**), 7.36-7.24 (m, 7H, **ArH**), 4.42 (m, 1H, **CHOH**), 3.69 (d, 1H, J= 10.7 Hz, **CH**CHO), 3.60 (ABX, 1H, J_{AB} = 10.8 Hz, J_{AX}= 5.1 Hz, J_{BX}= 5.8 Hz, **CH**CHOH), 3.36 (d, 1H, J= 10.7 Hz, **CH**CHO), 3.22 (d, 1H, J= 13.4 Hz, **CH_2**SPh), 3.17 (d, J= 10.9 Hz, **CH**CHO), 3.06 (d, 1H, J= 13.4 Hz, **CH_2**SPh), 2.43 (s, 3H, **CH_3**Ar). **^{13}CNMR** (91 MHz, $CDCl_3$) δ: 200.6 (CHO), 143.8 (*ipso*), 134.8 (*ipso*), 133.2 (*ipso*), 130.6 (ArH), 129.9 (ArH), 129.4 (ArH), 127.7 (ArH), 127.5 (ArH), 75.5 (CHOH), 60.5 (quat), 54.0 (CH_2), 50.4 (CH_2), 29.6 (CH_2) and 21.6 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{19}H_{25}O_4N_2S_2$ $[M+NH_4]^+$ 409.1250, found 409.1250.

2-hydroxy-1-(phenylthiomethyl)cyclopentyl(phenyl)methanone 269



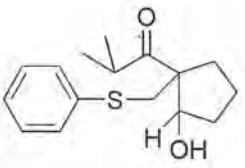
269

A solution of 5-benzoylhex-5-enol (0.080 g, 0.396 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) cinchonidine (0.012 g, 0.0396 mmol, 0.1 equiv) in dry toluene (0.5 mL). The mixture was srirred for 15 min at rt and the cooled to -20 °C. Then a solution of thiophenol (0.048 g, 44 μL, 0.436 mmol, 1.1 equiv) was added in dry toluene (0.5 mL) was added dropwise to the cooled solution at -20 °C. After being stirred for 4 h, Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O (2 x 50 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 10 % Et_2O, hexanes) afforded the title compound (113 mg, 92 %, 3:2 d.r *trans/cis*, 61 % e.e.) [iv] as a colorless solid; major

diastereomer *trans* **m.p.**= 89-91 °C (diethylether/ hexanes); **IR** (neat) cm^{-1}): υ_{max} 3465 (OH), 2955 (CH_2), 1670 (C=O), 1088 (C-O). Diastereomers were separated by column chromatography; *cis* diastereomer. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.88-7.83 (m, 2H, **ArH**), 7.49 (m, 1H, **ArH**), 7.42-7.36 (m, 2H, **ArH**), 7.20-7.09 (m, 5H, **ArH**), 4.62 (t, 1H, J= 6.6 Hz, **CHOH**), 3.67 (d, 1H, J= 12.4 Hz, **CH_2**SPh), 3.43 (d, 1H, J= 12.4 Hz, **CH_2**SPh), 2.39-1.50 (m, 6H, 3 x **CH_2**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 205.6 (C=O), 136.8 (*ipso*), 136.4 (*ipso*), 132.1 (ArH), 130.1 (ArH), 128.8 (ArH), 128.7 (ArH), 128.2 (ArH), 126.5 (ArH), 78.0 (CHOH), 61.6 (quat), 38.8 (CH_2), 34.0 (CH_2), 32.2 (CH_2) and 20.7 (CH_2). *trans* diastereomer. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.82-7.79 (m, 2H, **ArH**), 7.52-7.46 (m, 1H, **ArH**), 7.43-7.36 (m, 2H, **ArH**), 7.20-7.09 (m, 5H, **ArH**), 4.56 (m, 1H, **CHOH**), 3.37 (d, 1H, J= 12.6 Hz, **CH_2**SPh), 3.24 (d, 1H, J= 12.6 Hz, **CH_2**SPh), 3.13 (br s, 1H), 2.49 (m, 1H, 1 x **CH**), 2.22-1.93 (m, 3H, 1 x **CH_2**, 1 x **CH**), 1.84-1.75 (m, 2H, 1 x **CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 206.0 (C=O), 137.6 (*ipso*), 135.9 (*ipso*), 131.8 (ArH), 130.1 (ArH), 128.7 (ArH), 128.4 (ArH), 128.1 (ArH), 126.4 (ArH), 79.5 (CHOH), 63.7 (quat), 41.3 (CH_2), 32.2 (CH_2), 32.0 (CH_2) and 21.5 (CH_2). **HRMS** (ES+) *m/z* calculated for $C_{19}H_{21}O_2S$ $[M+H]^+$ 313.1257, found 313.1258. **HPLC** (Chiralcel AD-H, hexane/ethanol= 90/10, 1.0 mL/min, λ= 254 nm, retention time) *cis*-diastereomer (11.4, 17.2 mins), *trans*-diastereomer (14.6, 16.3 mins).

[iv] See Appendix for enantiomeric excess for compound **269**.

1-(2-hydroxy-1-(phenylthiomethyl) cyclopentyl)-2-methylpropan-1-one 291



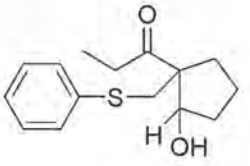
291

A solution of 7-methyl-5-methylene-6-oxooctanol (0.100 g, 0.594 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) quinine (0.019 g, 0.0594 mmol, 0.1 equiv) in dry toluene (0.5 mL). The mixture was srirred for 15 min at rt and the cooled to -20 °C. Then a solution of thiophenol (0.072 g, 66 μL, 0.654 mmol, 1.1 equiv) in dry toluene (0.5 mL) was added dropwise to the cooled solution at -20 °C. After being stirred for 6 h, Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O (2 x 100 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 10 % Et_2O, hexanes) afforded the title compound (142 mg, 86 %, 7:1 d.r.,70 % e.e.)[iii]) [v] as a colorless oil; IR (neat)/ cm^{-1}): υ_{max} 3462 (OH), 1696 (C=O), 1090 (C-O). Inseparable mixture of diastereomers. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.32-7.15 (m, 5H, **ArH**), 4.37 (m, 1H, **CHOH**), 3.20 (d, 1H, J= 12.2 Hz, **CH_2**SPh), 3.05 (d, 1H, J= 12.5 Hz, **CH_2**SPh), 3.06-2.95 (sept, 1H, **CH**$(CH_3)_2$), 2.14-1.44 (m, 6H, 3 x **CH_2**), 1.07 (d, 6H, J= 6.6 Hz, **$(CH_3)_2$**CH). *trans* diastereomer diagnostic peaks: **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 4.25 (m, 1H, **CHOH**), 3.43 (d, 1H, J= 11.9 Hz, **CH_2**SPh), 3.22 (d, 1H, J= 11.9 Hz, **CH_2**SPh). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 219.7 (C=O), 218.1 (C=O), 136.7 (*ipso*), 136.7 (*ipso*), 129.5 (ArH), 129.3 (ArH), 129.0 (ArH), 129.0 (ArH), 126.4 (ArH), 126.3 (ArH), 78.7 (CHOH), 75.9 (CHOH), 64.6 (quat), 63.1 (quat), 39.7 (CH_2), 37.4 ($CH(CH_3)_2$), 36.8 (CH_2), 36.1 ($CH(CH_3)_2$), 32.3 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 21.1 (CH_2), 20.5 (CH_2), 20.4 (CH_3) and 19.8 (CH_3). **HRMS** (ES+) *m/z* calculated for $C_{16}H_{23}O_2S$ $[M+H]^+$ 279.1413, found 279.1410. **HPLC** (Chiralcel AD-H, hexane/isopropanol= 90/10, 1.0

mL/min, λ = 254 nm, retention time) *trans*-minor diastereomer (6.2, 7.2 mins), *cis*-major diastereomer (7.8, 16.8 mins).

[v] See Appendix for enantiomeric excess for compound **291**.

