Cinchona Alkaloid-Mediated Asymmetric Synthesis of Amino Acids and Aziridines

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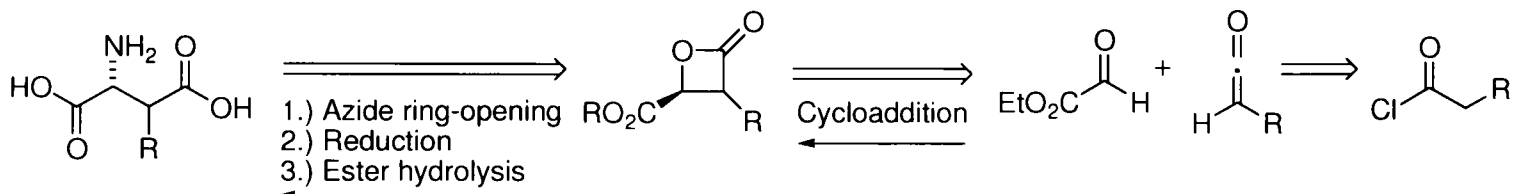
Contents

Abstract

In recent years the use of cinchona alkaloids as effective organocatalysts has been realised. The commercial availability and easy modification of these privileged structures establish them as attractive compounds for use in synthesis. For these reasons we were eager to apply cinchona alkaloid catalysis to the enantioselective synthesis of two important classes of molecule, β-amino acids and aziridines.

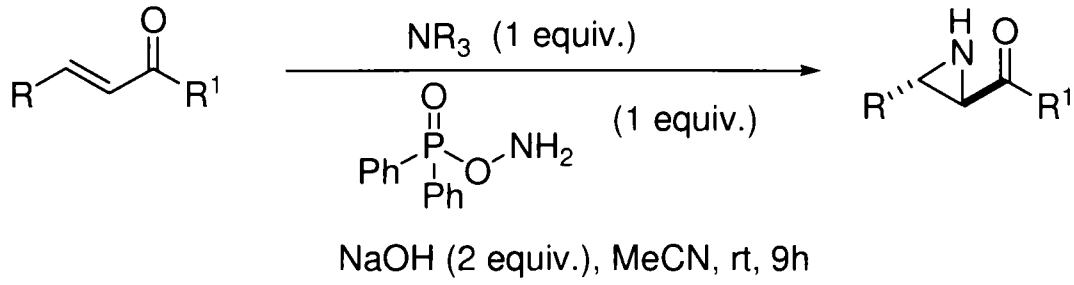
(A) Synthesis of β-Alkylaspartates via β-Lactone Ring-Opening

The cinchona alkaloid-catalysed reaction of ethyl glyoxylate with substituted ketenes, formed *in situ* from acid chloride precursors, gives *cis*-disubstituted β-lactones in moderate yield and high enantiomeric excess. Glyoxylate has rarely been used in the amine-catalysed ketene cycloaddition and this chemistry allowed for the direct installation of an ester functionality into the product. Subsequent azide ring opening, reduction and ester hydrolysis allow access to chiral β-alkyl aspartates.



(B) Synthesis of Aziridines from α,β–Unsaturated Ketone Derivatives

Our group has developed an organocatalytic reaction which furnishes unprotected aziridines in good yield from α,β–unsaturated ketone derivatives. Screening of chiral tertiary amines derived from the cinchona alkaloid motif allowed reasonable levels of enantioselectivity to be achieved. The substrate scope of the reaction was probed to incorporate a range of different alkene derivatives.



Acknowledgments

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Thank you to Dick Sheppard and Pete Haycock from the Imperial College NMR support service for all of their help throughout my studies, and to all staff from the Imperial College Mass Spectrometry Service.

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Finally I would like to thank my family; Dad, Mum, Patrick and Lauren, Nanny and Grandad Jenner and Grandma and Grandad Hudson, and my amazing boyfriend Stephen, for their constant love, support and encouragement.

Abbreviations

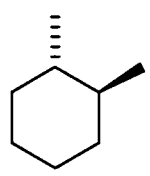
^{1}H	Proton
^{13}C	Carbon-13
Å	Angstrom(s)
Ac	Acetyl
aq.	Aqueous
Ar	Aryl substituent
Boc	*tert*-Butoxycarbonyl
t-Bu	*tert*-Butyl
Bn	Benzyl
BTF	Benzotrifluoride
cat	Catalyst/Catalytic
CI	Chemical Ionisation
CBz	Benzyl carbamate
Cp	Cyclopentadiene
d	Doublet
DEAD	Diethylazodicarboxylate
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMF	*N,N'*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
d.e	Diastereomeric excess
d.r	Diastereoisomeric ratio
e.e	Enantiomeric excess
Equiv.	Equivalent(s)
EI	Electron Ionisation
ES	Electrospray Ionisation
Et	Ethyl
FAB	Fast Atom Bombardment

Fmoc	9-Fluorenylmethyl carbamate
GC/MS	Gas Chromatography Mass Spectrometry
hmbc	Heteronuclear Multi-Bond Correlation
Hünig's base	*N*,*N*-Diisopropylethylamine
Hz	Hertz
IR	Infrared
IPA	Isopropylalcohol
J	Coupling constant (in Hz)
LC/MS	Liquid Chromatography Mass Spectrometry
m	*Meta*
m	Multiplet
M	Molar
Me	Methyl
MHz	Megahertz
m.p.	Melting point
Ms	Methanesulfonyl
m/z	Mass/charge ratio (in mass spectrometry)
NMM	*N*-Methylmorpholine
NMR	Nuclear Magnetic Resonance
o-Ns	*o*-Nitrobenzenesulfonamide
Nuc	Nucleophile
o	*Ortho*
p	*Para*
petrol	Petroleum ether (b.p. 40-60°C)
Ph	Phenyl
ppm	Part(s) per million
i-Pr	*Iso*-Propyl
q	Quartet
QD	Quinidine
r.t.	Room temperature
s	Singlet

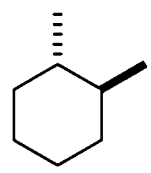
SES	2-Trimethylsilylethanesulfonyl
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*t*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

Stereochemical Notation

Throughout this thesis, the pictorial representation of stereochemistry is consistent with the conventions proposed by Maehr.* Thus, solid wedges and broken lines represent absolute configuration, where greater narrowing of the solid wedge indicates distance from the viewer. In contrast, structures drawn with solid/broken lines represent racemates.



single enantiomer



racemate

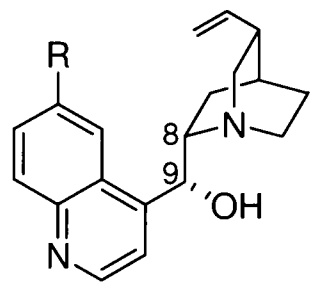
* Maehr, J. *J. Chem. Ed.* **1985**, *62*, 114.

General Introduction

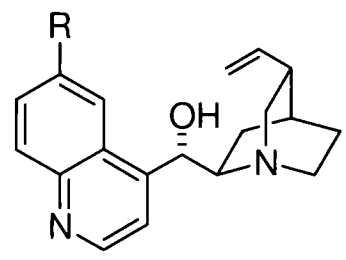
General Introduction

Over the past two decades the cinchona alkaloids (Figure 1) and their derivatives have emerged as a class of privileged structures known to effect a range of asymmetric transformations.[1] Their use as versatile chiral ligands, basic catalysts and chromatographic selectors demonstrate the vast number of applications of such compounds. The alkaloids are commercially available, inexpensive and easily modified for a range of asymmetric reactions.

Cinchona alkaloid pairs, quinine and quinidine, and the so called Cinch bases cinchonidine and cinchonine, are described as pseudoenantiomeric species differing at stereocentres C8 and C9. The result of this unique structural motif allows access to both enantiomeric forms of the product in the majority of cinchona alkaloid catalysed reactions.



Quinine: R=OMe
Cinchonidine: R=H



Quinidine: R=OMe
Cinchonine: R=H

Figure 1

Modifications of these alkaloid species have generally focused around the C9-O functionality, the tertiary quinuclidine nitrogen and the remote quinuclidine olefinic side chain. The C9 hydroxy motif lends itself well to etherification, esterification and inversion,[2] as well as more recent thiourea substitutions.[3] The quinuclidine nitrogen may be quaternised to give cinchona alkaloid-derived phase transfer catalysts which in turn can be applied to a number of asymmetric reactions, including the α-alkylation of carbonyl compounds and the epoxidation of enones.[4] Finally, the terminal quinuclidine alkene readily provides access to both the 10, 11-dihydro- alkane and the 10, 11 didehydro- alkyne[5] derivatives. This vinylic side chain also allows attachment of the

cinchona motif to polymer chains which has led to the development of a diverse range of polymer supported asymmetric chemistry.[1]

Given the wide synthetic applicability of these structures it was hoped that we could utilise the cinchona alkaloids in our own chemistry, and more specifically in the asymmetric synthesis of two sets of small target molecule; β-alkyl aspartates and aziridines.

1. Organocatalytic Synthesis of β–Alkylaspartates *via* β–Lactone Ring Opening

1.1 Introduction

1.1.1 β-Alkyl Aspartates

The β-alkyl aspartates (**1**) are a class of non-proteinogenic amino acids whose diverse biological and biochemical activities make them interesting and relevant synthetic targets.[6] Independently they are known to be selective inhibitors of glutamate transporters.[7] However, they are also often found embedded in larger natural product molecules. For example, β-methyl aspartic acid **1** (R=Me) is a component of the phosphatase inhibitor motuporin **2** (Figure 2).[8]

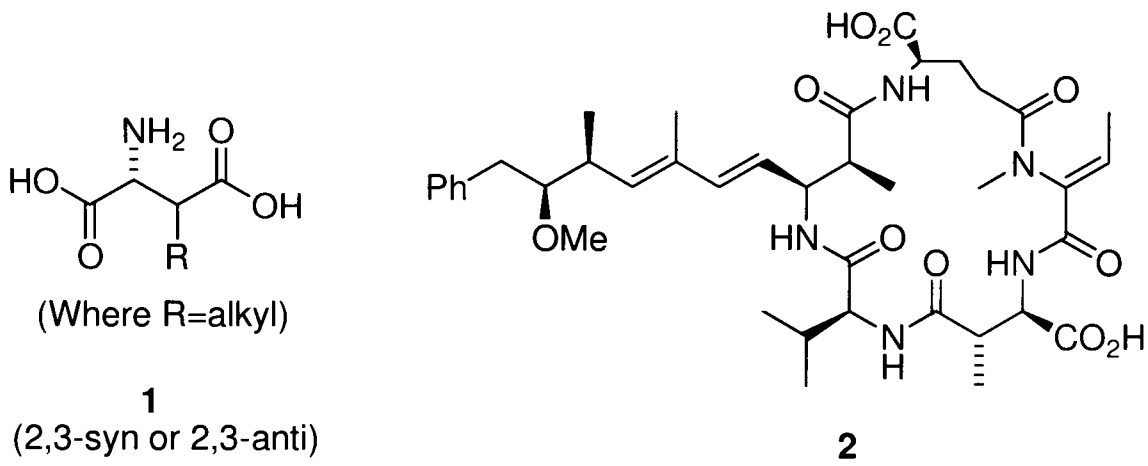
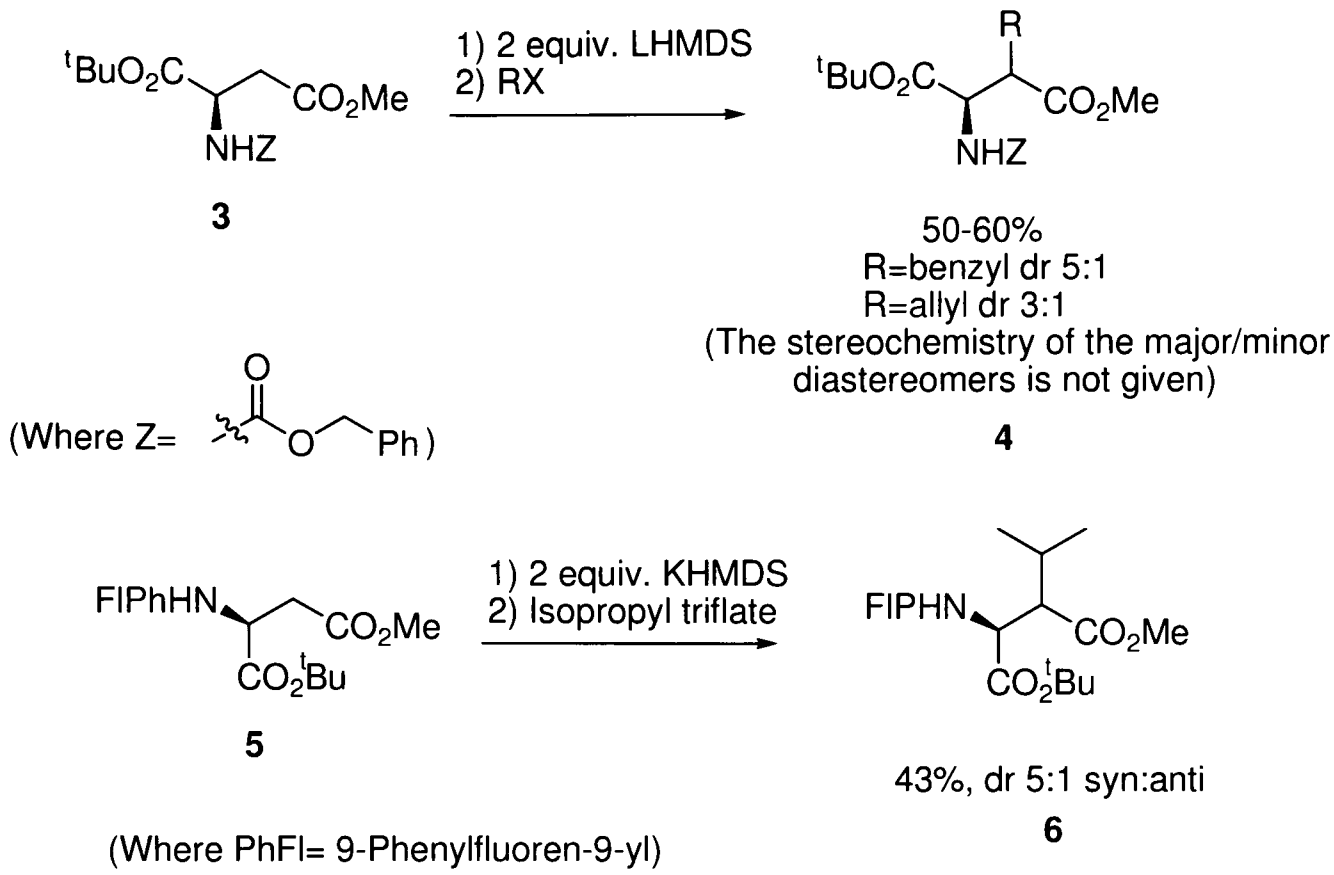


Figure 2

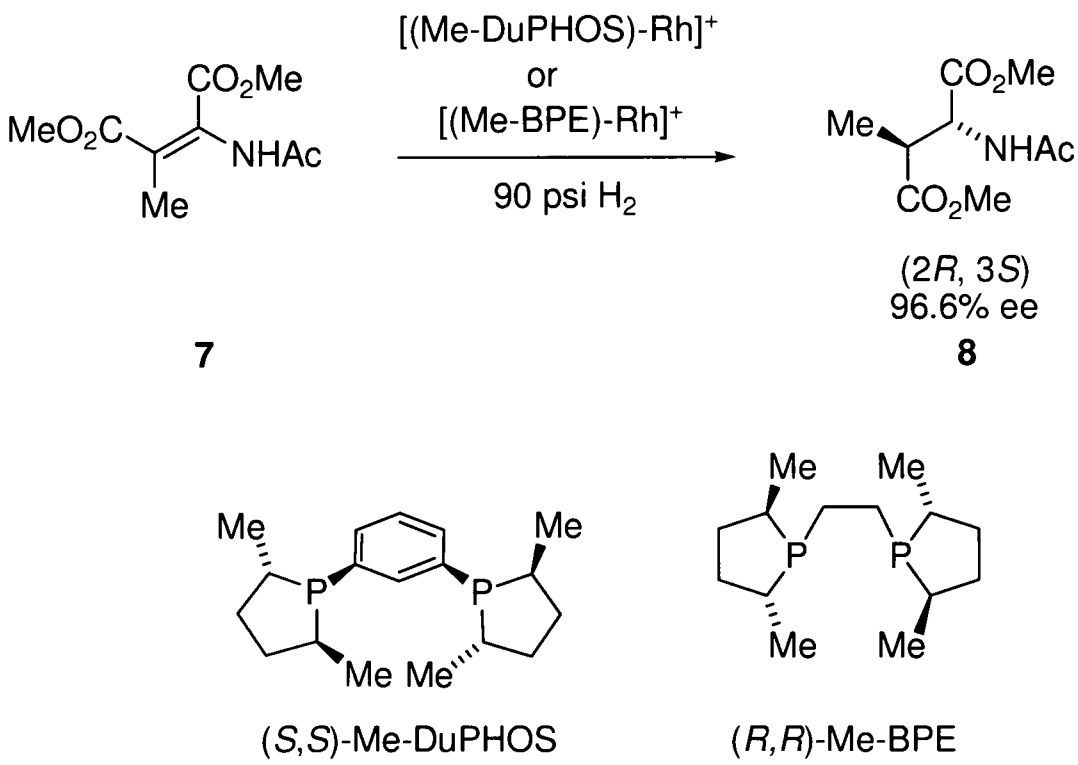
1.1.1.1 Synthesis of β–Alkyl Aspartates

There are a number of methods available for the synthesis of the β-alkyl aspartates. The alkylation of aspartate ester-derived anions (**3** and **5**) proceeds in moderate yield (40-60%) but diastereoselectivities are generally poor.[9,10] Additionally the use of highly electrophilic reagents is required, for example benzyl or allyl bromide, or isopropyl triflate (Scheme 1).



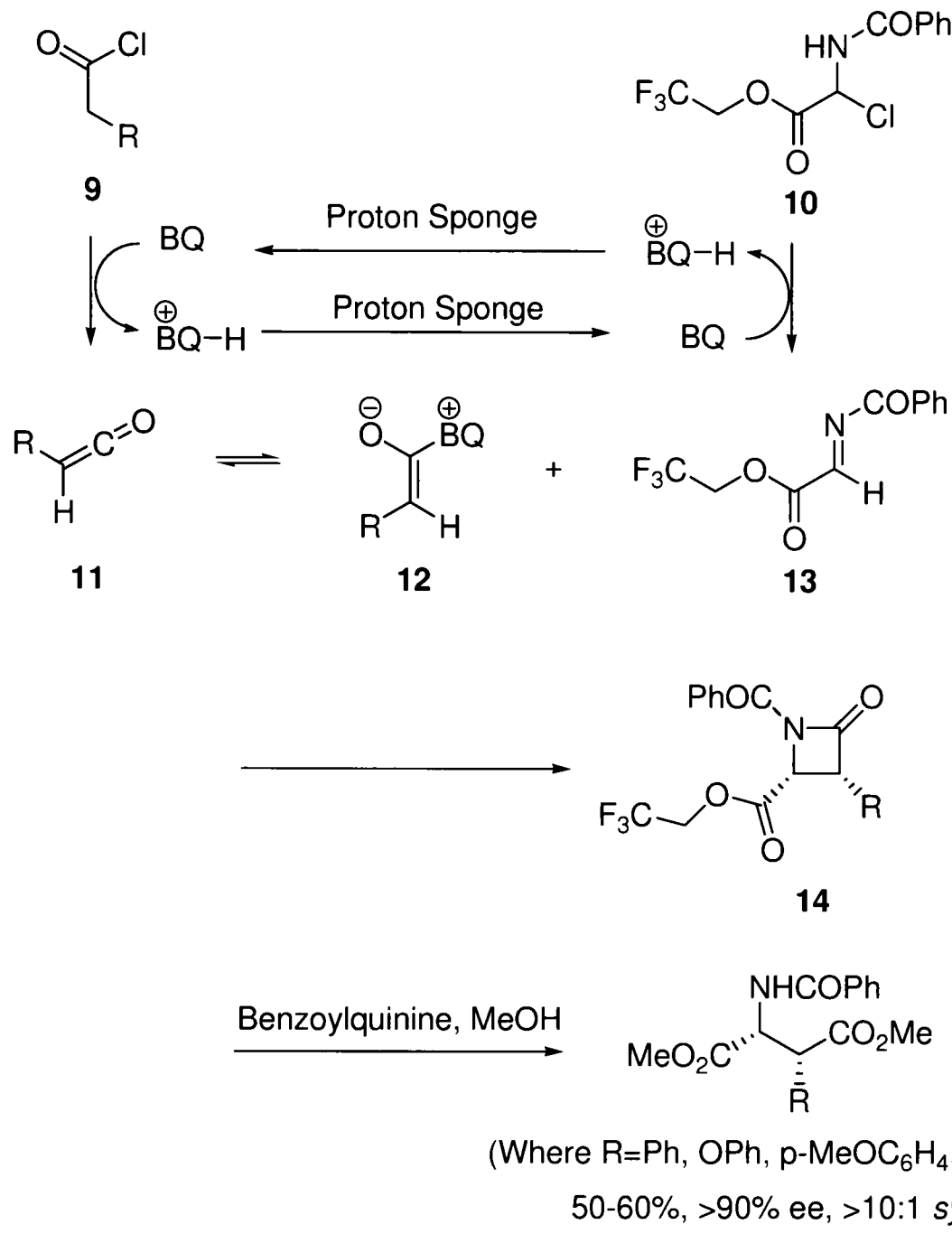
Scheme 1

Catalytic hydrogenation of tetrasubstituted amidoacrylates (**7**) provides a highly enantioselective route to the formation of β-alkyl aspartate derivatives.[11] However, this method suffers from the need to synthesise a geometrically pure amidoacrylate precursor in order for the reaction to proceed with high diastereoselectivities (Scheme 2).



Scheme 2

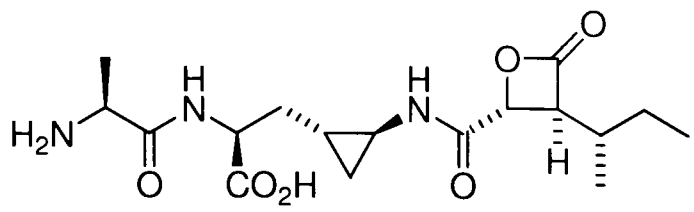
Lectka *et al.* have developed a versatile one-pot organocatalytic lactamisation, ring-opening sequence that provides access to the β-alkyl aspartate motif in reasonable yield (50-60%) and excellent diastereo- (>10:1 *syn:anti*) and enantio- (>90% *e.e*) selectivity.[12] β-Lactams were prepared from *N*-acyl-α-chloroglycine ester and acid chloride in the presence of a benzoylquinine catalyst (BQ) which acts to dehydrohalogenate both components to give *N*-acylimine **13** and ketene **11** respectively. Benzoylquinine then serves as a catalyst for the [2+2] cycloaddition reaction between the reactive species to give *cis*-disubstituted β-lactam products. Ring-opening and transesterification of these products provides access to the desired substituted aspartates. The *cis*-stereochemistry of the 2,3- disubstituted lactam products subsequently determines the stereochemical outcome of the ring-opening reaction, and hence this sequence gives access to the 2,3-*syn* product diastereomer only (Scheme 3).



Scheme 3

1.1.1.2 The Application of β-Lactone Methodology to the Synthesis of β-Alkyl Aspartates

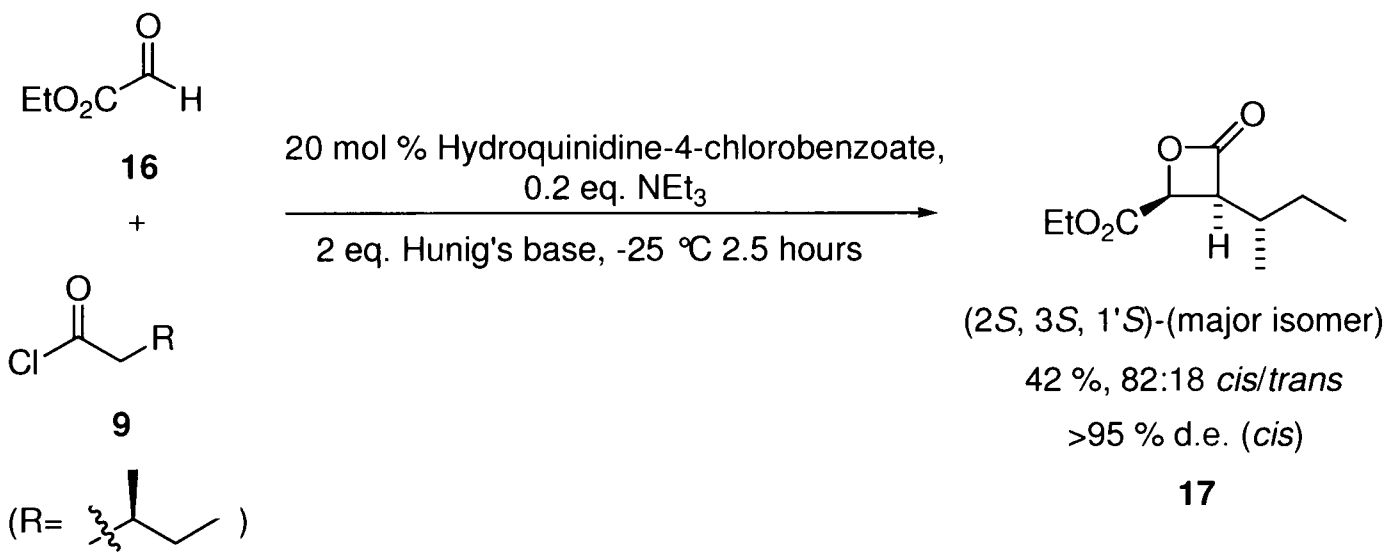
Our work towards the β-alkyl aspartates originally stemmed from a total synthesis project within the group. The synthesis of the 20*S*-proteasome inhibitor belactosin A (Figure 3)[13,14] required the formation of a 2,3-*trans* disubstituted β-lactone moiety.



Belactosin A

Figure 3

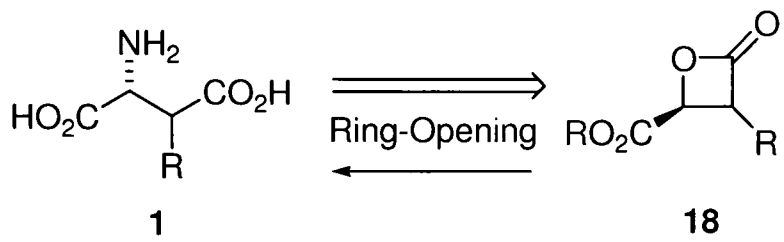
Based on literature precedent[15] the group hoped to utilise a cinchona alkaloid mediated net [2+2] cycloaddition reaction between a ketene and an activated aldehyde to access the *trans*-disubstituted lactone product. Ethyl glyoxylate (**16**), rarely used in such reactions previously, was selected as the activated aldehyde component as this would allow direct installation of an ester functionality at C2. Ketene formation would be achieved *in situ via* the dehydrochlorination of an acid chloride. However, initial experimentation using the conditions shown in Scheme 4, showed the formation of the 2,3-*cis* disubstituted β-lactone as the major product (>95:5 *d.e*). Evidence for the formation of the *cis* isomer was based upon ^{1}H NMR coupling constants where *J* 7.0 for EtO_2CCH (typical literature values: $^{3}J_{cis}$= approx. 6.5 Hz, $^{3}J_{trans}$= approx. 4.0-4.5 Hz).



Scheme 4

Although these results prevented the use of this methodology in the total synthesis project it was noted that this reaction may provide an efficient route to the β-alkyl aspartates **1** *via* β-lactone ring-opening with a nitrogen nucleophile (Scheme 5). To this end a fuller study of the scope of the glyoxylate-ketene cycloaddition was undertaken, the results of which are described in this thesis. Additionally, given that the β-lactone motif may offer a

novel starting point for the synthesis of β-alkylaspartates the introduction to this chapter focuses upon key methodology for the synthesis of β-lactones and subsequent ring-opening reactions.



1 18

Scheme 5

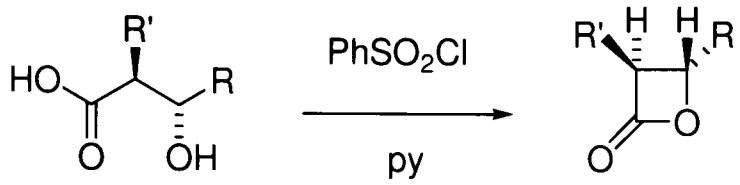
1.1.2 Traditional Methods for the Synthesis of β-Lactones[16,17]

Einhorn was the first to isolate and characterise a monosubstituted β-lactone in 1883,[18] with the first synthesis of the simple lactone, 2-oxetanone, occurring in 1916.[19] Both of these early methods utilise the cyclisation of β-halo acids in aqueous media in order to form the 4-membered lactone ring *via* C-O alkyl bond formation. Since this early experimental work took place the area has developed significantly and currently there are three main methods for the synthesis of β-lactones:

1. Lactonisation by C-O acyl bond formation.
2. Lactonisation by C-O alkyl bond formation.
3. [2+2] cycloadditions
    (i) Concerted cycloaddition by Lewis acid catalysis.
    (ii) Net [2+2] cycloaddition by nucleophilic catalysis.

1.1.2.1 Lactonisation by C-O Acyl Bond Formation

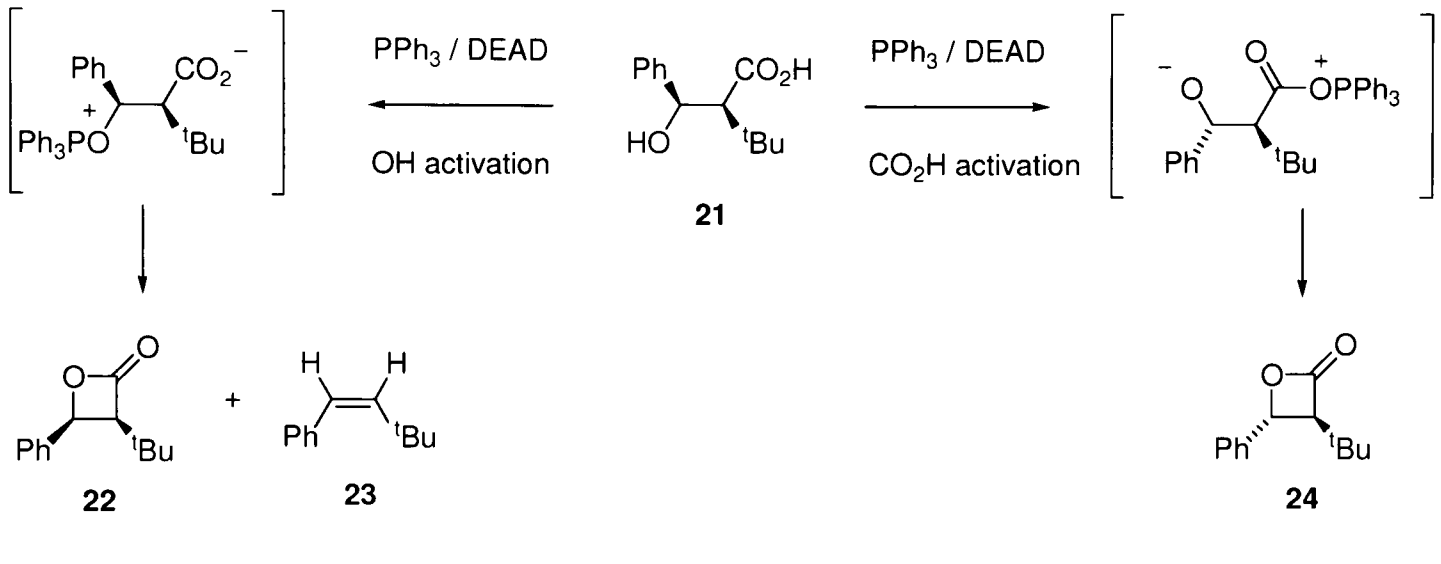
The cyclisation of 3-hydroxycarboxylic acids (**19**), and ester derivatives thereof,[20] provides a reliable method for the synthesis of the β-lactone moiety (**20**) *via* C-O acyl bond formation (Scheme 6). The reaction proceeds *via* an anhydride intermediate. Activation of the carboxylic acid group, with subsequent attack by the nucleophilic hydroxy oxygen, gives the β-lactone product with retention of configuration.



19 **20**

Scheme 6

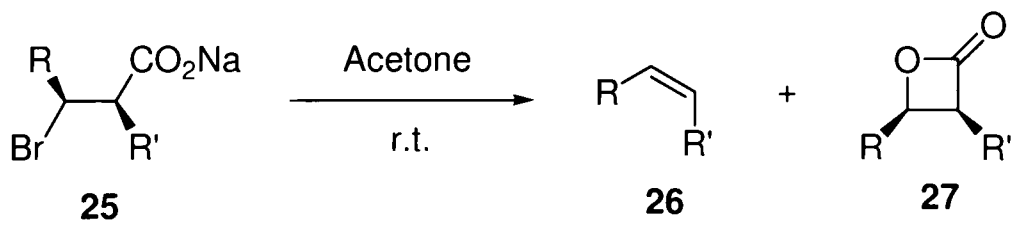
Mitsunobu conditions can be employed to enable C-O acyl bond formation[21] (Scheme 7). However, this lactonisation method is generally not favoured due to the competing C-O alkyl bond formation reaction that occurs upon activation of the hydroxy group, and gives rise to a diastereomer (**22**) of the product formed upon C-O acyl bond formation (**24**).



Scheme 7

1.1.2.2 Lactonisation by C-O Alkyl Bond Formation

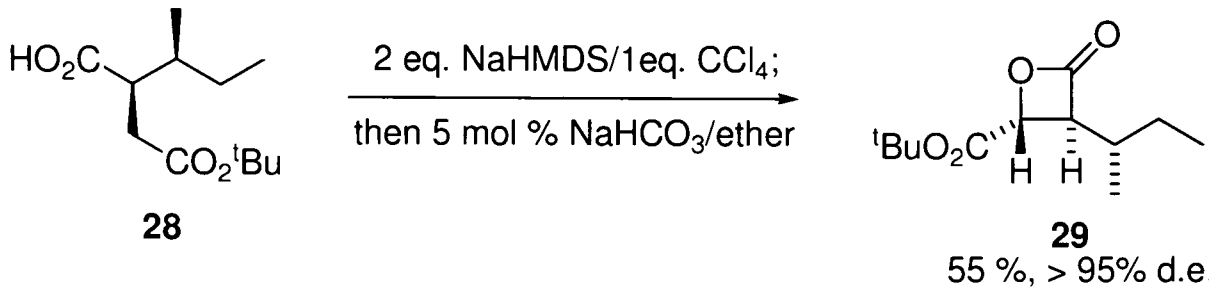
β-Halocarboxylic acids (**25**) may be used to form β-lactones with inversion of configuration at the carbon atom bearing the halogen substituent[20] (Scheme 8). However, the major products formed in such a reaction are often olefinic (**26**), produced as a result of β-lactone decarboxylation or elimination of the halogen halide with loss of CO_2.[22]



25 **26** **27**

Scheme 8

A further example of lactonisation *via* C-O alkyl bond formation comes from our recent total synthesis of (+)-belactosin A.[13] A one pot chlorination-ring closure reaction afforded the disubstituted β-lactone **29**, in reasonable yield and with excellent diastereoselectivity (Scheme 9).



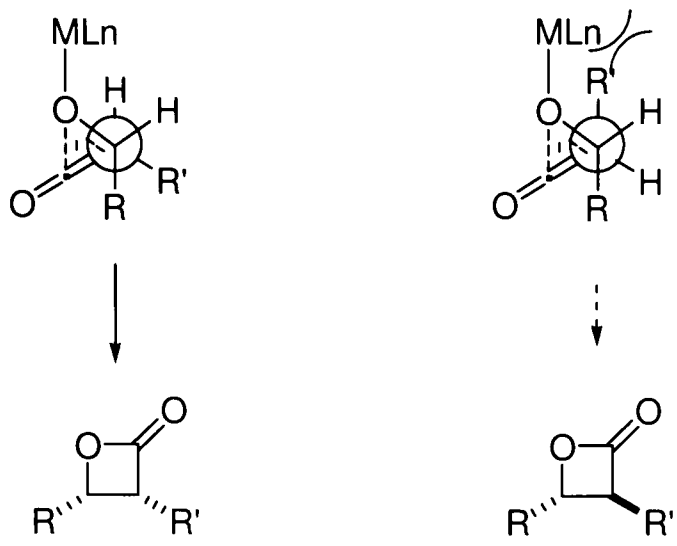
28 **29**
55 %, > 95% d.e.

Scheme 9

As shown Mitsunobu conditions can also be applied to β-lactonisation *via* C-O alkyl bond formation (Scheme 7). However, due to the undesirable product distribution observed in the reaction this procedure is rarely used as a method for the synthesis of β-lactones.

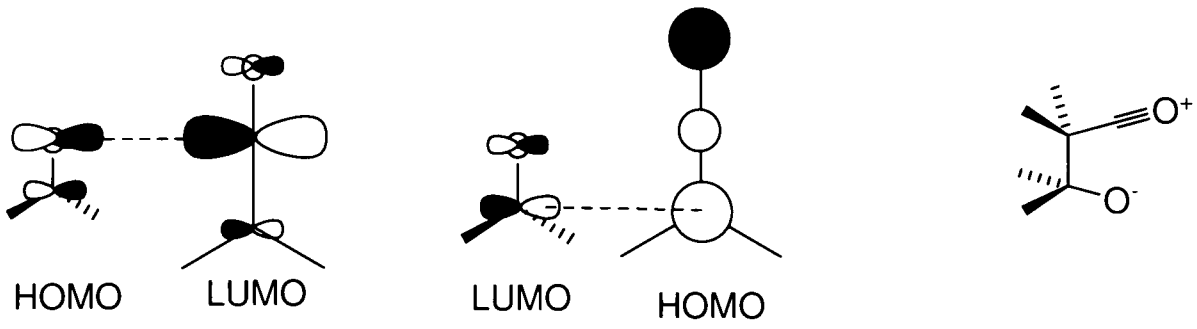
1.1.2.3 Lewis Acid Catalysed [2+2] Cycloadditions

The [2+2] cycloaddition reaction that occurs between a ketene and a carbonyl compound was first reported by Staudinger in 1911.[23] The reaction was further developed in 1975 by Zaisteva, who introduced the use of Lewis acids and silyl ketenes in such reactions.[24] More recent advances have seen the development of asymmetric variants of the Lewis acid mediated [2+2] cycloaddition, all of which appear to be highly *cis* selective due to the steric requirements of both the catalyst and the R group of the ketene in question[25] (Scheme 10).



Scheme 10

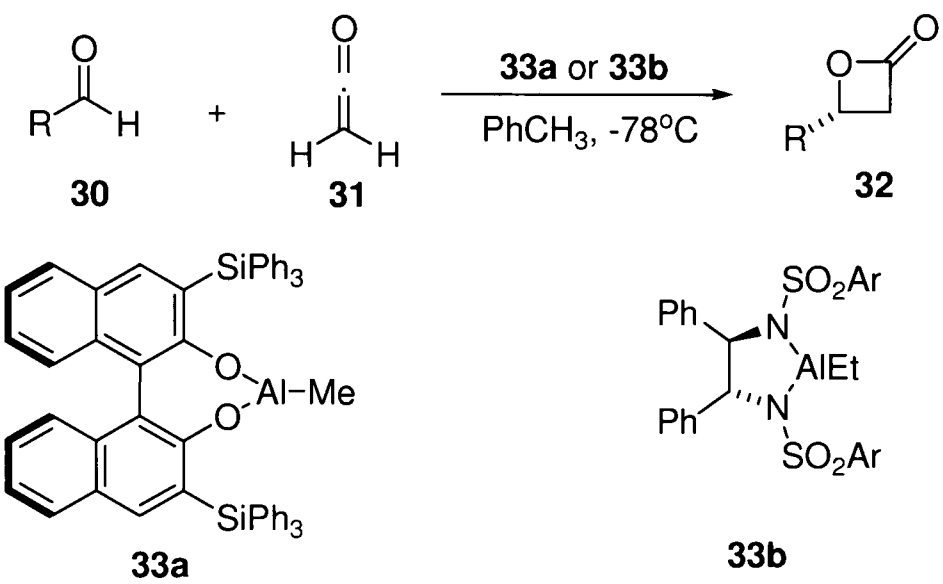
In contrast to other similar reactions (for example the reaction of ketenes with alkenes or imines, or the dimerisation of ketenes) little attention has been focused upon the elucidation of the mechanism for this specific [2+2] cycloaddition. It has been proposed that the formation of the β-lactone may occur *via* a transition state where both HOMO(carbonyl)/LUMO(ketene) and HOMO(ketene)/LUMO(carbonyl) interactions are important (**A**); in this case the geometric requirements of the ketene orbitals would be likely to result in an orthogonal approach of the ketene onto the activated carbonyl. However, there is also the possibility that a two-step reaction pathway may be functioning with the formation of a zwitterionic intermediate (**B**) (Scheme 11).[26,27]



Scheme 11

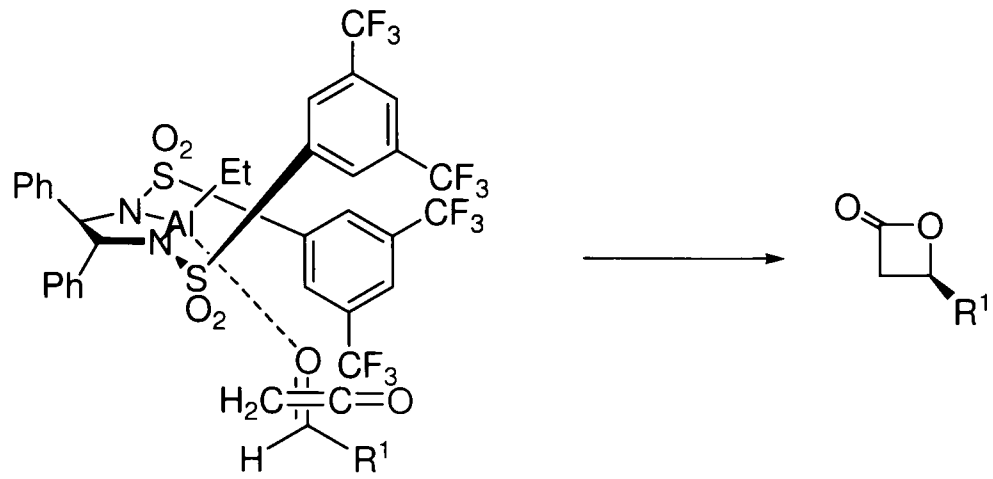
In 1994, Miyano *et al.* described the use of stoichiometric amounts of chiral aluminium complexes (**33a** and **33b**) in an asymmetric variant of the [2+2] cycloaddition reaction between ketene (**31**) and a range of aldehydes.[28] Variable yields (33-91%), and poor-to-moderate enantioselectivities (17-56% *e.e*) were obtained for a range of aliphatic (R=Me,

Et, *n*-Pr, *n*-Bu), branched aliphatic (R=*i*-Pr, *t*-Bu), aromatic (R=Ph) and cyclic (R=cyclohexyl) R groups. Subsequently, this group went on to report the first asymmetric [2+2]-cycloaddition reaction catalysed by 10 mol% of aluminium bissulfonamide complex (**33b**).[29] Low to excellent yields (13-94%) and enantioselectivities (14-74% *e.e*) were obtained, with higher *e.e* values observed for aldehydes with bulky R groups (Scheme 12).



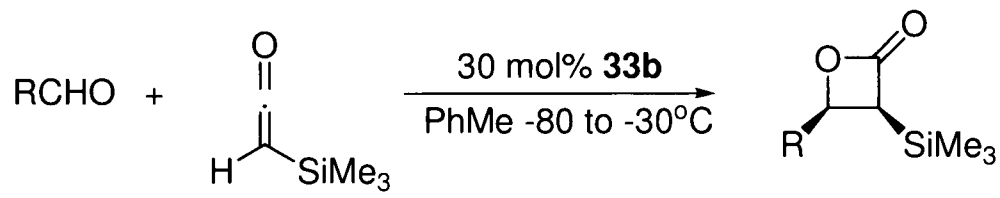
Scheme 12

Coordination of the aldehyde to the catalyst occurs *via* the oxygen lone pair in a manner *anti* to the R^1 substituent. Bulky R groups (R= *t*-Bu, *i*-Pr, cyclohexyl) show a greater propensity to adopt this conformation hence the decreased enantioselectivity observed for aldehydes where R=Me or Et. Nucleophilic attack of the ketene to the activated aldehyde proceeds *via* the exposed *re*-face, avoiding the sterically bulky bis(trifluromethyl)phenyl group at the back of the diazaaluminolidine ring. Note the orthogonal approach of the ketene in relation to the aldehyde as predicted by orbital requirements.



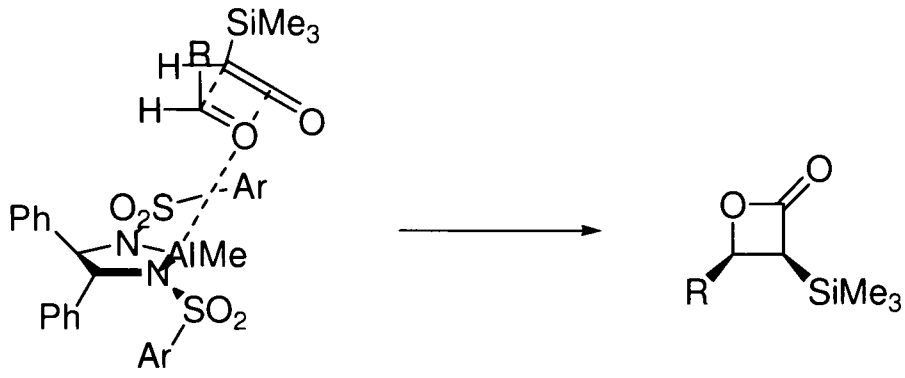
Scheme 13

Further developments saw the use of the more inherently stable silyl ketene species **34** as an alternative reaction partner to ketene itself. In 1996 Kocienski *et al.* reported the use of silyl ketene (**34**) in the asymmetric [2+2] cycloaddition reaction with a range of aldehydes promoted by 30 mol % of catalyst **33b**.[30] Yields ranged from 43 to 82% for a number of aromatic (R=$PhCH_2$, p-$MeOPhCH_2$, $PhCH_2CH_2$) and cyclic saturated (R=c-C_6H_{11}) R groups, with variable enantioselectivity (36-83% *e.e*) and moderate to high diastereoselectivities (63:31 to 99:1 *cis:trans*) for the *cis*-silylated β-lactones (**35**), (Scheme 14).



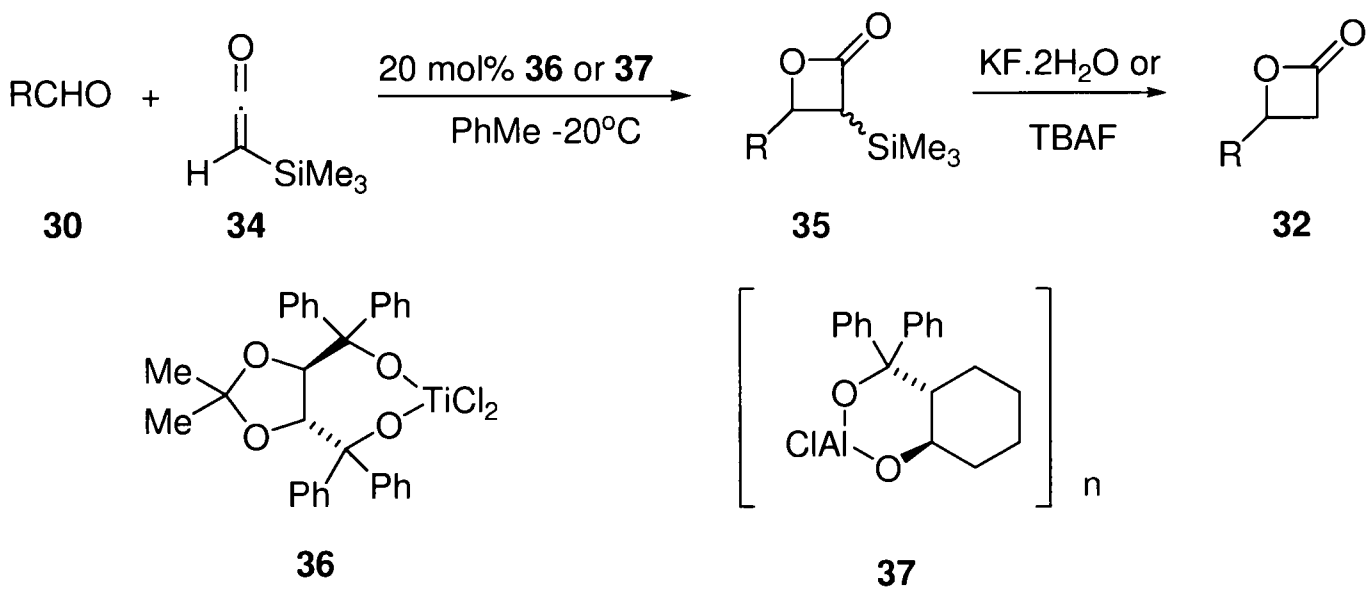
Scheme 14

Synperiplanar approach of the nucleophilic ketene to the electrophilic, Lewis acid coordinated aldehyde, from the top face of the complex, gives the predicted absolute configuration for the major product (Scheme 15). Although the non-orthogonal approach of the silylketene to the carbonyl component is slightly unexpected, the possibility of a zwitterionic intermediate (Scheme 11, **B**) means that this is not an absolute requirement in order for the reaction to occur.



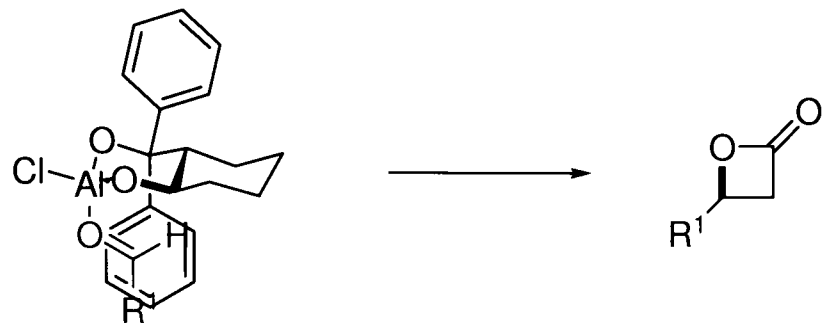
Scheme 15

Romo *et al.*[31,32] also studied the use of silyl ketene in the [2+2] cycloaddition reaction using the tartrate derived dichlorotitanium-TADDOL catalyst **36**, and the aluminium based catalyst **37**. Again, the cycloaddition was found to give exclusively the *cis*-silylated lactone (**35**) in moderate yield (45-78%, two steps after desilylation) and poor to good enantioselectivity (9-85% *e.e*) for numerous aliphatic and aromatic R groups (Scheme 16).



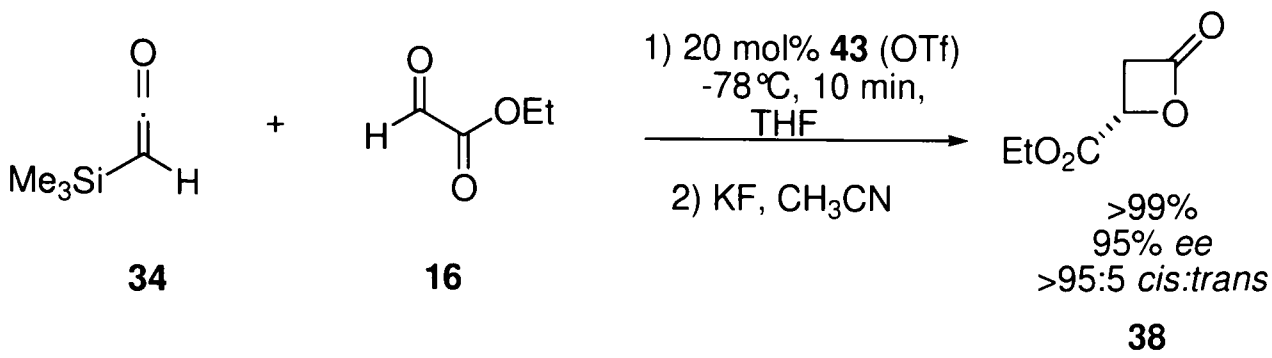
Scheme 16

The high level of selectivity observed in the [2+2] cycloaddition is thought to originate from the catalyst-aldehyde complex shown in Scheme 17. The pseudoaxial phenyl group at the back of the structure effectively blocks the *re* face of the aldehyde allowing preferential attack by the ketene on the more exposed *si* face (Scheme 17).



Scheme 17

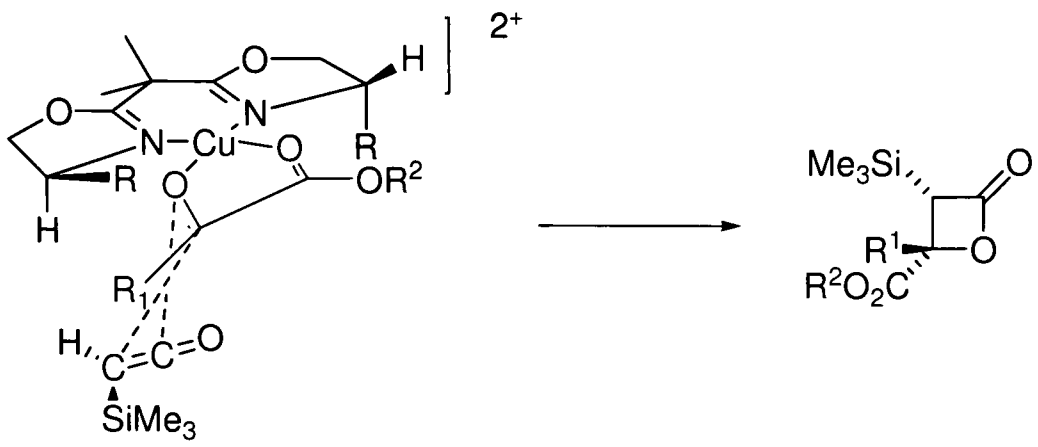
Work by Evans *et al.*[33] expanded further on this silyl ketene approach to the [2+2] cycloaddition reaction. Cu (II) bis(oxazoline) complex **43** is used to promote the reaction between silyl ketene and a number of different carbonyl compounds including ethyl glyoxylate (**16**), α-keto esters (**39**) and α-diketones (**41**) (Scheme 18). In the case of the α-keto esters an increase in the steric bulk of the acyl substituent (R^1=*i*-Bu, *i*-Pr, Ph) led to a slight decrease in enantioselection (79-87% *e.e* from 95% and 99% *e.e* respectively with R^1=Me and Et). All substrates gave moderate to excellent yields (79- >99%) and consistently high *e.e* values (83-99%).



34 **16** **38** **39** **40** **41** **42** **43**

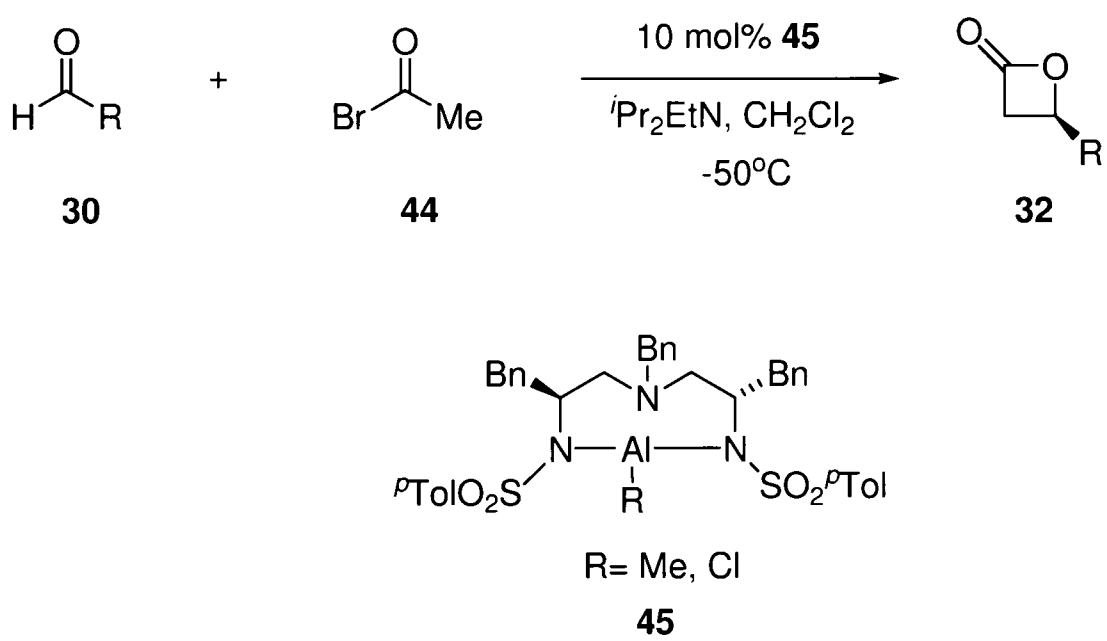
Scheme 18

The orthogonal approach of the ketene onto the activated carbonyl component, from the less hindered *si*-face of the catalyst complex gives the observed stereochemistry (Scheme 19). The high *cis*-selectivity is explained by assuming placement of the TMS substituent away from the large catalyst-substrate complex (Scheme 19).



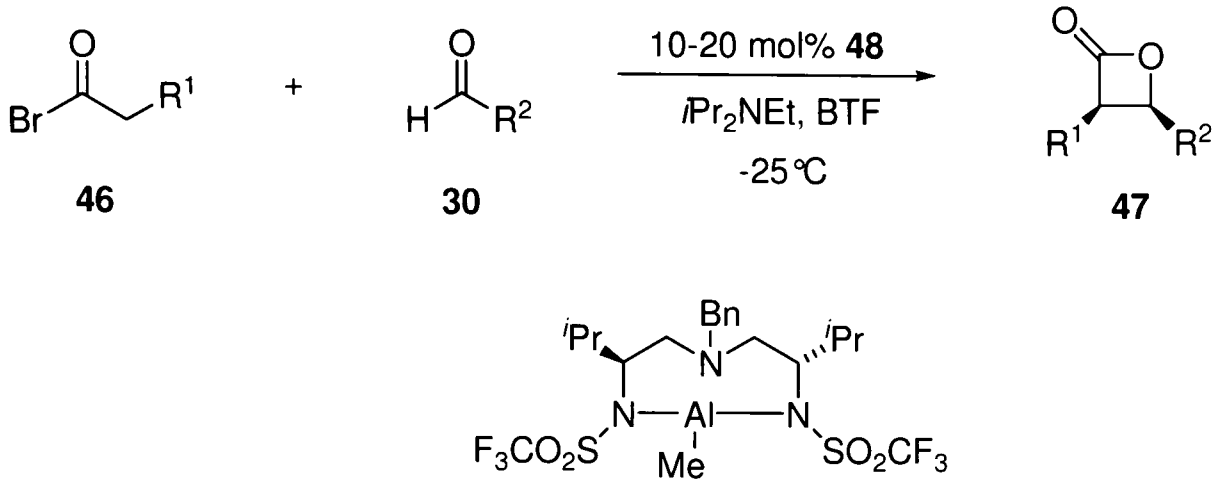
Scheme 19

Nelson *et al.*[34] further expanded upon the [2+2] Lewis acid mediated cycloaddition, moving away from the use of silyl ketenes and favouring instead the *in situ* deprotonation of acyl halides to give the reactive ketene species. The Al (III)-triamine complex **45** was used to effect the reaction between a range of straight chain, β-branched, and alkoxy-substituted aldehydes (**30**), and acetyl bromide (**44**) (Scheme 20). Base was required in order to promote ketene formation *via* deprotonation of **44**. All monosubstituted β-lactones (**32**) were obtained in moderate to high yields (56-91%) and with excellent enantioselectivities (89-95% *e.e*).



Scheme 20

The development of the modified catalyst **48**, along with the use of substituted acyl bromides (**46**), allowed the synthesis of 2,3-disubstituted β-lactones (**47**) in good yield (71-88%) with moderate to excellent *d.e* (72- >98% *cis*), and consistently high *e.e* values (88-96%) (Scheme 21).[35,36]



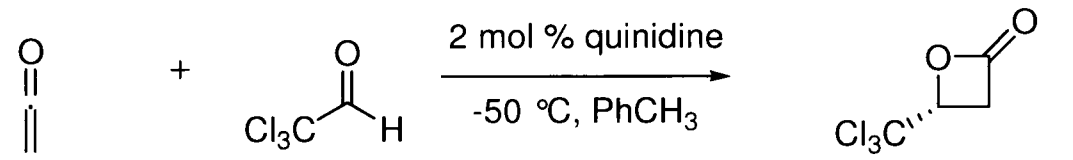
46 **30** **47**

48

Scheme 21

1.1.2.4 Net [2+2] Cycloadditions by Nucleophilic Catalysis

In 1982 Wynberg *et al.*[37,38] set the precedent for the synthesis of asymmetric β-lactones using the nucleophilic cinchona alkaloid promoters, quinine and quinidine (Figure 1 and Scheme 22). Both pseudoenantiomeric catalysts give high reaction yields, 76 and 98% respectively, and result in the synthesis of opposite enantiomers, quinidine leading to the *2R* product, quinine leading to the *2S* product. Proof of configuration was established by conversion of the β-lactone to the known (*S*)-(-) and (*R*)-(+)-malic acids, with subsequent comparison of optical rotation.

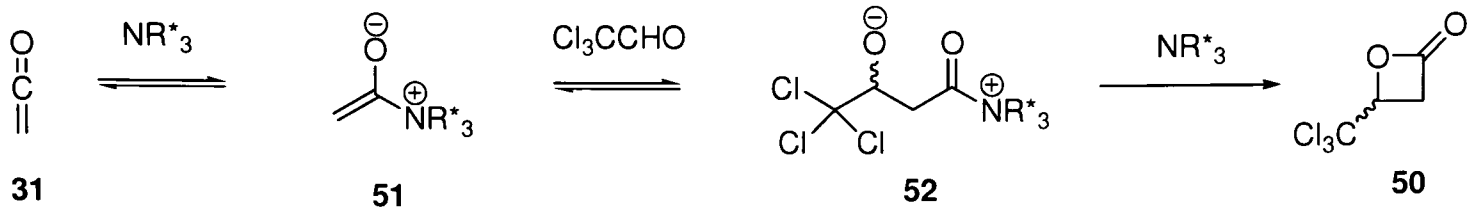


31 **49** *2R*-**50**
98%, 98% ee

Scheme 22

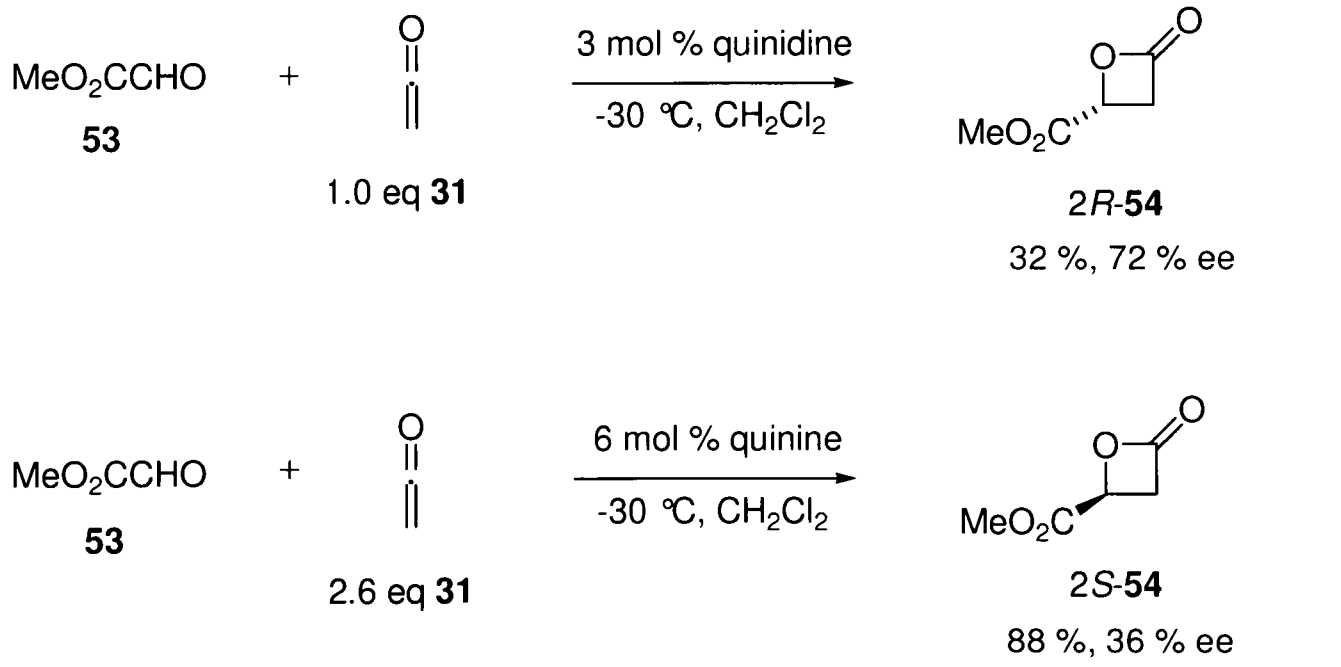
The reaction mechanism is thought to proceed *via* ammonium ion enolate **51**, generated upon the addition of the tertiary amine to the ketene species. This is followed by an aldol lactonisation with subsequent release of the amine catalyst (Scheme 23). In order for the reaction to proceed in good yield a highly electrophilic aldehyde component is required, hence the use of chloral in Wynberg's original procedure. This stringent requirement is thought to be due to the low energy and nucleophilicity of the ammonium enolate **51**, which is required to react with the aldehyde in order to produce the intermediate aldol

product (**52**). The aldehyde component is also not activated by the presence of a Lewis acid and consequently will be less reactive itself.



Scheme 23

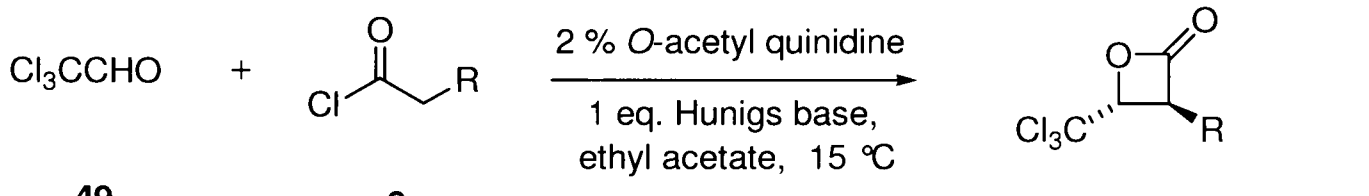
Guérin *et al.*[39] have demonstrated the use of cinchona alkaloid catalysis to mediate the reaction between gaseous ketene **31** and methyl glyoxylate **53** to give methyl ester monosubstituted β-lactones **54** (Scheme 24). However, in order to obtain reasonable reaction yields a large excess of ketene was required. Additionally, selectivity in the quinine case was low even at higher catalyst loadings. The absolute configurations assigned to the products are identical to those given by Wynberg[19(b)] for the chloral reaction. However, from the data provided it remains unclear as to how the stereochemistry of 2*R*-**54** and 2*S*-**54** was determined.



Scheme 24

Examples of disubstituted β-lactones formed *via* this organocatalytic method appear to be uncommon in the literature and to date only one non-bicyclic example of such a reaction has been found.[15] Indeed it was this precedent that formed the basis of our initial studies toward the synthesis of the 2,3-*trans* disubstituted β-lactone required for the total

synthesis of belactosin A (Figure 3). The method describes the asymmetric synthesis of a 2,3-disubstituted β-lactone (**55**) using chloral (**49**), propionyl chloride (**9**, R=Me) and an *O*-acetyl quinidine catalyst (Scheme 25). The product was identified as the *trans* isomer, by comparison to literature ^{1}H NMR data,[40] and was obtained with respectable *trans*-selectivity (71:29 *anti*:*syn*), excellent *e.e* (>95%), and in moderate yield (50%). The (2*R*, 3*S*) absolute stereochemistry of the product was determined by ring-opening followed by conversion to a compound of known optical rotation. It is noteworthy that this example shows the first use of *in situ* ketene generation (for this type of organocatalytic β-lactonisation) *via* dehydrochlorination of acid chlorides using a stoichiometric amount of non-nucleophilic Hünig's base. Triethylamine, being less sterically hindered and more nucleophilic, was thought to act as a competing, achiral organocatalyst and hence gave much lower enantioselectivities.

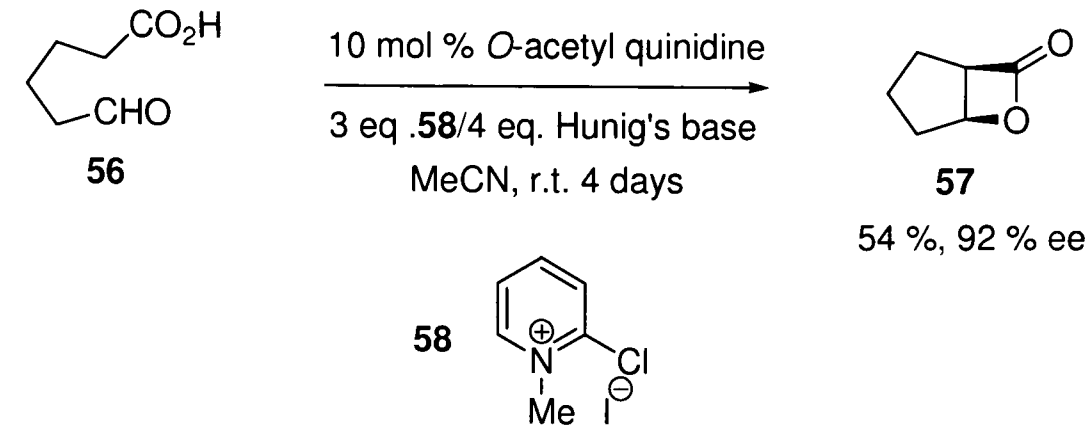


49 **9** (2*R*, 3*S*)-(major isomer)-**55**

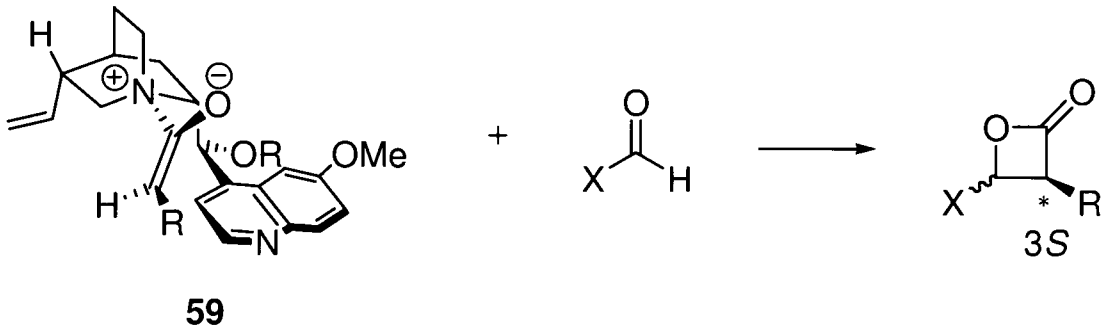
50%, >95% ee, 71:29 *trans/cis*

Scheme 25

In 2001 Romo *et al.*,[41] set the precedent for the use of unactivated aldehydes in an intramolecular version of the organocatalytic cyclisation. The ketene component is formed directly from the carboxylic acid using Mukaiyama's reagent **58**. In this case the constraints of the bicyclic system allow formation of the *cis* product only (**57**) (Scheme 26). The reaction was carried out on a number of substituted oxo-acid precursors with varying yields (36-68%) and generally high *e.e* values (>80%).



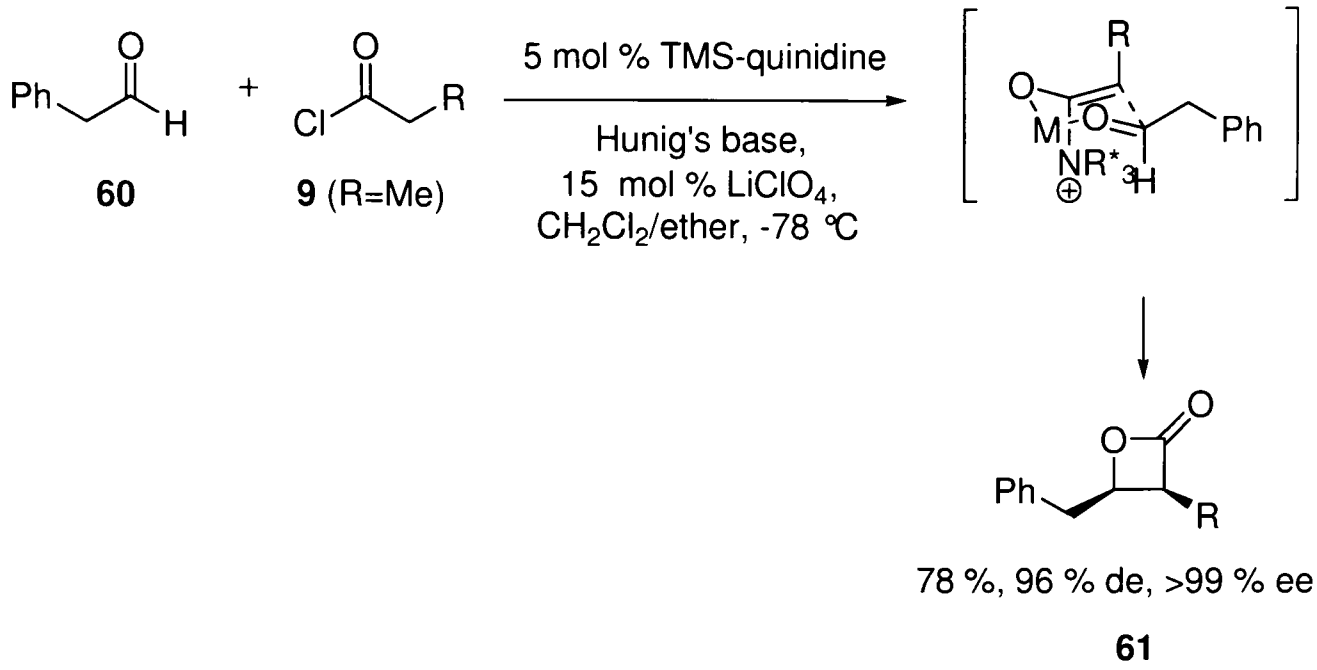
Scheme 26



Scheme 27

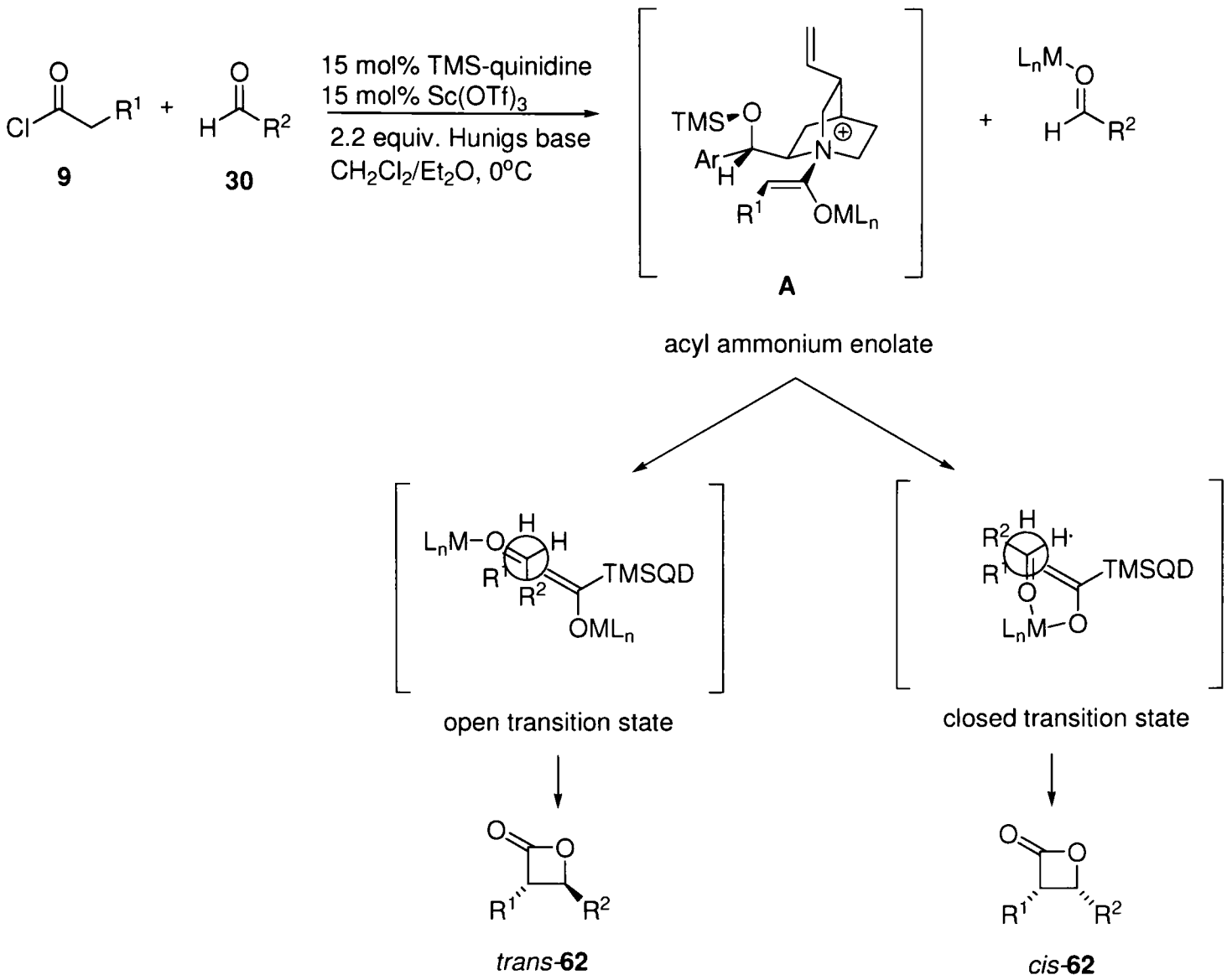
A model has been proposed by Calter[42] and Romo[41] to account for the observed 3*S* stereoselectivity obtained with a quinidine catalyst. A so called app-open quinidine-ketene complex is invoked (**59**). Formation of the *Z*-enolate is imposed by approach of the chiral amine opposite to the ketene substituent, which orientates itself into open space away from the ethylene bridge of the quinuclidine ring. Effective shielding of the *re*-face of the enolate leaves the opposite *si*-face accessible to the incoming aldehyde, inducing 3*S* stereoselectivity (Scheme 27).

More recently both Nelson and Calter have undertaken work towards the formation of disubstituted β-lactones using a diverse range of unactivated aldehydes along with a stoichiometric amount of tertiary amine, a catalytic amount of a cinchona alkaloid derivative and a Lewis acid. Nelson's procedure[43] uses lithium perchlorate as the Lewis acid of choice and shows a highly *cis* selective reaction, the stereochemistry of which is postulated to arise from a closed transition state mediated by the presence of the Lewis acid (Scheme 28).



Scheme 28

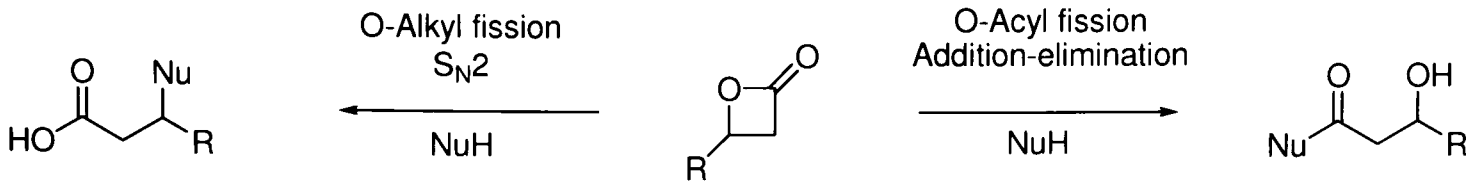
Alternatively Calter[44] has described the use of scandium triflate to form *trans* disubstituted β-lactones from a range of aliphatic acid chlorides (**9**) and aromatic aldehydes (**30**), in high yield (75-80%) and with excellent *d.e* (>9:1 in all cases) and *e.e* (92-99%). Models have been advanced to explain the configuration at both C2 and C3. The stereochemistry obtained at the C2 centre is dependent upon the metal, proceeding *via* either an open or a closed transition state leading to the *trans* or the *cis* isomer respectively. It was noted that higher concentrations of Lewis acid favoured the formation of the *trans* isomer, indicating that the transition state leading to this isomer involves two molecules of Lewis acid (Scheme 29). The C3 stereochemistry is reliably predicted using the so called app-open ammonium *Z*-enolate model (**A**), identical to that put forward by Calter and Romo to rationalise the 3*S* induction in the intramolecular reaction (Scheme 27).



Scheme 29

1.1.3 Nucleophilic Ring Openings of β-Lactones[45]

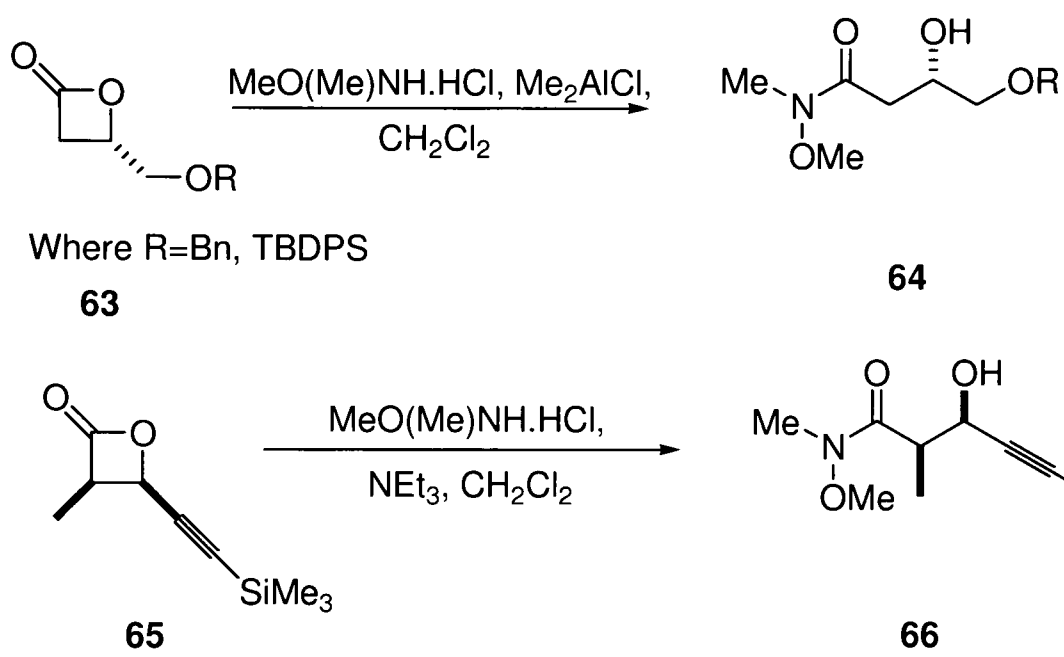
The ring strain inherent in the 4-membered β-lactone system makes it highly susceptible to nucleophilic attack followed by ring opening. The use of a hard nucleophile in such a reaction results in the cleavage of the C-O acyl bond *via* an addition-elimination mechanism, with formation of an aldol product. However, soft nucleophiles generally attack in an S_N2 manner with cleavage of the C-O alkyl bond. In this case β-substituted carboxylic acids are the major product (Scheme 30). This section seeks to highlight some of the more recent examples of such reactions.



Scheme 30

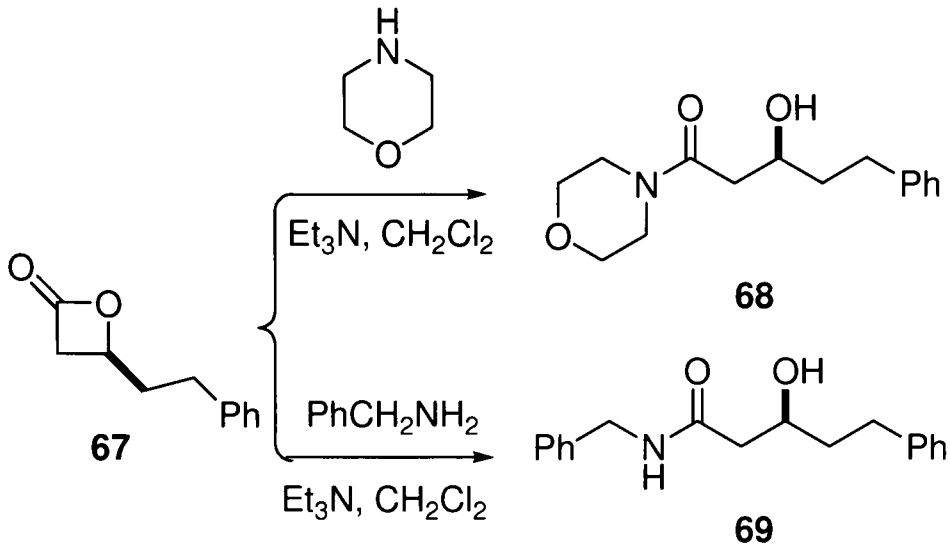
1.1.3.1 O-Acyl Cleavage

Nelson *et al.*[46] have shown two examples of mono- and disubstituted β-lactone ring openings *via* amine-mediated addition-elimination, using *N,O*-dimethylhydroxylamine, to give the corresponding Weinreb amides (**64** and **66**). All products were delivered with consistently high yields (83-97%) (Scheme 31).



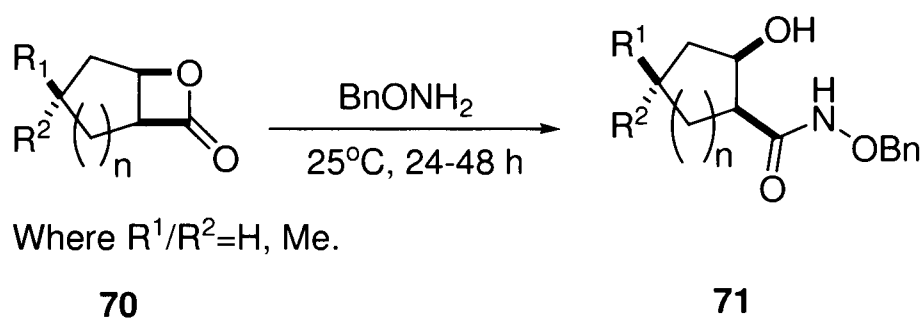
Scheme 31

Morpholine and benzyl amide were also used as examples of efficient nucleophiles for the addition-elimination reaction, giving the resultant aldol products (**68** and **69**) in high yield (95% and 88% respectively) (Scheme 32).



Scheme 32

Romo *et al.*[47] have also used hydroxylamine nucleophiles to study the acyl C-O cleavage of bicyclic β-lactone systems. *O*-Benzylhydroxylamine was selected as the reagent of choice and used with a number of bicyclic substrates to facilitate the ring-opening reaction, yielding hydroxamic acid derivatives (**71**) in moderate yield (45-50%) (Scheme 33).

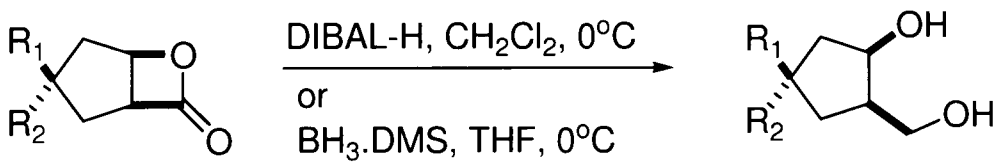


Where R^1/R^2=H, Me.

70 **71**

Scheme 33

The reductive opening of bicyclic β-lactones is also demonstrated using both di-isobutylaluminium hydride and a borane-dimethylsulfide complex to yield the corresponding diols[47] (**72**) (Scheme 34).

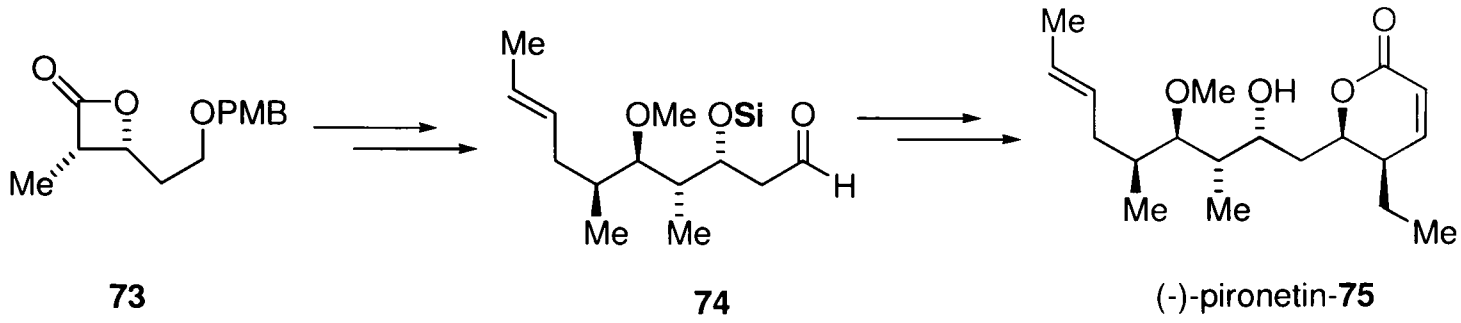


Where R_1/R_2=H, Me, OCH_2CH_2O.

70 **72**

Scheme 34

Nelson *et al.*[48] employed the *O*-acyl cleavage approach in the enantioselective total synthesis of (-)-pironetin (**75**) (Scheme 35). The synthesis involves a series of acyl halide-aldehyde cyclocondensation (AAC) reactions used to form a number of stereochemically defined β-lactone rings. These lactones are subsequently opened using hard nucleophiles, such as *N*, *O*-dimethylhydroxylamine, in order to build the extended propionate skeleton of the target molecule.

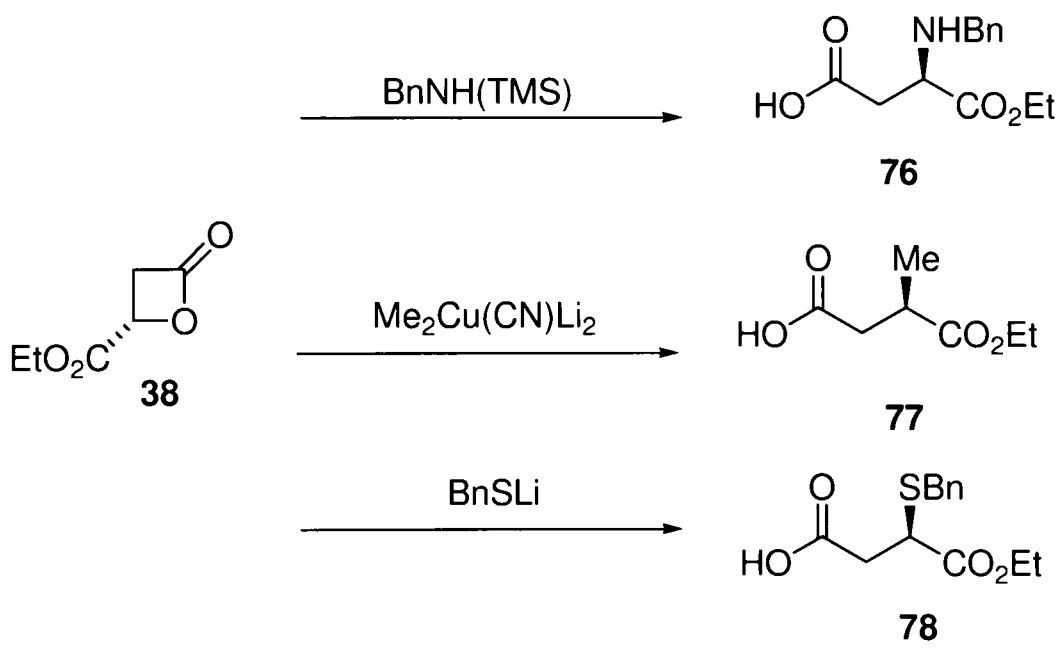


73 **74** (-)-pironetin-**75**

Scheme 35

1.1.3.2 S_N2 O-Alkyl Cleavage

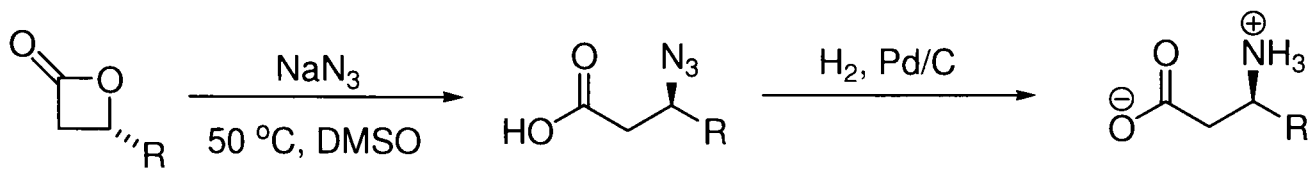
Work by Evans *et al.*[33] has shown that the S_N2 *O*-alkyl fission reaction may be facilitated with a range of different nucleophiles (Scheme 36), including *N*-benzyl-*N*-(trimethylsilyl)amine, the organocuprate $Me_2Cu(CN)Li_2$, and lithium benzylsulfide. All products were obtained in good yield (> 83%).



Scheme 36

Nelson *et al.*[49] set the precedent for the use of soft nitrogen based nucleophiles, such as the azide anion, to effect exclusive S_N2 alkyl bond cleavage with a number of

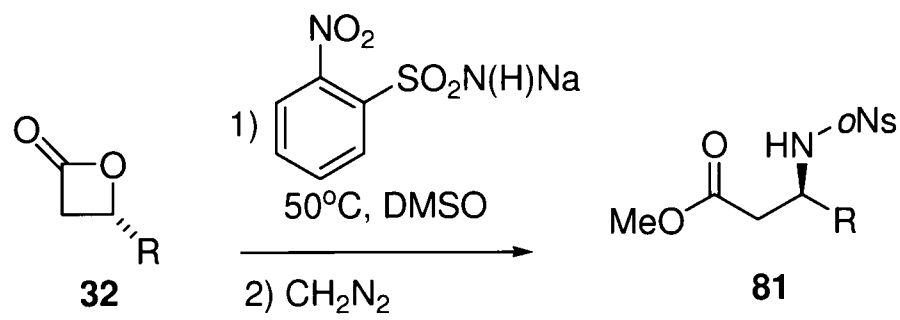
monosubstituted β-lactones, where R=alkyl, branched alkyl and aromatic chains. (Scheme 37). Highly regioselective nucleophilic addition to the C2 centre is observed. Additionally the azido acid product can be isolated and purified with the use of a simple extractive workup, the products being obtained in high yield (83-94%) and with excellent *e.e* (92-97% for those determined). Subsequent azide reduction (H_2, Pd/C) provides access to chiral substituted β–amino acids.



32 **79** **80**

Scheme 37

Furthermore, Nelson has described the use of the *o*-nitrobenzenesulfonamide anion to install an amine bearing an easily removable protecting group at C2.[49] A number of monosubstituted β-lactones (R=alkyl, branched alkyl and aromatic chains) were shown to work well in this reaction giving moderate yields (43-83%) with high *e.e* values (93-95% for those determined) (Scheme 38). However, the substituent R group appears to have a significant bearing upon the regioselectivity of the reaction. Lactones with increased steric bulk at C2, for example where R=*c*-C_6H_{11}, suffer significant competition between the S_N2 and the carbonyl addition pathways, a problem not encountered when using azide.

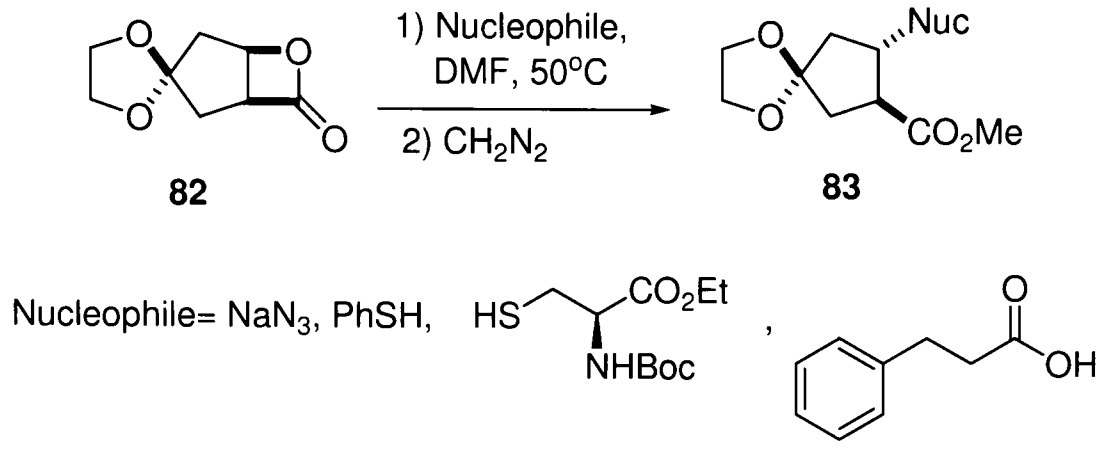


32 **81**

Scheme 38

Romo *et al.*[47] has demonstrated the use of a range of soft nucleophiles in the S_N2 ring cleavage of bicylic β–lactones to give *trans*-β-substituted cyclopentane esters (**83**) (Scheme 39). Yields for the reaction proved to be variable with the *N*-Boc-cysteine ethyl

ester giving a yield of just 14%, whereas benzenethiol, sodium azide and hydrocinnamic acid gave much improved results of 81%, 76% and 58% respectively.



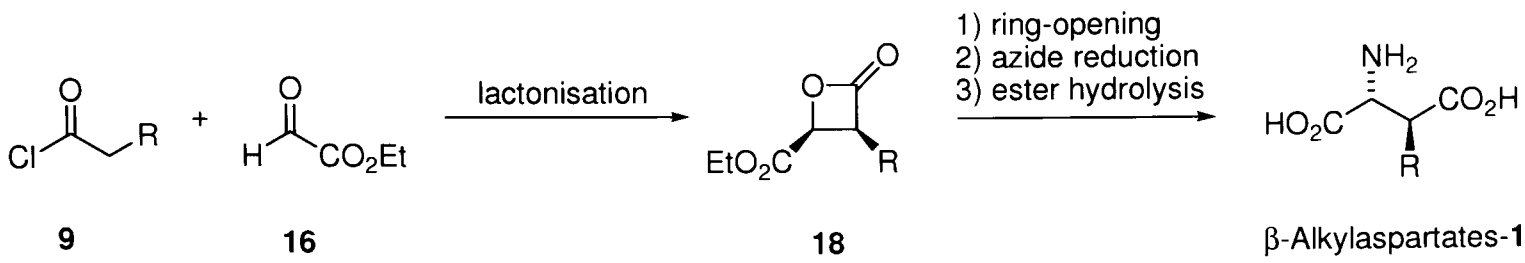
Scheme 39

1.1.4 Project Aims

As previously discussed in Section 1.1.1.2 we proposed to optimise the original *cis*-β-lactone ring-forming reaction (Scheme 4). It was suggested that initial experimental work be carried out using three simple, commercially available acid chlorides where R=Me, *i*-Pr and Bn. Once optimal reaction conditions had been established it was envisaged that the scope of the lactonisation procedure, using ethyl glyoxylate (**16**) and a range of both commercially and non-commercially available acid chlorides (**9**), could be tested. It was thought that the proposed S_N2 C2 lactone ring-opening would occur using a soft nitrogen nucleophile and literature precedent suggested that azide may be a good selection with this reaction in mind. Simple functional group manipulation (azide reduction and ester hydrolysis) should then allow access to the biologically significant β-alkyl aspartate motif.

As we had predicted, based upon literature precedent,[15] that our initial experimental work would provide the *trans* diastereomer of the disubstituted β-lactone, we were initially surprised to obtain the *cis* product almost exclusively. With this observation in mind it was proposed that the stereochemical outcome of the cycloaddition reaction should be considered in detail. It was also hoped that the synthesis of a literature compound, β-methylaspartic acid **1** (where R=Me), would allow the absolute configuration of the lactone starting material to be determined (Scheme 40). Comparison of the $[\alpha]_D$ values of the literature compound and the synthetic compound, produced using the lactonisation-

S_N2 ring-opening methodology described, should allow the lactone configuration to be deduced with ease.

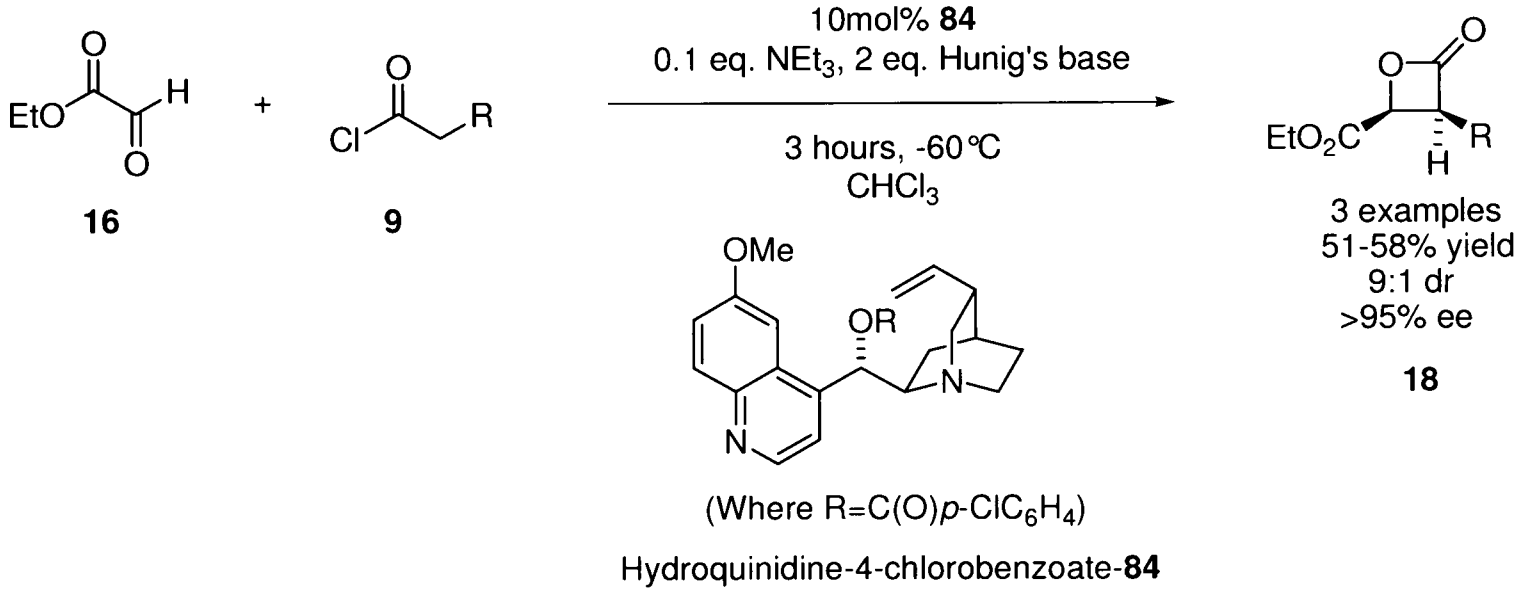


Scheme 40

1.2. Results and Discussion

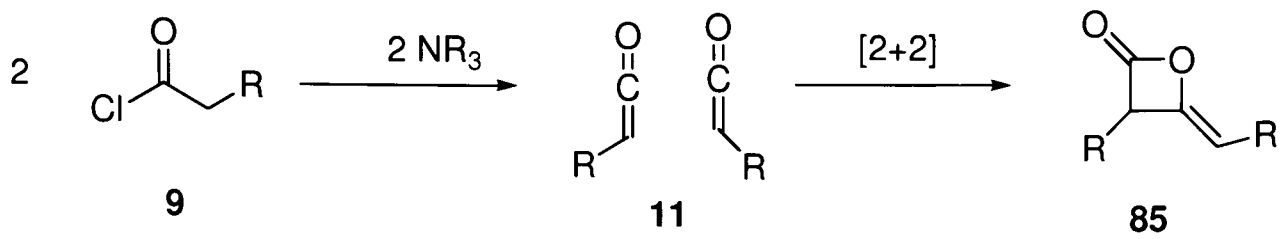
1.2.1 Previous Results-Optimisation of the Lactonisation Reaction

In this section, initial work carried out by co-workers, focusing upon the establishment of a reliable set of reaction conditions, is discussed. The original lactonisation procedure optimised[50,51] for acid chlorides where R=Me, *i*-Pr, Bn, is highlighted in Scheme 41. A mixture of ethyl glyoxylate (50% solution in toluene) and acid chloride in chloroform is added dropwise over 30 minutes to a stirred solution of triethylamine, Hünig's base and catalyst in chloroform at -60°C. The mixture is then stirred for 2.5 hours, after which time removal of solvent and subsequent column chromatography allows access to the desired lactone products.



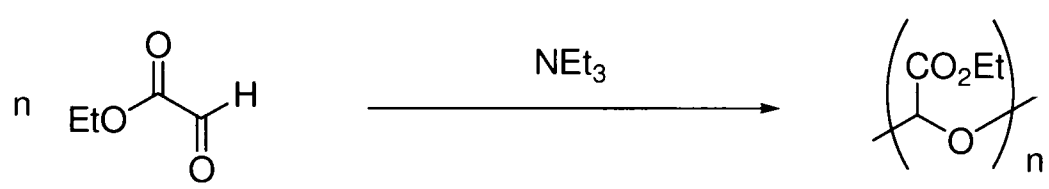
Scheme 41

Initial results proved several aspects of the reaction to be important in order to achieve consistently good yields. The success of the reaction was very much dependent upon the order of reactant addition. Ketene dimer **85**, formed *via* the deprotonation of acid chloride **9**, with a subsequent [2+2] cycloaddition, was found to be the major product of the reaction when either glyoxylate was added to the base/acid chloride mixture, or acid chloride was added to the base/glyoxylate mixture (Scheme 42). The amount of ketene dimer formed could only be measured in a qualitative manner by TLC analysis as decomposition on a silica column prevented its isolation.



Scheme 42

Formation of dimer **85** upon addition of the glyoxylate to the base/acid chloride mixture simply suggested an alternative reaction pathway whereby the presence of base alongside acid chloride led to formation of the ketene with subsequent dimerisation before either component could react with the glyoxylate. Dimer formation upon addition of the acid chloride to the base/glyoxylate mixture was thought to be due to the consumption of glyoxylate by a base assisted polymerisation reaction[52] (Scheme 43), hindering the desired lactonisation pathway.

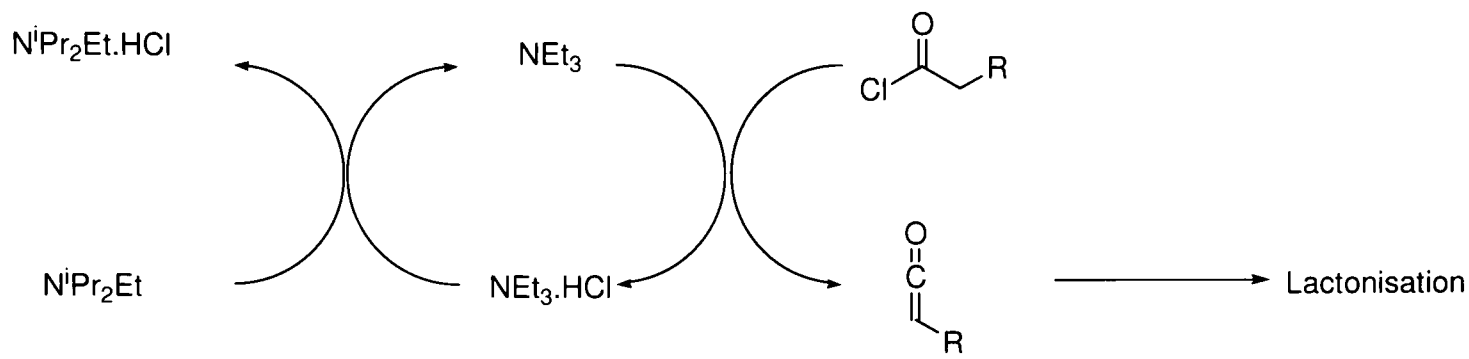


Scheme 43

Co-workers attempted to minimise both the dimerisation and polymerisation pathways. Accordingly yields were found to improve when the glyoxylate/acid chloride mixture was added to the Hünig's base/NEt_3 solution. This was encouraging and after further optimisation it was found that yields of between 50-60% could be achieved upon dropwise addition of the glyoxylate/acid chloride mixture to the basic catalytic system over a period of 0.5 hours.[51]

Additionally, the presence of both Hünig's base and triethylamine were found to be key in order for the reaction to proceed with consistently reasonable yields and high *e.e* values. Co-workers[51] have shown that the more sterically bulky Hünig's base is incapable of dehydrochlorinating acid chlorides to form the desired ketene. Furthermore, although triethylamine was able to form the required ketene there was evidence that this smaller, more nucleophilic base could also act as a competing organocatalyst in the lactonisation

process, eroding the *e.e* of the final product. Using 2 equivalents of Hünig's base and a catalytic amount of triethylamine (10 mol%) bypasses this problem, with the NEt_3HCl salt, formed upon generation of the ketene, being recycled by the stoichiometric quantity of Hünig's base (Scheme 44).



Scheme 44

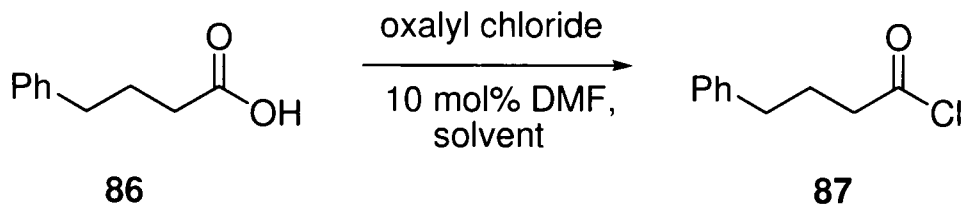
Prior to the start of any new work on this project it was deemed important to be able to repeat the initial successful results obtained in the lactonisation reaction, again using the three acid chlorides (R=Me, *i*-Pr, Bn, Scheme 41) tested in the preliminary optimisation studies. Disappointingly upon repetition of these primary results yields of less than 30% were consistently observed. It was proposed that polymerisation of the commercially available glyoxylate starting material (quoted as a 50% solution in toluene) may be preventing the reaction from giving the higher yields (50-60%) previously reported by co-workers. Indeed ^{1}H NMR analysis showed the glyoxylate solution to be ca. 1.4 M in glyoxaldehyde. Adjusting the quantity of glyoxylate used upon the basis of this analysis saw a subsequent increase in reaction yield to levels equivalent to those previously observed.

Now, comfortable with the reliable reaction conditions in hand, a number of acid chlorides were synthesised in order to test the scope of the lactonisation procedure.

1.2.2 Acid Chloride Synthesis

A range of acid chlorides were selected for testing in the lactonisation reaction. Alkyl, branched alkyl, aromatic and silyl protected hydroxy substituents would provide a wide selection of functionality that we hoped would allow us to screen the steric and electronic

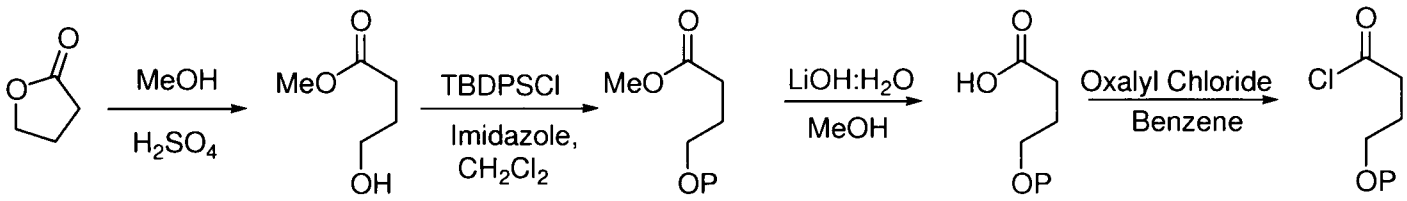
effects of the chemistry. Propionyl, isovaleryl, hydrocinnamoyl, butyryl and 3, 3-dimethyl-butyryl chloride were all obtained directly from a commercial source. 4-Phenyl butyryl chloride (**87**) was synthesised in excellent yield (97%) from the corresponding carboxylic acid (**86**) using standard oxalyl chloride chemistry[53,54] (Scheme 45).



86 **87**

Scheme 45

Silyloxy-substituted acid chloride **92** was obtained in 4 steps from commercially available γ-butyrolactone (**88**). Ring-opening with methanol to form methyl ester **89**, followed by TBDPS (*t*-butyldiphenylsilyl ether) protection, gave **90** in 40% yield over 2 steps. Subsequent ester hydrolysis allowed the synthesis of carboxylic acid **91** (88%) which was then readily transformed to acid chloride **92** using standard conditions (quantitative yield) (Scheme 46).[55-57]



88 **89** **90** **91** **92**

(Where P=TBDPS)

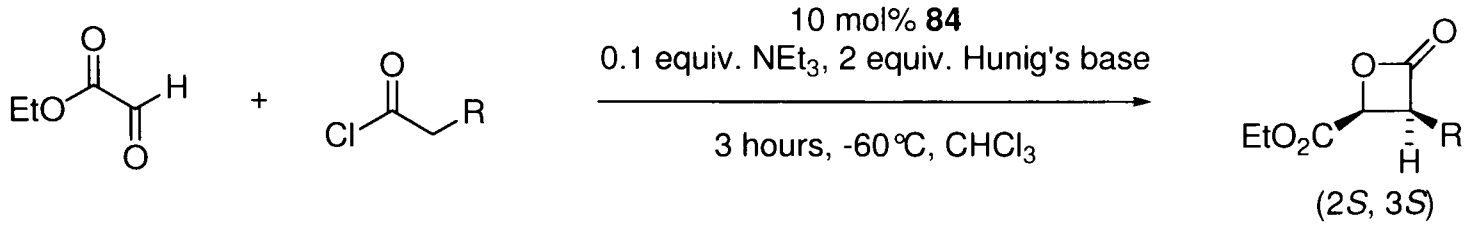
Scheme 46

With a range of substituted acid chlorides now in hand we planned to test the substrate scope of the lactonisation reaction.

1.2.3 Synthesis of *cis*-2, 3-Disubstituted β-lactones

As previously described the simple acid chlorides where R=Me, *i*-Pr, Bn were tested first, using the quinidine derived catalyst **84**, giving promising results (entries 1, 4 and 6). Elongation of the alkyl chain to incorporate R=Et (entry 2) and R=CH_2Bn (entry 7) was well tolerated. Additionally we were encouraged by the result shown in entry 8 where a

silyl protected hydroxyl functionality was successfully incorporated at C3. Entries 3 and 5 demonstrate that the pseudoenantiomeric catalyst hydroquinine-4-chlorobenzoate can be used to obtain the opposite enantiomer of the lactone product. The use of 3, 3-dimethyl-butyryl chloride (entry 9) in the reaction gave none of the desired product. It is postulated that the *cis*-disubstituted β-lactone does not form due to steric congestion caused by the large *t*-Bu group.

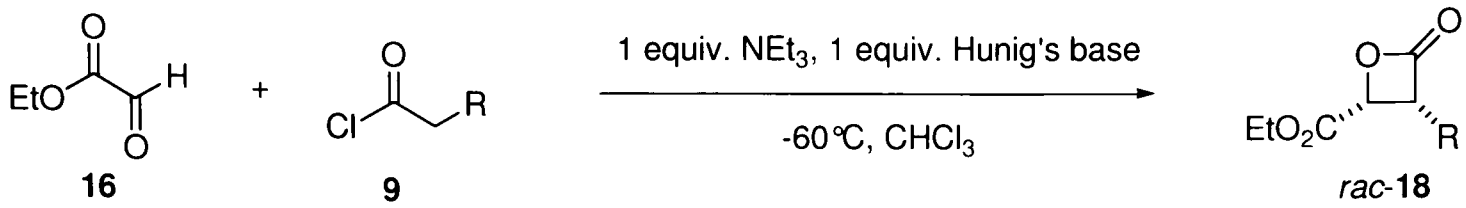


Entry	R Group	Yield (%)	*cis:trans*[(b)]	*e.e* (%)[(c)]
1	Me	55	>95:5	>95
2	Et	50	>95:5	>95
3	Et[(a)]	58	>95:5	>95[(a)]
4	*i*-Pr	59	>95:5	>95
5	*i*-Pr[(a)]	60	>95:5	>95[(a)]
6	Bn	48	>95:5	>95
7	CH_2Bn	54	>95:5	>95
8	$(CH_2)_2OSi^tBuPh_2$	47	>95:5	>95
9	*t*-Bu			

[(a)] Hydroquinine-4-chlorobenzoate used as catalyst to give the enantiomeric product to that obtained using **84**; [(b)]*cis:trans* ratio measured by ^{1}H NMR analysis; [(c)] Enantiomeric purity measured by chiral shift NMR using Eu(hfc)$_3$.

Table 1

Diastereomeric ratios were determined by the integration of peaks from ^{1}H NMR spectra, with the *cis/trans* isomers being identified *via* the analysis of coupling constants (General literature values: $^3J_{cis}$= approx. 6.5 Hz, $^3J_{trans}$= approx. 4.0-4.5 Hz). Enantiomeric ratios were determined by chiral shift ^{1}H NMR using Eu(hfc)$_3$. In order to establish the enantiomeric purity of the chiral series of lactones an identical racemic series was synthesised using 1 equivalent of triethylamine in place of the chiral cinchona alkaloid catalyst **84** (Scheme 47). Yields of the racemic lactones were lower than those of their enantiomerically pure counterparts (34% and 55% respectively, where R=Me) due to an increase in diketene formation upon using stoichiometric quantities of triethylamine.



Scheme 47

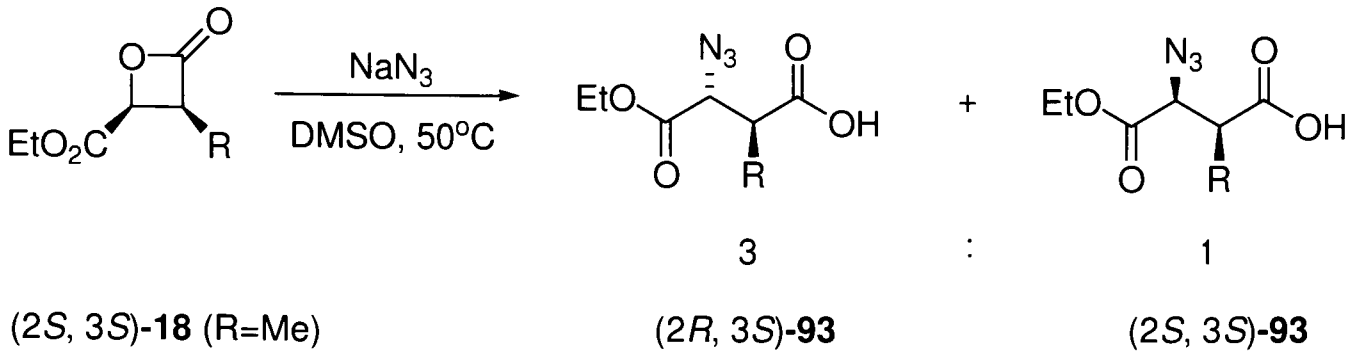
Having established the scope of the lactonisation reaction we now wanted to consider the potential of these enantioenriched products to undergo ring-opening.

1.2.4 Azide Mediated Ring-Opening *via* S_N2 O-Alkyl Cleavage

Based on literature precedent set by Nelson *et al.*[49] (Scheme 37), sodium azide was selected as the nucleophile of choice for the β-lactone ring-opening reaction. This would allow direct installation of *N*-functionality at the C2 position. Furthermore it was anticipated that subsequent catalytic hydrogenation would allow access to the free amine. Nelson's original work focused upon the ring-opening of C2-monsubstituted β-lactones. In contrast our system requires the ring-opening of disubstituted derivatives, which may prove more challenging due to steric constraints, so with this in mind we chose to conduct initial test reactions on the 2,3-disubstituted methyl lactone **18**, R=Me.

The methyl substituted lactone **18**, in DMSO, was added to a stirred solution of NaN_3 in DMSO at 50°C. The reaction was allowed to stir for 4 hours, until all of the lactone starting material had been consumed as judged by TLC analysis. Using a simple acid-base extraction procedure the desired azido acid product was obtained in reasonable yield (60%). Unfortunately, the diastereoselectivity of the reaction was poor, 3:1, ((2*R*, 3*S*)-**93**): ((2*S*, 3*S*)-**93**), as judged by integration of ^{1}H NMR peaks (Scheme 48). As no literature data were available for the two observed diastereomers ((2*R*, 3*S*)-**93** and (2*S*, 3*S*)-**93**) it was assumed that the major isomer was the (2*R*, 3*S*) ring-opened product. This assumption seems valid based upon the expected C2 S_N2 inversion upon ring-opening of the (2*S*, 3*S*)-lactone starting material. It is postulated that the moderate diastereoselectivity observed in the reaction can be attributed to one of two possible causes; either the desired (2*R*, 3*S*)-**93** product forms and subsequently epimerises under

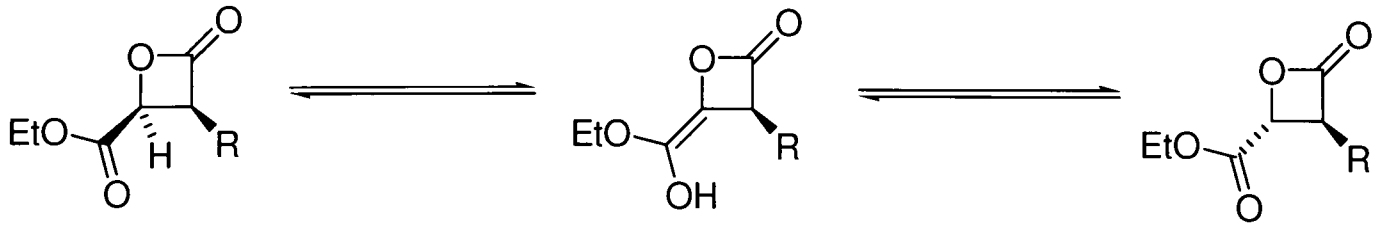
the reaction conditions; or the (2*S*, 3*S*) lactone starting material (**18**) epimerises upon heating leading to the observed mixture of diastereomeric products.



(2*S*, 3*S*)-**18** (R=Me) (2*R*, 3*S*)-**93** (2*S*, 3*S*)-**93**

Scheme 48

In order to test this hypothesis the original 3:1 mixture of diastereomers ((2*R*, 3*S*)-**93** and (2*S*, 3*S*)-**93**) was subjected to the standard reaction conditions for 2 hours. After work-up, ^{1}H NMR analysis of the reaction mixture indicated no change in the diastereomeric ratio of products. This result seems to indicate that the observed 3:1 ratio does not result from the interchange of product diastereomers during the reaction, unless this is the true thermodynamic ratio of products. Therefore it seems likely that the poor observed diastereoselectivity of the reaction arises *via* epimerisation of the starting material at the C2 centre. With this in mind a sample of the diastereomerically pure methyl substituted β–lactone (**18**) (>95:5 *cis:trans* by ^{1}H NMR), was stirred continuously in DMSO at 50°C for 1.5 hours. TLC analysis showed the appearance of one new spot and subsequent ^{1}H NMR analysis confirmed that the product was indeed a 3:1 mixture of the *cis:trans* disubstituted lactone. This suggests that epimerisation of the lactone starting material occurs upon heating, possibly *via* enolisation as shown in Scheme 49.



(2*S*, 3*S*)-**18** **94** (2*R*, 2*S*)-**18**

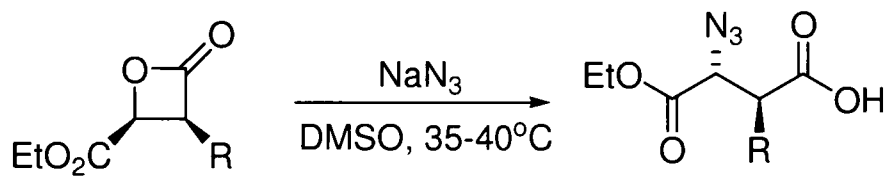
Scheme 49

Pleasingly, decreasing the reaction temperature to between 35-40°C resulted in an increase in the diastereomeric ratio from 3:1 to 9:1 ((2*R*, 3*S*)-**93**): ((2*S*, 3*S*)-**93**), again

with a reasonable product yield of 60%. Having established a reliable set of conditions the scope of the reaction could now be expanded to the use of some of the β-lactones synthesised in the initial section of this project.

1.2.4.1 Scope of the Azide Mediated Ring-Opening Reaction

Lactones with alkyl, branched alkyl and aromatic R groups (R=Et, *i*-Pr and CH_2Bn) were selected in order to test the tolerance of the reaction to various substitution patterns. Again this methodology proved to be fairly general and all β-azido acids were obtained in good yield and with high diastereoselectivities (Table 2).



Entry	R Group	Yield (%)	((2*R*, 3*S*)-**93**): ((2*S*, 3*S*)-**93**)[a]
1	Me	60	9:1
2	Et	74	9:1
3	*i*-Pr	61	9:1
4	CH_2Bn	66	9:1

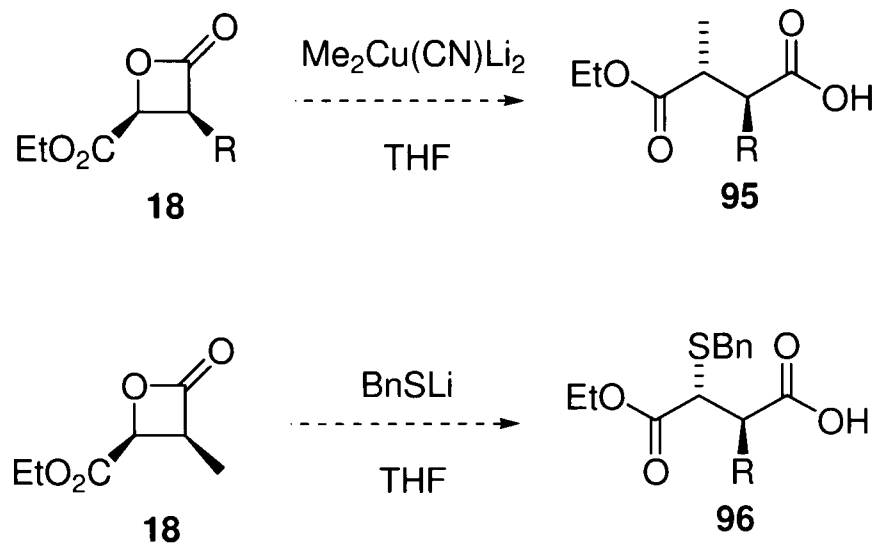
[a] ((2*R*, 3*S*)-**93**): ((2*S*, 3*S*)-**93**) determined by ^1H NMR.

Table 2

Initially it was thought that lactones with larger, bulkier substituents in the C3 position may require increased reaction times or higher temperatures due to the increased steric congestion adjacent to the reaction centre. However, results showed that all substituted lactones reacted within 4 hours at temperatures of no more than 40°C.

In addition to the use of azide in the ring-opening reaction, and inspired by work detailed by Evans *et al.* (Scheme 36)[33] on the ring-opening of monosubstituted β-lactones using organocuprates and soft sulfur nucleophiles, we also attempted to use the cuprate $Me_2Cu(CN)Li_2$, and lithium benzylsulfide BnSLi, in our own ring-opening procedure. Again, the less sterically hindered methyl substituted lactone (**18**) was selected for use in initial test reactions. In both cases product peaks could not be unambiguously assigned in

the ^{1}H NMR spectra of the crude reaction mixtures. In the reaction using lithium benzylsulfide no starting material was present at the end of the reaction as judged by ^{1}H NMR. In the organocuprate case a minimal amount of starting material was still visible in the ^{1}H NMR spectrum after the reaction was terminated (δ=4.93 ppm, (1H, d, *J* 6.9, EtO_2CCH)). Purification of the multi-spot reactions proved difficult (Scheme 50).

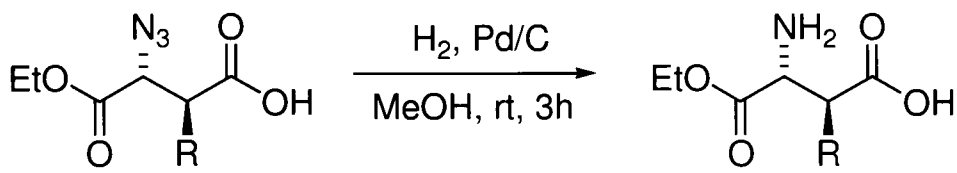


Scheme 50

Having synthesised a number of azido acid substrates it was hoped that a simple reduction procedure would allow access to the β–amino acid moiety required for the synthesis of the target β-alkyl aspartates.

1.2.5 Reduction of Substituted Azido Acids

Catalytic hydrogenation using palladium on carbon in methanol provided access to the β-amino acid esters (**97**) in excellent yield with no erosion of diastereoselectivity (Table 3).



Entry	R Group	Yield (%)	(2*R*, 3*S*)-**97**: (2*S*, 3*S*)[a]
1	Me	99	9:1
2	Et	Quantitative	9:1
3	*i*-Pr	Quantitative	9:1
4	CH_2Bn	92	9:1

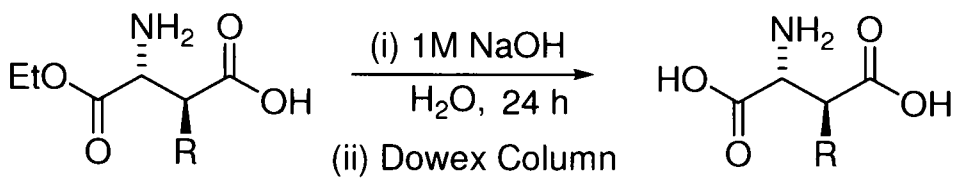
[a] (2*R*, 3*S*): (2*S*, 3*S*) determined by ^{1}H NMR.

Table 3

1.2.6 Synthesis of β-Methyl Aspartic Acid and Conformation of Stereochemistry

At this stage the predicted (2*R*, 3*S*) configuration of the β–amino acid esters (**97**) was based upon the expected S_N2 inversion of configuration in the (2*S*, 3*S*)-β-lactone ring-opening step. In order to confirm this prediction we hoped to synthesise a literature compound enabling the comparison of optical rotation values, and hence allowing us to establish the absolute stereochemistry of our synthetic β-amino acids.

To this end we proposed the synthesis of β-methylaspartic acid (**1**, where R=Me), a component of the phosphatase inhibitor, motuporin (**2**) (Figure 2). The synthesis of **1** was readily achieved using a simple ester hydrolysis procedure (NaOH, H_2O), freeing the amino acid product using a Dowex® ion exchange column (Scheme 51).

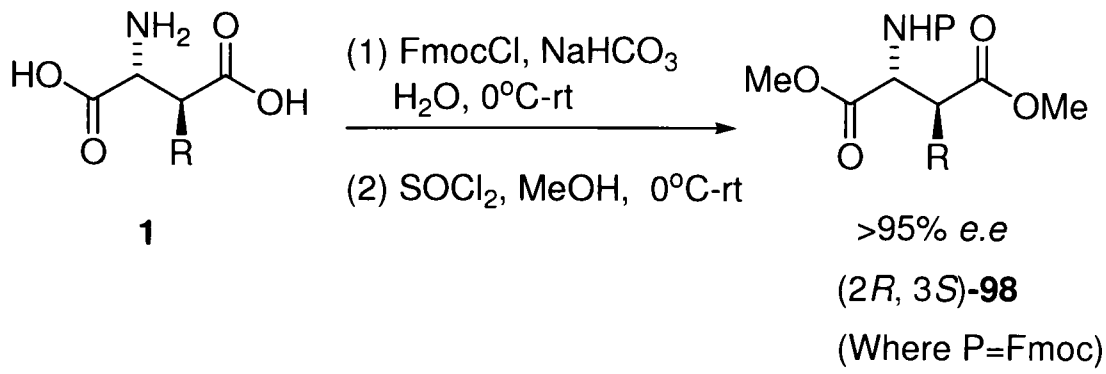


97 (2*R*, 3*S*)-**1**

Scheme 51

β-Methylaspartic acid has previously been synthesised *via* a multistep route to give both the syn- and anti- diastereomers.[7] ^{1}H NMR Data are reported for both diastereomers and we were pleased to note that the ^{1}H NMR spectrum of our synthetic sample matched well with that reported for the anti-isomer. Additionally, the optical rotation of our sample ($[\alpha]_D^{21}$ -31.0 (*c* 2.00, 5M HCl)) was almost equal, and opposite, to that of the (2*S*, 3*R*) product reported in the literature ($[\alpha]_D^{21}$ +34.3 (*c* 2.05, 5M HCl)), suggesting that indeed our β-amino acid product (**1**) has an absolute configuration of (2*R*, 3*S*), and thus that the β -lactone starting material has a configuration of (2*S*, 3*S*). In order to confirm the optical purity of our sample *N*-Fmoc protected dimethylester **98** was synthesised in two steps (30% overall yield) from **1** (where R=Me) (Scheme 52). Chiral HPLC analysis confirmed that our sample was essentially enantiomerically pure (>95%), (*rac*-**98** was synthesised

for HPLC analysis *via* an identical route from racemic lactone starting material (Scheme 47)).

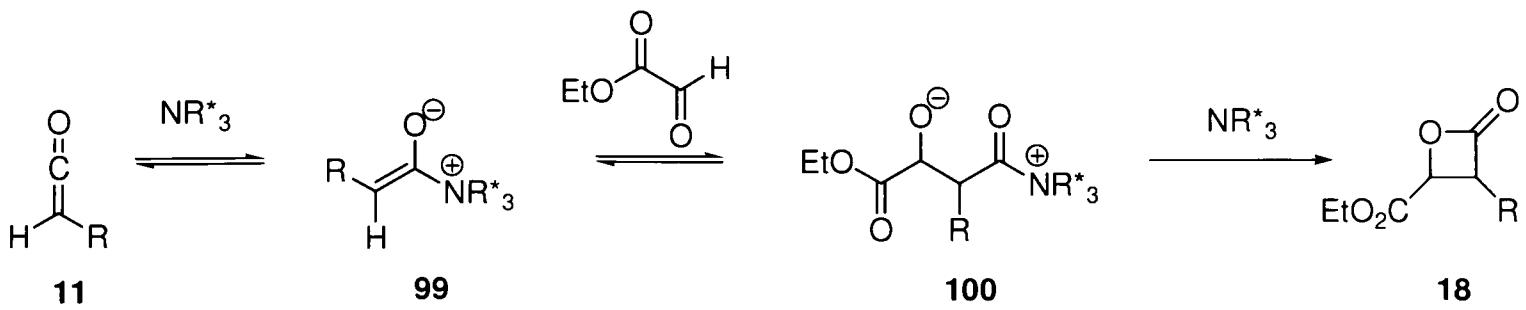


Scheme 52

The confirmed (2*S*, 3*S*) absolute configuration of the lactone product, obtained with catalyst **84**, can be explained using two models.

1.2.6.1 Models for the Apparent (2*S*, 3*S*) Stereoselectivity of the Lactonisation Reaction

The stereoselectivity at the C3 centre is explained using the model put forward by Calter[42] and Romo[41] for 3*S* induction in constrained bicyclic systems (Scheme 27). The *Z*-ammonium ion enolate (**99**), formed upon addition of the quinidine-derived chiral tertiary amine to the ketene species (Scheme 53), sits with the *si*-face exposed and the *re*-face protected by the so called app-open conformation of the catalyst. This prevents attack from the back face, resulting in selective attack of the glyoxylate from the *si*-face to give 3S selectivity at this centre (Figure 4). In contrast, quinine catalysis is predicted to give the opposite 3*R* enantiomer.



Scheme 53

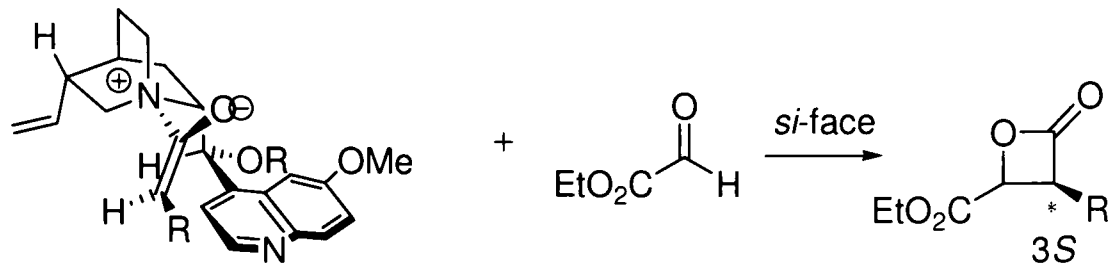
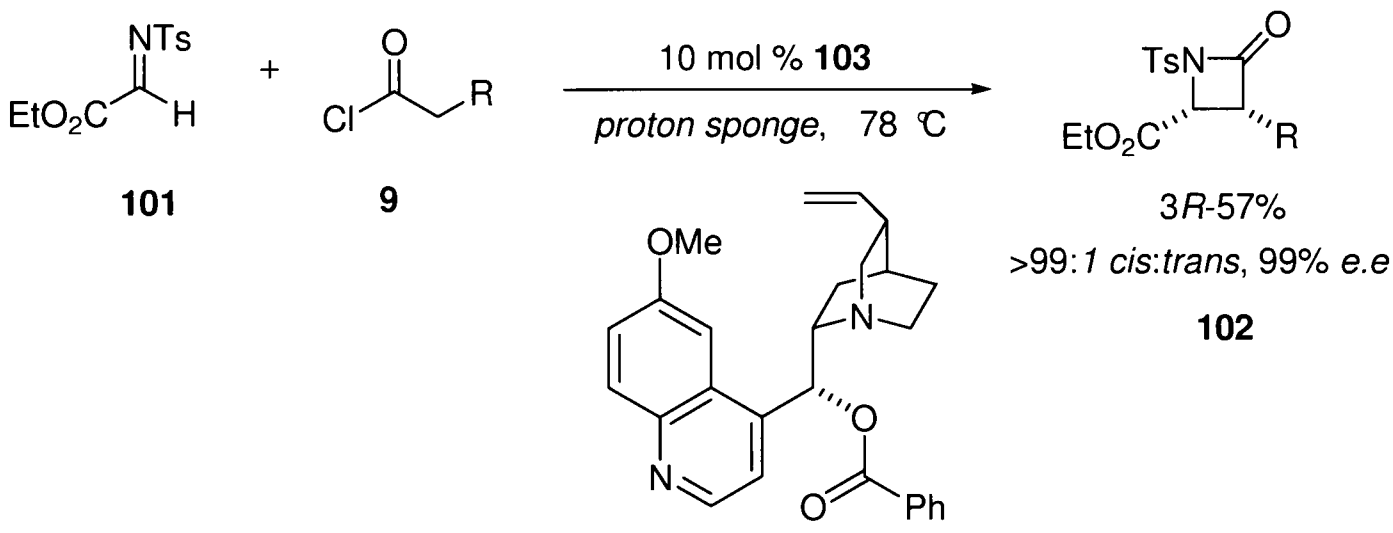


Figure 4

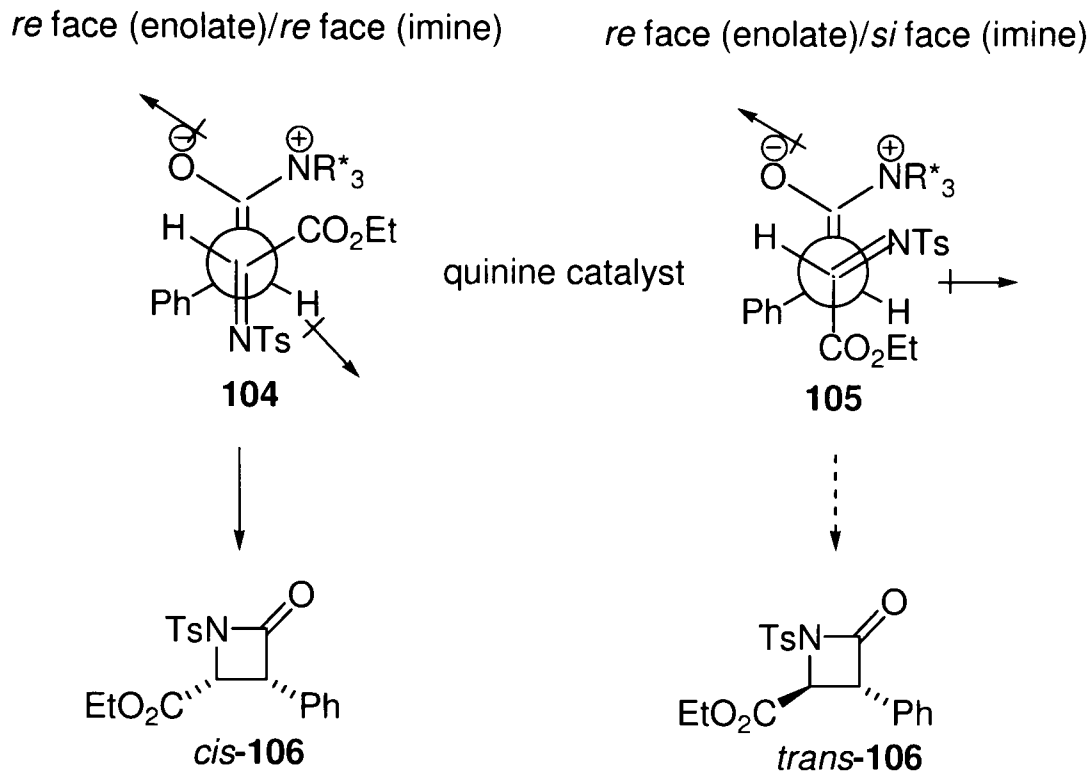
The C2-(*cis*) stereoselectivity is more difficult to rationalise, particularly since the use of chloral as an electrophile gives the *trans*-isomer as the major product (71:29 *trans:cis*) (Scheme 25).[15] However, a tentative model for the stereoinduction at this centre is proposed[50] based on Lectka's closely related *cis*-selective lactamisation reaction (Scheme 54).[58,59] The net [2+2] cycloaddition reaction between imine **101** and a range of ketenes, generated *in situ* from acid chlorides, provides *cis*-β-lactams in reasonable yield (36-65%) and with excellent enantioselectivity (99:1 or >99:1). As would be predicted from the model for stereoinduction at C3 (Figure 4), the quinidine derived catalyst provides access to the 3*S* stereocentre with quinine catalysis leading to the opposite sense of induction to give the 3*R* product.



Scheme 54

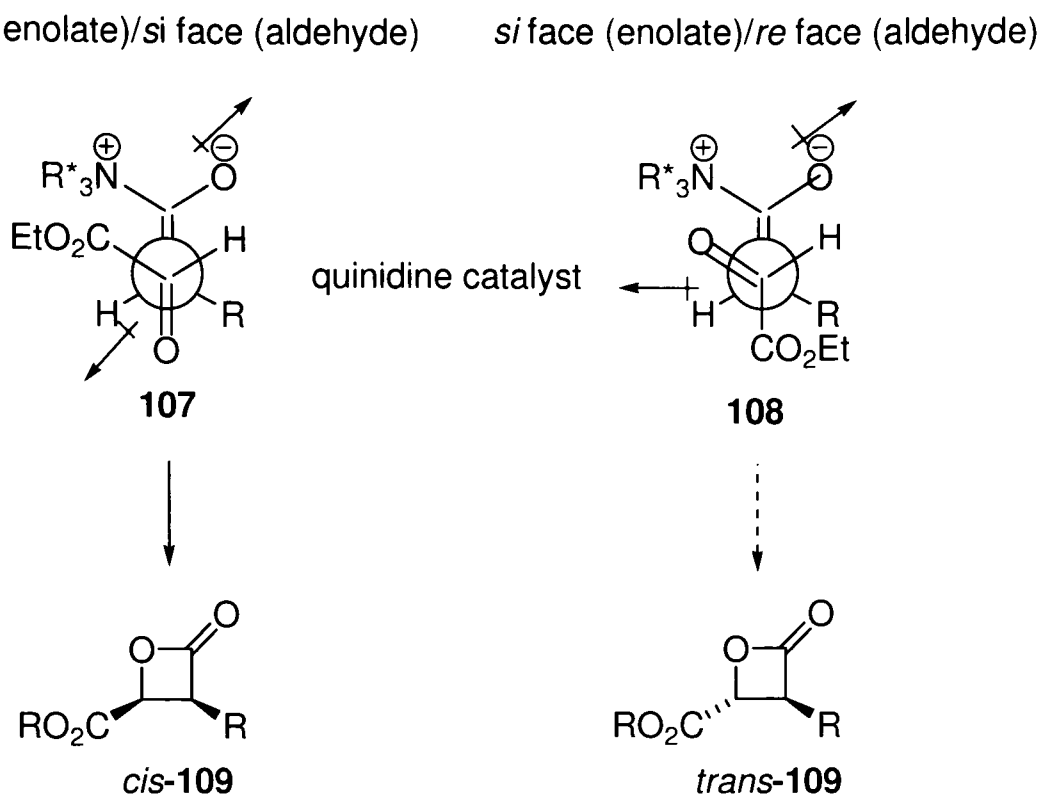
Leckta models the open transition-state for the reaction (based on a quinine-derived catalyst) using Macromodel, AMBER force field, docked at a 2.2 Å transition state distance. Results show that the lowest energy configurations, leading to the *cis*-**106** and

trans-**106** products respectively, are **104** and **105**, with **104** being lower in energy than **105** (Scheme 55). Although Leckta provides no explanation as to why configuration **104** is lower in energy than **105**, it is postulated that the difference may arise from the more effective maximisation of dipole-repulsions within **104**.



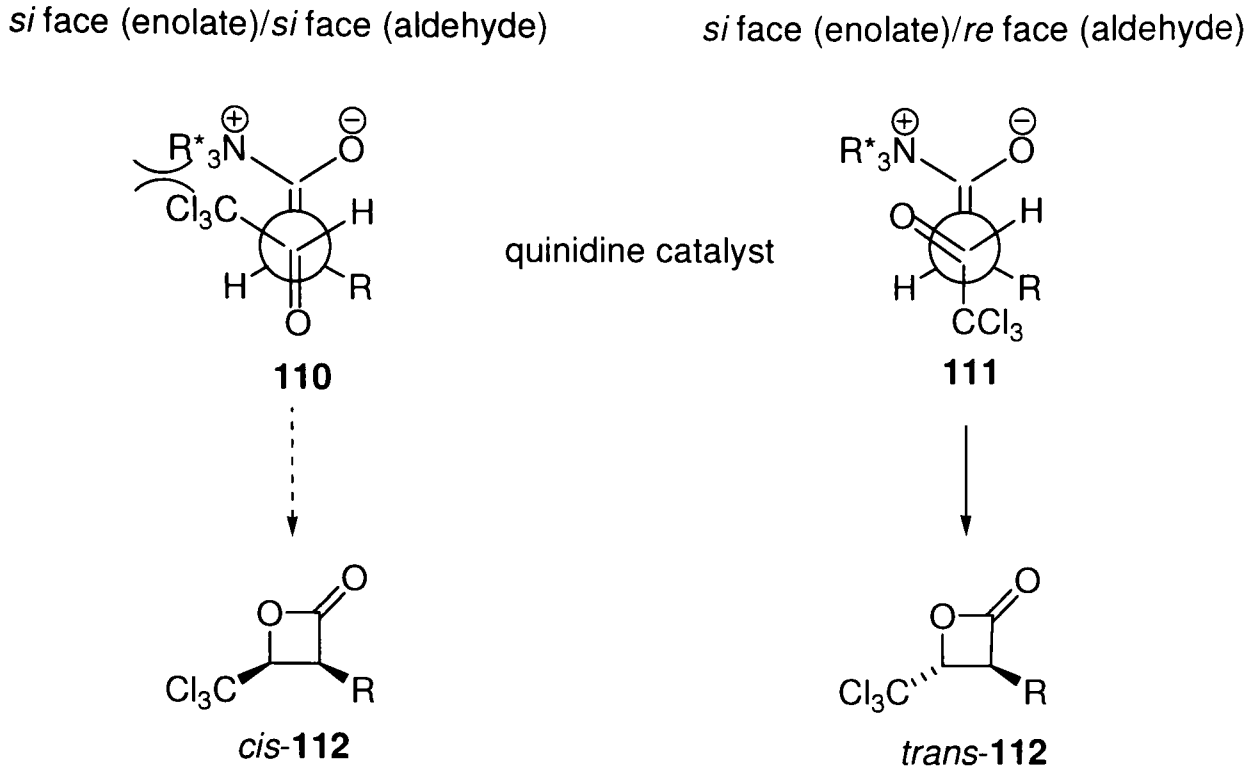
Scheme 55

Application of this model to the β-lactone system gives **107** and **108** as the two lowest energy reactive configurations, with **107** displaying more effective maximization of dipole-dipole repulsions and therefore being lower in energy than **108.** As observed, this results in the formation of *cis*-**109** as the major product. In line with the use of quinidine derived catalyst **84** in the lactonisation reaction, configuration **107** shows a *si-si* interaction, while configuration **108** depicts a *si-re* interaction (Scheme 56).



Scheme 56

This model can also be used to explain the observed *trans*-selectivity in the analogous literature reaction using chloral as an electrophile (Scheme 25).[15] In this case the transition state **110**, leading to the *cis* product **112**, is strongly disfavoured by the severe steric clash of the trichloromethyl group and the quinidine catalyst (Scheme 57). Additionally, A-values suggest that the proposed steric argument is valid, the A-value of CO_2Et being 1.1-1.2 kcal/mol, with the value of the CF_3 group, used as a direct comparison to the CCl_3 group whose A-value was not available, being significantly higher at 2.4-2.5 kcal/mol.[60,61] This model also provides a rationale for the observed 2*R* (quinidine)/2*S* (quinine) stereoinduction observed in Wynberg's original synthesis of monosubstituted β-lactones using chloral (Scheme 22).[37,38] Our results appear to successfully validate these two predictive models.



Scheme 57

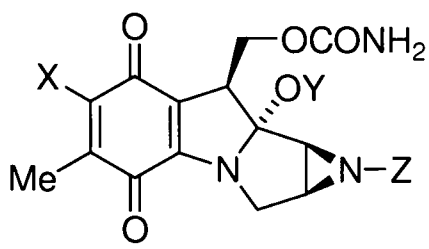
1.2.7 Conclusions

In summary, the synthesis of a range of *cis*-2,3-disubstituted β-lactones was accomplished *via* the net [2+2] addition of ethyl glyoxylate to ketenes, generated *in situ* from acid chlorides. This cinchona alkaloid-mediated approach provided the desired lactone products in reasonable yield and with excellent diastereo- and enantioselectivities. Subsequent lactone ring-opening using the soft nitrogen nucleophile sodium azide, followed by catalytic hydrogenation of the azide functionality, allowed access to a number of β-amino acid esters in good yield and with high diastereomeric ratios. Ester hydrolysis of β-amino acid ester **97** (where R=Me), completed the synthesis of the biologically significant, known compound, β–methyl aspartic acid, and allowed comparison of optical rotation values confirming the predicted configuration of the product to be (2*R*, 3*S*).[62]

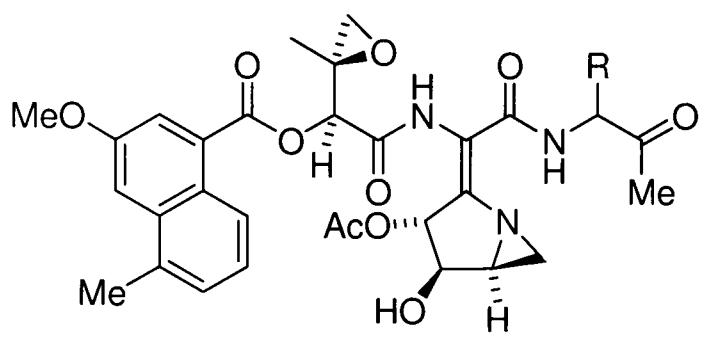
2. Organocatalytic Aziridination of Enones

2.1 Introduction

Aziridines are three-membered, saturated, *N*-containing heterocycles whose prevalence in natural product molecules, such as the mitosanes (Figure 5), makes them attractive synthetic targets. Additionally, the strain inherent in the three ring system allows facile, stereocontrolled ring opening with a range of nucleophiles, providing access to *N*-containing products.[63,64]



mitomycin A-C

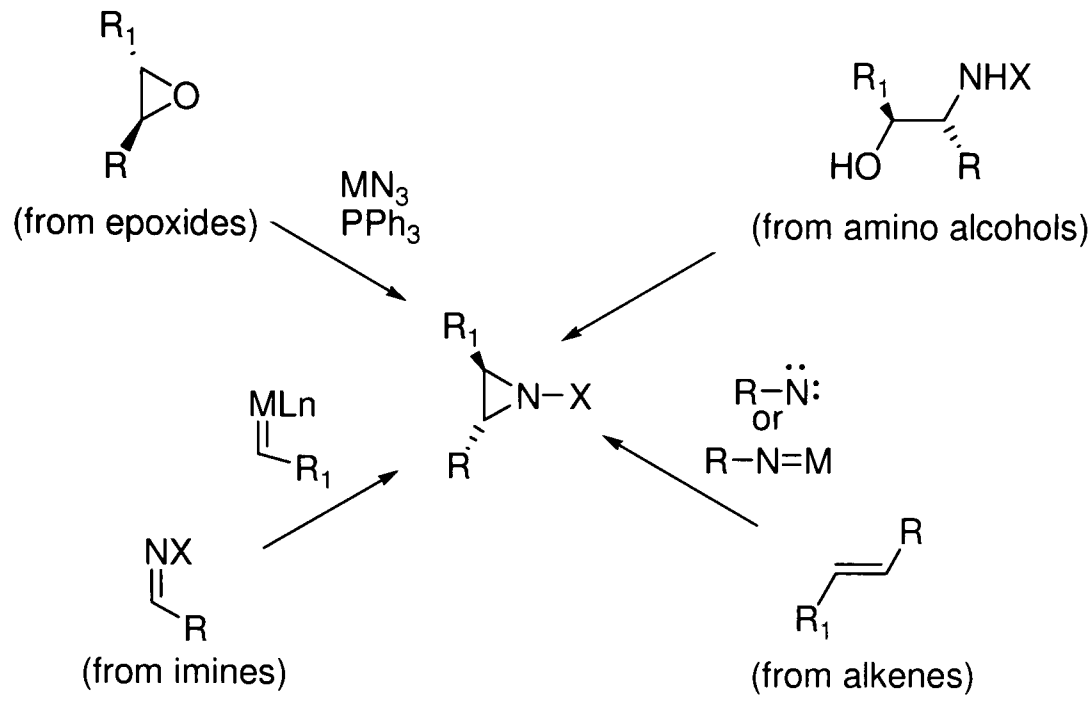


azinomycin A-B

Figure 5

2.1.1 Synthesis of Aziridines[63,65-67]

Generally there are fewer reliable methods available for the synthesis of aziridines compared to their oxygen analogues, the epoxides. This is particularly true in reference to asymmetric aziridination reactions. The most popular methods for the preparation of aziridines are as shown in Scheme 58.

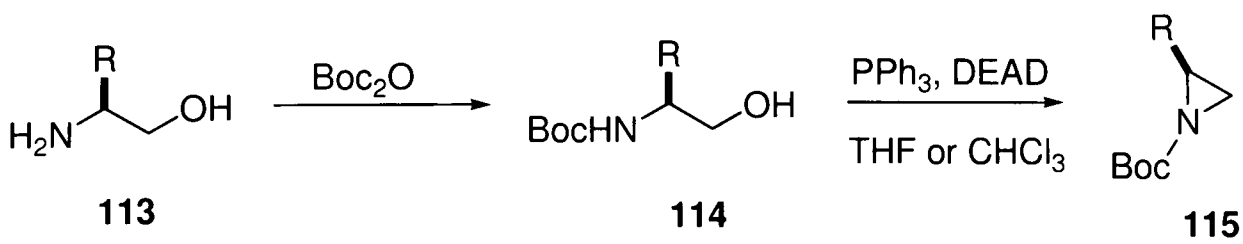


Scheme 58

This section seeks to briefly outline key work on the synthesis of aziridines from amino alcohols, epoxides and imines with the remainder of the section focusing upon synthetic routes directly from alkene substrates.

2.1.1.1 From Amino Alcohols

1,2-Amino alcohols provide a route into the aziridine framework *via* activation of the hydroxyl functionality followed by ring closure utilizing either the *N*-amine lone pair or the amide anion. The commercial availability and range of synthetic methods for the preparation of chiral 1,2-amino alcohols allows this technique to be rendered asymmetric. Methods for the activation of the hydroxyl functionality include Mitsunobu conditions which allow the synthesis of a range of *N*-Boc protected aziridines in high yield (73-86%, where R= CH_2OBn, $(CH_2)_2CO_2Bn$, $(CH_2)_2CHMe_2$, Bn) (Scheme 59). [68]

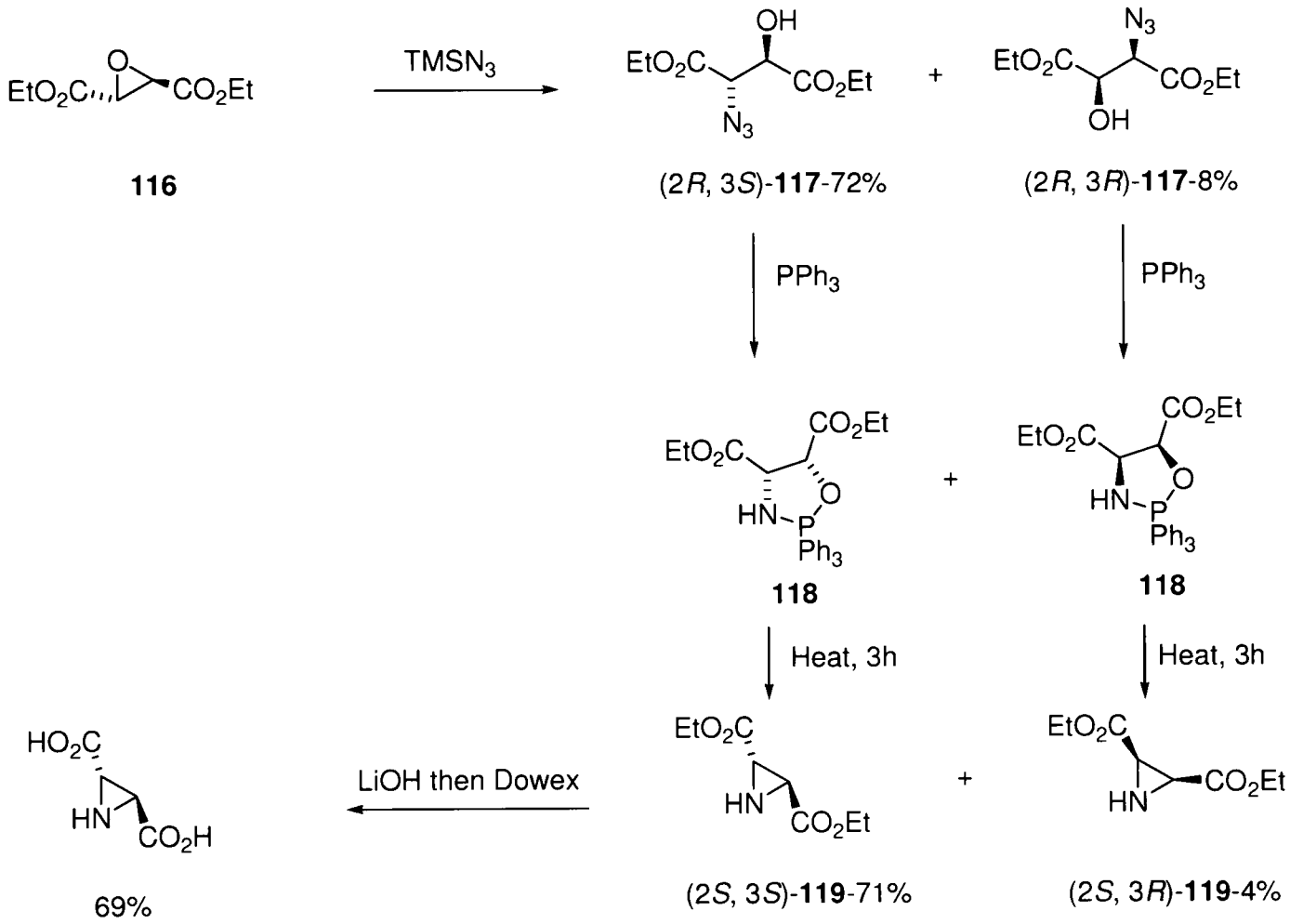


113 **114** **115**

Scheme 59

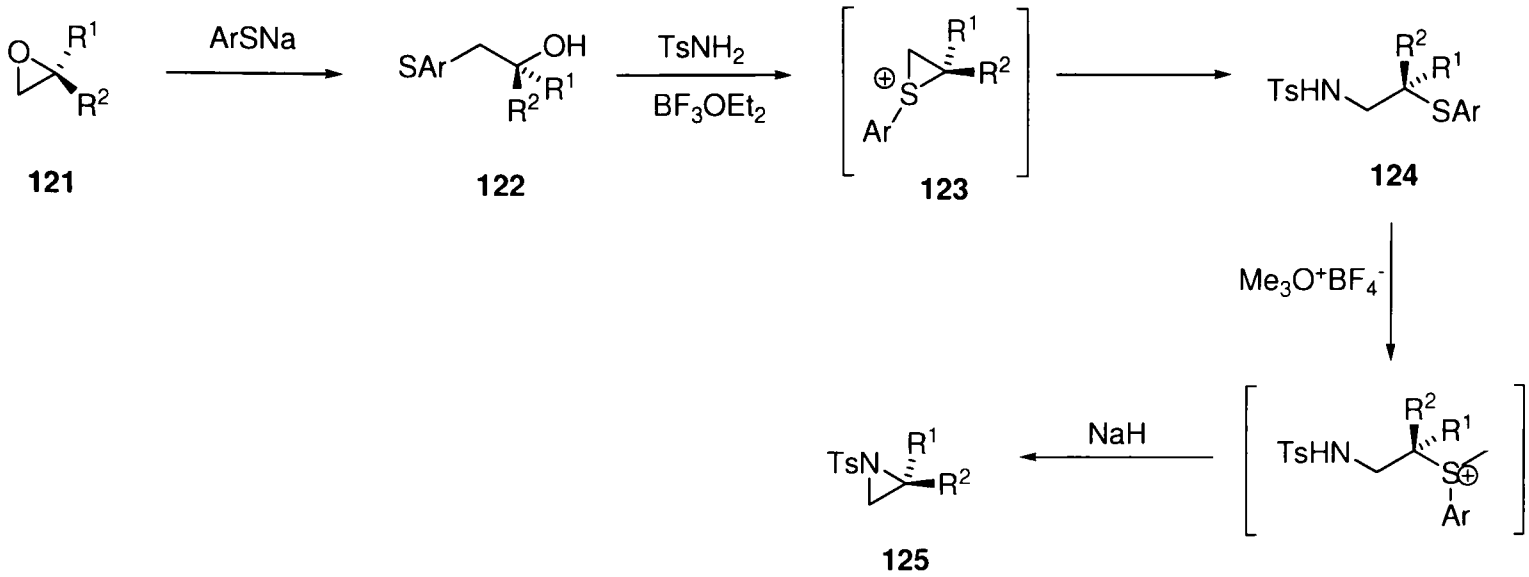
2.1.1.2 From Epoxides

Azide ring-opening of epoxides gives azido alcohols. Subsequent Staudinger reduction initially forms an imino phosphorane, followed by an oxazaphospholine intermediate (**118**) which then undergoes a thermally induced cyclisation to give the desired aziridine product. Again, the range of methods available for the synthesis of optically active epoxides makes this procedure widely applicable to the synthesis of asymmetric products. Zwanenburg *et al.*[69] demonstrate this methodology in the synthesis of the aziridine containing natural product (2*S*, 3*S*)-(+)-aziridine-2, 3-dicarboxylic acid **120** (Scheme 60).



Scheme 60

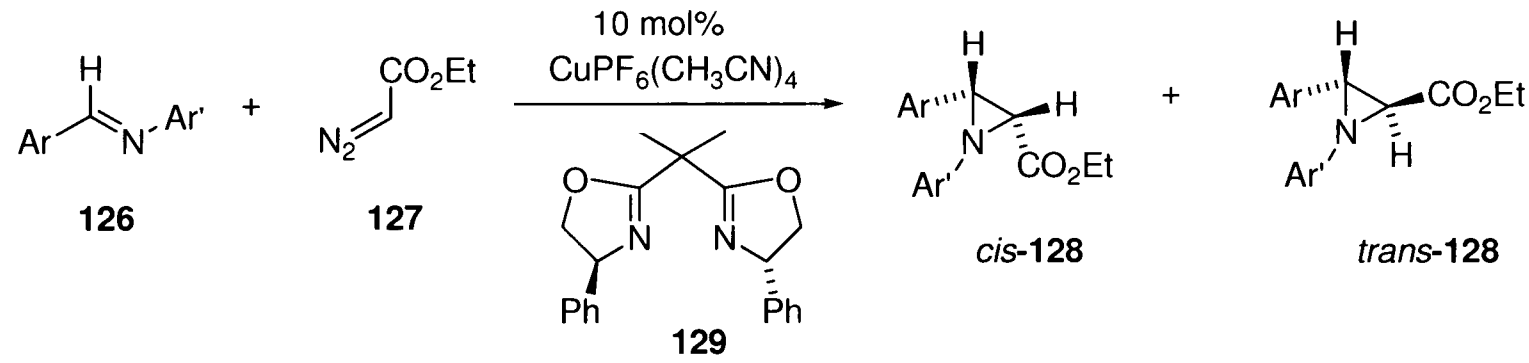
Additionally, chiral episulfonium intermediates (**123**) offer an alternative pathway for the formation of chiral aziridine products from epoxides.[70] Double S_N2 inversion provides access to the product with retention of stereochemistry in reasonable to high yield (52-94%) and with good *e.e* values (77-97%) for R^1/R^2=H or Ar (Scheme 61).