1-(2-hydroxy-1-(phenylthiomethyl) cyclopentyl) propan-1-one 299



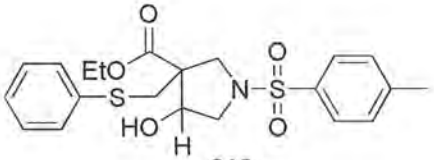
299

A solution of 5-methylene-6-oxooctanal (0.080 g, 0.519 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) quinine (0.017 g, 0.0519 mmol, 1 equiv) in dry toluene (0.5 mL). The mixture was stirred for 15 min at rt and the cooled to -40 °C. Then a solution of thiophenol (0.063 g, 58 μL, 0.570 mmol, 1.1 equiv) dry toluene (0.5 mL) was added dropwise to the cooled solution at -40 °C. After being stirred for 8 h, Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O (2 x 100 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 15 % Et_2O, hexanes) afforded the title compound as an inseparable mixture of diastereomers. (108 mg, 79 %, 3:2 d.r.) [v] as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3466 (OH), 2928 (CH_2), 1671 (C=O), 1088 (C-O). **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.36-7.15 (m, 10H, **ArH**), 4.26 (m, 1H, **CHOH**), 3.21 (d, 1H, J= 12.3 Hz, **CH_2**SPh), 3.04 (d, 1H, J= 12.3 Hz, **CH_2**SPh), 2.59-2.49 (dq, 4H, J= 3.4, 7.1 Hz, **CH_2**CH_3), 2.25-1.62 (m, 12H, 6 x **CH_2**), 0.99 (dt, 3H, J= 2.9, 7.1 Hz, (**CH_3**CH_2). Minor diastereomer diagnostic peaks: **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 4.37 (m, 1H, **CHOH**), 3.47 (d, 1H J= 12.3 Hz, **CH_2**SPh), 3.25 (d, 1H, J= 12.4 Hz, **CH_2**SPh). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 215.0 (C=O), 214.1 (C=O), 136.4 (*ipso*), 136.3 (*ipso*), 129.9 (ArH), 129.6 (ArH), 129.0 (ArH), 126.6 (ArH), 126.5 (ArH), 125.5 (ArH), 79.2 (CHOH), 76.0

(CHOH), 63.8 (quat), 62.4 (quat), 40.3 (CH_2), 37.0 (CH_2), 34.7 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 30.8 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 20.9 (CH_2), 20.3 (CH_2), 7.8 (CH_3) and 7.5 (CH_3). **HRMS** (EI) *m/z* calculated for $C_{15}H_{20}O_2S$ [M] 264.1186, found 264.1178. **HPLC** (Chiralcel AD-H, hexane/isopropanol= 95/5, 1.0 mL/min, λ= 254 nm, retention time) *cis-trans* diastereomers (12.0, 12.7, 13.8, 28.9 mins).

[v] See Appendix for enantiomeric excess for compound **299**.

Ethyl-4-hydroxy-3-(phenylthiomethyl)-1-tosylpyrrolidine-3-carboxylate 310

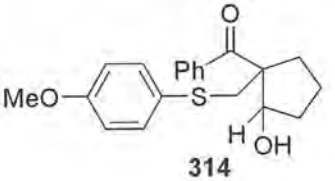


310

A solution of Ethyl-2-((4-methyl-N-(2-oxoethyl) phenylsulfonamide) methylacrylate (0.050 g, 0.154 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) quinine (0.005 g, 0.0154 mmol, 0.1 equiv) in dry toluene (0.5 mL). The mixture was srirred for 15 min at rt. Then a solution of thiophenol (0.019 g, 17 μL, 0.169 mmol, 1.1 equiv) was added in dry toluene (0.5 mL) was added dropwise to the solution at. After being stirred for 8 h, Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O (2 x 100 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 20 % EtOAc, hexanes) afforded the title compound (46 mg, 68 %, 5:4 d.r, 25 % e.e.) as a colorless oil. **IR** (neat)/ cm^{-1}): υ_{max} 3449 (OH), 2925 (CH_2), 1731 (C=O), 1161 (C-O). Diastereomers were separated by column chromatography. Major diastereomer. **^{1}H NMR** (250 MHz,$CDCl_3$) δ: 7.67 (2H, d, J= 8.2 Hz, **ArH**), 7.32-7.22 (m,7H, **ArH**), 4.52 (m, 1H, **CHOH**), 3.82 (q, 2H, J= 7.1 Hz, **CH_2**CH_3), 3.76 (d, 1H, J= 7.5 Hz, **CH**COH), 3.58 (ABX, 1H, J_{AB}= 10.8 Hz, J_{AX}= 5.2 Hz, J_{BX}= 5.6 Hz, **CH**COH), 3.31 (d, 1H, J= 12.9 Hz,

CH_2SPh), 3.25 (1H, d, J= 3.0 Hz, **CH**C=O), 3.19 (1H, d, J= 3.0 Hz, **CH**C=O), 3.04 (1H, d, J= 13.0 Hz, **CH_2SPh**), 2.39 (3H, s, **CH_3Ar**), 1.09 (3H, t, J = 7.2 Hz, **CH_3CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 171.7 (COO), 143.6 (*ipso*), 135.1 (*ipso*), 133.6 (*ipso*), 131.0 (ArH), 129.6 (ArH), 129.0 (ArH), 127.5 (ArH), 127.1 (ArH), 72.7 (CHOH), 61.6 (CH_2CH_3), 58.2 (quat), 54.1 (CH_2), 52.9 (CH_2), 35.4 (CH_2), 21.5 (CH_3Ar) and 13.8 (CH_3CH_2). Minor diastereomer. **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 7.72-7.67 (d, 2H, J= 8.3 Hz, **ArH**), 7.31-7.18 (m, 7H, **ArH**), 4.29 (m, 1H, **CHOH**), 3.88 (q, 2H, J= 7.2 Hz, **CH_2CH_3**), 3.59 (s, 2H, **CH_2C=O**), 3.26 (d, 1H, J= 2.3 Hz, **CH**COH), 3.21 (d, 1H, J= 2.3 Hz, **CH**COH), 3.11 (d, 1H, J= 13.3 Hz, **CH_2SPh**), 2.91 (d, 1H, J= 13.3 Hz, **CH_2SPh**), 2.38 (s, 3H, **CH_3ArH**), 1.1 (t, 3H, J= 7.2 Hz, **CH_3CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 171.0 (COO), 143.7 (*ipso*), 135.0 (*ipso*), 133.5 (*ipso*), 130.6 (ArH), 129.7 (ArH), 129.0 (ArH), 127.5 (ArH), 127.0 (ArH), 74.6 (CHOH), 61.7 (CH_3CH_2), 58.6 (quat), 53.4 (CH_2), 51.3 (CH_2), 38.5 (CH_2), 21.5 (CH_3Ar) and 13.8 (CH_3CH_2). **HRMS** (ES+) *m/z* calculated for $C_{21}H_{26}O_5NS_2$ $[M+H]^+$ 436.1247, found 436.1249. **HPLC** (Chiralcel AD-H, hexane/isopropanol = 90/10, 1.0 mL/min, λ= 254 nm, retention time) minor diastereomer (36.3, 80.1 mins), major diastereomer (44.2, 47.4 mins).

2-hydroxy-1-((4-methoxyphenylthio) methyl) cyclopentyl (phenyl) methanone 314

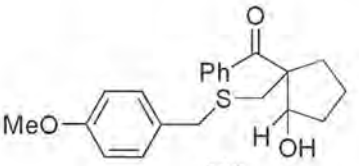


314

A solution of 5-benzoylhex-5-enol (0.072 g, 0.356 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) quinine (0.012 g, 0.0356 mmol, 0.1 equiv) in dry toluene (0.5 mL). The mixture was srirred for 15 min. Then a solution of 4-methoxybenzenethiol (0.055 g, 48 μL, 0.392 mmol, 1.1 equiv) in dry toluene (0.5 mL) was added dropwise to the solution at -40 °C. After being stirred for 12 h, Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more

portions of Et_2O (2 x 100 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 20 % Et_2O, hexanes) afforded the title compound (85 mg, 70 %, 3:1 d.r.) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3487 (OH), 2959 (CH_2), 1671 (C=O), 1088 (C-O). Diastereomers were separated by column chromatography; minor diastereomer **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.87-7.77 (m, 2H, **ArH**), 7.54-7.35 (m, 3H, **ArH**), 7.15-7.07 (m, 2H, **ArH**), 6.73-6.66 (m, 2H, **ArH**), 4.54 (m, 1H, **CHOH**), 3.74 (s, 3H,**OCH_3**Ar), 3.29 (d, 1H, J= 12.8 Hz, **CH_2**SPh), 3.17 (d, 1H, J= 12.9 Hz, **CH_2**SPh), 2.54-1.66 (m, 6H, 3 x **CH_2**). **^{13}C NMR** (91 MHz,$CDCl_3$) δ: 205.3 (C=O), 159.1 (OMe *ipso*), 136.8 (*ipso*), 134.1 (ArH), 133.7 (ArH), 132.0 (*ipso*), 128.7 (ArH), 128.2 (ArH), 114.5 (ArH), 77.9 (CHOH), 61.9 (quat), 55.3 (OCH_3), 41.0 (CH_2), 34.2 (CH_2), 32.3(CH_2), 20.8 (CH_2). Major diastereomer. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.87-7.83 (m, 2H, **ArH**), 7.58-7.36 (m, 3H, **ArH**), 7.15-7.10 (m, 2H, **ArH**), 6.72-6.67 (m, 2H, **ArH**), 4.62 (m, 1H, **CHOH**), 3.75 (s, 3H, **OCH_3**Ar), 3.59 (d, 1H, J= 12.7 Hz, **CH_2**SPh), 3.37 (d, 1H, J= 12.7 Hz, **CH_2**SPh), 2.41-1.56 (m, 6H, 3 x **CH_2**). **^{13} C NMR** (91 MHz, $CDCl_3$) δ: 206.1 (C=O), 159.1 (OMe *ipso*), 137.8 (*ipso*), 133.8 (ArH), 131.9 (*ipso*), 128.7 (ArH), 128.4 (ArH), 128.2 (ArH), 114.5 (ArH), 79.6 (CHOH), 64.1 (quat), 55.3 (OCH_3), 43.6 (CH_2), 32.5 (CH_2), 32.2 (CH_2) and 21.7 (CH_2). **HRMS** (ES+) *m/z* calculated for $C_{20}H_{22}O_3S$ 342.1283, found 342.1284. **HPLC** (Chiralcel AD-H, hexane/isopropanol= 99/1, 1.0 mL/min, λ= 254 nm, retention time) mixture of diastereomers minor (42.2, 49.9 mins), major (48.7, 56.3 mins).