Scheme **61**

2.1.1.3 From Imines

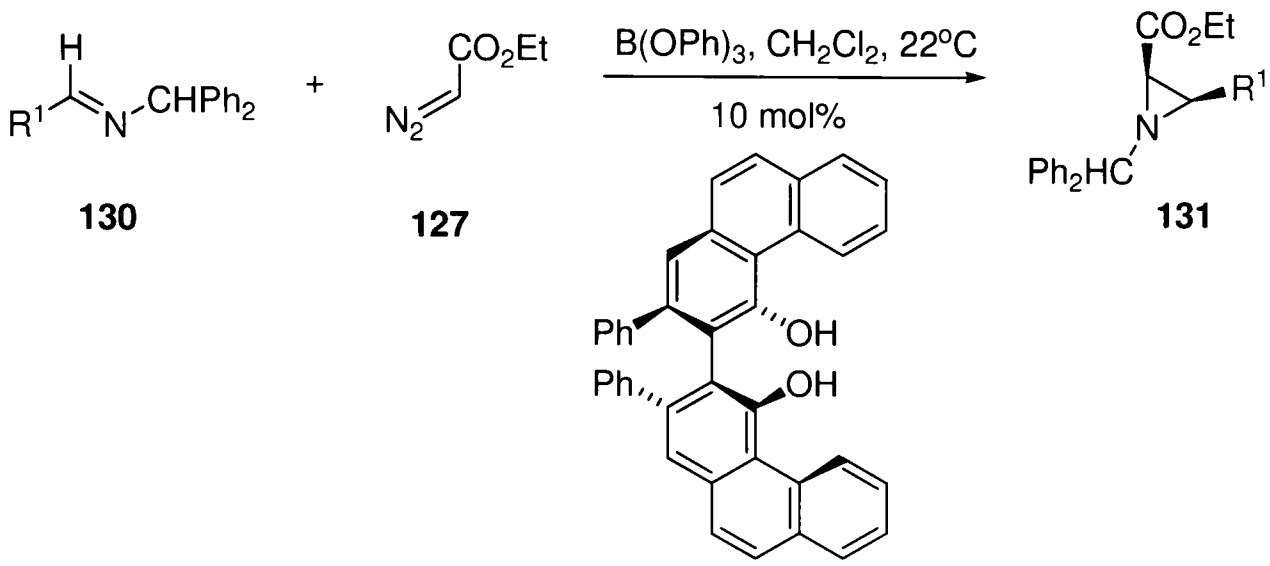
An alternative approach to the *N*-protected aziridine framework is provided *via* the addition of a carbene, or a carbene equivalent such as an ylide, to an imine. Jacobsen *et al.*[71] detailed the first asymmetric example of this strategy using the metallocarbene derived from ethyl diazoacetate (**127**), and copper(I)hexafluorophosphate alongside the chiral bisoxazaline ligand **129**. However, only meagre reaction yields (10-65%) were obtained. Additionally, diastereoselectivities (2:1 ->10:1 *cis*:*trans*) and *e.e* values (<67%) were generally poor (Scheme 62).



Scheme 62

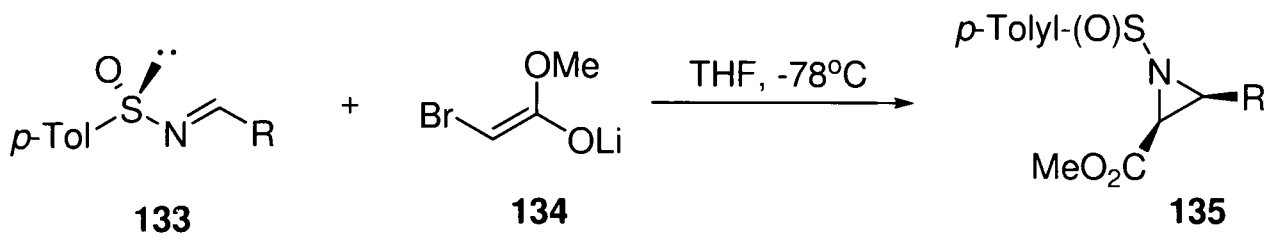
Wulff *et al.*[72,73] took a slightly different approach to the problem making further advances by employing axially chiral ligands (**132**) complexed to boron Lewis acids to catalyse the addition of ethyl diazoacetate to *N*-benzhydryl protected imines (**130**). This strategy benefits from much improved *e.e* values (>91%) diastereoselectivities (generally >30:1 *cis*:*trans*), reasonable yields (51-77%) and wide reaction scope, where both aromatic and

aliphatic imines are tolerated (Scheme 63). However, the reaction is restricted by the use of the benzhydryl protecting group which is not an aziridine activator and hence requires a further two step deprotection-protection procedure to be employed if aziridine ring-opening is required.



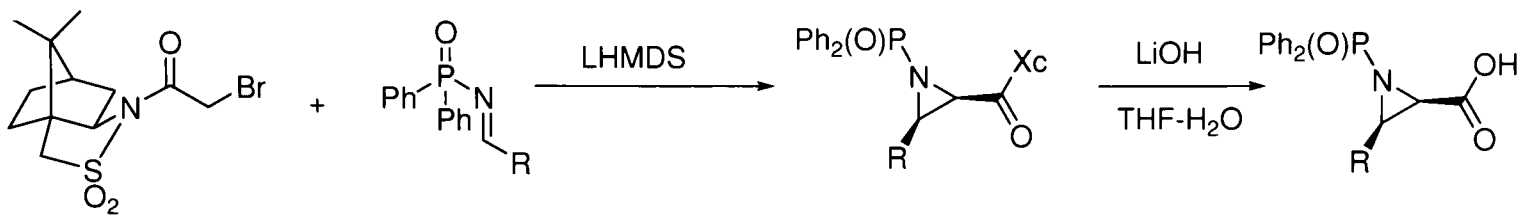
Scheme 63

Additionally, the asymmetric aza-Darzens reaction allows the formation of chiral *N*-substituted aziridines from imines *via* addition of an enolate with a substituent leaving group, generally formed from a α–halocarbonyl compound. In 1994 Davis *et al.*[74] reported the addition of achiral α–bromoenolates (**134**) to chiral *N*-sulfimines (**133**) to give aziridine products in reasonable yield (64-77%) and with good diastereoselectivities (88:12 to 99:1 *cis:trans*) (Scheme 64). Oxidation of the product aziridines with *m*-CPBA gives access to *N*-tosyl protected aziridines which are activated towards ring opening.



Scheme 64

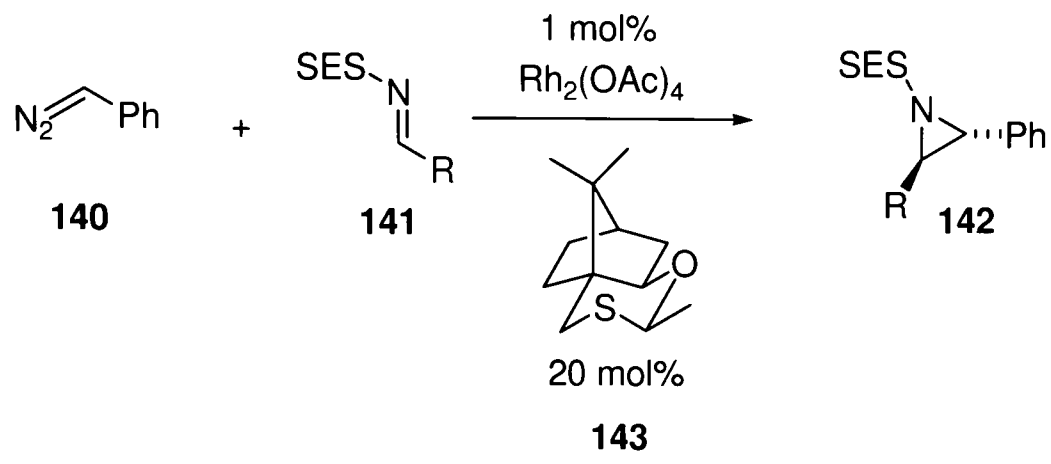
Sweeney *et al.*[75] took a very similar approach using diphenylphosphinyl imines and chiral enolates derived from bromoacetylcamphorsultam (**136**), to obtain *N*-Dpp aziridine products in reasonable to high yield (40-77%) and with *cis*-diastereoselectivity for a range of R groups (R=Aromatic and *t*-Bu). Subsequent removal of the chiral auxiliary under basic conditions gives access to a range of aziridine carboxylates (**139**) (Scheme 65).



136 **137** **138** **139**

Scheme 65

Further significant work has been done in the area of aziridination from imine precursors, particularly with regard to the use of sulfur ylides as carbene equivalents. In 1996 Aggarwal *et al.*[76] described a novel asymmetric, catalytic system in which a chiral sulfide (**143**) is used to mediate metal carbenoid addition to imines. Aziridination occurs in average to excellent yield (47-91%), with *e.e* values being particularly noteworthy (>88%), for a range of aromatic R groups and where R=C_6H_{11}.[77] However, diastereoselectivities are meagre (3:1 to 5:1 *trans:cis*) and although subsequent publications have detailed an increase in the levels of *trans:cis* selectivity (up to 8:1 *trans:cis*)[78] they remain less than desirable (Scheme 66).

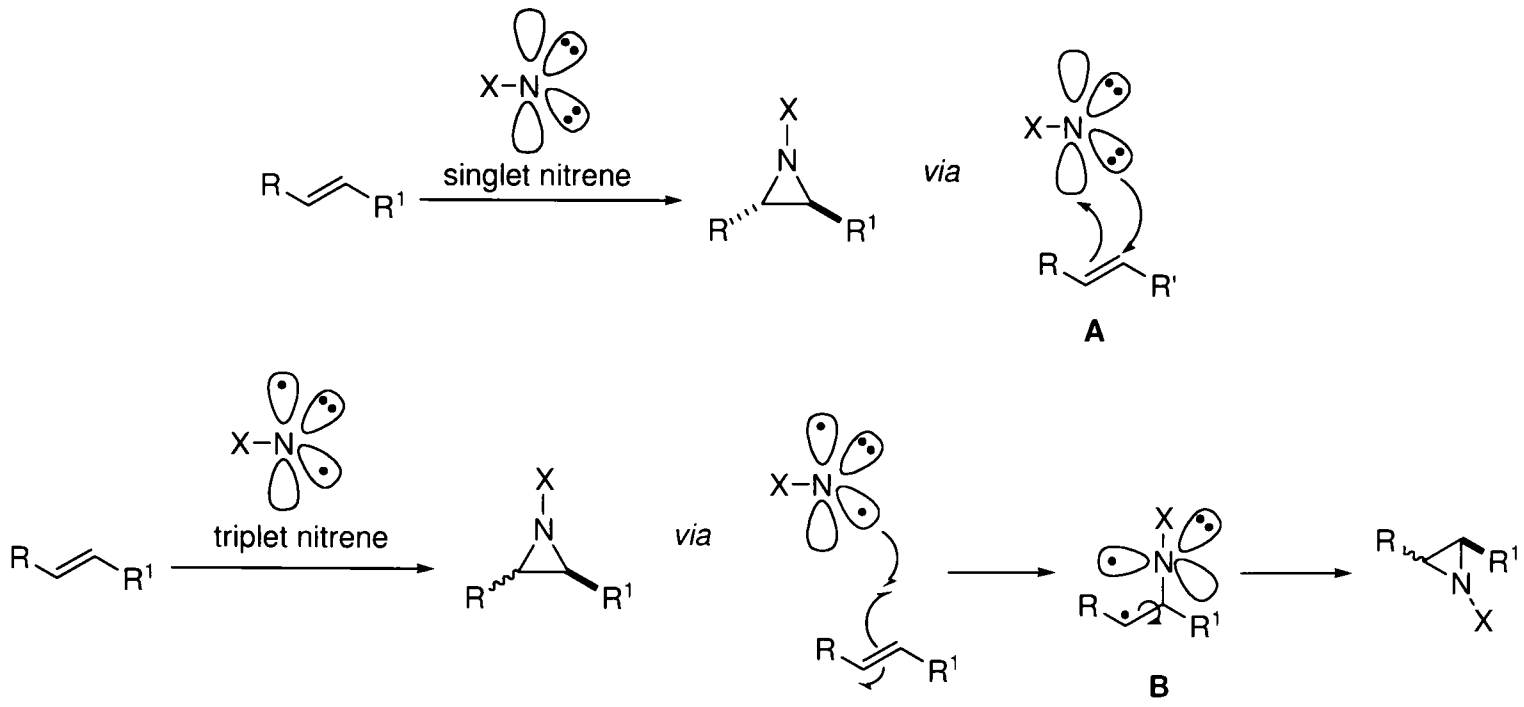


140 + 141 → 142 (143)

Scheme 66

2.1.1.4 From Alkenes

The synthesis of aziridines from alkene substrates involves the direct addition of a nitrene, or a nitrene equivalent, to the unsaturated hydrocarbon component. Free nitrene methods are notoriously limited in terms of the poor stereochemical control exhibited in the reaction, giving a mixture of both *cis* and *trans* products. Such products are formed due to rapid interconversion between the triplet and singlet nitrene states. A singlet nitrene holds its two non-bonded electron pairs in two separate orbitals with both electron pairs having anti parallel spin. A singlet nitrene adds stereospecifically to an alkene *via* a concerted process (**A**). However, a triplet nitrene holds its non-bonded electrons in three orbitals, one with a pair of anti parallel electrons with the other two containing a single electron of parallel spin. Consequently a triplet nitrene adds in a stepwise manner to the alkene substrate *via* a transient diradical species (**B**) which may bond rotate, resulting in poor stereospecificity in the product aziridine (Scheme 67). Triplet nitrenes are generally more stable than their singlet counterparts and hence conversion of the singlet to the triplet state is facile, resulting in a mixture of *cis/trans* aziridine products.

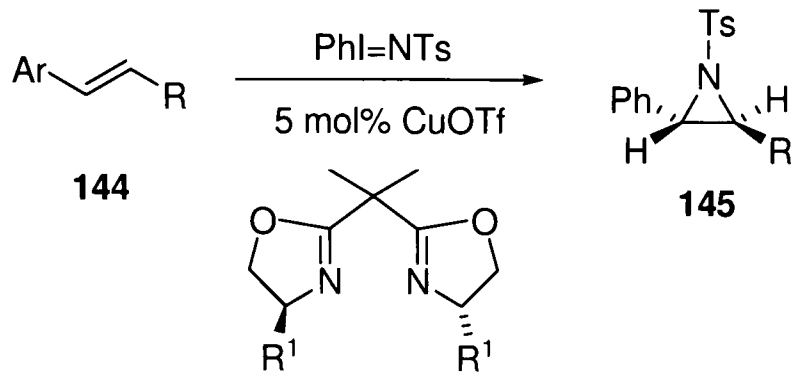


Scheme 67

The harsh reaction conditions required to generate free nitrenes, for example by the thermal or photolytic decomposition of the corresponding azide, and the stereochemical limitations outlined above led to the development of metal and non-metal based nitrene equivalents. This review focuses on the key methodology currently available in this area with particular emphasis on those methods that are, or have the potential to become, asymmetric.

2.1.1.4.1 Metal Nitrenoids

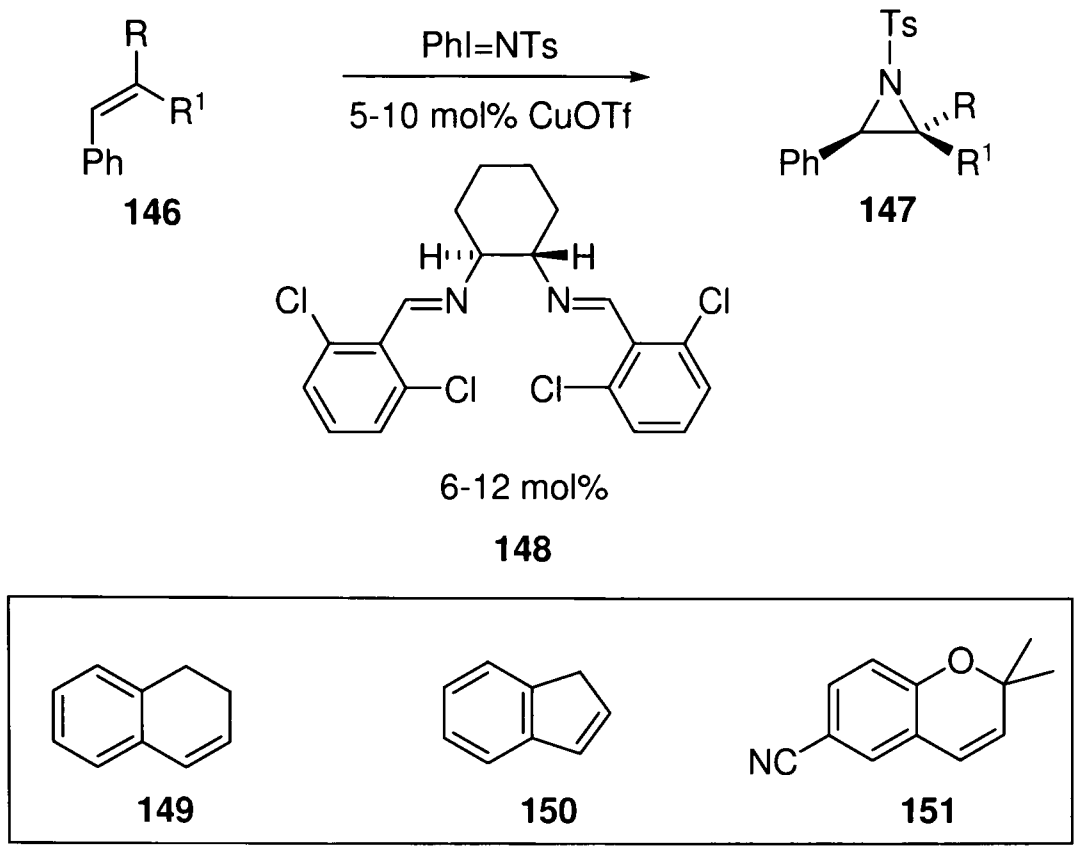
In 1993 seminal work by Evans *et al.*[79] detailed the use of bisoxazoline-copper complexes as effective asymmetric catalysts in the enantioselective aziridination of both electron poor and electron rich alkenes with (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane, PhI=NTs. A range of cinnamate esters (**144**) were readily aziridinated (where R=CO_2Me, CO_2Ph, $CO_2{}^tBu$) to give reasonable yields of the *N*-tosyl aziridine product (63-76%) with excellent enantioselectivities (>94%). However, the method is less reliable when extended to the use of simple olefinic substrates such as *trans*–β-methylstyrene and styrene itself, with these substrates giving significantly lower *e.e* values (70% and 63% respectively) (Scheme 68).



129

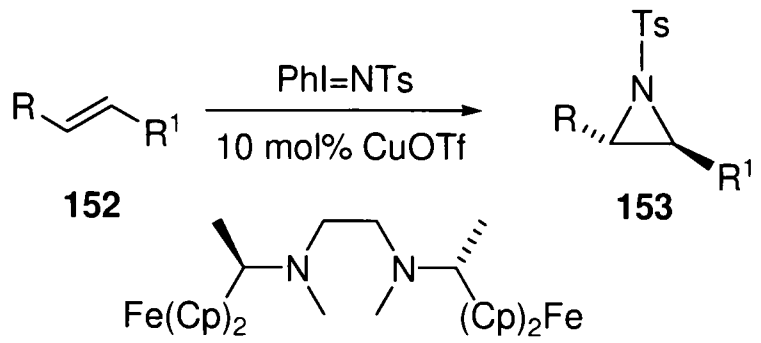
Scheme 68

1993 also saw the publication of work by Jacobsen[80] on a similar CuOTf system using readily available diimine-based catalysts as promoters of the PhI=NTs aziridination of a range of alkenes. Ligand **148** was found to be the most effective giving reasonable to good yields (50-79%) and meagre to excellent enantioselectivities (58->98%). Substrates include 1,2-dihydronapthalene (**149**), indene (**150**) and 6-cyano-2,2-dimethylchromene (**151**) (Scheme 69). However, simple olefins again presented a problem for the system with styrene and *cis*-β-methylstyrene giving a mixture of *cis*:*trans* products (3:1 *cis*:*trans* for both substrates). It is noteworthy that this system provides an alternative to the method developed by Evans in that *cis* olefins appear to be better substrates for the diimine system, whereas *trans* precursors are more effective in the bisoxazoline case.



Scheme 69

Diimines are again employed in methodology developed by Kim *et al.*[81] in which ligand **154** and CuOTf are seen to effect the aziridination of simple olefinic substrates (styrene, *trans*-stilbene, *trans*-β-methylstyrene, 1-hexene) to give *N*-tosyl aziridines in good yield (65-88%) (Scheme 70). Although enantioselectivities are not as high as modern-day standards dictate, they are equal to, or an improvement upon, those obtained for the same substrate in the Evans' methodology[79] (styrene: 88% yield, 74% *e.e. cf.* Evans' methodology 89% yield, 63% *e.e*). Additionally, the reaction does not suffer from poor stereoselectivities as observed in the Jacobsen work.[80] However, in order to obtain the reported yields a 10-fold excess of olefin is required in addition to 10 mol% catalyst loading, the upper limit of that used in the Jacobsen procedure.

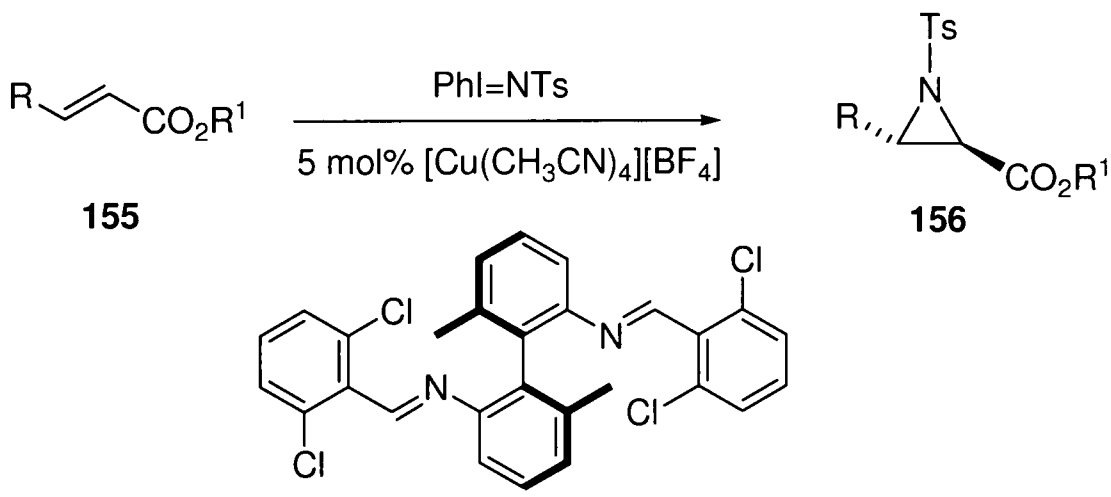


152 **153**

154

Scheme 70

Biaryl Schiff base complexes have also been developed in the context of asymmetric aziridination using metal nitrenoids. Scott *et al.*[82,83] used monomeric copper complexes formed using ligand **157**, to catalyse the aziridination of several cinnamate esters in reasonable to high yield for most substrates (45-89%) and with excellent enantioselectivities (>88%) (Scheme 71). Application of this system to the aziridination of styrenic alkenes proves less fruitful, and although yields are reasonable (60-80%), *e.e* values are low (<54%) and in some cases *cis-trans* isomerisation is noted. The authors attribute this observation to a lack of secondary binding in these unfunctionalised substrates. Although the selectivity of Scott's diimine methodology is similar to that of those previously mentioned[79-81] this particular system is significantly more reactive, with all reactions proceeding within minutes at room temperature.



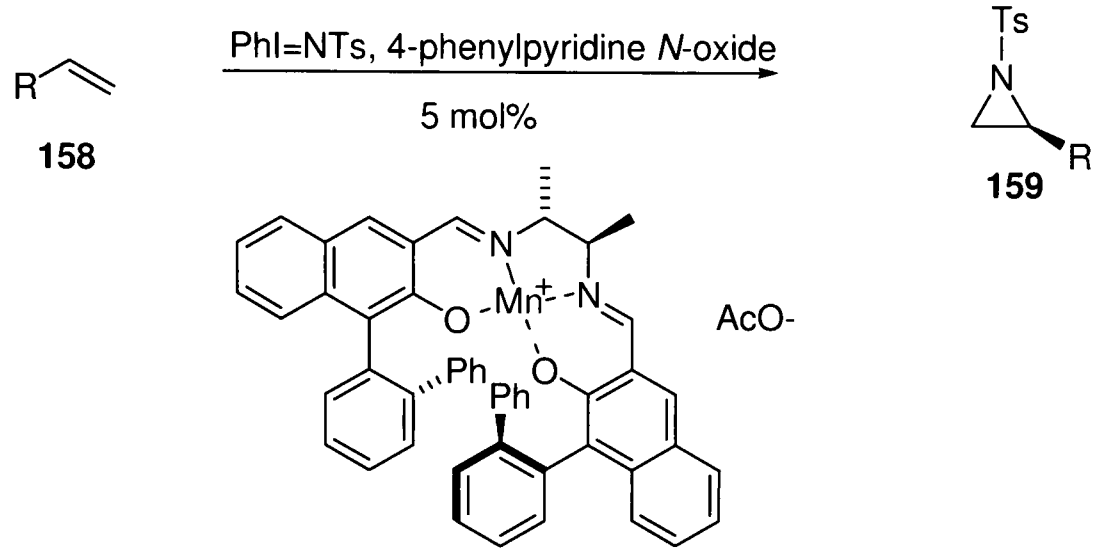
155 **156**

157

Scheme 71

While copper is by far the most popular metal used in metal nitrenoid additions to alkenes other transition metals such as manganese, rhodium and ruthenium have also

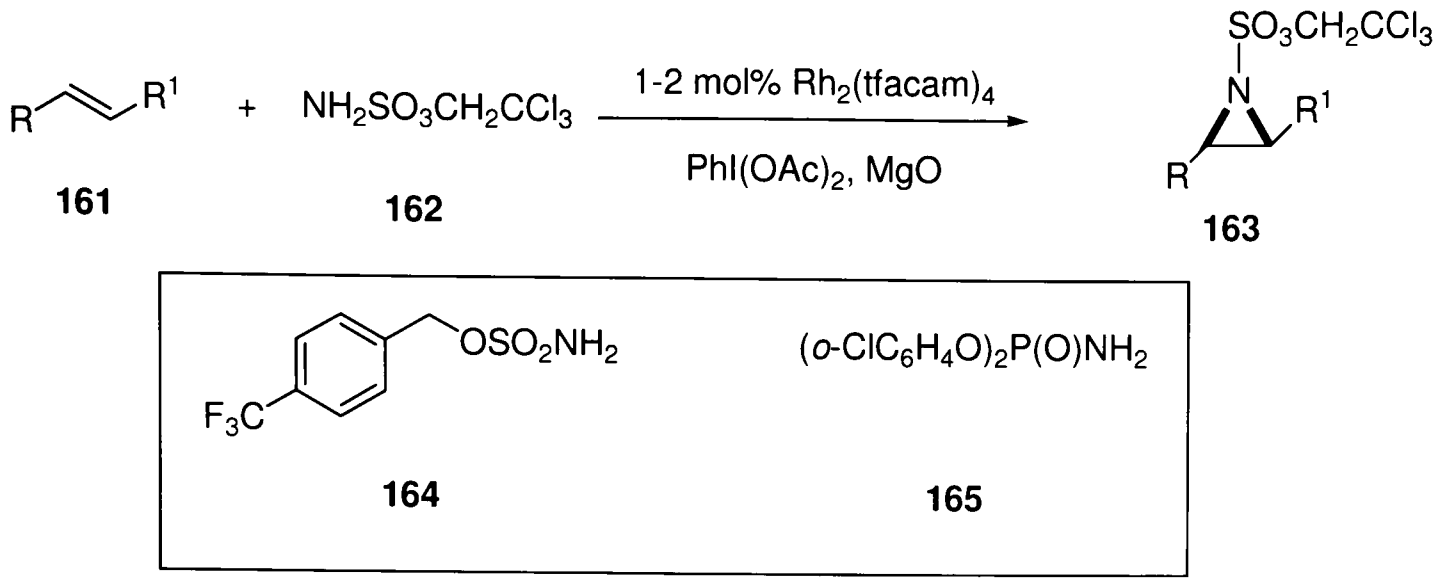
been applied to this methodology. A report worthy of note, in the main for the observed complementary selectivity for styrenic olefins, is that of Katsuki *et al.*[84] This work described the asymmetric aziridination of styrene, and derivatives there of, using the (salen)manganese(III) complex **160**. Yields are high (>70% for styrene, *p*-chlorostyrene and *p*-methylstyrene) and enantioselectivities good to excellent (81-94%) (Scheme 72).



160

Scheme 72

In terms of rhodium catalysis a noteworthy report is that by Du Bois *et al.*[85] in which an achiral Rh(II) catalytic species is employed in order to promote the aziridination of a range of alkenes (both aromatic and aliphatic) using trichloroethylsulfamate ester (**162**) as a nitrogen source. The reaction proceeds in reasonable to excellent yield (57-95%) and is stereospecific with *trans* and *cis*-β-methylstyrene (Scheme 73). It is noted that the Rh(II) catalyst of choice, $Rh_2(tfacam)_4$ (tfacam=CF_3CONH), is highly selective for π–bond functionalisation over σ-CH insertion, an alternative pathway often observed using similar Rh catalysts. Additionally the reaction can be extended to the use of alternative sulfamate esters (**164**) and phosphoramidates (**165**) as aziridinating agents. This allows for diversity in terms of methods for *N*-deprotection at a later stage. Although currently there are no reports of an enantioselective version of this methodology it shows potential for compatibility with asymmetric ligands.



Scheme 73

Many other catalytic metal-ligand systems have been developed for the direct aziridination of alkenes.[65] However, it is clear that there is still a significant amount of work to be carried out in this area before the quality of aziridine chemistry matches that of the epoxides. Many of the above methods are severely limited in terms of poor stereoselectivity, particularly with styrenic substrates, and the need to use excess alkene in some cases. Additionally, much of this methodology leads to the synthesis of *N*-protected aziridine products, and although this may be useful in some cases for subsequent ring-opening reactions, many of these groups require harsh reactions conditions for their removal, for example *N*-Ts.

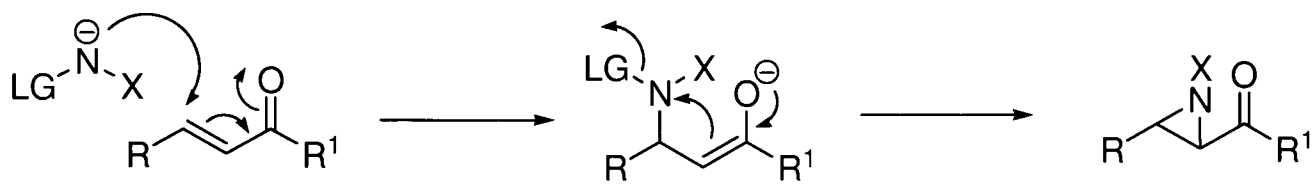
2.1.1.4.2 Non-Metal Nitrenoids

The use of non-metal nitrenoids to form aziridines from olefinic species is not as well documented as that of metal nitrenoids. However, such methods have the potential to provide an attractive synthetic alternative to metal mediated routes, with many non-metal *N*-delivering reagents being more tolerant to water and air. It is also often the case that non-metal methodology is suited to different classes of substrate than metal based work, so broadening the scope of the general reaction class. There are a number of interesting publications regarding this topic detailed in the literature, including methods for the electrochemical aziridination of olefins,[86] bromine catalysed redox aziridination developed by Sharpless and co-workers,[87] and the more recent methodology on iodine-catalysed synthesis of unprotected aziridines using ammonia as a nitrogen source

formulated by De Vos *et al.*.[88] However, this section seeks to focus solely upon nucleophilic aziridinating agents.

2.1.1.4.2.1 Nucleophilic Aziridinating Agents

Nucleophilic aziridinating agents generally possess a substituted nitrogen atom attached directly to a good leaving group. Once the nitrogen is deprotonated such reagents are known to react *via* a Michael type addition reaction to α,β–unsaturated carbonyl compounds (**166**), delivering an intermediate enolate anion (**167**) which then closes down to form the desired aziridine product (**168**) (Scheme 74). A variety of *N*-substituted reagents allows the synthesis of both *N*-protected (where X=Ts, Cbz or Ar) and *N*-free aziridines, a reaction characteristic uncommon in the metal nitrenoid methodologies previously discussed.



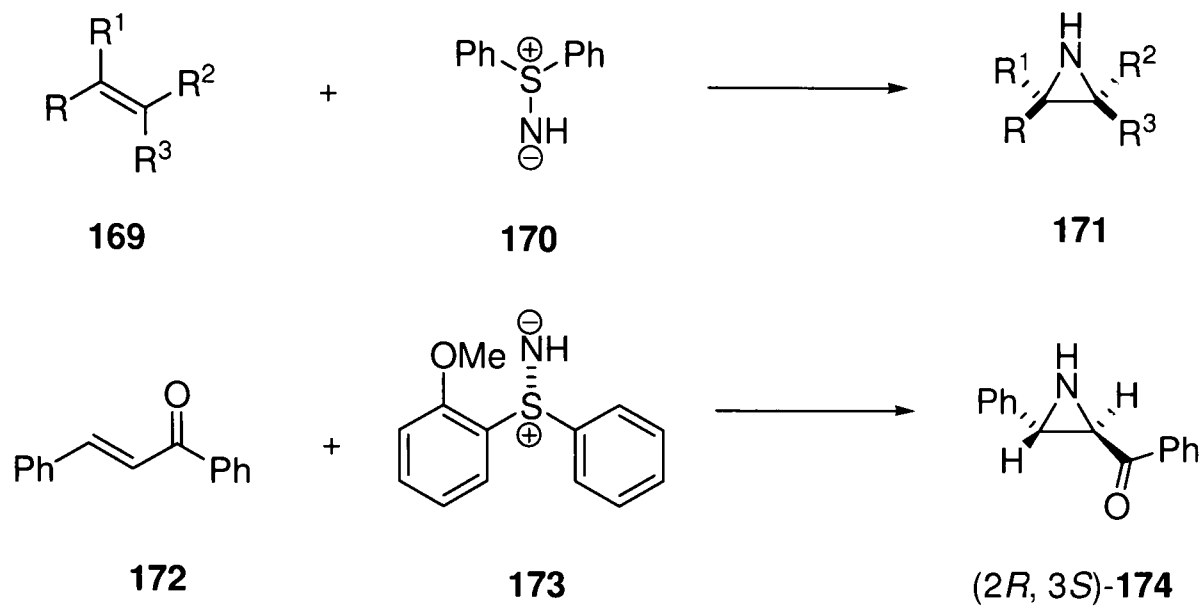
Scheme 74

The *N*-based nucleophilic reagents available for such transformations include sulfilimides, hydroxylamines and hydrazine derivatives.

2.1.1.4.2.1.1 Sulfimides

Sulfimides have not been widely used in the context of the nucleophilic aziridination of alkenes. However, a notable publication is that by Oae *et al.*[89] in which the reaction of a free sulfimide with a range of α,β-unsaturated ketones, to form *N*-unprotected aziridines, is detailed. Diphenyl sulfimide (**170**) is readily synthesised from diphenyl-*N*-*p*-tosylsulfimide and concentrated sulfuric acid.[90] Reaction of ylide **170** with electron deficient olefins, including *trans*-chalcone, dimethyl fumarate and maleate, and *cis*- and *trans*-dibenzoylethylene, resulted in the formation of the aziridine products in generally reasonable yield (40-73%) (Scheme 75). Preparation of the chiral, free sulfimide, *o*-

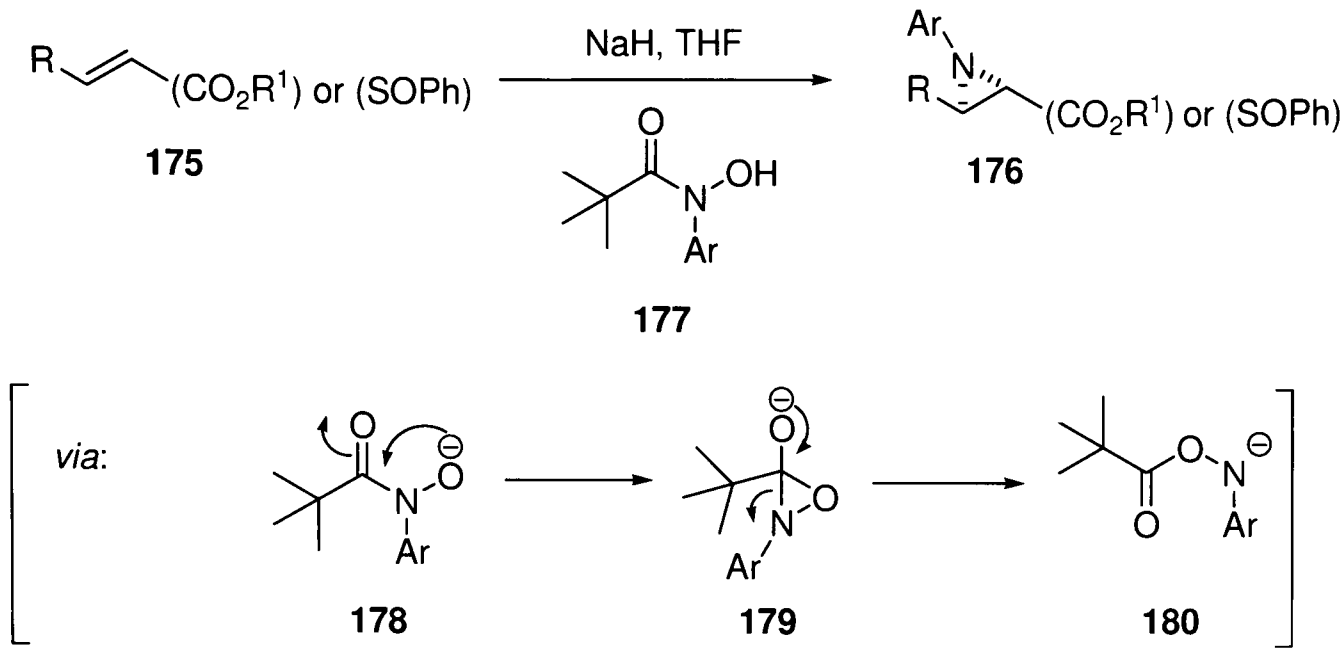
methoxyphenylphenyl-*N*-*p*-tosylsulfimide (**173**), is also described. Application of ylide **173** to the aziridination reaction using *trans*-chalcone gives the desired product ((2*R*, 3*S*)-**174**) in up to 96% yield and 32.6% optical purity after optimisation.



Scheme 75

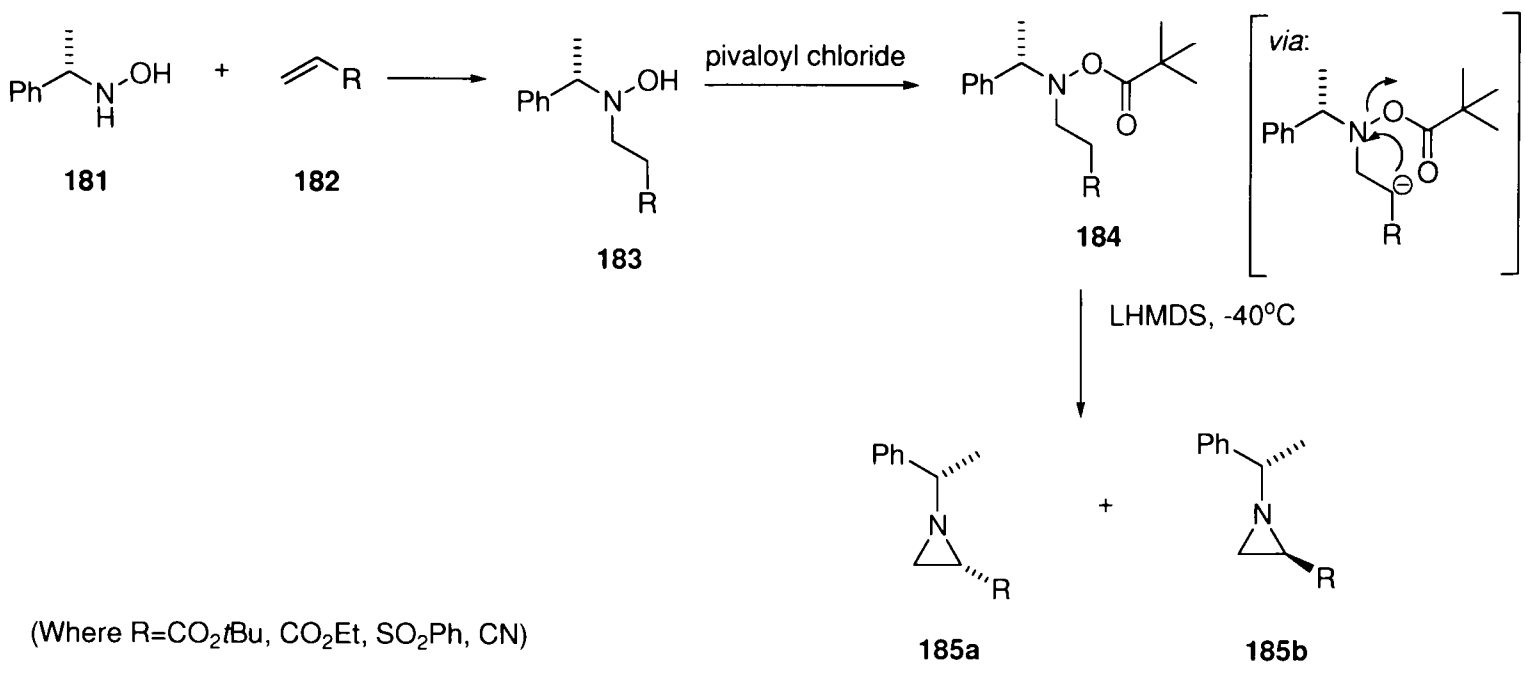
2.1.1.4.2.1.2 Hydroxylamines

In 1993 Prabhakar and co-workers[91] reported the use of *N*-hydroxy-*N*-pivaloylanilines (**177**) as novel aziridinating reagents. The *in situ* formation of the sodium salt of **177** is used to aziridinate a range of α,β-unsaturated esters and vinyl sulfoxides. The reaction is tolerant to a number of different aromatic substituents on the hydroxamic acid including *p*-bromo-, chloro-, nitro-, methyl- and methoxyphenyl. Yields are generally good to excellent (60-95%) and the reaction is highly stereospecific, with dimethyl maleate and fumerate giving exclusively the *cis*- and *trans*-aziridine products respectively. The mechanism of the reaction is thought to proceed *via* a thermodynamically driven isomerisation[92] of the hydroxamate anion (**178**) to the corresponding *N*-acyloxyaniline anion (**180**) with subsequent Michael addition to the unsaturated substrate (Scheme 76).



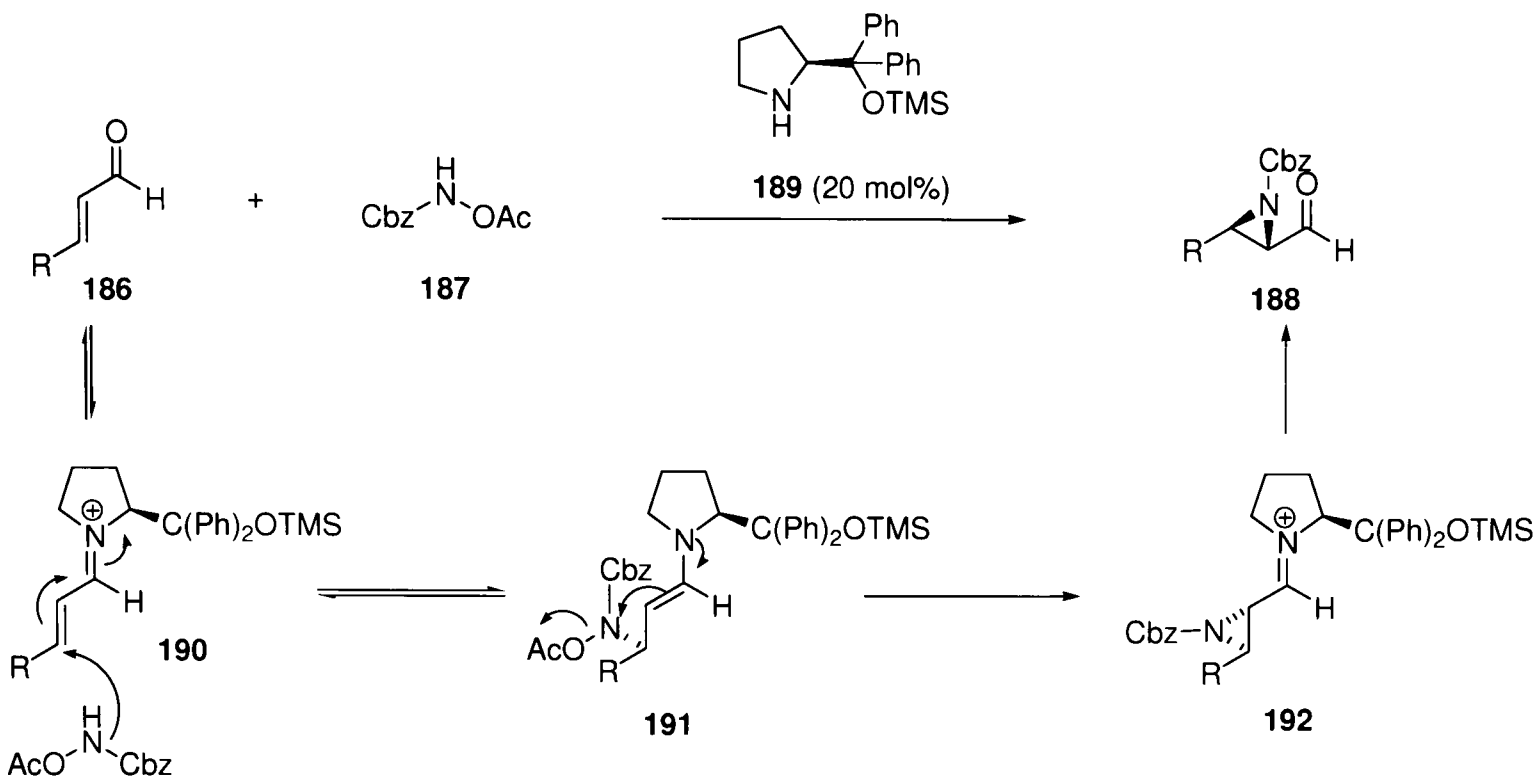
Scheme 76

Bew *et al.*[93] take a similar approach to Prabhakar this time using chiral substituted hydroxylamines to induce enantioselectivity. Conjugate addition of (*S*)-*N*-α-methylbenzyl hydroxylamine (**181**) to a range of acrylate esters, and other electron deficient olefins (where R=SO_2Ph and CN), gave the corresponding products (**183**) in excellent yield (91-100%). Acylation of these products with pivaloyl chloride allowed formation of (*S*)-*N*-(α-methylbenzylamine)-*O*-pivaloyl hydroxylamines (**184**) again with consistently high yields (75-93%). The subsequent deprotonation of these species with LHMDS, followed by ring closure, allows access to optically active *N*-substituted aziridines in reasonable yield (42-67%). Initially poor diastereoselectivities (67:33 **185a** -78°C to rt) were improved upon after temperature screening (93:7 **185b** at -40°C) where R=$CO_2{}^tBu$ (Scheme 77).



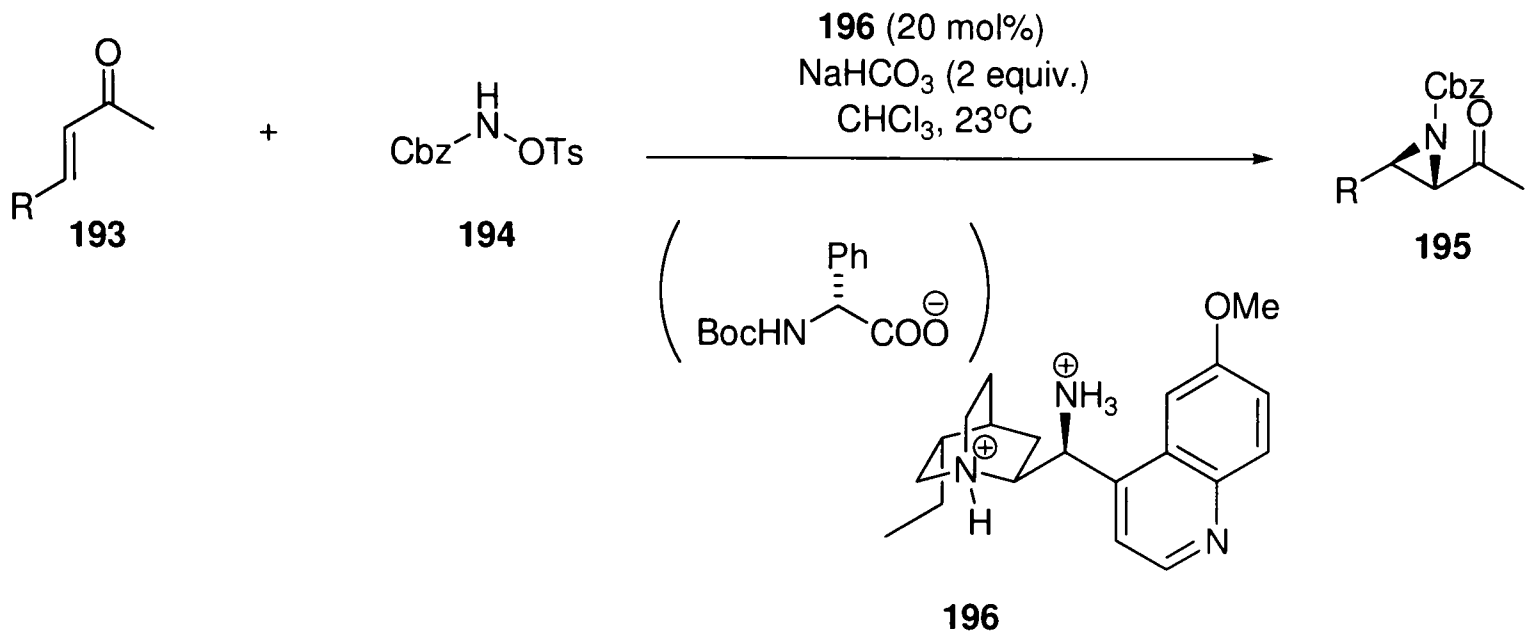
Scheme 77

A recent publication by Cordova *et al.*[94] described the enantioselective synthesis of *N*-substituted aziridines from enals using hydroxylamines. However, in this case the product chirality is not induced by a substituent on the hydroxylamine itself but by the prolinol derivative **189**. Formation of the chiral iminium species **190** is followed by conjugate addition of the Cbz-hydroxylamine (**187**) to the β-carbon. The proposed shielding of the *Si* face of the intermediate **190** by the aromatics of catalyst **189** allows stereoselective *Re* face addition of the hydroxylamine to the iminium. Enamine **191** is then free to close back down to form the aziridinated product (**192**) with subsequent cleavage of the chiral auxiliary. The reaction scope was found to be fairly general with alkyl, aromatic, ester and *O*-Bz protected functionality being tolerated on the enal substrate. Yields and diastereoselectivities are reasonable (54-78% and 4:1 to 10:1), with the reaction displaying excellent enantioselectivities (84-99%) (Scheme 78). Issues with product stability were encountered, with short reaction times (<40 min) being required for most substrates in order to prevent decomposition.



Scheme 78

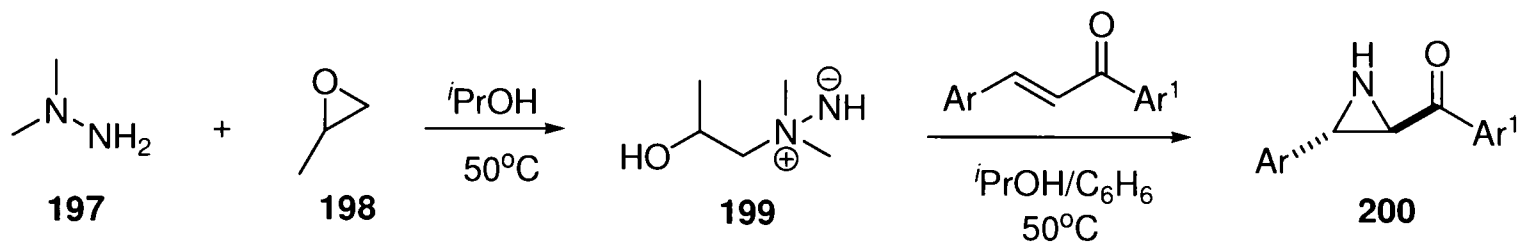
More recently Melchiorre *et al.*[95] have developed a related method for the hydroxylamine mediated aziridination of aliphatic and aromatic substituted enones (where R= pentyl, Me, CO_2Et, Ph, *p*-$NO_2C_6H_4$), thought to proceed *via* a similar mechanism to that proposed by Cordova (Scheme 78).[94] The cinchona alkaloid derived salt **196** is utilized as a catalyst, alongside the *N*-tosyl protected hydroxylamine **194**, as a nitrogen source (Scheme 79). Yields for the *N*-Cbz protected aziridine products are good (74-96%) with consistently high diastereomeric ratios (19:1 or greater) and moderate to excellent *e.e* values (73-99%). Additionally this method proved successful in the aziridination of β-methylcyclohexenone.



Scheme 79

2.1.1.4.2.1.3 Hydrazine Derivatives

In 1980 Ikeda and co-workers[96] reported a facile, one pot aziridination of chalcones using aminimides or *N-N* ylide species. The aziridinating reagent **199** was formed *via* ring-opening of 2-methyloxirane (**198**) with dimethylhydrazine (**197**) followed by proton transfer from the primary amine to the hydroxy anion to form the reactive species. Subsequent addition of chalcone, or derivatives thereof (Ar=Ph, *p*-NO_2, *o*-Cl and Ar^1=Ph, *p*-Cl), to the reaction vessel gave the desired *trans*-products (as determined by ^{1}H NMR coupling constants where J_{trans}=2-3 Hz)[97] in good yield (67-89%) (Scheme 80). However, volatile starting materials require the reaction to be conducted in a sealed tube with heating to a moderate temperature of 50°C.

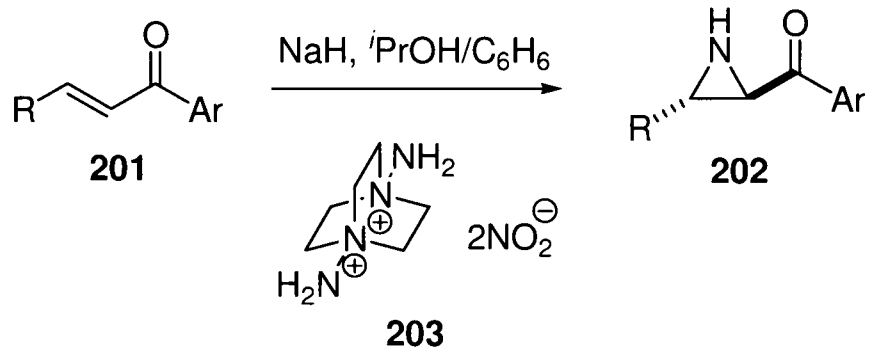


197 198 199 200

Scheme 80

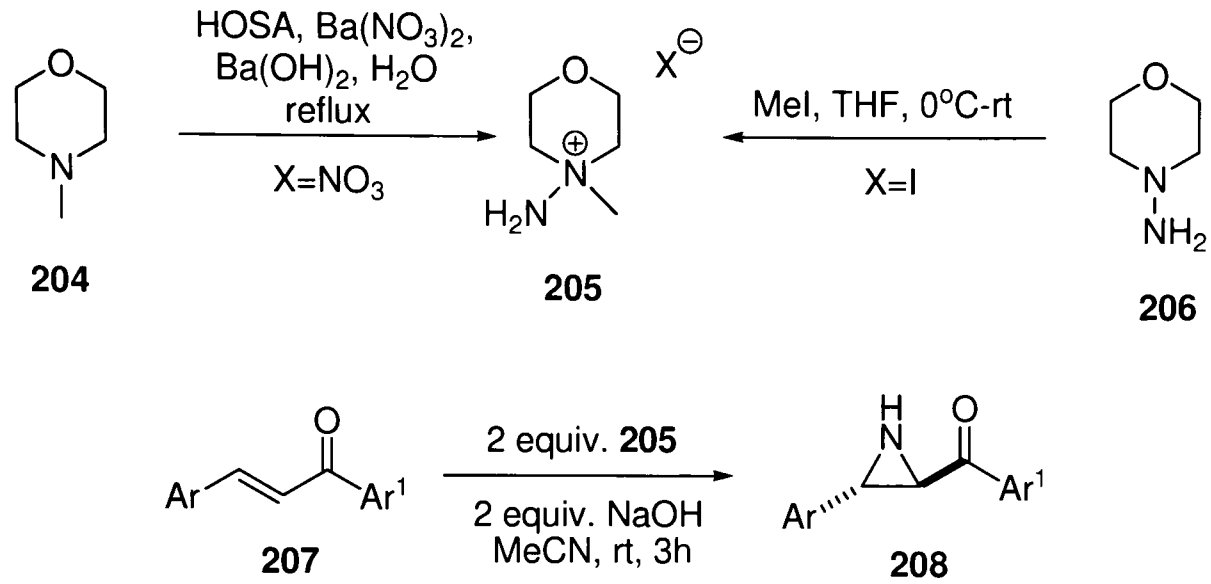
Prior to the start of work in our own group only one other report of aziridination using hydrazine derivatives was found in the literature. Xu *et al.*[98] describe the aziridination of α,β-unsaturated ketones using the diaminated DABCO derivative *N,N'*-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate (Scheme 81). In this work the *N-N* bond of the

aziridinating agent is not derived from starting materials, as is the case for the Ikeda methodology using dimethylhydrazine,[96] but by direct amination of a tertiary amine species. Preparation and isolation of the hydrazinium salt (**203**) is simple and further purification is not required.[99] Aziridination of a range of ketones (R=Me, Ph, *o*-Cl/NO_2 phenyl, p-MeO/Cl/Br/Me/NO_2 phenyl and Ar=Ph, *p*-Cl/Br/Me/MeO phenyl) is readily achieved using derivative **203** and base, with the mechanism being postulated to proceed *via* the standard Michael addition, ring-closure pathway (Scheme 74). *Trans* products were obtained, as deduced from ^{1}H NMR coupling constants. Yields are consistently high for chalcone and derivatives with electron donating groups present on the aromatic rings (76-99%), but disappointing for both the *para*- and the *ortho*- substituted nitro chalcones (15% and 17% respectively). Additionally, the aziridination of α,β-unsaturated esters and amides could not be achieved under the standard reaction conditions.



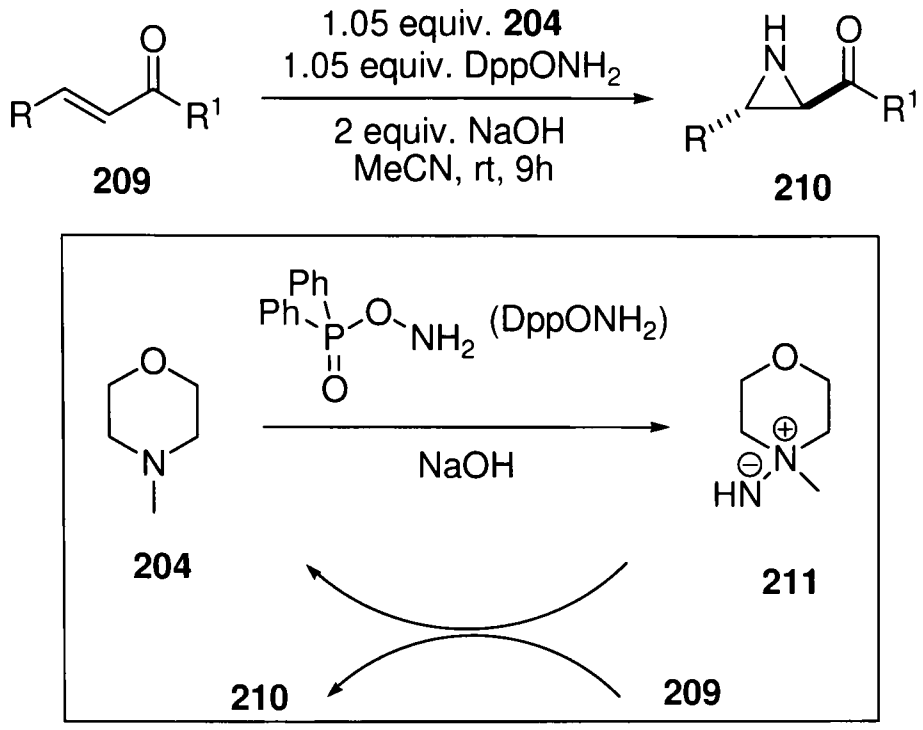
Scheme 81

In 2006 our group published work on the synthesis of aziridines using hydrazinium salts (**205**) derived from the morpholine framework.[100] The salts are formed either by the methylation of commercially available *N*-aminomorpholine or *via* the amination of *N*-methylmorpholine with hydroxylamine-*O*-sulfonic acid (HOSA). Once isolated the morpholinium salt can be used to aziridinate a range of aromatic α,β-unsaturated ketones in reasonable to excellent yield (42-95%), giving predominantly the *trans*-aziridine product (>90:10, based on ^{1}H NMR *J* values) (Scheme 82).

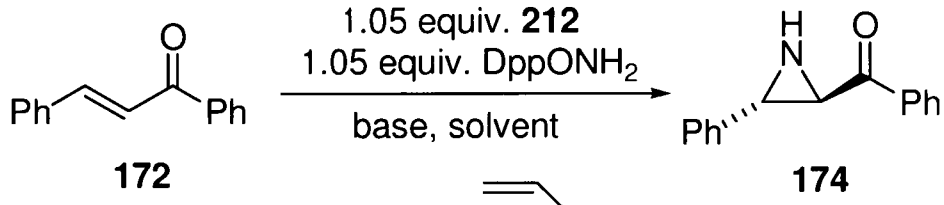


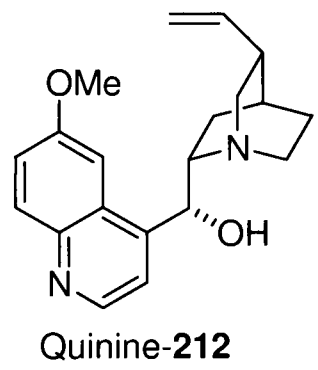
Scheme 82

On the basis of this initial paper we subsequently published further work describing an *in situ* salt formation-aziridination method.[101] Amination of *N*-methylmorpholine using *O*-(diphenylphosphinyl) hydroxylamine ($DppONH_2$), followed by *N*-deprotonation, gave aminimine ylide **211**. Subsequent 1,4-addition of the ylide to the olefin substrate with ring closure, gave the *trans*-aziridine product (as determined by ^1H NMR coupling constants) in generally good to excellent yield (62-97%), and with regeneration of tertiary amine **204** (Scheme 83). Significantly, our system has been shown to tolerate both aromatic, aliphatic and ester substituted enones. Work towards a catalytic system is also described with the efficient aziridination of chalcone occurring with 25 mol% amine (66% yield). Perhaps more importantly still, the publication describes our efforts towards an asymmetric aziridination procedure. Quinine (**212**) was found to be an effective tertiary amine promoter giving the aziridinated product of chalcone in 64% yield and 56% *e.e* (major enantiomer is (2*R*, 3*S*) by comparison of optical rotations)[102] (Scheme 83). We believed this preliminary result to be very promising in terms of our prospects for increased enantioselectivity in the system. This has formed the basis for much of our current work in this area.



Asymmetric Approach:



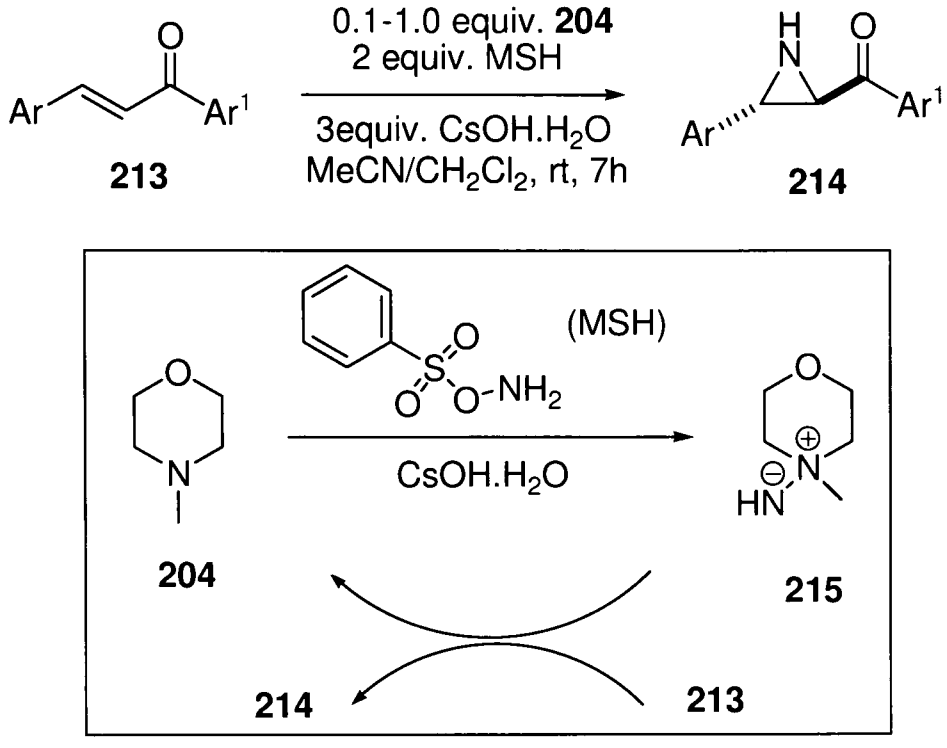


Quinine-**212**

Scheme 83

Just prior to the publication of our later work Shi *et al.*[103] published methodology detailing the aziridination of a range of aromatic α,β-unsaturated ketones, using a morpholinium species, generated *in situ* from *N*-methylmorpholine (**204**) and *O*-mesitylenesulfonylhydroxylamine (MSH) (Scheme 84). Amination of amine **204** with subsequent *N*-deprotonation provided ylide species **215**. This ylide is then free to undergo Michael addition to the electron deficient olefin (**213**) to yield the desired aziridine product (21-85% yield with 1.0-0.1 equiv. amine) and regenerate amine **204**. All substrates are aromatic with no mention of the method being applied to aliphatic systems. Additionally, the publication describes work towards an asymmetric synthesis of aziridines using the chiral tertiary amine (+)-Troger's base (**216**). Amination of amine

216 with subsequent aziridination of the substrate gave enantiomerically enriched products for a limited number of α,β-unsaturated enones (55-67% *e.e*). The absolute configuration of the major enantiomer was found to be (2*R*, 3*S*) as determined by comparison to the rotation of a known compound[104] (Scheme 84).



Scheme 84

2.1.2 Project Aims

The initial aim of the project was to expand the scope of the aziridination reaction using *N*-methylmorpholine as a promoter. The reaction had shown excellent tolerance to aromatic α,β–unsaturated ketones and it was hoped that we could expand the substrate scope to other alkyl substituted enones, α,β-unsaturated amides, dienones, and other electron deficient olefins, for example cinnamonitrile. Additionally we hoped to develop

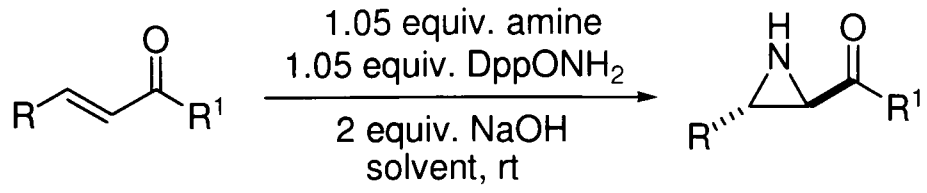
a cinchona alkaloid-mediated approach to the enantioselective aziridination of enones, based on our first promising result obtained with quinine.[101]

2.2 Results and Discussion

As previously discussed (Scheme 82 and Scheme 83), our group has developed an organocatalytic method for the synthesis of *N*-unsubstituted aziridines from enone precursors. At this stage we considered the two main areas of this work requiring further development to be; the advancement of an asymmetric system, based on our first promising result obtained with quinine, and the expansion of the substrate scope in the *N*-methyl morpholine (NMM)/*N*-methyl pyrolidine (NMP) aziridination procedure. Our results in both areas of this project are described, beginning with the exploration of the substrate scope for the achiral reaction.

2.2.1 *N*-Methyl Morpholine Promoted Aziridination

Table 4 details the substrate scope of the NMM/NMP mediated reaction prior to the beginning of the work described in this thesis.[101] Chalcone, and a range of substituted aromatic variants (R=*m*-NO_2Ph, *p*-CNPh, *p*-MePh, *p*-OMePh, 1-naphthyl, 3-furyl and R1=*p*-ClPh, *p*-MePh, *p*-OMePh), proved to be excellent substrates for the reaction giving consistently reasonable yields (62-97%, entries 1-10). Pleasingly, aliphatic enones also appeared to work well in the reaction, again producing moderate to high yields of the desired aziridine product (62-83%, entries 11 13). Finally, the procedure was shown to work using ester substituted derivatives (entries 14 and 15).



Entry	R	R^1	Amine; Solvent	Time (h)	Yield (%)
1	Ph	Ph	NMM; MeCN	9	88
2	*m*-NO_2Ph	Ph	NMM; MeCN	10	75
3	*p*-CNPh	Ph	NMM; MeCN	10	62
4	*p*-MePh	Ph	NMM; MeCN	10	78
5	*p*-OMePh	Ph	NMP; CH_2Cl_2	24	79
6	Ph	*p*-ClPh	NMM; MeCN	10	90
7	Ph	*p*-MePh	NMM; MeCN	24	86
8	Ph	*p*-OMePh	NMM; MeCN	24	97
9	1-naphthyl	Ph	NMP; CH_2Cl_2	24	67
10	3-furyl	Ph	NMM; MeCN	6	90
11	*n*-Bu	Ph	NMM; CH_2Cl_2	22	83
12	*i*-Bu	Ph	NMM; CH_2Cl_2	22	78
13	CH_2CH_2Ph	Ph	NMM; CH_2Cl_2	16	62
14	H	O*t*Bu	NMM; CH_2Cl_2	10	80
15	Ph	O*t*Bu	NMM; CH_2Cl_2	40	32

Table 4

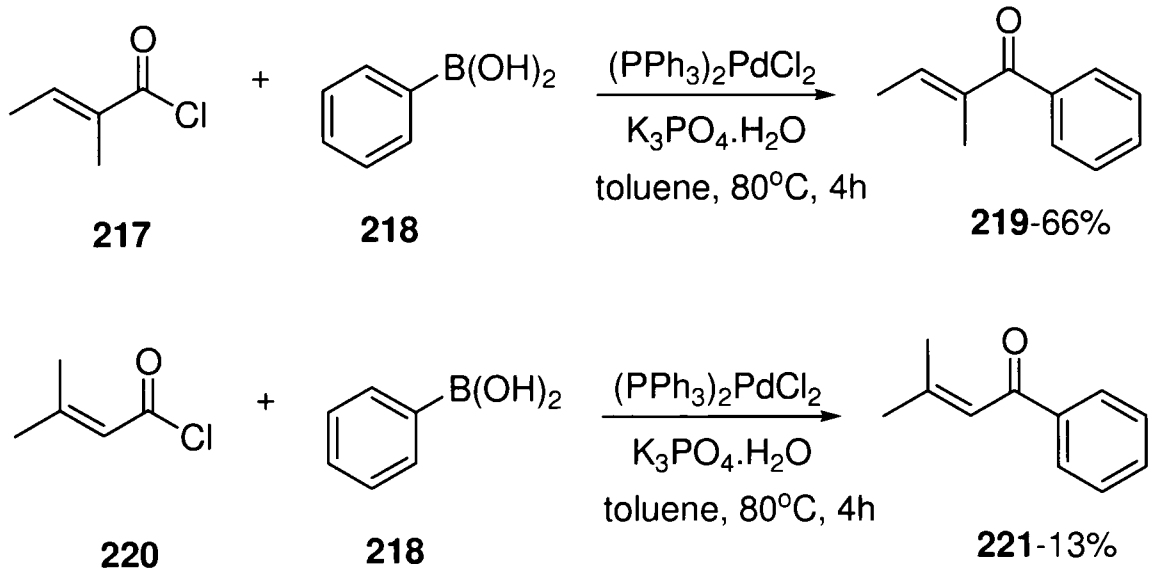
With these results in mind we began to consider expanding the scope of the achiral aziridination procedure. Currently only disubstituted enones had been tested in the reaction and immediately this led us to consider the potential for the aziridination of trisubstituted derivatives, with both aromatic and aliphatic substitution patterns. The three aliphatic, acyclic substrates (entries 11-13) had proven to be successful in the reaction and to this end we proposed testing a number of cyclic derivatives. Additionally, we hoped to vary the R^1 substituent, adjacent to the ketone moiety of the substrate, to incorporate a wider range of electron withdrawing functionality.

As NMM/NaOH in acetonitrile had provided a consistently reasonable set of results with chalcone, and a number of other substrates, we chose this system as our standard for further substrate screening. The specific substrates identified for testing were either obtained from commercial sources or synthesised *via* literature procedures as detailed.

2.2.1.1 Trisubstituted Enones

Trisubstituted derivatives offered an interesting class of substrate to test in the aziridination reaction, in part due to the issue of *cis-/trans-* selectivity, and additionally as such substrates have the potential to form products containing quaternary centres. Aliphatic and aromatic substituted derivatives were tested in order to probe the steric and electronic effects that these groups may exert upon the reaction. Most of the derivatives tested in this section of work were not commercially available, therefore requiring expedient synthesis from readily available starting materials.

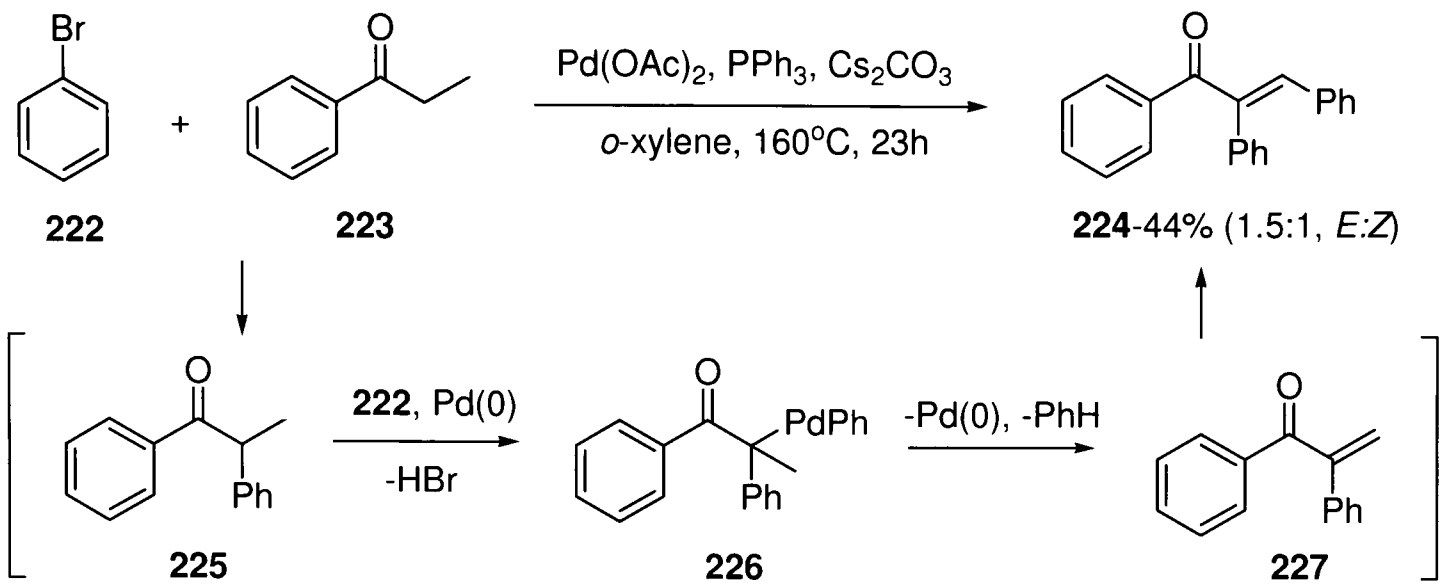
The dimethyl substituted α,β-unsaturated ketones **219** and **221** were synthesised *via* a Suzuki-Miyaura type coupling of acid chlorides **217** and **220** with phenyl boronic acid (**218**) in the presence of hydrated K_3PO_4 as base (Scheme 85).[105] The poor yield obtained for the β,β-disubstituted derivative **221** was as expected as the literature reports that substrates with no α-substitution suffer from polymerisation under the reaction conditions.



Scheme 85

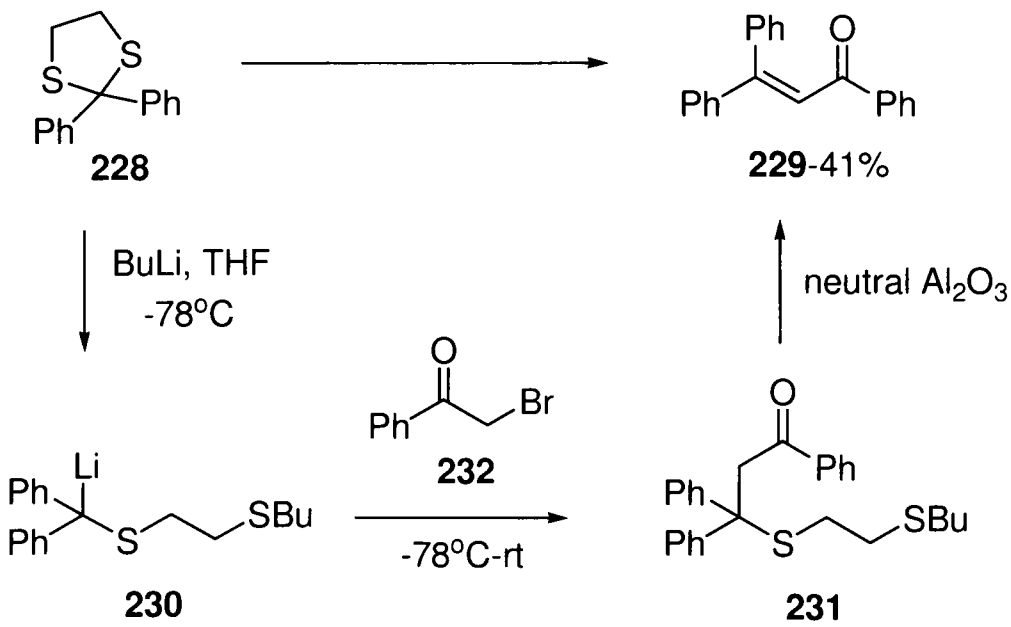
Aromatic trisubstituted derivative **224** was also synthesised using palladium catalysis. The multiple arylation of aromatic ketone **223** is reported to proceed *via* a so-called oxidative unsaturation pathway.[106] Arylation of **223** at the α-position is followed by reaction of the enolate of **225** with phenyl palladium bromide; this gives species **226** which undergoes elimination of PhPdH to provide the α,β-unsaturated ketone **227** with

liberation of Pd(0) and benzene. Subsequent phenylation at the β-position gives the desired α,β-unsaturated product **224** as a separable mixture of *E/Z* isomers, both of which can be tested in the aziridination reaction (Scheme 86).



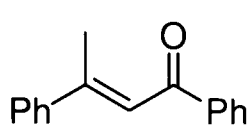
Scheme 86

Finally, the β,β-diphenyl substituted enone **229** was synthesised according to literature precedent *via* the coupling of benzophenone dithioacetal **228** and α–bromoketone **232**.[107] Initial addition of *n*-BuLi to the dithioacetal promotes ring-opening to give the lithiated species **230**, subsequent addition of ketone **232** provides the isolable intermediate **231**, which, after addition of neutral alumina, undergoes elimination to give the unsaturated product **229** (Scheme 87).

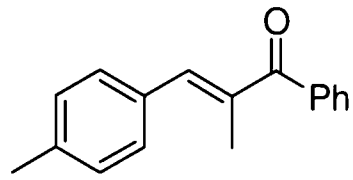


Scheme 87

Two further trisubstituted enones were tested in this section of work. Ketone **233** and **234** were obtained from commercial sources (Figure 6).



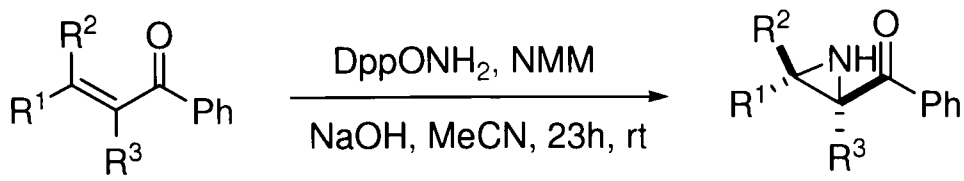
233



234

Figure 6

Having synthesised a range of trisubstituted enones we tested these derivatives under the standard NMM aziridination conditions (Table 5). As chalcone had previously been shown to be a good substrate for the NMM aziridination reaction we began by looking at similar derivatives possessing a β-substituent. Enones **233** and **221** (entries 1 and 2), were subjected to the aziridination conditions with disappointing results. No aziridine product was isolated in either case, with the mass balance of both reactions being low. It was postulated that the presence of potentially acidic gamma-protons in both substituents may be resulting in competing substrate decomposition. With this in mind we chose to test the β-phenyl substituted enone **229** (entry 3), containing no gamma–protons. In this case only starting material was recovered from the reaction after 23 hours. Having had no success with β-substituted chalcone derivatives we chose to move on to look at α–substitution patterns, again starting with the α-methyl substituted derivative **234** (entry 4). Pleasingly enone **234** proved to be a good substrate for the NMM aziridination reaction (58% yield). As an interesting comparison to this result we then chose to test the *E/Z* α-phenyl substituted derivatives *E/Z*-**224** (entries 5 and 6). Unfortunately the results obtained using these substrates were disappointing, with only starting material being recovered from both of the reactions. Finally the 2,3-dimethyl substituted enone **219** was tested as an aliphatic comparison, containing gamma-protons. As with substrates **233** and **221** (entries 1 and 2) no aziridine product was isolated, and a low reaction mass balance was observed.



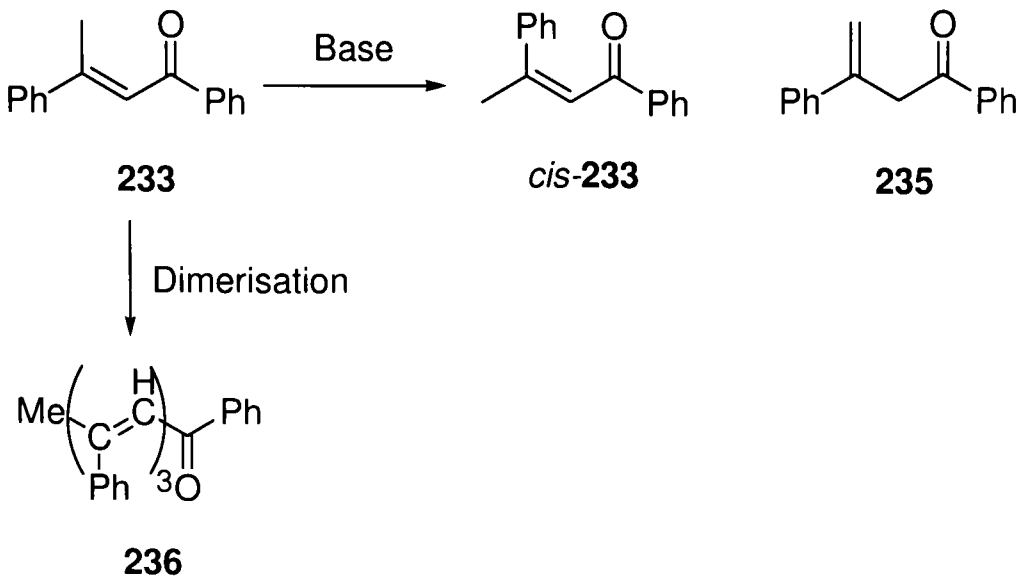
Entry	Enone	R^1	R^2	R^3	Yield (%)	Recovered Starting Material (%)[a]
1	**233**	Ph	Me	H	0	41
2	**221**	Me	Me	H	0	0
3	**229**	Ph	Ph	H	0	100
4	**234**	*p*-MeC_6H_4	H	Me	58	30
5	***E*-224**	Ph	H	Ph	0	100
6	***Z*-224**	H	Ph	Ph	0	100
7	**219**	Me	H	Me	0	22

[a] Percentage recovered starting material after column chromatography.

Table 5

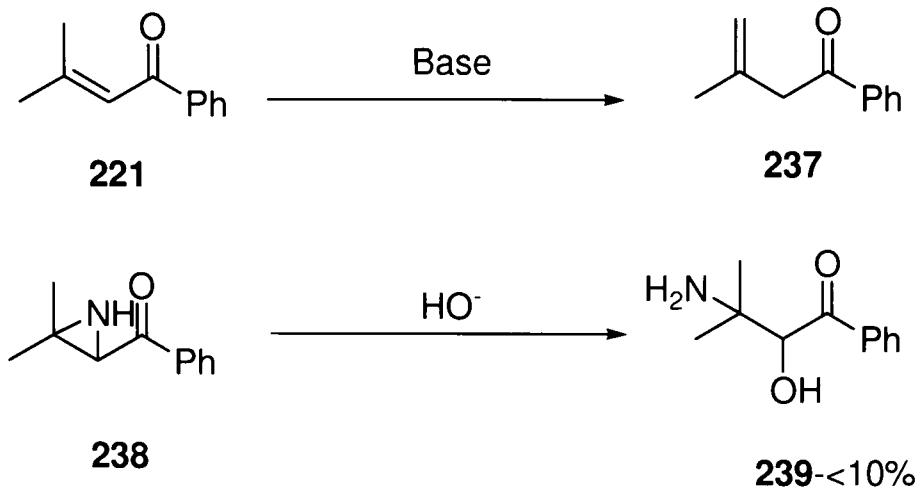
As previously described we suspected the low reaction mass balance obtained with substrates **233**, **221** and **219** (entries 1, 2 and 7) to be due to the presence of acidic gamma–protons resulting in the decomposition of these derivatives under basic reaction conditions. With this in mind we chose to analyse the crude reaction mixtures using GC/MS (EI^+) in order to identify any key products formed during the reaction. All relevant GC/MS data for this section of work are given in the experimental section of this thesis.

GC/MS (EI^+) analysis of the crude reaction mixture obtained using enone **233** showed the presence of three peaks corresponding to the mass of the starting material. It was postulated that these may arise *via* an alkene isomerisation pathway to give products *cis*-**233** and **235**, an unconjugated system unlikely to undergo aziridination (Scheme 88). A literature report was uncovered detailing the condensation of acetophenone, monitored by GLC-MS, a product of which is shown to be enone **233**.[108] Dimerisation of derivative **233** was shown to give compound **236** ($[M]^+$=426); a peak corresponding to this mass can also be identified in the GC/MS spectrum obtained from our crude reaction.



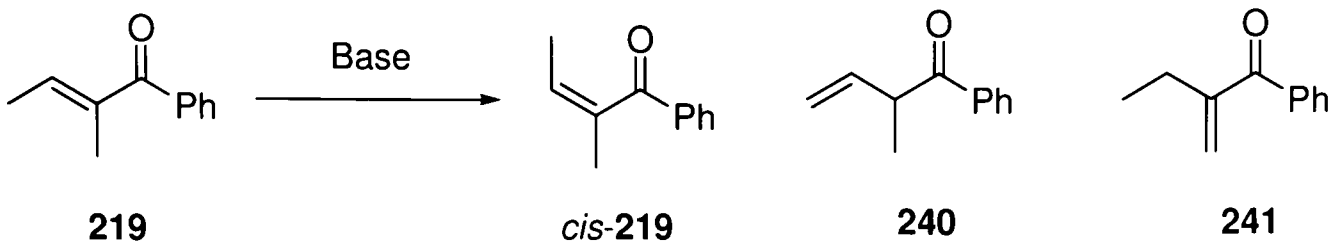
Scheme 88

The reaction of 3,3-dimethyl enone **221** was also studied by GC/MS. ^{1}H NMR analysis of the crude reaction mixture showed that the starting material had been fully consumed after 23 hours. However, GC/MS (EI^+) gave two intense peaks the mass of which corresponded to the starting alkene **221**. Again, it was postulated that the basic reaction conditions may be promoting alkene isomerisation to give **237**, a non-conjugated system that is unlikely to be aziridinated under the reaction conditions (Scheme 89), although this suggestion is not corroborated due to lack of alkene signals in the ^{1}H NMR of the crude mixture. Alternatively, if the starting material is degraded *via* a polymerisation pathway these mass peaks may correspond to a fragmented polymer of enone **221**. A product, thought to correspond to the ring opened aziridine **239** (as confirmed by accurate mass analysis), was isolated in low yield (<10 %) (Scheme 89). No aziridine product was observed.



Scheme 89

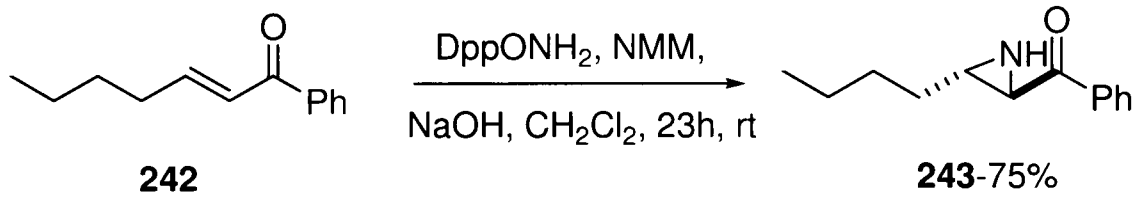
Finally, the reaction of the 2,3-dimethyl substituted enone **219** was also studied by GC/MS. Little information could be gained from the complex ^{1}H NMR spectrum of the crude reaction mixture. However, signals representative of the starting material and a number of other alkene protons (δ_H= 5-6 ppm) were visible. GC/MS (EI^+) analysis of the crude reaction displayed two major components the mass of both of which corresponded to that of the starting material. Again, it was postulated that under basic reaction conditions enone **219** may be undergoing isomerisation to *cis*-**219**, **240** or **241** (Scheme 90). However, after referring back to the ^{1}H NMR of the crude reaction it was clear that none of the visible alkene signals corresponded to these known compounds (*cis*-**219**, **240** and **241**),[109-111] suggesting that either the peaks present in the GC/MS do not relate to these products as initially thought, or that they are only minor components in the system. Alternatively the basic reaction conditions could lead to polymerisation of the starting material alkene with these peaks representing fragments of polymerisation products. In order to establish whether the proposed substrate decomposition was mediated by base alone, enone **219** was subjected to NaOH (2 equiv.) in MeCN. The ^{1}H NMR of the crude reaction mixture showed the same alkene protons as observed in our original aziridination reaction (5-6 ppm), with the GC/MS (EI^+) spectrum displaying three peaks with the same mass as the starting material. This result indicates that the apparent substrate degradation is base-promoted and occurs even in the absence of aminating agent.



219 *cis*-**219** **240** **241**

Scheme 90

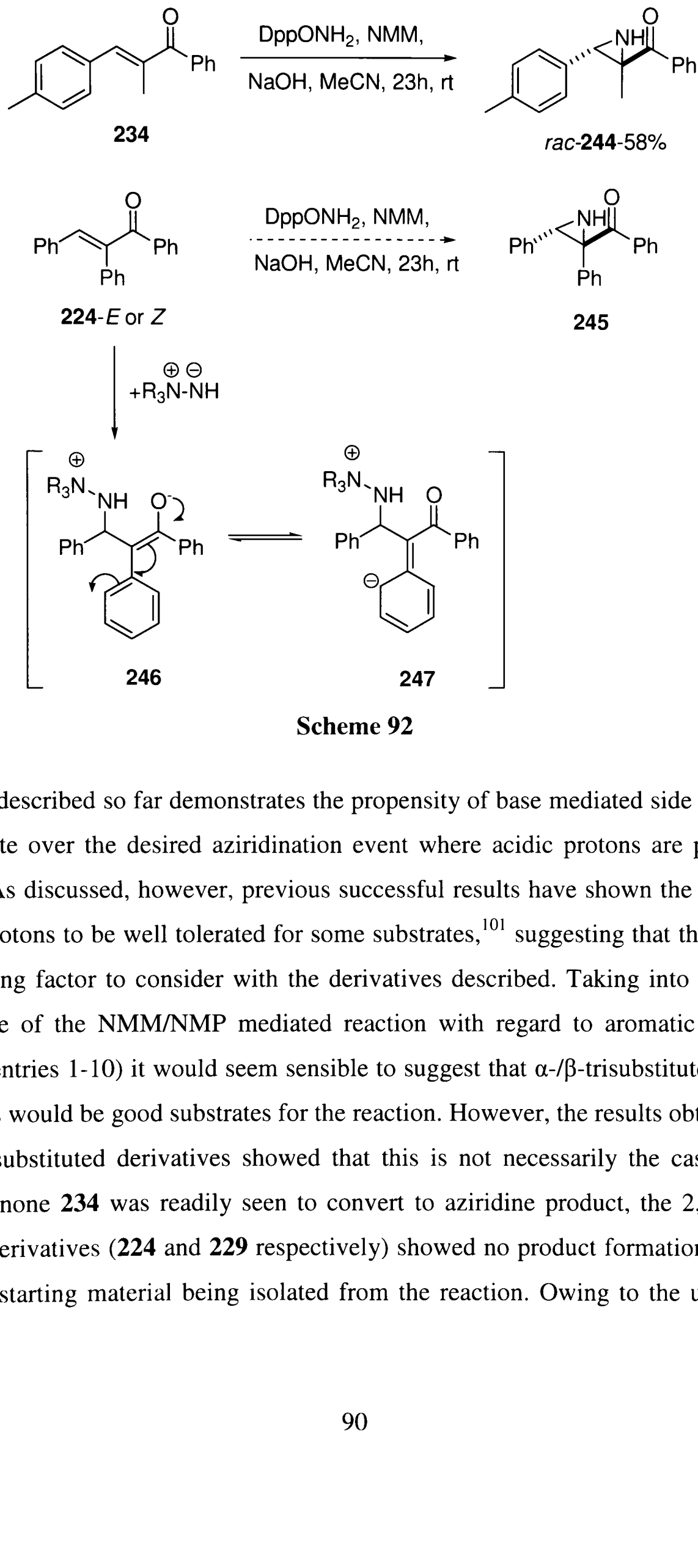
The seemingly incompatible nature of our basic aziridination system with substrates **233**, **221** and **219** was somewhat surprising as previous work had shown other substrates possessing gamma–protons (Table 4, entries 11-13) to work well in the NMM mediated aziridination. Substrate **242** was re-tested under the conditions specified in Table 4 in order to establish that the results obtained with our new aliphatic substituted derivatives were reliable. Aziridine **243** was isolated in good yield (75%, Scheme 91, *cf.* previous work (Table 4, entry 11) 83%)[101] showing that the results were indeed reliable. The fact that some substrates containing acidic protons are successfully aziridinated under these conditions, suggests that the presence of gamma-protons is not the only factor affecting the instability of these derivatives.



242 **243**-75%

Scheme 91

Two interesting results worthy of comparison are those obtained using enones **234** and *E*-/*Z*-**224** (Scheme 92, Table 5, entries 4 and 5/6). While an α–phenyl group appears to prevent aziridination from occurring, the α–methyl substituted derivative reacts well to give the desired product. In the case of the aromatic variant this result suggests that the formation of aziridine product is not competitive. The additional phenyl group would be expected to stabilize the intermediate enolate, increasing the rate of aminimine addition, while decreasing the rate of ring closure. The fact that the reaction is unsuccessful suggests that the nucleophilicity of the intermediate enolate is an important factor in the ring-closure process. The nucleophilicity of intermediate **246** may be reduced *via* delocalisation onto the α-aromatic (Scheme 92).



Scheme 92

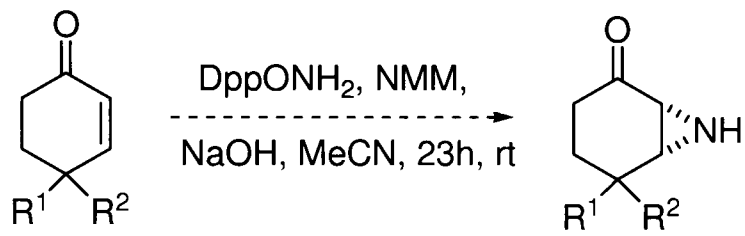
The work described so far demonstrates the propensity of base mediated side reactions to predominate over the desired aziridination event where acidic protons are present in a substrate.As discussed, however, previous successful results have shown the presence of gamma–protons to be well tolerated for some substrates,[101] suggesting that this is not the only limiting factor to consider with the derivatives described. Taking into account the wide scope of the NMM/NMP mediated reaction with regard to aromatic derivatives (Table 4, entries 1-10) it would seem sensible to suggest that α-/β-trisubstituted chalcone derivatives would be good substrates for the reaction. However, the results obtained using phenyl trisubstituted derivatives showed that this is not necessarily the case, and that although enone **234** was readily seen to convert to aziridine product, the 2,3- and 3,3-diphenyl derivatives (**224** and **229** respectively) showed no product formation, with only recovered starting material being isolated from the reaction. Owing to the unpromising

results obtained so far with trisubstituted enones, we began to consider a different substrate class for the reaction.

2.2.1.2 Cyclic Enones

Previously only acyclic derivatives had been tested in the NMM mediated aziridination reaction and with this in mind we chose to look at simple cyclic enones as possible substrates. Although some cyclic enones possess acidic protons, a factor previously suspected to cause problems with substrate degradation in the aziridination reaction, we were still keen to test these derivatives.

Cyclohexenone (Table 6, entry 1) was selected for initial testing. As we anticipated problems regarding the presence of acidic gamma-protons we also chose to test 4,4-dimethylcyclohexenone (Table 6, entry 2). Unfortunately both reactions proved to be unsuccessful with no aziridine product being isolated in either case (Table 6).



Entry	R^1	R^2	Yield (%)	Recovered Starting Material (%)[a]
1	H	H	0	0
2	Me	Me	0	0

[a] Percentage recovered starting material after column chromatography.

Table 6

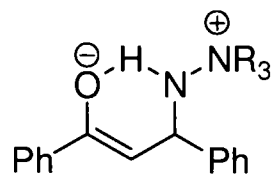
Again the lack of aziridine product formation, teamed with a low mass balance for both reactions, prompted us to investigate other possible reaction products using GC/MS (EI^+) analysis. For the reaction of cyclohexenone, column chromatography allowed the isolation of one spot only, which proved to be a mixture of products. GC/MS (EI^+) analysis of the crude mixture showed the presence of three peaks with masses corresponding to starting material, cyclohexenone dimer and a mono-aziridinated product of this dimer. No starting material was recovered. Again, it was thought that the presence

of acidic protons in the starting material may lead to product decomposition *via* a base induced polymerisation pathway. Upon subjecting cyclohexenone to base (NaOH) in MeCN for 17 hours, GC/MS (EI^+) analysis of the crude reaction mixture showed peaks corresponding to the mass of a cyclohexenone dimer. Additionally, a peak corresponding to the mass of a trimer of the starting material was also visible. This suggests that indeed substrate decomposition is base-mediated and occurs in the absence of the aminating agent $DppONH_2$.

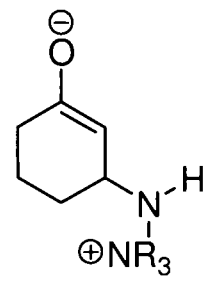
It was considered that by altering the order of addition of components, or by decreasing the amount of base used in the reaction, we may be able to prevent product decomposition from occurring. The hydrazinium salt was prepared as standard *via* addition of NMM to $DPPONH_2$ in MeCN with stirring for 30 minutes.[101] However, instead of the simultaneous addition of base and α,β–unsaturated ketone, the base (NaOH, 2 equiv.) was added after hydrazinium formation was complete (30 minutes) and 45 minutes prior to enone addition. It was hoped that this would reduce the contact time between the base and the substrate and hence eliminate the suggested base mediated decomposition pathway. After stirring for 23 hours only a trace amount of aziridine product was seen by ^1H NMR. In a separate reaction the amount of base used was decreased to 1 equivalent but disappointingly this proved no more successful in providing higher yields of the desired product. The aziridination of 4,4-dimethylcyclohexenone (Table 6, entry 2) proved to be equally problematic, with no products being isolated after column chromatography.

Although these results suggest that the basic nature of the aziridination system teamed with the acidic protons present in the substrates may be resulting in decomposition, preliminary computational calculations[112] imply the absence of a stabilising H-bonding interaction may prevent these cyclic substrates from reacting regardless of the presence of gamma–protons. For the standard substrate chalcone, calculations have shown that upon formation of the intermediate enolate species a hydrogen bond is formed between the N-*H* and the O^- (**248**). This interaction markedly lowers the TS-energy for both the aminimine addition and for the ring-closure step. However, cyclic enones are

conformationally restricted, so preventing the formation of this favourable hydrogen bond (**249**) (Scheme 93).



248



249

Scheme 93

The disappointing results obtained in this section led us to move away from cyclic substrates, considering instead derivatives with different electron withdrawing functionality adjacent to the ketone moiety of the substrate. Previous work (Table 4, entries 1-10 and entries 14 and 15) has shown the success of both aromatic and ester groups in this position and we were keen to extend this work to incorporate other activating groups.

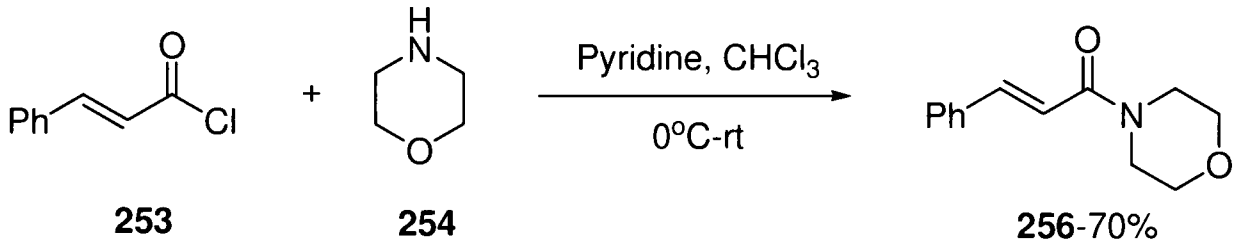
2.2.1.3 Derivatives Containing Other Activating Groups

The presence of a strong electron withdrawing group in the substrate would be expected to stabilise the intermediate enolate formed upon aminimine addition. It was predicted that this stabilisation would affect the two key reaction steps differently, increasing the rate of aminimine addition, and in turn decreasing the rate of ring-closure. It was postulated that trends in the substrate scope would provide information regarding the likely rate determining step of the aziridination reaction. We hoped to use pKa values[113] as an approximate guide to the electron withdrawing capacity of each group.

The commercially available nitrile (**250**, Table 7, entry 3), sulfone (**251**, Table 7, entry 4) and nitro (**252**, Table 7, entry 5) derivatives were selected for initial testing. These substrates were deemed interesting, both in terms of the potential for ring-opening of their aziridinated products, and also due to the terminal functionality offering further

routes for manipulation. To the best of our knowledge no literature preparations are reported for the synthesis of the sulfone- or nitro- substituted aziridines, with only one report available detailing a indirect method for the synthesis of the nitrile derivative *via* bromination of cinnamonitrile, followed by addition of ammonia gas with subsequent ring-closure.[114] α,β-Unsaturated amides also represented an interesting class of substrate containing an activating group. Again, the presence of the amide functionality makes these derivatives attractive in terms of further manipulation after aziridination has occurred. The morpholino amide **256** (Scheme 94, Table 7, entry 6) was selected as a substrate easily synthesised from readily available materials. Additionally we wanted to test oxazolidinone **258** (Scheme 95, Table 7, entry 7) as such derivatives have the potential to be easily synthesised with incorporation of chiral centres on the oxazolidinone ring.

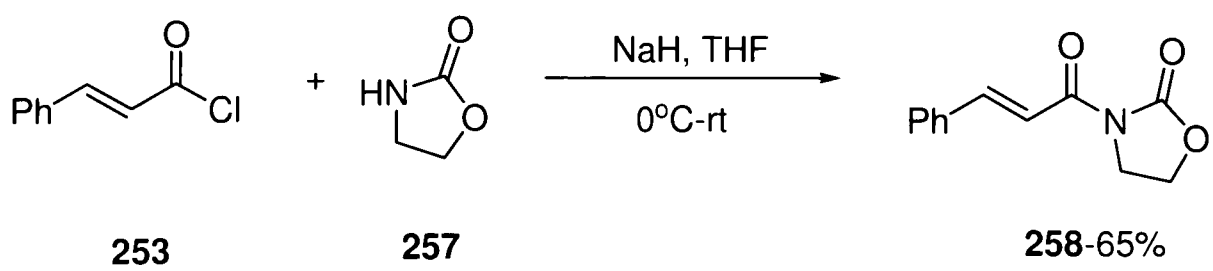
Amide **256** was synthesised *via* a simple literature procedure.[115] Addition of morpholine to cinnamoyl chloride (**253**), in the presence of pyridine as base, gave the desired product in reasonable yield (70%) (Scheme 94).



253 **254** **256**-70%

Scheme 94

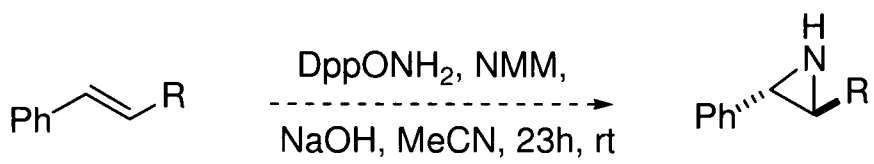
Oxazolidinone **258** was readily synthesised in moderate yield (65%) from cinnamoyl chloride and 2-oxazolidinone, in the presence of base (NaH, 60% in mineral oil) (Scheme 95).[116]

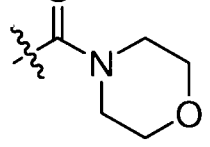
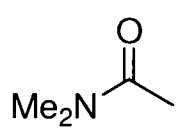
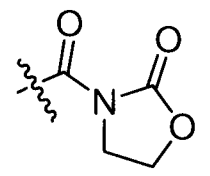
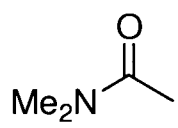


253 **257** **258**-65%

Scheme 95

All substrates were subjected to the standard NMM aziridination conditions (Table 7). Entries 1 and 2 are included for comparison as previous successful substrates (Table 4, entries 1 and 15).[101] The results obtained from this section of work were disappointing. Nitrile **250** (entry 3), sulfone **251** (entry 4) and morpholine **256** (entry 6) failed to produce any of the desired aziridine product with only starting material being recovered from the reaction. Nitro derivative **252** (entry 5) and oxazolidinone **258** (entry 7) gave no product and appeared to decompose under the reaction conditions.



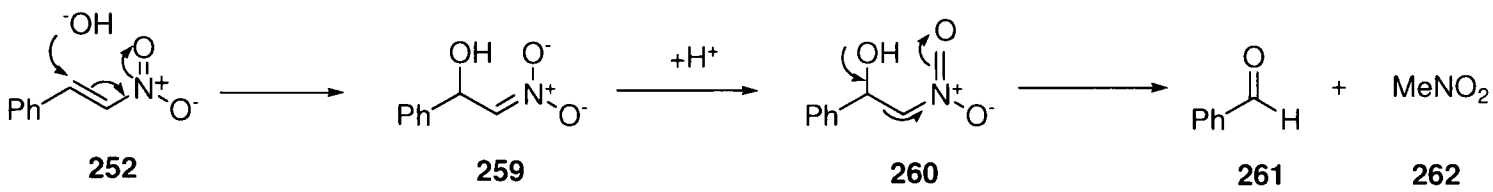
Entry	Enone	R	pKa of corresponding subunit in DMSO	Yield (%)	Recovered Starting Material (%)[a]
1[b]	-	Ph	24.7 (MeCOPh)	88	-[c]
2[b]	-	CO_2tBu	30.3 ($MeCO_2tBu$)	32	-[c]
3	**250**	CN	31.3 (MeCN)	0	>90
4	**251**	SO_2Ph	29.0 ($MeSO_2Ph$)	0	100
5	**252**	NO_2	17.2 ($MeNO_2$)	0	-[c]
6	**256**		35.0 	0	100
7	**258**		35.0 	0	-[c]

[a]Percentage recovered starting material after column chromatography; [b]Tested as part of previous work by co-workers; [c]Not measured.

Table 7

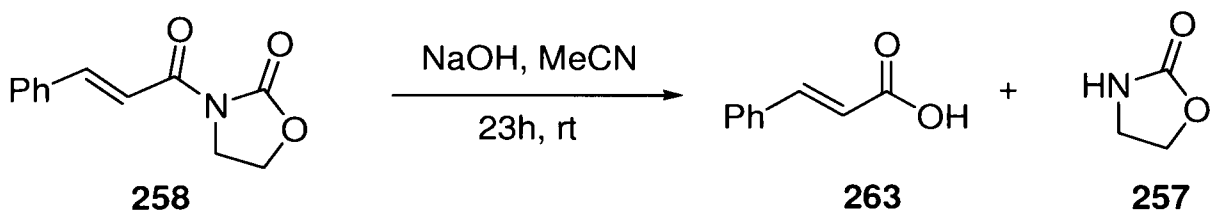
The pKa values of the corresponding subunits for all new substrates (entries 3-7) do not appear to be within a range between the two successful substrates (entries 1 and 2), apart from sulfone **251** which has a pKa value of 29.0. The nitro derivative **252** (entry 5, pKa 17.2), has a pKa value less than that of the lower limit set by the phenyl ketone derivative (entry 1, pKa 24.7), and the nitrile derivative **250** (entry 3, pKa 31.3), and both amides **256** and **258** (entries 6 and 7, pKa 35.0), have pKa values higher than the upper limit set by the *t*-butyl ester derivative (entry 2, pKa 30.3).

Both nitro derivative **252** (entry 5) and oxazolidinone **258** (entry 7) appeared to be unstable under the aziridination conditions. With this in mind we chose to submit both crude reaction mixtures for GC/MS (EI^+) analysis in order to gain information with regard to possible modes of decomposition. GC/MS analysis of the reaction of derivative **252** identified the presence of benzaldehyde which was further substantiated by an aldehyde peak at δ_H= 10.1 ppm in the ^1H NMR spectrum of the crude mixture. Decomposition of styrene derivative **252** is postulated to occur *via* the retro-Henry type reaction represented in Scheme 96; such a mechanism would account for the presence of benzaldehyde in the crude reaction mixture. Indeed stirring substrate **252** in the presence of base for 20 hours showed decomposition. Again benzaldehyde was clearly identified in both the ^1H NMR and GC/MS (EI^+) spectra of the crude reaction mixture.



Scheme 96

^1H NMR and GC/MS (EI^+) analysis of the crude material from the reaction of oxazolidinone derivative **258** showed peaks corresponding to cinnamic acid (**263**) and 2-oxazolidinone (**257**), suggesting that substrate **258** is unstable under the reaction conditions. Indeed, subjecting amide **258** to basic conditions (NaOH) showed decomposition to the component parts; cinnamic acid and 2-oxazolidinone, as identified by ^1H NMR and GC/MS (EI^+) analysis (Scheme 97).

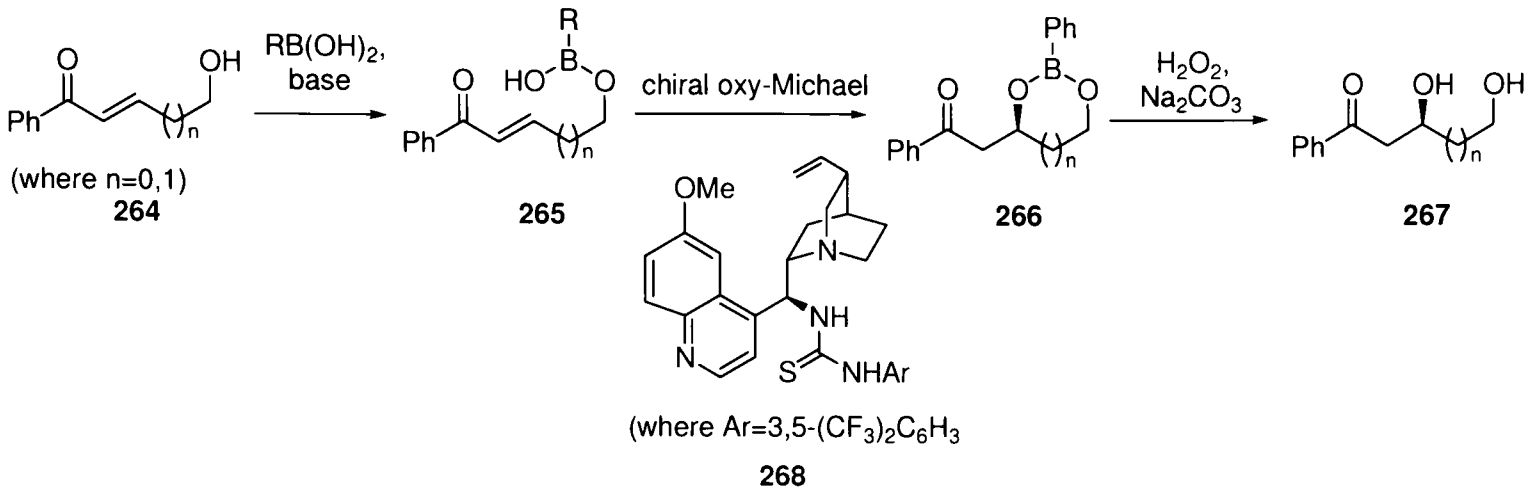


Scheme 97

Due to the lack of correlation between pKa and substrate substitution it was difficult at this stage to draw any firm conclusions regarding the rate determining step of the reaction. However, the fact that a number of reactions (Table 5, entries 3, 5 and 6 and Table 7, entries 3, 4 and 6) resulted in the recovery of 100% starting material suggested that the preliminary aminimine addition step was not occurring or was reversible. With this in mind we began to consider the potential for introducing some sort of directing group into the substrate which might aid the initial aminimine addition.

2.2.1.4 γ-Hydroxy substituted enones

Our preliminary thoughts were that the incoming nucleophile could be directed by H-bonding. We considered that the introduction of a delta-hydroxy group into the substrate may allow a H-bond to form between the substrate and the aminimine. While we were unaware of similar directing effects, a related concept proved successful in recent work by Falck *et al.*,[117] in which a cinchona alkaloid-mediated, enantioselective, oxy-Michael addition to γ/δ-hydroxy-α,β-enones was described. Falck details the synthesis of boronic acid hemiester **265**, generated *in situ* from a γ/δ–hydroxy enone (**264**) and a standard boronic acid. The intramolecular Michael addition then proceeds *via* complexation of adduct **265** to a chiral amine catalyst, in this case a thiourea derivative of quinine (**268**). Mild oxidative removal of the boronate functionality then exposes the product chiral diol (**267**) (Scheme 98). The catalyst is thought to act in a bifunctional ("push/pull") manner, with coordination of the thiourea moiety to the carbonyl group of adduct **265** ("pull") and complexation of the tertiary nitrogen of the catalyst to the boron ("push") giving the product diols in high yields (71-95%) and with excellent *e.e* values (87-99%) (Figure 7). On the basis of this report we hoped to test a range of similar substrates in the NMM-promoted aziridination reaction.



Scheme 98

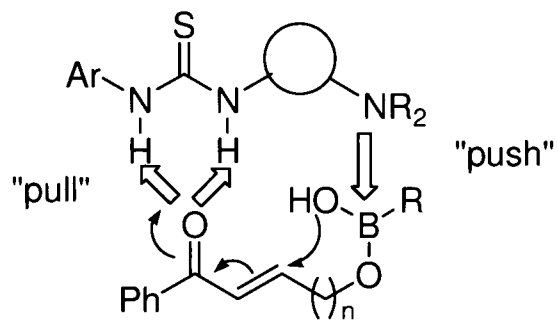
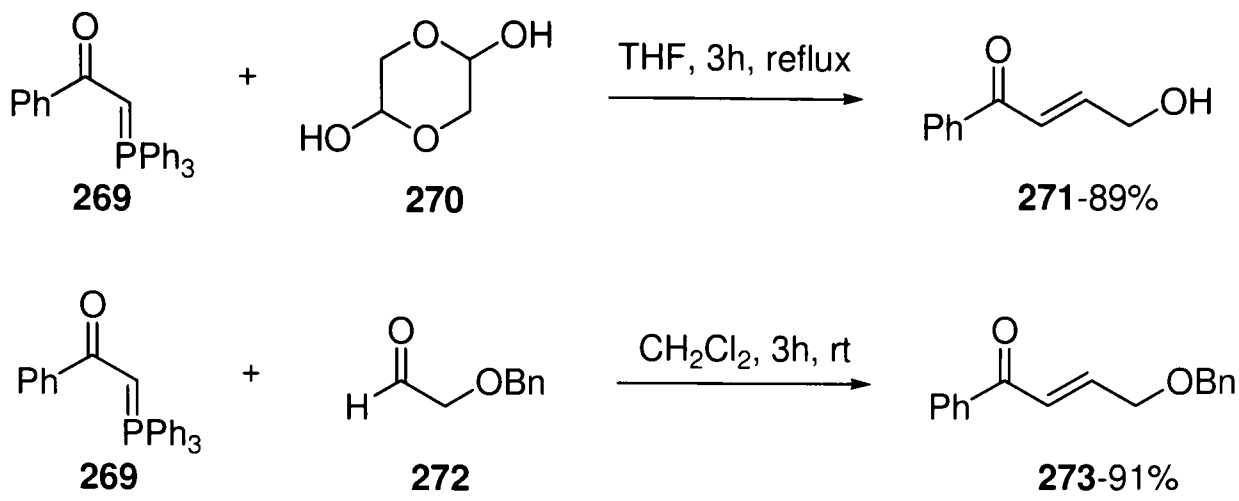


Figure 7

We began with the synthesis of γ-hydroxy enone **271** following the literature procedure used by Falck and co-workers.[118] The protocol utilises standard Wittig chemistry to install the unsaturated system. Glycoaldehyde dimer (**270**) was added to a solution of ylide **269** in THF with heating to reflux for 3 hours (Scheme 99). The product enone was isolated in good yield (89%) despite literature suggestions[118] that such substrates are susceptible to decomposition to the corresponding furan. Additionally we chose to synthesise the benzyl protected derivative **273** as a control substrate to investigate the role of hydrogen bonding. The synthesis of **273** was completed using standard Wittig chemistry to give the desired product in excellent yield (91%) (Scheme 99).



Scheme 99

Enones **271** and **273** were subjected to the standard NMM-promoted aziridination conditions (Table 8). Disappointingly both reactions were unsuccessful. No aziridine product was isolated in either case with both starting materials seemingly decomposing under the reaction conditions.

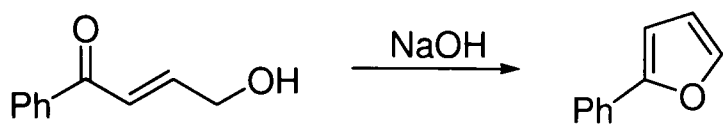
Entry	Enone	R	Yield (%)	Recovered Starting Material (%)[a]
1	**271**	H	0	0
2	**273**	Bn	0	0

[a] Percentage recovered starting material after column chromatography; [b] Not measured.

Table 8

Again, the low reaction mass balance of both reactions prompted us to submit the crude reaction mixtures for GC/MS (EI^+) analysis in order to identify any key products formed *via* side reactions. Analysis of the crude mixture recovered from the reaction of enone **271** showed the presence of a component of mass corresponding to the desired product. However, the ^1H NMR spectrum of the same mixture showed no evidence of characteristic aziridine peaks (typically δ_H= 3-4 ppm for C*H*NH), suggesting that the extent of desired product formation is not significant under these conditions. Additionally a peak with a mass corresponding to the furan derivative **274**, formed upon ring closure of the substrate, is visible by GC/MS. This suggests that under the basic reaction

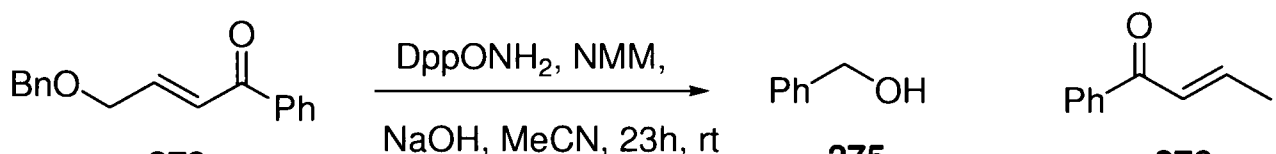
conditions the γ-hydroxy enone (**271**) may be decomposing to give product **274**, therefore preventing the desired aziridination pathway from occurring (Scheme 100).



271 **274**

Scheme 100

It was thought that the benzyl protecting group present in enone **273** may prevent cyclisation to the undesired furan product. Substrate consumption was complete after 23 hours with the ^{1}H NMR of the crude reaction proving to be complex with no identifiable characteristic aziridine peaks. GC/MS (EI^{+}) analysis of the crude reaction mixture showed peaks corresponding to the mass of benzyl alcohol **275** and enone **276**, again suggesting that the substrate decomposes under the reaction conditions (Scheme 101).



273 **275** **276**

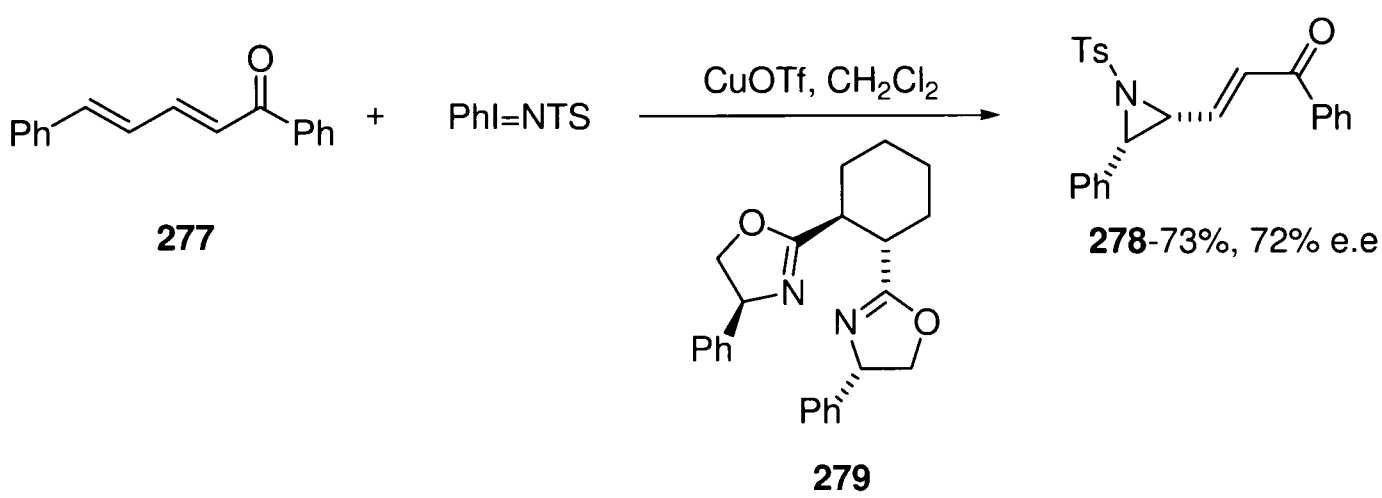
Identified by GC/MS (EI^{+})

Scheme 101

Although initially we had hoped that the pendant hydroxyl functionality of these γ-hydroxy substituted enones may prove beneficial in terms of exerting a directing effect over the incoming aminimine, ultimately these substrates proved highly unstable under the aziridination reaction conditions. At this stage we considered the successful results previously obtained by co-workers (Table 4). Aromatic substituted derivatives were consistently seen to give good results in the achiral aziridination reaction (Table 7, entries 1-10). However, only one example of a heteroaromatic substituent was available (Table 7, entry 10). With this in mind we proposed testing a range of different heteroaromatic substituted substrates. Additionally we were interested in introducing an extra alkene unit into the substrate in order to extend the reaction scope to dienones.

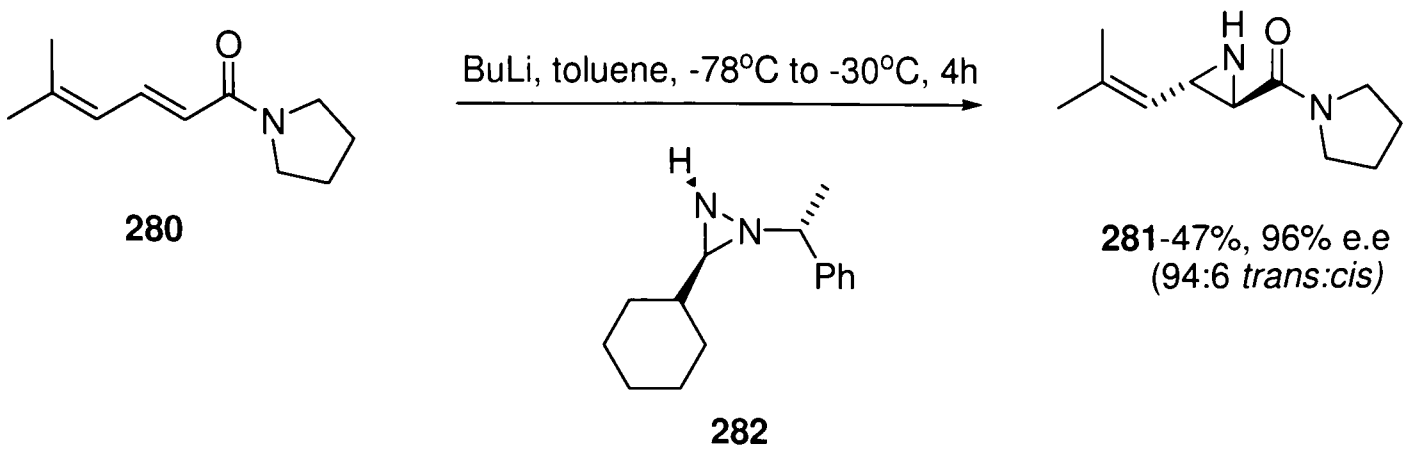
2.2.1.5 Dienones

Dienones represent an interesting class of substrate for the aziridination reaction, potentially yielding vinyl aziridine products. Vinyl aziridines lend themselves to a range of transformations, including Lewis acid catalysed, [1,3]-sigmatropic rearrangements to give 3-pyrrolines[119] and ring expansion leading to piperidines,[120] making them a synthetically appealing target class. To the best of our knowledge very few reports of the aziridination of dienones exist. Two key examples of such work are described here. Xu *et al.*[121] presented the asymmetric aziridination of 1,3-dienes catalysed by bisoxazoline CuOTf complexes with PhI=NTs as a nitrene source. Yields (21 73%) and enantioselectivities (up to 80% *e.e*) were variable, but diastereoselectivities were high (>99%, generally for the *cis*-product). Interestingly the reaction was highly regioselective for the γ,δ-alkene unit (Scheme 102).



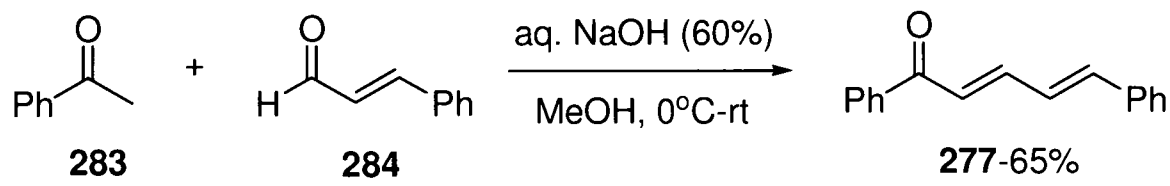
Scheme 102

A second report by Katsuki and co-workers[122] described the asymmetric aziridination of α,β,γ,δ-unsaturated amide **280** with diaziridine **282**. The reaction proceeded in moderate yield and with excellent enantioselectivity (47% and 96% respectively). Additionally the procedure was found to be highly selective for the *trans* aziridine product (94:6 *trans:cis*), and in contrast to the work presented by Xu *et al.*,[121] was regioselective for the α,β-alkene unit (Scheme 103).



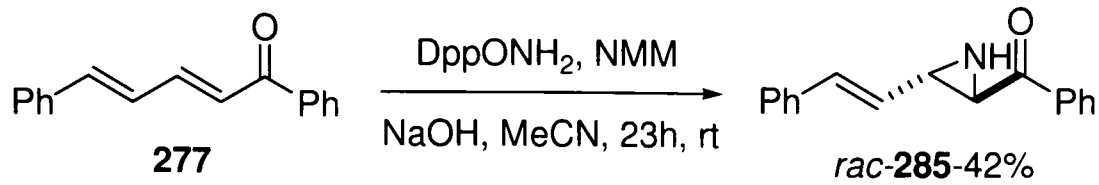
Scheme 103

The regioselectivity of the aziridination process was a significant point of interest at this stage, and although we were unable to find examples of the nucleophilic aziridination of dienones, the polyleucine based nucleophilic epoxidation of such substrates[123,124] suggested that our reaction would be selective for the α,β–alkene unit. In order to test the compatibility of the dienone functionality with our own aziridination conditions we began with the synthesis of chalcone derivative **277**. This was simply achieved *via* the aldol condensation of acetophenone (**283**) with cinnamaldehyde (**284**) to give the desired product in reasonable yield (65%) (Scheme 104).[125]



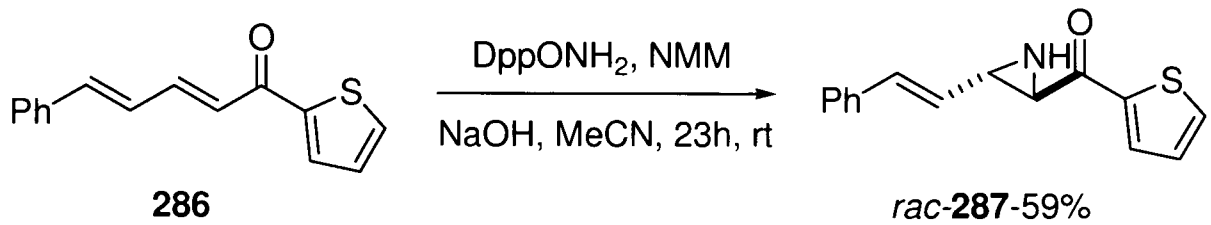
Scheme 104

Subjecting diene **277** to the standard NMM aziridination conditions gave the *trans*-aziridine product **285** in moderate yield (Scheme 105). Hmbc analysis, showing a long range coupling between the carbonyl group (δ_C=197.0 ppm) and one of the hydrogens present on the aziridine ring (δ_H=3.77 ppm), along with distinctive chemical shift values for the alkene hydrogens (δ=6.82 and 6.07 ppm), confirmed that aziridination does indeed occur on the alkene unit adjacent to the ketone functionality.



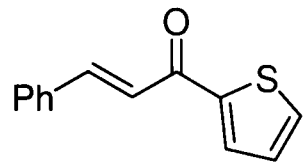
Scheme 105

With this promising result in hand we now sought to test a range of other derivatives. As the substituted thiophene **286** was found be one of the only commercially available dienones we selected this as the starting point for further testing. Pleasingly dienone **286** proved to be a good substrate for the aziridination system, giving aziridine **287** in reasonable yield (Scheme 106).

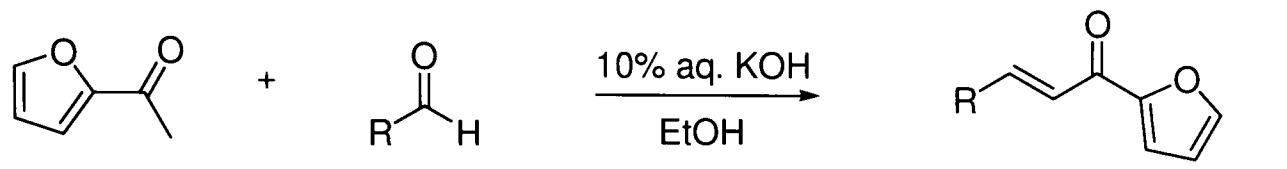


Scheme 106

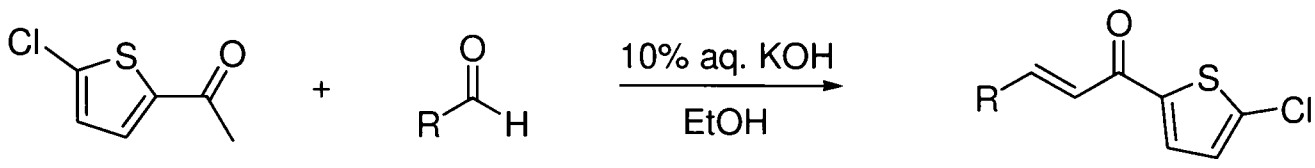
Based on the successful results obtained so far we were now keen to test a range of other dienone derivatives, with heteroaromatic substituents adjacent to the ketone moiety, and their mono alkene equivalents. Thiophene derivative **288** was obtained from a commercial source as a comparison to diene **286**. The initial successful reaction of the commercially available thiophene substrate **286** (Scheme 106) prompted us to look at the effect of furan substituted derivatives on the reaction. The synthesis of furanyl enone **291** (where R=Ph) and diene **292** (where R=PhCH=CH), were readily achieved *via* the aldol condensation of 2-acetyl furan (**289**) and the respective aldehyde component **290**, where R=Ph for the mono alkene product and R=PhCH=CH for the diene product (Scheme 107).[126] We were also keen to see if further substitution on the heteroaromatic would have any effect upon the reaction and to this end we chose to synthesise the chloro- and methyl- substituted thiophene derivatives **294** and **297** (where R=Ph) and **295** and **298** (where R=PhCH=CH) (Scheme 107).



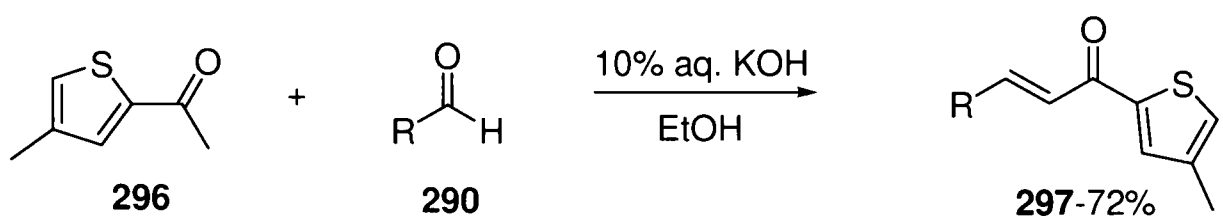
288



289 + **290** → **291**-88%, **292**-52%



293 + **290** → **294**-45%, **295**-36%



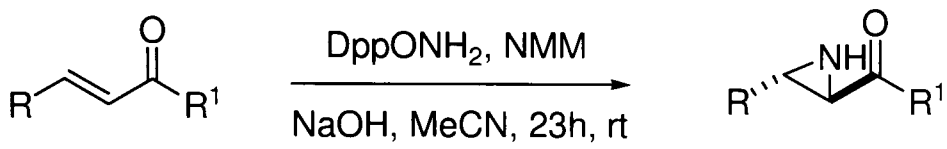
296 + **290** → **297**-72%, **298**-58%

(Where R=Ph for **291**, **294**, **297** and R=Ph(H)C=CH for **292**, **295**, **298**)

Scheme 107

The aziridination results obtained in this section of work are summarised in Table 9. Thiophene substituted dienone **286** (entry 3) gave a higher yield (59%) than that of its phenyl substituted counterpart (entry 1, 42%), while the furan derivative **292** (entry 5) produced a much lower yield of only 22%. With the mono alkene substrates the higher yield was provided by the furan derivative **291** (entry 4, 73%), while thiophene derivative **288** (entry 2) gave only 40% product yield (*cf.* chalcone under the same conditions: 88%). No clear pattern is observed in terms of which substrate, the enone or the dienone, gives higher product yields, with the thiophenyl monoalkene giving a lower yield than its dienone equivalent (entries 2 and 3, 40% *vs* 59%), and the furanyl monoalkene producing a significantly higher yield than its dienone counterpart (entries 4 and 5, 73% *vs* 22%). The addition of a further substituent to the heteroaromatic ring resulted in a drop in yield (entries 6-9). It is clear from the low reaction mass balance, in most cases, that alternative

undesired pathways are operating. However, at this stage no alternative side products were identified. It should be noted that all reactions in Table 9 were run over a period of 23 hours; it is possible that higher yields may well have been obtained for some of the substrates with longer reaction times.



Entry	Enone	R	R^1	Yield (%)	Recovered Starting Material (%)[(a)]
1	**277**	PhCH=CH	Ph	42	12
2	**288**	Ph	2-thiophenyl	40	32
3	**286**	PhCH=CH	2-thiophenyl	59	25
4	**291**	Ph	2-furyl	73	0
5	**292**	PhCH=CH	2-furyl	22	20
6	**294**	Ph	5-chloro-2-thiophenyl	25	0
7	**295**	PhCH=CH	5-chloro-2-thiophenyl	41	21
8	**297**	Ph	4-methyl-2-thiophenyl	22	21
9	**298**	PhCH=CH	4-methyl-2-thiophenyl	27	40

[(a)] Percentage recovered starting material after column chromatography.

Table 9

2.2.1.6 Summary of the Scope of the NMM Mediated Aziridination Reaction

Unsuccessful substrates that showed evidence of decomposition under the reaction conditions are shown in Table 10. Enones possessing gamma-protons proved generally to be poor substrates for the achiral aziridination reaction. Such derivatives seemingly undergo base mediated decomposition, preventing formation of the desired product. However, previous work conducted by co-workers (Table 4, entries 11-13)[101] has shown three substrates containing acidic protons to readily provide aziridine products. Although the reasons for this notable difference in reactivity are currently unknown, clearly the presence or absence of gamma-protons is not the sole factor in determining the stability of a compound under the NMM-mediated aziridination conditions. Substrates without

gamma-protons, such as nitro alkene **252** and oxazolidinone **258**, were also seen to decompose under the reaction conditions *via* alternative base mediated pathways. Cyclic substrates were unstable to the reaction conditions; computational studies have suggested that aziridination of these substrates is likely to be difficult due to their inability to form a favourable H-bonding interaction in the enolate intermediate.

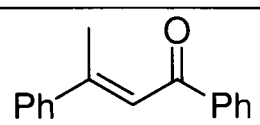
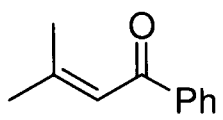
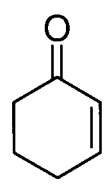
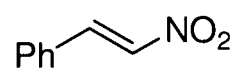
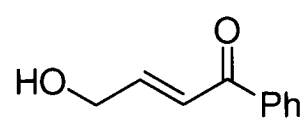
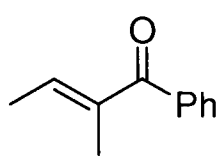
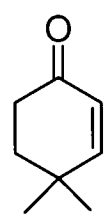
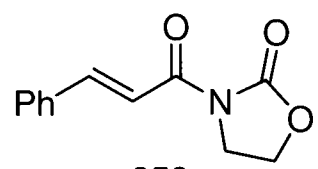
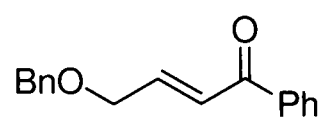
Trisubstituted Enones	Cyclic Enones	Derivatives Containing Other Activating Groups	γ-Hydroxy Substituted Enones
 **233**			
 **221**		 **252**	 **271**
 **219**		 **258**	 **273**

Table 10

Further unsuccessful substrates for which there was no evidence of decomposition are shown in Table 11. None of these substrates possess gamma–protons. In an attempt to establish a trend relating the pKa of a derivative to its reactivity under the given conditions we tested a number of substrates possessing different electron withdrawing functionality. The results of these reactions were compared to the previous results obtained by co-workers, using phenyl ketone and *t*-butyl ester motifs, (Table 4, entries 1-5, 9 and 10, 14 and 15).[101] However, no correlation was observed with regard to the pKa values of successful and unsuccessful substrates.

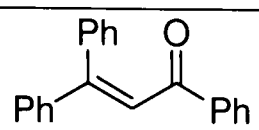
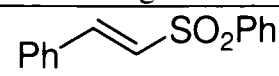
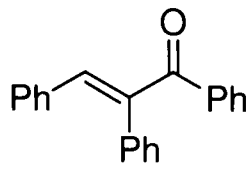
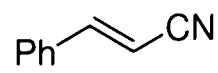
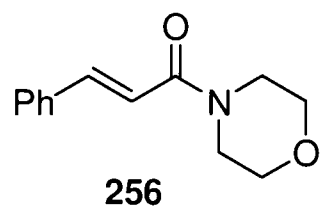
Trisubstituted Enones	Derivatives Containing Other Activating Groups
 **229**	 **251**
 **224**-(*E* or *Z*)	 **250**
	 **256**

Table 11

Successful aziridination substrates are summarised in Table 12 (substrates previously tested by co-workers are included for completion). In line with results from previous work (Table 4, entries 1-10),[101] aromatic substituted derivatives were seen to be a successful class of substrate for the achiral aziridination reaction Enone **234** provides the first example of the NMM-mediated aziridination of a trisubstituted derivative. Additionally, heteroaromatic substituted enones and dienones worked well in the reaction.

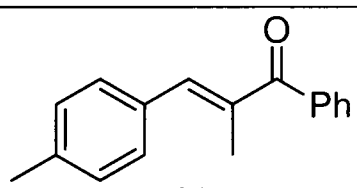
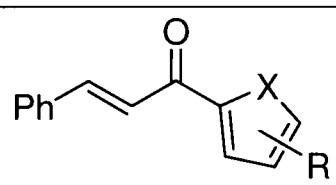
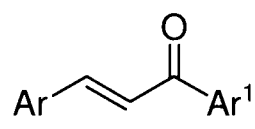
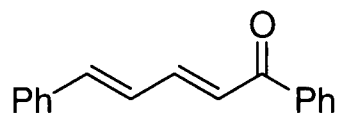
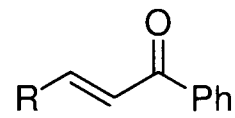
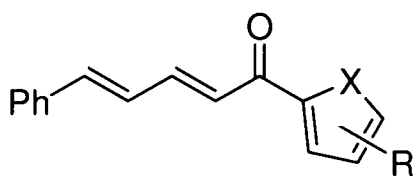
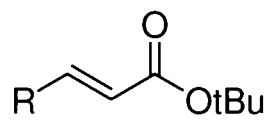
Trisubstituted Enones	Heteroaromatic Enones and Dienones	Substrates Previously Tested by Co-workers
 **234**		
		 (Where R=*n*-Bu, *i*-Bu, $(CH_2)_2Ph$)
	 (Where X=O, S and R=H, 4-methyl, 5-chloro)	 (Where R=H, Ph)

Table 12

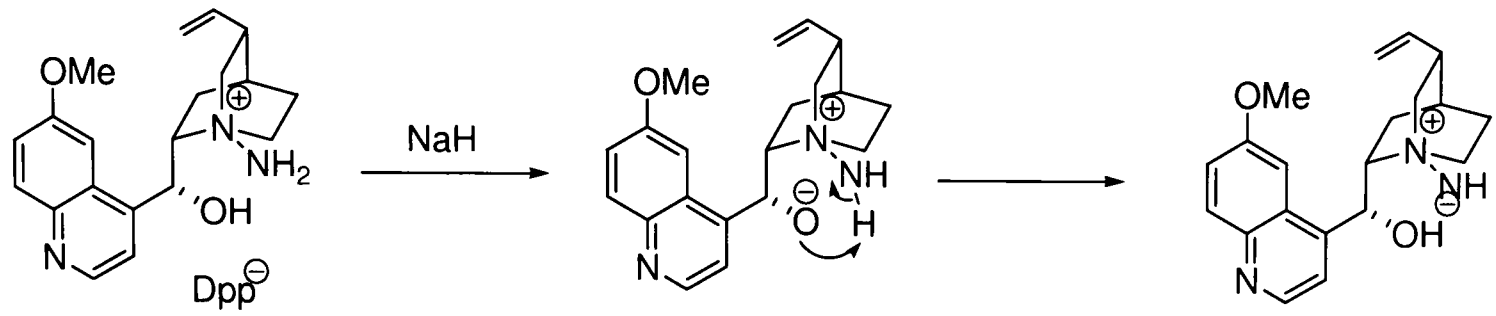
Having studied a wide range of substrates in the NMM mediated aziridination reaction we now turned our attention to the asymmetric reaction.

2.2.2 Asymmetric Aziridination

The initial promising result obtained using quinine as a promoter showed that it is indeed possible to effect asymmetric induction in the aziridination reaction (Scheme 83).[101] Preliminary solvent/base screening conducted by co-workers[127] had shown the presence of isopropoxide to have a positive influence upon the reaction yield and *e.e* compared to NaOH (64% yield, 56% *e.e* using NaH/IPA/CH_2Cl_2, *cf.* 59% yield, 46% *e.e* using NaOH/CH_2Cl_2). With this result in mind we began by conducting some preliminary studies on the effect of IPA upon the asymmetric system.

2.2.2.1 The Effect of IPA on the Asymmetric Aziridination Reaction

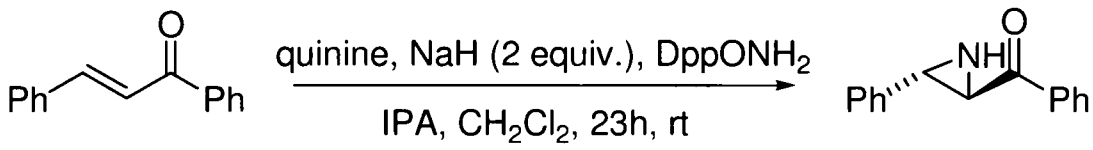
We considered that a possible explanation for the positive effects observed upon reaction yield and *e.e* with the IPA/NaH system, compared to the NaOH system, may be the formation of water as a by-product in the latter case. The lower yields and *e.e* values noted using NaOH as base may simply be due to the fact that water exerts an undesirable effect upon the reaction, possibly aiding protonation of the intermediate enolate or ring-opening of the aziridine product. Further consideration of the reaction system led to the proposal that the hydroxyl functionality of quinine itself may be functioning in the same capacity as the original alcohol. In this scenario we would envisage the formation of the hydrazinium salt **299** as usual. This would be followed by the NaH-mediated deprotonation of the quinine C9 hydroxy group, resulting in the formation of the cinchona derived alkoxide **300**, which would subsequently deprotonate the primary NH_2 moiety in order to form the reactive aminimine species **301** (Scheme 108). Clearly this pathway of events is dependent upon the acidity of the *N*-NH_2 functionality of the aminated catalyst compared to that of the C9 hydroxy moiety.



299 300 301

Scheme 108

Given that the results of the reaction conducted with IPA were superior to those obtained with NaOH we reasoned that increasing the amount of alcohol available may improve the system. Alternatively, if the C9 hydroxy functionality of the catalyst could indeed function as an IPA "equivalent", could less alcohol be used? Additionally, we wondered whether varying the amount of IPA available in the system would have any effect upon the levels of enantioselectivity observed. Three experiments were conducted; the first using a large excess of alcohol (entry 1), the second using 1 equivalent of IPA (entry 3) and the third in the absence of IPA (entry 4). A control reaction using the standard 2 equivalents of IPA is included for comparison (entry 2) (Table 13).



Entry	IPA (equiv.)	Yield (%)	Recovered Starting Material (%)[a]	*e.e.* (%)[b]
1	Excess[c]	-[d]	12	
2	2	69	18	54
3	1	64	16	42
4	0	32	13	48

[a] Percentage recovered starting material after column chromatography; [b] Enantiomeric excess measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H); [c] IPA used as sole reaction solvent; [d] Trace of product visible by crude ^{1}H NMR, no product was isolated after column chromatography.

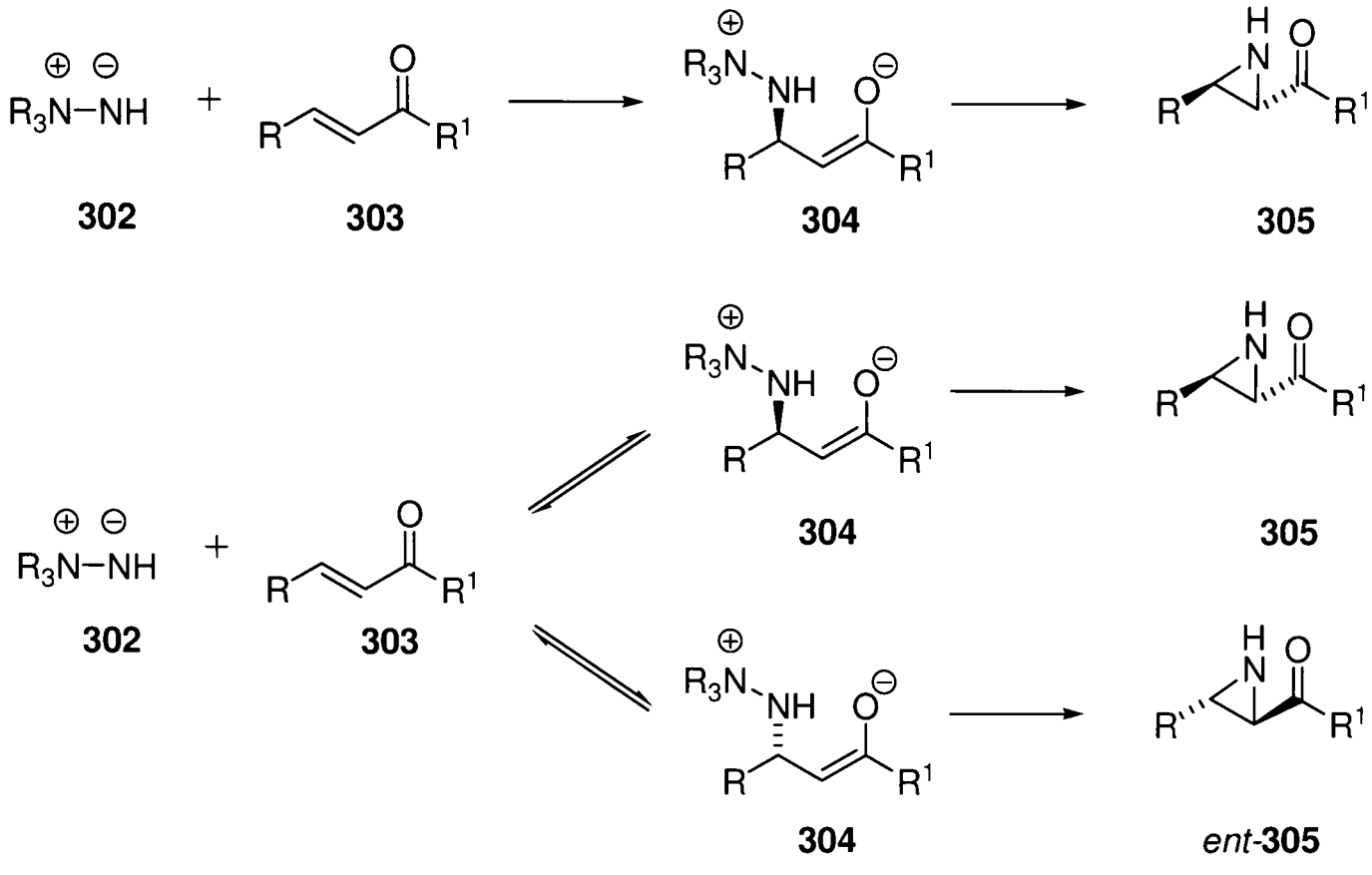
Table 13

The results showed the use of a large excess of alcohol to be detrimental; only a trace amount of aziridine product, along with 12% of starting material, was recovered (entry

1). This suggested substrate decomposition under the reaction conditions. Use of 1 equivalent of IPA appeared to have little effect on the yield although the *e.e* value of the reaction was notably lower than that achieved under the standard conditions (entry 2 *vs.* entry 3). Eliminating the use of IPA altogether (entry 4) significantly reduced the reaction yield with the observed *e.e* value still being similar to that achieved using 2 equivalents of alcohol, and slightly higher than that obtained with the NaOH system (46% *e.e*). Since altering the number of equivalents of IPA did not improve the reaction yield or enantioselectivity we decided to use the original conditions established by co-workers[101] (2 equiv. NaH/IPA in CH_2Cl_2) in all subsequent reactions. With these conditions in hand we began to consider the asymmetric reaction in more detail, with particular regard to the effect of substrate structure upon the enantioselectivity of the reaction.

2.2.2.2 Substrate Structure *v* Enantiomeric Excess of the Asymmetric Aziridination Reaction

As our previous work on the NMM mediated system had shown, in order to understand the aziridination reaction more thoroughly we needed to determine where the rate limiting step of the reaction occurs, and with regard to the asymmetric system, at which point in the reaction the product asymmetry is introduced. In relation to this problem there are two possibilities (Scheme 109). In the first pathway the initial aminimine conjugate addition step is irreversible and the facial selectivity, and subsequent *e.e*, is determined at this stage. Ring closure gives access to the aziridine product with the same *e.e* value as the intermediate enolate **304**. The second pathway depicts a reversible Michael addition. In this case the factors determining the *e.e* value of the final product include the stability, and hence the concentration, of both enolate adducts and the energy barrier to the ring closure step. Although this scheme appears to be a reasonable starting point, realistically this is likely to be an overly simplistic view of the true reaction mechanism. Other factors, such as the equilibria between the intermediate enolate and its protonated form, are likely to play a key role in the result.



Scheme 109

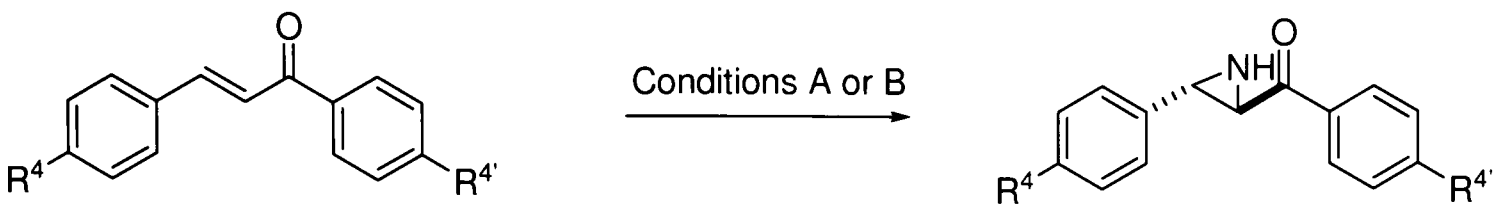
At this stage we considered that in the absence of any information regarding a transition state model, the rate determining step of the reaction, or indeed where the product asymmetry is introduced, a survey of substrate structure *versus e.e* of the quinine mediated reaction may provide important information. With this in mind we began by screening a range of electron rich and electron poor chalcone derivatives.

2.2.2.2.1 Electron Rich and Electron Poor Chalcone Derivatives

A range of commercially available *para*- substituted (4 and 4'(substitution on the phenyl ring adjacent to the ketone functionality)) derivatives were selected for initial testing under the standard asymmetric aziridination conditions (Conditions B) (Table 14). In all cases the absolute configuration of the major enantiomer is assumed to be (2*R*, 3*S*) by analogy to the result obtained with chalcone and quinine.[101] Judging by the low mass balance of the majority of the reactions other undesirable reaction pathways are occurring to prevent full conversion of starting material to product. This proposal is investigated as part of subsequent work on the asymmetric system and results will be discussed consequently. Where authentic racemic product samples were not available from previous work they were synthesised, using the general NMM aziridination procedure

(Conditions A), in order to provide standards for HPLC analysis of the enantioenriched products.

We began by testing derivatives possessing electron donating and electron withdrawing groups in the R^4 position (entries 1 7). The observed *e.e* values for substrates with electron donating groups proved to be consistently higher than those of substrates with electron withdrawing groups (for example, entry 2 (55%) *vs* entry 7 (37%)). Similar $R^{4'}$ derivatives were subjected to the standard set of conditions (entries 8-13); again substrates with electron donating groups on the aromatic ring provided higher *e.e* values than their electron withdrawing counterparts (entry 9 (66%) *vs* entry 13 (25%)). Substitution on the aromatic ring adjacent to the ketone moiety ($R^{4'}$) delivered slightly higher levels of enantioselectivity compared to substitution on the other aromatic (R^4) (for example, entry 2 (55%) *vs* entry 9 (66%)). We considered these findings to be promising, particularly with regard to the result acquired using 4'-methoxychalcone (entry 9) in which the reaction *e.e* obtained was higher than that observed with chalcone under the same conditions (66% (entry 9) *cf.* 56% with chalcone).[101]



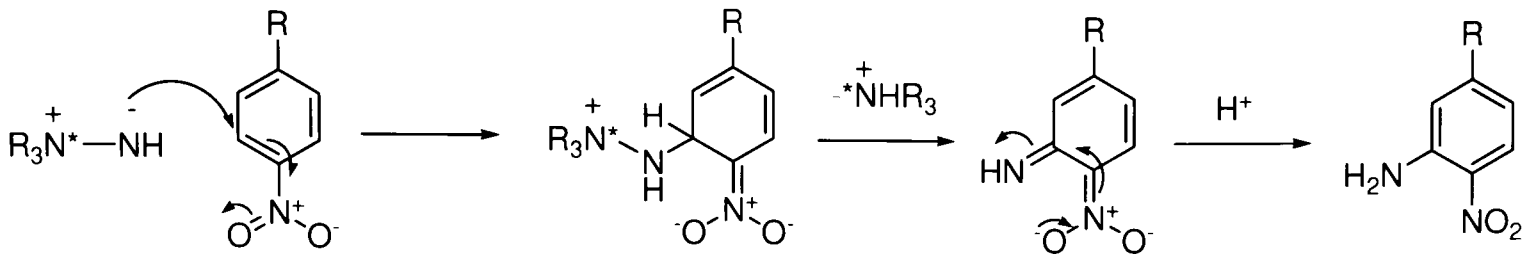
Conditions A: $DppONH_2$, NMM, NaOH, MeCN, 23h, rt
Conditions B: $DppONH_2$, Quinine, NaH/IPA, CH_2Cl_2, 23h, rt

Entry	R^4	$R^{4'}$	Conditions	Yield (%)	Recovered Starting Material (%)[a]	*e.e.* (%)[b]
1	OMe		A	22	78	
2	OMe		B	35	22	55
3	Cl		A	16	77	
4	Cl		B	54	7	48
5	Me		B	55	4	52
6	NO_2		A	45	32	
7	NO_2		B	43	9	37
8		OMe	A	23	35	
9		OMe	B	48	-[c]	66
10		Cl	B	62	-[c]	46
11		Me	B	68	25	59
12		NO_2	A	9	29	
13		NO_2	B	<1	2	25

[a] Percentage recovered starting material after column chromatography; [b] Enantiomeric excess measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H). Major enantiomer assumed to be (2*R*, 3*S*) by analogy to the result obtained with chalcone under the same conditions; [c] Not measured.

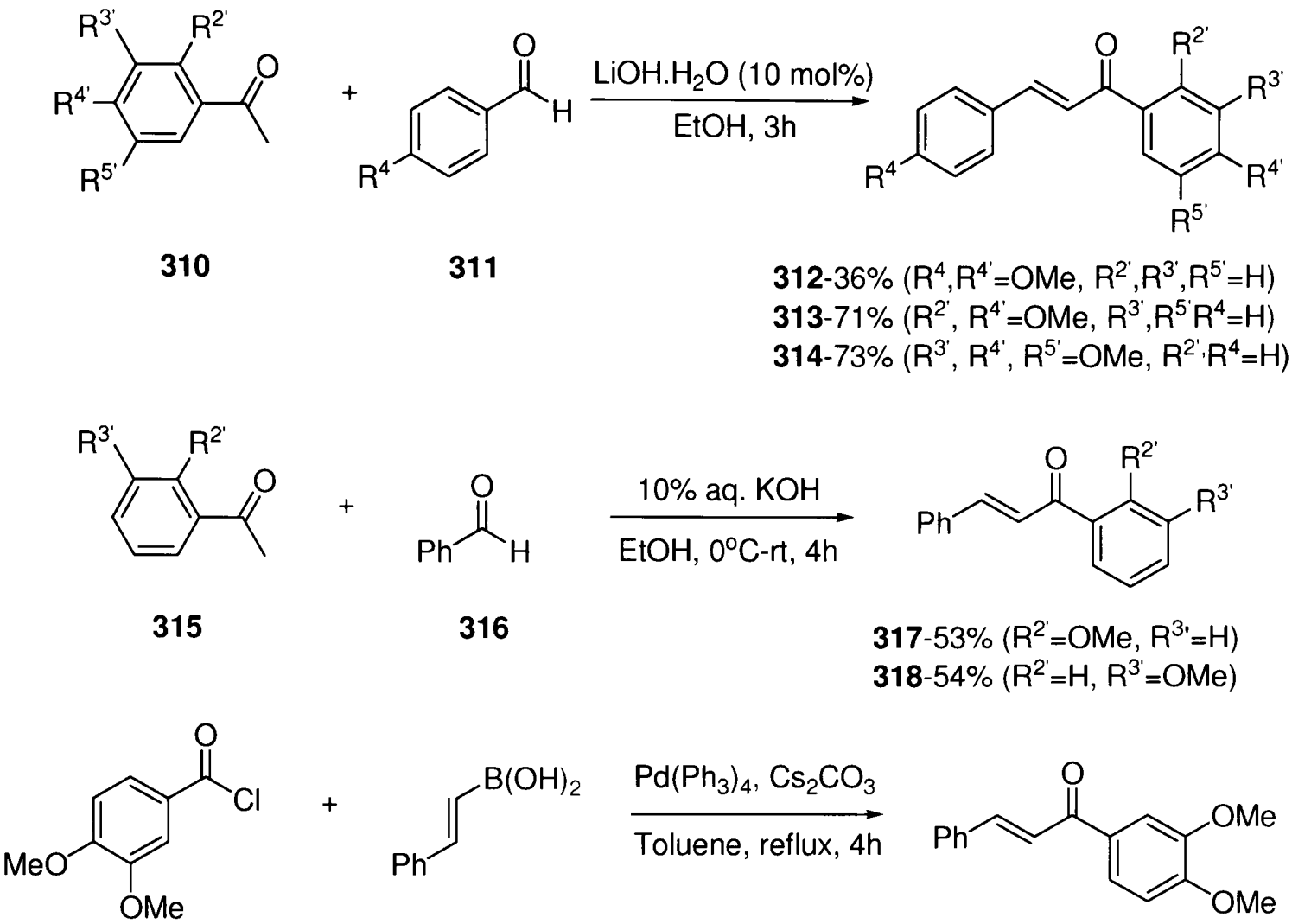
Table 14

Finally, a result that we considered to be of interest was that obtained using 4'-nitrochalcone (entry 13) in which the yield of the desired aziridine product was very poor (<1%) and only 2% starting material was recovered. One possible explanation for the low mass balance observed in this reaction is the operation of a competing vicarious nucleophilic substitution reaction (Scheme 110). It is known that electron poor aromatics undergo such a reaction,[128-130] although at this stage, in the interests of time, we chose not to pursue this hypothesis further and no reaction products were characterised.



Scheme 110

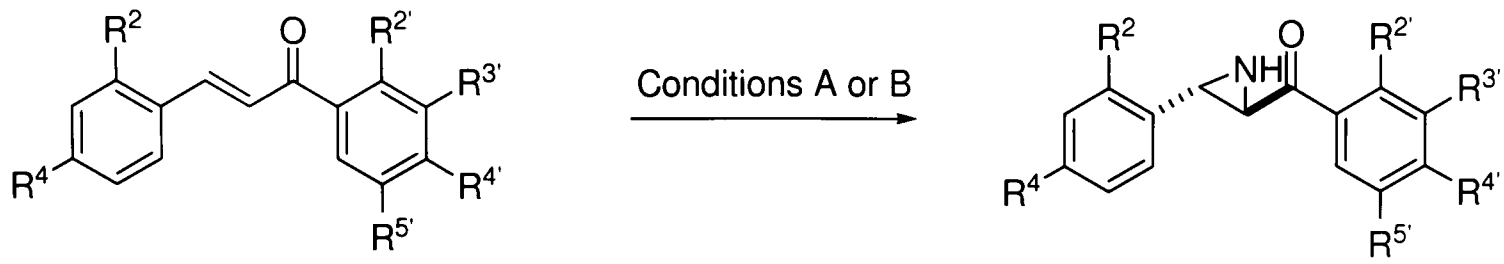
The results displayed in Table 14 clearly show substrates with electron donating groups, particularly those substituted on the aromatic ring adjacent to the ketone moiety, to be superior in terms of the *e.e* values achieved in the asymmetric aziridination reaction. With this in mind several methoxy substituted enones were synthesised with a variety of different *ortho-*, *meta-*, *para-* substitution patterns. An aldol condensation was the method of choice employed for the preparation of the majority of such compounds, with the desired products being obtained in generally reasonable yield (36-73%) using either $LiOH.H_2O$ or KOH (10% aq.) as base, depending on the literature procedure followed.[131,132] Enone **321** could not be synthesised using standard aldol chemistry; instead this product was prepared using palladium coupling between acid chloride **319** and boronic acid **320** (Scheme 111).[133]



Scheme 111

All substrates were tested under the standard asymmetric conditions (Table 15, Conditions B). Again, the absolute configuration of the major enantiomer, in all cases, is assumed to be (2*R*, 3*S*) by analogy to the result with chalcone and quinine.[101] The racemic aziridines were prepared *via* the NMM aziridination procedure (Conditions A) in order to provide a set of standards that would allow reliable HPLC analysis of the enantioenriched products. As substitution on the aromatic adjacent to the ketone moiety of the substrate ($R^{4'}$) had previously given higher *e.e* values than substitution on the other aromatic, we began by testing the *ortho*- ($R^{2'}$, entry 2) and *meta*- ($R^{3'}$, entry 4) substituted derivatives. Comparison of the *e.e* values obtained for the *ortho*- (53% *e.e*), *meta*- (48% *e.e*) and *para*- (Table 14, entry 9, 66% *e.e*) substrates showed substitution in the $R^{4'}$ position to give the highest levels of enantioselectivity, while the levels of selectivity obtained with the *ortho*- and *meta*- substituted derivatives were essentially the same. We then considered that introducing further electron donating substituents may increase

levels of asymmetric induction further. Disubstituted derivatives with varying substitution patterns were initially screened (entries 5-10). The results showed that 4,4' (entry 6, 63% *e.e*) and the 2'4'- (entry 8, 57% *e.e*) substitution gave slightly elevated levels of selectivity, although not to any significant degree above the level obtained with chalcone under the same conditions (56% *e.e*).[101] Trisubstituted derivative **314** (entry 12, 60% *e.e*) was also subjected to the reaction conditions, but again the observed enantioselectivity was similar to that of chalcone. Finally, we looked at substitution on the other aromatic ring, using the commercially available 2-methoxy substituted derivative (entry 14). Comparison of this substrate (60% *e.e*) with its *para*-substituted counterpart (Table 14, entry 2, 55% *e.e*) showed an insignificant difference between the two *e.e* values obtained, suggesting that the position of substituents on this ring is not a major factor in determining enantioselectivity.