1-((4-methoxybenzythio)methyl-2-hydroxycyclopentyl)phenylmethanone 311

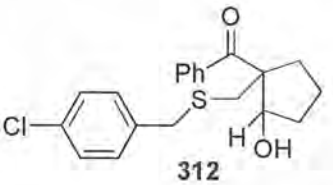


311

A solution of 5-benzoylhex-5-enol (0.070 g, 0.346 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) quinine (0.012 g, 0.0346 mmol, 0.1 equiv) in dry toluene (0.5 mL). The mixture was srirred for 15 min. Then a solution of 4-methoxytoluenethiol (0.059 g, 53 μL, 0.381 mmol, 1.1 equiv) in dry toluene (0.5 mL) was added dropwise to the solution at -40 °C. After being stirred for 48 h, Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O, and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 20% Et_2O, hexanes) afforded the title compound (83 mg, 67 %, 3:2 d.r) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3458 (OH), 2916 (CH_2), 1671 (C=O), 1095 (C-O); Inseparable mixture of diastereomers. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.86-7.77 (m, 4H, **ArH**), 7.58-7.51 (m, 2H, **ArH**), 7.47-7.37 (m, 4H, **ArH**), 7.07-7.00 (m, 4H, **ArH**), 6.78-6.73 (m, 4H, **ArH**), 4.45 (m, 1H, **CHOH**), 3.78 (s, 6H, **OCH_3**Ar), 3.44 (s, 2H, **CH_2**Ar), 2.81 (d, 1H, J= 12.9 Hz, **CH_2**SPh), 2.70 (d, 1H, J= 12.9 Hz, **CH_2**SPh), 2.20-1.51 (m, 12H, 6 x **CH_2**). Minor diastereomer diagnostic peaks: **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 4.56 (m, 1H, **CHOH**), 3.09 (d, 1H, J= 12.6 Hz **CH_2**SPh), 2.90 (d, 1H, J= 12.6 Hz, **CH_2**SPh). **^{13} C NMR** (91 MHz, $CDCl_3$) δ: 206.5 (C=O), 205.8 (C=O), 158.7 (OMe *ipso*), 158.6 (OMe *ipso*), 137.8 (*ipso*), 136.9 (*ipso*), 132.0 (ArH), 131.9 (ArH), 129.8. (ArH), 129.8. (ArH), 129.6 (ipso), 129.5 (ipso), 128.6 (ArH), 128.3 (ArH), 128.2 (ArH), 128.2 (ArH), 113.8 (ArH), 113.8 (ArH), 79.7 (CHOH), 76.8 (CHOH), 63.8 (quat), 61.5 (quat), 55.2 (CH_3), 37.4 (CH_2), 37.1 (CH_2), 36.9 (CH_2), 35.0 (CH_2), 34.1 (CH_2), 32.4 (CH_2), 32.1 (CH_2) 32.0 (CH_2), 21.5 (CH_2). and 20.6 (CH_2). **HRMS** (EI) *m/z* calculated

for $C_{21}H_{24}O_3S$ [M] 356.1445, found 356.1440. **HPLC** (Chiralcel AD-H, hexane/isopropanol= 95/5, 1.0 mL/min, λ= 254 nm, retention time) mixture of diastereomers (42.0, 46.2, 51.5 mins).

1-((4-chlorobenzythio)methyl-2-hydroxycyclopentyl)phenylmethanone 312

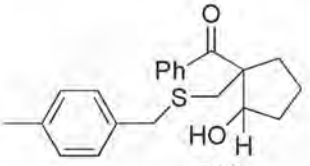


312

A solution of 5-benzoylhex-5-enol (0.060 g, 0.297 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) quinine (0.010 g, 0.0297 mmol, 0.1 equiv) in dry toluene (0.5 mL). The mixture was srirred for 15 min. Then a solution of 4-chlorobenzenemethanethiol (0.052 g, 44 μL, 0.327 mmol, 1.1 equiv) was added in dry toluene (0.5 mL) was added dropwise to the solution at -40 °C. After being stirred for 42 h, Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O (2 x 100 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 30 % Et_2O, hexanes) afforded the title compound (89 mg, 78 %, 4:3 d.r) as a colorless oil; **IR** (neat)/cm^{-1}): υ_{max} 3464 (OH), 2916 (CH_2), 1671 (C=O), 1091 (C-O). Inseparable mixture of diastereomers. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.86-7.75 (m, 4H, **ArH**), 7.61-7.35 (m, 6H, **ArH**), 7.19-7.12 (m, 4H, **ArH**), 7.05-6.99 (m, 4H, **ArH**), 4.56 (t, 1H, J= 6.2 Hz, **CHOH**), 3.44 (s, 4H, 1 x **CH_2**Ar), 2.79 (d, 1H, J= 12.7 Hz, **CH_2**SPh), 2.68 (d, 1H, J= 12.7 Hz, **CH_2**SPh), 2.46-2.34 (m, 4H, 2 x **CH_2**), 2.28-2.18 (m, 4H, 2 x **CH_2**), 2.11-1.52 (m, 4H, 2 x **CH_2**). Minor diastereomer diagnostic peaks: **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 4.44 (m, 1H, **CHOH**), 3.10 (d, 1H, J= 12.5 Hz, **CH_2**SPh), 2.87 (d, 1H, J= 12.5 Hz, **CH_2**SPh). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 206.3 (C=O), 205.5 (C=O), 137.6 (*ipso*), 136.8 (*ipso*), 136.7 (*ipso*), 136.3 (*ipso*), 136.1 (*ipso*), 133.4 (ArH), 132.7 (*ipso*), 132.1 (ArH), 130.2 (ArH), 130.1 (ArH), 128.8 (ArH), 128.7

(ArH), 128.6 (ArH), 128.5 (ArH), 128.4 (ArH), 128.3 (ArH), 79.8 (CHOH), 76.8 (CHOH), 63.6 (quat), 61.4 (quat), 37.5 (CH_2), 36.9 (CH_2), 36.7 (CH_2), 35.2 (CH_2), 34.2 (CH_2), 33.4 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 21.5 (CH_2) and 20.7 (CH_2). **HRMS** (EI) *m/z* calculated for $C_{20}H_{21}O_2ClS$ [M] 360.0949, found 360.0945. **HPLC** (Chiralcel AD-H, hexane/isopropanol= 90/10, 1.0 mL/min, λ= 254nm, retention time) mixture of diastereomers (24.5, 30.1, 37.3, 39.8 mins).

1-((4-methylbenzythio)methyl-2-hydroxycyclopentyl)phenylmethanone 313



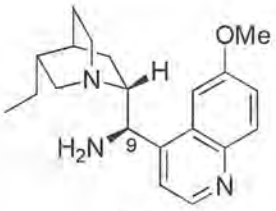
313

A solution of 5-benzoylhex-5-enol (0.065 g, 0.321 mmol, 1 equiv) in toluene (1 mL) was added to a stirred solution of (-) quinine (0.011 g, 0.0321 mmol, 0.1 equiv) in dry toluene (0.5 mL). The mixture was stirred for 15 min. Then a solution of 4-toluenemethanethiol (0.049 g, 53 μL, 0.353 mmol, 1.1 equiv) in dry toluene (0.5 mL) was added dropwise to the solution at -40 °C. After being stirred for 42 h, Et_2O is added and the mixture is washed with water. The aqueous layer is extracted with two more portions of Et_2O (2 x 50 mL), and the combined organic layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 30% Et_2O, hexanes) afforded the title compound (80 mg, 73 %, 3:2 d.r., 32 % e.e.) as a colorless oil; **IR** (neat)/ cm^{-1}): υ_{max} 3406 (OH), 1668 (C=O), 1094 (C-O). Diastereomers were separated by column chromatography; minor diastereomer **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.85-7.76 (m, 2H, **ArH**), 7.54-7.36 (m, 3H, **ArH**), 7.04-6.98 (m, 4H, **ArH**), 4.45 (m, 1H, **CHOH**), 3.45 (s, 2H, **CH_2**Ar), 2.81 (d, 1H, J= 12.9 Hz, **CH_2**SPh), 2.70 (d, 1H, J= 12.9 Hz, **CH_2**SPh), 2.30 (s, 3H, **CH_3**Ar),

2.12-1.48 (m, 6H, 3 x **CH_2**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 206.6 (C=O), 137.9 (*ipso*), 137.0 (*ipso*), 134.5 (*ipso*), 131.9 (ArH), 129.1 (ArH), 128.7 (ArH), 128.4 (ArH), 128.2 (ArH), 79.7 (CHOH), 63.8 (quat), 37.5 (CH_2), 37.2 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 21.5 (CH_3), 21.1 (CH_2). Major diastereomer **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 7.84-7.80 (m, 2H, **ArH**), 7.55-7.36 (m, 3H, **ArH**),7.04 (s, 4H, **ArH**), 4.55 (m, 1H, **CHOH**), 3.45 (s, 2H, **CH_2**Ar), 2.91 (d, 1H, J= 12.5 Hz, **CH_2**SPh), 2.91 (d, 1H, J= 12.5 Hz, **CH_2**SPh), 2.31 (s, 3H, **CH_3**Ar), 2.51-1.49 (m, 6H, 3 x **CH_2**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 205.8 (C=O), 137.0 (*ipso*), 136.6 (*ipso*), 134.6 (*ipso*), 132.0 (ArH), 129.1 (ArH), 128.6 (ArH), 128.4 (ArH), 128.2 (ArH), 76.9 (CHOH), 61.5 (quat), 37.1 (CH_2), 35.1 (CH_2), 34.1 (CH_2), 32.1 (CH_2), 21.1 (CH_3) and 20.7 (CH_2). **HRMS** (EI) *m/z* calculated for $C_{21}H_{24}O_2S$ [M] 340.14908, found 340.14915. **HPLC** (Chiralcel AD-H, hexane/isopropanol= 95/5, 1.0 mL/min, λ= 254 nm), retention time: minor diastereomer (12.5, 16.3 mins), major diastereomer (13.8, 17.9 mins).