Conditions A: $DppONH_2$, NMM, NaOH, MeCN, 23h, rt
Conditions B: $DppONH_2$, Quinine, NaH/IPA, CH_2Cl_2, 23h, rt

Entry	R^2	R^4	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$	Conditions	Yield (%)	Recovered Starting Material (%)[a]	*e.e.* (%)[c]
1			OMe				A	61	34	
2			OMe				B	41	13	53
3				OMe			A	71	16	
4				OMe			B	28	19	48
5		OMe			OMe		A	24	53[b]	
6		OMe			OMe		B	26	30	63
7			OMe		OMe		A	78	-[d]	
8			OMe		OMe		B	<5	37	57
9				OMe	OMe		A	<5	36	
10				OMe	OMe		B	<5	85	31
11				OMe	OMe	OMe	A	73	73[b]	
12				OMe	OMe	OMe	B	59	14	60
13	OMe						A	79	16	
14	OMe						B	22	16	60

[a] Percentage recovered starting material after column chromatography; [b] Percentage conversion by ^1H NMR; [c] Enantiomeric excess measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H). Major enantiomer assumed to be (2*R*, 3*S*) by analogy to the result obtained with chalcone under the same conditions; [d] Not measured.

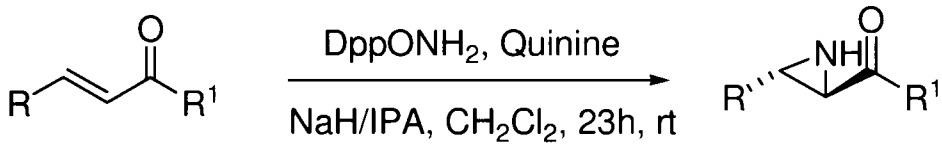
Table 15

We now wanted to extend the survey of substrate structure *versus e.e* to the dienones previously found to be successful candidates for the NMM-mediated aziridination reaction.

2.2.2.2.2 Dienones

All substrates synthesised in Section 2.2.1.5 were tested under the standard asymmetric aziridination reaction conditions (Table 16). In all cases the absolute configuration of the major enantiomer is assumed to be (2*R*, 3*S*) by analogy to the result with chalcone and quinine.[101] The yields obtained were generally poor (4-47%) and again the low mass balance observed for all examples indicated that side reactions were likely to be

occurring. In general the *e.e* values achieved for the dienones and their enone equivalents appeared to be within a similar range to one another, which suggested that the extra alkene unit of the diene had little effect upon the level of asymmetric induction observed. Thiophene substituted derivatives (entries 2 and 3, 72% *e.e* and 71% *e.e* respectively) gave slightly higher levels of enantioselectivity than their furan substituted counterparts (entries 4 and 5, 71% *e.e* and 52% *e.e* respectively), and with this in mind it appeared logical to test the substituted thiophene derivatives **294**, **295**, **297** and **298** (entries 6-9). Increasing the electron density of the heteroaromatic, *via* the addition of a methyl substituent, resulted in improved levels of *e.e* (entries 8 and 9, 77% *e.e* and 72% *e.e cf.* entries 2 and 3, 72% *e.e* and 71% *e.e*, respectively), while the addition of a chloro substituent gave a slight decrease in the levels of selectivity (entries 6 and 7, 64% *e.e* and 58% *e.e* respectively). These results show that, in general, varying the substituent adjacent to the ketone moiety of the substrate has a favourable effect upon the levels of enantioselectivity obtained compared to the result achieved with chalcone under the same conditions.[101]

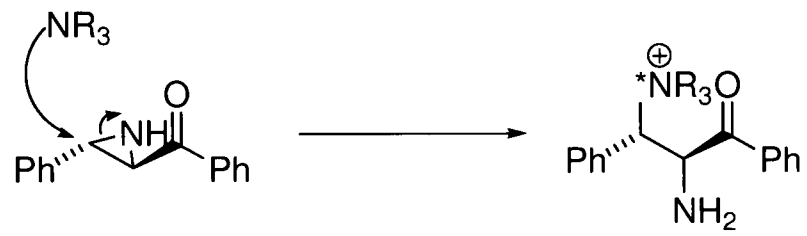


Entry	Enone	R	R^1	Yield (%)	Recovered Starting Material (%)[a]	*e.e.* (%)[b]
1	**277**	PhCH=CH	Ph	25	42	52
2	**288**	Ph	2-thiophenyl	47	14	72
3	**286**	PhCH=CH	2-thiophenyl	30	12	71
4	**291**	Ph	2-furyl	41	0	71
5	**292**	PhCH=CH	2-furyl	13	0	52
6	**294**	Ph	5-chloro-2-thiophenyl	27	10	64
7	**295**	PhCH=CH	5-chloro-2-thiophenyl	26	0	58
8	**297**	Ph	4-methyl-2-thiophenyl	46	30	77
9	**298**	PhCH=CH	4-methyl-2-thiophenyl	4	23	72

[a] Percentage recovered starting material after column chromatography; [b] Enantiomeric excess measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H). Major enantiomer assumed to be (2*R*, 3*S*) by analogy to the result obtained with chalcone under conditions B

Table 16

This work has highlighted the poor mass balance observed for most of the quinine-mediated asymmetric aziridination reactions. In order to investigate this observation further we ran a standard asymmetric reaction using chalcone as a substrate ($NaH/IPA/CH_2Cl_2$), and submitted the crude material (after work-up) for LC/MS (ES^+) analysis. The resultant spectra showed two significant peaks of similar retention time (t_R=4.96 and 5.07 min), with mass values of $[M]^+$=548.2914 and $[M]^+$=548.2898 respectively. Additionally, both peaks corresponded to the molecular formula $C_{35}H_{38}N_3O_3$. Initially we proposed that the structure correlating to this mass was that of the aziridine ring-opening product **322** (Scheme 112). This hypothesis was tested by resubmitting pure aziridine to the standard asymmetric reaction conditions. LC/MS (ES^+) analysis failed to show any peaks with a mass of 548, or indeed the mass of any other potential ring-open products.

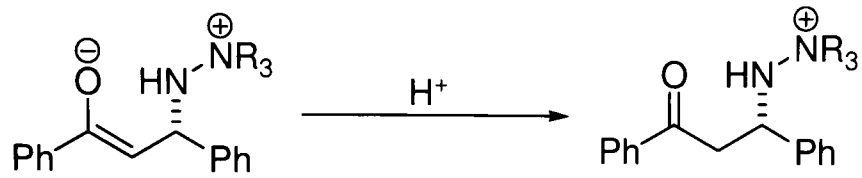


174 **322**-[M=548]

(Where NR_3= Quinine)

Scheme 112

As an alternative, it was proposed that the peaks of mass 548, observed in the LC/MS spectrum of the crude reaction mixture, represented the ketone adduct **324** (Scheme 113), a protonated form of the intermediate enolate adduct **323**. If protonation is assumed to occur upon work-up this may indicate that species **323** is unreactive, potentially due to the poor leaving group ability of quinine.

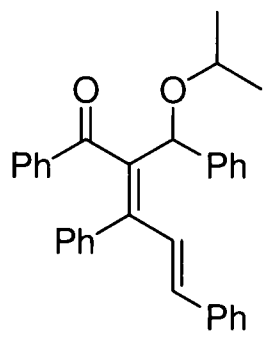


323 **324**

Scheme 113

At this stage the crude material was purified in order to remove aziridine product and remaining starting material. The column was subsequently flushed with a more polar solvent to give a residue of polar material which we believed would contain adduct **324**. This mixture was then stirred under basic conditions (2 equiv. NaH/IPA, 23h) in an attempt to effect ring-closure of the intermediate enolate. This proved to be unsuccessful with LC/MS (ES^+) analysis showing no evidence of aziridine product or enolate adduct.

A peak at t_R=3.98 min ($[M]^+$=458.2452), in the original LC/MS (ES^+) spectrum of the crude asymmetric reaction, was thought to correspond to a product of the base catalysed polymerization of chalcone (**325**, $[M]^+$=458) (Figure 8). In order to investigate this idea further LC/MS (ES^+) analysis was used to identify the products formed upon mixing chalcone and base (2 equiv. NaH/IPA, 23h). TLC analysis of the reaction mixture showed only a trace of remaining chalcone after 23 hours, and although the LC/MS (ES^+) spectrum showed no peaks with mass corresponding to **325**, $[M]^+$=458, there were a number of intense peaks with higher mass numbers that may correlate to other polymerisation products, ($[M]^+$=1095 (t_R=8.15 min), 859 (t_R=8.35 min), 933 (t_R=8.59 min). This is clearly not conclusive evidence for the polymerisation of chalcone but it does show that the substrate is unstable to the basic reaction conditions.



325

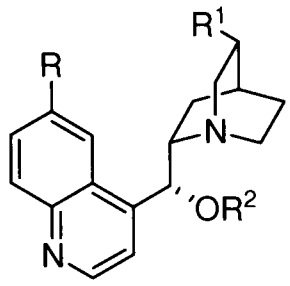
Figure 8

At this stage we elected to move away from substrate variation and instead focus upon the initial promising result obtained with quinine in the asymmetric reaction (Scheme 83, 64%, 56% *e.e*).[101] Using this result as a benchmark for further catalyst modification we hoped to improve upon the selectivity and to progress towards a transition state model for the reaction.

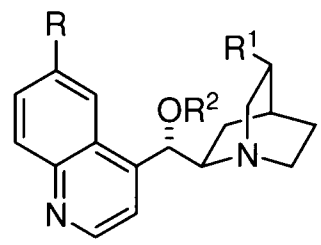
2.2.2.3 Cinchona Alkaloid Promoters

We began by screening several commercially available cinchona alkaloids in order to see if the observed *e.e* values obtained in previous reactions could be improved (Figure 9). Additionally, it was hoped that conducting such a screen would highlight the functionality responsible for asymmetric induction. The parent compounds, quinine and quinidine, were selected to provide two benchmark results in both pseudoenantiomeric series. The dihydro derivatives, in which the terminal alkene unit is fully saturated, would also be tested in order to see if subtle alterations to this remote functionality had any effect upon the *e.e* values obtained in the reaction. Cinchonidine and cinchonine, the so-called Cinch bases, possess a hydrogen atom in place of the electron donating methoxy group, on the quinoline ring. These derivatives would allow us to probe the importance of electron density on the aromatic portion of the catalyst. Quincorine and quincoridine, derivatives of the parent compounds containing no quinoline ring, would be tested in order to probe the significance of the aromatic unit of the catalyst. Finally, the hydro ether derivatives, hydroquinine-4-methyl-2-quinolyl ether and its pseudoenantiomeric partner, along with the ketone derivative, quininone, were selected for testing in order to see if manipulation of the free hydroxyl group had any effect upon the enantioselectivity of the reaction.

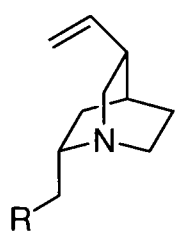
A co-worker conducted a preliminary screen of a small number of cinchona alkaloid catalysts prior to the work described in this thesis.[127] All previous results were repeated, as part of this work, under identical conditions in order to ensure accuracy. The results of the tertiary amine screen are as shown in Table 17.



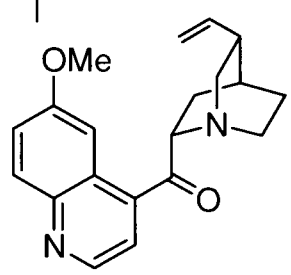
Quinine: R=OMe, R^1= $CH{=}CH_2$, R^2= H
Hydroquinine: R=OMe, R^1= CH_2CH_3, R^2= H
Cinchonidine: R=H, R^1= $CH{=}CH_2$, R^2= H
Hydroquinine-4-methyl-2-quinolyl ether:
R=H, R^1= CH_2CH_3, R^2=



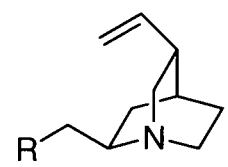
Quinidine: R=OMe, R^1= $CH{=}CH_2$, R^2= H
Hydroquinidine: R=OMe, R^1= CH_2CH_3, R^2= H
Cinchonine: R=H, R^1= $CH{=}CH_2$, R^2= H
Hydrocinchonine: R=H, R^1= CH_2CH_3, R^2= H
Hydroquinidine-4-methyl-2-quinolyl ether:
R=H, R^1= CH_2CH_3, R^2=



Quincorine: R= OH
OBz-Quincorine: R= OBz

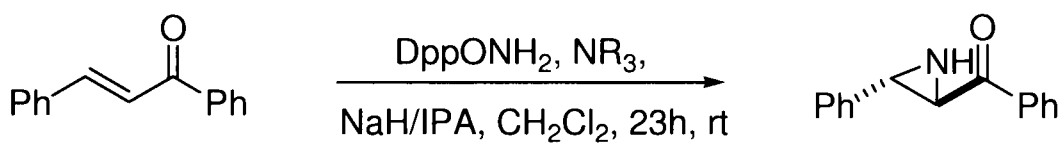


Quininone



Quincoridine: R= OH

Figure 9



Entry	NR_3	Yield (%)	*e.e.* (%)[a]
1[b]	quinine	63	57 (2*R*,3*S*)
2[b]	quinidine	31	50 (2*S*, 3*R*)
3	hydroquinine	49	50 (2*R*,3*S*)
4	hydroquinidine	32	30 (2*S*, 3*R*)
5[b]	cinchonidine	38	42 (2*R*,3*S*)
6	cinchonine	42	41 (2*S*, 3*R*)
7	hydrocinchonine	50	26 (2*S*, 3*R*)
8	quincorine	44	1 (2*S*, 3*R*)
9	quincoridine	85	0
10	OBz-quincorine	<10%	6 (2*S*, 3*R*)
11	hydroquinine-4-methyl-2-quinolyl ether	6	27 (2*S*, 3*R*)
12	hydroquinidine-4-methyl-2-quinolyl ether	7	8 (2*S*, 3*R*)
13	quininone	16	3 (2*S*, 3*R*)

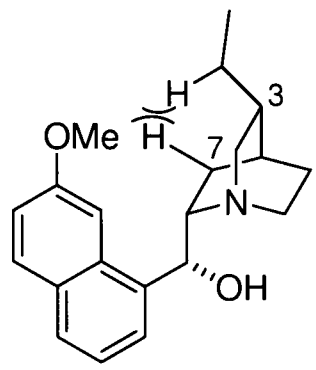
[a] Enantiomeric excess measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H). Configuration of the product is given in parentheses and based upon the result obtained using quinine to give the (2*R*, 3*S*-(t_R (minor)=15.96 min, t_R (major)=18.82 min)) as the major enantiomer; [b]In accord with results obtained previously.

Table 17

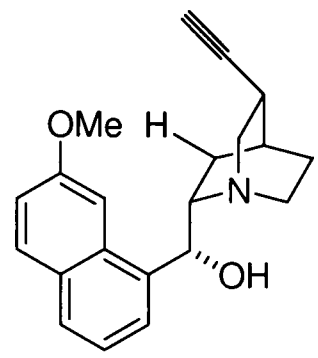
As expected, the pseudoenantiomeric pairs of each tertiary amine generally gave products with opposite absolute configuration (quinine derivatives (2*R*, 3*S*); quinidine derivatives (2*S*, 3*R*)). This was true in every case apart from the 4-methyl-2-quinolyl ether derivatives (entries 11 and 12) where both pseudoenantiomers were found to give (2*S*, 3*R*) products. However, it should be noted that the *e.e* for the hydroquinidine case is very low (entry 12). Additionally in the cases of quincorine (entry 8), its *O*-benzoate equivalent (entry 10) and quininone (entry 13), we would expect the major product enantiomer to have the (2*R*, 3*S*) configuration as all three structures are quinine derived. However, these tertiary amines gave (2*S*, 3*R*) products, but again with very low levels of enantioselectivity.

The parent compounds quinine (entry 1) and quinidine (entry 2) were tested and found to give approximately equal, and opposite *e.e* values as expected (57% and 50% *e.e* respectively). The hydro- derivatives (entries 3 and 4) gave slightly reduced *e.e* values (50% and 30% respectively) compared to those obtained using quinine and quinidine. Initially we found this observation surprising given the remote location of the alkene moiety. However, upon further investigation we found work in the literature describing the effect that altering this group can have over the overall structure of the alkaloid.[134] The A value of an ethyl group is substantially higher than that of either an ethenyl or an alkynyl substituent (A values: $-CH_2CH_3$ 7.49 kJ mol^{-1}, $-CH=CH_2$ 6.23-7.00 kJ mol^{-1}, $-C\equiv CH$ 1.71-2.18 kJ mol^{-1}),[134] and this is thought to result in increased 1,3-syn repulsion, between C3 and C7 of the quinuclidine ring, in the fully hydrogenated derivatives (Figure 10).[134] In line with this reasoning, X-ray crystal structures have shown that ethyl-quinuclidines are consistently more twisted than their vinyl and alkynyl analogues (overall torsion angles (i.e., the sum of the three quinuclidine torsion angles)= 65° ethyl, 60° ethenyl and 26°-49° alkynyl).[134] This effect will certainly alter the basicity of the quinuclidine nitrogen, and potentially the efficiency of the catalyst, and may go some way towards explaining the lower *e.e* values observed when using the hydroquinine and hydroquinidine derivatives in our own reaction. However, it should be noted that this effect is quite subtle and, in regard to literature reactions, no large generalisations can be

made in terms of whether the parent compound or its hydro derivative will give the best results in a reaction. For example, Jørgensen's recent asymmetric synthesis of bisphosphonate derivatives *via* a cinchona alkaloid-catalysed Michael-type addition reaction, showed the opposite outcome to our own findings, with hydroquinine found to be superior to quinine in terms of both yield and *e.e* (80%, 48% *e.e* for quinine *cf.* 84%, 56% *e.e* for hydroquinine under the same conditions).[135]



Hydroquinine-**326**

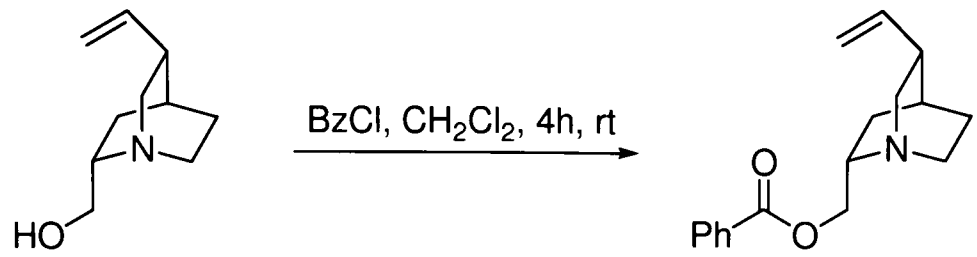


Didehydroquinine-**327**

Figure 10

The *e.e* values obtained using cinchonidine and cinchonine were lower than those achieved using quinine and quinidine (entries 5 and 6, 42% and 41% *cf.* 57% and 50%, respectively), suggesting that increased electron density on the quinoline ring is important, at least to some extent, in acquiring higher levels of enantioselectivity. Although the results described so far were noteworthy, we considered our observations made using the other cinchona alkaloid derivatives (entries 8-13) to be of greater consequence. With these catalysts we saw a significant decrease in the amount of asymmetric induction observed in the reaction.

Quincorine and quincoridine both gave essentially racemic products (entries 8 and 9). These results suggest that the aromatic portion of the catalyst is important and to this end we chose to synthesise derivative **329** incorporating an *O*-benzoate protecting group into the catalyst (Scheme 114).[136]

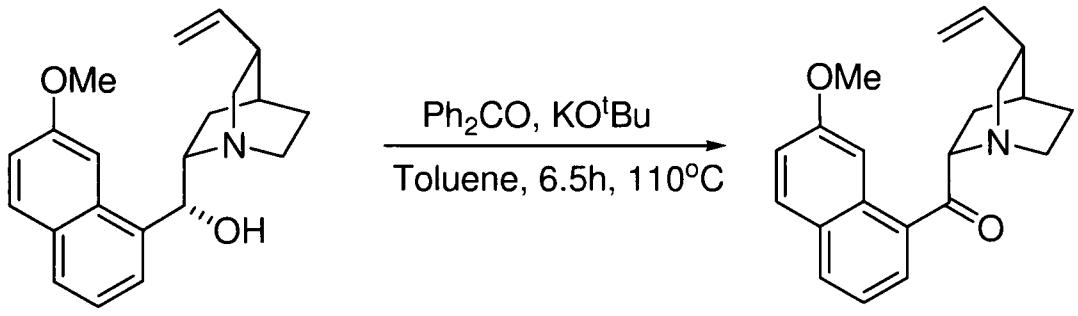


328 **329**-84%

Scheme 114

It was initially thought that the presence of the aromatic benzoate group would be a reasonable substitute for the quinoline ring of the parent compound, therefore improving the levels of enantioselectivity observed in the reaction. However, the results obtained using catalyst **329** (entry 10) were disappointing, returning a low product yield and *e.e* value (<10%, 6% *e.e*).

The second key set of results showed that protection of the C9 hydroxy moiety as an aromatic ether gave a large decrease in reaction *e.e* values when compared to the parent alkaloids (entries 11 and 12, 27% *e.e* hydroquinine-4-methyl-2-quinolyl ether, 7% *e.e* hydroquinine-4-methyl-2-quinolyl ether *cf.* 57% *e.e* quinine, 50% *e.e* quinidine). Additionally the ketone, quininone **330** (entry 13) synthesised from quinine in a simple one step oxidation procedure (Scheme 115),[137] showed very poor levels of enantioselectivity (3% *e.e*). Clearly this suggests that the free C9 hydroxy substituent is key in order to achieve reasonable levels of enantioselectivity in the reaction.

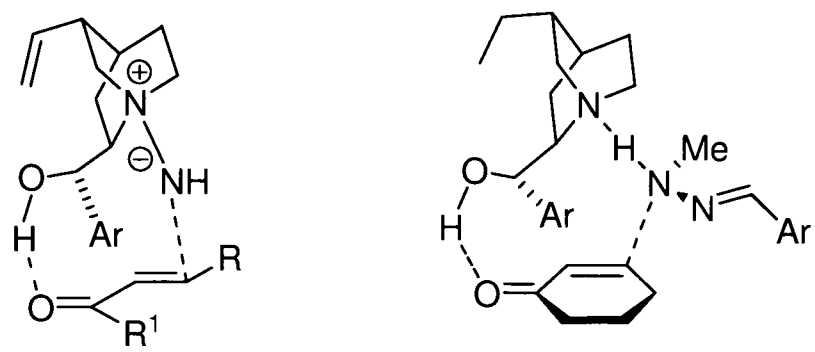


212 **330**-65%

Scheme 115

Analysis of our results at this stage showed quinine to be the best promoter of the asymmetric aziridination reaction in terms of enantioselectivity. Additionally, the

necessity for the presence of the free C9 hydroxyl moiety was noted, with protection or oxidation at this position leading to a large decrease in reaction *e.e* values. Although, as mentioned previously, the enantioselectivity-determining step of the reaction is currently not known, we postulated that one possibility for this stringent requirement may be the participation of the hydroxyl functionality in hydrogen bonding with the ketone moiety of the substrate (Figure 11, **A**). A similar interaction is proposed by Jørgensen and co-workers[138] for the cinchona alkaloid-mediated aza-Michael addition of hydrazones to cyclic enones (Figure 11, **B**).



A **B**

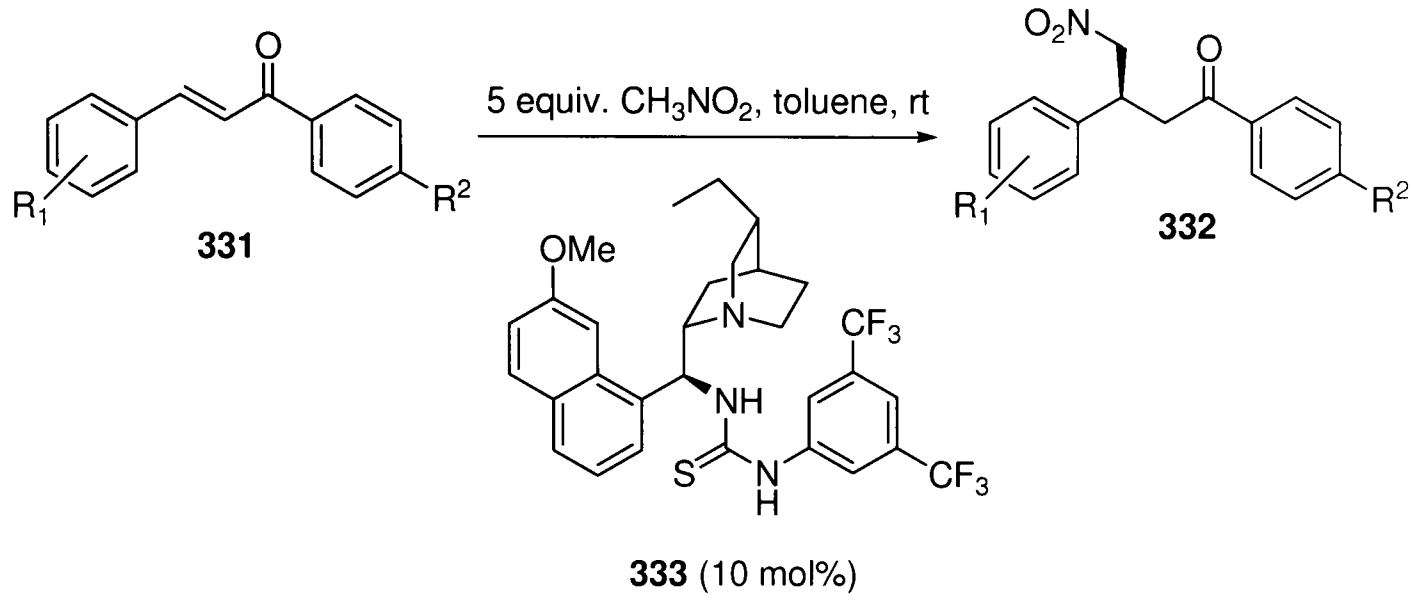
Figure 11

In order to investigate this proposal further we wanted to synthesise a number of cinchona alkaloid derivatives possessing functionality with varying H-bonding ability in the C9 position.

2.2.2.3.1 Cinchona Alkaloid-Derived Hydrogen Bond Donors

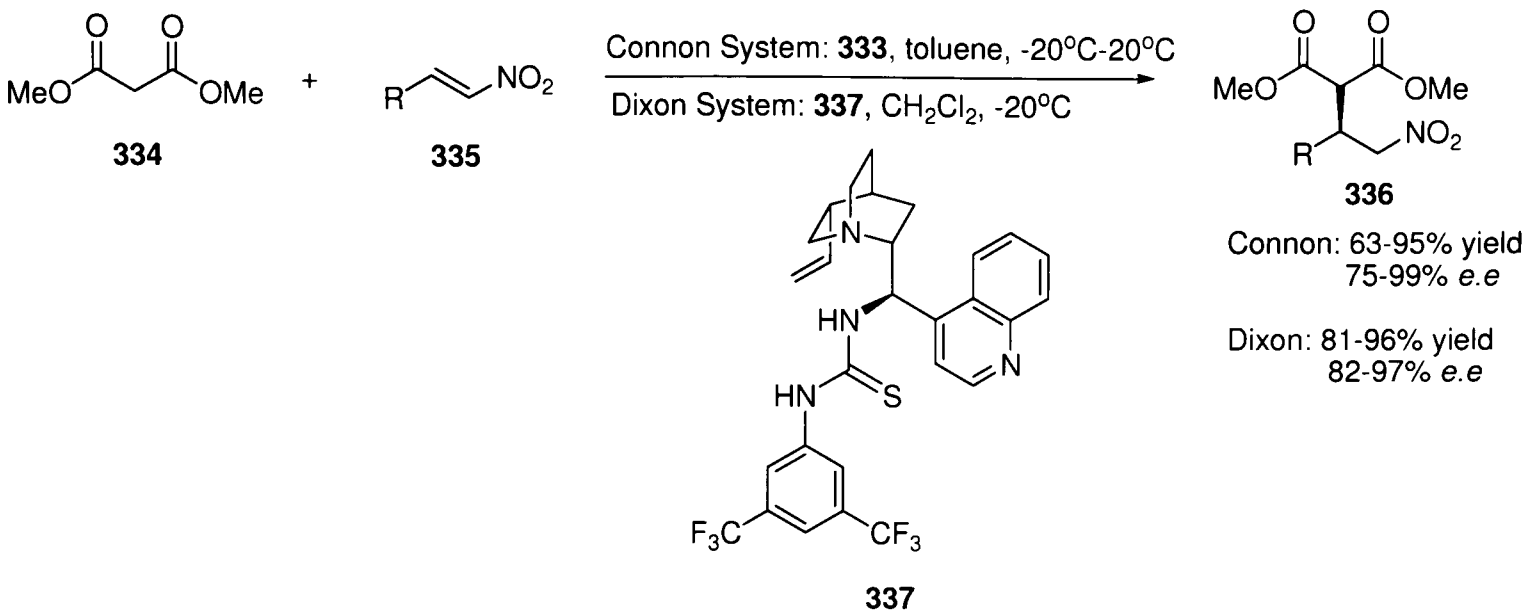
A review of the recent literature uncovered three key papers on the use of H-bond donor, thiourea, cinchona alkaloid derivatives to affect asymmetric catalysis with excellent *e.e* values. Soos *et al.*[139] detailed the enantioselective conjugate addition of nitromethane to chalcones using a bifunctional thiourea derivative of epiquinine (**333**) (the unnatural configuration of the parent alkaloid at C9) to achieve excellent product yields (80-94%) and *e.e* values (89-98%) (Scheme 116). The Lewis basic quinuclidine nitrogen and the C9 secondary alcohol moiety are held within a well-defined chiral environment. Replacement of the hydroxyl functionality with a more effective H-bond donor, such as a

thiourea, allows such compounds to act as bifunctional catalysts. Additionally, Soos probed the influence of the relative stereochemistry of the Lewis basic and Lewis acid groups by inverting the C9 centre (for example, in quinine from the natural configuration (8*S*, 9*R*) to the unnatural configuration (8*S*, 9*S*)).



Scheme 116

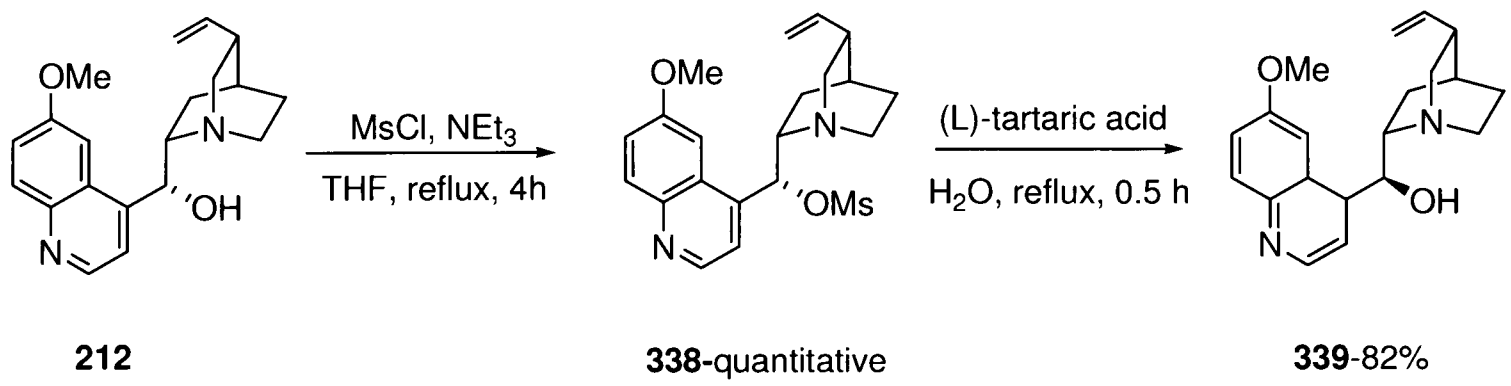
Connon[140] and Dixon[141] independently investigated the use of the cinchona scaffold to promote the Michael addition of malonate esters to nitro olefins. Both catalysts are again based upon the bifunctional thiourea moiety, with Dixon using the cinchonine derivative **337** (10 mol% loading), and Connon using the same epidihydroquinine structure (**333**, 2-5 mol% loading) as previously described in the work of Soos.[139] Both reactions give high product yields and excellent *e.e* values (Scheme 117). The bifunctional nature of the catalyst is thought to allow *N*-quinuclidine assisted deprotonation of the malonate, followed by attack of this species onto the thiourea-bound, nitroolefin electrophile, which sits in a chiral environment with a single face exposed for addition.



Scheme 117

Based upon this precedent we hoped to synthesise a range of effective H-bond donor, cinchona alkaloid derivatives, with both the natural and unnatural configuration at C9, for testing in the asymmetric aziridination reaction.

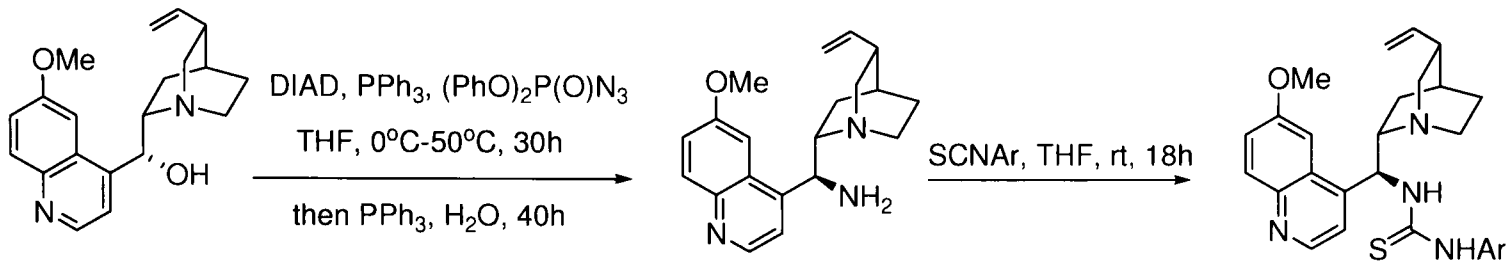
We began with the synthesis of epiquinine (**339**)[2] which would be independently tested but would also allow a route into a range of derivatives. Initial *O*-mesylation of quinine was followed by inversion at the C9 centre using (L)-tartaric acid in water. S_N2 displacement by water was thought to proceed with assistance from local H-bonding involving the protonated quinuclidine nitrogen (Scheme 118).



Scheme 118

The common protocol used for the synthesis of thiourea derivatives involves a Mitsunobu inversion at the C9 hydroxy centre, using an azide nucleophile, followed by an *in situ*

Staudinger reduction. This provides a free amine moiety at the C9 centre. Addition of isothiocyanate allows access to the desired thiourea product.[139] As quinine was readily available and we now had epiquinine in hand, we would have access to both the natural and the unnatural configuration of any thiourea derivative. We began with the synthesis of the unnatural analogue **268** from quinine **212** (Scheme 119). Depending on the initial results obtained using catalyst **268** as a promoter, we would return to this protocol in order to synthesise similar derivatives.

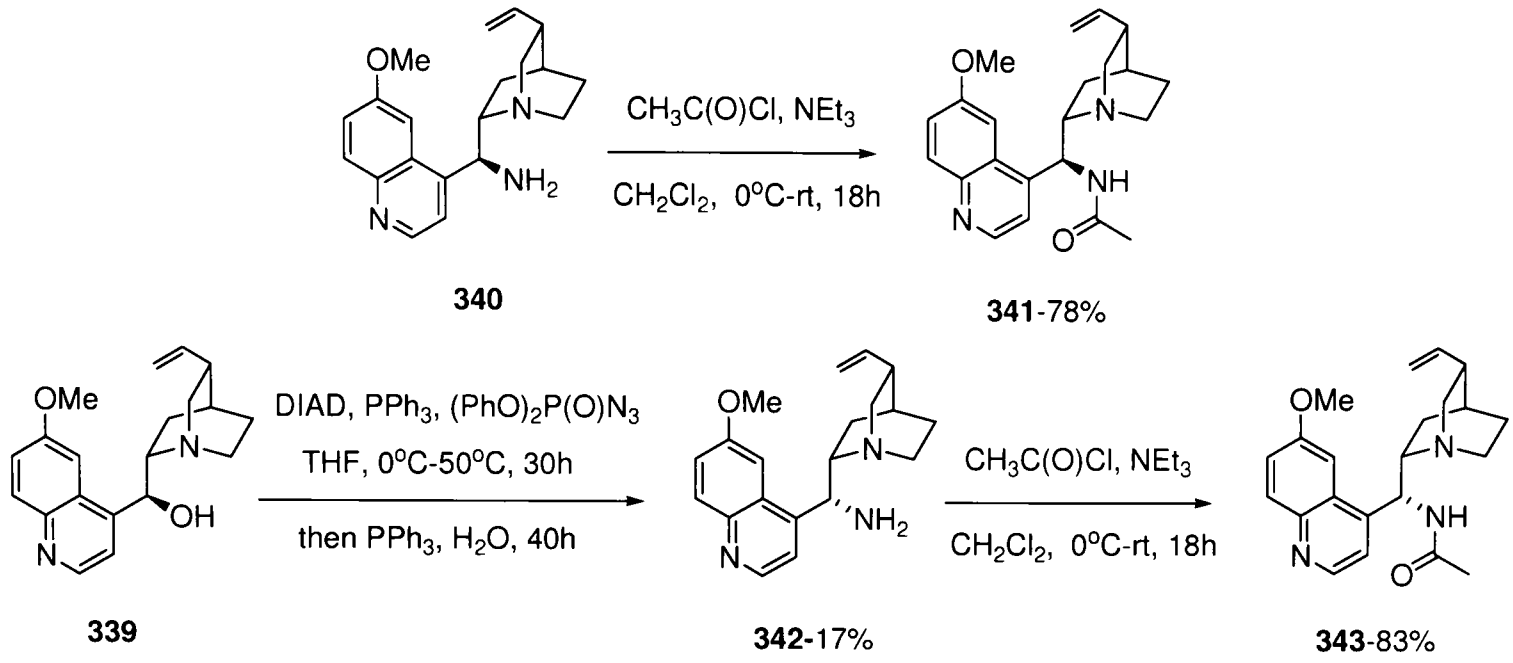


212 **340**-59% **268**-62%

(Where Ar= 3,5-bis(trifluoromethyl)phenyl)

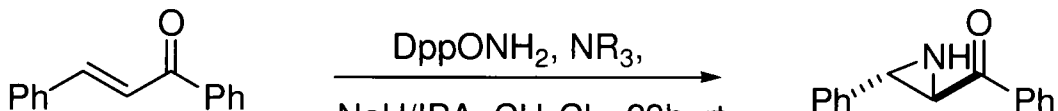
Scheme 119

Although the use of cinchona acetamide derivatives is not as well documented in the literature as their thiourea counterparts, we reasoned that such compounds may also have the potential to act as enhanced H-bond donors. With this in mind we synthesised both the naturally and the unnaturally configured acetamides of quinine.[142] Addition of acetyl chloride to amine **340** allowed access to the unnatural analogue **341**. The naturally configured material (**343**) was synthesised *via* the Mitsunobu inversion/Staudinger reduction of epiquinine **339**, followed by addition of acetyl chloride to free amine **342** (Scheme 120).



Scheme 120

At this stage we elected to test the derivatives that we had synthesised so far. The standard asymmetric aziridination conditions were utilised with each derivative being tested in turn (Table 18).



Entry	NR_3	Yield (%)	Recovered Starting Material (%)[a]	*e.e.* (%)[c]
1	Epiquinine (**339**)	28	74	11 (2*S*,3*R*)
2	thiourea (unnatural config.) (**268**)	0	100[b]	
3	acetamide (natural config.) (**343**)	0	100	-
4	acetamide (unnatural config.) (**341**)	8	>90	14 (2*S*, 3*R*)

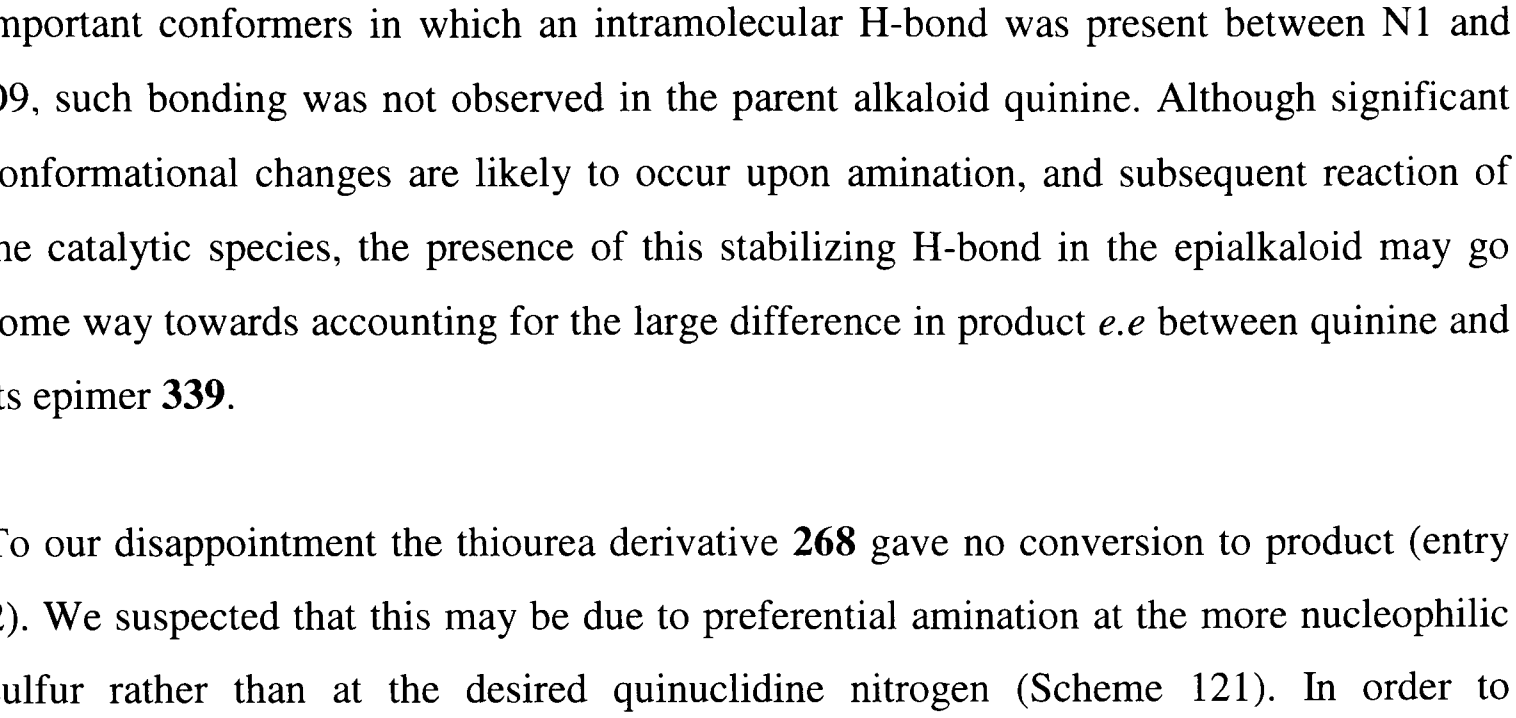
[a] Percentage recovered starting material after column chromatography; [b] As judged by TLC; [c] Enantiomeric excess measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H). Assumed configuration of the product is given in parentheses and based upon the result obtained using quinine to give the (2*R*, 3*S*-(t_R (minor)=15.96 min, t_R (major)=18.82 min)) enantiomer as the major product.

Table 18

Epiquinine (entry 1) gave a product *e.e* value of 11%, clearly indicating that the stereochemistry at the C9 centre is important in terms of enantioselectivity. A report by Caner *et al.*[143] used semiempirical PM3 calculations to probe the conformational spaces of the epicinchona alkaloids. The results obtained for epiquinine showed a number of

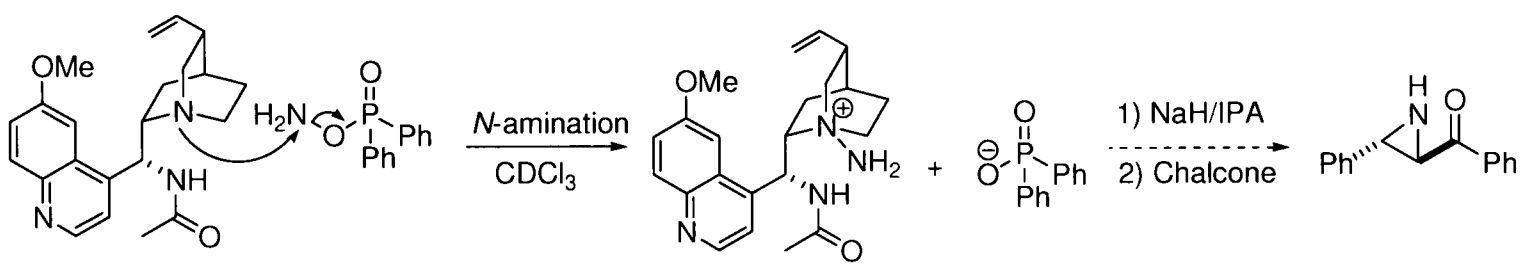
important conformers in which an intramolecular H-bond was present between N1 and O9, such bonding was not observed in the parent alkaloid quinine. Although significant conformational changes are likely to occur upon amination, and subsequent reaction of the catalytic species, the presence of this stabilizing H-bond in the epialkaloid may go some way towards accounting for the large difference in product *e.e* between quinine and its epimer **339**.

To our disappointment the thiourea derivative **268** gave no conversion to product (entry 2). We suspected that this may be due to preferential amination at the more nucleophilic sulfur rather than at the desired quinuclidine nitrogen (Scheme 121). In order to investigate this result further commercially available thiourea **346** was subjected to the standard aminating agent $DppONH_2$ (**344**) whilst the reaction was monitored by ^1H NMR. Thiourea **346** alone shows a characteristic singlet at δ_H=3.10 ppm (10 mol% TMS as a standard (TMS: thiourea, 1:2.3)). After only 20 minutes ^1H NMR showed the appearance of a new singlet peak at δ_H=3.18 ppm (TMS: thiourea: new product peak, 1:1.2:0.9). It was suggested that this new signal may correspond to the *S*-aminated compound **347** (Scheme 121). As this presumed pathway would most likely prevent the desired aziridination from occurring no further thiourea derivatives were tested as part of this work.



Scheme 121

Both acetamide **341** and **343** proved to be poor promoters of the reaction (entries 3 and 4), with derivative **341** giving a yield of 8% and an *e.e* value of 14%, whilst species **343** provided 0% conversion of starting material to desired product. Catalyst **343** was subjected to the aminating agent **344** in $CDCl_3$. The reaction was monitored by ^1H NMR in order to observe the rate of catalyst amination. The results of this work showed that the catalyst was indeed aminated, presumably at the more nucleophilic quinuclidine nitrogen. ^1H NMR spectra showed that conversion to the aminated quinine species **348** was incomplete after 24 hours (approximately 1:1 catalyst (**343**): aminated catalyst (**348**)). After this time base (NaH/IPA) and chalcone were subsequently added to the reaction with only minimal product formation being observed by TLC after a further 23 hours. Column chromatography allowed isolation of starting material only (Scheme 122). Due to the low activity of these promoters we chose not to pursue this route any further.



343 344 348 174

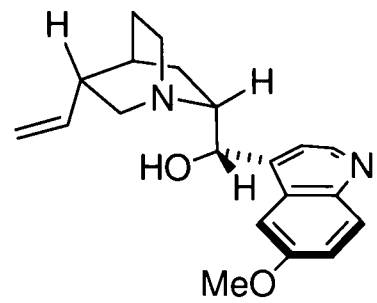
Scheme 122

It is thought that the incomplete amination of the amide catalysts is at least partially responsible for the lack of product formation using such promoters. However, these results may also imply that the presence of an H-bond donor at C9 does not play as an important a role as initially proposed. We considered an alternative hypothesis whereby the relative bulk of the C9 group alters the preferred catalyst conformation, resulting in varying levels of reaction enantioselectivity.

2.2.2.3.2 Effect of Catalyst Conformation upon Enantioselectivity

A number of conformational studies have been conducted on the cinchona alkaloids using molecular modelling and nOe enhancements.[143-145] Dijkstra *et al.*[144,145] described a

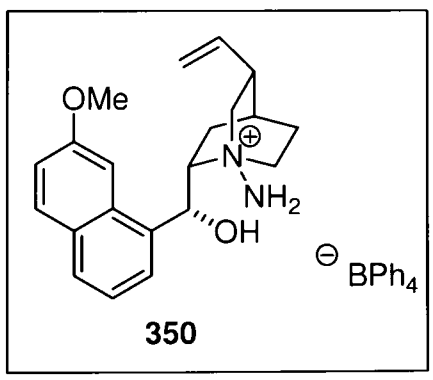
combined NMR-molecular orbital approach, and have shown the anti-open conformation **349** (Figure 12, shown for quinidine) to be favoured in the parent alkaloids in all solvents.



349
Quinidine anti-open conformation

Figure 12

At this stage a co-worker was able to isolate and recrystallise the tetraphenylborate salt of aminated quinine (**350**) allowing us to establish the preferred conformation of our catalyst in crystal form (Figure 13, ethanol is present as the solvent of recrystallisation. Atom numbering follows that given for the actual x-ray structure rather than the standard cinchona alkaloid numbering scheme).[146]



350

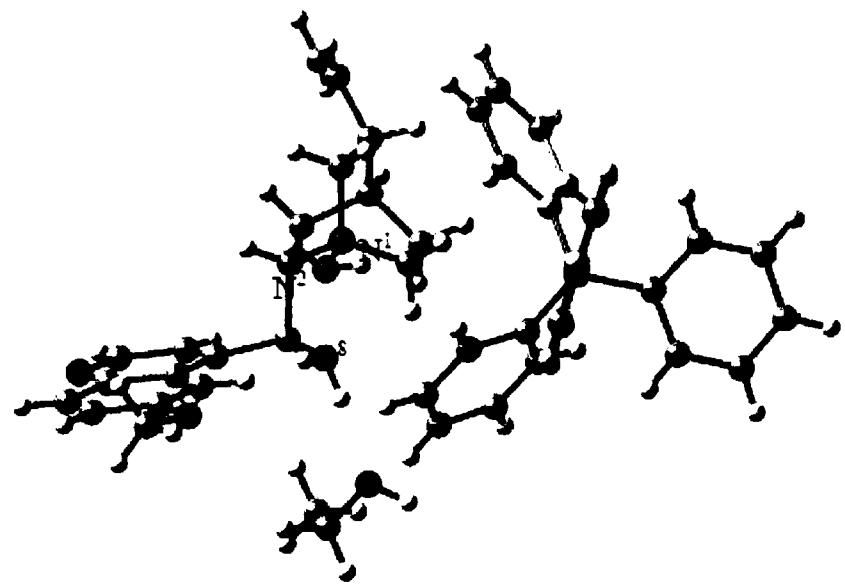


Figure 13

Comparison of crystallographic data[146] with values obtained using a semiempirical PM3 method,[143] suggest that quinidinium salt **350** also adopts the anti-open conformation as

predicted by Dijkstra. If we assume that aminimine addition is the enantiomer-determining step, and that this anti-open conformation is retained upon *N*-deprotonation to form the aminimine ylide, then we can predict a transition state model as shown in Figure 14 (**A** (favoured, giving the (2*R*, 3*S*) product as the major product), **B** (disfavoured, giving the (2*S*, 3*R*) product as the major enantiomer)). It was postulated that aromatic-aromatic interactions, between R^1 and the quinoline ring of the catalyst, may be important in the transition states shown. Such interactions would account for the necessity of the quinoline ring in obtaining reasonable *e.e* values for the reaction (*cf.* quincorine 1% *e.e.*, Table 17, entry 8), and the significant effect upon *e.e* observed when varying the substituent adjacent to the ketone moiety of the substrate (Table 16). In the favoured transition state (**A**) the R^1 group of the substrate resides in a plane above the quinoline ring. The disfavoured transition state (**B**) positions the R^1 aromatic away from the quinoline ring, so disrupting the postulated aromatic-aromatic interaction.

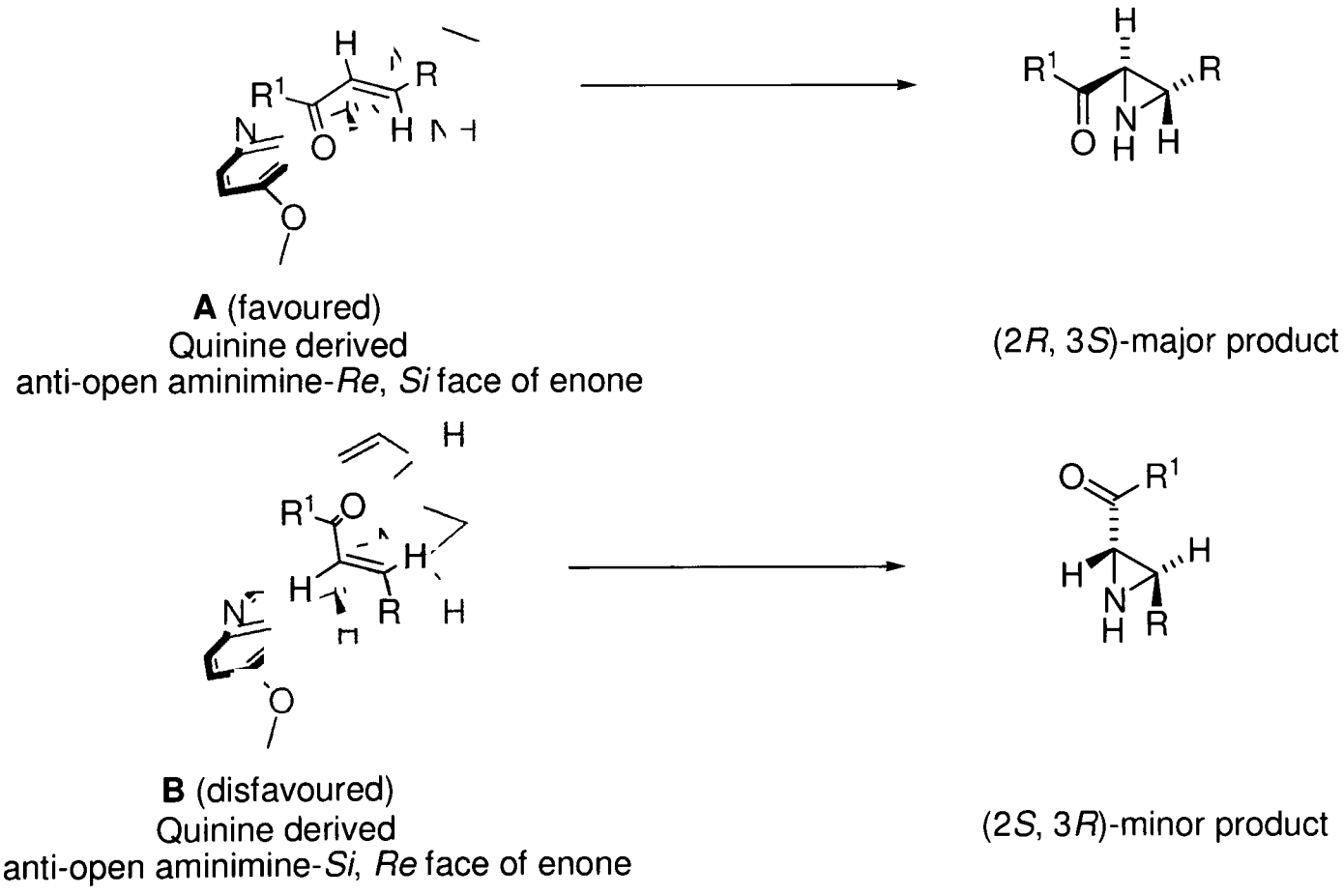
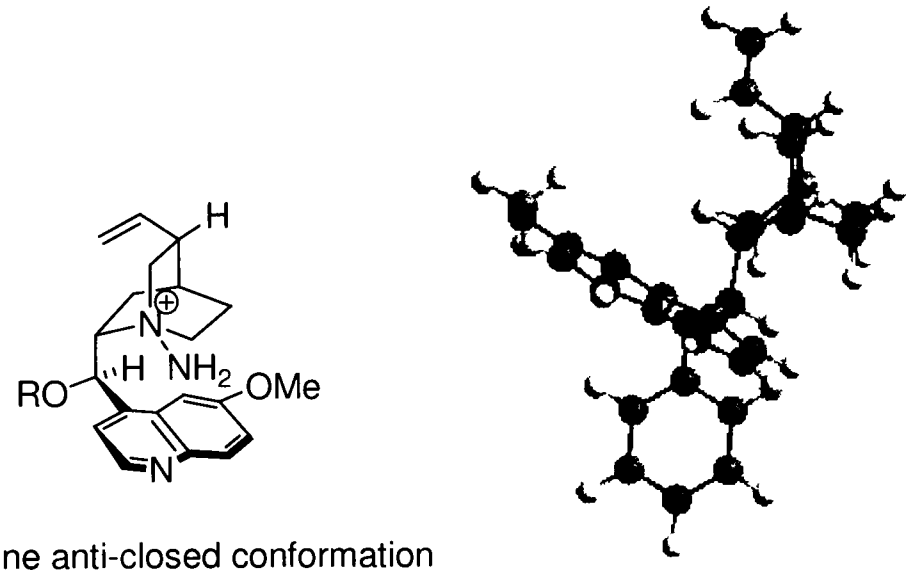


Figure 14

We proposed that the steric bulk of the group at the C9 position would affect the catalyst conformation, a hypothesis which seemed reasonable in light of the results described in

Table 17 (entries 11 and 12), in which a marked decrease in enantioselectivity was observed upon protecting the C9 hydroxy functionality as a bulky aromatic ether. When the hydroxyl functionality is not protected it is small and remains towards the back face of the catalyst, as shown in Figure 14. However, upon O9 protection the steric bulk of the group is increased which in turn is likely to cause significant conformational change in the catalyst. The hydroxyl group is predicted to rotate (*via* the C8-C9 bond) to prevent steric clash with the quinuclidine ring, causing the quinoline ring to be pushed forward. This rotation would disrupt the proposed aromatic-aromatic interaction between the R^1 substituent and the quinoline ring of the catalyst, resulting in decreased levels of enantioselectivity as the catalyst adopts the so called anti-closed conformation as shown in Figure 15. An MMF conformer search in Spartan, based upon the *N*-aminated quinine derivative where R=Ph, showed that all of the lowest enery conformers adopted conformations where the OPh group is in this position with some flexibility in the open/closed arrangement of the quinoline ring.[147]



quinine anti-closed conformation

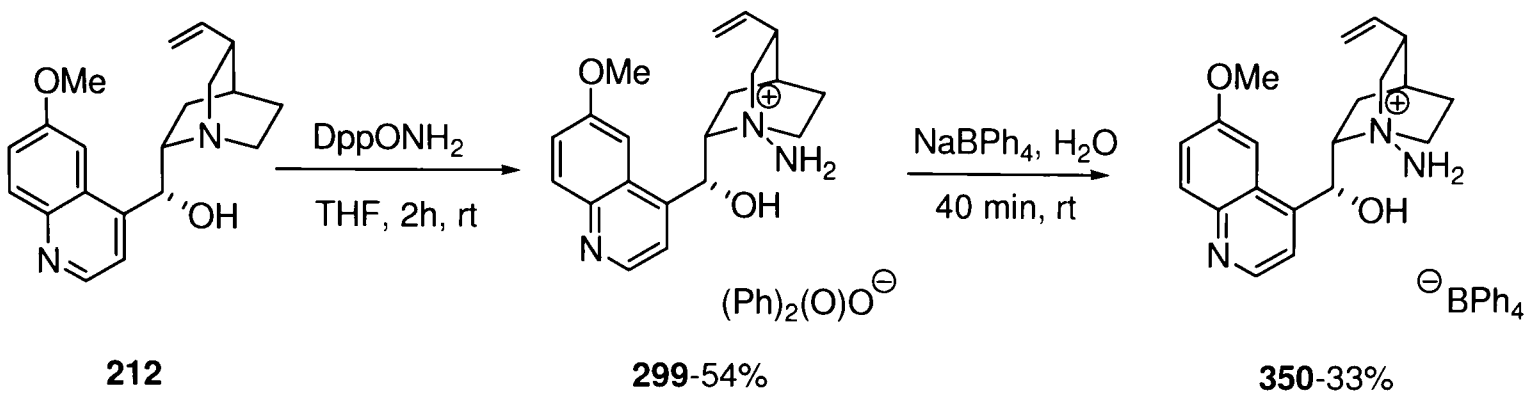
Figure 15

However, the true reaction transition state is likely to be more complex than that portrayed in Figure 14. Deprotonation to form the aminimine ylide, and subsequent Michael addition to the chalcone substrate, is likely to induce a significant degree of conformational change in the catalyst. Therefore it is quite possible that the crystal structure obtained (Figure 13) is not representative of the true reactive catalyst conformation.

At this stage we returned to consider the disappointing results obtained with the acetamide catalysts **341** and **343**, (Section 2.2.2.3.1), where slow and incomplete catalyst amination was believed to be a significant factor in achieving low reaction yields. This led us to contemplate moving away from the original *in situ* amination-aziridination procedure, instead focusing upon the isolation of the hydrazinium salt before the addition of the substrate chalcone and base. This would also allow us to explore a range of strong bases, anhydrous conditions and apolar solvents, and study the subsequent effects upon reaction *e.e.*

2.2.2.3.3 Isolation of Aminated Quinine Salts and Subsequent Application to the Asymmetric Aziridination of Chalcone

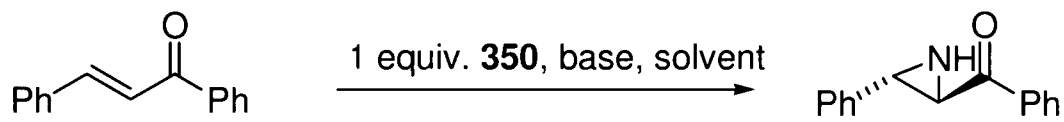
^{1}H NMR experiments previously conducted within the group, to monitor the rate of quinine amination under the standard conditions (1 equiv. $DppONH_2$, $CDCl_3$, rt), had shown that after 30 minutes the amination was approximately 76% complete.[146] It was hoped that isolation of the hydrazinium salt, before use in the aziridination reaction, would increase reaction yields. The diphenylphosphine salt of *N*-aminated quinine (**299**) was readily accessed *via* the addition of $DppONH_2$ to a solution of quinine in THF. The salt rapidly precipitated out of solution after the addition of the aminating agent. As the diphenylphosphine salt (**299**) was seen to have poor solubility in organic solvents it was suggested that counter ion exchange using the less polar anion, tetraphenylborate, would be beneficial. Addition of $NaBPh_4$ to a stirred solution of quinidinium diphenylphosphinate (**299**) in H_2O saw the precipitation of the desired product (**350**) as a white solid (Scheme 123).



212 **299**-54% **350**-33%

Scheme 123

As well as testing the hydrazinium salt under the standard NaH/IPA conditions we also wanted to probe the effect upon the reaction of using stronger aprotic bases such as *n*-BuLi or KO*t*Bu. It was postulated that the absence of a proton source in the reaction would prevent quenching of the intermediate enolate **323**, potentially resulting in higher reaction yields. The results of this study are shown in Table 19. Entry 1 shows the standard reaction conditions, using the well established base system NaH/IPA (2 equiv.). We also wanted to examine the use of KO*t*Bu in DMSO as an alternative system (entry 2) as this had previously been shown to work well in the achiral aziridination reaction.[100] Finally, we selected *n*-BuLi for testing as a suitably strong base (entries 3-6).



Entry	Base (equiv.), Solvent	Temperature (°C)	Yield (%) (*e.e* (%))[(a)]
1	NaH/IPA (2), toluene	rt	0
2	KO*t*Bu (2), DMSO	-78 to rt	0
3	*n*-BuLi (1), THF	-78	0
4	*n*-BuLi (2), THF	-78	0
5	*n*-BuLi (1), THF	-78 to rt	0
6	*n*-BuLi (2), THF	-78 to rt	71 (31)

[(a)] Where product was isolated enantiomeric excess was measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H). The *e.e.* value is given in parentheses with the assumed configuration of the product being based upon the result obtained using quinine to give the 2*R*, 3*S*-(t_R (minor)=15.96 min, t_R (major)=18.82 min)) enantiomer as the major product.

Table 19

The result obtained using NaH/IPA (entry 1) was surprising as no aziridine product was isolated, with only starting material being observed by TLC. Under the same $DppONH_2$ *in situ* conditions we observed a 64% yield and a product *e.e* value of 41%. The result

obtained using KO*t*Bu as base (entry 2) proved to be equally disappointing. with no product formation being observed, despite complete disappearance of starting material as judged by TLC analysis. Both the ^{1}H NMR and LC/MS (ES^+) analysis of the crude reaction mixture were complex, preventing the identification of any side products. This result was particularly surprising as this system had previously been shown to work well in the achiral reaction using the hydrazinium iodide salt of NMM.[100] Entries 3-6 demonstrated that product formation does not occur at lower temperatures and that 2 equivalents of *n*-BuLi are required in order to achieve ylide formation. Entry 6 shows an improvement upon the reaction yield achieved with the *in situ* NaH/IPA/CH_2Cl_2 system (71% *cf.* 63%), although this increase is not significant and the *e.e* value of the product was seen to decrease from 57%, under the standard conditions, to 31% with *n*-BuLi as base (*n.b. In situ* NaOH/THF conditions gave no aziridine product).[101] Currently it is unclear as to why 2 equivalents of a strong, aprotic base, such as *n*-BuLi, are required in order to affect aziridination. The synthesis of a dianionic species is possible if deprotonation of the C9 hydroxy functionality occurs initially, with subsequent *N*-NH_2 deprotonation with the second equivalence of base. Again, such a hypothesis depends upon the respective pKa values of the C9 hydroxy and the *N*-NH_2 proton An approximate value for the pKa of the quinine hydroxyl group, based on other non-aromatic alcohols,[113] is 30 (DMSO), and although the pKa of the *N*-NH_2 group is not currently known it is predicted to be less acidic than the hydroxyl functionality. All of the conditions described in Table 19 failed to show any significant improvement in yield and *e.e* compared to the original *in situ* system. With this in mind, and because using *n*-BuLi as base would make it difficult to realise a catalytic variant of the asymmetric aziridination, the *in situ* reaction remained the procedure of choice.

2.2.3 Conclusions and Future Work

The substrate scope of the achiral, NMM-mediated aziridination was probed with generally disappointing results. Many substrates appeared to be unstable to the reaction conditions, with decomposition of starting material inevitably resulting in little or no reaction to form desired product. However, two new classes of substrate, the dienones,

and their mono alkene equivalents, with heterocyclic functionality adjacent to the ketone, proved to give good results under both the achiral and asymmetric aziridination conditions, with *e.e* values surpassing those achieved with any other previously tested substrate. Work towards further improving the enantioselectivities obtained with such substrates, and the subsequent application of these products to aziridine ring-opening reactions continues. A range of electron rich and electron poor enones were subjected to the standard asymmetric reaction conditions with results showing a slight increase in *e.e* values for methoxy substituted derivatives. Initial catalyst screening has shown the quinoline ring of the cinchona alkaloid derivatives, and the C9 hydroxy functionality, to be the two key components in achieving reasonable levels of enantioselectivity in the aziridination reaction. A preliminary transition state model can be put forward for the reaction based upon our initial observations and the crystal structure of aminated quinine. However, further catalyst synthesis and screening is required in order to formulate a more accurate working model. In order to progress towards our ultimate goal of achieving excellent *e.e* values for the reaction we will not only concentrate our efforts on the derivatisation of the cinchona alkaloid motif, but also upon other potential promoters such as chiral NMM and NMP derivatives. Additionally it is hoped that molecular modelling and further mechanistic investigation will provide us with important information with regards to building a reliable transition state model.

3. Experimental

3. Experimental

3.1 General Procedures

^{1}H and ^{13}C NMR analyses were performed on Brüker AV400 (400 MHz (^{1}H), 100 MHz (^{13}C)) and Brüker AV500 (500 MHz (^{1}H), 125 MHz (^{13}C)) spectrometers at ambient temperatures. Chemical shifts (δ_H, δ_C) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are recorded to the nearest 0.1 Hz. Carbon spectra are supported by DEPT-135 analysis with peaks assigned as C, CH or CH_2.

Infrared spectra were recorded on a Mattson Satellite FT-IR spectrometer or on a Perkin Elmer Spectrum 100 FT-IR Spectrometer as a thin film between NaCl plates, as a nujol mull where necessary or as a solid. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

Mass spectrometry was carried out using CI (NH_3), ES^+, EI^+ or FAB^+ and were recorded using Micromass Platform II or AutoSpecQ instruments. Only molecular ions and fragments from molecular ions are reported.

HPLC analyses were performed on an Agilent 1100.

Specific rotations (α) were recorded on an Optical Activity Autopolarimeter. 0.5 dm, at the stated temperature (°C) and concentration (*c*) measured in units of g/100mL. Specific rotations were converted to optical rotations $[\alpha]_D$ *via* the equation:

$$[\alpha]_D = 100\alpha / (l \times c)$$

Melting points were determined using a Reichert hot plate microscope and are uncorrected.

Thin layer chromatography (TLC) was performed using glass backed plates pre-coated with silica gel 60 F_{254}. Flash chromatography was carried out on silica gel (VWR Prolabo).

All reactions were carried out under a positive pressure of N_2 or Ar unless otherwise stated. Solvents were freshly distilled before use from calcium hydride ($CHCl_3$, CH_2Cl_2) or sodium/benzophenone (ether/THF). All acid chlorides were purified by Kugelrohr distillation and stored at -5 °C under N_2. All other reagents were purified in accordance with the instructions in D. Perrin and W. Armarego, "Purification of Laboratory Chemicals", Pergamon Press, 4th Ed., 1998 or used as obtained from commercial sources.

3.2 Experimental Procedures

3.2.1 Experimental for the Organocatalytic Synthesis of β–Alkylaspartates *via* β–Lactone Ring Opening

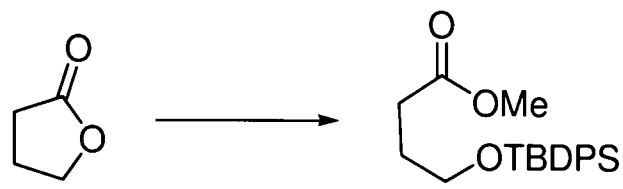
3.2.1.1 General Procedure for the Preparation of Acid Chlorides

4-Phenyl butyryl chloride (87)[54]

87

To a rapidly stirred solution of 4-phenyl butyric acid (0.80 g, 4.9 mmol) and dimethyl formamide (40 μL, 0.49 mmol, 10 mol%) in CH_2Cl_2 (6 mL) at 0 °C was added oxalyl chloride (0.46 mL, 5.4 mmol). The reaction was allowed to warm to rt with stirring for 1.5 h. Solvent and excess oxalyl chloride were removed *in vacuo* and the crude was then purified by Kugelrohr distillation to afford acid chloride **87** (0.39 g, 2.1 mmol, 97%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 7.34-7.19 (5H, m, ArH), 2.92 (2H, t, *J* 7.2, CH_2COCl), 2.72 (2H, t, *J* 7.2, CH_2Ar), 2.07 (2H, m, CH_2CH_2Ar). ^1H NMR data correspond to literature compound.

4-(*tert*-Butyl-diphenylsilanyloxy)-butyric acid methyl ester (90)[55]

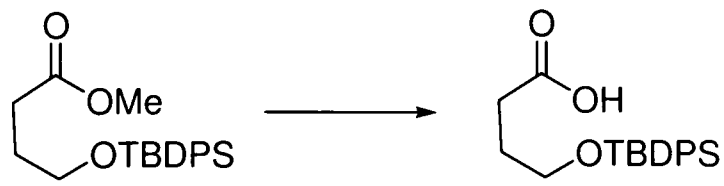


90

To a rapidly stirred solution of γ-butyrolactone (0.50 mL, 6.5 mmol) was added conc. H_2SO_4 (10 drops) and MeOH (12 mL). The mixture was heated under reflux for 5 h and the resulting solution was diluted with water (15 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were combined and washed with saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous NaCl (15 mL). The solvent was removed *in vacuo* to afford the crude 3-hydroxy-butyric acid methyl ester as a pale yellow oil, which was used in the next step without further purification.

To a rapidly stirred solution of 3-hydroxy-butyric acid methyl ester (0.53 g, 4.5 mmol) and imidazole (0.61 g, 9.0 mmol) in CH_2Cl_2 (30 mL) was added *t*-butyldiphenylsilyl chloride (1.2 mL, 4.5 mmol) dropwise over 5 min. The resulting solution was left to stir at rt for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (6:1 petrol:ether) to afford the *title compound* **90** (0.93 g, 3.4 mmol, 40%) as a pale yellow oil; δ_H (500 MHz, $CDCl_3$) 7.69-7.67 (4H, m, ArH), 7.45-7.39 (6H, m, ArH), 3.71 (2H, t, *J* 6.1, $CH_2OSiPh_2{}^tBu$), 3.68 (3H, s, CO_2CH_3), 2.49 (2H, t, *J* 7.4, $CH_2CO_2CH_3$), 1.91 (2H, tt, *J* 7.4, 6.1, $CH_2CH_2CO_2CH_3$), 1.07 (9H, s, $OSiPh_2C(CH_3)_3$). ^1H NMR data correspond to literature compound.

4-(*tert*-Butyl-diphenylsilanyloxy)-butyric acid (91)[56]

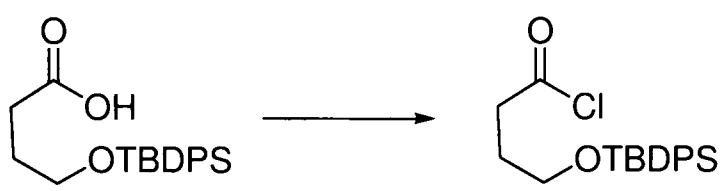


91

To a rapidly stirred solution of 4-(*tert*-butyl-diphenylsilanyloxy)-butyric acid methyl ester (1.2 g, 4.4 mmol) in MeOH (40 mL) was added lithium hydroxide monohydrate

(0.91 g, 21 mmol). The reaction was allowed to stir at rt overnight. Water (8 mL) was added and the resulting mixture was stirred for a further 30 min, after which time it was concentrated *in vacuo* to approximately 5 mL. The pH was then lowered to 3 using 1.0 M hydrochloric acid. The solution was extracted with EtOAc and dried over sodium sulfate. The remaining solvent was removed *in vacuo* to give the crude product which was purified by flash column chromatography (2:1 petrol:ether) to afford the *title compound* **91** (1.0 g, 3.8 mmol, 88%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.67-7.64 (4H, m, ArH), 7.43-7.38 (6H, m, ArH), 3.70 (2H, t, *J* 6.2, $CH_2OSiPh_2{}^tBu$), 2.53 (2H, t, *J* 7.3, CH_2CO_2H), 1.89 (2H, tt, *J* 7.3, 6.2, $CH_2CH_2CO_2H$), 1.05 (9H, s, $OSiPh_2C(CH_3)_3$). ^1H NMR data correspond to literature compound.

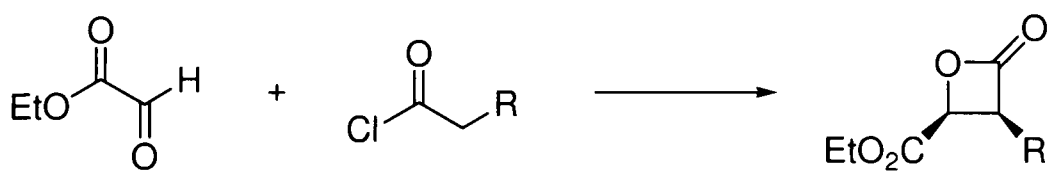
4-(*tert*-Butyl-diphenylsilanyloxy)-butyryl chloride (92)[57]



92

A solution of 4-(*tert*-butyl-diphenylsilanyloxy)-butyric acid (0.78 g, 3.0 mmol) in benzene (8 mL) was treated with oxalyl chloride (1.5 mL, 18 mmol). The reaction was allowed to stir at rt for 18 h, after which time the solvent and excess oxalyl chloride were removed *in vacuo* and the crude product purified by Kugelrohr distillation to afford the *title compound* **92** (0.85 g, 3.0 mmol, quantitative yield) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 7.66-7.63 (4H, m, ArH), 7.44-7.37 (6H, m, ArH), 3.69 (2H, t, *J* 6.2, $CH_2OSiPh_2{}^tBu$), 3.05 (2H, t, *J* 7.3, CH_2CO_2Cl), 1.94 (2H, tt, *J* 7.3, 6.2, $CH_2CH_2CO_2Cl$), 1.05 (9H, s, $OSiPh_2C(CH_3)_3$). ^1H NMR data correspond to literature compound.

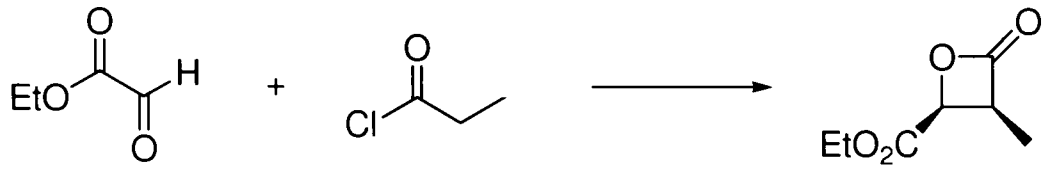
3.2.1.2 General Procedure for Catalytic Enantioselective β-Lactone Synthesis



To a rapidly stirred solution of NEt_3 (14 μL, 0.10 mmol), Hünig's base (0.35 mL, 2.0 mmol) and catalyst (47 mg, 0.10 mmol) in chloroform (1 mL), at -60 °C, was added a

mixture of ethyl glyoxylate (0.71 mL of 1.4 M in toluene, 1 mmol) and acid chloride (1.5 equiv.) in chloroform (1 mL) over 0.5 h. The reaction was then stirred for 2.5 h at which point most of the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography (2:1 petrol:ether) to afford β-lactone. For the synthesis of the (2*R*, 3*R*) substrates hydroquinine-4-chlorobenzoate was used as an alternative catalyst.

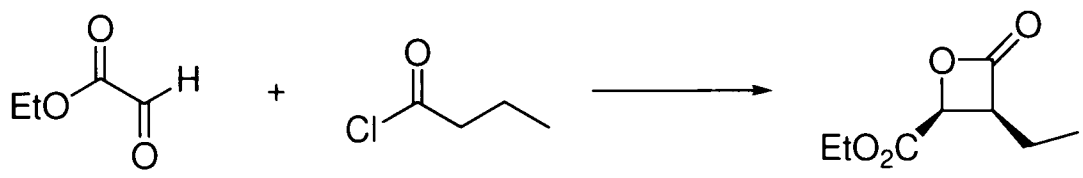
(2*S*, 3*S*)-Ethyl 3-methyl-4-oxooxetane-2-carboxylate (351)



(2*S*, 3*S*)-**351**

Propionyl chloride (0.13 mL, 1.5 mmol) was used as described to afford the (2*S*, 3*S*)-lactone **351** (0.09 g, 0.52 mmol, 55%) as a colourless oil; $[\alpha]^{22}_{D}$ -30.3 (*c* 1.78, $CHCl_3$); >95% *e.e.* (determined by ^{1}H NMR in the presence of 40 mol% Eu(hfc)$_3$); ν_{max}/cm^{-1}(film) 2985, 1841, 1754, 1211, 1115, 1026; δ_H (400 MHz, $CDCl_3$) 4.93 (1H, d, *J* 6.9, EtO_2CCH), 4.32 (2H, dq, *J* 14.2, 7.1, $CH_3CH_2O_2C$), 4.08 (1H, quin, *J* 7.2, EtO_2CCHCH), 1.31 (3H, t, *J* 7.1, $CH_3CH_2O_2C$), 1.27 (3H, d, *J* 7.8, $CHCHCH_3$); δ_C (100 MHz, $CDCl_3$) 169.9 (C), 167.2 (C), 70.4 (CH), 62.0 (CH_2), 50.2 (CH), 14.2 (CH), 9.4 (CH); m/z (CI (NH_3)) 176 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 176.0924 $C_7H_{14}NO_4$ requires $[M+NH_4]^+$, 176.0923.

(2*S*, 3*S*)-Ethyl 3-ethyl-4-oxooxetane-2-carboxylate (352)

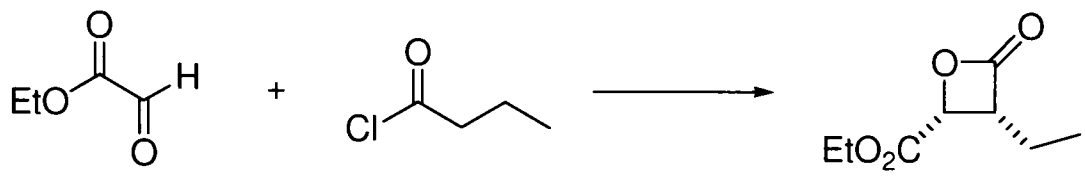


(2*S*, 3*S*)-**352**

Butyryl chloride (0.16 mL, 1.5 mmol) was used as described to afford the (2*S*, 3*S*)-lactone **352** (0.09 g, 0.52 mmol, 50%) as a colourless oil; $[\alpha]^{22}_{D}$ -16.5 (*c* 4.25, $CHCl_3$); >95% *e.e.* (determined by ^{1}H NMR in the presence of 10 mol% Eu(hfc)$_3$); ν_{max}/cm^{-1}(film) 2974, 2940, 2881, 1840, 1755, 1209, 1030; δ_H (400 MHz, $CDCl_3$) 4.96 (1H, d, *J* 6.9,

EtO_2CCH), 4.33 (2H, q, *J* 7.3, $CH_3CH_2O_2C$), 3.93-3.87 (1H, m, EtO_2CCHCH). 1.85-1.68 (2H, m, $CHCH_2CH_3$), 1.35 (3H, t, *J* 7.3, $CH_3CH_2O_2C$), 1.08 (3H, t, *J* 7.3, $CHCH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 169.3 (C), 167.4 (C), 70.1 (CH), 62.1 (CH_2), 56.9 (CH), 18.8 (CH_2), 14.2 (CH), 11.4 (CH); m/z (CI (NH_3)) 190 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 190.1078 $C_8H_{16}NO_4$ requires : 190.1079.

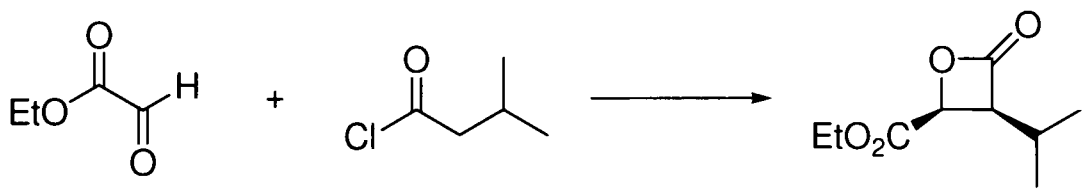
(2*R*, 3*R*)-Ethyl 3-ethyl-4-oxooxetane-2-carboxylate (352)



(2*R*, 3*R*)-**352**

Butyryl chloride (0.16 mL, 1.5 mmol) was used as described to afford the (2*R*, 3*R*)-lactone **352** (0.10 g, 0.59 mmol, 58%) as a colourless oil; $[\alpha]^{22}_D$ +29.9 (*c* 1.67, $CHCl_3$); >95% *e.e.* (determined by ^1H NMR in the presence of 10 mol% $Eu(hfc)_3$); ν_{max}/cm^{-1}(film) 2980, 2940, 2908, 1843, 1742, 1208, 1028; δ_H (400 MHz, $CDCl_3$) 4.95 (1H, d, *J* 6.8, EtO_2CCH), 4.32 (2H, q, *J* 7.3, $CH_3CH_2O_2C$), 3.90-3.84 (1H, m, EtO_2CCHCH), 1.85-1.67 (2H, m, $CHCH_2CH_3$), 1.35 (3H, t, *J* 7.3, $CH_3CH_2O_2C$), 1.08 (3H, t, *J* 7.3, $CHCH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 169.3 (C), 167.4 (C), 70.1 (CH), 62.1 (CH_2), 56.9 (CH), 18.8 (CH_2), 14.2 (CH), 11.4 (CH); m/z (CI (NH_3)) 190 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 190.1076 $C_8H_{16}NO_4$ requires : 190.1079.

(2*S*, 3*S*)-Ethyl 3-isopropyl-4-oxooxetane-2-carboxylate (353)

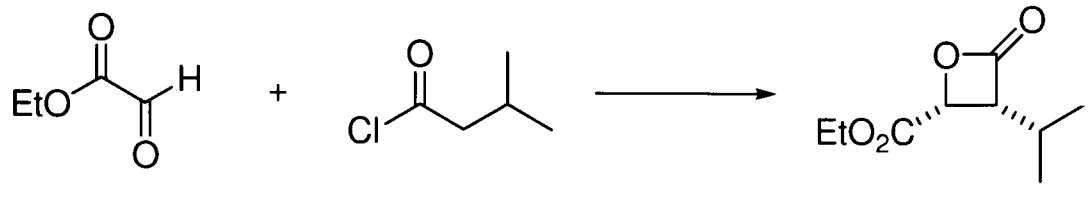


(2*S*, 3*S*)-**353**

Isovaleryl chloride (0.19 mL, 1.5 mmol) was used as described to afford the (2*S*, 3*S*,)-lactone **353** (0.11 g, 0.59 mmol, 59%) as a colourless oil; $[\alpha]^{22}_D$ +2.3 (*c* 1.77, $CHCl_3$); >95% *e.e.* (determined by ^1H NMR in the presence of 20 mol% $Eu(hfc)_3$); ν_{max}/cm^{-1}(film) 2968, 2940, 2878, 1840, 1753, 1210, 1022; δ_H (400 MHz, $CDCl_3$) 4.91 (1H, d, *J* 6.8, EtO_2CCH), 4.31 (2H, dq, *J* 14.3, 7.2, $CH_3CH_2O_2C$), 3.67 (1H, dd, *J* 10.1, 6.8,

EtO_2CCHCH), 2.12 (1H, dsept, *J* 10.1, 6.8, $CH(CH_3)_2$), 1.33 (3H, t, *J* 7.2, $CH_3CH_2O_2C$), 1.12 (3H, d, *J* 6.8, $CH(CH_3)_2$), 0.92 (3H, d, *J* 6.8, $CH(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 168.6 (C), 167.6 (C), 69.8 (CH), 62.1 (CH_2), 26.0 (CH), 26.0 (CH), 21.1 (CH), 19.9 (CH), 14.0 (CH); m/z (CI (NH_3)) 204 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 204.1230 $C_9H_{18}NO_4$ requires : 204.1236.

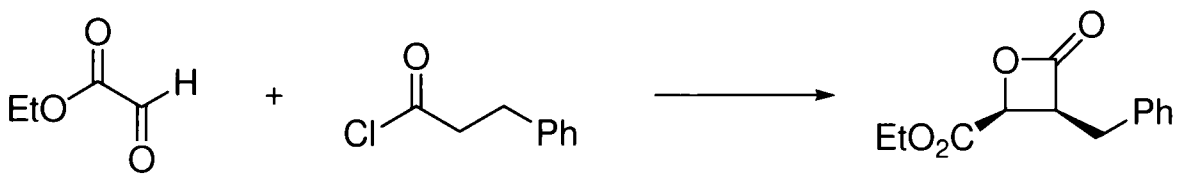
(2*R*, 3*R*)-Ethyl 3-isopropyl-4-oxooxetane-2-carboxylate (353)



(2*R*, 3*R*)-**353**

Isovaleryl chloride (0.19 mL, 1.5 mmol) was used as described to afford the (2*R*, 3*R*,)-lactone **353** (0.11 g, 0.59 mmol, 60%) as a colourless oil; $[\alpha]^{22}_D$ -2.3 (*c* 1.71, $CHCl_3$); >95% *e.e.* (determined by ^1H NMR in the presence of 30 mol% Eu(hfc)$_3$); ν_{max}/cm^{-1}(film) 2969, 2941, 2878, 1841, 1753, 1210, 1104, 1022; δ_H (400 MHz, $CDCl_3$) 4.91 (1H, d, *J* 6.8, EtO_2CCH), 4.31 (2H, dq, *J* 14.3, 7.3 $CH_3CH_2O_2C$), 3.67 (1H, dd, *J* 10.7, 6.8, EtO_2CCHCH), 2.14 (1H, dsept, *J* 10.7, 6.8 $CH(CH_3)_2$), 1.34 (3H, t, *J* 7.3, $CH_3CH_2O_2C$), 1.12 (3H, d, *J* 6.8, $CH(CH_3)_2$), 0.92 (3H, d, *J* 6.8, $CH(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 168.8 (C), 167.7 (C), 70.3 (CH), 62.7 (CH), 62.1 (CH_2), 26.0 (CH), 21.1 (CH), 19.9 (CH), 14.0 (CH); m/z (CI (NH_3)) 204 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 204.1240 $C_9H_{18}NO_4$ requires: 204.1236.

(2*S*, 3*S*)-Ethyl 3-benzyl -4-oxooxetane-2-carboxylate (354)

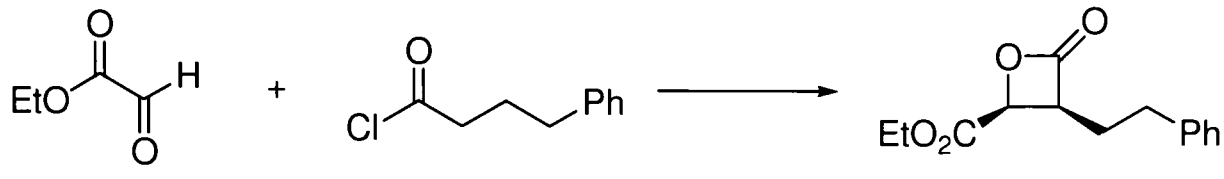


(2*S*, 3*S*)-**354**

Hydrocinnamoyl chloride (0.22 mL, 1.5 mmol) was used as described to afford the (2*S*, 3*S*)-lactone **354** (0.11 g, 0.47 mmol, 48%) as a colourless oil; $[\alpha]^{22}_D$ +20.0 (*c* 4.00, $CHCl_3$); >95% *e.e.* (determined by ^1H NMR in the presence of 40 mol% Eu(hfc)$_3$); ν_{max}/cm^{-1}(film) 2923, 2852, 1858, 1724, 1076, 1045; δ_H (400 MHz, $CDCl_3$) 7.33-7.18 (5H, m, ArH), 4.97 (1H, d, *J* 6.8, EtO_2CCH), 4.34-4.23 (2H, m, $CH_3CH_2O_2C$), 4.20-4.13

(1H, m, EtO_2CCHCH), 3.18 (1H, dd, *J* 15, 7.9, $CHCH_2Ph$), 3.04 (1H, dd, *J* 15, 7.9, $CHCH_2Ph$), 1.22 (3H, t, *J* 7.3, $CH_3CH_2O_2C$); δ_C (100 MHz, $CDCl_3$) 168.7 (C), 167.3 (C), 136.1 (C), 128.8 (CH), 128.5 (CH), 127.1 (CH), 70.1 (CH), 62.2 (CH), 56.0 (CH_2), 30.7 (CH_2), 13.1 (CH); m/z (CI (NH_3)) 252 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 252.1247 $C_{13}H_{18}NO_4$ requires : 252.1236.

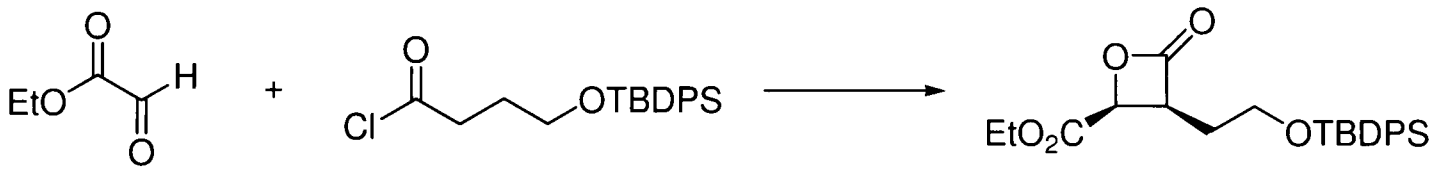
(2*S*, 3*S*)-4-Oxo-3-phenethyl-oxetane-2-carboxylic acid ethyl ester (355)



(2*S*, 3*S*)-**355**

4-Phenyl butyryl chloride (0.23 g, 1.5 mmol) was used as described to afford the (2*S*, 3*S*)-lactone **355** (0.12 g, 0.48 mmol, 47%) as a colourless oil; $[\alpha]^{22}_D$ -6.0 (*c* 2.32, $CHCl_3$); >95% *e.e.* (determined by ^1H NMR in the presence of 20 mol% $Eu(hfc)_3$); ν_{max}/cm^{-1}(film) 2983, 2939, 1839, 1753, 1209, 1106, 1037; δ_H (400 MHz, $CDCl_3$) 7.35-7.19 (5H, m, ArH), 4.94 (1H, d, *J* 6.9, EtO_2CCH), 4.33 (2H, dq, *J* 14.5, 6.9 $CH_3CH_2O_2C$), 4.00-3.93 (1H, m, EtO_2CCHCH), 2.88-2.72 (2H, m, CH_2Ph), 2.20-2.07 (1H, m, 1 × CH_2CH_2Ph), 2.02-1.93 (1H, m, 1 × CH_2CH_2Ph), 1.36 (3H, t, *J* 6.9, $CH_3CH_2O_2C$); δ_C (100 MHz, $CDCl_3$) 169.2 (C), 167.3 (C), 139.7 (C), 128.6 (CH), 128.4 (CH), 126.5 (CH), 69.9 (CH), 62.1 (CH_2), 54.1 (CH), 32.4 (CH_2), 26.8 (CH_2), 14.1 (CH); m/z (CI (NH_3)) 266 (100%) $[M+NH_4]^+$, found : $[M+H]^+$, 249.1132 $C_{14}H_{17}O_4$ requires : 249.1127.

(2*S*, 3*S*)-3-[2-(*tert*-Butyl-diphenylsilanyloxy)-ethyl]-4-oxo-oxetane-2-carboxylic acid ethyl ester (356)

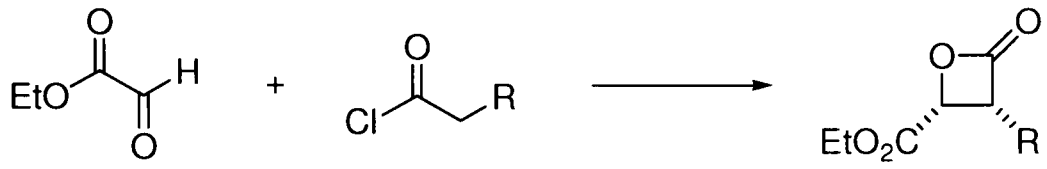


(2*S*, 3*S*)-**356**

4-(*tert*-Butyl-diphenylsilanyloxy)-butyryl chloride (0.64 g, 1.5 mmol) was used as described to afford (2*S*, 3*S*)-lactone **356** (0.20 g, 0.47 mmol, 47%) as a colourless oil; $[\alpha]^{22}_D$ -3.6 (*c* 1.10, $CHCl_3$); >95% *e.e.* (determined by ^1H NMR in the presence of 5

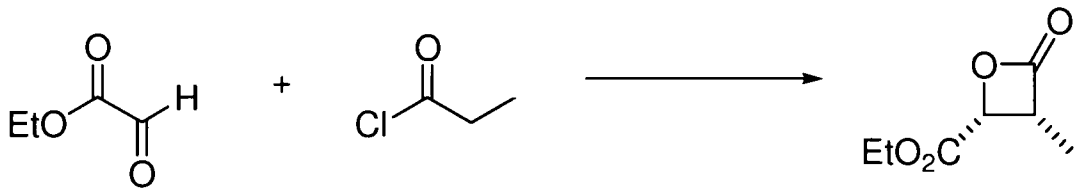
mol% $Eu(hfc)_3$); ν_{max}/cm^{-1}(film) 2959, 2932, 2858, 1843, 1755, 1428; δ_H (400 MHz, $CDCl_3$) 7.70-7.68 (4H, m, ArH), 7.50-7.40 (6H, m, ArH), 4.93 (1H, d, *J* 6.9, EtO_2CCH), 4.38 (2H, q, *J* 7.1, $CH_3CH_2O_2C$), 4.32-4.22 (1H, m, EtO_2CCHCH), 3.89-3.83 (1H, m, 1 × $CH_2CH_2OSiPh_2{}^tBu$), 3.75-3.70 (1H, m, 1 × $CH_2CH_2OSiPh_2{}^tBu$), 2.09-2.01 (1H, m, 1 × $CH_2OSiPh_2{}^tBu$), 2.00-1.88 (1H, m, 1 × $CH_2OSiPh_2{}^tBu$), 1.29 (3H, t, *J* 7.1, $CH_3CH_2O_2C$), 1.11 (9H, s, $OSiPh_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 169.5 (C), 167.5 (C), 135.5 (CH), 133.2 (C), 133.1 (C), 129.9 (CH), 127.8 (CH), 70.0 (CH), 62.1 (CH_2), 60.0 (CH_2), 51.9 (CH), 28.2 (CH_2), 26.9 (CH), 14.2 (CH); m/z (CI (NH_3)) 444 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 444.2204 $C_{24}H_{34}NO_5Si$ requires : 444.2206.

3.2.1.3 General Racemic β-Lactonisation Procedure



To a rapidly stirred solution of NEt_3 (1 equiv.) and Hünig's base (1 equiv.) in $CHCl_3$ (half solvent volume), at -60 °C, was added ethyl glyoxylate (1 equiv. of 1.4 M in toluene) and acid chloride (1.5 equiv.) in $CHCl_3$ (half solvent volume) over 0.5 h. The reaction was then stirred for 2.5 h at which point the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography (2:1 petrol:ether) to afford the β-lactone.

(2*R, 3*R**)-Methyl 3-isopropyl-4-oxooxetane-2-carboxylate (*rac*-351)**

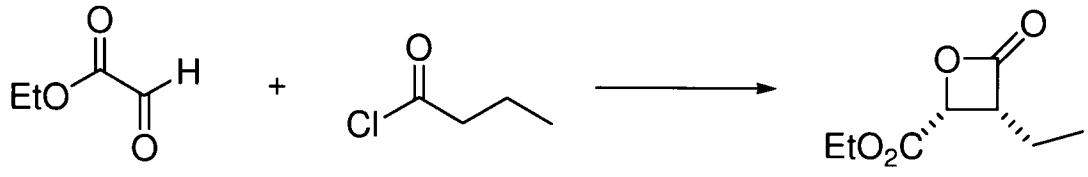


***rac*-351**

Propionyl chloride (0.39 mL, 4.5 mmol) in $CHCl_3$ (2.5 mL (half solvent volume)) was used as described to afford lactone ***rac*-351** (0.16 g, 1.0 mmol, 34%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 4.95 (1H, d, *J* 6.9, EtO_2CCH), 4.33 (2H, dq, *J* 14.2, 7.1, $CH_3CH_2O_2C$), 4.08 (1H, quin, *J* 7.2, EtO_2CCHCH), 1.34 (3H, t, *J* 7.1, $CH_3CH_2O_2C$),

1.30 (3H, d, *J* 7.8, CHCHCH_3). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

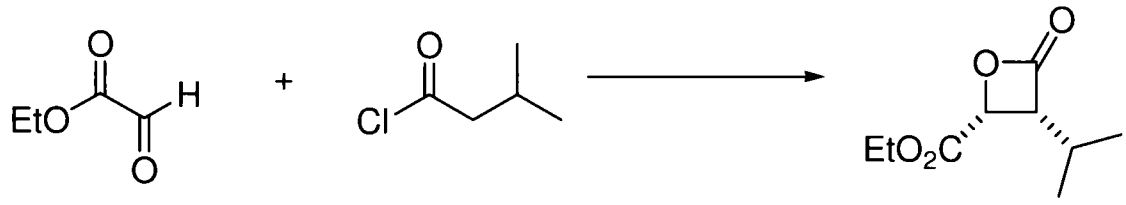
(2*R, 3*R**)-Ethyl 3-ethyl-4-oxooxetane-2-carboxylate (*rac*-352)**



rac-**352**

Butyryl chloride (0.16 mL, 1.5 mmol) in $CHCl_3$ (1 mL (half solvent volume)) was used as described to afford lactone ***rac*-352** (40 mg, 0.23 mmol, 21%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 4.96 (1H, d, *J* 6.9, EtO_2CCH), 4.32 (2H, q, *J* 7.3, $CH_3CH_2O_2C$), 3.94-3.89 (1H, m, EtO_2CCHCH), 1.85-1.65 (2H, m, $CHCH_2CH_3$), 1.34 (3H, t, *J* 7.3, $CH_3CH_2O_2C$), 1.07 (3H, t, *J* 7.3, $CHCH_2CH_3$). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

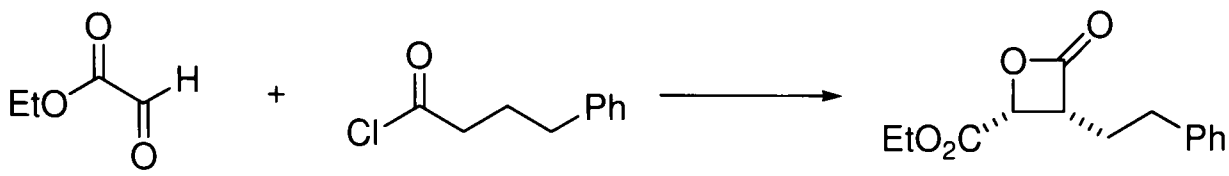
(2*R, 3*R**)-Ethyl 3-isopropyl-4-oxooxetane-2-carboxylate (*rac*-353)**



rac-**353**

Isovaleryl chloride (0.37 mL, 3.0 mmol) in $CHCl_3$ (2.5 mL (half solvent volume)) was used as described to afford lactone ***rac*-353** (0.18 g, 0.97 mmol, 32%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 4.92 (1H, d, *J* 6.8, EtO_2CCH), 4.32 (2H, dq, *J* 14.4, 7.2, $CH_3CH_2O_2C$), 3.67 (1H, dd, *J* 10.1, 6.8, EtO_2CCHCH), 2.14 (1H, dsept, *J* 10.1, 6.8, $CH(CH_3)_2$), 1.34 (3H, t, *J* 7.2, $CH_3CH_2O_2C$), 1.13 (3H, d, *J* 6.8, $CH(CH_3)_2$), 0.93 (3H, d, *J* 6.8, $CH(CH_3)_2$). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

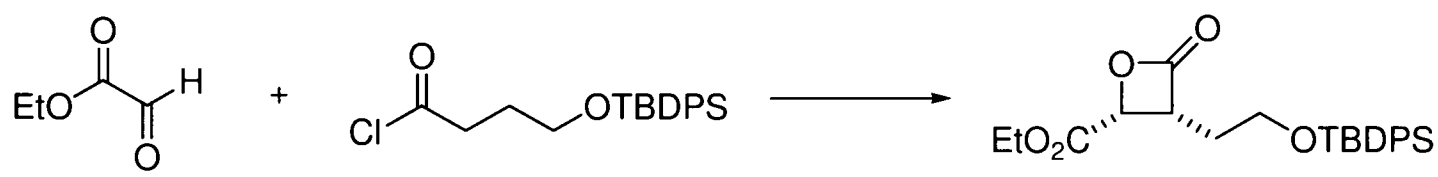
(2*R, 3*R**)-4-Oxo-3-phenethyl-oxetane-2-carboxylic acid ethyl ester (*rac*-355)**



***rac*-355**

4-Phenyl butyryl chloride (0.55 g, 3.0 mmol) in $CHCl_3$ (2 mL (half solvent volume)) was used as described to afford lactone ***rac*-355** (0.11 g, 0.44 mmol, 23%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.33-7.17 (5H, m, ArH), 4.93 (1H, d, *J* 6.9, EtO_2CCH), 4.37-4.27 (2H, m, $CH_3CH_2O_2C$), 4.00-3.90 (1H, m, EtO_2CCHCH), 2.86-2.75 (2H, m, CH_2Ph), 2.17-2.05 (1H, m, 1 × CH_2CH_2Ph), 2.00-1.87 (1H, m, 1 × CH_2CH_2Ph), 1.34 (3H, t, *J* 6.9, $CH_3CH_2O_2C$). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

(2*R, 3*R**)-3-[2-(*tert*-Butyl-diphenylsilanyloxy)-ethyl]-4-oxo-oxetane-2-carboxylic acid ethyl ester (*rac*-356)**

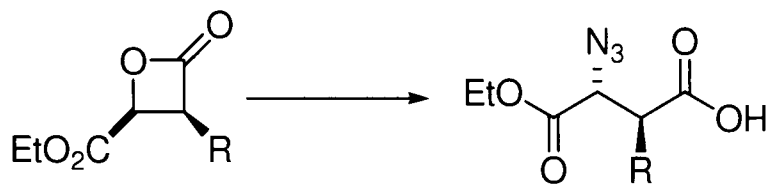


***rac*-356**

4-(*tert*-Butyl-diphenyl-silanyloxy)-butyryl chloride (0.50 g, 1.8 mmol) in $CHCl_3$ (1 mL (half solvent volume)) was used as described to afford lactone ***rac*-356** (0.19 g, 0.45 mmol, 37%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.70-7.67 (4H, m, ArH), 7.50-7.40 (6H, m, ArH), 4.92 (1H, d, *J* 6.9, EtO_2CCH), 4.37 (2H, q, *J* 7.1, $CH_3CH_2O_2C$), 4.32-4.22 (1H, m, EtO_2CCHCH), 3.87-3.81 (1H, m, 1 × $CH_2CH_2OSiPh_2C(CH_3)_3$), 3.75-3.68 (1H, m, 1 × $CH_2CH_2OSiPh_2{}^tBu$), 2.08-2.00 (1H, m, 1 × $CH_2OSiPh_2{}^tBu$), 1.97-1.87 (1H, m, 1 × $CH_2OSiPh_2{}^tBu$), 1.29 (3H, t, *J* 7.1, $CH_3CH_2O_2C$), 1.10 (9H, s, $OSiPh_2C(CH_3)_3$). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

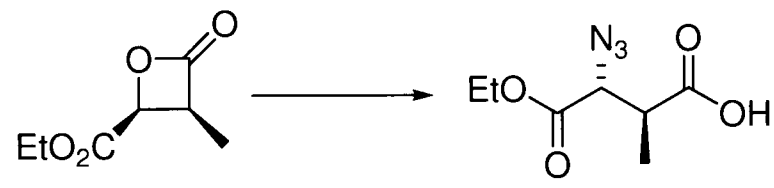
The percentage of chiral shift reagent, $Eu(hfc)_3$, required to split the enantiomeric peaks for these products was established and used in this work in order to determine the *e.e.* of the lactone products. Ethyl 3-benzyl-4-oxooxetane-2-carboxylate was also synthesised as a racemic mixture as part of previous experimental work.[51]

3.2.1.4 General Azide Ring Opening Procedure



To a solution of sodium azide (2 equiv.) in anhydrous DMSO (half solvent volume), at 40 °C was added β-lactone (1 equiv.) in DMSO (half solvent volume). The solution was stirred for 4 h, or until the starting material had been consumed as judged by TLC. The reaction was cooled to rt and saturated aqueous $NaHCO_3$ was added to give a heterogeneous solution which was then triturated with water until all precipitate dissolved. The resulting mixture was extracted with EtOAc (2 × 15 mL) and the aqueous layer acidified to pH 0 with 1 M HCl. The acidic aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organics were then washed with water (2 × 10 mL) and saturated aqueous NaCl (2 × 10 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the β-azido acid.

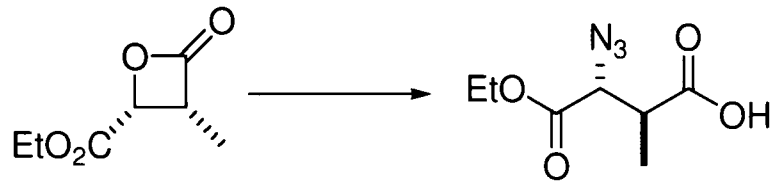
(2*R*, 3*S*)-2-Azido-3-methyl-succinic acid 1-ethyl ester (357)



357

β-Lactone (0.14 g, 0.89 mmol) in DMSO (1.5 mL (half solvent volume)) was used as described to afford the (2*R*, 3*S*)-product **357** (0.11 g, 0.55 mmol, 60%) as a pale yellow oil in a >9:1 ratio of diastereomers; $[\alpha]^{22}_D$ +62.9 (*c* 0.35, $CHCl_3$); ν_{max}/cm^{-1}(film) 2987, 2116, 1742, 1741, 1268; δ_H (400 MHz, $CDCl_3$) 9.49 (1H, s, COOH), 4.29 (2H, dq, *J* 14.4, 7.2, $CH_3CH_2O_2C$), 4.18 (1H, d, *J* 6.1, CHN_3), 3.08 (1H, dq, *J* 6.1, 7.1, $CHCH_3$), 1.31 (3H. t, *J* 7.2, $CH_3CH_2O_2C$), 1.27 (3H, d, *J* 7.1, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 178.6 (C), 168.6 (C), 63.7 (CH), 62.4 (CH_2), 41.6 (CH), 14.1 (CH), 13.2 (CH); m/z (CI (NH_3)) 219 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 219.1087 $C_7H_{15}N_4O_4$ requires : 219.1093.

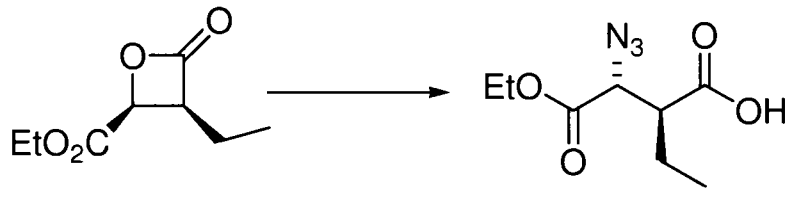
(2*R, 3**S*)-2-Azido-3-methyl-succinic acid 1-ethyl ester (*rac*-357)**



rac-**357**

β-Lactone (0.23 g, 1.44 mmol) in DMSO (5 mL (half solvent volume)) was used as described in the general procedure for azide ring opening to afford (2*R**, 3*S**)–***rac*-357** product (0.12 g, 0.60 mmol, 41%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 9.49 (1H, s, COOH), 4.29 (2H, dq, *J* 14.3, 7.2, $CH_3CH_2O_2C$), 4.21 (1H, d, *J* 6.1 , CHN_3), 3.05 (1H, app. dq, *J* 6.1, 7.1, $CHCH_3$), 1.35 (3H. t, *J* 7.2, $CH_3CH_2O_2C$), 1.31 (3H, d, *J* 7.1, $CHCH_3$). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

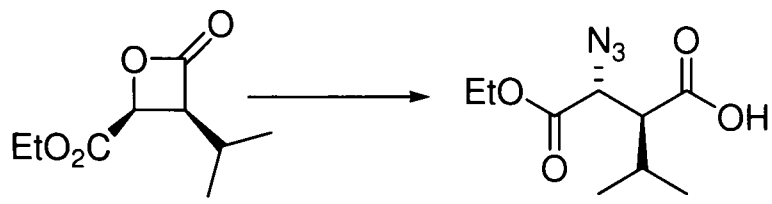
(2*R*, 3*S*)-2-Azido-3-ethyl-succinic acid 1-ethyl ester (358)



358

β-Lactone (0.20 g, 0.85 mmol) in DMSO (2 mL (half solvent volume)) was used as described to afford the (2*R*, 3*S*)-product **358** (0.19 g, 0.88 mmol, 74%) as a pale yellow oil in a >9:1 ratio of diastereomers; $[\alpha]^{22}_D$ +48.0 (*c* 1.38, $CHCl_3$); ν_{max}/cm^{-1}(film) 2978, 2941, 2111, 1737, 1719, 1266, 1207; δ_H (400 MHz, $CDCl_3$) 10.81 (1H, s, COOH), 4.28 (2H, dq, *J* 14.3, 7.2, $CH_3CH_2O_2C$), 4.11 (1H, d, *J* 7.0, CHN_3), 2.91-2.86 (1H, m, $CHCH_2CH_3$), 1.84-1.75 (1H, m, 1 × CH_2CH_3), 1.67-1.59 (1H, m, 1 × CH_2CH_3), 1.31 (3H, t, *J* 7.2, $CH_3CH_2O_2C$), 1.01 (3H, t, *J* 7.5, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 178.2 (C), 168.9 (C), 62.3 (CH), 62.2 (CH_2), 48.5 (CH), 21.6 (CH_2), 14.0 (CH), 11.6 (CH); m/z (CI (NH_3)) 233 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 233.1253 $C_8H_{17}N_4O_4$ requires : 233.1250.

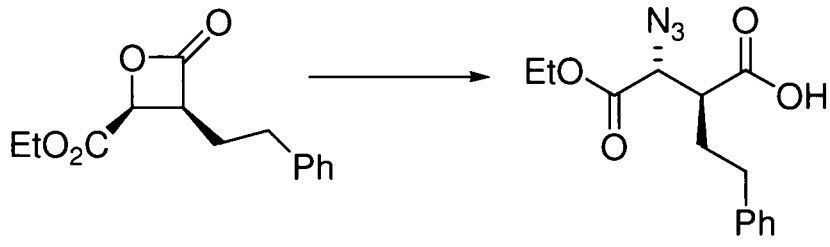
(2*R*, 3*S*)-2-Azido-3-isopropyl-succinic acid 1-ethyl ester (359)



359

β-Lactone (0.20 g, 1.2 mmol) in DMSO (2 mL (half solvent volume)) was used as described to afford the (2*R*, 3*S*)-product **359** (0.15 g, 0.66 mmol, 61%) as a pale yellow oil in a >9:1 ratio of diastereomers; $[\alpha]^{22}_{D}$ +29.0 (*c* 0.97, $CHCl_3$); ν_{max}/cm^{-1}(film) 2970, 2113, 1739, 1712, 1263, 1205; δ_H (400 MHz, $CDCl_3$) 10.85 (1H, s, COOH), 4.29-4.25 (2H, m, $CH_3CH_2O_2C$), 4.13 (1H, d, *J* 7.8, CHN_3), 2.83-2.80 (1H, m, $CHCH(CH_3)_2$), 2.08-2.00 (1H, m, $CH(CH_3)_2$), 1.31 (3H, t, *J* 7.1, $CH_3CH_2O_2C$), 1.11-0.97 (6H, m, $CH(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 177.5 (C), 169.0 (C), 62.3 (CH_2), 61.6 (CH), 53.0 (CH), 27.6 (CH), 20.7 (CH), 19.1 (CH), 14.0 (CH); m/z (CI (NH_3)) 247 (100%) $[M+NH_4]^+$, found : $[M+NH_4]^+$, 247.1404 $C_9H_{19}N_4O_4$ requires : 247.1406.

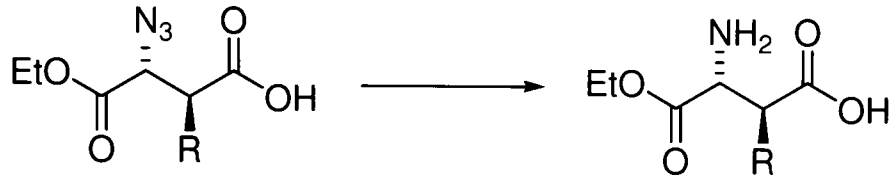
(2*R*, 3*S*)-2-Azido-3-phenethyl-succinic acid 1-ethyl ester (360)



360

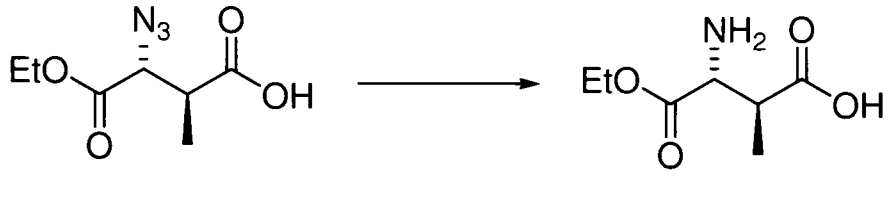
β-Lactone (0.21 g, 0.85 mmol) in DMSO (2 mL (half solvent volume)) was used as described to afford the (2*R*, 3*S*) product **360** (0.14 g, 0.48 mmol, 66%) as a pale yellow oil in a 9:1 ratio of diastereomers; $[\alpha]^{22}_{D}$ +22.1 (*c* 0.91, $CHCl_3$); ν_{max}/cm^{-1}(film) 2983, 2113, 1742, 1712, 1265, 1211; δ_H (400 MHz, $CDCl_3$) 10.85 (1H, s, COOH), 7.36-7.22 (5H, m, ArH), 4.30 (2H, q, *J* 7.0, $CH_3CH_2O_2C$), 4.21 (1H, d, *J* 6.3 , CHN_3), 3.07-3.02 (1H, m, $CHCH_2CH_2Ph$), 2.85-2.69 (2H, m, CH_2CH_2Ph), 2.22-2.13 (1H, m, 1 × CH_2CH_2Ph), 1.97-1.90 (1H, m, 1 × CH_2CH_2Ph), 1.33 (3H, t, *J* 7.0, $CH_3CH_2O_2C$); δ_C (100 MHz, $CDCl_3$) 178.2 (C), 168.7 (C), 140.5 (C), 128.6 (CH), 128.4 (CH), 126.4 (CH), 62.6 (CH), 62.4 (CH_2), 46.4 (CH), 33.3 (CH_2), 29.8 (CH_2), 14.0 (CH); m/z (CI (NH_3)) 220 (100%), 309 (90%, $[M+NH_4]^+$), found : $[M+NH_4]^+$, 309.1567 $C_{14}H_{21}N_4O_4$ requires : 309.1563.

3.2.1.5 General Azide Reduction Procedure



To a solution of azido acid (1 equiv.) in MeOH (10 mL) was added Pd/C (10% by mass). The reaction was stirred under a positive pressure of hydrogen, using a H_2 balloon, for 3 h then filtered through Celite® and washed with MeOH (25 mL). The solvent was removed *in vacuo* to afford the β-amino acid.

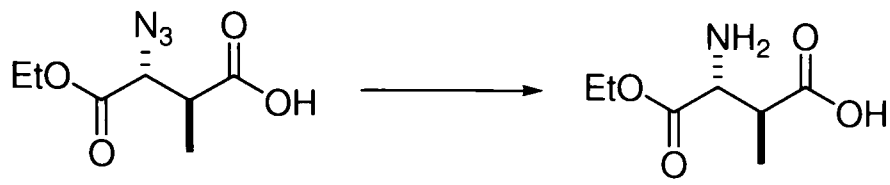
(2*R*, 3*S*)-2-Amino-3-methyl-succinic acid 1-ethyl ester (361)



361

Azido acid (0.12 g, 0.59 mmol) was used as described to afford the (2*R*, 3*S*) product **361** (0.10 g, 0.57 mmol, 99%) as a white solid in a >9:1 ratio of diastereomers; $[\alpha]^{22}_D$ -8.5 (*c* 3.28, MeOH); ν_{max}/cm^{-1}(neat) 3390, 2981, 2940, 1739, 1586; δ_H (400 MHz, D_2O) 4.30-4.16 (2H, m, $CH_3CH_2O_2C$), 4.09 (1H, d, *J* 4.3, $CHNH_2$), 3.03 (1H, dq, *J* 4.3, 7.6, $CHCH_3$), 1.22 (3H, d, *J* 7.6, $CHCH_3$); 1.21 (3H. t, *J* 7.1, $CH_3CH_2O_2C$); δ_C (100 MHz, D_2O/20 mol% MeOH) 180.4 (C), 171.9 (C), 64.0 (CH), 56.1 (CH_2), 42.3 (CH), 14.5 (CH), 13.8 (CH); m/z (CI (NH_3)) 176 (100%) $[M+H]^+$, found : $[M+H]^+$, 176.0928 $C_7H_{14}NO_4$ requires : 176.0923.

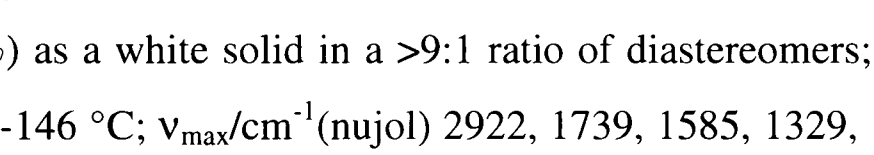
(2*R, 3*S**)-2-Amino-3-methyl-succinic acid 1-ethyl ester (*rac*-361)**



rac-**361**

Azido acid (0.12 g, 0.59 mmol) was used as described in the general procedure for azide reduction to afford (2*R**, 3*S**)-***rac*-361** (0.10 g, 0.57 mmol, 97%) as a pale yellow oil; δ_H (400 MHz, D_2O) 4.21 (2H, dq, *J* 14.2, 7.1, $CH_3CH_2O_2C$), 4.09 (1H, d, *J* 4.3, $CHNH_2$), 3.03 (1H, dq, *J* 4.3, 7.6, $CHCH_3$), 1.22 (3H, d, *J* 7.6, $CHCH_3$); 1.21 (3H, t, *J* 7.1, $CH_3CH_2O_2C$). ^{1}H NMR data corresponds to that of the enantiomerically enriched compound.

(2*R*, 3*S*)-2-Amino-3-ethyl-succinic acid 1-ethyl ester (362)



362

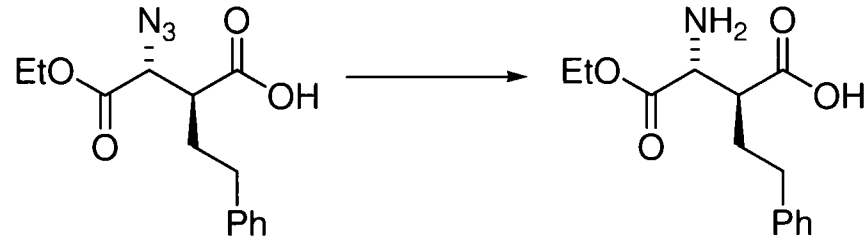
Azido acid (0.12 g, 0.55 mmol) was used as to afford the (2*R*, 3*S*) product **362** (0.12 g, 0.63 mmol, >99%) as a white solid in a >9:1 ratio of diastereomers; $[\alpha]^{22}_D$ +4.1 (*c* 0.99, MeOH); m.p. 144-146 °C; ν_{max}/cm^{-1}(nujol) 2922, 1739, 1585, 1329, 1197; δ_H (400 MHz, D_2O) 4.19-4.09 (2H, m, $CH_3CH_2O_2C$), 4.05 (1H, d, *J* 4.2, $CHNH_2$), 2.71 (1H, dt, *J* 4.2, 7.7, $CHCH_2CH_3$), 1.67-1.56 (1H, m, 1 × CH_2CH_3), 1.52-1.43 (1H, m, 1 × CH_2CH_3), 1.13 (3H. t, *J* 7.2, $CH_3CH_2O_2C$), 0.85 (3H, t, *J* 7.4, CH_2CH_3); δ_C (100 MHz, D_2O/20 mol% MeOH) 179.3 (C), 170.1 (C), 63.7 (CH_2), 53.6 (CH), 48.5 (CH), 22.4 (CH_2), 13.3 (CH), 11.4 (CH); m/z (CI (NH_3)) 190 (100%) $[M+H]^+$, found : $[M+H]^+$, 190.1081 $C_8H_{16}NO_4$ requires : 190.1079.

(2*R*, 3*S*)-2-Amino-3-isopropyl-succinic acid 1-ethyl ester (363)

363

Azido acid (0.13 g, 0.57 mmol) was used as described to afford the (2*R*, 3*S*) product **363** (0.12 g, 0.59 mmol, >99%) as a white solid in a >9:1 ratio of diastereomers; $[\alpha]^{22}_{D}$ +10.7 (*c* 0.38, MeOH); m.p. 165-166 °C; ν_{max}/cm^{-1}(nujol) 2922, 2361, 2342, 1751; δ_H (400 MHz, D_2O) 4.25-4.11 (2H, m, $CH_3CH_2O_2C$), 4.22 (1H, d, *J* 3.4, $CHNH_2$), 2.42 (1H, dd, *J* 10.5, 3.4, $CHCH(CH_3)_2$), 1.72 (1H, dsept, *J* 10.5, 6.6, $CH(CH_3)_2$), 1.16 (3H, t, *J* 7.2, $CH_3CH_2O_2C$), 0.91 (3H, d, *J* 6.6, 1 × $CH(CH_3)_2$), 0.88 (3H, d, *J* 6.6, 1 × $CH(CH_3)_2$); δ_C (100 MHz, D_2O/20 mol% MeOH) 179.3 (C), 170.7 (C), 64.3 (CH_2), 54.9 (CH), 52.8 (CH), 27.6 (CH), 21.1 (CH), 19.9 (CH), 13.8 (CH); m/z (CI (NH_3)) 204 (100%) $[M+H]^+$, found : $[M+H]^+$, 204.1237 $C_9H_{18}NO_4$ requires : 204.1236.

(2*R*, 3*S*)-2-Amino-3-phenethyl-succinic acid 1-ethyl ester (364)

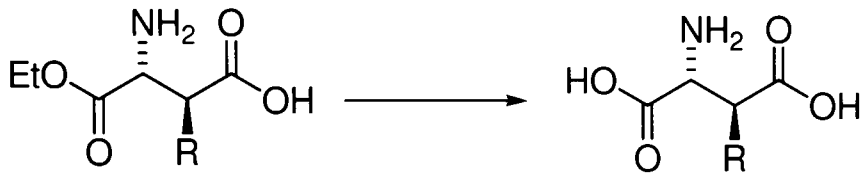


364

Azido acid (0.12 g, 0.46 mmol) was used as described to afford the (2*R*, 3*S*) product **364** (0.11 g, 0.42 mmol, 92%) as a white solid in a >9:1 ratio of diastereomers; $[\alpha]^{22}_{D}$ -24.1 (*c* 0.42, MeOH); m.p. 166-168 °C; ν_{max}/cm^{-1}(nujol) 2923, 2853, 1738, 1574, 1190, 1094, 1018; δ_H (400 MHz, D_2O) 7.32-7.20 (5H, m, ArH), 4.20 (2H, dq, *J* 14.3, 7.2, $CH_3CH_2O_2C$), 4.12 (1H, d, *J* 4.3 , $CHNH_2$), 2.91-2.86 (1H, m, $CHCH_2CH_2Ph$), 2.66 (2H, t, *J* 7.7, CH_2CH_2Ph), 2.01-1.92 (1H, m, 1 × CH_2CH_2Ph), 1.87-1.78 (1H, m, 1 × CH_2CH_2Ph), 1.17 (3H, t, *J* 7.2, $CH_3CH_2O_2C$); δ_C (100 MHz, D_2O/20 mol% MeOH) 178.5 (C), 170.1 (C), 141.7 (C), 129.4 (CH), 129.2 (CH), 127.0 (CH), 64.3 (CH_2), 54.3 (CH), 46.5 (CH), 33.2 (CH_2), 30.9 (CH_2), 13.8 (CH); m/z (CI (NH_3)) 266 (100%) $[M+H]^+$, found : $[M+H]^+$, 266.1393 $C_{14}H_{20}NO_4$ requires : 266.1392.

3.2.1.6 Ester Hydrolysis Procedure

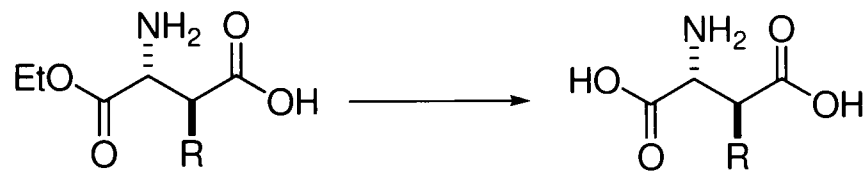
(2*R*, 3*S*)-2-Amino-3-methyl-succinic acid (1, R=Me)



1 (R=Me)

To a solution of amino acid ester (0.85 g, 4.9 mmol) in water (100 mL) was added 1 M NaOH (15 mL). The reaction was stirred at rt for 24 h after which time the solution was acidified to pH 0 with 1 M HCl. The solvent was removed *in vacuo* and the resulting white solid freed from the HCl salt using a column of Dowex® 50WX8-100 ion exchange resin to afford (2*S*, 3*R*)-**1** (R=Me) (0.48 g , 3.3 mmol, 69%) as an off-white solid in a >9:1 ratio of diastereomers; $[\alpha]^{22}_{D}$ -23.5 (*c* 2.73, 5 M HCl); literature value for 2-Amino-3-methyl-succinic acid (2S, 3R) $[\alpha]^{21}_{D}$ +34.3 (*c* 2.05, 5 M HCl);[34] ν_{max}/cm^{-1}(nujol) 3429-2854, 2353, 2248, 1588, 1414, 1348; δ_H (400 MHz, D_2O) 3.65 (1H, d, *J* 5.3, C*H*NH_2), 2.87 (1H, dq, *J* 5.3, 7.5 C*H*CH_3)), 1.26 (3H, d, *J* 7.5, CHC*H*$_3$); δ_C (100 MHz, D_2O/20 mol% MeOH) 181.4 (C), 174.3 (C), 58.0 (CH), 42.1 (CH), 15.6 (CH); m/z (ES^-) $[M-H]^-$, found : $[M-H]^-$, 146.0446 $C_5H_8NO_4$ requires : 146.0453.

(2*R, 3**S*)-2-Amino-3-methyl-succinic acid (*rac*-1, R=Me)**

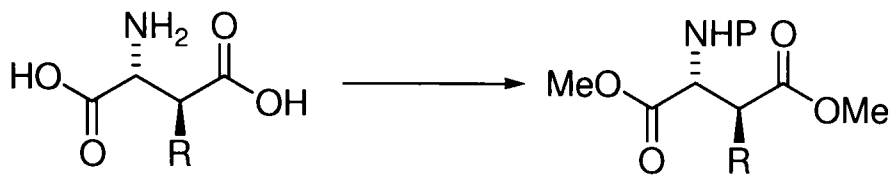


rac-**1** (R=Me)

Amino acid ester (0.11 g, 0.63 mmol) was used as described in the ester hydrolysis procedure to afford (2*R**, 3*S**)-***rac*-1** (R=Me) (60 mg, 0.41 mmol, 65%) as an off-white solid; δ_H (400 MHz, D_2O) 7.00 (1H, br s, COOH), 3.68 (1H, d, *J* 5.3, C*H*NH_2), 2.88 (1H, dq, *J* 5.3, 7.5 C*H*CH_3), 1.24 (3H, d, *J* 7.5, CHC*H*$_3$). ^{1}H NMR data corresponds to that of the enantioenriched compound.

3.2.1.7 Determination of Enantiomeric Excess for 1 (R=Me)

(2*R*, 3*S*)-Dimethyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methylsuccinate (98, R=Me)



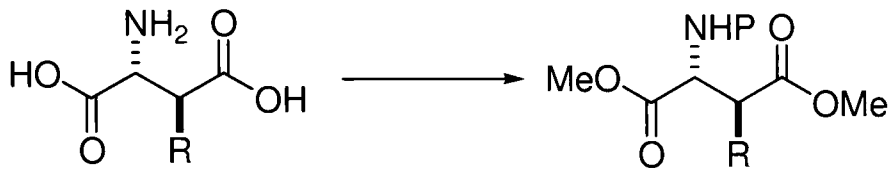
98 (R=Me)

(Where P= Fmoc)

To a solution of amino acid (20 mg, 0.14 mmol) in water (0.5 mL) was added $NaHCO_3$ (23 mg, 0.27 mmol) with stirring. The resulting solution was cooled to 5 °C and FmocCl (50 mg, 0.20 mmol) is added slowly as a solution in dioxane (0.5 mL). The mixture was then stirred at 0 °C for 1 h and allowed to warm to rt overnight. Water (2 mL) was added to the solution and the aqueous layer extracted with EtOAc (2 × 10 mL). The organic layer was back extracted with saturated aqueous $NaHCO_3$ (2 × 10 mL) and the combined aqueous layers acidified to pH 0 with 1 M HCl. The acidic aqueous layer was extracted with EtOAc (3 × 15 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the crude Fmoc protected amino acid which was taken directly onto the next step. Thionyl chloride (16 μL, 0.22 mmol) was added to a solution of the *N*-protected amino acid (40 mg, 0.11 mmol) in MeOH (4 mL) at 0 °C. The reaction was allowed to stir overnight after which time the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (2:1 petrol:EtOAc) to afford *N*-Fmoc-dimethyl ester **98** (R=Me) (13 mg, 0.03 mmol, 30%) as a colourless oil; $[\alpha]^{22}_D$ -7.34 (*c* 2.73, $CHCl_3$); >95% *e.e.* t_R (major)= 68.91 min (determined by HPLC analysis with comparison to an authentic racemic sample (column: OJ-H, flow rate: 0.8, gradient: 98:2 injection vol.: 2 μL); ν_{max}/cm^{-1}(nujol) 1734, 1708, 1509, 1450, 1326, 1269, 1215, 1091, 1058, 760, 739; δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 7.5, ArH), 7.67 (2H, t, *J* 7.5, ArH), 7.44 (2H, t, *J* 7.5, ArH), 7.36 (2H, t, *J* 7.5, ArH), 5.89 (1H, d, *J* 9.6, NH), 4.68 (1H, dd, *J* 9.6, 3.8, C*H*NHP), 4.53-4.42 (2H, m, CH_2CHAr), 4.31 (1H, t, *J* 7.2, CH_2CHAr), 3.79 (3H, s, CH_3O_2C), 3.75 (3H, s, CH_3O_2C), 3.35 (1H, qd, *J* 7.4, 3.8, C*H*CH_3), 1.33 (3H, d, *J* 7.4, CHCH_3); δ_C (100 MHz, $CDCl_3$) 174.4 (C), 171.3 (C), 156.7 (C), 143.7 (C), 141.3

(C), 127.8 (CH), 127.1 (CH), 125.2 (CH) 120.0 (CH), 67.3 (CH_2), 55.9 (CH), 52.7 (CH), 52.2 (CH), 47.2 (CH), 41.3 (CH), 13.8 (CH); m/z (CI, NH_3) 176 (84%), 398 (20%, $[M+H]^+$), 420 (100%), 573 (93%), found : $[M+H]^+$, 398.1602 $C_{22}H_{24}NO_6$ requires : 398.1604.

(2*R, 3*S**)-Dimethyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methylsuccinate (*rac*-98, R=Me)**



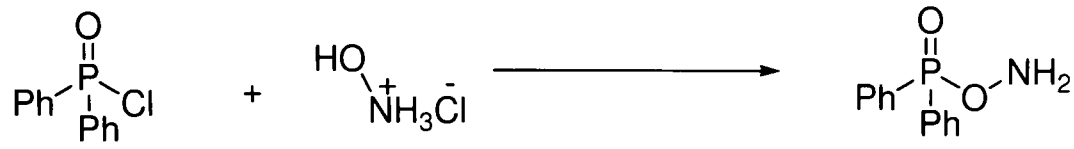
rac-**98** (R=Me)

(Where P= Fmoc)

Amino acid (0.54 g, 1.5 mmol) was used as described in the enantiomeric excess determination for **1** (R=Me) to afford (2*R**, 3*S**)-***rac*-98** (R=Me) (0.30 g, 0.76 mmol, 51%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 7.5, ArH), 7.65 (2H, t, *J* 7.5, ArH), 7.43 (2H, t, *J* 7.5, ArH), 7.35 (2H, t, *J* 7.5, ArH), 5.79 (1H, d, *J* 9.6, NH), 4.63 (1H, dd, *J* 9.6, 3.8, C*H*NHP), 4.52-4.40 (2H, m, CH_2CHAr), 4.30 (1H, t, *J* 7.2, CH_2CHAr), 3.80 (3H, s, CH_3O_2C), 3.76 (3H, s, CH_3O_2C), 3.35 (1H, qd, *J* 7.4, 3.8, C*H*CH_3), 1.31 (3H, d, *J* 7.4, CHCH_3). ^{1}H NMR data corresponds to that of the enantioenriched compound.

3.2.2 Experimental for the Organocatalytic Aziridination of Enones

Preparation of $DppONH_2$ (344)[148]

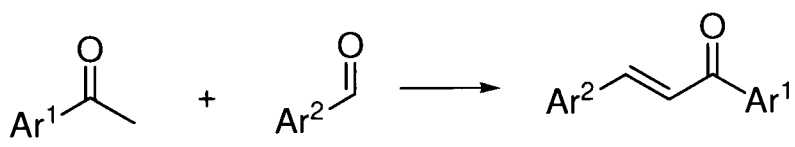


344

Aqueous NaOH (1.94 g in 7.0 mL) was added to a stirred solution of hydroxylamine hydrochloride (3.96 g, 57.0 mmol) in water (8.5 mL). Diphenylphosphinic chloride (5.00 g, 21.1 mmol) in dioxane (25 mL) was added in one portion with vigorous stirring. Stirring continued for 4 min as copious precipitation ensued. Water (30 mL) was added and the slurry was filtered and washed with cold water (30 mL). The white solid was dried under vacuum for 3 h then purified by stirring as a slurry with aqueous NaOH (50 mL, 0.25 M) at 0 °C for 30 min. The product was filtered and washed with cold water (30 mL), then dried under vacuum in a desiccator to give the product **344** (0.85 g, 3.7 mmol, 17%) as a white solid; m.p. >135 °C gradual decomp. (lit., >130 °C gradual decomp.); δ_H (400 MHz, $CDCl_3$) 7.90-7.85 (4H, m, ArH), 7.60-7.48 (6H, m, ArH), 6.0 (2H, br s, NH_2); m/z (FAB^+) 234 (100%), $[M+H]^+$. Data matches previously reported values.

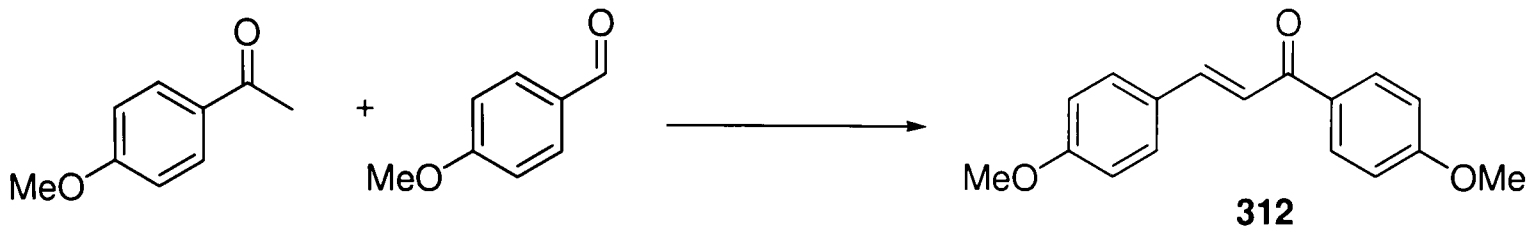
3.2.2.1. α,β-Unsaturated Ketone Synthesis

General Procedure 1 for α,β-Unsaturated Ketone Synthesis



Ketone (1 equiv.) in EtOH (half solvent volume) was treated with $LiOH.H_2O$ (10 mol%) and stirred for 10 min at rt. Aldehyde (1 equiv.) in EtOH (half solvent volume) was added and the mixture was allowed to stir for 3 h. EtOH was removed *in vacuo* and the reaction was diluted with water (10 mL), neutralised with aqueous HCl (2%), extracted with EtOAc (3 × 10 mL), washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was crystallised from EtOH.

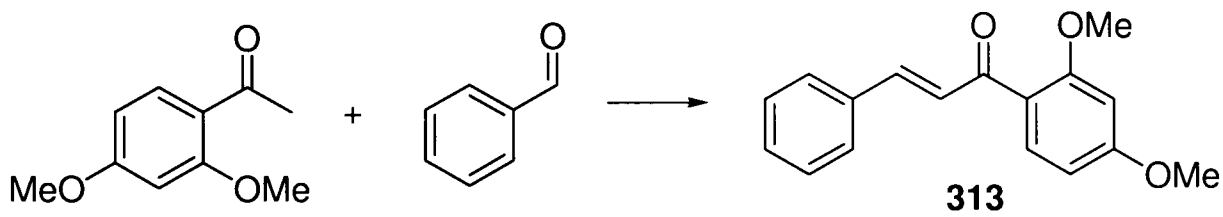
4,4'-Dimethoxychalcone (312)[131]



312

4-Methoxyacetophenone (150 mg, 1.0 mmol) in EtOH (0.5 mL) was treated according to the general procedure 1 for α,β-unsaturated ketone synthesis to give enone **312** (100 mg, 0.36 mmol, 36%) as a yellow solid; m.p. 100-101 °C (lit., 100-101 °C); δ_H (400 MHz, $CDCl_3$) 8.05 (2H, d, *J* 8.8, ArH), 7.80 (1H, d, *J* 15.6, CH), 7.62 (2H, d, *J* 8.8, ArH), 7.45 (1H, d, *J* 15.6, CH), 7.00 (2H, d, *J* 8.8, ArH), 6.96 (2H, d, *J* 8.8, ArH), 3.91 (3H, s, OCH_3), 3.88 (3H, s, OCH_3); m/z (CI (NH_3)) 269 (100%) $[M+H]^+$, found : $[M+H]^+$, 269.1184 $C_{17}H_{17}O_3$ requires : 269.1178. Data matches previously reported values.

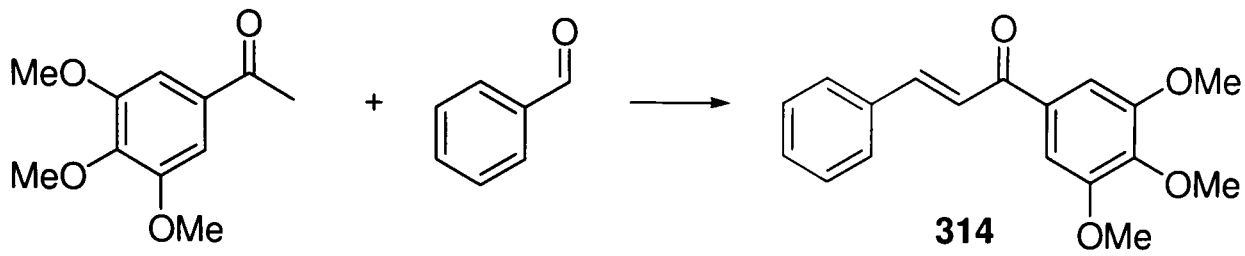
2',4'-Dimethoxychalcone (313)



313

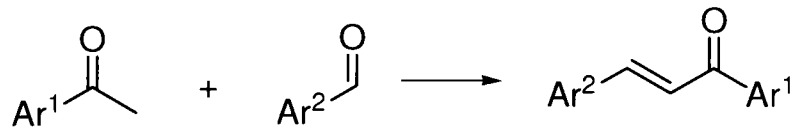
2',4'-Dimethoxyacetophenone (1.8 g, 10 mmol) in EtOH (5 mL) was treated according to the general procedure 1 for α,β-unsaturated ketone synthesis to give enone **313** (1.9 g, 7.1 mmol, 71%) as a yellow solid; m.p. 77-79 °C; ν_{max}/cm^{-1}(nujol) 2310, 1577, 1252, 1024, 822; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 8.7, ArH), 7.71 (1H, d, *J* 15.8, CH), 7.64-7.62 (2H, m, ArH), 7.55 (1H, d, *J* 15.8, CH), 7.45-7.40 (3H, m, ArH), 6.59 (1H, dd, *J* 8.7, 2.2, ArH), 6.53 (1H, d, *J* 2.2, ArH), 3.94 (3H, s, OCH_3), 3.90 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 190.6 (C), 164.2 (C), 160.4 (C), 142.0 (CH), 135.5 (C), 132.9 (CH), 130.0 (CH), 128.8 (CH), 128.3 (CH), 127.2 (CH), 122.2 (C), 105.2 (CH), 98.7 (CH), 55.8 (CH), 55.6 (CH); m/z (CI (NH_3)) 269 (100%) $[M+H]^+$, found : $[M+H]^+$, 269.1183 $C_{17}H_{17}O_3$ requires : 269.1178.

3',4',5'-Trimethoxychalcone (314)



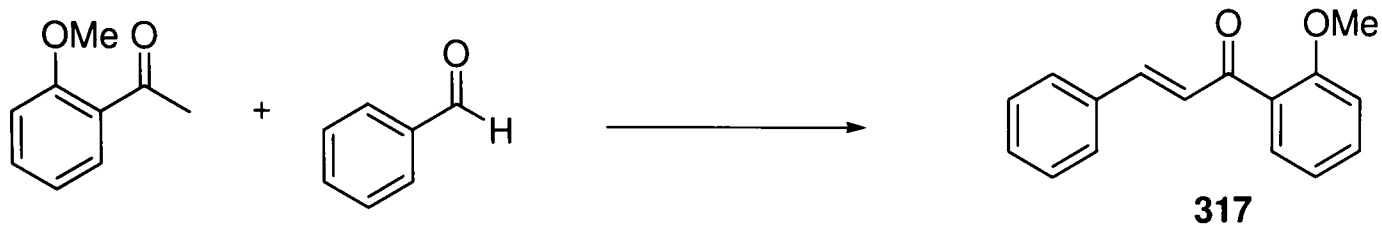
3',4',5'-Trimethoxyacetophenone (1.0 g, 4.8 mmol) in EtOH (6 mL) was treated according to the general procedure 1 for α,β-unsaturated ketone synthesis to give enone **314** (1.1 g, 3.7 mmol, 73%) as a yellow solid; m.p. 77-78 °C (lit., 79-80 °C); ν_{max}/cm^{-1}(nujol) 1655, 1574, 1337, 1122, 992; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, d, *J* 15.7, CH), 7.70-7.67 (2H, m, ArH), 7.51 (1H, d, *J* 15.7, CH), 7.50-7.45 (3H, m, ArH), 7.30-7.29 (2H, m, ArH), 3.98 (6H, s, OCH_3), 3.97 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 189.3 (C), 153.18 (C), 144.8 (CH), 142.5 (C), 134.9 (C), 133.5 (C), 130.6 (CH), 129.0 (CH), 128.5 (CH), 121.8 (CH), 106.1 (CH), 61.0 (CH), 56.4 (CH); m/z (CI (NH_3)) 299 (100%) $[M+H]^+$, found : $[M+H]^+$, 299.1289 $C_{18}H_{19}O_4$ requires : 299.1283.

General Procedure 2 for α,β-Unsaturated Ketone Synthesis



Ketone (1 equiv.) in EtOH (10 mL) was added slowly to a solution of KOH (30 mL 10% aqueous) at 0 °C with stirring for 15 min. Aldehyde (1 equiv.) was then added and the mixture was allowed to stir for a further 15 min at 0 °C. The reaction was stirred for 4 h then diluted with water (10 mL), neutralised with aqueous HCl (10%), extracted with EtOAc (3 × 20 mL), washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*. Purification by column chromatography gave the desired product.

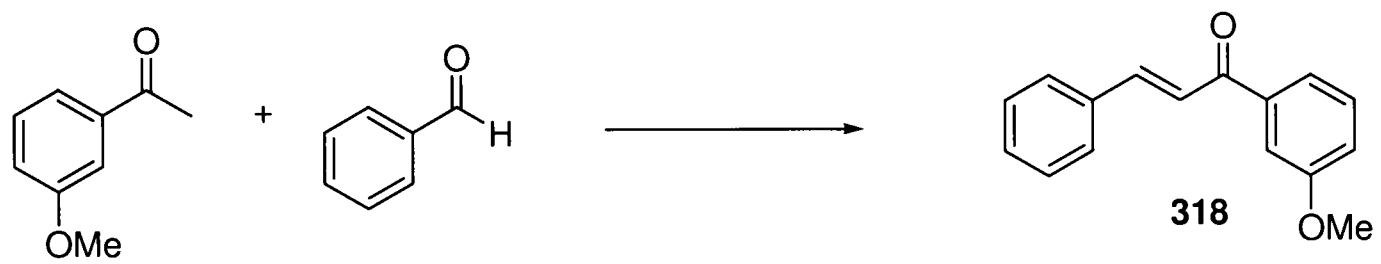
2'-Methoxychalcone (317)[126]



317

2-Methoxyacetophenone (1.4 mL, 10 mmol) in EtOH (10 mL) was treated according to the general procedure 2 for α,β-unsaturated ketone synthesis. Purification by column chromatography (19:1 petrol:EtOAc) gave enone **317** (1.3 g, 5.3 mmol, 53%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.66-7.02 (11H, m, 9 × ArH, 1 × CHCO, 1 × CHAr), (3H, s, OCH_3); m/z (CI (NH_3)) 239 (100%) $[M+H]^+$, found : $[M+H]^+$, 239.1076 $C_{16}H_{15}O_2$ requires : 239.1072. Data matches previously reported values.

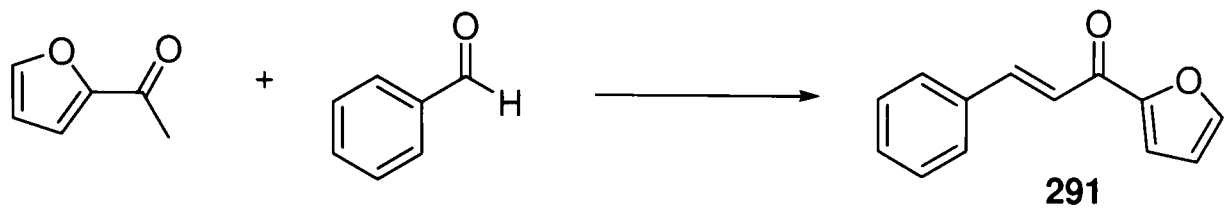
3'-Methoxychalcone (318)[149]



318

3-Methoxyacetophenone (1.4 mL, 10 mmol) in EtOH (10 mL) was treated according to the general procedure 2 for α,β-unsaturated ketone synthesis. Purification by column chromatography (19:1 petrol:EtOAc) gave enone **318** (1.3 g, 5.4 mmol, 54%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* 15.7, CH), 7.68-7.66 (2H, m, ArH), 7.64-7.62 (1H, m, ArH), 7.58-7.56 (1H, m, ArH), 7.54 (1H, d, *J* 15.7, CH), 7.46-7.42 (4H, m, ArH), 7.17-7.15 (1H, m, ArH), 3.91 (3H, s, OCH_3); m/z (CI (NH_3)) 239 (100%) $[M+H]^+$, found : $[M+H]^+$, 239.1079 $C_{16}H_{15}O_2$ requires : 239.1072. Data matches previously reported values.

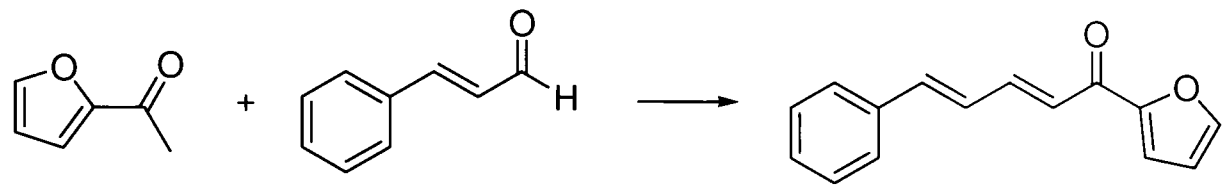
(*E*)-1-(Furan-2-yl)-3-phenylprop-2-en-1-one (291)[150]



291

2-Acetyl furan (0.54 g, 4.9 mmol) in EtOH (5 mL) was added to aqueous KOH (15 mL 10%) and treated according to the general procedure 2 for α,β-unsaturated ketone synthesis, with stirring for 20 h. Purification by column chromatography (100:6 petrol:EtOAc) gave enone **291** (0.86 g, 4.3 mmol, 88%) as a colourless solid; m.p. 84-86 °C (lit., 81-83 °C);δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 15.8 CH=CH), 7.63-7.61 (3H, m, ArH), 7.45 (1H, d, *J* 15.8, CH=CH), 7.40-7.38 (3H, m, ArH), 7.34-7.33 (1H, m, ArH), 6.57 (1H, m, ArH); m/z (CI (NH_3)) 199 (100%) $[M+H]^+$, found : $[M+H]^+$, 199.0762 $C_{13}H_{11}O_2$ requires : 199.0759. Data matches previously reported values.

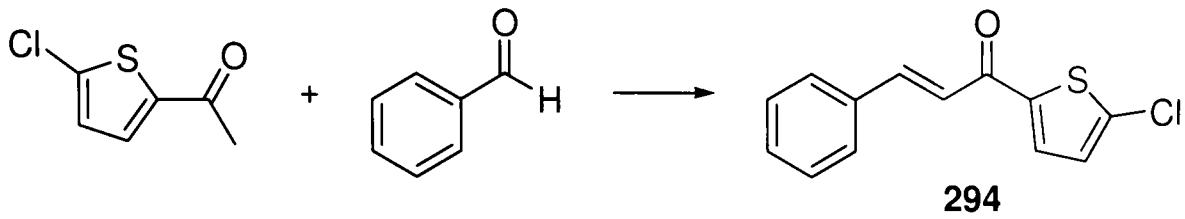
(2*E*, 4*E*)-1-(Furan-2-yl)-5-phenylpenta-2,4-dien-1-one (292)



292

2-Acetyl furan (0.5 g, 4.5 mmol) in EtOH (5 mL) was added to aqueous KOH (15 mL 10%) and treated with cinnamaldehyde (0.57 mL, 4.5 mmol) according to the general procedure 2 for α,β-unsaturated ketone synthesis, with stirring for 20 h. Purification by column chromatography (100:6 petrol:EtOAc) gave enone **292** (0.53 g, 2.4 mmol, 52%) as a yellow solid; m.p. 103-105 °C; ν_{max}/cm^{-1}(solid) 1655, 1582, 1465, 1002, 760; δ_H (400 MHz, $CDCl_3$) 7.66-7.59 (2H, m, 1 × CH=CH and ArH), 7.45-7.44 (2H, m, ArH), 7.35-7.27 (4H, m, ArH), 7.00-6.94 (3H, m, 3 × CH=CH), 6.52 (1H, dd, *J* 3.5, 1.7, ArH); δ_C (100 MHz, $CDCl_3$) 178.0 (C), 153.7 (C), 146.5 (CH), 143.9 (CH), 142.1 (CH), 136.1 (C), 129.3 (CH), 128.9 (CH), 127.4 (CH), 126.8 (CH), 124.7 (CH), 117.4 (CH), 112.5 (CH); m/z (CI (NH_3)) 225 (100%) $[M+H]^+$, found : $[M+H]^+$, 225.0927 $C_{15}H_{13}O_2$ requires : 225.0916.

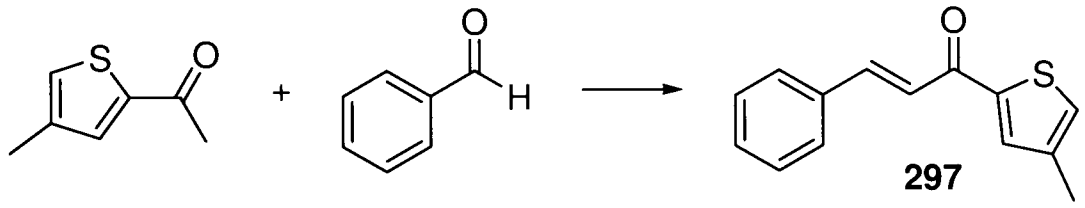
(*E*)-1-(5-Chlorothiophen-2-yl)-3-phenylprop-2-en-1-one (294)



294

2-Acetyl-5-chlorothiophene (0.5 g, 3.1 mmol) in EtOH (5 mL) was added to aqueous KOH (15 mL 10%) and treated with benzaldehyde (0.32 mL, 3.1 mmol) according to the general procedure 2 for α,β-unsaturated ketone synthesis, with stirring for 23 h. Purification by column chromatography (100:3 petrol:EtOAc) gave enone **294** (0.35 g, 1.4 mmol, 45%) as a white solid; m.p. 94-96 °C; ν_{max}/cm^{-1}(solid) 1645, 1592, 1576, 1424, 1233; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 15.6, CH=CH), 7.61 (1H, d, *J* 4.1, ArH), 7.58-7.56 (2H, m, ArH), 7.38-7.37 (3H, m, ArH), 7.30 (1H, d, *J* 15.6, CH=CH), 6.95 (1H, d, *J* 4.1, ArH); δ_C (100 MHz, $CDCl_3$) 180.9 (C), 144.4 (CH), 144.3 (C), 139.7 (C), 134.4 (C), 131.4 (CH), 130.8 (CH), 129.0 (CH), 128.6 (CH), 127.8 (CH), 120.2 (CH); m/z (CI (NH_3)) 249 (100%) $[M+H]^+$, found : $[M+H]^+$, 249.0151 $C_{13}H_{10}OSCl$ requires : 249.0141.

(*E*)-1-(4-Methylthiophen-2-yl)-3-phenylprop-2-en-1-one (297)

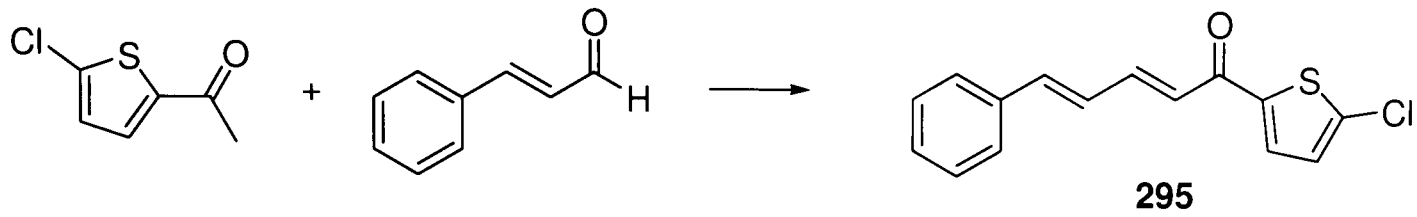


297

2-Acetyl-4-methylthiophene (0.5 mL, 4.4 mmol) in EtOH (5 mL) was added to aqueous KOH (15 mL 10%) and treated with benzaldehyde (0.45 mL, 4.4 mmol) according to the general procedure 2 for α,β-unsaturated ketone synthesis, with stirring for 23 h. Purification by column chromatography (100:2.5 petrol:EtOAc) gave enone **297** (0.72 g, 3.2 mmol, 72%) as an off-white solid; m.p. 96-98 °C; ν_{max}/cm^{-1}(solid) 1645, 1599, 1572, 1424, 1230; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, d, *J* 15.6, CH=CH), 7.69 (1H, br s, ArH), 7.66-7.63 (2H, m, ArH), 7.43-7.41 (3H, m, ArH), 7.42 (1H, d, *J* 15.6, CH=CH), 7.27 (1H, br s, ArH), 2.33 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 182.0 (C), 145.0 (C), 143.8 (CH), 139.1 (C), 134.8 (C), 134.0 (CH), 130.6 (CH), 130.0 (CH), 129.0 (CH), 128.5

(CH), 121.6 (CH), 15.7 (CH); m/z (CI (NH_3)) 229 (100%) $[M+H]^+$, found : $[M+H]^+$, 229.0685 $C_{14}H_{13}OS$ requires : 229.0687.

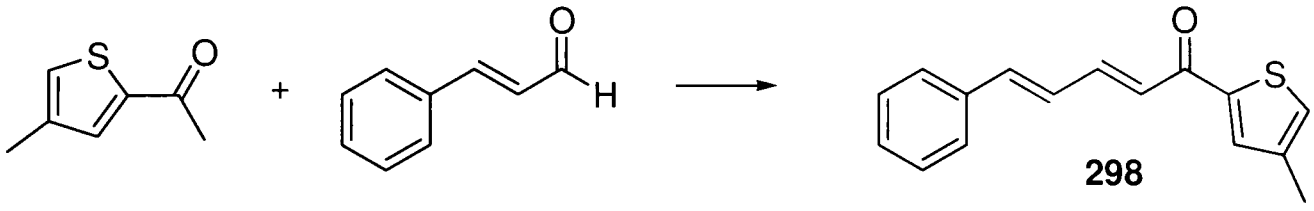
(2*E*, 4*E*)-1-(5-Chlorothiophen-2-yl)-5-phenylpenta-2,4-dien-1-one (295)



295

2-Acetyl-5-chlorothiophene (0.5 g, 3.1 mmol) in EtOH (5 mL) was added to KOH (15 mL 10% aqueous) and treated with cinnamaldehyde (0.39 mL, 3.1 mmol) according to the general procedure 2 for α,β-unsaturated ketone synthesis, with stirring for 23 h. Recrystallisation from EtOAc gave enone **295** (0.30 g, 1.1 mmol, 36%) as a yellow solid; m.p. 153-155 °C; ν_{max}/cm^{-1}(solid) 1634, 1572, 1423, 1254, 1012; δ_H (400 MHz, $CDCl_3$) 7.67-7.61 (1H, m, CH=CH), 7.58 (1H, d, *J* 4.0, ArH), 7.53-7.52 (2H, m, ArH), 7.42-7.34 (3H, m, ArH), 7.04-7.01 (3H, m, 2 × CH=CH and 1 × ArH), 6.92 (1H, d, *J* 14.8, CH=CH); δ_C (100 MHz, $CDCl_3$) 181.1 (C), 144.5 (CH), 144.4 (C), 142.6 (CH), 139.5 (C), 136.0 (C), 130.9 (CH), 129.4 (CH), 128.9 (CH), 127.7 (CH), 127.4 (CH), 126.5 (CH), 123.7 (CH); m/z (CI (NH_3)) 275 (100%) $[M+H]^+$, found : $[M+H]^+$, 275.0306 $C_{15}H_{12}OSCl$ requires : 275.0297.

(2*E*, 4*E*)-1-(4-Methylthiophen-2-yl)-5-phenylpenta-2,4-dien-1-one (298)

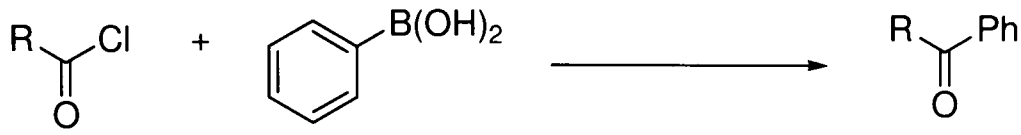


298

2-Acetyl-4-methylthiophene (0.5 mL, 4.4 mmol) in EtOH (5 mL) was added to KOH (15 mL 10% aqueous) and treated with cinnamaldehyde (0.55 mL, 4.4 mmol) according to the general procedure 2 for α,β-unsaturated ketone synthesis, with stirring for 23 h. Recrystallisation from EtOAc gave enone **298** (0.65 g, 2.6 mmol, 58%) as a yellow solid; m.p. 115-117 °C; ν_{max}/cm^{-1}(solid) 1638, 1576, 1424, 1351, 1137; δ_H (400 MHz, $CDCl_3$) 7.65-7.58 (2H, m, 1 × ArH and 1 × CH=CH), 7.50-7.48 (2H, m, ArH), 7.40-7.33 (3H, m, ArH), 7.24 (1H, s, ArH), 7.00-6.96 (3H, m, 3 × CH=CH), 2.31 (3H, s, CH_3); δ_C (100

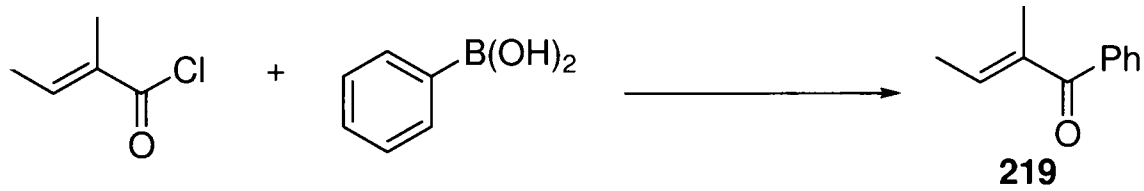
MHz, $CDCl_3$) 182.0 (C), 145.2 (C), 143.8 (CH), 141.9 (CH), 139.1 (C), 136.1 (C), 133.7 (CH), 129.7 (CH), 129.3 (CH), 128.9 (CH), 127.4 (CH), 126.7 (CH), 125.1 (CH), 15.7 (CH); m/z (CI (NH_3)) 255 (100%) $[M+H]^+$, found : $[M+H]^+$, 255.0852 $C_{16}H_{15}OS$ requires : 255.0844.

General Procedure for 3 for α,β-Unsaturated Ketone Synthesis



To a mixture of phenylboronic acid (1.2 equiv.), $(Ph_3P)_2PdCl_2$ (0.02 equiv.) and $K_3PO_4.H_2O$ (1.2 equiv.) in toluene (10 mL) was added acid chloride (1 equiv.). The reaction mixture was heated at 80 °C for 4 h. After removal of the insolubles by filtration, purification of the filtrate by silica gel column chromatography (hexane:EtOAc, 100:1) gave the desired product.

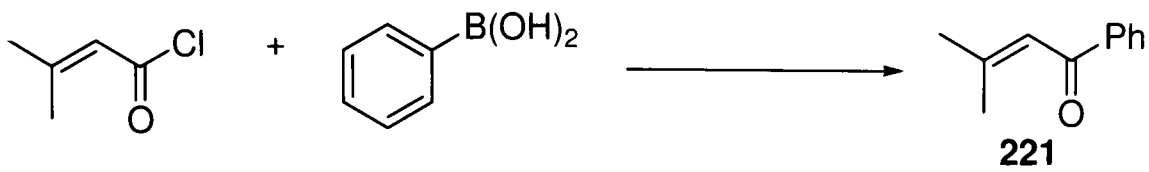
(*E*)-2-Methyl-1-phenylbut-2-en-1-one (219)[105]



219

Tigloyl chloride (0.3 g, 2.53 mmol) was treated according to the general procedure 3 for α,β-unsaturated ketone synthesis for NMM aziridination to give enone **219** (0.26 g, 1.6 mmol, 66%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.64-7.62 (2H, m, ArH), 7.53-7.49 (1H, ArH), 7.44-7.41 (2H, m, ArH), 6.42 (1H, qq, *J* 7.0, 1.0, C*H*CH_3), 1.99 (3H, br m, CH_3), 1.90 (3H, br dd, *J* 7.0, 1.0, CH_3); m/z (CI (NH_3)) 178 (100%) $[M+NH_4]^+$, found : $[M+H]^+$, 161.0972 $C_{11}H_{13}O$ requires : 161.0966. Data matches previously reported values.