Synthesis of cinchona alkaloid catalysts

(1*R*)-(8-ethylquinuclidin-2-yl) (6-methoxyquinolin-4-yl) methanamine 101



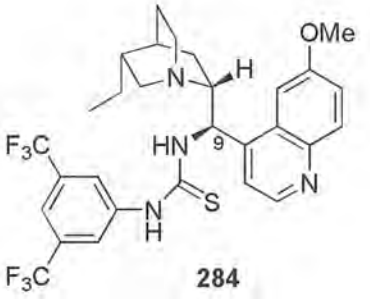
101

Hydroquinine (3.5 g, 10.7 mmol, 1 equiv) and triphenylphosphine (3.38 g, 12.9 mmol, 1.2 equiv) were dissolved in 50 mL of dry THF and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (2.61 g, 12.9 mmol, 1.2 equiv) was added all at once. Then a solution of diphenyl phosphoryl azide (3.56 g, 12.9 mmol, 1.2 equiv) in 20 mL of dry THF was added dropwise at 0 °C. The mixture was allowed to warm to rt. After being stirred for 12 h, the solution was heated to 50 °C for 2 h. Then triphenylphosphine (3.65 g, 13.91 mmol, 1.3 equiv) was added and heating was maintained until gas evolution had ceased (2 h). The solution was cooled to room temperature and 1 mL of water was added and the solution was stirred for 3 h. Solvents were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and 10% HCl (1:1, 100 mL). The aqueous phase was washed with CH_2Cl_2 (4 x 50 mL). Then the aqueous phase was made alakline with excess cc. aqueous ammonia and was washed with CH_2Cl_2 (4 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, EtOAc/ MeOH/ cc. aq. NH_4OH= 50/ 50/ 1) afforded the title compound (3.02 g, 87 %) as a yellowish viscous oil. **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 8.73 (d, 1H, J= 4.7Hz, **ArH**), 8.11 (d, 1H, J= 9.1Hz, **ArH**), 7.70 (br, s, 1H, **ArH**), 7.65 (d, 1H, J = 4.4Hz, **ArH**), 7.49 (d, 1H, J= 2.7, 9.2Hz, **ArH**), 4.77 (d, 1H, J= 10.2Hz, **CH**NH_2), 4.00 (s, 3H, O**C**H_3), 3.33 (dddd, 1H, J= 2.2, 7.8, 10.5, 15.5Hz, **CH**), 3.29 (dd, 1H, J= 9.8, 13.6Hz, **CH**), 3.19 (q, 1H, J= 10.7Hz, **CH**), 2.85 (ddd, 1H, J= 4.9, 13.7, 15.5 Hz, **CH**), 2.61 (ddd, 1H, J= 2.3, 4.7, 13.5Hz, **CH**), 1.71-1.33 (m, 8H),

0.89 (t, 3H, J= 7.3Hz, **CH_3CH_2**).[13] **C NMR** (91MHz, $CDCl_3$)δ: 157.9 (OMe *ipso*), 147.4 (*ipso*), 146.5 (ArH), 143.2 (*ipso*), 129.6 (ArH), 128.2 (*ipso*), 121.5 (ArH), 119.2 (ArH), 101.0 (ArH), 61.3 (CHN), 56.8 (CH_2), 54.3 (OCH_3), 50.4 ($CHNH_2$), 39.9 (CH_2), 36.7 (CH), 27.4 (CH_2CH_3), 26.7 (CH_2), 24.9 (CH_2), 24.7 (CH) and 10.4 (CH_3CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [18]

1-(3, 5-bis (trifluoromethyl) phenyl)-3-3(*R*)-(8-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)thiourea 284



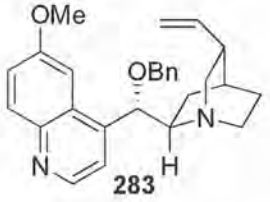
284

To a solution of 9-amino(9-deoxy)*epi*-hydroquinine **101** (0.5 g, 1.54 mmol, 1 equiv) in dry THF (5 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.422 g, 1.54 mmol, 1 equiv) in 5 mL of dry THF at ambient temperature. The mixture was stirred overnight and the solvent was removed in vacuo. Purification by column chromatography (SiO_2, EtOAc/ MeOH/ cc. aq. NH_4OH= 300/ 5/ 1) afforded the title compound (716 mg, 78 %) as an off white amorphous solid; **^{1}H NMR** (250 MHz, CDOD) δ: 8.58 (d, 1H, J= 4.7Hz, **ArH**), 8.00 (br, s, 2H, **ArH**), 7.96 (d, 1H, J= 2.6Hz, **ArH**), 7.94 (d, 1H, J= 9.3Hz, **ArH**), 7.49 (br, s, 1H, **ArH**), 7.47 (d, 1H, J= 4.8Hz, **ArH**), 7.36 (dd, 1H, J= 2.7, 9.3Hz, **ArH**), 6.31 (d, 1H, J= 11.0Hz, **CH**NH_2), 3.91 (s, 3H, O**CH_3**), 3.45 (dddd, 1H, J= 2.3, 7.8, 10.5, 15.6Hz, **CH**ax), 3.26 (q, 1H, J= 10.7Hz, **CH**eq), 3.17 (dd, 1H, J= 9.9, 13.6 Hz, **CH**N), 2.71 (ddd, 1H, J= 4.9, 13.8, 15.6Hz, **CH**eq), 2.43 (ddd, 1H, J= 2.3, 4.7, 13.6Hz, **CH**N), 1.59 (br, m, 2H, CH_2), 1.41 (br m, 1H, **CH**CH_2), 1.28 (br m, 1H, **CH**), 1.27 (ddd, 1H, J= 2.7, 10.4, 13.3Hz,

CHeq), 1.21 (m, 2H, **CH$_2$**CH$_3$), 0.75 (t, 3H, J= 7.3Hz, **CH$_3$**CH$_2$), 0.61 (dd, 1H, J= 10.4, 13.3Hz, **CH**ax). **^{13}C NMR** (91 MHz, CDOD) δ:180.7 (C=S), 157.8 (OMe *ipso*), 146.4 (ArH), 145.5 (*ipso*), 143.3 (*ipso*), 141.2 (*ipso*), 130.6 (q, J_{CF}= 33.0 Hz, ipso), 129.4 (ArH), 128.3 (*ipso*), 121.8 (q, J_{CF}= 272.2 Hz, CF_3), 121.3 (ArH), 121.1 (ArH), 119.3 (ArH), 115.0 (ArH), 102.3 (ArH), 59.6 (CHN), 56.5 (CH_2), 54.7 (OCH_3), 54.1 (CH_2), 41.2 (CH_2), 36.3 ($CHCH_2$), 27.1 (CH_2), 26.4 (CH_2CH_3), 24.7 (CH_2), 24.5 (CH_2) and 10.4 (CH_3CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [19]

2-((*S*)-benzyloxy (6-methoxyquinolin-4-yl) methyl)-8-vinylquinuclidine 283



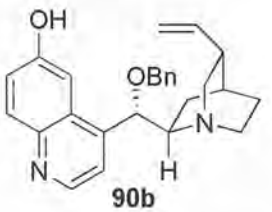
283

To a solution of (+) quinidine (1.0 g, 3.08 mmol, 1 equiv) in DMF (10 mL) was added NaH (0.300 g, 60% suspension in mineral oil, 2.5 equiv). The resulting mixture was stirred at room temperature for 1 h, benzylchloride (0.429 g, 3.39 mmol, 1.1 equiv) was added dropwise via syringe over 10 minutes. The resulting mixture was stirred overnight. When the reaction was complete, brine was added carefully and the resulting mixture was extracted with EtOAc. The organic phase was washed with brine and the combined layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 95 % EtOAc/ MeOH) afforded the title compound (1.05 g, 82 %) as yellowish oil; **^{1}H NMR** (360 MHz, $CDCl_3$) δ: 8.68 (d, 1H, J= 4.5 Hz, **ArH**), 7.97 (d, 1H, J= 9.3 Hz, **ArH**), 7.40 (d, 1H, J= 4.5 Hz, **ArH**), 7.32-7.20 (m,7H, **ArH**), 5.90 (m, 1H, **CH**=CH_2), 5.24 (br, 1H, 1 x **CH**), 4.93 (m, 1H, **CH**=CH_2), 4.89 (s, 1H, **CH**=CH_2), 4.41 (d, 1H, J= 11.4 Hz, **CH$_2$**OBn),