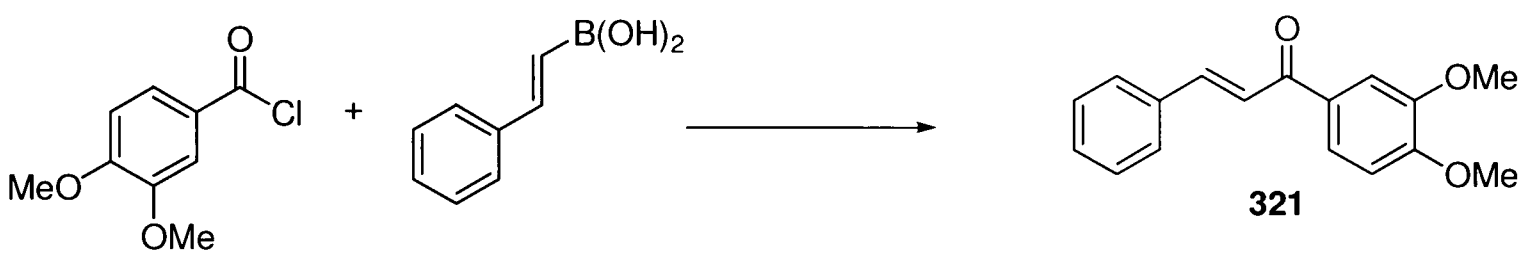
3-Methyl-1-phenylbut-2-en-1-one (221)[105]



221

3,3-Dimethylacryloyl chloride (0.28 mL, 2.53 mmol) was treated according to the general procedure 3 for α,β-unsaturated ketone synthesis for NMM aziridination to give enone **221** (50 mg, 0.3 mmol, 13%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.96-7.94 (2H, m, ArH), 7.56-7.52 (1H, m, ArH), 7.48-7.44 (2H, m, ArH), 6.77-6.76 (1H, br t, *J* 1.3, CHCOPh), 2.23 (3H, br d, *J* 0.9, 1 × $C(CH_3)_2$), 2.04 (3H, br d, *J* 0.9, 1 × $C(CH_3)_2$); m/z (CI (NH_3)) 161 (100%, $[M]^+$), 178 (91%, $[M+NH_4]^+$), found : $[M+H]^+$, 161.0965 $C_{11}H_{13}O$ requires : 161.0966. Data matches previously reported values.

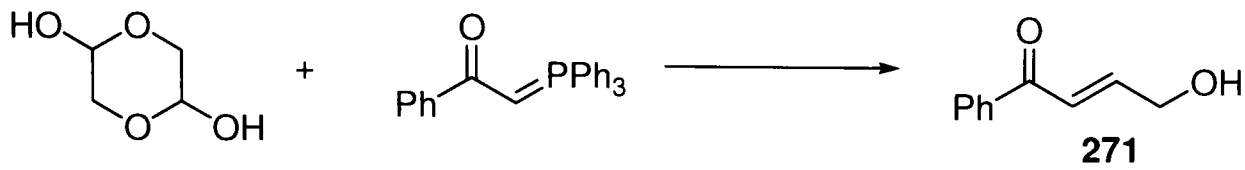
3',4'-Dimethoxychalcone (321)



321

A mixture of *trans*-phenylvinyl boronic acid (148 mg, 1.0 mmol), 3,4-dimethoxybenzoyl chloride (400 mg, 2.0 mmol), tetrakis(triphenylphosphine)palladium(0) (35 mg, 3 mol%), caesium carbonate (1.6 g, 5.0 mmol) and toluene (15 mL) was heated at reflux for 4 h. After cooling, the organic phase was diluted with EtOAc (30 mL) then washed with saturated aqueous $NaHCO_3$ (30 mL) then with water (30 mL) and dried over Na_2SO_4. Solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (10:4 petrol:ether) to afford enone **321** (69 mg, 0.26 mmol, 26%) as a yellow oil; ν_{max}/cm^{-1}(film) 3082, 2254, 1658, 1605, 1514; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* 15.6, CH), 7.71-7.64 (4H, m ArH), 7.57 (1H, d, *J* 15.6, CH), 7.44-7.42 (3H, m, ArH), 6.93 (1H, d, *J* 8.4, ArH), 3.98 (3H, s, OCH_3), 3.97 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 188.6 (C), 153.3 (C), 149.3 (C), 144.0 (CH), 135.1 (C), 131.3 (C), 130.4 (CH), 128.9 (CH), 128.4 (CH), 123.1 (CH), 121.7 (CH), 110.8 (CH), 110.0 (CH), 56.1 (CH), 56.1 (CH); m/z (CI (NH_3)) 269 (100%) $[M+H]^+$, found : $[M+H]^+$, 269.1186 $C_{17}H_{17}O_3$ requires : 269.1178.

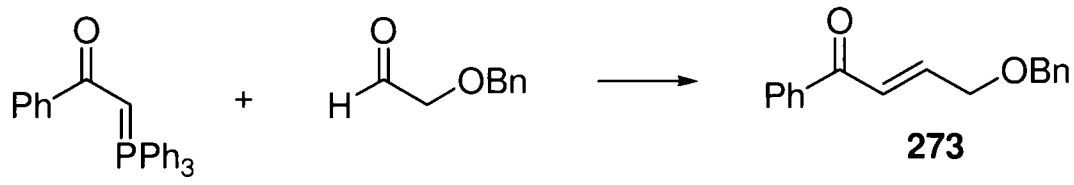
(*E*)-4-Hydroxy-1-phenylbut-2-en-1-one (271)[117]



271

To a solution of (benzoylmethylene)triphenyl phosphorane (0.2 g, 0.53 mmol) in THF (3 mL) was added glycoaldehyde dimer (50 mg, 0.44 mmol), and the resulting solution was heated under reflux for 3 h. The solution was cooled and the solvent removed *in vacuo*. The product was purified by chromatography (Florisil, 1:1 hexane:EtOAc) to give enone **271** as a yellow oil (62 mg, 0.38 mmol, 89%); δ_H (400 MHz, acetone-d_6) 8.02-8.00 (2H, m, ArH), 7.66-7.62 (1H, m, ArH), 7.57-7.53 (2H, m, ArH), 7.30 (1H, dt, *J* 15.4, 2.1, CH=CH), 7.12 (1H, dt, *J* 15.4, 3.7, CH=CH), 4.43-4.41 (2H, br m, C*H*$_2$OH), 3.79 (1H, s, CH$_2$O*H*); m/z (CI (NH_3)) 163 (47%, $[M+H]^+$), 180 (100%, $[M+NH_4]^+$), found : $[M+H]^+$, 163.0765 $C_{10}H_{11}O_2$ requires : 163.0759. Data matches previously reported values.

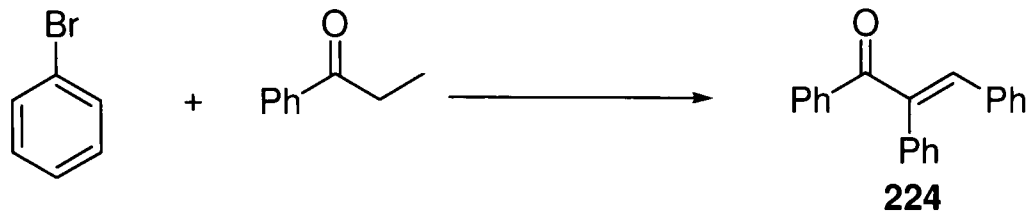
(*E*)-4-(Benzyloxy)-1-phenylbut-2-en-1-one (273)



273

To a solution of ylide (0.2 g, 0.53 mmol) in CH_2Cl_2 (2 mL) was added benzyloxyacetaldehyde (0.15 mL, 1.1 mmol) in CH_2Cl_2 (1 mL) dropwise. The solution was allowed to stir for 3 h at rt after which time the solvent was removed in *vacuo*. The crude product was purified by silica gel column chromatography (petrol:EtOAc, 100:2) to give enone **273** (0.12 g, 0.48 mmol, 91%) as a colourless oil; ν_{max}/cm^{-1}(film) 3067, 3032, 2857, 1671, 1625, 1579, 1447, 1284; δ_H (400 MHz, $CDCl_3$) 8.01-7.98 (2H, m, ArH), 7.61-7.57 (1H, m, ArH), 7.52-7.48 (2H, m, ArH), 7.42-7.33 (5H, m, ArH), 7.26 (1H, dt, *J* 15.5, 2.0, CH=CH), 7.11 (1H, dt, *J* 15.5, 4.0, CH=CH), 4.66 (2H, s, CH_2Ph), 4.32 (2H, dd, *J* 4.0, 2.0, C*H*$_2$CH); δ_C (100 MHz, $CDCl_3$) 190.4 (C), 144.5 (CH), 137.8 (C), 137.7 (C), 132.9 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 124.9 (CH), 73.0 (CH_2), 69.2 (CH_2); m/z (CI (NH_3)) 253 (83%, $[M+H]^+$), 270 (100%, $[M+NH_4]^+$), found : $[M+H]^+$, 253.1233 $C_{17}H_{17}O_2$ requires : 253.1229.

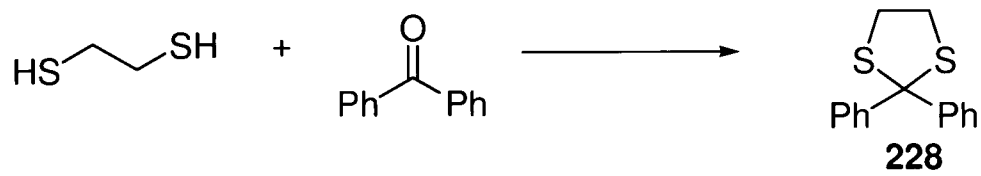
(*E*)-1, 2, 3-Triphenylprop-2-en-1-one (224)[151]



224

Propiophenone (0.25 mL, 1.88 mmol) was added to a solution of bromobenzene (0.79 mL, 7.52 mmol) in the presence of $Pd(OAc)_2$ (20 mg, 0.09 mmol), PPh_3 (0.10 g, 0.38 mmol) and Cs_2CO_3 (2.45 g, 7.52 mmol) with *o*-xylene (5 mL) as solvent. The reaction was heated under reflux for 24 h after which time the solution was allowed to cool before being filtered over a pad of Celite®. Solvents were removed under vacuum and the crude product was purified by silica gel column chromatography (hexane:EtOAc, 100:1) to give enone **(*E*)-224** (0.14 g, 0.51 mmol, 27%) and enone **(*Z*)-224** (0.1 g, 0.35 mmol, 17%) as yellow oils; **(*E*)-224** ν_{max}/cm^{-1}(film) 1650, 1252; δ_H (400 MHz, $CDCl_3$) 8.00-7.91 (2H, m, ArH), 7.51-7.13 (14H, m, 2 × CH=CH and ArH); m/z (CI (NH_3)) 285 (100%) $[M+H]^+$, found : $[M+H]^+$, 285.1271 $C_{21}H_{17}O$ requires : 285.1279; **(*Z*)-224** ν_{max}/cm^{-1}(film) 1660, 1224; δ_H (400 MHz, $CDCl_3$) 8.07-8.05 (2H, m, ArH), 7.54-7.17 (14H, m, 2 × CH=CH and ArH); m/z (CI (NH_3)) 285 (100%) $[M+H]^+$, found : $[M+H]^+$, 285.1268 $C_{21}H_{17}O$ requires : 285.1279. Data matches previously reported values.

2,2-Diphenyl-1,3-dithiolane (228)[152]

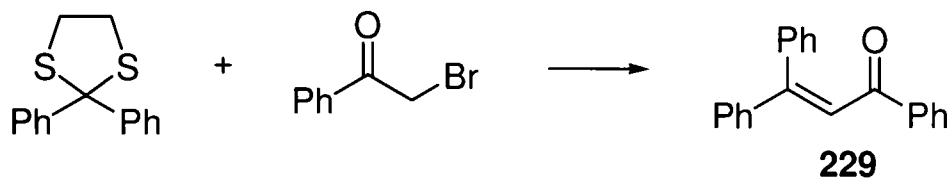


228

Benzophenone (1.0 g, 5.48 mmol) and 1,2-ethanedithiol (0.92 mL, 11.0 mmol) were combined and stirred, followed by the addition of BF_3.HOAc (0.76 mL, 5.48 mmol). The solution rapidly solidified and was left to stir rapidly for 15 min. The mixture was diluted with hexane (30 mL) and washed with $NaHCO_3$ (3 × 30 mL), aqueous NaOH (15% by mass, 3 × 30 mL) and saturated aqueous NaCl (3 × 30 mL). The organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (100:5 hexane:ether) to give enone **228** (1.4 g, 5.43 mmol, 98%) as a

white solid; m.p. 104-105 °C (lit., 105 °C); δ_H (400 MHz, $CDCl_3$) 7.64-7.62 (4H, m, ArH), 7.33-7.24 (6H, m, ArH), 3.45 (4H, s, 2 × CH_2O); m/z (CI (NH_3)) 259 (100%) $[M+H]^+$, found : $[M+H]^+$, 259.0621 $C_{15}H_{15}S_2$ requires : 259.0615. Data matches previously reported values.

1,3,3-Triphenylprop-2-en-1-one (229)[153]



229

To a THF solution (60 mL) of dithioacetal (0.3 g, 1.16 mmol) at -78 °C was added *n*-BuLi (0.8 mL, 1.28 mmol, 1.6 M in hexanes). The mixture was stirred at this temperature for 1 h after which time α–bromoacetphenone (0.23 g, 1.16 mmol) in THF (5 mL) was added. The reaction was gradually warmed to rt and stirred for 18 h. Neutral alumina (5 g) was then added and the slurry was stirred for 30 min. After filtration and evaporation of the solvent under vacuum the crude product was purified by neutral alumina column chromatography (100:2-100:5 hexane:ethyl acetate) to give enone **229** (0.13 g, 0.46 mmol, 41%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.99-7.97 (2H, m, ArH), 7.55-7.51 (1H, m, ArH), 7.47-7.41 (7H, m, ArH), 7.34-7.30 (3H, m, ArH), 7.29-7.24 (2H, m, ArH), 7.19 (1H, s, CH); m/z (EI^+) 283 (100%) $[M-H]^+$, found : $[M]^+$, 284.1191 $C_{21}H_{16}O$ requires : 284.1193. Data matches previously reported values.

(*E,E*)-Cinnamylideneacetophenone (277)[125]

277

To a solution of acetophenone (0.5 mL, 4.3 mmol) in MeOH (30 mL) was slowly added NaOH (25 mL, aqueous solution 60% by mass) at 0 °C. After allowing the reaction to warm to rt, cinnamaldehyde (0.65 mL, 5.15 mmol) was added. The mixture was stirred for 20 h, then poured into H_2O (100 mL), ice (100 g) and conc. HCl (pH adjusted to ca. 5). The obtained solid was removed by filtration, dissolved in $CHCl_3$ (150 mL) and washed with aqueous $NaHCO_3$ (5% by mass, 2 × 100 mL). The organic layer was

collected, dried over Na_2SO_4 and the solution evaporated to dryness. The residue was purified by silica gel column chromatography (100%, CH_2Cl_2) and recrystallised from EtOH to give enone **277** (0.65 g, 2.78 mmol, 65%) as an orange solid; m.p. 103-105 °C (lit., 102-103 °C); δ_H (400 MHz, $CDCl_3$) 8.01-7.99 (2H, m, ArH), 7.66-7.58 (2H, m, 1 × CH=CH and 1 × ArH), 7.54-7.50 (4H, m, ArH), 7.42-7.33 (3H, m, ArH), 7.12 (1H, d, *J* 14.9, CH=CH), 7.06-7.05 (2H, m, 2 × CH=CH); m/z (EI^+) 234 (100%) $[M]^+$, found : $[M]^+$, 234.1039 $C_{17}H_{14}O$ requires : 234.1045. Data matches previously reported values.

(*E*)-1-Morpholin-4-yl-3-phenylprop-2-en-1-one (256)[115]

256

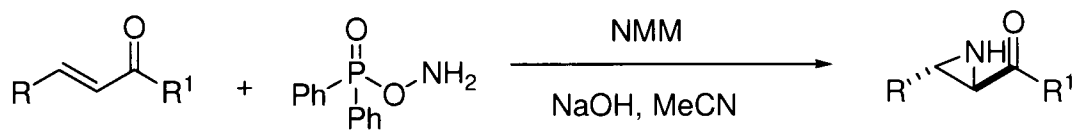
To a stirred solution of *trans*-cinnamoyl chloride (0.43 g, 2.6 mmol) in $CHCl_3$ (20 mL) was added morpholine (0.23 mL) in $CHCl_3$ (1 mL). The mixture was cooled to 0 °C and pyridine (0.21 mL) was added dropwise. Stirring was continued for 24 h at rt, the mixture was then evaporated under reduced pressure. The residue was diluted with 1:1 CH_2Cl_2:Et_2O (20 mL) and washed with saturated aqueous NaCl (30 mL) containing sufficient 2 M HCl to remove the amines. The solution was then washed with saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford enone **256** (0.39 g, 1.80 mmol, 70%) as a cream solid; m.p. 89-91 °C; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 15.4, CH=CH), 7.49-7.47 (2H, m, ArH), 7.34-7.28 (3H, m, ArH), 6.82 (1H, d, *J* 15.4, CH=CH), 3.65-3.61 (8H, br s, CH_2); m/z (ES^+) $[M]^+$, found : $[M+H]^+$, 218.1185 $C_{13}H_{16}NO_2$ requires : 218.1181. Data matches previously reported values.

(*E*)-3-Cinnamoyloxazolidin-2-one (258)[116]

258

NaH (60% in mineral oil, 0.12 g, 3 mmol) was added portion wise to a stirred solution of 2-oxazolidinone (0.22 g, 2.5 mmol) in THF (7 mL) at 0 °C. After complete addition, the solution was allowed to stir for 30 min at 0 °C. A solution of cinnamoyl chloride (0.46 g, 2.8 mmol) in THF (2 mL) was then added dropwise at 0 °C over 10 min and the solution stirred for 20 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (3 × 20 mL). The extracts were combined, washed with saturated aqueous NaCl (2 × 5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (3:1 petrol:EtOAc) to give enone **258** (0.35 g, 1.62 mmol, 65%) as a white solid; m.p. 153-155 °C (lit., 151-152.5 °C); δ_H (400 MHz, $CDCl_3$) 7.92 (1H, d, *J* 15.7, CH=CH), 7.85 (1H, d, *J* 15.7, CH=CH), 7.63-7.61 (2H, m, ArH), 7.41-7.39 (3H, m, ArH), 4.44 (2H, t, *J* 8.2, CH_2CH_2), 4.12 (2H, t, *J* 8.2, CH_2CH_2); m/z (CI (NH_3)) 235 (100%) $[M+NH_4]^+$, found : $[M+H]^+$, 218.0820 $C_{12}H_{12}NO_3$ requires : 218.0817. Data matches previously reported values.

3.2.2.2 NMM Promoted Aziridination

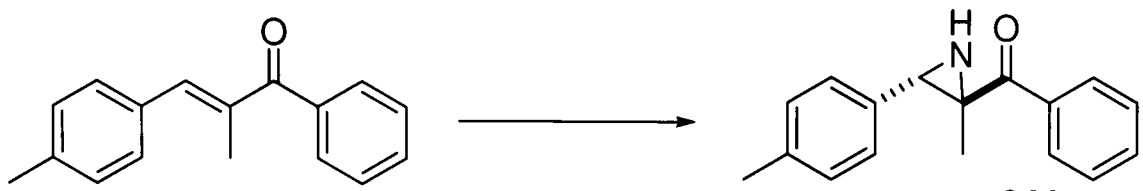


NMM Aziridination Procedure[101]

N-Methyl morpholine (1.0 equiv.) was added dropwise over 1 min to a solution of $DppONH_2$ (1 equiv.) in MeCN (2 mL or 4 mL) at rt. The white mixture was allowed to stir for 30 min, then NaOH (2 equiv.) and α,β-unsaturated ketone (1 equiv.) were added sequentially. The mixture was allowed to stir at rt for 23 h and was then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL), the organics combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification

by column chromatography (100% petrol to 2.5% to 5% EtOAc (unless otherwise stated) gave the aziridine.

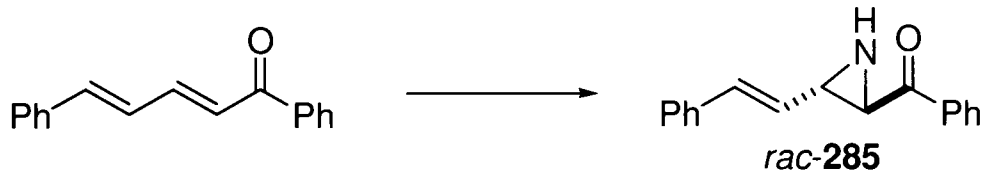
(*E*)-((2*R, 3*S**)-2-Methyl-3-*p*-tolylaziridin-2-yl)(phenyl)methanone (*rac*-244)**



rac-**244**

(*E*)-1-Phenyl-3-*p*-tolylprop-2-en-1-one (40 mg, 0.17 mmol) was used as described in the NMM aziridination procedure to afford aziridine ***rac*-244** (25 mg, 0.10 mmol, 58%) as a yellow oil; ν_{max}/cm^{-1}(film) 3280, 2931, 2875, 1670, 1453, 1275, 709; δ_H (400 MHz, $CDCl_3$) 7.84-7.81 (2H, m, ArH), 7.62-7.58 (1H, m, ArH), 7.53-7.49 (2H, m, ArH), 7.39-7.37 (2H, d, *J* 8.0, ArH), 7.29-7.25 (2H, m, ArH), 3.26 (1H, s, CH), 2.90 (1H, br s, NH), 2.42 (3H, s, $ArCH_3$), 1.32 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 202.2 (C), 137.5 (C), 135.8 (C), 132.9 (CH), 132.6 (C), 129.2 (CH), 128.9 (CH), 128.6 (CH), 127.8 (CH), 47.3 (C), 46.0 (CH), 21.2 (CH), 15.8 (CH); m/z (EI^+) 251 (72%) $[M]^+$, found : $[M]^+$, 251.1311 $C_{17}H_{17}NO$ requires : 251.1310.

(*E*)-Phenyl((2*R, 3*S**)-3-styrylaziridin-2-yl)methanone (*rac*-285)**

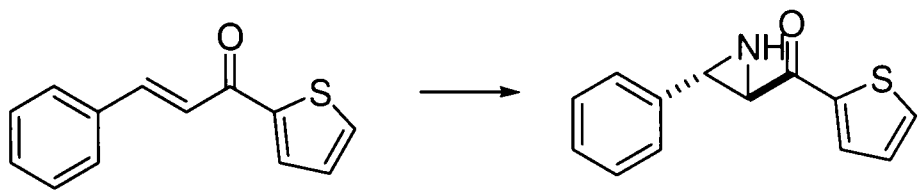


rac-**285**

(*E,E*)-Cinnamylideneacetophenone was used as described in the NMM aziridination procedure. Purification by column chromatography (100:3 to 100:6 petrol:EtOAc) gave aziridine ***rac*-285** (30 mg, 0.05 mmol, 42%) as a yellow oil; ν_{max}/cm^{-1}(film) 3267, 1671, 1602, 1582, 1255, 966; δ_H (400 MHz, CD_3OD) 8.10-8.08 (2H, m, ArH), 7.69-7.65 (1H, m, ArH), 7.58-7.54 (2H, m, ArH), 7.45-7.43 (2H, m, ArH), 7.34-7.31 (2H, m, ArH), 7.27-7.23 (1H, m, ArH), 6.82 (1H, d, *J* 16.0, CH=CH), 6.07 (1H, dd, *J* 16.0, 8.2, CH=CH), 3.77 (1H, d, *J* 2.5, C*H*NH), 2.88 (1H, dd, *J* 8.2, 2.5, C*H*NH); δ_C (100 MHz, CD_3OD) 197.0 (C), 137.8 (C), 137.2 (C), 135.1 (CH), 135.0 (CH), 130.0 (CH), 129.7

(CH), 129.4 (CH), 129.0 (CH), 128.5 (CH), 127.4 (CH), 44.3 (CH), 41.9 (CH); m/z (ES^+) found : $[M+H]^+$, 250.1241 $C_{17}H_{60}NO$ requires : 250.1232.

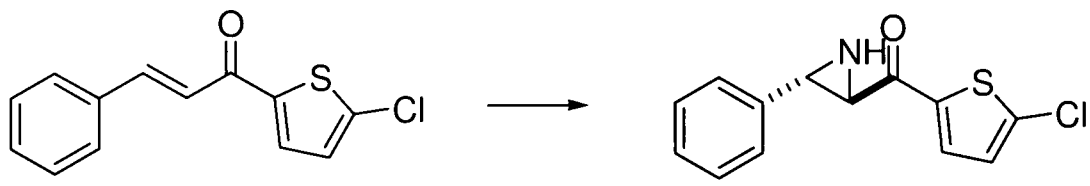
((2*R, 3*S**)-3-phenylaziridin-2-yl)(thiophen-2-yl)methanone (*rac*-365)**



rac-**365**

(*E*)-3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one was used as described in the NMM aziridination procedure. Purification by column chromatography (100:3 to 100:20 petrol:EtOAc) gave aziridine ***rac*-365** (18 mg, 0.08 mmol, 40%) as a white solid; m.p. 114-116 °C; ν_{max}/cm^{-1}(solid) 1645, 1523, 1500, 1420, 1261, 960; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, dd, *J* 4.0, 0.9, ArH), 7.76 (1H, dd, *J* 5.1, 0.9, ArH), 7.39-7.31 (5H, m, ArH), 7.19 (1H, dd, *J* 5.1, 4.0, ArH), 3.42 (1H, d, *J* 2.2, C*H*NH), 3.29 (1H, d, *J* 2.2, C*H*NH), 2.45 (1H, br s, CHN*H*); δ_C (125 MHz, $CDCl_3$) 188.2 (C), 142.8 (C), 138.2 (C), 134.8 (CH), 132.9 (CH), 128.5 (CH), 128.5 (CH), 127.8 (CH), 126.2 (CH), 44.3 (CH), 43.2 (CH); m/z (ES^+) found : $[M+H]^+$, 230.0647 $C_{13}H_{12}NOS$ requires : 230.0640.

(5-Chlorothiophen-2-yl)(2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-366)**

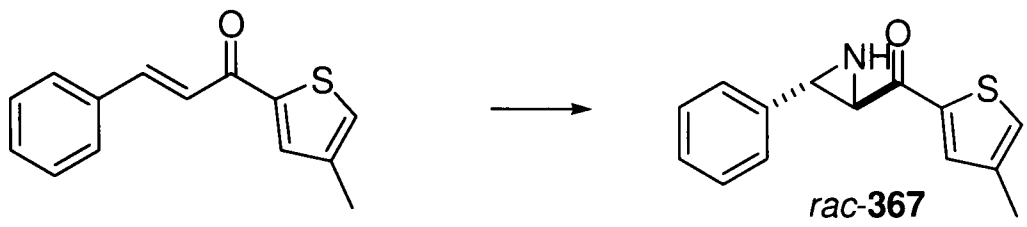


rac-**366**

(*E*)-1-(5-Chlorothiophen-2-yl)-3-phenylprop-2-en-1-one was used as described in the NMM aziridination procedure. Purification by column chromatography (100:3 petrol:EtOAc) gave aziridine ***rac*-366** (13 mg, 0.05 mmol, 25%) as a white solid; m.p. 83-85 °C; ν_{max}/cm^{-1}(solid) 1634, 1427, 1271, 1019, 833; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 4.1, ArH), 7.40-7.33 (5H, m, ArH), 7.01 (1H, d, *J* 4.1, ArH), 3.32 (1H, d, *J* 2.1, C*H*NH), 3.28 (1H, d, *J* 2.1, C*H*NH), 2.25 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 187.3 (C), 141.3 (C), 141.1 (C), 138.0 (C), 132.5 (CH), 128.6 (CH), 128.0 (CH), 128.0 (CH),

126.2 (CH), 43.8 (CH), 43.4 (CH); m/z (ES^+) found : $[M+H]^+$, 264.0252 $C_{13}H_{11}NOSCl$ requires : 264.0252.

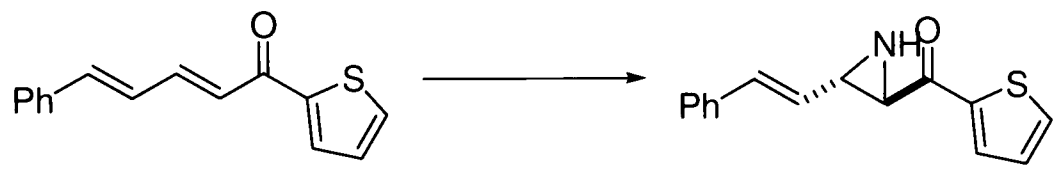
(4-Methylthiophen-2-yl)((2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-367)**



rac-**367**

(*E*)-1-(4-Methylthiophen-2-yl)-3-phenylprop-2-en-1-one was used as described in the NMM aziridination procedure. Purification by column chromatography (100:2.5 to 100:5 petrol:EtOAc) gave aziridine ***rac*-367** (5 mg, 0.02 mmol, 22%) as a yellow oil; ν_{max}/cm ^{1}(film) 1644, 1421, 1266, 1213, 756; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, s, ArH), 7.38-7.32 (6H, m, ArH), 3.37 (1H, d, *J* 2.0, C*H*NH), 3.26 (1H, d, *J* 2.0, C*H*NH), 2.31 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 188.2 (C), 142.3 (C), 139.4 (C), 138.3 (C), 134.8 (CH), 130.8 (CH), 128.5 (CH), 127.9 (CH), 126.2 (CH), 44.3 (CH), 43.2 (CH), 15.6 (CH); m/z (CI (NH_3)) 244 (100%) $[M]^+$, found : $[M]^+$, 244.0807 $C_{14}H_{14}NOS$ requires : 244.0796.

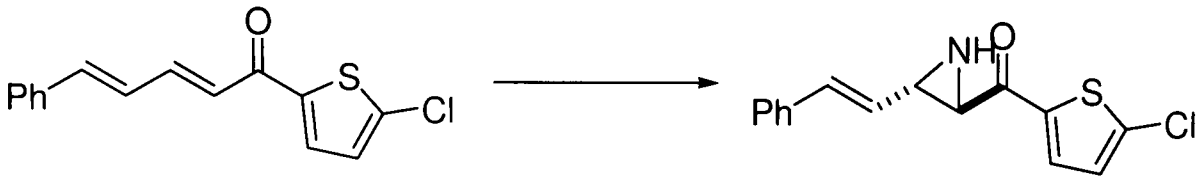
(*E*)-((2*R, 3*S**)-3-Styrylaziridin-2-yl)(thiophen-2-yl)methanone (*rac*-287)**



rac-**287**

(*E,E*)-5-Phenyl-1-(thiophen-2-yl)penta-2,4-dien-1-one was used as described in the NMM aziridination procedure. Purification by column chromatography (100:2 to 100:5 to 100:20 petrol:EtOAc) gave aziridine ***rac*-287** (12 mg, 0.05 mmol, 59%) as a yellow oil; ν_{max}/cm^{-1}(film) 1645, 1522, 1503, 1416, 1257, 909; δ_H (400 MHz, CD_3OD) 8.14-8.12 (1H, br m, ArH), 7.98-7.96 (1H, br m, ArH), 7.43-7.41 (2H, br m, ArH), 7.34-7.27 (4H, br m, ArH), 6.85-6.79 (1H, br m, CH=CH), 6.06-6.02 (1H, br m, CH=CH), 3.70 (1H, br d, *J* 7.2, C*H*NH), 2.95 (1H, br m, C*H*NH); δ_C (100 MHz, CD_3OD) 189.7 (C), 137.8 (C), 136.5 (CH), 135.3 (C), 135.0 (CH), 135.0 (CH), 129.9 (CH), 129.7 (CH), 129.0 (CH), 128.4 (CH), 127.4 (CH), 44.0 (CH), 42.0 (CH); m/z (CI (NH_3)) 256 (100%) $[M]^+$, found : $[M]^+$, 256.0805 $C_{15}H_{14}NOS$ requires : 256.0796.

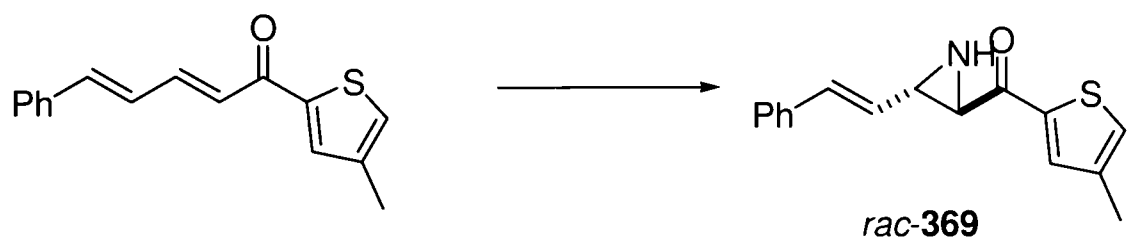
(5-Chlorothiophen-2-yl)((2*R, 3*S**)-3-((*E*)-styryl)aziridin-2-yl)methanone (*rac*-368)**



rac-**368**

(2*E*, 4*E*)-1-(5-Chlorothiophen-2-yl)-5-phenylpenta-2,4-dien-1-one was used as described in the NMM aziridination procedure. Purification by column chromatography (100:3 to 100:5 petrol:EtOAc) gave aziridine ***rac*-368** (12 mg, 0.04 mmol, 41%) as a yellow oil; ν_{max}/cm^{-1}(film) 1645, 1424, 1254, 1026, 957; δ_H (400 MHz, CD_3OD) 7.99 (1H, d, *J* 4.1, ArH), 7.44-7.42 (2H, m, ArH), 7.33 (2H, t, *J* 7.3, ArH), 7.28-7.24 (1H, m, ArH), 7.18 (1H, d, *J* 4.1, ArH), 6.83 (1H, d, *J* 16.0, CH=CH), 6.02 (1H, dd, *J* 16.0, 8.2, CH=CH), 3.65 (1H, d, *J* 2.0, C*H*NH), 2.95 (1H, dd, *J* 8.2, 2.0, C*H*NH); δ_C (100 MHz, CD_3OD) 187.6 (C), 141.5 (C), 140.2 (C), 136.4 (C), 133.7 (CH), 133.5 (CH), 128.4 (CH), 128.3 (CH), 127.6 (CH), 126.9 (CH), 126.0 (CH), 42.8 (CH), 40.0 (CH); m/z (CI (NH_3)) 290 (100%) $[M]^+$, found : $[M]^+$, 290.0416 $C_{15}H_{13}NOSCl$ requires : 290.0406.

(4-Methylthiophen-2-yl)((2*R, 3*S**)-3-((*E*)-styryl)aziridin-2-yl)methanone (*rac*-369)**

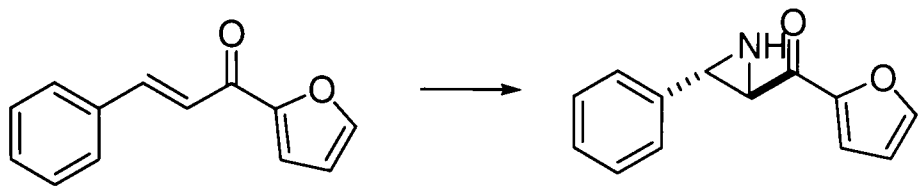


rac-**369**

(2*E*, 4*E*)-1-(4-Methylthiophen-2-yl)-5-phenylpenta-2,4-dien-1-one was used as described in the NMM aziridination procedure. Purification by column chromatography (100:2.5 to 100:5 petrol:EtOAc) gave aziridine ***rac*-369** (7 mg, 0.03 mmol, 27%) as a yellow oil; ν_{max}/cm^{-1}(film) 1646, 1457, 1426, 1254, 968, 867; δ_H (400 MHz, CD_3OD) 7.94 (1H, br s, ArH), 7.55 (1H, br s, ArH), 7.43 (2H, d, *J* 7.5, ArH), 7.33 (2H, t, *J* 7.5, ArH), 7.27-7.23 (1H, m, ArH), 6.81 (1H, d, *J* 15.9, CH=CH), 6.03 (1H, dd, *J* 15.9, 8.2, CH=CH), 3.66 (1H, br s, C*H*NH), 2.92 (1H, dd, *J* 8.2, 2.3, C*H*NH), 2.33 (3H, s, CH_3); δ_C (100 MHz, CD_3OD) 189.6 (C), 143.4 (C), 141.0 (C), 137.8 (C), 136.8 (CH), 135.0 (CH), 132.4 (CH),

129.7 (CH), 129.0 (CH), 128.4 (CH), 127.4 (CH), 44.0 (CH), 41.9 (CH), 15.4 (CH); m/z (CI (NH_3)) 270 (100%) $[M]^+$, found : $[M]^+$, 270.0950 $C_{16}H_{16}NOS$ requires : 270.0953.

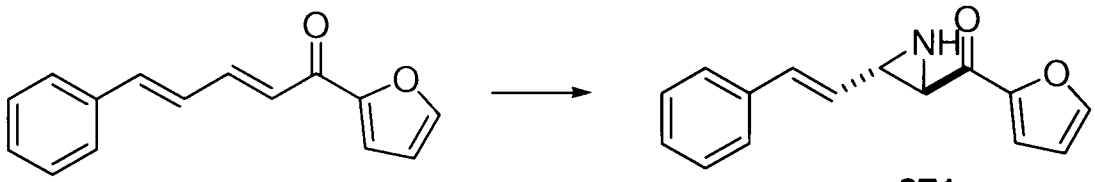
Furan-2-yl-((2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-370)**



rac-**370**

(*E*)-1-(Furan-2-yl)-3-phenylprop-2-en-1-one was used as described in the NMM aziridination procedure. Purification by column chromatography (100:3 to 100:6 to 100:20 petrol:EtOAc) gave aziridine ***rac*-370** (31 mg, 0.15 mmol, 73%) as a white solid; m.p. 82-84 °C; ν_{max}/cm^{-1}(solid) 1648, 1565, 1468, 1399, 1282, 1002, 764; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 1.2, ArH), 7.38-7.33 (6H, m, ArH), 6.62 (1H, dd, *J* 3.5, 1.6, ArH), 3.46 (1H, d, *J* 2.1, C*H*NH), 3.28 (1H, d, *J* 2.1, C*H*NH), 2.54 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 184.4 (C), 152.2 (C), 147.5 (CH), 138.3 (C), 128.5 (CH), 127.8 (CH), 126.3 (CH), 118.5 (CH), 112.7 (CH), 43.6 (CH), 43.4 (CH); m/z (CI (NH_3)) 214 (100%) $[M]^+$, found : $[M]^+$, 214.0871 $C_{13}H_{12}NO_2$ requires : 214.0868.

Furan-2-yl-((2*R, 3*S**)-3-((*E*)-styryl)aziridin-2-yl)methanone (*rac*-371)**

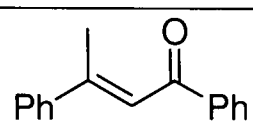
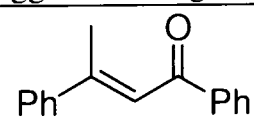
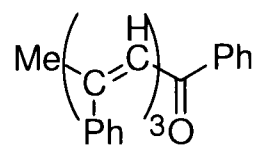
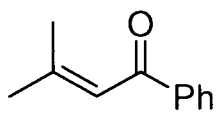
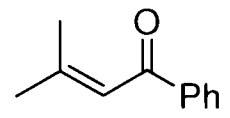
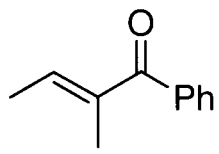
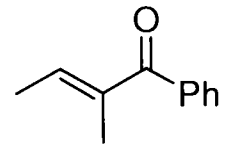
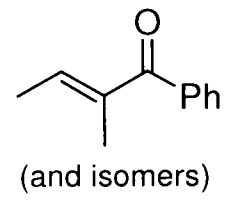
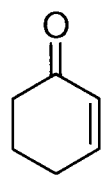
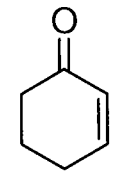
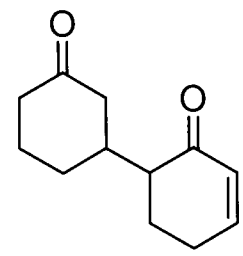
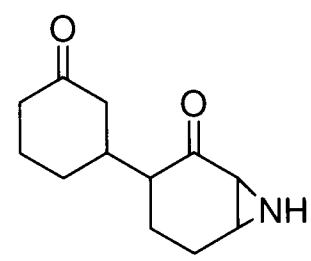


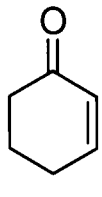
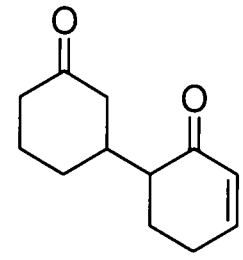
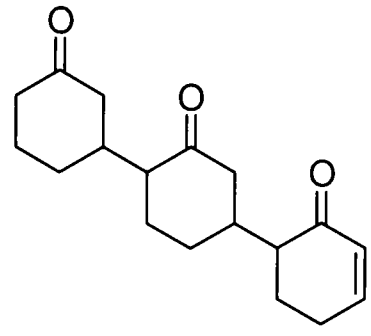
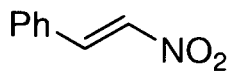
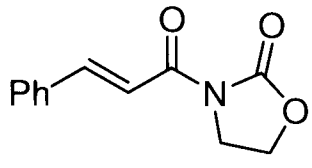
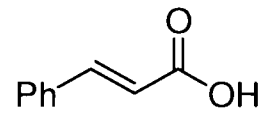
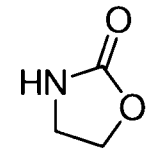
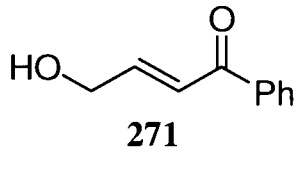
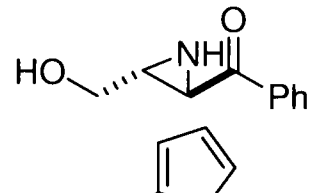
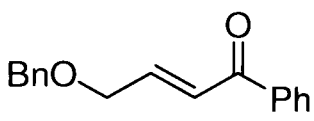
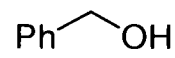
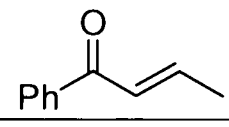
rac-**371**

(2*E*, 4*E*)-1-(Furan-2-yl)-5-phenylpenta-2,4-dien-1-one was used as described in the NMM aziridination procedure. Purification by column chromatography (100:4 to 100:20 petrol:EtOAc) gave aziridine ***rac*-371** (5 mg, 0.02 mmol, 22%) as a yellow oil; ν_{max}/cm^{-1}(oil) 1665, 1579, 1465, 1420, 1272; δ_H (400 MHz, MeOD) 7.90 (1H, br s, ArH), 7.58 (1H, d, *J* 3.5, ArH), 7.43-7.41 (2H, m, ArH), 7.32 (2H, t, *J* 7.3, ArH), 7.27-7.23 (1H, m, ArH), 6.81 (1H, d, *J* 16.0, CH=CH), 6.72 (1H, dd, *J* 3.5, 1.4, ArH), 6.01 (1H, dd, *J* 16.0, 8.1, CH=CH), 3.61 (1H, d, *J* 2.5, C*H*NH), 2.94 (1H, dd, *J* 8.1, 2.5, C*H*NH); δ_C (100 MHz, MeOD) 184.4 (C), 152.3 (C), 148.6 (CH), 136.7 (C), 134.0 (CH), 128.6 (CH),

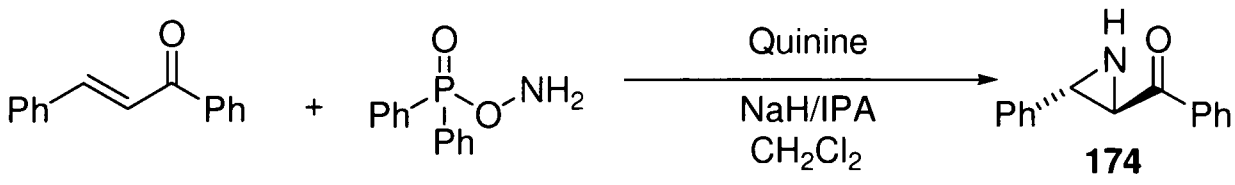
127.9 (CH), 127.3 (CH), 126.3 (CH), 119.5 (CH), 112.8 (CH), 43.0 (CH), 40.5 (CH); m/z (CI (NH_3)) 240 (100%) $[M]^+$, found : $[M]^+$, 240.1033 $C_{15}H_{14}NO_2$ requires : 240.1025.

3.2.2.3 GC/MS Data for the NMM Promoted Aziridination

Entry	Enone	Mass Peaks	t_R (min)	Suggested Assignment
1	 **233**	221 $[M-H]^+$ 222 $[M]^+$ 221 $[M-H]^+$	18.99 19.51 20.44	 (and isomers)
		426 $[M]^+$	29.93	
2	 **221**	161 $[M+H]^+$ 160 $[M]^+$	12.91 13.60	 (and isomers)
3	 **219**	160 $[M]^+$ 160 $[M]^+$	12.10 13.52	 (and isomers)
4	**219** with base only	160$[M]^+$ 160$[M]^+$ 161$[M+H]^+$	8.63 12.12 12.35	 (and isomers)
5		96 $[M]^+$	11.06	
		192 $[M]^+$	18.15	
		208 $[M+H]^+$	18.92	

7	 with base only	192 $[M]^+$	18.65	
				
		288 $[M]^+$	24.25	
8	 **252**	106 $[M]^+$	1.90	PhCHO
9	 **258**	148 $[M]^+$	13.96	
		87 $[M]^+$	4.53	
10	 **271**	177 $[M]^+$	17.43	
		144 $[M]^+$	6.46	
11	 **273**	108 $[M]^+$	2.48	
		146 $[M]^+$	22.73	

3.2.2.4 Variation in Equivalents of IPA in the Asymmetric Aziridination Reaction



174

***In situ* Hydrazinium Salt Formation and Enantioselective Aziridination**

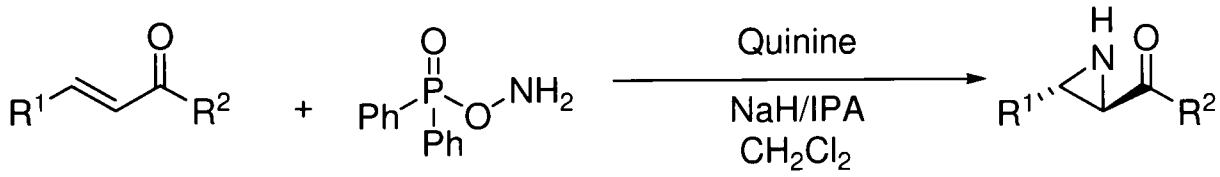
Quinine (1.0 equiv.) was added in one portion to a solution of $DppONH_2$ (1 equiv.) in CH_2Cl_2 (2 mL) at rt. The white mixture was allowed to stir for 30 min, then IPA (0 or 1 equiv.), NaH (60% dispersion in mineral oil, 2 equiv.) and chalcone (1 equiv.) were

added sequentially. The mixture was allowed to stir at rt for 23 h and was then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL), the organics combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (100% petrol to 2.5% to 5% EtOAc gave the aziridine. Optical purity determined by chiral HPLC analysis in comparison with authentic racemic material. Conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H.[101]

Chalcone (25 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination with 0 equiv. of IPA, to afford aziridine **174** (9 mg, 0.04 mmol, 32%) as an off-white solid; Assay of enantiomeric excess: (t_R (minor)=13.44 min, t_R (major)=15.33 min) 48% *e.e.* Data matches previously reported values.[101]

Chalcone (25 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination with IPA (10 μL, 0.13, 1 equiv.) to afford aziridine **174** (17 mg, 0.08 mmol, 64%) as an off-white solid; Assay of enantiomeric excess: (t_R (minor)=13.47 min, t_R (major)=15.37 min) 42% *e.e.* Data matches previously reported values.

3.2.2.5 Quinine Promoted Aziridination

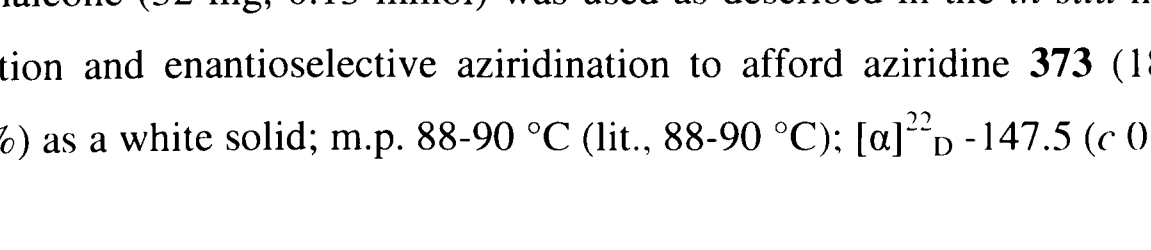


***In situ* Hydrazinium Salt Formation and Enantioselective Aziridination[101]**

Quinine (1.0 equiv.) was added in one portion to a solution of $DppONH_2$ (1 equiv.) in CH_2Cl_2 (2 mL) at rt. The white mixture was allowed to stir for 30 min, then IPA (2 equiv.), NaH (60% dispersion in mineral oil, 2 equiv.) and α,β-unsaturated ketone (1 equiv.) were added sequentially. The mixture was allowed to stir at rt for 23 h and was then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The solution was

extracted with CH_2Cl_2 (3 × 10 mL), the organics combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (100% petrol to 2.5% to 5% EtOAc (unless otherwise stated) gave the aziridine. Optical purity determined by chiral HPLC analysis in comparison with authentic racemic material. Conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H (unless otherwise stated). The absolute configuration of the major enantiomer is assumed to be (2*R*, 3*S*) by analogy to the result with chalcone and quinine.[101,102]

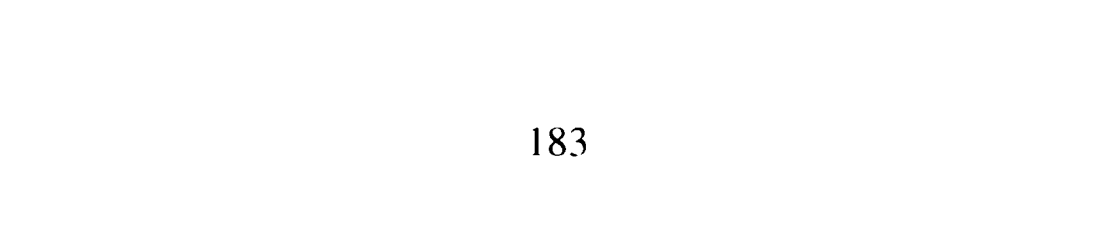
((2*R*, 3*S*)-(3-(4-Methoxyphenyl)aziridin-2-yl)(phenyl)methanone (372)[101]



372

4-Methoxychalcone (31 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **372** (12 mg, 0.05 mmol, 35%) as an orange sticky oil; $[\alpha]^{22}_D$ -379.3 (*c* 0.12, MeOH); δ_H (400 MHz, $CDCl_3$) 8.02 (2H, d, *J* 7.4, ArH), 7.64 (1H, t, *J* 7.4, ArH), 7.52 (2H, t, *J* 7.9, ArH), 7.32 (2H, d, *J* 8.7, ArH), 6.92 (2H, d, *J* 8.7, ArH), 3.84 (3H, s, OCH_3), 3.50 (1H, br m, C*H*NH), 3.16 (1H, br m, C*H*NH), 2.67 (1H, br m, CHN*H*); m/z (CI (NH_3)) 254 (100%) $[M+H]^+$, found : $[M+H]^+$, 254.1185 $C_{16}H_{16}NO_2$ requires : 254.1181; Assay of enantiomeric excess: (t_R (minor)=23.25 min, t_R (major)=26.74 min) 55% *e.e.* Data matches previously reported values.

((2*R*, 3*S*)-3-(4-Chlorophenyl)aziridin-2-yl)(phenyl)methanone (373)[103]

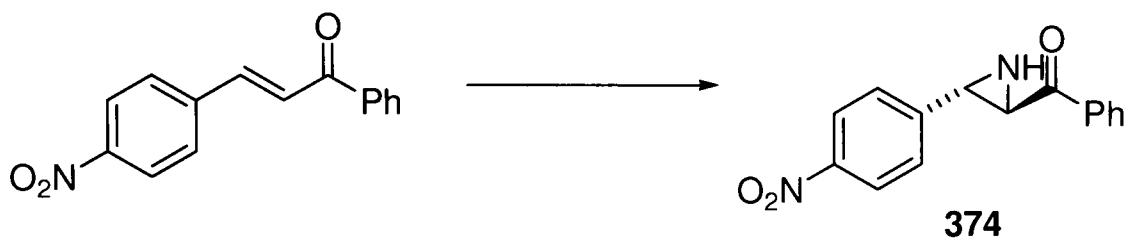


373

4-Chlorochalcone (32 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **373** (18 mg, 0.07 mmol, 54%) as a white solid; m.p. 88-90 °C (lit., 88-90 °C); $[\alpha]^{22}_D$ -147.5 (*c* 0.8, MeOH);

δ_H (400 MHz, $CDCl_3$) 8.00 (2H, d, *J* 7.1, ArH), 7.65 (1H, t, *J* 7.1, ArH), 7.52 (2H, t, *J* 7.9, ArH), 7.37-7.32 (4H, m, ArH), 3.47 (1H, dd, *J* 7.8, 2.2 C*H*NH), 3.17 (1H, dd, *J* 9.3, 2.2 C*H*NH), 2.70 (1H, br m, CHN*H*); m/z (CI (NH_3)) 258 (100%) $[M+H]^+$, found : $[M+H]^+$, 258.0689 $C_{15}H_{13}NOCl$ requires : 258.0686; Assay of enantiomeric excess: (t_R (minor)=16.27 min, t_R (major)=27.86 min) 48% *e.e.* Data matches previously reported values.

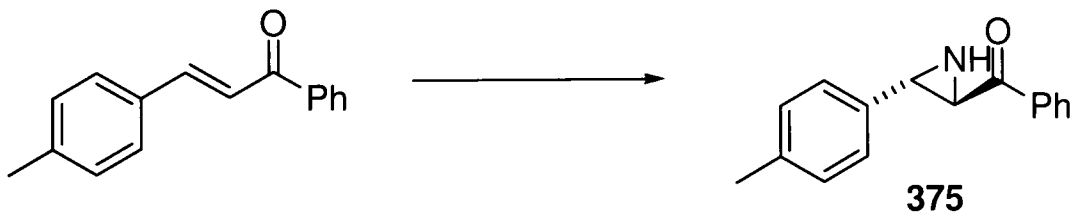
((2*R*, 3*S*)-3-(4-Nitrophenyl)aziridin-2-yl)(phenyl)methanone (374)[103]



374

4-Nitrochalcone (33 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **374** (15 mg, 0.06 mmol, 43%) as a yellow solid; m.p. 139-141 °C (lit., 141-143 °C); $[\alpha]^{22}_D$ -103.3 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.25-8.23 (2H, m, ArH), 8.02-8.00 (2H, m, ArH), 7.68-7.65 (1H, m, ArH), 7.58-7.51 (4H, m, ArH), 3.53 (1H, dd, *J* 7.8, 2.1, C*H*NH), 3.28 (1H, dd, *J* 8.8, 2.1, C*H*NH), 2.80 (1H, br m, CHN*H*); m/z (CI (NH_3)) 269 (100%) $[M+H]^+$, found : $[M+H]^+$, 269.0928 $C_{15}H_{13}N_2O_3$ requires : 269.0926; Assay of enantiomeric excess: (t_R (minor)=37.18 min, t_R (major)=76.34 min) 37% *e.e.* Data matches previously reported values.

Phenyl((2*R*, 3*S*)-3-*p*-tolylaziridin-2-yl)methanone (375)[101]

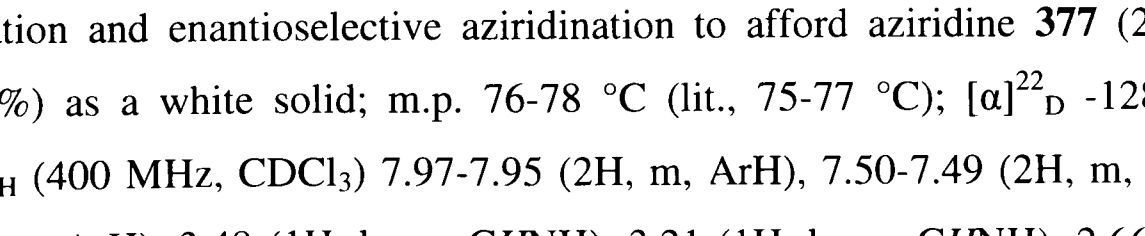


375

4-Methylchalcone (29 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **375** (17 mg, 0.07 mmol, 55%) as a cream solid; m.p. 106-108 °C (lit., 106-107 °C); $[\alpha]^{22}_D$ -99.4 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.02-8.01 (2H, m, ArH), 7.65-7.61 (1H, m, ArH), 7.52-

7.49 (2H, m, ArH), 7.30-7.28 (2H, m, ArH), 7.21-7.19 (2H, m, ArH), 3.51 (1H, br s, C*H*NH), 3.17 (1H, br s, C*H*NH), 2.68 (1H, br, NH), 2.39 (3H, s, CH_3); m/z (CI (NH_3)) 238 (100%) $[M+H]^+$, found : $[M+H]^+$, 238.1241 $C_{16}H_{16}NO$ requires : 238.1232; Assay of enantiomeric excess: (t_R (minor)=13.25 min, t_R (major)=15.99 min) 52% *e.e.* Data matches previously reported values.

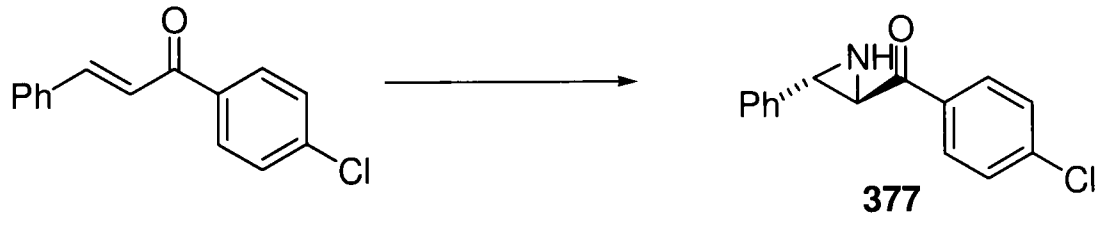
(4'-Methoxyphenyl)((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (376)[101]



376

4'-Methoxychalcone (31 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **376** (16 mg, 0.06 mmol, 48%) as a white solid; m.p. 71-72 °C (lit., 71-73 °C); $[\alpha]^{22}_D$ 138.9 (*c* 0.36, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.02-8.00 (2H, m, ArH), 7.39-7.28 (5H, m, ArH), 6.99-6.97 (2H, m, ArH), 3.90 (3H, s, OCH_3), 3.48 (1H, dd, *J* 8.0, 2.3, C*H*NH), 3.17 (1H, dd, *J* 9.3, 2.3, C*H*NH), 2.66 (1H, br dd, *J* 9.3, 8.0, CHN*H*); m/z (CI (NH_3)) 254 (100%) $[M+H]^+$, found : $[M+H]^+$, 254.1185 $C_{16}H_{16}NO_2$ requires : 254.1181; Assay of enantiomeric excess: (t_R (minor)=32.24 min, t_R (major)=42.16 min) 66% *e.e.* Data matches previously reported values.

(4'-Chlorophenyl)((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (377)[101]

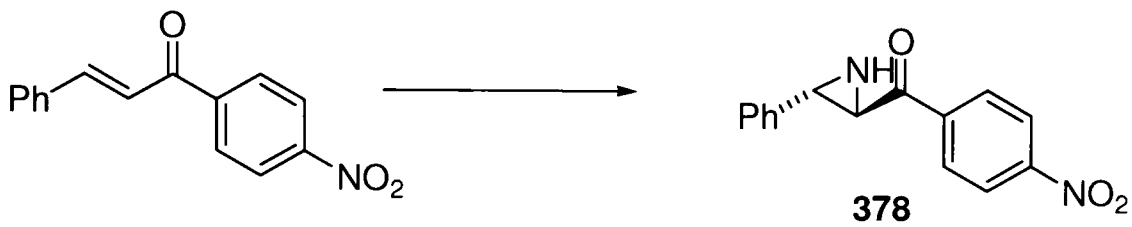


377

4'-Chlorochalcone (32 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **377** (20 mg, 0.08 mmol, 62%) as a white solid; m.p. 76-78 °C (lit., 75-77 °C); $[\alpha]^{22}_D$ -128.0 (*c* 0.63, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.97-7.95 (2H, m, ArH), 7.50-7.49 (2H, m, ArH), 7.40-7.34 (5H, m, ArH), 3.48 (1H, br m, C*H*NH), 3.21 (1H, br m, C*H*NH), 2.66 (1H, br m,

CHN*H*); m/z (CI (NH_3)) 258 (100%) $[M+H]^+$, found : $[M+H]^+$, 258.0690 $C_{56}H_{13}NOCl$ requires : 258.0686; Assay of enantiomeric excess: (t_R (major)=16.61 min. t_R (minor)=17.73 min) 46% *e.e.* Data matches previously reported values.

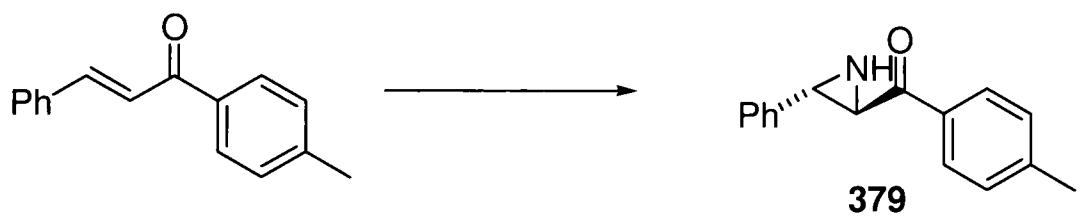
(4'-Nitrophenyl)((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (378)[101]



378

4'-Nitrochalcone (33 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **378** (0.2 mg, < 1%) as a yellow oil; $[\alpha]^{22}_D$ +66.7 (*c* 0.03, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.37-8.35 (2H, m, ArH), 8.18-8.15 (2H, m, ArH), 7.41-7.40 (5H, m, ArH), 3.51 (1H, dd, *J* 7.5, 1.8, C*H*NH), 3.28 (1H, dd, *J* 9.0, 1.8, C*H*NH), 2.77-2.73 (1H, br s, NH); m/z (CI (NH_3)) 269 (100%) $[M+H]^+$, found : $[M+H]^+$, 269.0936 $C_{15}H_{13}N_2O_3$ requires : 269.0926; Assay of enantiomeric excess: (t_R (major)=37.51 min, t_R (minor)=79.75 min) 25% *e.e.* Data matches previously reported values.

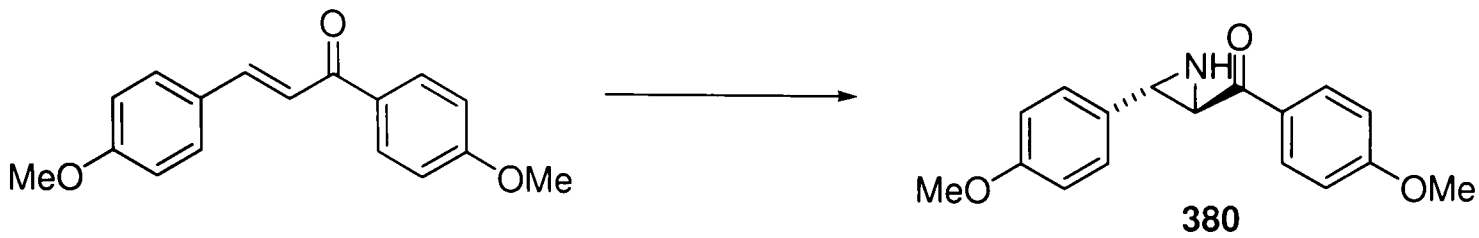
((2*R*, 3*S*)-3-Phenylaziridin-2-yl)(*p*-tolyl)methanone (379)[101]



379

4'-Methylchalcone (29 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **379** (21 mg, 0.09 mmol, 68%) as an off-white solid; m.p. 87-89 °C (lit., 89-90 °C); $[\alpha]^{22}_D$ -169.6 (*c* 0.63, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.93-7.91 (2H, m, ArH), 7.39-7.28 (7H, m, ArH), 3.51 (1H, dd, *J* 8.0, 2.3, C*H*NH), 3.18 (1H, dd, *J* 9.3, 2.3, C*H*NH), 2.70-2.66 (1H, br, NH), 2.45 (3H, s, CH_3); m/z (CI (NH_3)) 238 (100%) $[M+H]^+$, found : $[M+H]^+$, 238.1239 $C_{16}H_{16}NO$ requires : 238.1232; Assay of enantiomeric excess: (t_R (minor)=16.03 min, t_R (major)=21.5 min) 59% *e.e.* Data matches previously reported values.

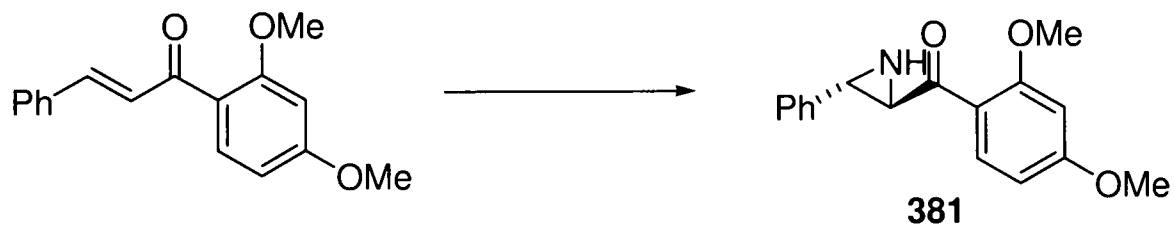
(4-Methoxyphenyl)(2*R*, 3*S*)-3-(4'-methoxyphenyl)aziridin-2-yl)methanone (380)



380

4,4'-Dimethoxychalcone (37 mg, 0.14 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:3 to 100:6 to 100:8 petrol:EtOAc) gave aziridine **380** (11 mg, 0.04 mmol, 26%) as a pale orange solid; m.p. 87-89 °C; $[\alpha]^{22}_{D}$ -185.9 (*c* 0.36, $CHCl_3$); ν_{max}/cm^{-1}(nujol) 1659, 1599, 1508, 1251, 1162, 1023, 801; δ_H (400 MHz, $CDCl_3$) 8.04 (2H, d, *J* 8.9, ArH), 7.31 (2H, d, *J* 8.7, ArH), 6.98 (2H, d, *J* 8.9, ArH), 6.92 (2H, d, *J* 8.7, ArH), 3.90 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.46-3.45 (1H, br m, C*H*NH), 3.14-3.13 (1H, br m, C*H*NH), 2.66-2.64 (1H, br m, NH); δ_C (100 MHz, $CDCl_3$) 194.0 (C), 164.1 (C), 159.4 (C), 130.7 (CH), 129.1 (C), 127.3 (CH), 114.0 (CH), 113.9 (CH), 113.8 (C), 55.6 (CH), 55.4 (CH), 43.8 (CH), 42.9 (CH); m/z (CI (NH_3)) 284 (100%) $[M+H]^+$, found : $[M+H]^+$, 284.1295 $C_{17}H_{18}NO_3$ requires : 284.1287; Assay of enantiomeric excess: (t_R (minor)=49.78 min, t_R (major)=59.89 min) 63% *e.e.*

(2',4'-Dimethoxyphenyl)((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (381)

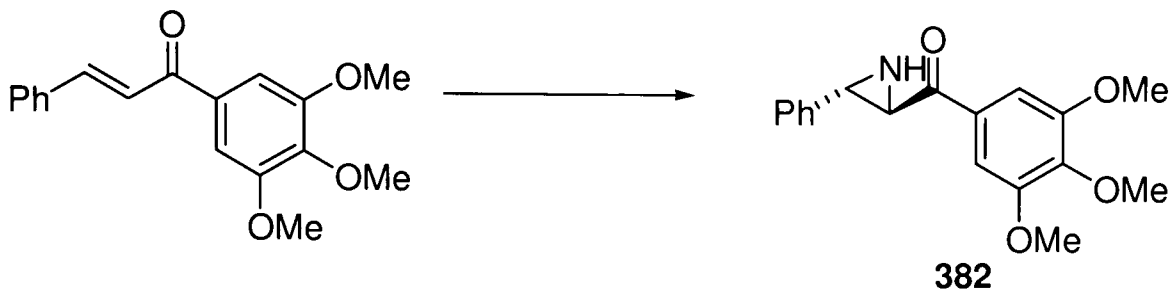


381

2',4'-Dimethoxychalcone (35 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:3 to 100:7.5 petrol:EtOAc) gave aziridine **381** (1 mg, <5%) as a yellow oil; $[\alpha]^{22}_{D}$ -34.78 (*c* 0.12, $CHCl_3$); ν_{max}/cm^{-1}(film) 1729, 1600, 1257, 1022, 803; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, d, *J* 8.7, ArH), 7.41-7.30 (5H, m, ArH), 6.59 (1H, dd, *J* 8.7, 2.2, ArH), 6.44 (1H, d, *J* 2.2, ArH), 3.89 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.57 (1H, br, C*H*NH), 3.12 (1H, br, C*H*NH), 2.73 (1H, br, NH); δ_C (100 MHz, $CDCl_3$) 195.5

(C), 165.2 (C), 161.6 (C), 139.4 (C), 132.8 (CH), 128.5 (C), 128.3 (CH), 127.4 (CH), 126.2 (CH), 105.5 (CH), 98.3 (CH), 55.6 (CH), 55.5 (CH), 48.2 (CH), 43.1 (CH); m/z (CI (NH_3)) 284 (100%) $[M+H]^+$, found : $[M+H]^+$, 284.1291 $C_{17}H_{18}NO_3$ requires : 284.1287; Assay of enantiomeric excess: (t_R (minor)=36.11 min, t_R (major)=39.82 min) 57% *e.e.*

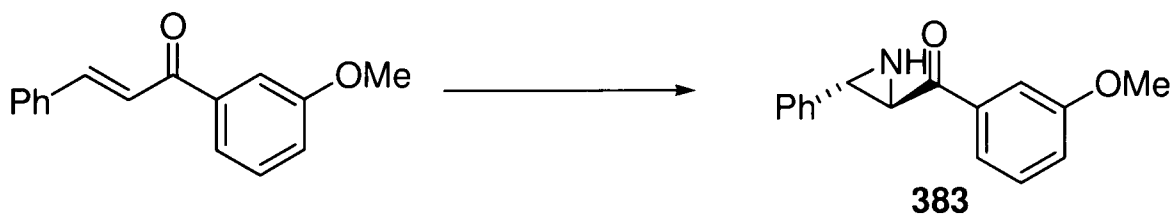
((2*R*, 3*S*)-3-Phenylaziridin-2-yl)(3', 4', 5'-trimethoxyphenyl)methanone (382)



382

3',4',5'-Dimethoxychalcone (39 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:7 to 100:10 petrol:EtOAc) gave aziridine **382** (24 mg, 0.08 mmol, 59%) as a yellow solid; m.p. 138-140 °C; $[\alpha]^{22}_D$ -13.30 (*c* 0.15, $CHCl_3$); ν_{max}/cm^{-1}(film) 1728, 1664, 1585, 1005; δ_H (400 MHz, $CDCl_3$) 7.40-7.23 (7H, m , ArH), 3.95 (3H, s, OCH_3), 3.90 (6H, br s, 2 x OCH_3), 3.46 (1H, br, C*H*NH), 3.21 (1H, br, C*H*NH), 2.70 (1H, br, NH); δ_C (100 MHz, $CDCl_3$) 194.6 (C), 153.3 (C), 143.4 (C), 138.3 (C), 131.2 (C), 128.6 (CH), 127.9 (CH), 126.2 (CH), 105.9 (CH), 61.8 (CH), 56.4 (CH), 43.8 (CH), 43.6 (CH); m/z (CI (NH_3)) 314 (100%) $[M+H]^+$, found : $[M+H]^+$, 314.1395 $C_{18}H_{20}NO_4$ requires : 314.1392; Assay of enantiomeric excess: (t_R (minor)=25.26 min, t_R (major)=28.95 min) 60% *e.e.*

(3'-Methoxyphenyl)((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (383)

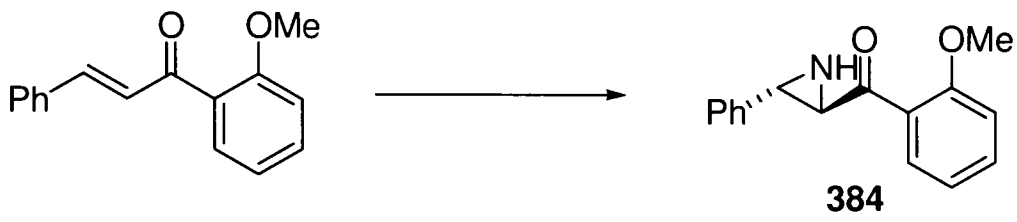


383

3'-Methoxychalcone (31 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:3.5 to 100:7 petrol:EtOAc) gave aziridine **383** (9 mg, 0.04 mmol, 28%) as a yellow oil; $[\alpha]^{22}_D$ -82.5 (*c* 0.32, $CHCl_3$); ν_{max}/cm^{-1}(film) 1667, 1598, 1455,

1433, 1264, 1030; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 7.7. ArH), 7.55-7.53 (1H, m, ArH), 7.44-7.33 (6H, m, ArH), 7.20-7.17 (1H, m, ArH), 3.88 (3H, s, OCH_3), 3.52 (1H, br d, *J* 1.8, C*H*NH), 3.21 (1H, br d, *J* 1.8, C*H*NH), 2.69 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 195.6 (C), 160.0 (C), 138.3 (C), 137.3 (C), 129.9 (CH), 128.6 (CH), 127.9 (CH), 126.2 (CH), 121.1 (CH), 120.3 (CH), 112.5 (CH), 55.5 (CH), 44.2 (CH), 43.6 (CH).; m/z (CI (NH_3)) 254 (100%) $[M+H]^+$, found : $[M+H]^+$, 254.1187 $C_{16}H_{16}NO_2$ requires : 254.1181; Assay of enantiomeric excess: (t_R (minor)=39.98 min, t_R (major)=63.27 min) 48% *e.e.*

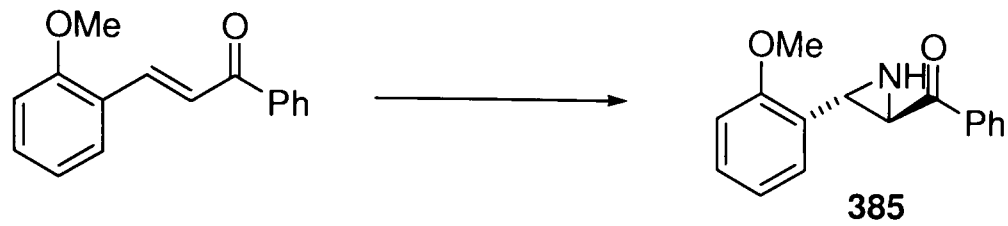
(2'-Methoxyphenyl)((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (384)



384

2'-Methoxychalcone (31 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **384** (14 mg, 0.05 mmol, 41%) as a yellow oil; $[\alpha]^{22}_D$ -86.8 (*c* 0.65, $CHCl_3$); ν_{max}/cm^{-1}(film) 1659, 1598, 1485, 1285; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* 7.7, 1.8, ArH), 7.55-7.50 (1H, m, ArH), 7.41-7.29 (5H, m, ArH), 7.07-7.04 (1H, m, ArH), 6.95 (1H, d, *J* 8.4, ArH), 3.64 (3H, s, OCH_3), 3.55 (1H, d, *J* 2.4, C*H*NH), 3.17 (1H, d, *J* 2.4, C*H*NH), 2.54 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 197.6 (C), 159.6 (C), 139.2 (C), 134.6 (CH), 130.6 (CH), 128.3 (CH), 127.5 (CH), 126.5 (C), 126.2 (CH), 120.8 (CH), 111.7 (CH), 55.5 (CH), 48.5 (CH), 43.6 (CH).; m/z (CI (NH_3)) 254 (100%) $[M+H]^+$, found : $[M+H]^+$, 254.1183 $C_{16}H_{16}NO_2$ requires : 254.1181; Assay of enantiomeric excess: (t_R (major)=19.09 min, t_R (minor)=21.61 min) 53% *e.e.*

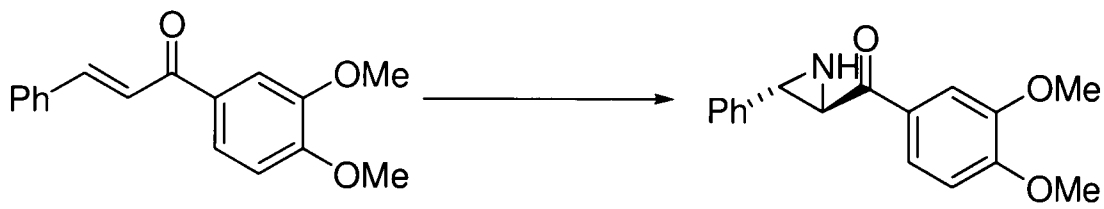
((2*R*, 3*S*)-3-(2-Methoxyphenyl)aziridin-2-yl)(phenyl)methanone (385)



385

2-Methoxychalcone (31 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination to afford aziridine **385** (7 mg, 0.03 mmol, 22%) as a white solid; m.p. 105-106 °C; $[\alpha]^{22}_{D}$ -19.1 (*c* 0.32, $CHCl_3$); ν_{max}/cm ^{1}(nujol) 1658, 1599, 1493, 1259; δ_H (400 MHz, $CDCl_3$) 8.08-8.06 (2H, m, ArH), 7.65-7.61 (1H, m, ArH), 7.53-7.49 (2H, m, ArH), 7.45-7.44 (1H, m, ArH), 7.33-7.29 (1H, m, ArH), 7.02-6.99 (1H, m, ArH), 6.92-6.90 (1H, m, ArH), 3.81 (3H, s, OCH_3), 3.47 (1H, d, *J* 2.3, C*H*NH), 3.42 (1H, d, *J* 2.3, C*H*NH), 2.50 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 196.6 (C), 158.3 (C), 136.2 (C), 133.6 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 126.8 (C), 126.6 (CH), 120.7 (CH), 110.1 (CH), 55.3 (CH), 43.2 (CH), 39.3 (CH).; m/z (CI (NH_3)) 254 (100%) $[M+H]^+$, found : $[M+H]^+$, 254.1181 $C_{16}H_{16}NO_2$ requires : 254.1181; Assay of enantiomeric excess: (t_R (minor)=11.13 min, t_R (major)=18.11 min) 60% *e.e.* (AS-H column).

(3', 4'-Dimethoxyphenyl)((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (386)



386

3',4'-Dimethoxychalcone (30 mg, 0.11 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:8 to 100:10 petrol:EtOAc) gave aziridine **386** (1 mg, 0.004 mmol, <5%) as a colourless oil; $[\alpha]^{22}_{D}$ -57.1 (*c* 0.04, $CHCl_3$); ν_{max}/cm^{-1}(film) 1651, 1415, 1261, 1022, 800; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, dd, *J* 8.5, 2.0, ArH), 7.58 (1H, d, *J* 2.0, ArH), 7.39-7.32 (5H, m, ArH), 6.91 (1H, d, *J* 8.4, ArH), 3.97 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.49 (1H, dd, *J* 9.0, 2.3, C*H*NH), 3.18 (1H, dd, *J* 9.0, 2.3, C*H*NH), 2.65 (1H, t, *J* 9.0, NH); δ_C (100 MHz, $CDCl_3$) 194.1 (C), 154.0 (C), 149.3 (C), 138.5 (C), 129.2 (C), 128.5 (CH), 127.8 (CH), 126.2 (CH), 123.4 (CH), 110.1 (CH), 110.1 (CH), 56.2 (CH),

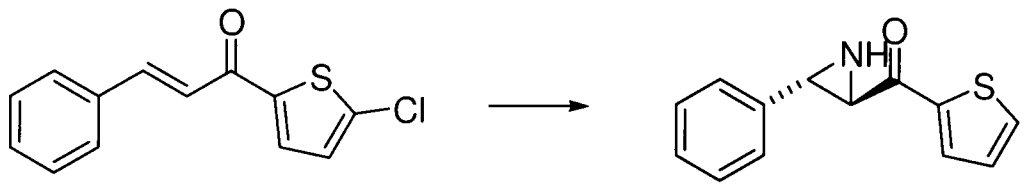
56.1 (CH), 43.6 (CH), 43.2 (CH); m/z (CI (NH_3)) 284 (100%) $[M+H]^+$, found : $[M+H]^+$, 284.1295 $C_{17}H_{18}NO_3$ requires : 284.1287; Assay of enantiomeric excess: (t_R (minor)=45.91 min, t_R (major)=55.52 min) 31% *e.e.*

(*E*)-Phenyl((2*R*, 3*S*)-3-styrylaziridin-2-yl)methanone (285)

285

(*E,E*)-Cinnamylideneacetophenone (30 mg, 0.13 mmol) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:3 to 100:6 petrol:EtOAc) gave aziridine **285** (8 mg, 0.03 mmol, 25%) as a yellow oil; $[\alpha]^{22}_D$ -126.3 (*c* 0.38, MeOH); δ_H (400 MHz, CD_3OD) 8.10 (2H, d, *J* 7.6, ArH), 7.68 (1H, t, *J* 7.4, ArH), 7.57 (2H, t, *J* 7.6, ArH), 7.44 (2H, d, *J* 7.4, ArH), 7.33 (2H, t, *J* 7.6, ArH), 7.28-7.24 (1H, m, ArH), 6.88 (1H, d, *J* 16.0, CH=CH), 6.07 (1H, dd, *J* 16.0, 8.2, CH=CH), 3.77 (1H, br s, C*H*NH), 2.89 (1H, dd, *J* 8.2, 2.3, C*H*NH); m/z (CI (NH_3)) 250 (100%) $[M+H]^+$, found : $[M+H]^+$, 250.1233 $C_{17}H_{16}NO$ requires : 250.1232; Assay of enantiomeric excess: (t_R (minor)=21.51 min, t_R (major)=22.96 min) 52% *e.e.* Data matches that of the racemic compound.

((2*R*, 3*S*)-3-Phenylaziridin-2-yl)(thiophen-2-yl)methanone (365)

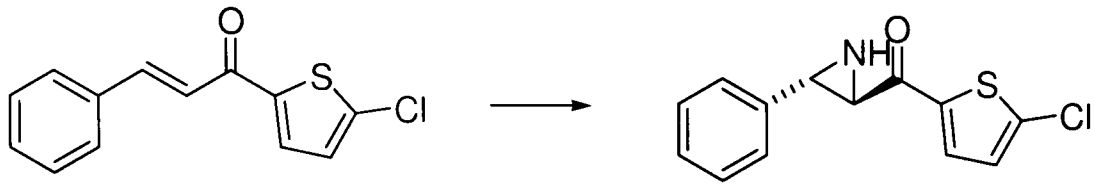


365

(*E*)-3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:4 petrol:EtOAc) gave aziridine **365** (23 mg, 0.1 mmol, 47%) as a white solid; $[\alpha]^{26}_D$ -319.0 (*c* 0.79, MeOH); δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 3.8, ArH), 7.76 (1H, dd, *J* 4.9, 0.7, ArH), 7.39-7.32 (5H, m, ArH), 7.19 (1H, dd, *J* 4.9, 4.0, ArH), 3.42 (1H, d, *J* 2.1, C*H*NH), 3.29 (1H, d, *J* 2.1, C*H*NH), 2.48 (1H, br s, CHN*H*); m/z (ES^+) found : $[M+H]^+$, 230.0647 $C_{13}H_{12}NOS$ requires : 230.0640; Assay of

enantiomeric excess: (t_R (minor)=22.75 min, t_R (major)=26.84 min) 72% *e.e.* Data matches that of the racemic compound.

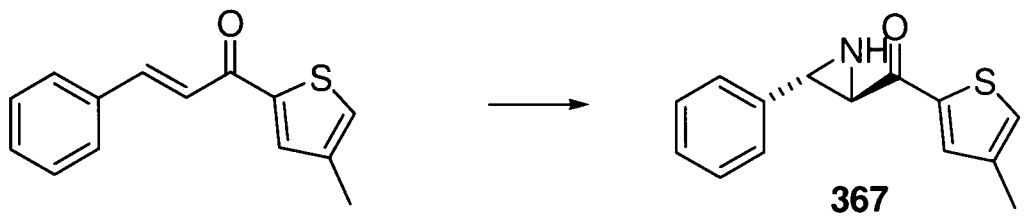
(5-Chlorothiophen-2-yl)(2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (366)



366

(*E*)-1-(5-Chlorothiophen-2-yl)-3-phenylprop-2-en-1-one was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:2.5 to 100:5 petrol:EtOAc) gave aziridine **366** (16 mg, 0.06 mmol, 27%) as a white solid; $[\alpha]^{22}_D$ -311.1 (*c* 0.54, MeOH); δ_H (400 MHz, CD_3OD) 7.90 (1H, d, *J* 4.1, ArH), 7.39-7.29 (5H, m, ArH), 7.14 (1H, d, *J* 4.1, ArH), 3.60 (1H, d, *J* 1.9, C*H*NH), 3.28 (1H, d, *J* 1.9, C*H*NH); m/z (ES^+) found: $[M+H]^+$ 264.0258 $C_{13}H_{11}NOSCl$ requires : 264.0257; Assay of enantiomeric excess: (t_R (major)=15.89 min, t_R (minor)=20.21 min) 64% *e.e.* Data matches that of the racemic compound.

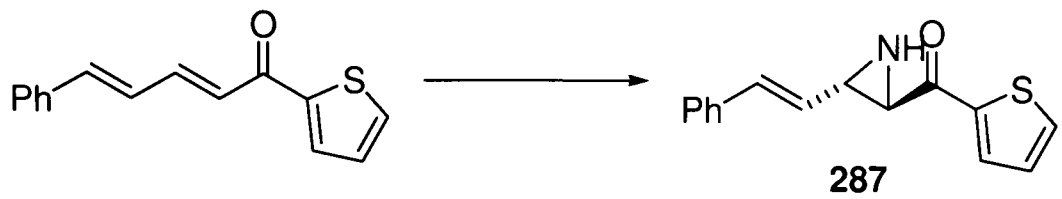
(4-Methylthiophen-2-yl)((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (367)



367

(*E*)-1-(4-Methylthiophen-2-yl)-3-phenylprop-2-en-1-one was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:2.5 to 100:5 petrol:EtOAc) gave aziridine **367** (12 mg, 0.05 mmol, 46%) as a yellow oil; $[\alpha]^{23}_D$ -536.4 (*c* 0.22, MeOH); δ_H (400 MHz, $CDCl_3$) 7.67 (1H, s, ArH), 7.38-7.32 (6H, m, ArH), 3.37 (1H, d, *J* 2.0, C*H*NH), 3.26 (1H, d, *J* 2.0, C*H*NH), 2.31 (3H, s, CH_3); m/z (CI (NH_3)) 244 (100%) $[M]^+$, found : $[M]^+$, 244.0800 $C_{14}H_{14}NOS$ requires : 244.0796; Assay of enantiomeric excess: (t_R (minor)=18.54 min, t_R (major)=25.42 min) 77% *e.e.* Data matches that of the racemic compound.

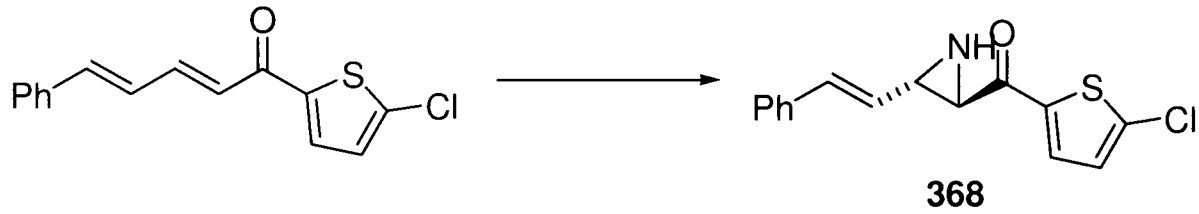
(*E*)-((2*R*, 3*S*)-3-Styrylaziridin-2-yl)(thiophen-2-yl)methanone (287)



287

(*E,E*)-5-Phenyl-1-(thiophen-2-yl)penta-2,4-dien-1-one was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:2.5 to 100:20 petrol:EtOAc) gave aziridine **287** (8 mg, 0.03 mmol, 30%) as a yellow oil; $[\alpha]^{26}_{D}$ -269.8 (*c* 0.06, MeOH); δ_H (400 MHz, CD_3OD) 8.12 (1H, d, *J* 3.8, ArH), 7.96 (1H, d, *J* 4.8, ArH), 7.45-7.43 (2H, m, ArH), 7.35-7.24 (4H, m, ArH), 6.82 (1H, d, *J* 16.0, CH=CH), 6.04 (1H, dd, *J* 16.0, 8.2, CH=CH), 3.70 (1H, br s, C*H*NH), 2.95 (1H, dd, *J* 8.2, 2.1, C*H*NH); m/z (CI (NH_3)) 256 (100%) $[M]^+$, found : $[M]^+$, 256.0801 $C_{15}H_{14}NOS$ requires : 256.0796; Assay of enantiomeric excess: (t_R (minor)=31.55 min, t_R (major)=34.45 min) 71% *e.e.* Data matches that of the racemic compound.

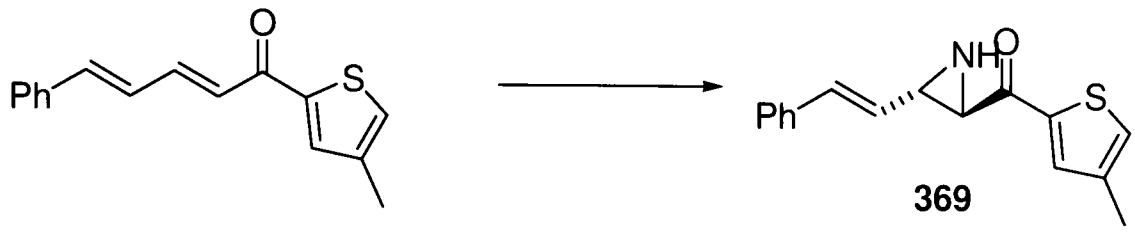
(5-Chlorothiophen-2-yl)((2*R*, 3*S*)-3-((*E*)-styryl)aziridin-2-yl)methanone (368)



368

(2*E*, 4*E*)-1-(5-Chlorothiophen-2-yl)-5-phenylpenta-2,4-dien-1-one was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:3 to 100:5 petrol:EtOAc) gave aziridine **368**, (9:1 *trans:cis* mixture of diastereomers, 16 mg, 0.05 mmol, 26%) as a yellow oil; $[\alpha]^{26}_{D}$ 259.2 (*c* 0.36, MeOH); δ_H (400 MHz, CD_3OD) 7.99 (1H, d, *J* 4.1, ArH), 7.44-7.42 (2H, m, ArH), 7.33 (2H, t, *J* 7.3, ArH), 7.28-7.24 (1H, m, ArH), 7.18 (1H, d, *J* 4.1, ArH), 6.82 (1H, d, *J* 16.0, CH=CH), 6.02 (1H, dd, *J* 16.0, 8.2, CH=CH), 3.66 (1H, d, *J* 2.3, C*H*NH), 2.95 (1H, dd, *J* 8.2, 2.3, C*H*NH); m/z (ES^+) found: $[M+H]^+$ 290.0417 $C_{15}H_{13}NOSCl$ requires : 290.0406; Assay of enantiomeric excess: (t_R (major)=24.49 min, t_R (minor)=31.64 min) 58% *e.e.* Data matches that of the racemic compound.

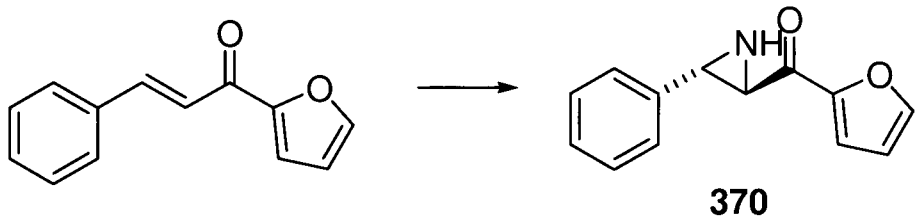
(4-Methylthiophen-2-yl)((2*R*, 3*S*)-3-((*E*)-styryl)aziridin-2-yl)methanone (369)



369

(2*E*, 4*E*)-1-(4-Methylthiophen-2-yl)-5-phenylpenta-2,4-dien-1-one was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:2.5 to 100:5 petrol:EtOAc) gave aziridine **369** (1 mg, 0.01 mmol, 4%) as a yellow oil; $[\alpha]^{26}_{D}$ -880.0 (*c* 0.05, MeOH); δ_H (400 MHz, CD_3OD) 7.96 (1H, br s, ArH), 7.56 (1H, br s, ArH), 7.44 (2H, d, *J* 7.5, ArH), 7.34 (2H, t, *J* 7.5, ArH), 7.28-7.24 (1H, m, ArH), 6.83 (1H, d, *J* 16.0, CH=CH), 6.04 (1H, dd, *J* 16.0, 8.2, CH=CH), 3.66 (1H, br s, C*H*NH), 2.93 (1H, dd, *J* 8.2, 2.2, C*H*NH), 2.34 (3H, s, CH_3); m/z (CI (NH_3)) 270 (100%) $[M]^+$, found : $[M]^+$, 270.0958 $C_{16}H_{16}NOS$ requires : 270.0953. Assay of enantiomeric excess: (t_R (minor)=31.87 min, t_R (major)=36.49 min) 72% *e.e.* Data matches that of the racemic compound.

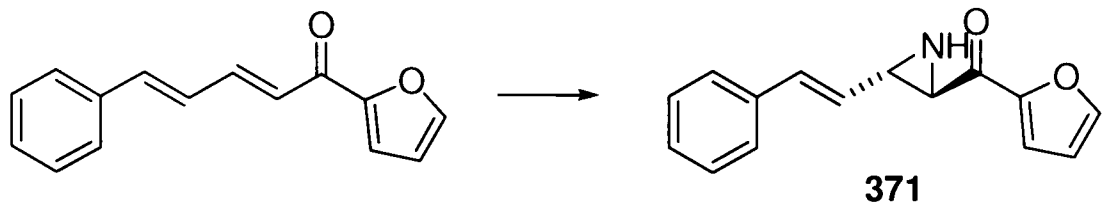
Furan-2-yl((2*R*, 3*S*)-3-phenylaziridin-2-yl)methanone (370)



370

(*E*)-1-(Furan-2-yl)-3-phenylprop-2-en-1-one was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:6 to 100:20 petrol:EtOAc) gave aziridine **370** (10 mg, 0.05 mmol, 41%) as a white solid; $[\alpha]^{22}_{D}$ -395.3 (*c* 0.4, MeOH); δ_H (400 MHz, $CDCl_3$) 7.67 (1H, br m, ArH), 7.37-7.30 (6H, m, ArH), 6.61 (1H, dd, *J* 3.5, 1.5, ArH), 3.45 (1H, d, *J* 2.0, C*H*NH), 3.27 (1H, d, *J* 2.0, C*H*NH), 2.28 (1H, br m, CHN*H*); m/z (CI (NH_3)) 214 (100%) $[M]^+$, found : $[M]^+$, 214.0871 $C_{13}H_{12}NO_2$ requires : 214.0868; Assay of enantiomeric excess: (t_R (minor)=18.31 min, t_R (major)=34.15 min) 71% *e.e.* Data matches that of the racemic compound.

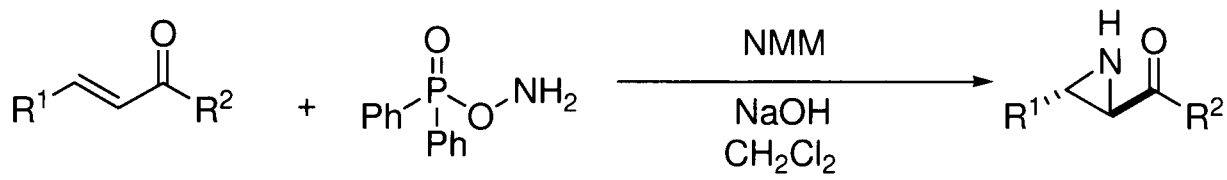
Furan-2-yl((2*R*, 3*S*)-3-((*E*)-styryl)aziridin-2-yl)methanone (371)



371

(2*E*, 4*E*)-1-(Furan-2-yl)-5-phenylpenta-2,4-dien-1-one was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination. Purification by column chromatography (100:4 to 100:20 petrol:EtOAc) gave aziridine **371** (3 mg, 0.01 mmol, 13%) as a yellow oil; $[\alpha]^{22}_{D}$ -26.6 (*c* 0.15, MeOH); δ_H (400 MHz, MeOD) 7.90 (1H, br s, ArH), 7.58 (1H, d, *J* 3.6, ArH), 7.44-7.42 (2H, m, ArH), 7.33 (2H, t, *J* 7.4, ArH), 7.27-7.23 (1H, m, ArH), 6.82 (1H, d, *J* 16.0, CH=CH), 6.73 (1H, dd, *J* 3.6, 1.5, ArH), 6.02 (1H, dd, *J* 16.0, 8.1, CH=CH), 3.61 (1H, br s, C*H*NH), 2.94 (1H, dd, *J* 8.1, 2.3, C*H*NH); m/z (CI (NH_3)) 240 (100%) $[M]^+$, found : $[M]^+$, 240.1022 $C_{15}H_{14}NO_2$ requires : 240.1025; Assay of enantiomeric excess: (t_R (minor)=30.35 min, t_R (major)=54.75 min) 52% *e.e.* Data matches that of the racemic compound.

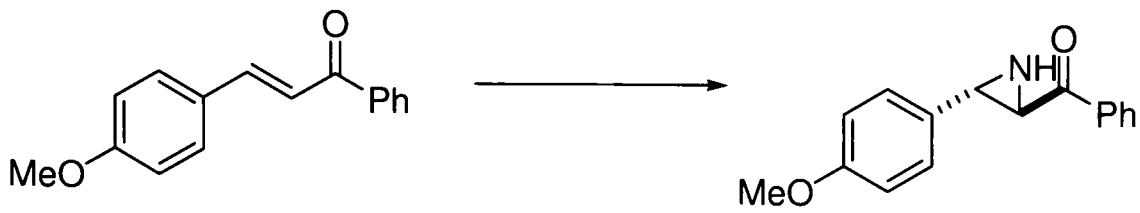
3.2.2.6 NMM Promoted Aziridination (preparation of substrates for HPLC)



NMM Aziridination Procedure[101]

N-Methyl morpholine (1.0 equiv.) was added dropwise over 1 min to a solution of $DppONH_2$ (1 equiv.) in CH_2Cl_2 (2 mL) at rt. The white mixture was allowed to stir for 30 min, then NaOH (2 equiv.) and α,β-unsaturated ketone (1 equiv.) were added sequentially. The mixture was allowed to stir at rt for 23 h and was then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL), the organics combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (100% petrol to 2.5% to 5% EtOAc (unless otherwise stated) gave the aziridine.

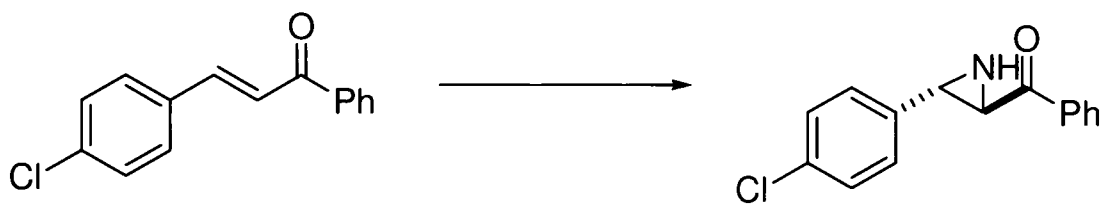
((2*R, 3*S**)-(3-(4-Methoxyphenyl)aziridin-2-yl)(phenyl)methanone (*rac*-372)**



rac-**372**

4-Methoxychalcone (29 mg, 0.13 mmol) was used as described in the NMM aziridination procedure to afford aziridine ***rac*-372** (7 mg, 0.03 mmol, 22%) as a white solid; δ_H (400 MHz, $CDCl_3$) 8.02 (2H, d, *J* 7.3, ArH), 7.63 (1H, t, *J* 7.3, ArH), 7.51 (2H, t, *J* 7.9, ArH), 7.31 (2H, d, *J* 8.7, ArH), 6.91 (2H, d, *J* 8.7, ArH), 3.84 (3H, s, OCH_3), 3.50 (1H, br m, C*H*NH), 3.16 (1H, br m, C*H*NH), 2.67 (1H, br m, CHN*H*). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

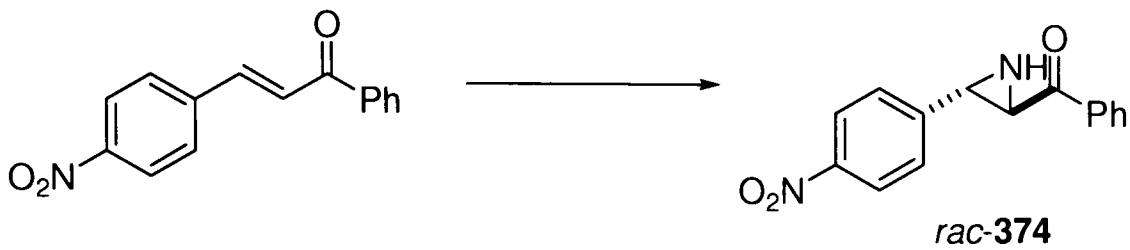
((2*R, 3*S**)-3-(4-Chlorophenyl)aziridin-2-yl)(phenyl)methanone (*rac*-373)**



rac-**373**

4-Chlorochalcone (30 mg, 0.13 mmol) was used as described in the NMM aziridination procedure to afford aziridine ***rac*-373** (5 mg, 0.02 mmol, 16%) as a white solid; δ_H (400 MHz, $CDCl_3$) 8.02-8.01 (2H, m, ArH), 7.67-7.64 (1H, m, ArH), 7.55-7.51 (2H, m, ArH), 7.50-7.34 (4H, m, ArH), 3.48 (1H, dd, *J* 8.0, 2.2 C*H*NH), 3.17 (1H, dd, *J* 9.2, 2.2 C*H*NH), 2.71 (1H, br m, CHN*H*). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

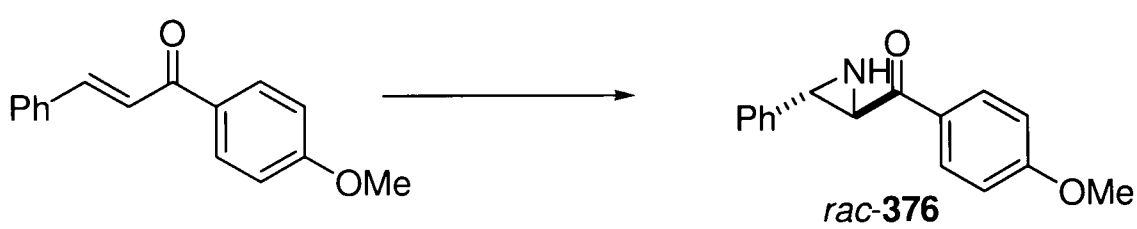
((2*R, 3*S**)-3-(4-Nitrophenyl)aziridin-2-yl)(phenyl)methanone (*rac*-374)**



rac-**374**

4-Nitrochalcone (30 mg, 0.13 mmol) was used as described in the NMM aziridination procedure to afford aziridine ***rac*-374** (16 mg, 0.06 mmol, 45%) as a yellow solid; δ_H (400 MHz, $CDCl_3$) 8.25-8.23 (2H, m, ArH), 8.02-8.00 (2H, m, ArH), 7.69-7.65 (1H, m, ArH), 7.58-7.51 (4H, m, ArH), 3.53 (1H, dd, *J* 8.2, 2.3, C*H*NH), 3.28 (1H, dd, *J* 9.2, 2.2, C*H*NH), 2.79 (1H, br m, CHN*H*). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

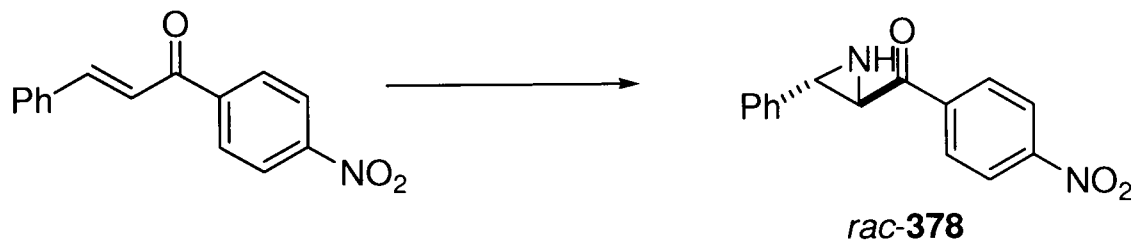
(4'-Methoxyphenyl)((2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-376)**



rac-**376**

4'-Methoxychalcone (29 mg, 0.13 mmol) was used as described in the NMM aziridination procedure to afford aziridine ***rac*-376** (8 mg, 0.03 mmol, 23%) as a white solid; δ_H (400 MHz, $CDCl_3$) 8.02-8.00 (2H, m, ArH), 7.39-7.28 (5H, m, ArH), 6.99-6.97 (2H, m, ArH), 3.90 (3H, s, OCH_3), 3.48 (1H, br m, C*H*NH), 3.17 (1H, br m, C*H*NH), 2.66 (1H, br m, CHN*H*). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

(4'-Nitrophenyl)((2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-378)**

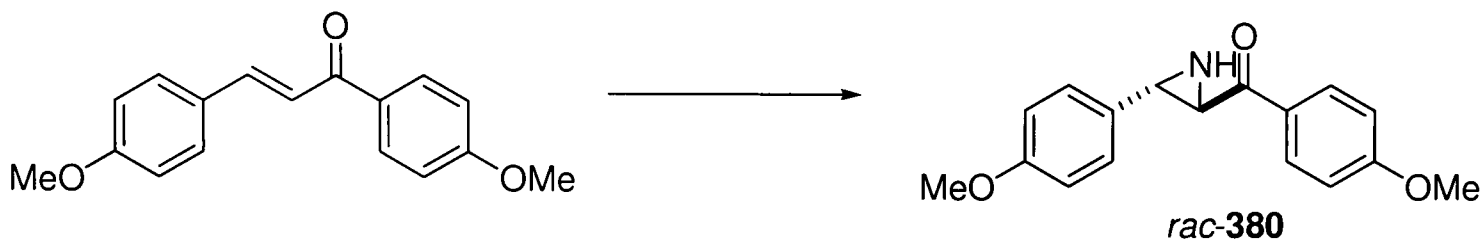


rac-**378**

4'-Nitrochalcone (20 mg, 0.08 mmol) was used as described in the NMM aziridination procedure. Purification by column chromatography (100:3 to 100:6 petrol:EtOAc) gave

aziridine ***rac*-378** (2 mg, 0.01 mmol, 9%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 8.38-8.35 (2H, m, ArH), 8.18-8.16 (2H, m, ArH), 7.42-7.36 (5H, m, ArH), 3.53 (1H, br s, C*H*NH), 3.29 (1H, br s, C*H*NH), 2.75 (1H, br s, NH). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

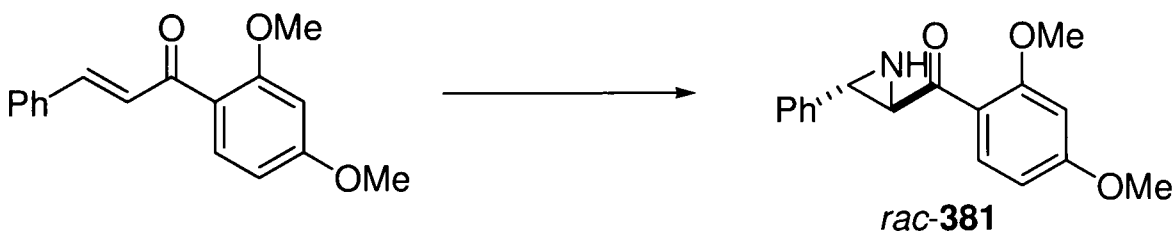
(4-Methoxyphenyl)((2*R, 3*S**)-3-(4'-methoxyphenyl)aziridin-2-yl)methanone (*rac*-380)**



rac-**380**

4,4'-Dimethoxychalcone (12 mg, 0.04 mmol) was used as described in the NMM aziridination procedure to afford aziridine ***rac*-380** (3 mg, 0.01 mmol, 24%) as a pale orange solid; δ_H (400 MHz, $CDCl_3$) 8.01 (2H, d, *J* 8.8, ArH), 7.31 (2H, d, *J* 8.8, ArH), 6.98 (2H, d, *J* 8.7, ArH), 6.92 (2H, d, *J* 8.7, ArH), 3.90 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.45 (1H, d, *J* 2.2, C*H*NH), 3.13 (1H, d, *J* 2.2, C*H*NH), 1.7 (1H, br, NH). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

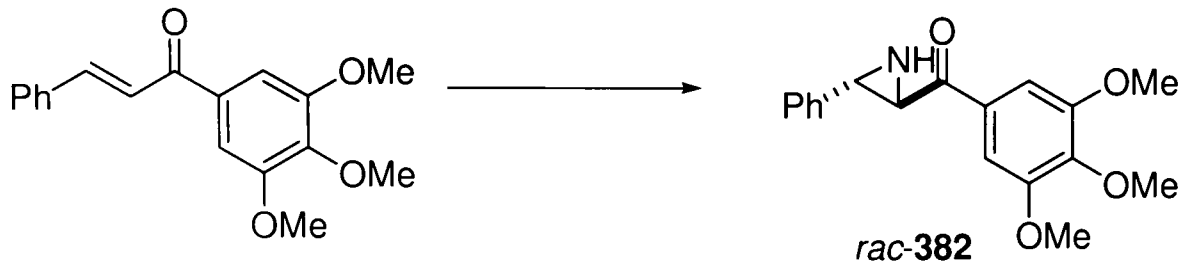
(2',4'-Dimethoxyphenyl)((2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-381)**



rac-**381**

2',4'-Dimethoxychalcone (35 mg, 0.13 mmol) was used as described in the NMM aziridination procedure. Purification by column chromatography (100:3 to 100:7.5 petrol:EtOAc) gave aziridine ***rac*-381** (29 mg, 0.10 mmol, 78%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* 8.8, ArH), 7.40-7.30 (5H, m, ArH), 6.58 (1H, dd, *J* 8.8, 2.3, ArH), 6.44 (1H, d, *J* 2.3, ArH), 3.88 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.58-3.56 (1H, br m, C*H*NH), 3.12-3.11 (1H, br m, C*H*NH), 2.75-2.71 (1H, br m, NH). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

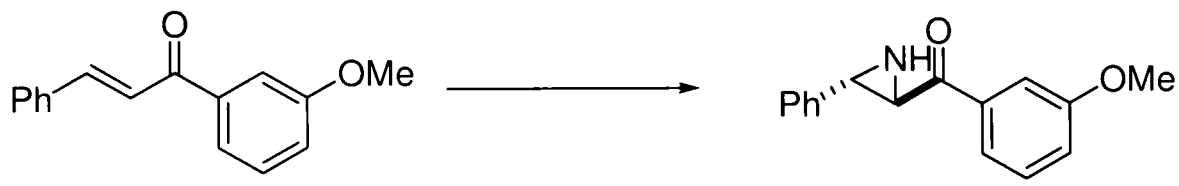
((2*R, 3S*)-3-Phenylaziridin-2-yl)(3', 4', 5'-trimethoxyphenyl)methanone (*rac*-382)



rac-**382**

3',4',5'-Dimethoxychalcone (39 mg, 0.13 mmol) was used as described in the NMM aziridination procedure. Purification by column chromatography (100:7 to 100:10 petrol:EtOAc) gave to afford aziridine ***rac*-382** (30 mg, 0.10 mmol, 73%) as a yellow solid; δ_H (400 MHz, $CDCl_3$) 7.42-7.29 (7H, m , ArH), 3.95 (3H, s, OCH_3), 3.90 (6H, br s, 2 x OCH_3), 3.46 (1H, d, *J* 1.83, C*H*NH), 3.22 (1H, br, C*H*NH), 2.70 (1H, br, NH). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

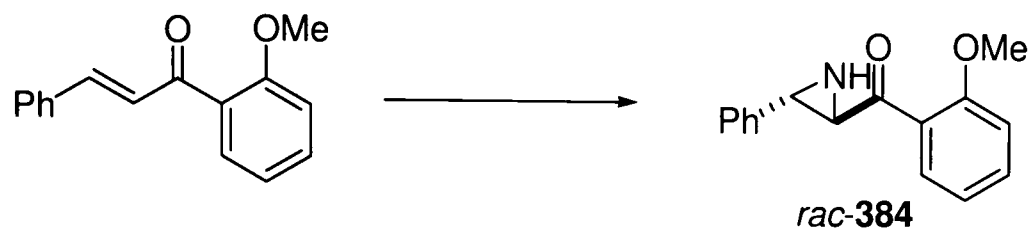
(3'-Methoxyphenyl)((2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-383)**



rac-**383**

3'-Methoxychalcone (29 mg, 0.13 mmol) was used as described in the NMM aziridination procedure. Purification by column chromatography (100:3.5 to 100:7 petrol:EtOAc) gave aziridine ***rac*-383** (23 mg, 0.09 mmol, 71%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 7.6, ArH), 7.55-7.53 (1H, m, ArH), 7.43-7.33 (6H, m, ArH), 7.20-7.17 (1H, m, ArH), 3.88 (3H, s, OCH_3), 3.52 (1H, br s, C*H*NH), 3.21 (1H, br s, C*H*NH), 2.69 (1H, br s, NH). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

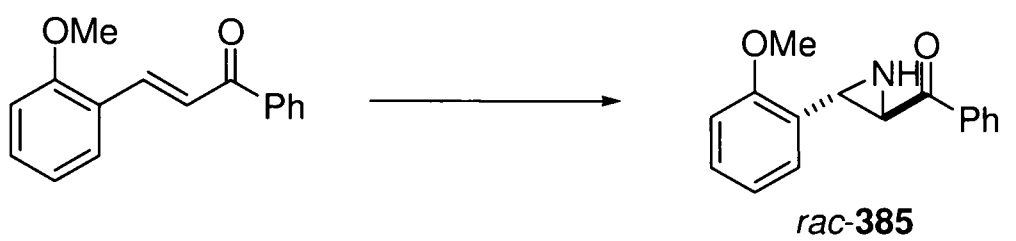
(2'-Methoxyphenyl)((2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-384)**



rac-**384**

2'-Methoxychalcone (30 mg, 0.13 mmol) was used as described in the NMM aziridination procedure to afford aziridine ***rac*-384** (20 mg, 0.08 mmol, 61%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* 7.7, 1.8, ArH), 7.54-7.51 (1H, m, ArH), 7.41-7.28 (5H, m, ArH), 7.07-7.03 (1H, m, ArH), 6.96 (1H, d, *J* 8.4, ArH), 3.64 (3H, s, OCH_3), 3.55 (1H, d, *J* 2.4, C*H*NH), 3.17 (1H, d, *J* 2.4, C*H*NH), 2.68 (1H, br s, NH). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

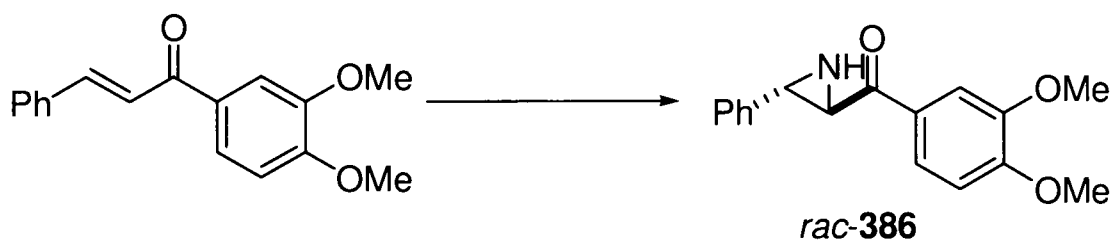
((2*R, 3*S**)-3-(2-Methoxyphenyl)aziridin-2-yl)(phenyl)methanone (*rac*-385)**



rac-**385**

2-Methoxychalcone (29 mg, 0.12 mmol) was used as described in the NMM aziridination procedure to afford aziridine ***rac*-385** (26 mg, 0.10 mmol, 79%) as a white solid; δ_H (400 MHz, $CDCl_3$) 8.08-8.06 (2H, m, ArH), 7.67-7.61 (1H, m, ArH), 7.53-7.49 (2H, m, ArH), 7.45-7.44 (1H, m, ArH), 7.32-7.28 (1H, m, ArH), 7.03-6.99 (1H, m, ArH), 6.92-6.90 (1H, m, ArH), 3.81 (3H, s, OCH_3), 3.48 (1H, br s, C*H*NH), 3.43 (1H, br s, C*H*NH), 2.58 (1H, br s, NH). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

(3',4'-Dimethoxyphenyl)((2*R, 3*S**)-3-phenylaziridin-2-yl)methanone (*rac*-386)**



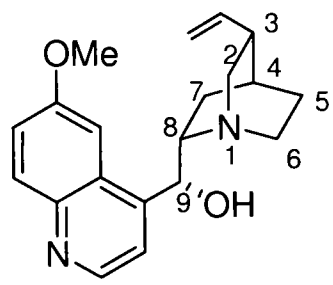
rac-**386**

3',4'-Dimethoxychalcone (26 mg, 0.10 mmol) was used as described in the NMM aziridination procedure. Purification by column chromatography (100:8 to 100:10

petrol:EtOAc) gave aziridine ***rac*-386** (1 mg, 0.004 mmol, <5%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, dd, *J* 8.4, 2.0, ArH), 7.58 (1H, d, *J* 2.0, ArH), 7.39-7.31 (5H, m, ArH), 6.91 (1H, d, *J* 8.4, ArH), 3.97 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.49 (1H, dd, *J* 9.0, 2.3, C*H*NH), 3.18 (1H, dd, *J* 9.0, 2.3, C*H*NH), 2.65 (1H, t, *J* 9.0, NH). ^{1}H NMR corresponds to that of the enantiomerically enriched compound.

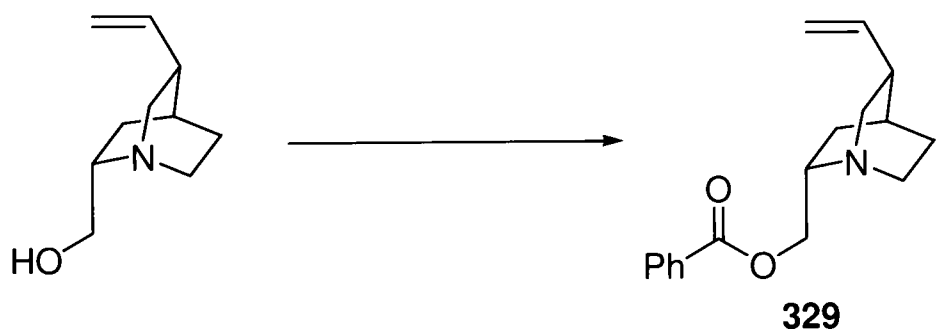
3.2.2.7 Synthesis of Cinchona Alkaloid Derivatives

(Where deduced, ^{1}H NMR assignments are given in accordance with the following scheme for the quinuclidine unit).



Quinine

Quincorine-*O*-Benzoate (329)[136]

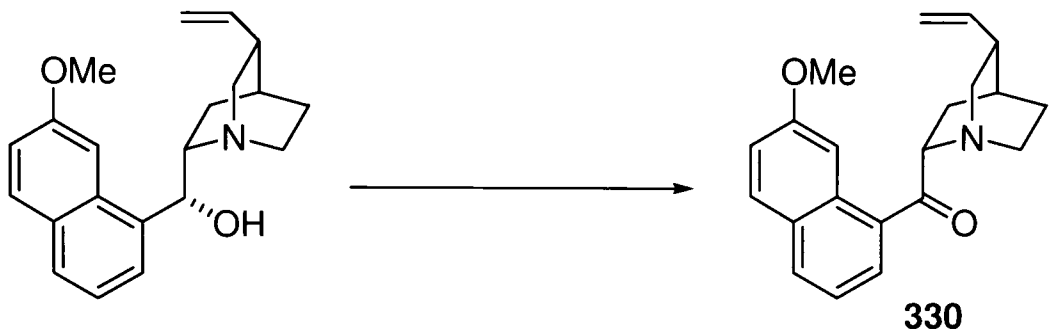


329

Quincorine (50 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. Benzoyl chloride (45 µL, 0.39 mmol) was added dropwise and the reaction was allowed to warm to rt with stirring for 4 h. Saturated aqueous $NaHCO_3$ (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (100:4:6 EtOAc:MeOH:NEt_3) to afford the *title compound* **329** (67 mg, 0.25 mmol, 84%) as a pale yellow oil; $[\alpha]^{22}_D$ +35.7 (*c* 1.6, CH_2Cl_2), lit. value: $[\alpha]_D$ +21 (*c* 1.4, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 8.07-8.05 (2H, m, ArH), 7.57-7.53 (1H, m, ArH), 7.45-7.41 (2H, m, ArH), 5.90 (1H, ddd, *J* 17.5, 10.1, 7.6, C*H*=CH_2), 5.10-5.04 (2H, m, CH=CH_2), 4.41 (1H,

dd, *J* 11.4, 8.1, 1 × CH_2CO_2Ph), 4.25 (1H, dd, *J* 11.4, 6.0, 1 × CH_2CO_2Ph), 3.27-3.18 (2H, m), 3.14-3.06 (1H, m), 2.77-2.70 (2H, m), 2.37-2.27 (1H, m), 2.00-1.92 (1H, m), 1.81-1.79 (1H, m), 1.60-1.55 (2H, m), 1.13-1.08 (1H, m); m/z (CI (NH_3)) 272 (100%) $[M+H]^+$, found : $[M+H]^+$, 272.1652 $C_{17}H_{22}NO_2$ requires : 272.1651. Data matches previously reported values.

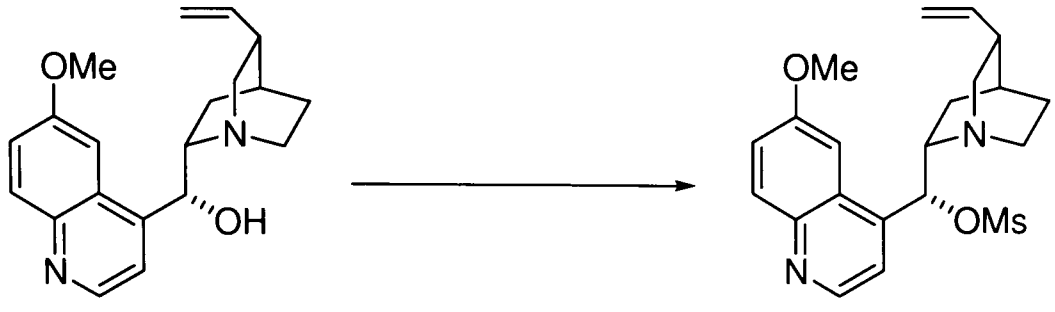
Quininone (330)[154]



330

To benzophenone (0.55 g, 3.1 mmol) in toluene (10 mL) was added quinine (0.5 g, 1.5 mmol) followed by KO*t*Bu (0.45 g, 3.9 mmol). The slurry was heated to reflux for 6.5 h and allowed to cool to rt overnight. The solution was cooled in an ice bath and 2 M HCl (5 mL) was added dropwise. The aqueous layer was collected and the organics were washed with 2 M HCl (2 × 5 mL). The combined aqueous layers were cooled to 0 °C and 5 M NaOH (10 mL) was added until the mixture reached pH 9. The solution was then extracted with $CHCl_3$ (3 × 25 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (100:4:6 EtOAc:MeOH:NEt_3) followed by recrystallisation from ether to give the *title compound* **330** (0.32 g, 1.0 mmol, 65%) as a pale yellow solid; m.p. 105-107 °C (lit., 102-104 °C); $[\alpha]^{22}_D$ +184.0 (*c* 0.5, $CHCl_3$), lit., value: $[\alpha]_D$ +219 (*c* 2.94, solvent not stated); δ_H (400 MHz, $CDCl_3$) 8.87 (1H, d, *J* 4.5, ArH), 8.05 (1H, d, *J* 9.2, ArH), 7.68-7.67 (2H, m, ArH), 7.42 (1H, dd, *J* 9.2, 2,8, ArH), 6.04-5.95 (1H, m, C*H*=CH_2), 5.10-5.05 (2H, m, CH=CH_2), 4.25-4.20 (1H, m, H-8), 4.00 (3H, s, OCH_3), 3.20-3.11 (1H, m), 2.97-2.90 (2H, m), 2.69-2.63 (1H, m), 2.41-2.27 (2H, m), 1.91-1.86 (1H, m), 1.74-1.68 (2H, m), 1.60-1.54 (1H, m); m/z (CI (NH_3)) 323 (100%) $[M+H]^+$, found : $[M+H]^+$, 323.1757 $C_{20}H_{23}N_2O_2$ requires : 323.1760. Data matches previously reported values.

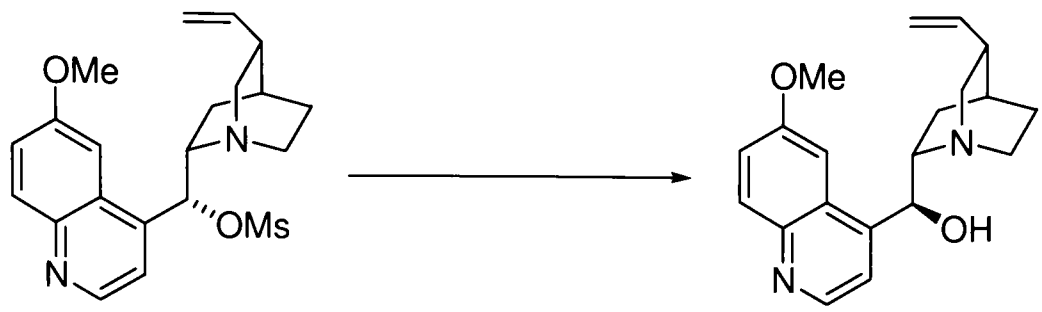
Quinine mesylate (338)



338

To a solution of quinine (1.0 g, 3.1 mmol) in THF (30 mL) was added MsCl (0.48 mL, 6.2 mmol) and NEt_3 (1.0 mL, 7.1 mmol). The reaction was heated to reflux for 4 h and then allowed to cool to rt after which time saturated aqueous $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL) and the combined organics were then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (9:1, ether:MeOH) to give the *title compound* **338** (1.2 g, 3.1 mmol, quantitative) as an off-white foam; $[\alpha]^{22}_D$ -61.2 (*c* 4.9, $CHCl_3$); ν_{max}/cm^{-1}(nujol) 3390, 2935, 1621, 1592, 1505, 1359, 1173; δ_H (400 MHz, $CDCl_3$) 8.83 (1H, d, *J* 4.5, ArH), 8.08 (1H, d, *J* 9.2, ArH), 7.47-7.39 (3H, m, ArH), 6.19 (1H, br s, CHOMs), 5.91-5.82 (1H, m, C*H*=CH_2), 5.06-5.02 (2H, m, CH=CH_2), 3.99 (3H, s, OCH_3), 3.47-3.40 (1H, br m, H-8), 3.18-3.09 (1H, br m, H-6), 3.00 (1H, dd, *J* 13.7, 10.2, H-2), 2.70-2.56 (5H, m, SO_2CH_3 and H-6 and H-2), 2.32-2.28 (1H, br m, H-3), 2.10-2.07 (1H, br m, 1 × H-5 or H-4), 1.95-1.94 (1H, br m, 1 × H-5 or H-4), 1.83-1.75 (1H, m, 1 × H-5 or H-4), 1.70-1.54 (2H, m, 2 × H-7); δ_C (100 MHz, $CDCl_3$) 158.4 (C), 147.5 (CH), 144.9 (C), 141.5 (CH), 132.2 (CH), 126.6 (C), 122.3 (CH), 119.3 (CH), 118.6 (C), 114.5 (CH_2), 100.9 (CH), 79.9 (CH), 60.2 (CH), 56.4 (CH_2), 55.7 (CH), 42.3 (CH_2), 39.5 (CH), 39.1 (CH), 27.6 (CH_2), 27.3 (CH), 25.0 (CH_2); m/z (ES^+) $[M+H]^+$, found : $[M+H]^+$, 403.1692 $C_{21}H_{27}N_2O_4S$ requires : 403.1692.

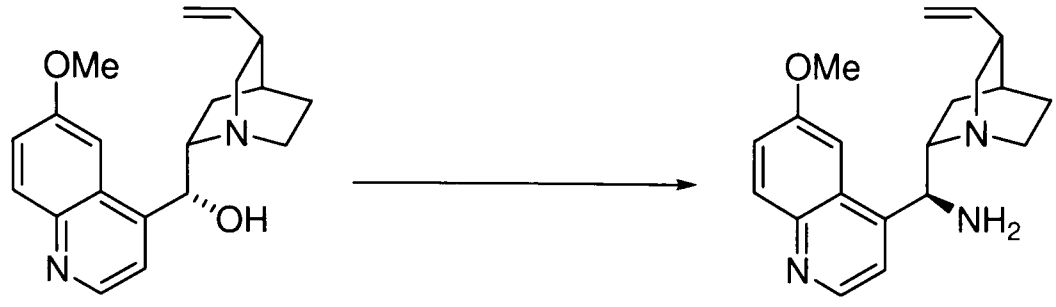
Epiquinine (339)



339

Quinine mesylate (0.63 g, 1.6 mmol) and (L)-tartaric acid (0.24 g, 1.6 mmol) in H_2O (8 mL) were heated to reflux for 30 min. The solution was cooled to rt and quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was then extracted with $CHCl_3$ (6 × 10 mL) and the organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc:MeOH, 4:1, then MeOH) to give the *title compound* **339** (0.42 g, 1.3 mmol, 82%) as a white foam; $[\alpha]^{22}_D$ + 27.1 (*c* 1.3, $CHCl_3$); ν_{max}/cm^{-1}(nujol) 3391, 2921, 1621, 1504, 1454, 1359, 1240; δ_H (400 MHz, $CDCl_3$) 8.68 (1H, d, *J* 4.5, ArH), 8.00 (1H, d, *J* 9.2, ArH), 7.62 (1H, d, *J* 2.8, ArH), 7.35 (1H, d, *J* 4.5, ArH), 7.32 (1H, dd, *J* 9.2, 2.8, ArH), 5.73-5.64 (1H, m, C*H*=CH_2), 4.98 (1H, d, *J* 10.0, C*H*OH), 4.95-4.88 (2H, m, CH=CH_2), 4.64 (1H, br, CHO*H*), 3.87 (3H, s, OCH_3), 3.20 (1H, dd, *J* 13.8, 10.0, H-2), 3.16-3.04 (2H, m, H-8 and H-6), 2.76-2.69 (2H, m, H-6 and H-2), 2.27-2.23 (1H, br, H-3), 1.65-1.63 (1H, br m, H-4), 1.56-1.52 (2H, m, 2 × H-5), 1.43-1.36 (1H, m, H-7), 0.89 (1H, dd, *J* 13.5, 7.8, H-7); δ_C (100 MHz, $CDCl_3$) 157.4 (C), 147.5 (CH), 144.8 (C), 144.5 (C), 141.4 (CH), 131.6 (CH), 128.2 (C), 121.3 (CH), 120.1 (CH), 114.6 (CH_2), 102.6 (CH), 71.4 (CH), 61.5 (CH), 55.9 (CH_2), 55.5 (CH), 40.8 (CH_2), 39.8 (CH), 28.0 (CH_2), 27.2 (CH), 25.1 (CH_2); m/z (CI (NH_3)) 325 (100%) $[M+H]^+$, found : $[M+H]^+$, 325.1926 $C_{20}H_{25}N_2O_2$ requires : 325.1916.

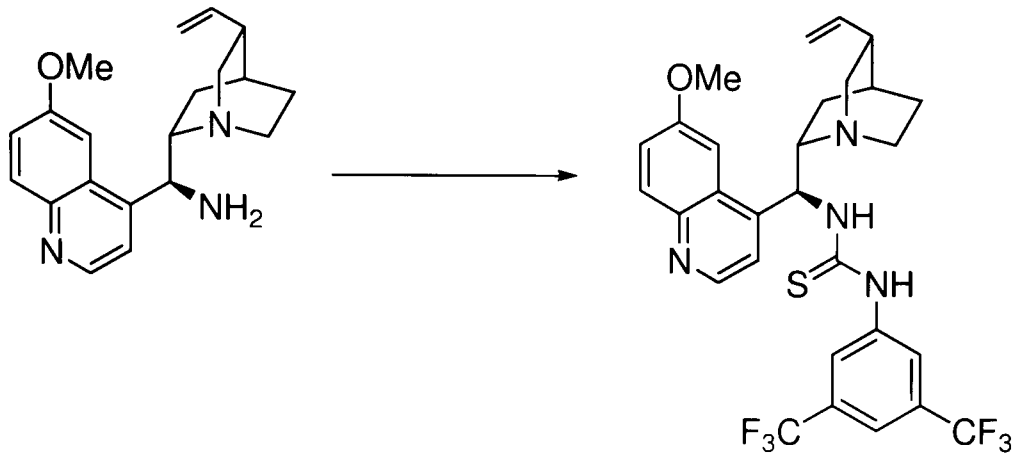
9-Amino(9-deoxy)-9-epiquinine (340)[155]



340

Quinine (0.1 g, 0.31 mmol) and PPh_3 (0.12 g, 0.47 mmol) were dissolved in dry THF (2.5 mL) and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (90 μL, 0.47 mmol) was added all at once. Then a solution of diphenyl phosphoryl azide (100 μL, 0.47 mmol) in THF (1.5 mL) was added dropwise. The mixture was allowed to warm to rt. After being stirred for 22 h the solution was heated to 50 °C for 7 h. PPh_3 (0.13 g, 1.6 mmol) was added and heating was maintained for a further 16 h, after which time another portion of PPh_3 (0.25 g, 3.0 mmol) was added and the reaction was stirred for another 6 h. The solution was allowed to cool to rt and water (0.3 mL) was added with stirring for 18 h. Solvents were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and 10% aqueous HCl (1:1, 4 mL). The aqueous phase was washed with CH_2Cl_2. (4 × 10 mL) then made alkaline with conc. aqueous NH_3. The aqueous phase was then washed with CH_2Cl_2 (4 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc:MeOH:conc. aqueous NH_4OH, 50:50:1) to afford the *title compound* **340** (59 mg, 0.18 mmol, 59%) as a pale yellow oil; $[\alpha]^{22}_D$ +88.4 (*c* 1.8, $CHCl_3$), lit., value: $[\alpha]^{25}_D$ +80 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.77 (1H, d, *J* 4.5, ArH), 8.05 (1H, d, *J* 9.2, ArH), 7.66 (1H, br s, ArH), 7.47 (1H, d, *J* 2.9, ArH), 7.40 (1H, dd, *J* 9.2, 2.9, ArH), 5.86-5.77 (1H, m, C*H*=CH_2), 5.04-4.97 (2H, m, CH=CH_2), 4.61 (1H, d, *J* 8.7, C*H*NH_2), 3.98 (3H, s, OCH_3), 3.32-3.19 (2H, m, H-6 and H-2), 3.11-3.09 (1H, br m, H-8), 2.84-2.78 (2H, m, H-6 and H-2), 2.30 (1H, br, H-3), 2.15 (2H, br, NH_2), 1.65-1.51 (3H, m, 2 × H-5 and H-4), 1.47-1.42 (1H, br m, H-7), 0.84-0.76 (1H, m, H-7); m/z (EI$^+$) 136 (100%), 187 (40%), 323 (5%, $[M]^+$), found : $[M]^+$, 323.1989 $C_{20}H_{25}N_3O$ requires : 323.1998. Data matches previously reported values.

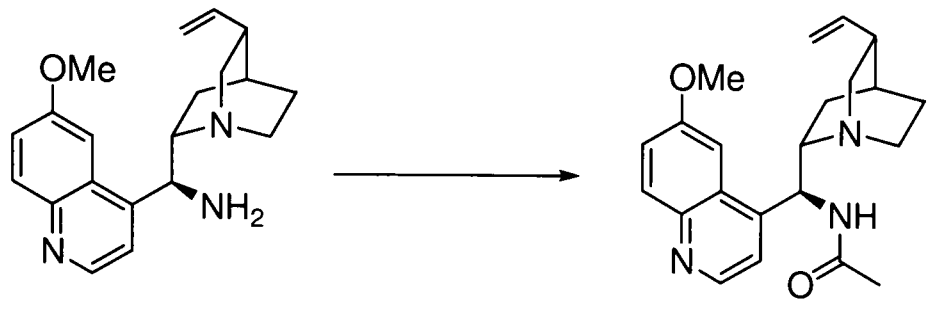
9-(3,5-Bis(trifluoromethyl)phenyl thiourea)-(9-deoxy)-9-epiquinine (268)[139]



268

To a solution of 9-amino epiquinine (32 mg, 0.1 mmol) in dry THF (0.3 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (18 μL, 0.1 mmol) in THF (0.2 mL) at ambient temperature. The mixture was stirred for 18 h and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc:MeOH:conc. aqueous NH_4OH, 300:5:1) to afford the *title compound* **268** (37 mg, 0.1 mmol, 62%) as an off-white solid; m.p. 117-119 °C; $[\alpha]^{22}_D$ -93.8 (*c* 1.9, $CHCl_3$), lit., value: $[\alpha]^{25}_D$ -127.9 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, MeOD) 8.69 (1H, d, *J* 4.7 ArH), 8.12 (2H, s, ArH), 8.10 (1H, d, *J* 2.1, ArH), 7.95 (1H, d, *J* 9.3, ArH), 7.61 (1H, br s, ArH), 7.58 (1H, d, *J* 4.7, ArH), 7.45 (1H, dd, *J* 9.3, 2.1, ArH), 6.38 (1H, d, *J* 10.8, C*H*NH), 5.86 (1H, ddd, *J* 17.4, 10.3, 7.4, C*H*=CH_2), 5.07-4.98 (2H, m, CH=CH_2), 4.03 (3H, s, OCH_3), 3.63-3.59 (1H, br m, H-6), 3.45 (1H, br m, H-8), 3.37-3.28 (1H, br m, H-2), 2.89-2.82 (2H, m, H-6 and H-2), 2.38 (1H, br m, H-3), 1.75-1.64 (3H, br m, 2 × H-5 and H-4), 1.51-1.46 (1H, br m, H-7), 0.90-0.86 (1H, br m, H-7); m/z (EI^+) 136 (100%), 271 (80%), 594 (25% $[M]^+$), found: $[M]^+$, 594.1898 $C_{29}H_{28}N_4OF_6S$ requires : 594.1888. Data matches previously reported values.

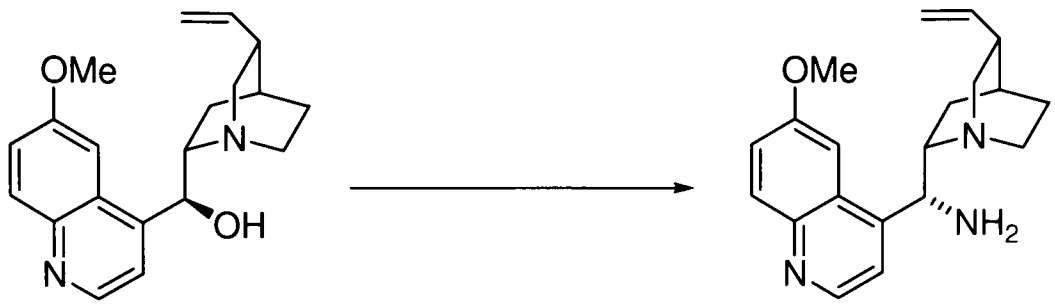
9-*N*-Acetamido(9-deoxy)-9-epiquinine (341)



341

9-Amino(9-deoxy)-9-epiquinine (35 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (0.7 mL) and NEt_3 (0.22 mL, 1.6 mmol) and the solution was cooled to 0 °C. Acetyl chloride (11 μL) in CH_2Cl_2 (0.3 mL) was added dropwise over 10 min. The reaction was then stirred at rt for 18 h. CH_2Cl_2 (1.5 mL) was added, the organic solution washed with saturated aqueous Na_2CO_3 (3 × 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc:MeOH:conc. aqueous NH_4OH, 50:50:1, followed by MeOH:EtOAc, 2:1) to afford the *title compound* **341** (29 mg, 0.1 mmol, 78%) as a yellow oil; $[\alpha]^{22}_D$ +16.6 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1}(nujol) 3245, 2960, 2927, 1650, 1508, 1027, 800, 665; δ_H (400 MHz, $CDCl_3$) 8.73 (1H, d, *J* 4.5, ArH), 8.02 (1H, d, *J* 9.2, ArH), 7.69 (1H, d, *J* 2.1, ArH), 7.39 (1H, dd, *J* 9.2, 2.1, ArH), 7.33 (1H, d, *J* 4.5, ArH), 6.76 (1H, br s, NH), 5.75 (1H, ddd, *J* 17.4, 10.2, 7.5, C*H*=CH_2), 5.37 (1H, br s, C*H*NH), 5.02-4.97 (2H, m, CH=CH_2), 3.99 (3H, s, OCH_3), 3.28 (1H, dd, *J* 13.7, 10.2, H-2), 3.20-3.10 (2H, br m, H-8 and H-6), 2.79-2.69 (2H, m, H-6 and H-2), 2.33-2.30 (1H, br m, H-3), 1.98 (3H, s, $COCH_3$), 1.68-1.61 (3H, m, 2 × H-5 and H-4), 1.47 (1H, br t, *J* 10.5, H-7), 0.92 (1H, br dd, *J* 13.5, 6.2, H-7); δ_C (100 MHz, $CDCl_3$) 170.1 (C), 157.8 (C), 147.5 (CH), 145.1 (C), 144.8 (C), 141.1 (CH), 131.7 (CH), 128.3 (C), 121.7 (CH), 119.2 (CH), 114.6 (CH_2), 101.9 (CH), 59.5 (CH), 56.0 (CH_2), 55.6 (CH), 51.1 (CH), 40.9 (CH_2), 39.4 (CH), 27.8 (CH_2), 27.3 (CH), 26.2 (CH_2), 23.2 (CH); m/z (EI$^+$) 136 (100%), 187 (20%), 230 (12%) 365 (2%, $[M]^+$), found : $[M]^+$, 365.2100 $C_{22}H_{27}N_3O_2$ requires : 365.2103.

9-Amino(9-deoxy)-quinine (342)

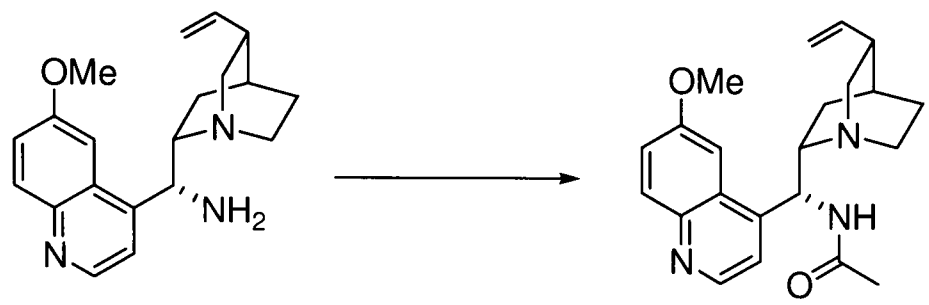


342

Epiquinine (0.23 g, 0.71 mmol) and PPh_3 (0.28 g, 1.07 mmol) were dissolved in dry THF (4 mL) and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (0.21 mL, 1.07 mmol) was added all at once. Then a solution of diphenyl phosphoryl azide (0.23 mL, 1.07 mmol) in THF (2 mL) was added dropwise. The mixture was allowed to warm to rt. After being stirred for 22 h the solution was heated to 50 °C for 2 h. PPh_3 (0.3 g, 1.14 mmol) was added and heating was maintained for a further 2 h, after which time another portion of PPh_3 (0.3 g, 1.14 mmol) was added and the reaction was stirred for another 2 h. The solution was allowed to cool to rt and water (0.5 mL) was added with stirring for 18 h. Solvents were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and 10% aqueous HCl (1:1, 4 mL). The aqueous phase was washed with CH_2Cl_2. (4 × 15 mL) then made alkaline with conc. aqueous NH_3. The aqueous phase was then washed with CH_2Cl_2 (4 × 15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc:MeOH:conc. aqueous NH_4OH, 50:50:1) to afford the *title compound* **342** (38 mg, 0.12 mmol, 17%) as a pale yellow oil; $[\alpha]^{22}_D$ -62.0 (*c* 1.5, $CHCl_3$); ν_{max}/cm^{-1}(nujol) 3380, 3080, 2970, 2880, 1605, 1500, 1225, 1258, 1022; δ_H (400 MHz, $CDCl_3$) 8.75 (1H, d, *J* 4.6, ArH), 8.03 (1H, d, *J* 9.2, ArH), 7.44 (1H, d, *J* 2.4, ArH), 7.38-7.36 (2H, m, ArH), 5.96 (1H, ddd, *J* 17.4, 10.3, 7.5, C*H*=CH_2), 5.10-5.05 (2H, m, CH=CH_2), 4.61 (1H, d, *J* 9.3, C*H*NH_2), 3.97 (3H, s, OCH_3), 3.22 (1H, app. q, *J* 8.4, H-8), 3.05 (1H, dd, *J* 13.7, 10.0, H-2), 3.00-2.94 (1H, br m, H-6), 2.70-2.65 (1H, br m, H-2), 2.60-2.53 (1H, m, H-6), 2.31-2.27 (1H, br m, H-3), 2.20-2.14 (1H, m, H-7), 1.91-1.90 (1H, br m, H-4), 1.76-1.64 (3H, m, H-7 and 2 × NH_2), 1.56-1.51 (2H, m , 2 × H-5); δ_C (100 MHz, $CDCl_3$) 157.7 (C), 149.3 (C), 148.0 (CH), 144.8 (C), 142.0 (CH), 132.0 (CH), 127.7 (C), 121.0 (CH), 118.3 (CH), 114.3 (CH_2), 101.2 (CH), 60.6 (CH),

56.3 (CH_2), 55.6 (CH), 53.9 (CH), 41.9 (CH_2), 39.8 (CH), 27.9 (CH_2), 27.8 (CH), 26.7 (CH_2); m/z (EI^+) 136 (100%), 187 (38%), 323 (5%, $[M]^+$), found : $[M]^+$, 323.2000 $C_{20}H_{25}N_3O$ requires : 323.1998.

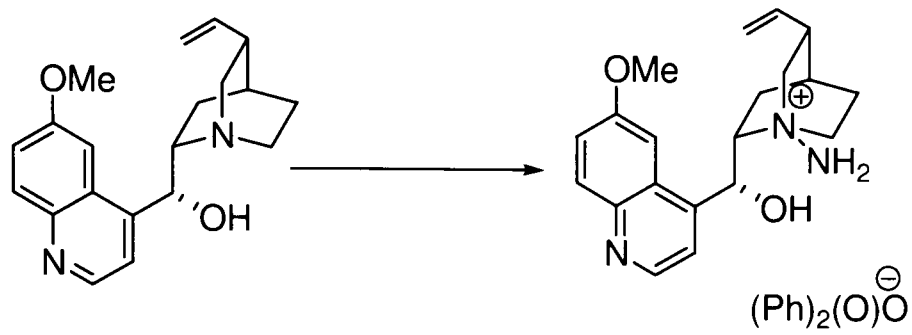
9-*N*-Acetamido-(9-deoxy)-9-quinine (343)



343

9-Amino-(9-deoxy)-9-quinine (30 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (1 mL) and NEt_3 (0.19 mL, 1.4 mmol) and the solution was cooled to 0 °C. Acetyl chloride (10 μL) in CH_2Cl_2 (1 mL) was added dropwise over 10 min. The reaction was then stirred at rt for 18 h. CH_2Cl_2 (1.5 mL) was added, the organic solution washed with saturated aqueous Na_2CO_3 (3 × 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc:MeOH, 3:1) to afford the *title compound* **343** (30 mg, 0.08 mmol, 83%) as a colourless oil; $[\alpha]^{22}_D$ -35.3 (*c* 1.4, $CHCl_3$); ν_{max}/cm^{-1}(nujol) 3566, 2926, 1652, 1558, 1373, 1228, 1028; δ_H (400 MHz, $CDCl_3$) 8.67 (1H, d, *J* 4.6, ArH), 7.95 (1H, d, *J* 9.2, ArH), 7.63 (1H, d, *J* 2.7, ArH), 7.34 (1H, dd, *J* 9.2, 2.7, ArH), 7.31 (1H, d, *J* 4.6, ArH), 6.01-5.87 (3H, m, C*H*=CH_2, C*H*NH and CHN*H*), 5.14-5.10 (2H, m, CH=CH_2), 3.97 (3H, s, OCH_3), 3.67 (1H, app. q, *J* 9.8, H-8), 3.12 (1H, dd, *J* 13.7, 10.0, H-2), 2.92-2.84 (1H, m, H-6), 2.79-2.74 (1H, m, H-2), 2.60-2.54 (1H, m, H-6), 2.32 (1H, br , H-3), 2.07-2.01 (1H, m , H-7), 1.94 (3H, s, COCH_3), 1.88-1.87 (1H, m, H-4), 1.80-1.72 (1H, m, H-5), 1.55-1.47 (2H, m, H-7 and H-5); δ_C (100 MHz, $CDCl_3$) 169.7 (C), 158.2 (C), 147.5 (CH), 144.8 (C), 144.5 (C), 142.0 (CH), 131.5 (CH), 128.4 (C), 122.2 (CH), 119.1 (CH), 114.5 (CH_2), 101.5 (CH), 57.5 (CH), 55.9 (CH), 55.8 (CH_2), 49.4 (CH), 41.4 (CH_2), 39.5 (CH), 27.5 (CH_2), 27.5 (CH), 25.4 (CH_2), 23.3 (CH); m/z (EI^+) 136 (100%), 187 (13%), 230 (5%) 365 (2%, $[M]^+$), found : $[M]^+$, 365.2105 $C_{22}H_{27}N_3O_2$ requires : 365.2103.

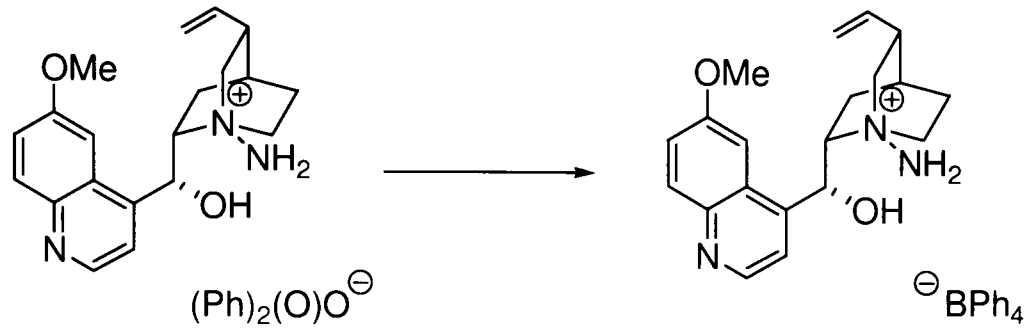
Quinidinium diphenylphosphinate (299)



299

Quinine (0.2 g, 0.62 mmol) was dissolved in dry THF (10 mL) and $DppONH_2$ (0.14 g, 0.62 mmol) was added in one portion to the stirred solution. After 5 min, a thick white precipitate appeared and a further 5 mL of THF was added to the mixture. After 2 h the reaction was filtered and the solvent was removed in *vacuo*. The residue was then dried under vacuum to give the *title compound* **399** (0.28 g, 0.50 mmol, 54%) as a white solid; m.p. 180-182 °C; $[\alpha]^{22}_{D}$ -61.5 (*c* 2.5, MeOH); ν_{max}/cm^{-1}(film) 3243, 1627, 1478, 1247, 1164, 1126; δ_H (400 MHz, $CDCl_3$) 8.73-8.70 (2H, m, ArH), 7.97 (1H, d, *J* 9.2, ArH), 7.72-7.67 (5H, m, ArH), 7.35-7.28 (3H, m, ArH and 2 × NH), 7.00-6.99 (5H, m, ArH), 6.91 (1H, d, *J* 2.5, ArH), 6.06 (1H, br s, OH), 5.39-5.30 (1H, ddd, *J* 17.1, 10.3, 6.9, C*H*=CH_2), 4.91 (1H, d, *J* 10.3, CH=CH_2), 4.90-4.78 (1H, m, H-9), 4.76 (1H, d, *J* 17.1, CH=CH_2), 3.87 (3H, s, OCH_3), 3.83-3.74 (2H, m, H-8 and H-6/2), 3.46 (1H, br s, H-6/2), 3.32-3.28 (1H, m, H-6/2), 2.74-2.69 (1H, m, H-6/2), 2.30-2.15 (3H, m, 2 × H-5/7 and H-3), 1.86-1.85 (1H, m, H-4), 1.76-1.71 (1H, m, H-5/7), 1.36-1.30 (1H, m, H-5/7); δ_C (100 MHz, $CDCl_3$) 157.5 (C), 147.6 (CH), 144.5 (C), 143.8 (C), 140.3 (C), 139.1 (C), 136.6 (CH), 131.5 (CH), 131.1 (CH), 131.0 (CH), 129.6 (CH), 127.7 (CH), 127.6 (CH), 125.6 (C), 121.4 (CH), 119.6 (CH), 117.2 (CH_2), 101.0 (CH), 72.4 (CH), 66.6 (CH_2), 62.9 (CH), 59.1 (CH_2), 55.7 (CH), 38.8 (CH), 30.34 (CH), 26.4 (CH), 26.2 (CH_2), 20.3 (CH_2); m/z (CI (NH_3)) 340 (100%) [MH^+-$Ph_2PO_2^-$], found : [MH^+-$Ph_2PO_2^-$], 340.2036 $C_{20}H_{26}N_3O_2$ requires : 340.2025.

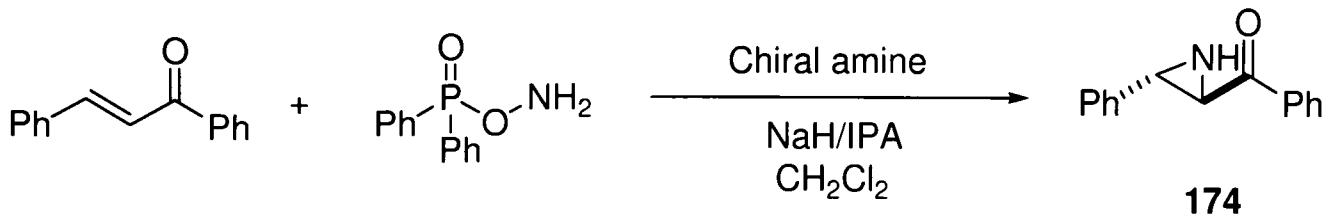
Quinidinium tetraphenylborate (350)



350

$NaBPh_4$ (0.13 g, 0.40 mmol) in H_2O (3 mL) was added to a solution of quinidinium diphenylphosphinate (0.2 g, 0.36 mmol) in H_2O (20 mL). A white precipitate was formed immediately. The reaction was allowed to stir for 40 min after which time the solid was filtered off and dried under vacuum in a desiccator to give the *title compound* **350** (80 mg, 0.12 mmol, 33%) as a white powder; m.p. 132-134 °C; $[\alpha]^{22}_D$ -25.0 (*c* 0.08, MeOH); ν_{max}/cm^{-1}(solid) 3499, 3257, 3055, 1621, 1509, 1242; δ_H (400 MHz, $CDCl_3$) 8.73 (1H, d, *J* 4.4 ArH), 8.07 (1H, d, *J* 9.2, ArH), 7.58-7.56 (8H, br m, ArH), 7.50-7.37 (3H, m, ArH), 7.15 (7H, t, *J* 7.3, ArH), 6.98-6.94 (5H, br m, ArH), 5.82 (1H, br s, OH), 5.44-5.37 (1H, m, C*H*=CH_2), 5.08-4.97 (3H, m, CH=CH_2 and H-9), 4.00-3.84 (2H, m, H-8 and H-2/6), 3.91 (3H, s, OCH_3), 3.10-2.99 (1H, m, H-2/6), 2.82-2.73 (1H, m, H-2/6), 2.55-2.50 (3H, br m, H-3 and H-2/6 and H-5/7), 2.13-2.08 (1H, br m, H-5/7), 1.92 (1H, br s, H-4), 1.73-1.65 (1H, m, H-5/7), 1.36-1.30 (1H, m, H-5/7); δ_C (100 MHz, $CDCl_3$) 163.8 (C), 163.4 (C), 158.2 (C), 147.4 (CH), 143.7 (C), 143.4 (C), 139.3 (C), 138.0 (C), 136.1 (CH), 135.9 (CH), 135.8 (CH), 135.3 (CH), 131.7 (CH), 130.8 (CH), 130.7 (CH), 130.0 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 126.4 (CH), 126.2 (CH), 125.3 (C), 122.3 (CH), 121.4 (CH), 119.1 (CH), 117.9 (CH_2), 100.9 (CH), 71.9 (CH), 67.0 (CH_2), 63.3 (CH), 58.5 (CH_2), 55.8 (CH), 38.8 (CH), 25.9 (CH), 25.6 (CH_2), 19.7 (CH_2); m/z (EI^+) 340 (100%) [MH^+-$^-BPh_4$], found : [MH^+-$^-BPh_4$], 340.2033 $C_{20}H_{26}N_3O_2$ requires : 340.2025.

3.2.2.8 Asymmetric Aziridination using Cinchona Alkaloid Derivatives



174

***In situ* Hydrazinium Salt Formation and Enantioselective Aziridination of Chalcone[101]**

Chiral amine (1.0 equiv.) was added in one portion to a solution of $DppONH_2$ (1 equiv.) in CH_2Cl_2 (2 mL) at rt. The white mixture was allowed to stir for 30 min, then IPA (2 equiv.), NaH (60% dispersion in mineral oil, 2 equiv.) and chalcone (1 equiv.) were added sequentially. The mixture was allowed to stir at rt for 23 h and was then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL), the organics combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (100% petrol to 2.5% to 5% EtOAc) gave the aziridine. Optical purity determined by chiral HPLC analysis in comparison with authentic racemic material. Conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H (unless otherwise stated).[101]

Quinine (41 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (19 mg, 0.09 mmol, 63%) as an off-white solid m.p. 102-104 °C (lit., 100-101 °C); $[\alpha]^{22}_D$ -113.0 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.03-8.00 (2H, m, ArH), 7.66-7.63 (1H, m, ArH), 7.51-7.49 (2H, m, ArH), 7.40-7.34 (5H, m, ArH), 3.54 (1H, dd, *J* 8.0, 2.3, C*H*NH), 3.21 (1H, dd, *J* 9.3, 2.3, C*H*NH), 2,70 (1H, br dd, *J* 9.3, 8.0, NH); m/z (CI (NH_3)) 224 (100%) $[M+H]^+$, found: $[M+H]^+$, 224.1083 $C_{15}H_{14}NO$ requires : 224.1075; Assay of enantiomeric excess: (t_R (minor)=15.96 min, t_R (major)=18.82 min) 57% *e.e.*. Data matches previously reported values.[101]

Quinidine (41 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford

aziridine **174** (9 mg, 0.04 mmol, 31%) as an off-white solid; $[\alpha]^{22}_{D}$ +197.8 (*c* 0.5, $CHCl_3$); Assay of enantiomeric excess: (t_R (major)=14.51 min, t_R (minor)=17.35 min) 50% *e.e.*. Data matches previously reported values.

Hydroquinine (42 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (14 mg, 0.06 mmol, 49%) as an off-white solid; $[\alpha]^{22}_{D}$ -96.5 (*c* 0.7, $CHCl_3$); Assay of enantiomeric excess: (t_R (minor)=15.01 min, t_R (major)=17.75 min) 50% *e.e.*. Data matches previously reported values.

Hydroquinidine (42 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (9 mg, 0.04 mmol, 32%) as an off-white solid; $[\alpha]^{22}_{D}$ +85.1 (*c* 0.5, $CHCl_3$); Assay of enantiomeric excess: (t_R (major)=15.14 min, t_R (minor)=18.01 min) 30% *e.e.*. Data matches previously reported values.

Cinchonidine (38 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (11 mg, 0.05 mmol, 38%) as an off-white solid; $[\alpha]^{22}_{D}$ -90.1 (*c* 0.6, $CHCl_3$); Assay of enantiomeric excess: (t_R (minor)=14.61 min, t_R (major)=16.47 min) 42% *e.e.*. Data matches previously reported values.

Cinchonine (38 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (12 mg, 0.05 mmol, 42%) as an off-white solid; $[\alpha]^{22}_{D}$ +101.6 (*c* 0.6, $CHCl_3$); Assay of enantiomeric excess: (t_R (major)=14.75 min, t_R (minor)=16.64 min) 41% *e.e.*. Data matches previously reported values.

Hydrocinchonine (41 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (17 mg, 0.08 mmol, 50%) as an off-white solid; $[\alpha]^{22}_{D}$ +55.8 (*c* 0.8, $CHCl_3$);

Assay of enantiomeric excess: (t_R (major)=14.89 min, t_R (minor)=16.81 min) 26% *e.e.*. Data matches previously reported values.

Hydroquinine-4-methyl-2-quinolyl ether (61 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (2 mg, 0.01 mmol, 6%) as an off-white solid; $[\alpha]^{22}_D$ negligible; Assay of enantiomeric excess: (t_R (major)=15.06 min, t_R (minor)=17.94 min) 27% *e.e.*. Data matches previously reported values.

Hydroquinidine-4-methyl-2-quinolyl ether (61 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (2 mg, 0.01 mmol, 7%) as an off-white solid; $[\alpha]^{22}_D$ negligible; Assay of enantiomeric excess: (t_R (major)=15.09 min, t_R (minor)=17.93 min) 85% *e.e.*. Data matches previously reported values.

Quincorine (20 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (12 mg, 0.05 mmol, 44%) as an off-white solid; $[\alpha]^{22}_D$ negligible; Assay of enantiomeric excess: (t_R (major)=14.45 min, t_R (minor)=17.31 min) 1% *e.e.*. Data matches previously reported values.

OBz Quincorine (35 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (2 mg, <10%) as an off-white solid; $[\alpha]^{22}_D$ +100.0 (*c* 0.1, $CHCl_3$); Assay of enantiomeric excess: (t_R (major)=14.82 min, t_R (minor)=16.84 min) 6% *e.e.*. Data matches previously reported values.

Quininone (42 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (4.5 mg, 0.02 mmol, 16%) as an off-white solid; $[\alpha]^{22}_D$ +35.5 (*c* 0.2,

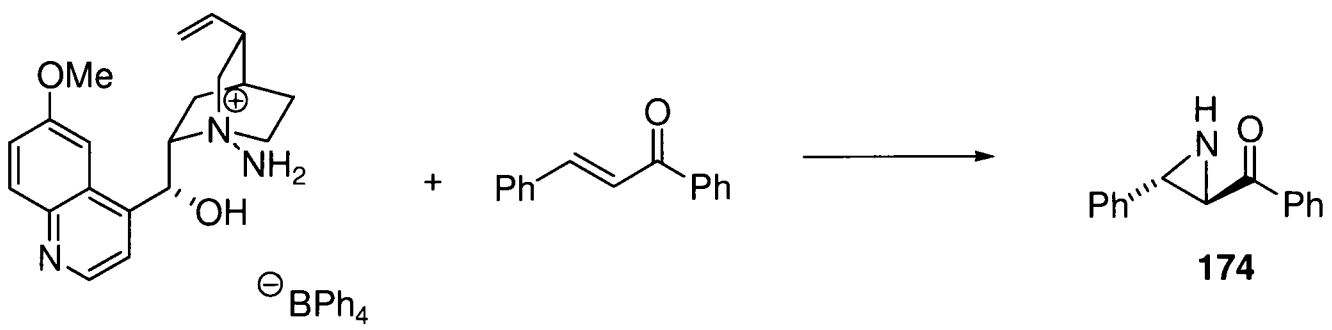
$CHCl_3$); Assay of enantiomeric excess: (t_R (major)=14.73 min, t_R (minor)=17.29 min) 3% *e.e.*. Data matches previously reported values.

Quincoridine (22 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (23 mg, 0.10 mmol, 85%) as a white solid with 0% *e.e.* Data matches previously reported values.

Epiquinine (51 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (8 mg, 0.04 mmol, 28%) as a white solid; $[\alpha]^{22}_D$ +14.5 (*c* 0.4, $CHCl_3$); Assay of enantiomeric excess: (t_R (major)=14.73 min, t_R (minor)=16.63 min) 11% *e.e.*. Data matches previously reported values.

9-*N*-Acetamido-(9-deoxy)-9-epiquinine (20 mg, 0.05 mmol) in CH_2Cl_2 (1.5 mL) was used as described in the *in situ* hydrazinium salt formation and enantioselective aziridination of chalcone to afford aziridine **174** (1 mg, 0.004 mmol, 8%) as a white solid; $[\alpha]^{22}_D$ negligible; Assay of enantiomeric excess: (t_R (major)=14.75 min, t_R (minor)=16.59 min) 14% *e.e.*. Data matches previously reported values.

3.2.2.9 Screening of Quinidinium Borate Salt 350



350 **174**

n-BuLi (44 μL, 1.36 M in hexanes, 0.06 mmol) was added to a solution of quinidinium borate **350** (20 mg, 0.03 mmol) in THF (1 mL) at -78 °C. After 10 min chalcone (6 mg, 0.03 mmol) in THF (0.5 mL) was added to the reaction dropwise. The reaction was

allowed to stir for 24 h at rt. NH_4Cl (2 mL) was added and organics were extracted with CH_2Cl_2 (3 × 10 mL). The solution was dried over Na_2SO_4 and the solvents removed *in vacuo*. The crude product was purified by silica gel chromatography (100:2.5 to 100:5 petrol:EtOAc) to give aziridine **174** (5 mg, 0.02 mmol, 71%) as a white solid; $[\alpha]^{22}_D$ negligible; δ_H (400 MHz, $CDCl_3$) 8.03-8.00 (2H, m, ArH), 7.66-7.34 (8H, m, ArH), 3.54 (1H, br s, C*H*NH), 3.21 (1H, br s, C*H*NH), 2.70 (1H, br s, NH); m/z (EI^+) 105 (98%), 118 (62%), 206 (72%) 223 (43%, $[M]^+$), found : $[M]^+$, 223.0991 $C_{15}H_{13}NO$ requires : 223.0997; Assay of enantiomeric excess: (t_R (minor)=14.54 min, t_R (major)=16.35 min) 31% *e.e.*. Data matches previously reported values.[101]

4. References

4. References

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