4.33 (d, 1H, J= 11.4 Hz, **CH_2**OBn), 3.84 (s, 3H, **OCH_3**), 3.22 (m, 1H,**CH**), 2.99 (m, 1H, **CH**), 2.90-2.63 (m, 3H, 3 x **CH**), 2.20-1.95 (m, 2H, 2 x **CH**), 1.68 (br, m, 1H, **CH**), 1.49-1.36 (m, 2H, 2 x **CH**) , 1.26-1.14 (m, 1H, 1 x **CH**). **^{13}C NMR** (91 MHz, $CDCl_3$) δ: 157.9 (OMe *ipso*), 147.7 (ArH), 144.8 (*ipso*), 144.7 (*ipso*), 140.6 ($CHCH_2$=), 137.9 (*ipso*), 131.9 (ArH), 128.5 (*ipso*), 128.0 (ArH), 127.9 (ArH), 127.6 (*ipso*), 121.9 (ArH), 119.1 (ArH), 114.6 (CH_2=), 101.3 (ArH), 80.6 (CHC-O), 71.4 (CH_2OBn), 60.2 (CHN), 55.8 (OCH_3), 50.2(CH_2), 49.5 (CH_2), 40.1 (CH), 28.2 (CH), 26.5 (CH_2) and 22.2 (CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [20]

4((*S*)-benzyloxy(8-vinylquinuclidin-2-yl) methyl) quinolin-6-ol, 90b



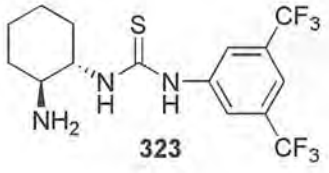
90b

A suspension of 2-((*S*)-benzyloxy (6-methoxyquinolin-4-yl) methyl)-8-vinylquinuclidine **283** (0.400 g, 0.965 mmol, 1 equiv) and NaSEt (0.324 g, 3.86 mmol, 4 equiv) in dry DMF was stirred at 110 °C until tlc analysis showed that the starting material had been consumed. The reaction mixture was cooled down to room temperature, mixed with sat NH_4Cl and H_2O. The resulting mixture was extracted with EtOAc. The organic phase was washed with brine and the combined layers are dried over magnesium sulphate, filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 98% EtOAc/ MeOH) then 90 % EtOAc/ MeOH) afforded the title compound (294 mg, 76 %) as a yellowish powder. **^{1}H NMR** (250 MHz, $CDCl_3$) δ: 10.83 (br, 1H, Ar**OH**), 8.58 (d, 1H, J= 4.5 Hz, **ArH**), 7.93 (d, 1H, J= 9.3 Hz, **ArH**), 7.77 (s, 1H, **ArH**), 7.35 (br, 1H, **ArH**), 7.27 (dd, 1H, J= 2.4, 8.8 Hz, **ArH**), 7.20-7.15 (m ,5H, **ArH**), 5.84

(m, 1H, **CH**=CH_2), 5.45 (br, 1H, 1 x **CH**), 4.87 (d, 1H, J= 10.0 Hz), 4.85 (s, 1H, 1 x **CH**), 4.25 (d, 1H, J= 11.4 Hz, $\mathbf{CH_2}$OBn), 4.18 (d, 1H, J= 11.4 Hz, $\mathbf{CH_2}$OBn), 3.47 (br, 1H, 1 x **CH**), 2.97-2.94 (m, 2H, 2 x **CH**), 2.79-2.70 (m, 2H, 2 x **CH**), 2.17-2.15 (m, 2H, 2 x **CH**) 1.65 (br, 1H, 1 x **CH**), 1.43-1.30 (m, 2H, 2 x **CH**), 1.02 (br, 1H, 1 x **CH**).**^{13}C NMR** (91 MHz, $CDCl_3$) δ: 157.2 (ArOH), 147.1 (ArH), 144.3 (*ipso*), 144.2 (*ipso*), 140.1 ($CHCH_2$=), 137.3 (*ipso*), 131.4 (ArH), 128.0 (*ipso*), 127.6 (ArH), 127.3 (ArH), 127.2 (*ipso*), 121.3 (ArH), 118.8 (ArH), 114.1 (CH_2=), 100.8 (ArH), 80.1 (CHCO), 71.0 (CH_2OBn), 58.7 (CHN), 48.8 (CH_2), 49.1 (CH_2), 39.7 (CH), 27.8 (CH), 26.0 (CH_2) and 21.7 (CH_2).

^{1}H NMR and ^{13}C NMR data was in agreement with the literature. [20]

1-(3, 5-bis (trifluoromethyl) phenyl-3-((1*S*, 2*S*)-2-aminocyclohexyl) thiourea 323 [21]



323

3,5-bistrifluoromethylphenylisothiocyanate (0.600 g, 2.21 mmol, 405 µl, 1 equiv) was added over a period of 1 h to a stirred solution of (1*S*, 2*S*)-(+)-1,2 diaminocyclohexane (0.252 g, 2.21 mmol, 1 equiv) in dry dichloromethane (11 mL). The reaction mixture was stirred for a further 3 h at rt. The solvent was concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 75 % EtOAc/EtOH) to afford the title compound (485 mg, 57 %) as a crystalline yellow solid; **m.p.** = 97-99 °C (EtOAc/ EtOH). **IR** (neat)/ cm^{-1}): υ_{max} 3252 (NH), 2936 (CH_2), 1587 (NH_2), 1176 (CF_3), 1132 (CF_3). **^{1}H NMR** (360 MHz, MeOH) δ: 8.23 (s, 2H, **ArH**), 7.67 (s, 1H, **ArH**), 4.26 (m, 1H, **CH**), 2.64 (m, 1H, **CH**), 2.19-2.05 (m, 2H, 1 x $\mathbf{CH_2}$), 1.82-1.79 (m, 2H, 1 x $\mathbf{CH_2}$), 1.42-1.32 (m, 4H, 2 x $\mathbf{CH_2}$). **^{13}C NMR** (91 MHz, MeOH) δ: 183.4 (C=S), 143.8 (*ipso*),

132.7 (q, CF_3, J= 190.4 Hz), 127.4 (ArH), 124.4 (ArH), 118.7 (ArH), 61.9 (CH), 56.4 (CHNC=S), 35.7 (CH_2), 33.0 (CH_2), 26.4 (CH_2) and 26.3 (CH_2).**[α]** $^{25}_{D}$=-76.2 (c= 1.0 in $CHCl_3$). **HRMS** (EI) *m/z* calculated for $C_{15}H_{17}N_3S_6$ [M] 385.1040, found 385.1041.

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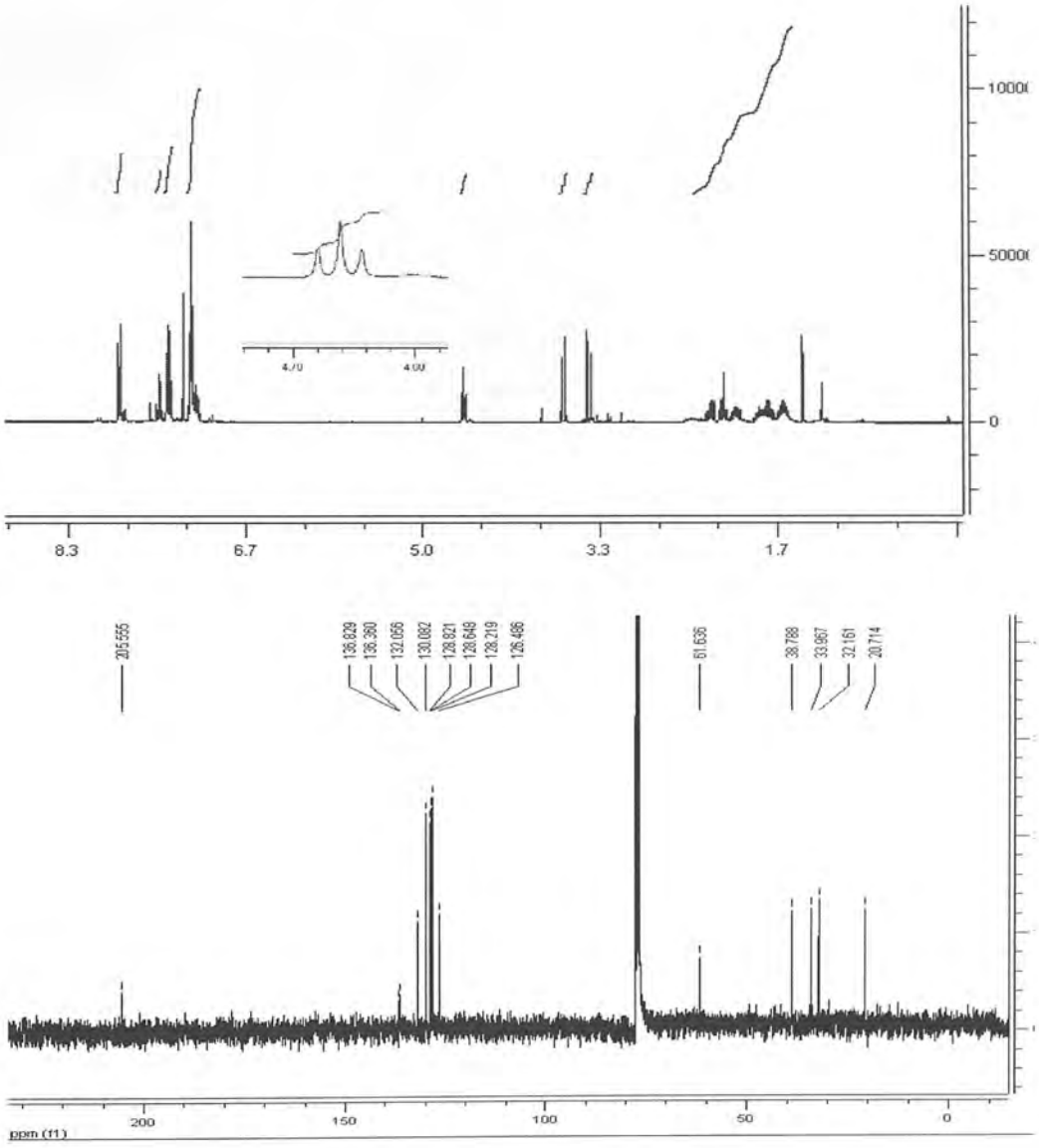
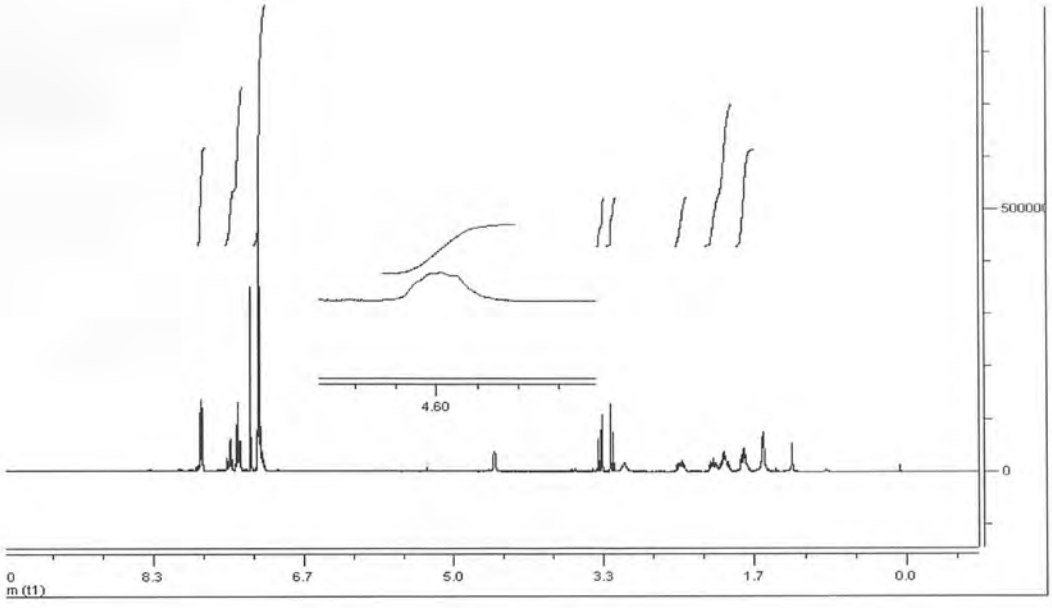
Appendix 1: ^{1}H and ^{13}C NMR Data

Spectroscopic Data

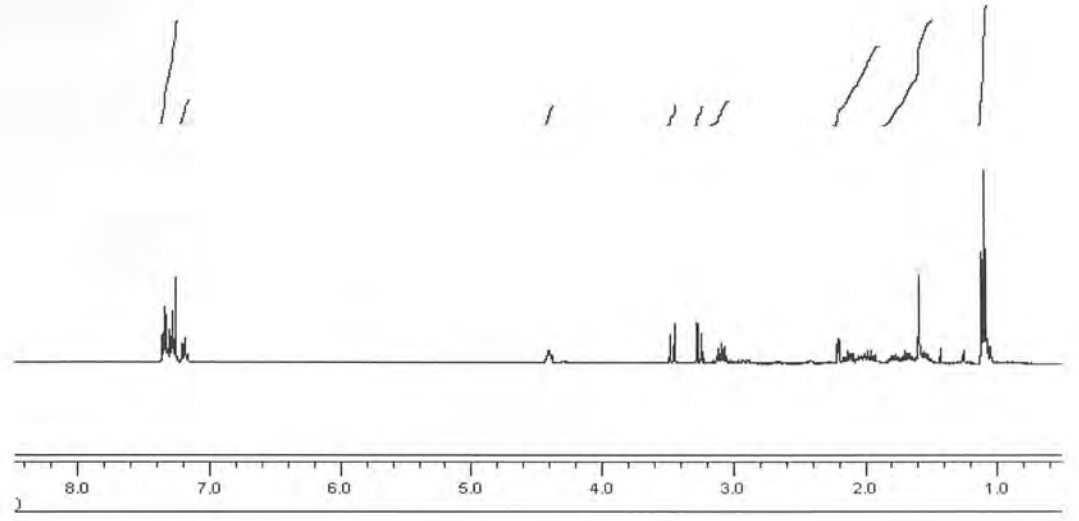
^{1}H NMR data for 2-hydroxy-1-(phenylthiomethyl)cyclopentyl(phenyl)methanone, **269**-*cis*

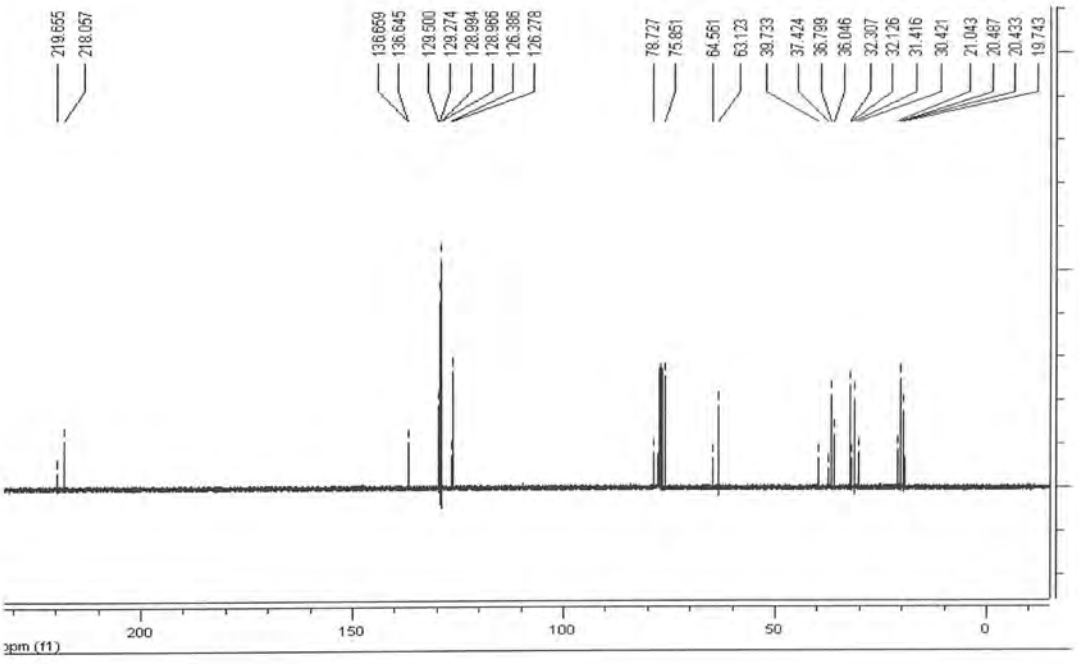


^{1}H NMR and ^{13}C NMR data for 2-hydroxy-1-(phenylthiomethyl)cyclopentyl(phenyl)methanone **269**-*trans*

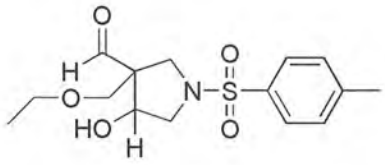


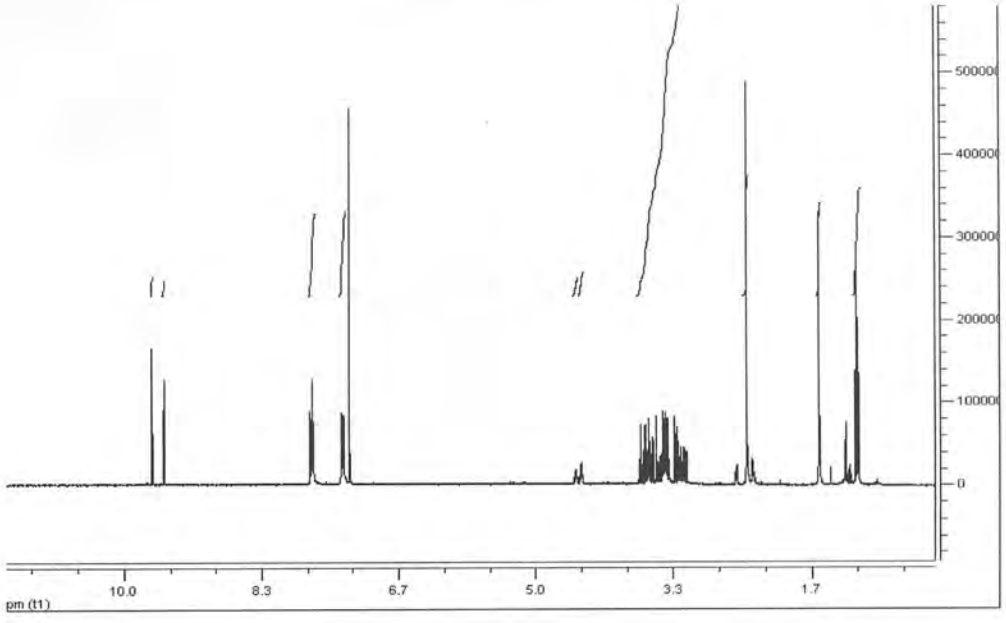
^{1}H NMR and ^{13}C NMR data for 1-(2-hydroxy-1-(phenylthiomethyl) cyclopentyl)-2-methylpropan-1-one, **291** *cis-trans*





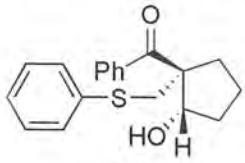
^{1}H NMR data for 3-(ethoxymethyl)-4-hydroxy-1-tosylpyrrolidine-3-carbaldehyde, **276** *cis-trans*



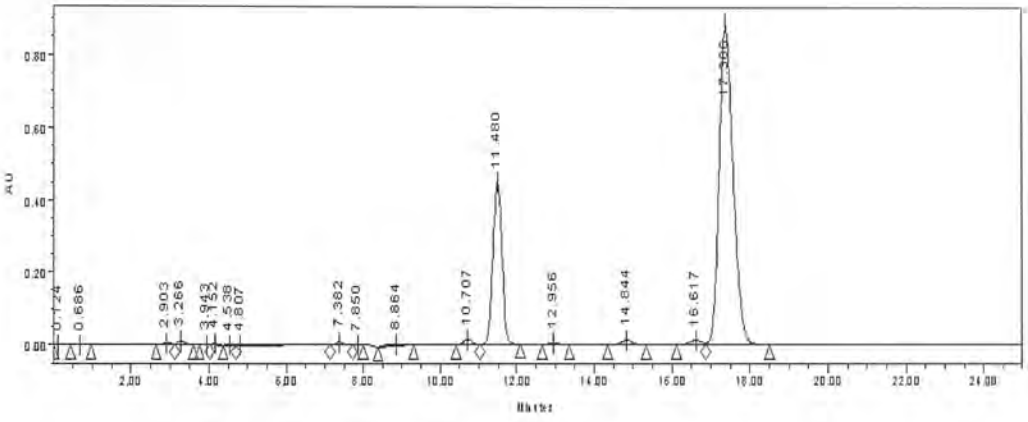


Appendix 2: Chiral HPLC Data

2.1. Chiral HPLC Data for 269 using (-) Quinine

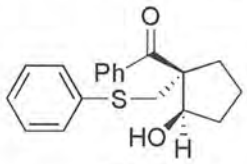


269-*cis*

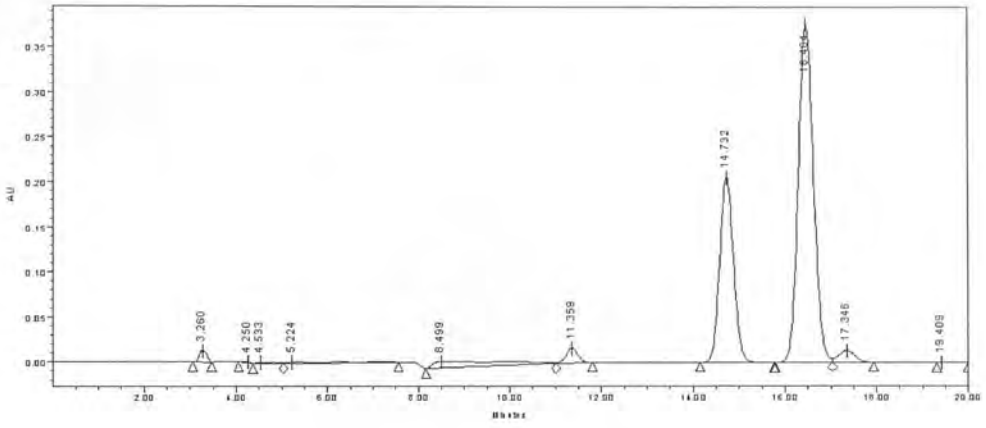


Peak #	Retention time(mins)	Area
1	11.480	24.04
2	17.386	70.74

2.2. Chiral HPLC Data for 269 using (-) Quinine

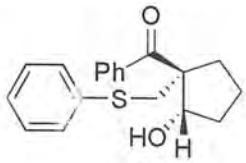


269-*trans*

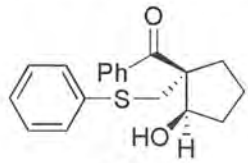


Peak #	Retention time(mins)	Area
1	14.793	45.06
2	16.545	28.29

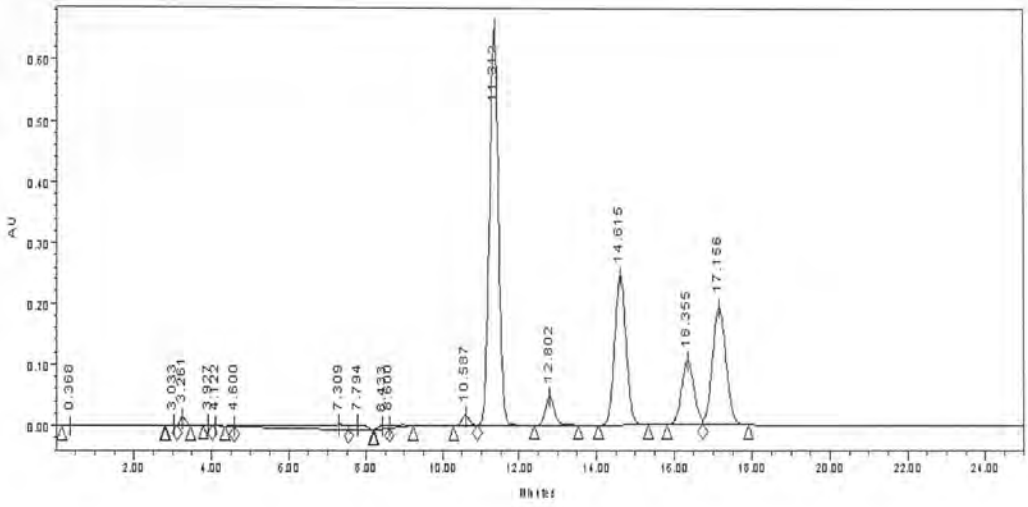
2.3. Chiral HPLC Data for 269 using (+) Quinidine



269-*cis*

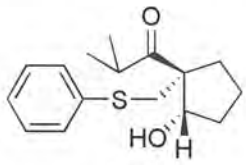


269-*trans*

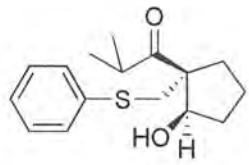


Peak #	Retention time(mins)	Area
1	11.312	42.58
2	14.615	19.94
3	16.355	9.29
4	17.156	18.40

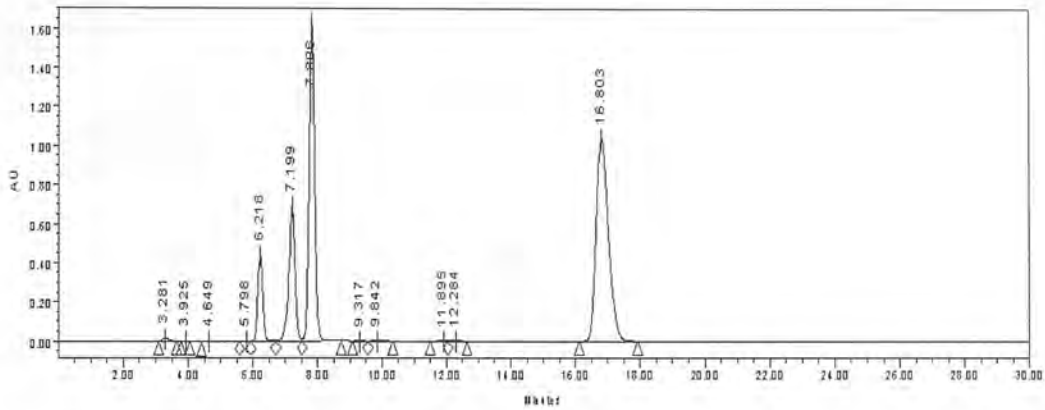
2.4. Chiral HPLC Data for 291 using (-) Quinine



291-*cis*

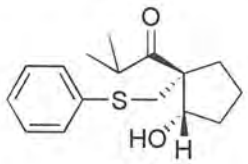


291-*trans*

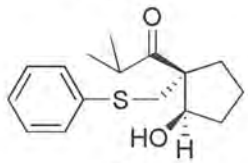


Peak #	Retention time(mins)	Area
1	6.218	7.60
2	7.199	14.79
3	7.806	32.06
4	16.803	44.88

2.5. Chiral HPLC Data for 291 using (+) Quinidine



291-*cis*



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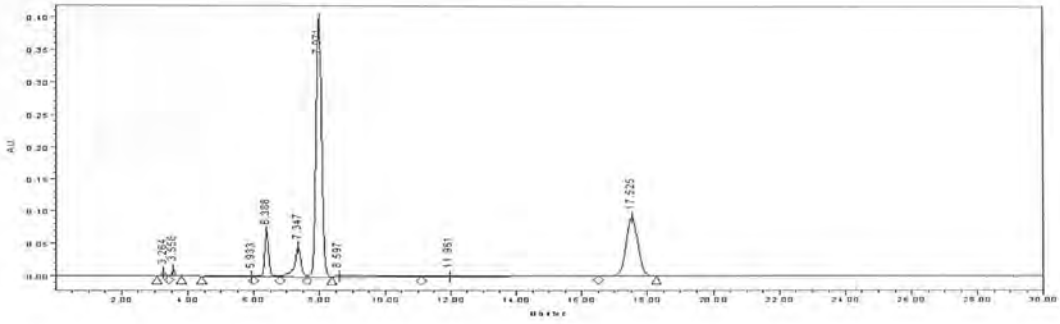
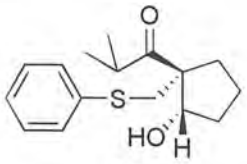
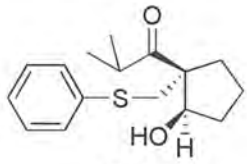


Peak #	Retention time(mins)	Area
1	6.388	7.18
2	7.347	7.55
3	7.971	51.55
4	17.525	25.74

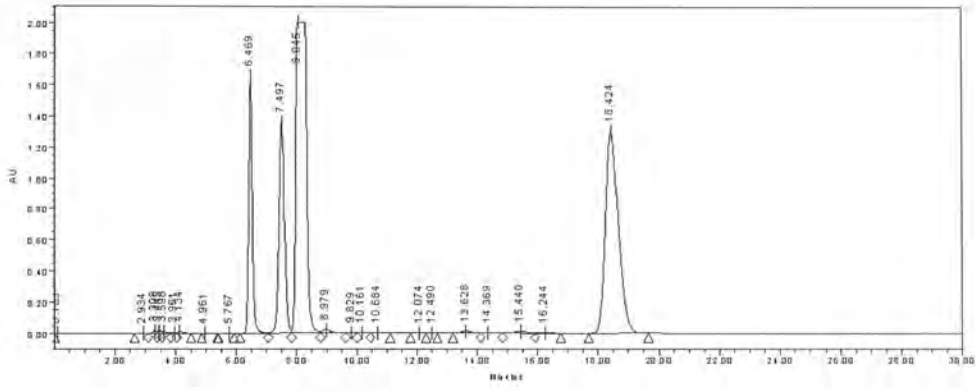
2.6 Chiral HPLC Data for 291 using (+) Cinchonine



291-*cis*

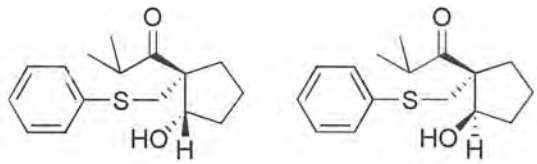


291-*trans*



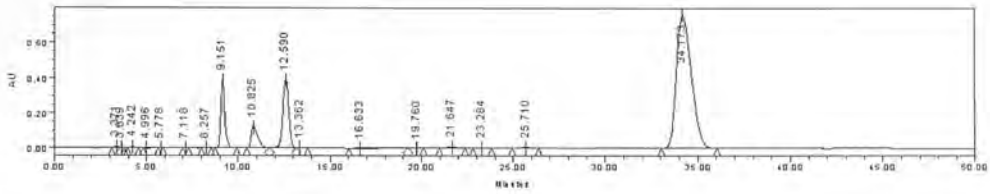
Peak #	Retention time(mins)	Area
1	6.469	11.45
2	7.497	14.22
3	8.045	40.45
4	18.424	32.30

2.7. Chiral HPLC Data for 291 using (-) Cinchonidine



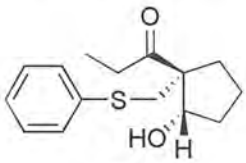
291-*cis*

291-*trans*

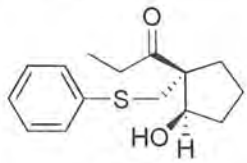


Peak #	Retention time(mins)	Area
1	9.151	9.38
2	10.825	4.89
3	12.590	13.12
4	34.173	72.1

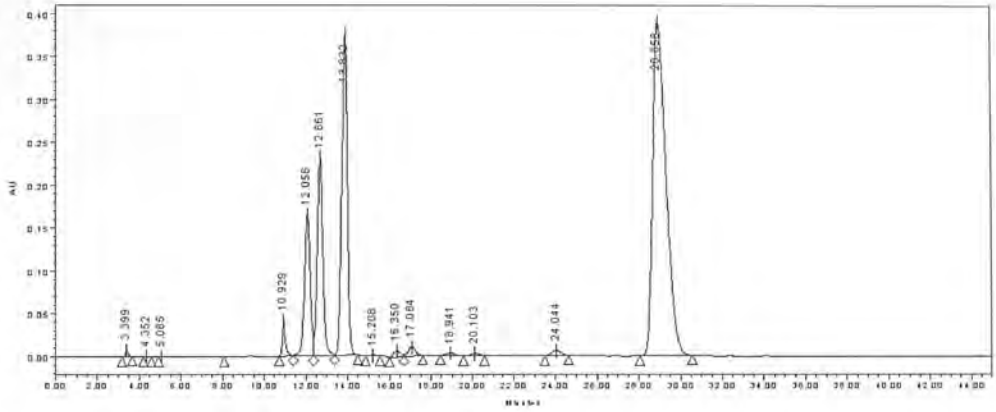
2.8. Chiral HPLC Data for 299 using (-) Quinine



299-*cis*

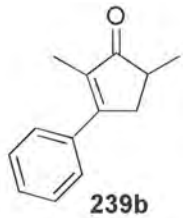


299-*trans*

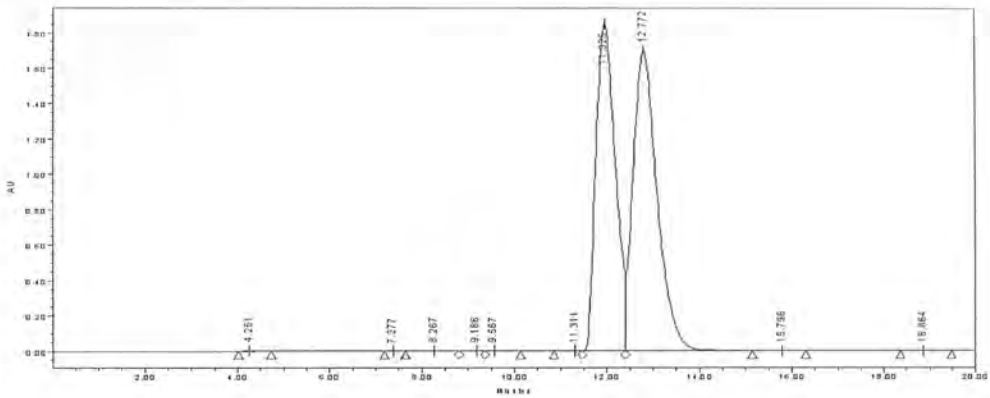


Peak #	Retention time(mins)	Area
1	12.056	9.76
2	12.661	13.10
3	13.832	21.02
4	28.858	52.14

2.9. HPLC Data for 239b

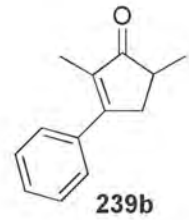


239b

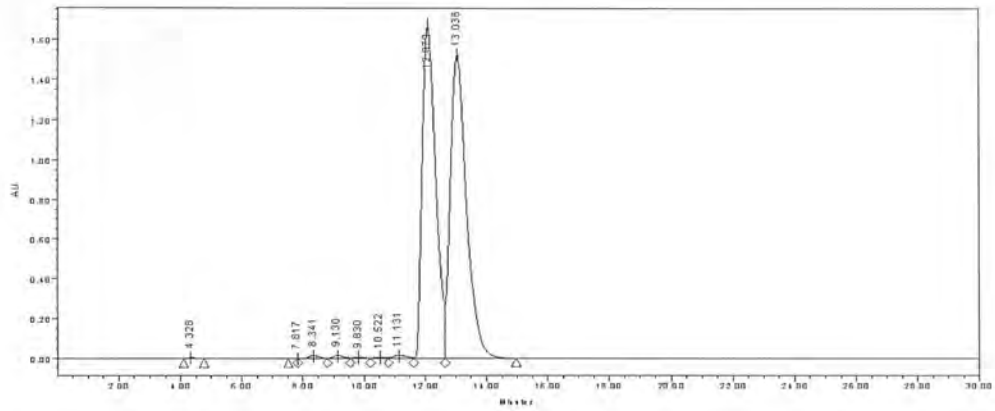


Peak #	Retention time(mins)	Area
1	11.925	46.50
2	12.772	53.10

2.10. Chiral HPLC Data for 239b



239b



Peak #	Retention time(mins)	Area
1	12.079	47.25
2	13.038	51.35